Intelligent Decision Support Systems in Ventilation Management

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Table of Contents

List of Tables

Chapter 2:

Chapter 3:

Chapter 5:

Chapter 6:

Chapter 7:

Appendix I:

Appendix II:

Appendix III:

Appendix IV:

Appendix V:

Appendix VII:

List of Figures

Chapter 2:

Chapter 5:

Chapter 6:

Chapter 7:

Appendix I:

Appendix II:

Appendix III:

Appendix IV:

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Declaration

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Abstract

Introduction: Intensive Care Unit (ICU) medical personnel, in an ongoing process termed ventilation management, utilize patient physiology and pathology data to define ventilator apparatus settings.

Aims: The aim of the research is to develop and evaluate in comparison hybrid ventilation advisor systems, that could support ventilation management process, specific to lung pathology for patients ventilated in control mode.

Methodology: A questionnaire was designed and circulated to Intensivists. Patient data, as defined by the questionnaire analysis, were collected and categorized into three lung pathologies. Three ICU doctors evaluated correlation analysis of the recorded data. Evaluation results were used for identifying models basic architecture. Two custom software toolboxes were developed for developing hybrid systems; namely the **EV**olution **O**f **F**uzzy **IN**ference **E**ngines (EVOFINE) and the **FU**zzy **N**eural (FUN) toolbox. Eight hybrid systems developed with EVOFINE, FUN, ANFIS and ANN techniques were evaluated against applied clinical decisions and patient scenarios.

Results: Seventeen (17) models were designed for each of the eight (8) modeling techniques. The modelled process consisted of twelve physiology variables and six ventilator settings. The number of models' inputs ranged from single to six based on correlation and evaluation findings. Evaluation against clinical recommendations has shown that ANNs performed better; mean average error as percentage for four of the applied techniques was 0.16%, 1.29% & 0.62 for ANN empirical, 0.05%, 2.23% & 2.30% for ANFIS, 0.93%, 2.33% & 1.89% for EVOFINE and 0.73%, 2.63% & 6.56 for FUN NM, in Normal, COPD and ALI-ARDS categories respectively. Additionally evaluation against clinical disagreement SD has shown that 70.6% of the NN empirical models were performing in 90% of their suggestions within clinical SD, while the percentages were 53%, 53% and 59% for the EVOFINE, ANFIS and NN Normalized models respectively. The EVOFINE and ANFIS produced Fuzzy Systems whose architecture is transparent for the user. Visual observation of ANFIS architectures revealed possibly hazardous advices. Evaluation against clinical disagreement has shown that the NN empirical was not producing hazardous advices, while EVOFINE, ANFIS and NN Normalized were shown to produce potentially hazardous advice in 17.6%, 23% and 5.8% of the developed models.

Abbreviations

A	Alveolar
a	Arterial
ALI	Acute Lung Injury
ANFIS	Adaptive network based fuzzy inference system
ANN	Artificial Neural Network
APRV	Airway Pressure Release Ventilation
ARDS	Acute respiratory distress syndrome
C	Airway & Lung Compliance
CI	cardiac index
CDSSs	Clinical Decision Support Systems
CMV	Continious Mandatory Ventilation
CO	Cardiac Output
COPD	Chronic obstructive pulmonary disease
CPAP	Continious Paositive Airway Pressure
CRS	Respiratory system static compliance
CVP	Central venous pressure
DB	Data Base
E	Elastance = 1/C
EA	Evolutionary Algorithms
EC	Evolutionary Computation
ECG	Electrocardiogram
ET	endotrachial tubing
E_TCO_2	End tidal capnography
EVOFINE	EVolution Of Fuzzy INference Engines
F	Gas Flow
FiO2	Fraction of Inspired Oxygen
FL	Fuzzy Logic
FLC	Fuzzy Logic Controller
Fmax	Flow Limitation, ventilator setting
FRBS	Fuzzy Rule Based System
FRC	Functional Residual Capacity
FS	Fuzzy Set
FUN	FUzzy Neural toolbox, training NN driven FL
G	Conductance = 1/R
GA	Genetic Algorithm
Gfuzzy	Genetic Fuzzy Algorithm
HCO3-	bicarbonate
HFV	High Frequency Ventilation

I/E	Inspiratory (time) / Expiratory (time) ratio
ICU	Intensive Care Unit
IDSSs	Intelligent Decision Support Systems
IMV	Intermittent Mandatory Ventilation
IPPB	Intermittent Possitive Pressure Breathing
IPPV	Intermittent Possitive Pressure Ventilation
KB	Knowledge Base
mae	mean absolute error
MMV	Mandatory Minute Volume
mse	mean square error
Neural	Neural Network
NoM	Nera of Maxima defuzzification technique
OI	Oxygenation Index
P	Pressure
PaCO2	Arterial Carbon Dioxide tension
PACO2	Alveolar Carbon Dioxide tension
Pao	airway opening pressure
PaO2	Arterial Oxygen tension
PAO2	Alveolar Oxygen tension
PAP	pulmonary artery pressure
Pb	barometric pressure
PCWP	pulmonary capillary wedge pressure
PEEP	Positive End Expiratory Pressure
Pex	Expiratory pressure (total PEEP)
pH	a measure of the activity of hydrogen ions (H^+) in a solution and, therefore, its acidity. pH=-log(H+)
P_{H2O}	water vapor pressure (47mmHg at 37o C)
PIP	Peak Inspiratory Pressure
Pmax	Pressure Limit, ventilator setting
Ppl	pleural pressure
Pplateau	end inspiratory pressure
PSV	Pressure Support ventilation
Q	Blood Volume
R	Airway & Lung Resistance
Raw	Airway resistance
RB	Rule Base
RI	Respiratory Index
rmse	root mean square error
RR	Respiration / Breathing Frequency in breaths per minute (BPM)
RRS	Respiratory system resistance

SaO_2	Oxygen Saturation of the hemoglobin of arterial blood
SC	Soft Computing, synergy of Artificial Intel. techniques
SIMV	Synchronized IMV
SOFLC	Self Organizing fuzzy logic controller
SpO_2	Oxygen Saturation as measured by pulse oximetry
T	Temperature
TI	Inspiration time
TSK	Takagi-Sugeno-Kang model
V	Gas Volume
v	Venous
V/Q	ventilation-perfusion ratio
VCO_2	CO_2 production
VD	Physiologic Dead Space
V_D	Dead Space volume
Ve	Expired Volume / min
VE	Minute Ventilation (L/min)
VO2	oxygen consumption
VO_2resp	Oxygen cost of breathing
Vpk	peak flow (L/min)
V_T	Tidal Volume
WOB	Work of breathing
τ	respiratory physiology the time constant

1. Introduction

Mechanical ventilation support is provided to critically ill ICU patients who are unable to maintain gas exchange. ICU Clinicians monitor and evaluate cardio-respiratory related physiology variables, in order to evaluate adequacy of mechanical ventilation. Since a patient's needs are continuously changing, clinicians have to adapt the ventilation strategy and drug administration on a regular basis. This ongoing process is described as ventilation management.

Clinicians examine physiology variables, and search for the optimum solution for the patient specific pathology. Due to the nature of the cardio-respiratory physiology, the number of involved variables is high. This is also true of the possible interventions (solutions) available to a clinician. An optimum set of ventilation variables is not described by a single solution, but rather by a range of solutions that could be beneficial to the patient.

The above process could be described as a search for an optimum solution to a clinical problem, which utilizes a large number of input variables (search space). Different methods have been applied for modelling mechanical ventilation. Tehrani and Roum (Tehrani F.T, Roum J.H, 2008), provide an overview of different methods in intelligent decision support systems (IDSSs) for the mechanical ventilation. Authors compare different methods from 1985 to present. Three categories of basic architectures are identified by the authors; namely Rule-based, Model-based and Rule-based plus model-based. IDSSs utilize available clinical and engineering knowledge for improving respiratory care. Intelligent systems provide a promising tool for the ICU clinicians for improving respiratory care quality, decreasing workload and minimizing medical errors.

1.1 Aims and objectives

The aim of the research is to develop, implement and evaluate hybrid intelligent decision support methods for ventilation management. This core research aim will be addressed with the following objectives:

- A literature review of current research into intelligent mechanical ventilation.
- Selection of optimal variables for ventilation management.

- Establishment of a verified patient data library based on the optimal variables.
- Development of hybrid systems for decision support problems.
- Evaluation of the systems on established benchmarks.
- Development of dedicated hybrid systems for ventilator management of a set of lung pathologies.
- Comparison of the performance of the hybrid systems with ICU domain experts.

1.2 Methodology

The proposed approach develops and evaluates models' performance based on the autonomous and synergetic use of genetic algorithms (GAs), neural networks (NN) and fuzzy logic (FL). This consortium of methodologies is commonly referred as Soft Computing.

The models are applied on control ventilated patients. The models do not account for temporal changes in data sets but the data presented to the models represent specific time instances of the physiology variables in a way similar to the method experienced intensivist apply changes to ventilator settings.

Development and optimization of hybrid systems requires first the identification of the appropriate input – output variables, second the evaluation of available architectures and decision making on the adapted system's architecture, and finally training and evaluation of the system with the assistance of experimental – recorded data. Input and output variables for the models were identified with the statistical analysis of questionnaires, developed for this purpose and circulated to eighteen (18) ICU doctors of three general hospitals. Questionnaire variables that scored high were candidates for participating in the development of the hybrid systems. These variables were collected in real ICU settings in two hospitals in Greece. Data recorded were used to establish the patients' database. Patients were further categorized into three major lung pathologies, namely COPD, ALI-ARDS and normal lungs. The purpose of this categorization was the difference in ventilation protocols among the different pathologies. Recorded data were randomly allocated into training (60%) and evaluation (40%) sets.

Collected data were further analyzed for identifying strong relationships between monitored variables and ventilation settings. Correlation analysis was performed on

the assumption that clinical decision making on ventilator settings is based on a subset of monitored physiology variables. Correlation results were evaluated by three ICU doctors from three different hospitals. Monitored variables that exhibited a high correlation degree (Correlation coefficient >0.5) and were accepted by the majority of the evaluators, were chosen to participate as inputs to the systems.

Two custom toolboxes were developed. The first was named EVOFINE (**EV**olution **O**f **F**uzzy **IN**ference **E**ngines) and utilizes Genetic Algorithms for identifying the optimum fuzzy system, based on available input-output training data. The second was named FUN (**FU**zzy **N**eural), and utilized a NN for substituting the rule base (RB) of a fuzzy system providing to the system the ability to learn from a given input-output data set. Both toolboxes were evaluated for their performance on non linear mathematical function and the cart pole system, prior to their application. Experiments were carried out for identifying the most efficient architecture of all the components involved in the hybrid systems. Evaluation of different architectures suggests that Evolved FRBSs perform adequately with a subset of the Rule Base, damping mutation rates reach faster an optimum solution and moderate number of Fuzzy Sets reduces complexity and increases performance. Similarly experiments performed on FUN architectures revealed that the choice of defuzzification technique is the determinant factor of model's performance. ANFIS and ANN performance was also tested against the same modelling problems and optimum architectures were identified. Neural networks with increased number of nodes and hidden layers, but sufficiently low to avoid overtraining, performed better. EVOFINE and FUN were benchmarked against the well established NN and ANFIS techniques. EVOFINE performed close to benchmarks while FUN could not succeed in cart pole stabilization.

Utilizing the recorded data training sets and the evaluation findings from the correlation analysis, different soft computing techniques have been applied for modeling the ventilation management process; namely EVOFINE, FUN, ANN and ANFIS. The resulted models were evaluated against the evaluation set. The performance of the models against the data set was measured in terms of mean square error and mean average error. Although the error between models' suggestions and clinical decisions is an important indicator of model's performance, it provides little evidence on whether the results are clinically acceptable. In order to accommodate for this problem three intensivists were presented with clinical

scenarios and were asked to advice on ventilator settings. The difference in their clinical decisions was analyzed for identifying the clinically acceptable difference among peers. The analysis of clinical decisions was used as measure of the models' performance.

1.3 Remainder of thesis

The thesis is organized into eight (8) chapters:

Chapter 2 presents background information necessary for the reader to understand mechanical ventilation principles and ICU decision making methods. The introduction to ventilation management is followed by a brief review on the necessity of clinical decision support systems in the ICU. The final part of the chapter describes briefly the methods used in clinical intelligent decision support systems, emphasizing to the soft computing methods.

Chapter 3 provides a literature review on respiration physiology models and mechanical ventilation controllers. Key research approaches and relevant research work undertaken by other authors is reviewed for the following approaches: Mathematical models and classical controllers, Expert systems, Hybrid and Fuzzy systems.

Chapter 4 describes the methods used for designing intelligent ventilation decision support systems. Specifically it describes the method for minimizing the systems' architecture, the method of data collection and analysis, the evaluation process, the custom hybrid models toolboxes development as well as the research ethics.

Chapter 5 presents the questionnaire development and evaluation. Based on the results of the questionnaire analysis, the data collection process is described. The final part of this chapter describes the analysis performed on collected data for further minimizing the models' architecture.

Chapter 6 describes the process of development, training and evaluating the hybrid systems against the recorded patient data. Evaluation of the EVOFINE, FUN, ANFIS and ANN systems is visually and numerically performed against clinical decision in the ICU. Furthermore the developed models are evaluated against ICU peers disagreement acquired based on real patient scenarios.

Chapter 7 presents and comments on the research findings. Research is discussed in terms of methodology used, models development and performance and comparison against other authors work on the same field.

Chapter 8 is presenting conclusions about the methods and the outcome of the research, providing insights of possible future applications and research work.
Appendix I provides the reader with detailed information on the clinical aspects of ventilation management.
Appendix II describes the architecture of the Matlab custom toolboxes developed for the purpose of the research.
Appendix III, evaluates the custom toolboxes against benchmark problems. The performance of the toolboxes is compared to established modelling methods, namely ANFIS and NNs.
Appendix IV provides the reader with additional information on the theory of AI methods.
Appendix V, provides a summary table (table V.1) of published research on ventilation management as well as the results.
Appendix VI presents the questionnaire used for collecting expert's opinion on ventilation management variables relative significance.
Appendix VII provides a table (VII.1) with the range of physiology variables and ventilator settings.

1.4 Contribution

Intelligent Decision Support (IDS) of ventilation management is a complex engineering problem involving a high number of participating variables, clinical expertise and human cardio-respiration physiology. The proposed research suggests a solution to the problem by introducing a two step method for modeling the ventilation management process.
Step one, is reducing the complexity of the problem. Since the number of participating variables is very high, the proposed approach decreases problem's search space by limiting the number of participating variables with the assistance of a questionnaire, correlation analysis and evaluation. Furthermore the proposed approach is designed to be pathology specific due to the differences in ventilation strategy according to pathology.
Data collected from three ICUs formed a real patient data base for three common lung pathologies. The developed database will be available to research community. Similarly the resulting architectures from the process of evaluating clinicians'

answers provides future researchers with appropriate input variables for each of the evaluated ventilator settings.

Step two evaluates the appropriateness of different soft computing methods for the task. Different soft computing techniques (EVOFINE, FUN, ANNs and ANFIS) have been applied and evaluated in parallel, for modelling the ventilation management process rather than the physiology, providing future research with sufficient evidence on the appropriateness of each technique for the task. The proposed approach is designed for modeling six rather than a single ventilator setting, providing a more holistical approach to ventilation management.

Additionally to the well established soft computing methods a new method for evolving FRBSs was suggested, and a new toolbox was designed and developed. EVOFINE was tested on benchmarking complex engineering problems in order to evaluate its' performance. The suggested evolution process has been shown to sufficiently map complex problems. Furthermore variable damping mutation rates have been applied. Results suggested that damping mutation rates reach an optimum FRBS architecture faster than constant rates.

2. Background

2.1 Mechanical Ventilatory Support

The major function of the respiratory system is to supply tissues with oxygen and dispose of carbon dioxide generated by metabolism.

Respiration includes four distinct processes, the **pulmonary ventilation** which is air movement into and out of the lungs, the **External respiration** which describes the gas exchange between blood and the alveoli air, the **Transport of gases** which is the transportation of blood gases between tissues and the lungs, accomplished by the cardiovascular system, and the **Internal respiration**, which describes cellular respiration, the exchange of gases between blood and cells (Marieb E.N. 1995).

Breathing, a term used to describe pulmonary ventilation, is a mechanical process divided into two phases. The inspiration phase is an active process leading to the enlargement of the thoracic cavity. During quiet breathing the intrapleural pressure decreases to about -6 mmHg (relative to atmospheric) and lungs expand. Airway pressure becomes negative in respect to atmospheric and air flows into the lungs (Ganong W.F. 1975). Expansion of thoracic cavity is accomplished with the activation of inspiratory muscles. The Diaphragm accounts for 75% of the change of intrathoracic volume during quiet breathing, while intercostals muscles contract to expand the thorax both laterally and in the anteroposterior plane (Ganong W.F. 1975). During quiet breathing the inspiration muscles activation expand the thoracic dimensions by few millimeters along each plane, as a result intrapulmonary pressure drops about 1 mmHg relative to atmospheric. The above process is described by ***Boyle's Law*** assuming that temperature is constant.

The quiet expiration phase in healthy individuals is a passive process that depends on lung elasticity. Inspiratory muscles relax and thoracic and intrapulmonary volumes decrease. Intrapulmonary pressure increases to about 1 mmHg above atmospheric, forcing gases out of the lungs.

Mechanical ventilatory support (which will be described from now as mechanical ventilation), is initiated when a patient's ability to maintain gas exchange has failed. Respiratory failure is categorized mainly to Hypoxemic and Hypercapnic. Hypoxemic is failure to oxygenate, while hypercapnic is failure of the ventilatory

pump. The term pump describes the mechanical and the neural control of respiration. Pump failure is described usually by a combination of failures such as:

- Inadequate muscle function: causes might be malnutrition, inadequate electrolyte balance, use of drugs such as calcium channel blockers.
- Excessive ventilatory load: patients with chronic obstructive disease increase load due to secretion accumulation, mucosal edema or bronchospasm.
- Impaired neuromuscular transmission and/or compromised central drive: drugs may depress or increase ventilatory drive. Metabolic acidosis could cause hypercapnia, resulting to dyspnea anxiety with increase respiration rate.

Hypoxemic failure is the failure to maintain arterial oxygenation. The basic mechanisms for this are the Ventilation-perfusion mismatch, right-left shunt, alveolar hypoventilation, diffusion effect and low concentrations of inspired O_2, termed as Fraction of Inspired Oxygen (FiO_2). Hypoxemia does not always call for mechanical ventilation; it is treatable with oxygenation support devices such as oxygen supply masks and continuous positive airway pressure (CPAP).

Support of patients with respiratory failure is given by medical devices described as mechanical ventilators, or artificial ventilators. The majority of mechanical ventilators provide the patient with a user defined mixture of fresh gases, by applying positive pressure in the upper airways. Since the pressure is above atmospheric, air flows into the lungs causing them to expand. Usually during the expiration phase pressure levels at the upper airways drop at atmospheric or maintained above atmospheric levels. The latter methodology is called Positive End Expiratory Pressure, abbreviated as PEEP. However this process is the invert of the physiological one, where inspiration is initiated due to sub-atmospheric pressure in lung compartment. This inversion is the cause of ventilator induced lung injuries. Barotraumas and volume trauma are lung injuries caused by alveolar over-distension; the former is due to excessive pressure and the latter due to high volume. Limiting maximum pressure and volume is the obvious solution to lung injuries. However limitation of these variables is not always advised due to abnormal lung mechanical properties. The reduction of cardiac output (C.O.) related to the increased intrathoracic pressure is another ventilator induced problem. Reduction is caused by the increased pulmonary vascular resistance, which decrease left ventricular filling (Pilbeam S.P. 1986). Prolong inhalation in respect to exhalation

decreases venous blood return to the heart. To decrease the effect of positive pressure ventilation on C.O., intensivists maintain a low mean airway pressure.

Positive pressure ventilators are classified according to control variables, phase variables and conditional variables. Control variables remain constant as the ventilatory load changes. According to this classification a ventilator could be pressure, volume, flow or time controlled. This is interpreted as maintaining a supply of gas mixture, during the inspiration phase, until a predefined level of the control variable is reached. Phase variables initiate some phase of the ventilation cycle. Phase variables are trigger, limit and cycle. Inspiration triggering could be voluntary from the patient, detected as drop in airway pressure or as gas flow into the lungs, or time triggered, controlled by the clinician. The limit variable is a threshold that cannot be exceeded. Inspiration phase is not always terminated when the limit is reached. Cycle variable terminates the inspiration when a threshold is reached. Conditional variables are those controlled by the ventilator logic. Synchronization to patient's efforts, permission for spontaneous breaths, and mandatory ventilation are examples of conditional variables. The flow chart in figure 2.1, taken from Hess and Kacmarek (Hess D.R., Kacmarek R.M. 2002), is a diagram for classifying mechanical ventilators.

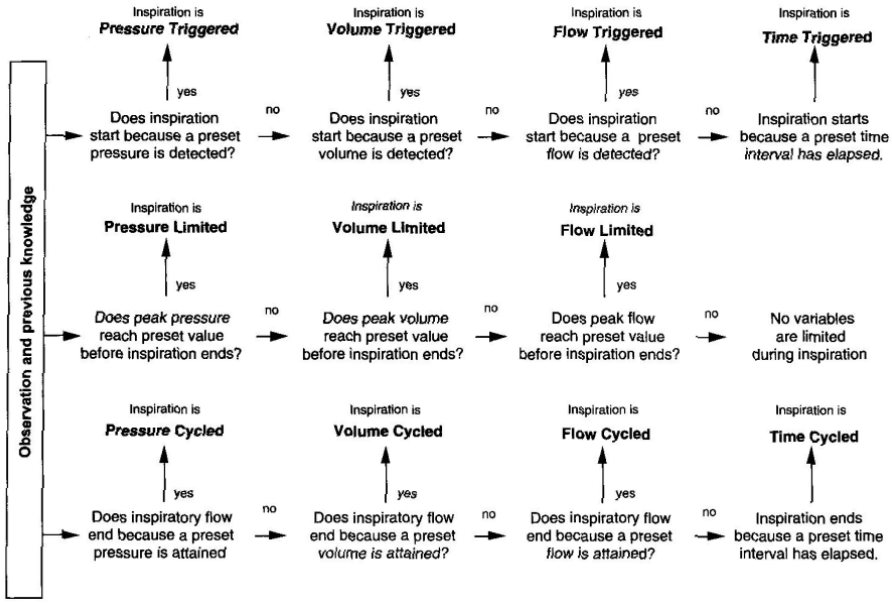

Figure 2.1: Classification of mechanical ventilators, taken from Hess D.R and Kacmarek R.M 2002.

Ventilators are further classified according to drive mechanism (McPherson S.P. 1995). Driving mechanism describes the technology of producing airflow into the lungs. The drive could be pneumatic, low or high pressure applied directly to the upper airways, Electric, usually pistons and compressors driven by servo or other electrical motors, and Bellows where high or low pressure is applied in the bellows chamber forcing it to collapse.

A modern ventilator is described as a block diagram in figure 2.2. The main modules of the ventilator are the Control Unit, a user interface for selecting settings, viewing variables and waveforms, and selecting modes of operation, a mixer, responsible for providing the correct concentrations of gases (Usually 100% O_2 with atmospheric air although Nitric Oxide was introduced lately to ICUs), the drive mechanism and the transducers for collecting flow, pressure, volume and oxygen concentration signals.

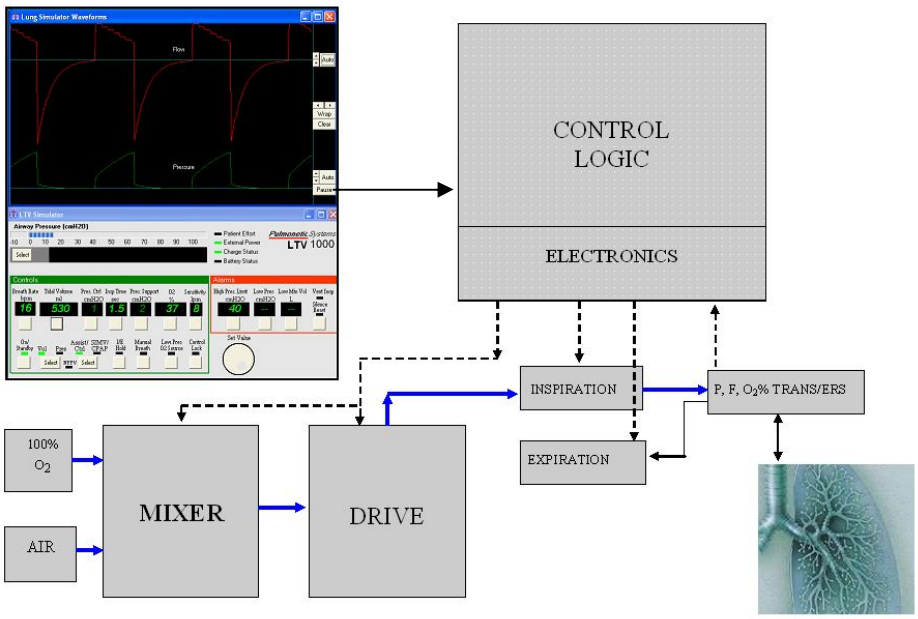

Figure 2.2: Ventilator block diagram.

Ventilators are capable of functioning as controllers, and/or assist devices. Several modes of operation have been developed in the last years, each having unique features designed for different respiratory problems and ventilation phases. The following modes are common to many manufacturers:

- **Control** ventilation: ventilator delivers preset volume or pressure controlled breaths, in predefined time intervals. Minute ventilation ($\overset{o}{V}_E$) is given by the product of tidal volume (V_T) multiplied by the respiration rate (RR):

$$\overset{0}{V}_E = V_T * RR \qquad \text{eq. 2.1}$$

- **Assist** ventilation: ventilator detects patient's effort for inspiration, either as pressure drop or flow at the upper airways, and provides pressure or volume controlled ventilation.
- Continuous Mandatory Ventilation (**CMV**): is an assist – control mode, were the clinician provides with a minimal rate of control ventilation, while the patient can trigger inspiration at a more rapid rate.
- Intermittent Mandatory Ventilation (**IMV**): delivers breaths at a set frequency similar to control mode. However the patient can breathe spontaneously between control breaths from a reservoir or demand system.
- Synchronized IMV (**SIMV**): works similar to assist mode. The difference is that it divides each minute into cycled time and to time where the patients effort to breathe will be assisted by synchronized mandatory breath. If patients fail to initiate a breath, for a given period, the system delivers mandatory breaths.
- Mandatory Minute Volume (**MMV**): system allows the patient to breath spontaneously. If the volume of spontaneous breaths has not reached a predefined threshold, then the remaining volume is provided mandatory.
- Continuous Positive Airway Pressure (**CPAP**): this is a spontaneous breathing mode. Clinicians decide upon a level of positive pressure throughout the ventilation cycle.
- Pressure Support ventilation (**PSV**): in this mode patient initiates inspiration phase. The ventilator assists the patient's effort until a predefined pressure level is reached. Some ventilators incorporate CMV, in case of patient's apnoea.
- Airway Pressure Release Ventilation (**APRV**): this is actually a CPAP mode which periodically lowers the pressure level to atmospheric level. This allows patient to exhale higher volumes; as baseline is restored patient is ventilated with higher volumes.
- High Frequency Ventilation (**HFV**): ventilates patients at high rates (above 60 BPM), with low volumes (Usually slightly higher than dead space volume).

Additionally to ventilation modes there are modifications to ventilation support. Positive End Expiratory Pressure (PEEP) is blocking exhalation when a preset pressure level is reached. Similar to PEEP is the Expiratory Retard, in which a resistance is applied to expiration tract, to maintain positive pressure in alveoli and prevent collapse. Inspiratory Hold ($P_{plateau}$) is a pause between inspiration and expiration phase, which allows gases to diffuse better in the alveoli.

The choice between mandatory and assist-spontaneous ventilation is patient specific. Mandatory ventilation is provided to patients with drug suppressed ventilation trigger, or when clinicians attempt to minimize breathing effort. Partial support is often used during weaning process. Weaning describes the phase of discontinuation of ventilation. In patients with Acute respiratory distress syndrome (ARDS), and Chronic obstructive pulmonary disease (COPD), control-assist modes are suggested such as CMV.

2.2 Ventilation Management

The care of critical ill mechanically ventilated patients requires regular gathering of clinical data for the evaluation of the ventilation strategy. Clinicians utilize the pathology and physiology data available for adapting ventilator settings to patient's needs. This process is described in bibliography as patient or ventilation management.

Patient's needs are continuously changing, and for this reason ventilation management is an ongoing process. The periods of evaluation range from several minutes to hours, depending on patient's health status and ventilation phase. It is common when clinicians initiate mechanical ventilation, to collect and evaluate data regularly, intervals of 15 to 30 minutes, in the first few hours, until the patient's physiology variables are stable. Time intervals between evaluations also adapt to changes in ventilation strategy. Frequent intervals are used when decisions are made for changes of ventilation modes.

Decision making of ICU clinicians concerning changes in ventilation support and drug administration, is supported by available clinical data, experience, and protocols. Appendix I provides with a detailed description on monitoring variables and ventilation targets during mechanical ventilation.

2.2.1 Decision Making - Ventilation Strategies – Protocols

The changes performed on ventilation settings and drug administration related to ventilation adequacy, are made based on a strategy. The strategy could be based on knowledge, expertise and experience, or on available guidelines and protocols, or more often as a combination of both.

Hancock and Durham (Hancock H.C., Durham L., 2007) addressed the theoretical background of clinical decision making. Three different approaches are described in the literature. These are: Analytical methodology, which is a linear process involving assessment of alternatives and selection of a course of action; Intuition, which is a holistic consideration of situations based on experience; practitioners have developed knowledge structures, enabling them to respond to a problem with the use of accumulated experience; and cognitive continuum theory which suggests that decision making is somewhere between the analytical and intuitive ends.

In contradiction to the theoretical approach of clinical decision making by Hancock and Durham (Hancock H.C., Durham L., 2007), Taylor (Taylor F, 2006) reported that ICU staff utilizes in action different approaches in decision making. He identified that hypothetico-deductive approach, concept of balance, pattern matching, intuition and trial and error, were used by the clinical staff participated in the research.

The subjective nature of decision making, as well as the multi-parametric nature of the ventilation management process, generates the need of protocols and guidelines. Carson et al (Carson E.R. et al 1991) focus on the need of converting measured data into information for clinicians. Their argument was supported by the substantial increase in the number of measured, derived and alarm variables in the ICU, over the past decades. Since humans have limited ability to estimate covariance between multiple variables (Morris A.H, Cook D.J, 1998), guidelines are necessary. Hypothesis, memory recall, prejudice, local cultural factors, local technical abilities and experience are all factors influencing caregiver decisions in the ICU.

Protocols usually present either as paper based flow diagrams, or paper - computerized decision support trees. Such algorithms developed for the ICU setting usually contain fuzzy terms such as “optimize PEEP”, which cannot be translated into executable instructions (Morris A.H, Cook D.J, 1998). Even more when decision trees are developed, it is difficult to implement them in different patient-clinical settings, leading to identical treatment decisions. The application of general

guidelines is associated with great variation in practice, due to individual clinical practice styles (Morris A.H, Cook D.J, 1998).

A different treatment strategy is adopted according to patient pathology. The most common health related patient categories found in ICU and potentially require some form of ventilation support, are the following (from: Hess D.R., Kacmarek R.M. 2002):

- Acute Lung Injury - Acute respiratory distress syndrome (ALI-ARDS).
- Chronic obstructive pulmonary diseases (COPD).
- Chest Trauma.
- Head Injury.
- Postoperative patients.
- Neuromuscular disease and chest wall deformities.
- Cardiac failure.
- Asthma.
- Burns and inhalation injury.
- Bronchopleural fistula.
- Drug overdose.

Although protocols - guidelines have been developed, there are diverse methods for dealing with the same problem (Brochard et al., 1994, Butter R et al., 1999, Horst H.M, 1998). The controversy surrounding mechanical ventilation is illustrated on ARDS ventilation management, thus reflecting a more general problem. ARDS is approached mainly by two different strategies. The open lung approach targets a specific pressure with pressure controlled ventilation (Amato M.B.P et al., 1998, Papadakos P.J, Lachmann B, 2002). High respiratory rates, high PEEP and permissive hypercapnia are used to maintain alveolar recruitment. A second approach named ARDSnet, or baby lung approach, focuses on the limitation of tidal volume using volume controlled ventilation (ARDS NETWORK, 2000). There is no convincing evidence that either approach is superior (East T, 1993, Shanhotz C). Figure 2.3 presents the protocol algorithms for both approaches.

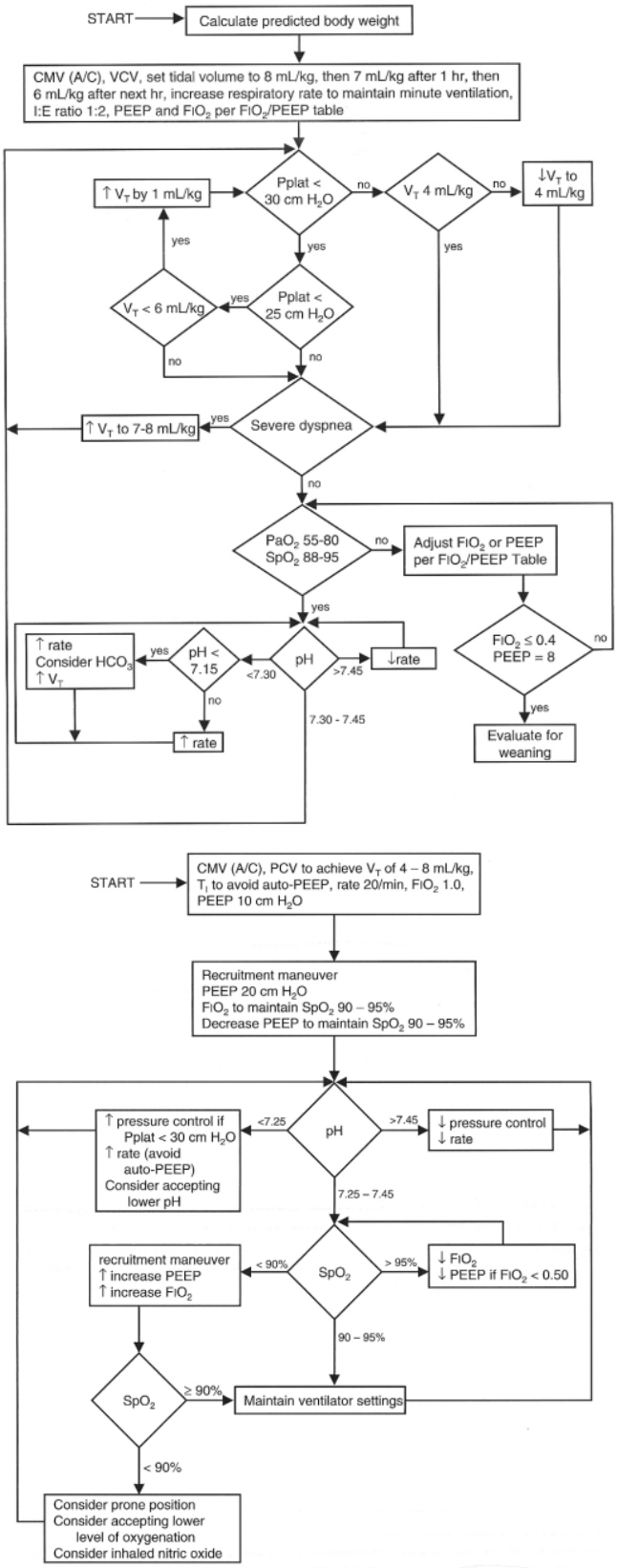

Figure 2.3: (Top) baby lung algorithm. (Bottom) open lung approach (taken from Hess D.R., Kacmarek R.M. 2002).

Wall et al (Wall R.J, et al 2001), reports that it has been demonstrated that implementation of protocols in the ICU, for specific clinical procedures, improves clinical outcomes. However it argues that clinicians are not constrained by the protocol since it focuses on common aspects of the patient's illness. Clinicians often need to deviate from the protocol, due to "subtleties inherent to each patient". Authors report that critics argue that protocols reduce the quality of care by reducing clinical judgment and degrading medical expertise.

We conclude that the multi-parametric nature of the ventilation management problem and the complexity of the cardio-respiration physiology call for medical guidelines - protocols. However the design and implementation of the protocols is compromised by the multi-strategy approaches, the ICU patients' case-mix (multiple pathologies) and the variation of clinicians' expertise and treatment styles.

2.3 An overview of common lung pathologies (ALI-ARDS & COPD)

Acute Lung Injury (ALI) and acute respiratory distress syndrome (ARDS) are clinical entities describing the diffuse pulmonary inflammation (Bellingan G & Finney S.J 2006). ARDS was first described by Ashbaugh and co-workers in 1967 (Lechin A.E. et al 1994). ALI is the less extreme manifestation of ARDS. Annual incidence of ALI-ARDS range from 8 to 70 cases per 100,000 population in developed countries (Bellingan G & Finney S.J 2006), while mortality ranges from 30-40% adults (Zwischenberger J.B 2006) and 30-75% in children (Hammer J 2006).

ALI-ARDS is the disruption of the normal alveolar-capillary barrier (Lechin A.E & Varon J 1994). Clinical manifestations are dyspnea, the severe hypoxemia due to mismatching of ventilation and perfusion, and lung stiffness manifested by increased compliance and WOB. ALI-ARDS could be caused by direct or indirect injury to the lung (Hammer J 2006). Sepsis is the basic etiology of ARDS in ICUs. Case mix (multiple risk factors) commonly develops ARDS and is usually the cause of patients' mortality rather than ARDS itself.

ALI-ARDS is usually treated with invasive mechanical ventilation and pharmacotherapeutic approaches. Pharmacotherapeutic approaches focus on the alveolar fluid balance and the reduction of inflammatory process. Ventilation

strategy influences mortality. Strategies focus on lung volumes, FiO_2, PEEP and ventilation modes (Bellingan G & Finney S.J 2006). Adjuncts to traditional mechanical ventilation include prone positioning, recruitment maneuvers to prevent or recruit lung collapse, surfactant administration to reduce surface tension in alveoli, high frequency ventilation and non invasive ventilation.

Chronic obstructive pulmonary disease (COPD) is "the airflow limitation due to narrowing and fibrosis of small airways and loss of airway alveolar attachment as a result of emphysema" (Barnes P.J 2006). Chronic airflow limitation is initiated by inflammation, airway hyperactivity, secretions and loss of the structural integrity of the lung parenchyma (Hess D.R, Kacmarek R.M 2002).

COPD affects 6% of the general population and is one of the top five causes of chronic morbidity and mortality in the USA (Amborosino N, Simonds A, 2007). A large percentage of COPD patients are admitted to ICU. 26-74% of them receive mechanical ventilation support (Gursel G 2005). Ventilation is initiated to prevent hypoxia and to control acidosis and hypercapnia (Plant P.K, Elliot M.W 2003). Research has shown that COPD patients ventilated with non-invasive mechanical ventilation have better results than intubation (Hibert G et al 1998, Plant P.K, Elliot M.W 2003).

Smoking, environmental and genetic factors are the main causes of COPD.

2.4 Overview & Necessity of Decision Support Systems (DSS) for mechanical ventilation

The controlled ventilation management process could be described as a closed control feedback system, where the controller is the ICU clinician and the controlled system is the patient. Clinicians gather clinical information utilizing multiple sources of data, such as blood gas analyzers, monitors, ventilators, patient's drug administration records and patient's pathology, and make decisions on the appropriate control adjustments to the ventilation apparatus. Clinical decisions are governed by expertise and experience. As it has already been stated the process of ventilation management, could be considered as a search of an optimum solution through a complex search space.

When modelling the clinician-patient system the researcher is faced with many obstacles. Cardio respiratory physiology is on its own a highly complex control

system to be modelled. Additionally clinician's decisions are made based on expertise and experience and a large number of available clinical data. Different lung pathologies are ventilated by utilizing different strategies. Strategies are not universally accepted, as described in section 2.2. Accumulated experience of the ICU clinical staff differs from one hospital to the other. ICU clinicians prioritize clinical data available to them with different hierarchy. Equipment type and measuring processes show a large variation among ICUs. Thus a system capable of mimicking doctor's decision making process should be able to learn both from experience and expertise. Furthermore the system should apply knowledge acquired in a general context and not in terms specific to a patient.

Automating the mechanical ventilation process has been suggested and applied as early as the first ventilation machines were introduced in the ICU. From 1957 (Saxton G.A and Myers G.A, 1957) up to today researchers have approached the goal of supporting the mechanical ventilation process by utilizing available technologies at the time. Although the variation of systems architecture is quite big, two main categories of mechanical ventilation support systems have been developed. The automated category consists of closed-loop systems, which automatically adjust ventilation settings based on a set of physiology measurements. In this category the number of controlled variables (the ventilator settings) and the number of input variables (the physiology measurements) ranges from single to multiple. Currently only two closed-loop systems are commercially available. Siemens-Draeger Medical and Hamilton Medical utilize adaptive algorithms for supporting delivered pressure and volume-frequency respectively. Siemens-Draeger uses a patented method known as Proportional Assist Ventilation (PAV, Younes M, 1992) which supports spontaneous breathing patients by adopting pressure support. Hamilton Medical, utilize a patented technology named Adaptive Support Ventilation (ASV, Tehrani F,T., 1991). ASV adjusts target volume and frequency based on respiratory mechanics, for minimizing work of breathing. Spontaneous breathing patients are supported with ASV, however when no breathing effort is initiated by the patient, the algorithm provides controlled ventilation.

Open-loop systems capture the patient's health status and provide suggestions on optimum ventilation settings. These systems are best described by the term Decision Support Systems (DSS). A more detailed description of DSS is provided in section 2.5. Capturing of physiology data could be performed either by manual entry of data,

or automatically from the monitoring and ventilation devices. Suggestions usually appear to the clinician most commonly through a graphical user interface.

Figure 2.4, presents graphically the closed-loop and open-loop basic architecture. The main difference between the two approaches is the feedback control loop of the ventilator apparatus (dashed line).

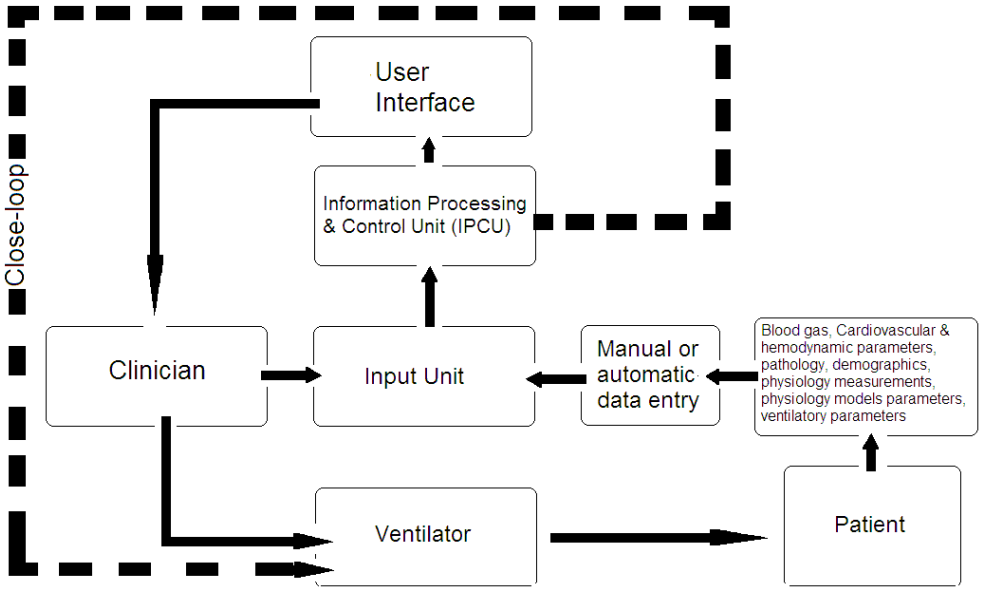

Figure 2.4: Diagram of open and close loop (dashed) systems.

The core of both system categories is the Information Processing and Control Unit (IPCU). The structure of the IPCU differs among researchers. However it can be categorized into four (4) main categories:

- Mathematical models of respiratory control. Such models were the early attempts to describe and automate the ventilation process.
- Classical controllers applied in mechanical ventilation. Control theory, such as Proportional-Integral-Deriviative (PID) controllers have been implemented for automating the mechanical ventilation process.
- Protocol and expert rule-based systems, commonly named Knowledge Base Systems (KBS). The available ventilation protocols and/or the clinicians' expertise are computerized. Decision trees and rule driven logic is often applied.
- Intelligent models. Intelligent systems that model the mechanical ventilation process. Intelligent models utilize artificial intelligence methods for

modelling the cardio-respiratory system, the decision making process of the clinician or as a combination of both.

The above categories have been implemented in combination. Examples of similar research are presented in the following sections.

Tehrani and Roum (Tehrani F.T, Roum J.H, 2008, "Intell. Dec. Sup.") provide a methodological review of intelligent decision support systems (IDSS). The key characteristics and the basic structure of IDSS is summarized by the authors in table 2.1 (Taken from Tehrani F.T, Roum J.H, 2008).

Table 2.1: IDSS main categories (Taken from Tehrani F.T, Roum J.H, 2008)

Key characteristics	Available alternatives		
Basis structure	Rule-based	Model-based	Rule-based + model-based
Applicable ventilation modes	Pressure support (PS)	SIMV or IMV + PS	Multiple modes
Patient types	Adults	Neonates	ARDS patients
Optimized parameters	Blood gases	Weaning time	Blood gases and weaning time
Type of technology	Open-loop (advisory)	Closed-loop (automatic)	Open-loop + closed-loop

Advisory expert systems and closed loop ventilation are gradually gaining acceptance (Wysocki M, 2007). The driving force for automating the process of ventilation management could be summarized in the following categories:

<u>Patient safety</u>: "*In the United States, the number of patients who died from medical error alone is equivalent to one airplane crash every day of the year*" (Wysocki M, 2007). Anesthetic incidents in the operating room are attributed between 70 to 82% to a human error (Dhillon B.S, 2000). Studies have shown (Giraud T et al, 1993), that a large percentage of ICU admitted patients (31%) has suffered iatrogenic complications. Schuh and colleagues (Schuh Ch, 2004) have shown that ICU staff reacts with long delays to hyper or hypoventilation, with mean delays of 127 and 50 minutes respectively. These are only few examples of the magnitude of medical errors complications. Alponso et al (Alponso A et al, 2007) evaluated ICU clinical staff and reported disturbing results about the difference among staff, in fundamental knowledge surrounding oxygen therapy. Since mechanical ventilation supports human life, errors caused by lack of appropriate training, experience and misjudgment, result in adverse effects for the patient.

<u>*Quality of care*</u>*:* Due to cardio respiratory system's complexity and ICU patients' case-mix, the process of ventilation management is demanding. In order to minimize

the diversity in ICU personnel knowledge level, protocols have been introduced to ventilation management. However protocols suffer from a long list of drawbacks, such as fuzziness in advice (Morris A.H, Cook D.J, 1998), diversity in acceptance (Brochard et al., 1994, Butter R et al., 1999, Horst H.M, 1998) and rapid change in ICU standards (Wysocki M, 2007). The need of protocols and guidelines is generated by the multi-parametric nature of the ventilation management process. Carson et al (Carson E.R. et al 1991) focus on the need of converting measured data into information for clinicians. Their argument is supported by the substantial increase in the number of measured, derived and alarm variables in the ICU, over the past decades. Since humans have limited ability to estimate covariance between multiple variables (Morris A.H, Cook D.J, 1998), guidelines are necessary. ICU clinicians prioritize clinical data available to them with different hierarchy. Taylor (Taylor F, 2006) in his research on decision making process reported that ICU staff utilizes in action different approaches in decision making. Hypothetico-deductive approach, Concept of balance, Pattern matching, Intuition and *trial and error*, were used by the clinical staff participated in the research. East et al (East TD et al 1999) have reported in a multicenter randomized trial that a computerized decision support system can significantly improve patient morbidity.

Resource limitation: In Greece ICUs operate with 20 to 30% of the appropriate clinical personnel according to European ICU standards (Roussos X, 2007). Due to this limitation a big percentage of ICU beds are left unused. The same problem is encountered in many European countries. In Sweden for example during April 2002, 782 ICU-beds were available (8.7 per 100 000 inhabitants). Almost 200 beds were not operative due to budgetary reasons or lack of personnel (Walther SM, Wickerts C.J, 2007). The resource limitations due to cost containment policies, has led ICU personnel working exhausting hours. Scott et al (Scott L.D et al, 2006) found that 86% of ICU nurses work overtime. When the number of available nurses per patient decreases there is an observed increase in the duration of ventilation (Thorens B.J et al, 1995), thus ICU costs increase and quality of care degrades.

The above evidence advocates the need of support tools for the process of ventilation management. Support tools could be in the form of decision making support or closed loop systems. Support should be provided in order to:

- Establish a baseline, in terms of quality of care.

- Minimize clinical errors in the ICU.
- Relieve partially ICU staff from the task of ventilation management.
- Minimize the need, in terms of numbers, of expert personnel and thus increase availability of beds.

In order to "mimic" the ventilation management process, support tools should rather model the process than the patient physiology. Modelling the process has several advantages. It includes available protocols that ICU staff employs in action, personnel experience and expertise and patient pathology and physiology.
Thus a system capable of supporting decision making in the ICU for the ventilation management process should have the following characteristics:

- **Learn from clinical decision making**, in order to incorporate protocols, experience and expertise.
- **Adapt to the patient needs**, thus frequently processing routinely monitored physiology data for producing advice.
- **Provide a holistic ventilation management**. Should not be concerned with part of the ventilator settings but with the total.
- **Be pathology specific**. Ventilation strategy is adapted to patient's pathology. Therefore the support tools should be able to do so.

2.5 Clinical Decision Support Systems (CDSSs)

Dr R. Hayward of the Center of Health Evidence of the University of Alberta (Canada) defines that "Clinical Decision Support systems link health observations with health knowledge to influence health choices by clinicians for improved health care". Although the term Diagnostic Decision Support Systems has been used, the CDSSs define a broader perspective and include Decision Support Systems (DSSs) in the areas of Administration, Management of Clinical Complexity, Cost Control and Medical Diagnosis (Perreault L, Metzger J. A, 1999).
CDSSs are divided into two major categories: The Knowledge Base Systems and the non Knowledge Base Systems. Knowledge-based systems (KBS) are widely used in the areas where knowledge is predominant rather than data (Pandey B, Mishra R.B, 2009). The Knowledge Base Systems incorporate existing knowledge either in the

form of massive databases including well established knowledge and past patient cases, or a set of expert defined rules. These systems are commonly known as expert systems. Non Knowledge Base Systems utilize Artificial Intelligence (AI) techniques for developing a DSS from available data sets.

The use of AI techniques for developing CDSSs has several advantages over the development of expert systems. One of the main problems of expert systems is the extraction of experts' knowledge. (Clancey W.J, 1983) This problem is termed knowledge acquisition bottleneck. Medical data often suffer from ambiguity and lack of complete information. These real life characteristics degrade expert systems performance. Additionally expert systems are hard to maintain. On the other hand AI techniques are capable of learning and training from real life data, thus eliciting "decision rules". Furthermore maintenance of AI systems usually involves retraining a developed system based on newly available data.

Soft Computing (SC) is a consortium of AI methods which work synergistically (Yardimci A, 2009). SC utilize a combination of well established AI techniques such as Fuzzy Logic (FL), Neural Networks (NN) and Genetic Algorithms (GAs) for producing flexible information systems for handling imprecision, uncertainty and partial truth in real life situations. The systems designed with an innovative combination of different AI techniques are commonly referred to as hybrid systems.

Fuzzy Logic (FL) was a term first coined by Zadeh (Cox E. 1994). FL is an inference engine, utilizing "IF premise THEN consequence" rules, similar to human reasoning. However numerical data are translated into degrees of membership for predefined fuzzy sets for a given variable domain. The inference engine makes decisions based on membership degrees to a given set.

Artificial Neural Networks (ANNs) or commonly described as Neural Networks (NNs) have been around nearly 50 years. NNs consist of interconnected information processing units called artificial neurons, modelled on biological neural neurons. The simplified NN is designed with three layers. The signals are propagated from the input layer to the neurons of the hidden layer. The hidden layers' neurons are linked to a weight. NN are trained by adapting neuron characteristics so as to adequately map an input-output relationship. Training is performed on available data sets, commonly based on a gradient descent back propagation method.

Genetic Algorithms (GAs) were first proposed by Holland in 1975 (Holland J.H, 1962 & 1975). GAs are search and optimization methods that emulate natural evolution

based on three fundamental processes: Mutation, Recombination and Selection. GAs operate as search algorithms that evolve possible solutions through search in complex spaces. Possible solutions to a problem are coded, traditionally in binary format, into chromosomes. An initial population of candidate solutions is submitted for evaluation on a given problem. The best performers have an increased probability of advancing to the next generation. Exchanging of code (crossover or mating) and mutation are operation for exploring alternative possible solutions to the problem. This process is repeated until a specific number of generations, or a good solution to a given problem has been reached.

Combination of these AI methods is commonly encountered in the form of NN-FL, NN-GA and FL-GA applications. NN-FL has two subcategories, the NN controlled by a FL or FL controlled by NN. Adaptive network fuzzy inference systems (ANFIS), was originally proposed by Jang (Jang J.S.R, 1993). ANFIS is actually a neural representation of Takagi-Sugeno-Kang model (TSK) fuzzy systems capable of learning through training data.

GA are used for pre-processing data sets to be used by a NN, but also GAs evolve a population of NNs to find the most appropriate architecture for a given problem.

Alternatively GAs have been used for evolving or tuning FL systems for generating a better mapping of fuzzy sets or an evolved rule base.

A more detailed description of the AI methods as well as their combinations is provided in *Appendix IV*.

Soft computing in medicine has been applied in many medical fields. In medicine FL-NN is used at a 68% rate, NN-GA at 27% rate and FL-GA at 5% rate according to Yardimci (Yardimci A, 2009), as shown in table 2.2. The combined AI techniques have been applied to many clinical disciplines including basic, Diagnostic, Clinical, Surgical science and Internal Medicine as shown in table 2.3.

Table 2.2: Applications of Soft Computing in medicine (taken from Yardimci A, 2009)

	Publication year									Total
	1995–1999	2000	2001	2002	2003	2004	2005	2006	2007	
FL	184	41	81	44	45	58	42	44	34	573
NN	641	160	171	172	192	239	194	211	186	2166
GA	43	20	18	17	14	28	29	40	36	245
FL–NN	29	6	23	13	14	8	14	21	16	144
NN–GA	17	2	5	5	6	6	8	11	9	56
FL–GA	3	1	–	1	1	1	–	4	–	11
FL–NN–GA	1	–	–	1	1	1	–	1	–	5

* FL: fuzzy logic, NN: neural networks, GA: genetic algorithms, FL–NN: fuzzy logic–neural networks, NN–GA: neural networks–genetic algorithms, FL–GA: fuzzy logic–genetic algorithms, FL–NN–GA: fuzzy logic-neural networks–genetic algorithms.

Table 2.3: SC in medical disciplines (taken from Yardimci A, 2009)

	SC methodologies			
	FL–NN	FL–GA	NN–GA	Total
Basic science				
Anatomy	–	–	–	–
Biochemisty	2	–	7	9
Biostatistics	8	1	4	13
Cytology	1	–	–	1
Embryology	–	–	–	–
Epidemiology	–	–	–	–
Genetics	5	2	4	11
Histology	–	–	1	1
Immunology	–	–	–	–
Microbiology	1	–	–	1
Neuroscience	–	–	–	–
Nutrition	–	–	–	–
Pathology	–	–	1	1
Pharmacology	4	–	4	8
Physiology	4	–	3	7
Toxicology	–	–	–	–
Diagnostic science				
Clinical Lab. Sciences				
Transfusion medicine	–	–	–	–
Cellular pathology	–	–	–	–
Clinical chemistry	–	–	1	1
Hematology	–	–	–	–
Clinical microbiology	–	–	–	–
Clinical immunology	–	–	–	–
Radiology				
Interventional radio	17	1	4	22
Nuclear medicine	–	–	1	1

	SC methodologies			
	FL–NN	FL–GA	NN–GA	Total
Clinical science				
Anesthesiology	3	1	1	5
Dermatology	1	–	–	1
Emergency medicine	1	–	–	1
Family medicine	–	–	–	–
Hospital medicine	–	–	–	–
Internal medicine				
Cardiology	13	–	–	13
Critical care medicine	6	–	–	6
Endocrinology	3	–	–	3
Gastroenterology	1	–	–	–
Geriatrics	–	–	–	–
Hematology	1	1	–	2
Hepatology	–	–	–	–
Infectious diseases	–	–	–	–
Nephrology	3	–	1	4
Oncology	8	–	1	9
Pulmonology	1	–	2	3
Rheumatology	–	–	–	–
Neurology	9	–	2	11
Gynecology	–	–	–	–
Palliative care	–	–	–	–
Pediatrics	1	–	–	1
Physical med. and reh.	4	1	1	6
Preventive medicine	–	–	–	–
Psychiatry	1	–	1	2
Radiation therapy	2	–	–	2
Surgical science				
General surgery	–	–	–	–
Cardiovascular surgery	–	–	–	–
Neurosurgery	–	–	–	–
Maxillofacial surgery	–	–	–	–
Ophthalmology	–	–	–	–
Orthopedic surgery	–	–	–	–
Otolaryngology	–	–	–	–
Pediatrics surgery	–	–	–	–
Plastic surgery	–	–	–	–
Surgical oncology	–	–	–	–
Urology	–	–	–	–
Vascular surgery	–	–	–	–

3. Review

3.1 Related work on modelling respiration physiology & mechanical ventilation control.

One of the early attempts to support the ventilation process was in 1957 by Saxton and Myers (Saxton G.A and Myers G.A, 1957). Researchers suggested and evaluated on poliomyelitis patients, a closed-loop iron lung ventilator. This early effort to automate the process of ventilation was adapting the iron lung negative pressure, based on end tidal carbon dioxide partial pressure (E_TCO_2).

Chatburn presented the summary of models' categories for the mechanical ventilation available at the time (Chatburn R.L, 2004). The models-systems were categorized into open-loop and closed-loop control systems. The author elaborated more on the closed-loop control category by dividing it into the following subcategories: set-point, auto set-point, servo, adaptive, optimal, knowledge base and artificial neural network control.

The following sections present a selection of research work on the development of systems that support artificial ventilation, based on the underlying design methods. Paragraphs 3.1.1 to 3.1.4, briefly describe the basic design principles encountered in the bibliography. The design principles are presented by providing a review of other authors' research. Paragraph 3.1.5 presents models based on AI, which are not directly related to ventilation management, but their design principles are considered relevant to the current work.

3.1.1 Mathematical Models of the Respiratory System and Classical Controllers.

Grodins et al, proposed a mathematical model of the respiratory control system (Grodins F.S et al, 1967). The model was designed with two major components: the controlling and the controlled system. The controlled system was sub-divided into three compartments, the lung, the brain and the tissue compartment. The controlling system included receptor elements, afferent nerves, neural centers, muscles and the thorax-lung pump, described in terms of chemical concentrations at receptors as inputs, and ventilation as the system's output. Mathematical equations of the system

included cardiopulmonary variables as well as delays in the form of time constants. The proposed model was the most complete approach of modelling the respiratory control at time. The major model limitation is that mathematical relationships could not describe the individual's physiology. The proposed model does not provide a holistic approach to respiration physiology, since it does not include dead space, respiration rate, venous admixture, and tissue circulation. Non-linear, complex, multi-parametric systems such as human physiology are not easily implemented by mathematical models.

Saunders et al adapted Grodins model to include dead space, shunt, cyclic ventilation, and muscle compartment. (Saunders K.B et al, 1980). The resulting five compartment model was described by 17 non-linear differential equations. The model was tested by simulating the following cases: CO2 loading, step changes in inspired CO2, step increase in CO2 in mixed venous blood, hypoxic mixtures, CO2 re-breathing and exercise. Performance was suboptimal in exercise and hypoxia experiments.

MacPuf developed by Dickinson in the 70s (Dickinson C.J, 1977), is one of the most complete mathematical attempts to describe respiration physiology in software. The model was written in the Fortran computer language and included blood circulation, gas exchanging system, ventilation control, and tissues metabolism. Through a user interface the model allows for changes in 31 respiration related variables, as well as options of artificial ventilation, subject's demographics and clinical disorders. The work of Dickinson has been used as a starting point of many modern models, including SOPA Vent, described in paragraph 3.1.3.

Techrani (Tehrani F.T, 2007), suggested a decision support system for mechanical ventilation. The system process input data, such as blood gas, lung mechanical properties, breathing variables and ventilator settings, and computes the optimal level of ventilation. The algorithm utilizes mathematical equations for predicting tidal volume, respiration rate, peak inspiratory pressure, inspiration and expiration time and FiO2 and PEEP levels. The system produces new ventilator variables as well as suggestions on weaning.

In the early attempts to automatically control patient's ventilation many articles were published on applications of Proportional/Integral/Derivative (PID) controllers, based on a single physiology variable as input to the system (Coles J.Ret al 1973, Coon R.L et al 1978, East T.D et al 1982, Ohlson K.B et al 1982). A representative work of the early

attempts is that of Chapman et al (Chapman F.W et al 1985). The proposed system is a PID feedback controller responding to changes of Expired End Tidal CO_2 Fraction (FET_{CO2}). The system's output is the minute ventilation, and is estimated by applying a transfer function utilizing previous controller output, current error (output value-target) as well as previous error. An empirical relationship was designed to graph tidal volume against respiration frequency (their product is the minute ventilation). Evaluations on dogs showed that the system reacts fast to hypercapnia and hypoxia events. The drawbacks of the model include: the single input variable, ventilation control cannot be based on end tidal CO2 alone (Westenskow D.R, 1981), there are medical cases where we deliberately change the targeted P_aCO_2 (e.g. permissive hypercapnia), assumptions were made about constant dead space and metabolic rate, and changes in lung mechanics may alter the relationship between arterial and end tidal CO_2.

Martinoni et al (Martinoni E.P et al 2004), proposed a similar model to Chapman, in terms of monitoring variable. However the design of the system was based on a human physiological model of oxygen and carbon dioxide exchange, transport and storage. The systems' output was the desired minute ventilation as well as prediction of FET_{CO2}. The system was also adjusting the tidal volume and respiration frequency based on constrains on the maximum inspiratory pressure. Systems evaluation was performed on 15 patients during general anesthesia. The performance was compared against a fuzzy-controller described by Schaublin and colleagues (discussed in section 3.1.4). Both systems maintained ventilation close to a set point. However the same restrictions apply as in Chapman's controller.

In 2004, Jandre et al (Jandre FC et al, 2004), proposed a closed loop controller for regulating $P_{ET}CO_2$, and minimizing elastance of the respiratory system (E_{rs}). The authors work was based on the "open-lung ventilation" protocol. The model was a combination of proportional and integral (PI) controller, mathematical models and explicit objective functions. Two distinct controllers were designed. The first optimized V_T and RR as well as inspiration and expiration time. The controller reduced the risk of lung injury by finding a balance between peak alveolar pressure and flow. The second controller was adjusting the PEEP value for minimizing E_{rs}. For this purpose a gradient descent law utilizing local derivatives of the elastance was implemented. The controller's gains were semi-automatically calculated prior to application. The system was evaluated on six paralyzed female piglets ventilated in

control mode (CMV). Authors concluded that the controller dynamics approximate physiological responses.

In 2004, Tehrani et al (Tehrani F et al 2005), proposed a system composed from two closed-loop controllers. The first controller uses PE_TCO_2, S_pO_2, C & R as input variables and automatically adjusts rate, volume and Inspiration over Expiration time ratio (I:E). Values of capnography and saturation are translated into blood gases partial pressures based on mathematical equations. A correction factor is used for introducing shift of haemoglobin association curve based on pH. A threshold value for arterial oxygen is set to 104 mmHg. If readings are lower than this value, the effect of oxygen to ventilation is zero. Ventilation frequency is derived by mathematical relationship and targets to keep work of breathing at minimum. Tidal volume calculation takes into consideration PEEP and respiratory elastance. The second controller is a PID controller that maintains S_pO_2 at predefined levels by adjusting F_iO_2. Evaluation of the system was performed on both computer simulation and Yorkshire pigs. Results showed good performance in hypercapnia and hypoxemia in both computer and animal experiments.

Laubscher et al (Laubscher T.P et al 1994), proposed a computerized method to be used for the start-up procedure (initial settings), for closed-loop ventilation. Evaluation was carried out in 25 adult and 17 children patients in ICU. Initial test breaths were given to derive ventilator settings for minute ventilation, V_T and RR. The values of these variables were proposed based on measured median values of dead space and expiratory time constant (RC). Calculation was based on mathematical formulas, using work of other authors, and minimal work of breathing approach. Results showed that the proposed settings were similar to physiological breathing pattern. Differences between intensivist settings and computer proposal were not significant. The proposed model is different from the models encountered in the bibliography since it focuses on the problem of automatic selection of initial settings.

A nonlinear model for mechanical ventilation (Polak A.G, Mroczka J, 2006) was proposed by Polak, and Mroczka. The model incorporated airway morphology, dynamic behavior of the lung and chest walls, nonlinearities due to turbulence and airway collapsing and time variance of mechanical properties. The model was implemented in Matlab software. Simulation was performed to observe results in comparison with published and experimental data. However resistance values, during simulation proven very small compared to normal values, and to compensate

the model error they were multiplied by three. The model of mechanical ventilation resulted that all variables behaved linear except for lung compliance. The proposed model is a suggestion for adapting ventilation according to pathology which affects lung mechanical properties.

Guerrisi et al (Guerrisi M et al 2005), proposed a dual-controlled ventilation system for optimizing pressure and flow delivered to patients, both in inspiration and expiration phase. Changes in airway and lung resistance and compliance were compensated by two controllers, namely: stationary and transient flow generator stabilizer (STFGS) and time varying airways pressure stabilizer (DRSS). The synergism of the two controllers was designed to ensure tidal volume delivered to the patient, independently from intensity of the patient's load. Laboratory tests showed successful compensation when respiration frequency was under 20 BPM. Tidal volume was shown to be independent from lung mechanical properties. Finally non conventional flow waveforms were applied in an attempt to mimic physiological breathing patterns. However the model has not been tested on human or animal subjects.

Spahija et al (Spahija J et al 2005) approached the problem of closed-loop ventilation on a different base. The input to their controller system was the Diaphragm electrical activity (EAdi). When EAdi exceeds an upper threshold Pressure Support Ventilation (PSV) is incrementally increased. When EAdi falls below the threshold, the controller decreases PSV. This mode of ventilation was named Target Drive Ventilation (TDV). The system was tested in eleven health individuals who were breathing through an increased workload (flow resistance) mouthpiece. During the first test the threshold of EAdi was identified by an average value. Following this test, subjects were assisted in their ventilation while using a bicycle ergometer. Results have shown that it is possible to adapt the level of ventilatory assist based on changes in the respiratory drive, detected using the EAdi signal. Limitations of the approach include the initial test for evaluating the threshold, in which the subject has to breathe unassisted, something not always feasible in ICU patients. In order to improve expiratory synchrony, the authors used a neural cycling-off algorithm. The uses of such an algorithm lead to constant breathing cycle times, in contrast to physiological ventilation where changes both in respiration frequency and volume occur to compensate for metabolic demands. Finally results gained from the use on healthy subjects do not automatically apply to patients with lung pathologies.

Proportional Assist ventilation (PAV) is a pressure support ventilation method that adapts pressure support level throughout the inspiration phase. The pressure support changes in relation to volume and flow, thus allowing patient to have full control over breathing. The proportionality between flow and airway pressure is determined by a clinicians' gain setting; the settings is set according to respiratory lung mechanics. PAV was first described by Younes et al (Younes M et al, 1992), utilising a piston ventilator. Similarly Chua et al (Chua L.P et al, 1997) and (Li N et al, 1997) utilized a linear actuator to collapse a bellow for producing the calculated pressure support. Lua and Shi (Lua A.C & Shi K.C, 2006) suggested a proportional solenoid valve (PSV) for regulating airflow to patients lungs. Based on lung mechanics the controller calculates a theoretical airway pressure target. The pressure target is used as a set point for a Proportional Integral Derivative (PID) controller, which utilizes actual airway pressures and deviation from the set point, for controlling the solenoid function. Authors have tested the PAV-PSV controller on breathing simulators capable of simulating changes in lung mechanics and on healthy volunteers with artificial change in lung mechanics. In both occasions PAV-PSV was capable of "comfortably" ventilating subjects. PAV is commercially available by Siemens-Draeger.

Luepschen et al (Luepschen H, 2007), developed a PID controller for automatically adjusting the FiO_2 for maintaining the oxygen saturation in the range of 90-92%. The controller was tested against an ARDS Simulink (Matlab) model, by varying the PEEP level. Authors concluded that their approach exhibited a trade-off between robustness and performance.

Rees et al (Rees S.E, Allerod C, Murley D et al, 2006), presented a DSS system for bedside use. The core of the system was a mathematical model of respiration physiology. However the model variables were fitted to patient specific physiology based on collected database physiology data. The systems interface allows clinicians to answer "What if" questions, by applying trial and error procedures on the physiology model rather than the patient. Additionally the system was capable of suggesting ventilator settings of tidal volume, respiration frequency and FiO_2. Suggestions were made based on mathematical functions, called penalty functions. Penalty functions quantify the clinical preference to the goals of ventilation. The DSS utilizes gradient descent method for optimizing ventilator settings. The systems' operation was illustrated by a single patient example. However no numerical data were provided on

the efficiency of the proposed ventilation. Additionally the penalty functions were designed with the input of experts, introducing subjectivity to the system.

Allerod et al (Allerod C et al 2008), evaluated a DSS system based on mathematical models of respiration physiology. The system produces advice on tidal volume, breathing frequency and FiO_2. Experimental procedures we used for estimating models' variables. This step is performed to make the model patient specific. The quality of the model is evaluated by comparing the measured and modelled values. The system was evaluated retrospectively against recorded data from 20 patients. The DSS suggestions were compared against the intensive care physician. The mathematical model evaluation performs very well with mean difference between measured and simulated values in the range of 0.0 to 3.0 However the DSS suggestions on ventilation settings exhibits large deviations from clinicians' suggestions. Tidal volume difference ranged from 0.2 to 0.9 ml/Kgr. FiO2 was persistently suggested lower than the clinicians' suggestion (0% in one case to 17%). Breathing rate suggestions closely followed clinical decisions.

3.1.2 Expert Systems for Ventilation Management.

In 1985, Miller (Miller P.L, 1985) suggested a ventilator management advisor system named VQ-ATTENDING. The system collects medical condition inputs from the physician, the current set of Arterial Blood Gases (ABSs), the ventilator settings and the physician's proposal for the new settings. The output of the system due to complexity of the task, as commented by the author, is limited to ventilator settings of F_iO_2, PEEP, RR, V_T and Dead Space. The output is not only a suggestion on new ventilator setup, but also a critical view on the strategy of patient's management. The system is built on multiple levels of "If .. THEN.." production rules. The systems goals adapt to patient needs depending on type and severity of disease and current ventilatory support. The rule base is in fact a "backwards-chaining" inference system, since the conclusions of rules become inferencing goals which the system confirms by investigating other production rules. However, the major drawback of such a system is that when multiple rules are simultaneously fired conflict on proposed solution might exist. The author overcomes this disadvantage by assigning priorities to goals. The system is based on binary logic, where crisp values are associated with premise and consequent. The method for the design of rules is not

analyzed. It is a complex approach of multidimensional production rules, but there is no presented evaluation of the proposed model.

In 1989, Shahsavar et al (Shahsavar N et al 1989) proposed an object oriented rule base system (KUSIVAR) for the support of three phases of ventilation management, initiation, treatment and weaning. The knowledge representation is structured in an object oriented format, where numeric values have been transformed into symbolic values (eg.P_aCO_2=9.05 kPa, is transformed to "Very High"), according to a crisp classifier. Rules have been added latter with the help of a knowledge acquisition tool named KAVE (Shahsavar N et al 1995). The knowledge base contains mathematical models for estimating and optimizing unavailable variables. However there is no reference or description of the models. The Inference engine works with forward chaining production rules. The model was evaluated in 1995 by Shahsavar et al (Shahsavar N et al 1995), once the rule base has been established. Evaluation of the system showed 75% agreement between system and clinical outcomes in initiation phase. During treatment and weaning phase the system made less wrong recommendations than the physicians.

East et al (East T.D et al, 1990) presented and evaluated a computerized protocol for mechanical ventilation. Flow chart protocols were developed with the feedback of clinical personnel. Paper flow charts for ARDS patients, were evaluated and computerized. The computerized protocols were initially tested against retrospectively collected patient data for validation purposes. The proposed system was tested on 61 adult ARDS patients. Researchers have shown that 83% of protocol decisions were followed clinically.

In 1993, Rutledge et al (Rutledge G.W et al 1993) developed a ventilator management advisor named VentPlan. The model incorporated both qualitative and quantitative values. The VentPlan consists of four components. A belief network named VPnet, which included diagnostic, monitored and intermediate nodes, a mathematical model, a plan evaluator and a graphical interface. The VPnet represented medical conditions such as Sepsis, Pneumonia, in binary format, with prior probabilities, and combined these diagnosis nodes with hemodynamic data to produce quantitative variables for the physiological model. VPnet classifies the diagnostic variables into classical sets and based on probability distribution produces mean and standard deviation values for the physiology model. The mathematical model is a first-order differential equation model, describing the exchange of oxygen and carbon dioxide

in lungs and tissues, and transport through the body. The model estimates the probability distribution of variables based on population prior variable distribution. The estimate is strongly influenced by the clinical context. Based on updated variable distributions and the ventilator settings, the model makes predictions for partial pressures of gases in each model compartment. The plan evaluator provides ranking of plans. The attributes of the model are F_iO_2, PEEP, RR, V_T. Determination of values is based on a function provided directly from physician's experience. Values are weighted to obtain an overall value. As commented by the authors "This value *assumes* that the predictions for an alternative plan are certain. Taken into account the *uncertainty of the model predictions*, the plan evaluator calculates the expected value for each plan from the distributions for the predictions of each attribute, by making the *assumption* that these distributions are independent". The authors have validated the components of the system based on clinical scenarios and sets of patient's data. However during mathematical model validation the model recorded very high standard errors for blood gases. Evaluation of recommendations was carried out retrospectively. The study included 10 ICU patients. Suggestions for F_iO_2 disagreed in only two cases, while the rest of settings disagreement was raised to seven (7) out of fifty five (55) adjustments, mainly due to *not* incorporating permissive hypercapnia in the model architecture.

Adaptive support ventilation (ASV) was introduced by Laubscher and colleagues (Laubscher T.P, Heinrichs W et al, 1994 IEEE & David M, 1994). ASV incorporates measurement tools and algorithms to select V_T and RR to minimize work of breathing. ASV combines different modes of ventilation since it switches between control and spontaneous breathing. Clinicians set the desired minute ventilation and ASV adopts tidal volume and respiration rate based on respiratory mechanics measurements. ASV safeguards against hypoventilation, auto-PEEP and lung over-distension trauma. ASV has been evaluated by Arnal et al (Arnal J.M et al, 2004) on 243 patients. Authors found that ASV was capable of selecting specific breathing volume and rate settings for COPD and ALI-ARDS patients. Iotti et al (Iotti G et al, 2005) tested ASV in more than 80 patients and found that ASV was achieving the same arterial partial pressure of Carbon Dioxide as the clinicians but with lower minute ventilation. ASV is commercially available by Hamilton.

Miksch et al (Miksch S et al 1996), presented a therapy planning system named VIE-VENT. VIE-VENT used temporal data abstraction techniques for validating patient

data and therapy planning. Patient data and data trends were classified into qualitative descriptions. The dynamic comparison algorithm used by the authors classifies data to a qualitative trend description. Based on the fitting of the data to the trend description the system suggests changes in therapeutic actions. The logic of the system is based on decision rules (" if …then …else") and classification of measured variables into classical sets. The system was evaluated retrospectively on clinical scenarios. However there is no numeric evidence provided for the efficacy of the proposed system.

Dojat et al in 1997 (Dojat M et al 1997) suggested a knowledge-based closed loop system (NeoGanesh) for the automatic control of pressure support ventilation. The system aims were to reduce the need for monitoring, improve weaning process and to reduce duration of ventilation. The system's crisp inputs were the Respiration Rate, the end tidal Capnography, expressed in pressure units, the pressure support level and the tidal volume. The input data were classified in diagnostic categories. The knowledge representation was expressed in temporal reasoning. Temporal reasoning, (Ramaux N et al 1997) compares predefined scenarios which represent the knowledge-base, to current events (sessions). The temporal reasoning proposed introduced the mechanisms of aggregation of similar situations and forgetting of non relevant information. Temporal abstractions were used to assess the time course of patient's disease status. Object oriented programming creates instances of subclasses to be matched by rule variables for a given rule. In this way a new rule base defined as a subclass inherits all the old rules. This was named inherited rule base, allowing knowledge base to evolve. Finally a subtask named Action Planning determines the new ventilator settings.

The initial target of the system was to maintain the ventilated patient in a comfort zone ($12<RR<28$, $V_T>300ml$, $E_TCO_2<55mmHg$). The second target was to assist weaning process. Recommendation for weaning to the clinician, was stated when pressure support drop bellow a threshold. Clinical evaluation of the model on ten (10) patients (Dojat M et al 2000), reveals that mean duration in ventilation support was slightly higher with the proposed model compared to standard procedure (24h compared to 23h). However automatic pressure support showed longer periods of ventilation in the comfort zone that standard ventilation (93% compared to 66% respectively). Overall results supported the research hypothesis that continuous support pressure adjustment may facilitate weaning process.

A second evaluation was performed in 2005 (Bouadma L et al 2005). In their work authors concluded based on results from 43 patients, that the system ventilated patients within comfort zone 64% of total time. The difference from the previous evaluation was attributed to technical problems in end tidal CO_2 acquisition. Weaning readiness was detected earlier than intensivists in 17 cases.

The distinct characteristic of NeoGanesh architecture is the knowledge base representation. However this was originally developed on available data and clinicians' expertise which limit the performance to clinical specific ventilation strategies. Furthermore the classification of input data to classes, named states by authors, is based on classical set theory (e.g. Normal set), which by itself provides binary representation to the forward chain rule base. Thus the main advantage of the knowledge base relies on the chain of events preexisting knowledge rather than on the representation of the current states.

Neurally adjusted ventilator assistance (NAVA, Sinderby C et al, 1999), collects electromyographic activity with the use of an esophageal catheter, to record the diaphragm activity. The system based on muscle effort generates a proportional airway pressure. NAVA results in a better patient – ventilator synchrony. The pressure support could be adjusted to patient needs.

Tehrani and Roum (Tehrani F.T, Roum J.H, 2008) presented a rule and model based DSS, named FLEX. FLEX use a predefined decision tree and a mathematical model for calculating ventilator settings. FLEX system is capable of weaning patients applied in a closed-loop setting. Many of the FLEX rules apply according to predefined thresholds, allowing flexibility based on patient's conditions. The system was tested against clinicians' recommendations in a 24h interval. Although authors present results and suggest small deviations from clinical recommendations, the disagreement of FLEX exhibits big variations. As authors comment:" Thus the predictive minute ventilation value for FLEX is well within the expected variability for this variable (20%), supporting the utility". FLEX provides decision support on minute ventilation, respiration rate, PIP, FiO_2, PEEP and I/E. The mathematical model as well as the decision rules utilize recorded (automatically or keyed) physiology variables; namely blood gases (P_aO_2 or SpO_2, P_aCO_2 or E_TCO_2), respiratory mechanics, ventilatory variables and ventilatory measured variables (spontaneous breathing rate, peak inspiratory pressure, tidal volume). The advantages of the proposed system are that it can be used in different modes of

ventilation, it can be applied to various pathologies and could be used as DSS or closed-loop weaning. The drawbacks could be summarized to the large variations of FLEX suggestions from the clinical data and the use of mathematical models for predicting desired outputs. The use of mathematical models includes coefficients which should be adjusted to the patients needs. However adjusting coefficients is on its own a problem of optimization.

3.1.3 Hybrid Models for Ventilation Management.

Kwok et al in 2003 (Mahfouf M 2006, Kwok H.F et al 2003) proposed the use of an Adaptive Fuzzy Inference System (ANFIS), for the control of the inspired F_iO_2. Their model utilized F_iO_2, PEEP and PaO_2 as inputs to their system. The ANFIS method utilized training data from different clinical scenarios. Respiratory measurements, hemodynamic data, ventilator settings, body temperature and hemoglobin level were collected from seventy one (71) measurements from three ICU patients. These measurements were presented to nine (9) anesthetists, who were asked to advise on the F_iO_2 level. They were also presented with recorded data and asked to advice on inspired O_2 fraction. A computer physiology simulator named SOPA Vent (Goode K.M, 1993, Mahfouf M 2006) calculated the resulted PaO_2, and the new scenario was presented to the anesthesiologist. The scenario values at each sampling point were used for training data for the ANFIS Sugeno-type fuzzy inference system. The training cost function was the mean square error (*mse*) between scenario value and systems output. The training process resulted into 11 rules for the inference engine. Simultaneously the authors developed a feed-forward multilayer perceptron (MLP), using the same training data. Evaluation of both systems and two previous designed models called FAVeM (Goode K.M et al 1998) and RBN-MB (Kwok H.F et al 2000) respectively, was made on data sets not used for training purposes. The output of all models was compared against clinicians' advice. Results have shown that MLP was the best modelling approach to clinicians' advice. The main drawback of this research lies in the simulation. As argued by the authors, clinicians' advice may be subject to constrain due to simulation process. Moreover the development of training and test sets was based on the accuracy of the computer model to predict new physiological values.

In 2004, the same authors described the architecture of a hybrid model for ventilation decision support system (Linkens D.A et al 2004).

Wang et al, in 2006, presented a new version of Simulation of Patients under Artificial Ventilation (SOPA Vent) model (Wang A et al 2006). SOPA Vent initially developed in 1993 (Goode K.M, 1993). The original SOPA Vent mathematically modelled the gas exchange during mechanical ventilation, by utilizing a large number of invasive and non-invasive measurements, demographic data and ventilator apparatus settings. The model consists of five compartments: the alveolar, the pulmonary, the arterial, the tissue and the venous compartment. The model equations are based on the work of Dickinson, which is briefly described in paragraph 3.1.1. Computing speed and need for invasive measurements were identified as the main limitations of the model. The new model does no longer utilize invasive measurements. To compensate for the non use of these measurements a neuro-fuzzy model was developed for the estimation of dead space. An ANFIS algorithm was used on data from control ventilated ICU patients, collected from the patient data management system of Royal Hallamshire Hospital ICU in Sheffiled UK. In order to identify model's inputs, physiology and ventilation variables were correlated to dead space; those that scored higher were incorporated as inputs to the model. $PaCO_2$, RR, tidal volume, Pinsp and PEEP were identified as inputs and were utilized for tuning the rule base of the fuzzy inference engine. The results have shown a good estimation of dead space. The same method was used for identifying input variables for the estimation of tidal volume. Patient's weight, PEEP, PIP, and RR were the input variables for developing and training with an ANFIS algorithm the inference engine. To validate the final model authors feed the ventilator settings, ventilator measurement, demographic data and blood gas measurements to the model and evaluated the predictions of $PaCO_2$ and PaO_2 against real measurements. Results show a good prediction of arterial oxygen, but not so realistic estimation of arterial CO_2.

Kwok et al (Kwok H.F et al 2004) presented an advisory system for the control of FiO_2, taking into consideration the bypass of venous blood to the arterial compartment, which is called a shunt. This can be measured clinically using a pulmonary artery catheter (PAC), but it is not routinely available. The authors proposed a non-invasively estimation of shunt based on high correlation (0.839) of respiratory index (RI) to shunt. RI is calculated by the following formula: $RI=(P_AO_2-PaO_2)/PaO_2$.

An ANFIS model and a linear regression model were fitted to the RI and shunt, based on data from ICU patient records of a teaching hospital. The mean estimation error of ANFIS model was lower than that of linear regression; this suggested that the relationship is non-linear. For the estimation of FiO_2 Newton's method, population median cardiac index and oxygen consumption were used. The evaluation of the FiO_2 advisor was carried out by simulation on the SOPA Vent model. The study aimed to evaluate the change in PaO_2 produced by the FiO_2 recommendation, taking into consideration effective shunt. Comparison of the two methods for shunt estimation showed that FiO_2 advisor made better recommendations when the ANFIS estimation was used. This is mainly due to the non-linear estimation of shunt. Limitations of the study include the uneven distribution of shunt values between the two groups during pseudorandom generation of groups, and the use of SOPA Vent model for testing advisor performance since models are a simplification of the respiration physiology.

Liu et al (Liu F et al 2006), proposed a Neuro-Fuzzy system for modelling the clinician FiO_2 setting process. The systems inputs were the current RR, PEEP and SaO_2, as well the current FiO_2 ventilator settings. The system was trained and evaluated retrospectively, based on a 20 day (1h sampling) record of BIPAP ventilated patients. The system utilized a Mamdani type FS. Initial rule base was updated when a new data sample was presented. The rules were ranked based on Hebbian learning rule. Additionally the system incorporated a rule reduction feature. The proposed system was benchmarked against other Neuro-Fuzzy systems showing superior performance both in terms of *rmse* and reduction of rules.

Chen and Chen (Chen AH, Chen G-T, 2007) presented a ventilator weaning prediction system named VWPS. The core of the system was an Artificial Neural network that utilized 16 weaning features. The back propagation algorithm was trained with different training algorithms with a subset of the 121 collected datasets ($2/3^{rds}$, 81 datasets). The system was evaluated based on accuracy and sensitivity, on the evaluation datasets. The accuracy and the sensitivity score was delivered by a ranking 2x2 matrix that incorporated the following fields: Actual weaning successful or failure, predict weaning successful or fail. The evaluation method is not encountered in other relevant papers. Results are summarized in table Appendix V, table V.1.

3.1.4 Fuzzy Systems for Ventilation Management.

In 1994, Sun, Kohane and Stark (Sun Y et al 1994), proposed an advisor FiO_2 fuzzy system for mechanically ventilated newborn infants. The target of the system was to maintain oxygen saturation at a predefined level. The system utilizes two inputs, directly measured from a Nellcor pulse oximeter. The inputs are the error between target and measured SpO_2 and the slope of SpO_2 trends. The input variables were assigned seven (7) and five (5) fuzzy sets respectively. A rule base was designed by expert neonatologists. The system utilized weighted mean deffuziffication method. The system was tested on infants, providing suggestion and not directly controlling inspired oxygen concentrations. Patients with shunt and vasoactive medication were excluded from the test. Preliminary results show adequate operation of the fuzzy system.

Schaublin et al (Schaublin J et al 1996) designed and evaluated a fuzzy closed-loop system for the automatic adjustment of tidal volume and respiration frequency during general anesthesia. The system's target was to maintain end tidal CO_2 at a predefined level, to minimize deviation of tidal volume and respiration frequency from normal values according to patient's weight, and to maintain an acceptable pressure plateau. The system used five inputs, namely: difference between desired and actual end tidal CO_2 fraction, the difference between actual and end tidal fraction of CO_2 recorded 60 seconds before, current respiration rate, tidal volume/Kgr, and plateau pressure. The outputs were the change in minute volume/Kgr, and the change in breathing rate. The original rule base was designed with the help of clinical experts and it was modified in pilot studies. Center of gravity was chosen as the defuzzification method. The study was performed on 30 patients. Fuzzy logic control was compared with human control. Control time intervals were allocated randomly to anesthesiologists and fuzzy controller. Both anesthesiologists and controller were tested against maintenance of target end tidal CO2 fraction, and step changes of target value. Results have shown that maintenance of target value was performed with similar precision by both controller and humans, while the fuzzy controller responded better to step changes. The tidal volume, respiration frequency and plateau pressure, defined by the controller were within acceptable ranges. Arterial blood samples were taken during the process and results were within clinical accepted limits.

Nemoto et al (Nemoto T et al 1999), proposed a fuzzy algorithm for controlling the level of pressure support ventilation. The proposed system was designed with six (6) inputs, namely heart rate, arterial oxygen saturation, tidal volume, respiration rate, and respiration frequency and heart rate rates of change (Trends). The first fuzzy module translated these reading to a fuzzy mapping of patients' condition rating from poor to good, divided into four categories. The second fuzzy module utilized heart rate and respiration rate trends as well as respiration rate values for producing Trend value. Trend fuzzy sets were assigned with stable, improving, deteriorating and crashing linguistic variables. The system's output was the proposed percentage change in the level of pressure support, based on Condition and Trend output from the previous two fuzzy modules. The system was tested retrospectively on 13 patients with chronic obstructive pulmonary disease (COPD). The fuzzy controllers' decisions were compared against actually implemented changes by the attending physician. The agreement, within +/-2 cmH_2O, for the first and second 24h period was 78% and 72% respectively. The architecture of the controller was based on non invasive variables and parameter trends. The choice of variables and fuzzy knowledge base was not based on a specific method. Furthermore the collection of variables was performed manually every hour by medical staff, which might have induced errors to the test data.

Belal et al used fuzzy trend template fitting model for producing advice on neonatal ventilation management alerts (Belal S.Y et al 2005). Eighteen (18), variables were automatically collected from monitoring and ventilation equipment. Only three (3) were used as inputs to the model, the rest were collected for future analysis. Arterial oxygen saturation (SaO2), Transcutaneous O2 and CO2 (tcpO2 & tcpCO2), were tagged either as valid or artifacts, using algorithms suggested by other authors. The model is composed of first a fuzzy classifier and second a Mamdani inference engine. Trend template fitting was used. Trends of SaO2, tcpO2 and tcpCO2, were expressed qualitatively and compared to predefined fuzzy templates. If the trends did not follow, both in terms of direction and time, the normal expected behavior expressed by templates, clinical intervention would be necessary. Variables were qualified into seven categories, not by assigning membership values to fuzzy sets, but rather fulfillment degrees. Fulfillment was defined as a real value in the range 0 to 1. The assignment of a fulfillment degree to a variable is based on the following logical approach: Fulfillment increases linearly from 0-1, when a variable is above

the target value, and decreases linearly when it is below the target. Targets for each variable are crisp values assigned by experts. The qualitative category was used as an input to the classifier. A similar method was adapted for the variables that qualitative describe trends. Variables were considered to follow under normal behavior an exponential function towards a normal range. If a variable converges in an expected way it may be qualitatively described as "normal", otherwise it could be described in terms such as "fast increase". If the slope (growth rate), falls between two growth limits, it is described as normal, otherwise is described as abnormal. Six qualitative categories were given for two scenarios, above and below target. Growth rate and growth limits were dynamically calculated every second. Qualitative trends were the second input to the classifier. A smoothing method was applied for calculating the qualitative categories for a specified time window. The time window was set by experts, but it was also user defined through software graphical interface. The Mamdani inference engine accepted as inputs the classifier output, and five user settings such as last ventilation change and suctioning. The inference engine produced alert advice on initiation of tcp calibration, suctioning, blood sampling and/or ventilation settings change. The system was validated against clinical staff decisions. Validation was made in terms of agreement, disagreement and no action, by direct comparison of produced advice to clinicians' actions. Overall agreement was high (93%).

Luepschen et al (Luepschen H et al 2005) presented a fuzzy logic controller capable of performing recruitment maneuvers for patients with Acute Respiratory Distress Syndrome (ARDS). The system was designed to perform the recruitment scheme called "open lung". The fuzzy systems' inputs were the Peak Inspiratory Pressure (PIP), the arterial oxygen partial pressure (PaO2), and its gradient (delta PaO2). The system was capable of controlling directly the pressure limit of a ventilator by incremental changes (d_PIP). The fuzzy controller incorporated a second output called "lung open", in order to specify the change in phase of recruitment maneuver. According to open lung approach the maneuver is composed of four (4) phases, namely: Opening, closing, re-opening, and steady state. Signals and images from Electrical impedance tomography and CT scan were used to verify the progress of the procedure. Tests were performed on three female pigs which were under general anesthesia. ARDS was simulated to pigs by multiple lavages of saline solution.

Results were not statistically supported, but as authors comment "presented results are promising".

In 2005 a fuzzy logic open-loop controller was presented for optimizing the respiratory rate and tidal volume ventilator settings (Tzavaras A et al 2005). The fuzzy system was designed in four interconnected sub-systems, in an effort to decrease knowledge base complexity. The system's inputs are: end tidal capnography, arterial oxygen saturation, cardiac output, body temperature, airways resistance and compliance, as well as patients' height, age and weight. The main Mamdani inference engine produced advice on minute ventilation and lung mechanics time constant (RC). Rule base was developed based on respiration physiology and mathematical models proposed by other authors. Minute ventilation and RC constant were feed into the second Mamdani controller, which produced an initial advice on respiration rate (RR). The RR value was adapted to patient age by a gradient d_RR, which was provided by a third Mamdani inference engine. Finally a Mamdani controller considered the patients' height and weight, and provided with a desired change in minute ventilation (d_VE).

The system was tested by changing input values as singles or as pairs. The model performed according to accepted knowledge of respiration physiology. It dynamically adapted ventilation settings for changes in lung mechanics, to compensate for deficiency to deliver large volumes by increasing respiration rate. Limitations include the derivation of rule base based on mathematical models, and the systems' testing in non-clinical conditions.

3.1.5 Hybrid Approaches in other Medical Fields.

Weller et al (Weller P.R et al 2002) designed and evaluated a genetically tuned fuzzy controller for the intra-aortic balloon pump. The fuzzy inference engine was developed with two inputs (mean diastolic pressure and peak systolic pressure), and one output, the deflation time before the end of the cardiac cycle. Rules as well as input domains were designed with the assistance of a domain expert. Three fuzzy linguistic variables were assigned to each input-output. The system was trained and tested with the help of a standard cardiac model modified to simulate failing and intra-aortic balloon assisted heart. The membership functions were evolved for 100

generations. The final best individuals were tested successfully on the simulation model.

Shieh et al developed and evaluated two genetically tuned controllers for the close-loop control of bispectral index (BIS) during general anesthesia (Shieh J.S et al 2006). The first controller was developed on PID technology, while the second was a fuzzy inference engine. Both controllers were adapting drug infusion rate to the needs of simulated patients. GAs were used for tuning proportional, integral and derivative gain of the PID controller, and for tuning the shape (constant center) of the fuzzy engine membership functions. PID GAs initial population was randomly initialized, and gain variables were randomly chosen in the domain of 0 to 10. FLC was designed with input variables, namely error of BIS index, and change in error between current and previous samples. The FLC output was the change in drug (propofol) infusion rate. Each FLC variable was divided into five (5) linguistic membership functions. Rule base was developed with the assistance of domain experts, resulting into 25 rules. For testing purposes a patient model was developed based on genetic fuzzy clustering of clinical data from 12 surgical patients. The patient model was designed with two inputs, the propofol infusion rate and the body weight, and three outputs, the heart rate, the systolic arterial pressure and the BIS index. The systems fitness function was the mean square error (mse). The model incorporated trends of vital signs; if fitness function was optimal and trends did not agree with clinical data then the model was identified as not being optimal. Seventy two (72), virtual operations showed that both controllers were maintaining target BIS better than manual control in target level of BIS=50. The limitation of the method is the use of a patient model which is representative to the population used for its development.

Curatolo et al (Curatolo M et al 1996) designed a fuzzy logic system for the control of the inspired oxygen and isoflurane concentrations during minimal flow anesthesia in 30 patients. They developed two fuzzy controllers, controlling oxygen and isoflurane delivered concentration, based on a target value. The oxygen FLC utilized the error between the desire and actual concentration and the fresh gas flow as inputs. The isoflurane FLC utilized three inputs; the error between desired and actual concentration, its integral and the fresh gas flow. The authors do not provide detailed information about the FLCs. Both controllers were directly controlling a PID servo controller which was calibrated and exhibited linear response in the range of 0.5 – 5

L/min. Patients were randomly allocated into standard and control groups. Anesthesia was performed to the standard group by another technique due to lack of personnel experience. This difference in methods does not allow for direct comparison between the two groups. Another method for limitation is the use of different values for the control methods by clinical staff and FLCs. Clinical staff evaluated the end tidal concentration while the FLC operated based on delivered concentrations. However general assumptions could be made for the performance of the FLC. Results have shown that O_2 concentrations remained between 28-30 vol% (target was 30 vol%), for a longer period than in the standard group. During steady state of isoflurane delivery, the controller maintained delivered concentrations +/- 0.1 of target vol% in 94% of time.

Linkens et al suggested a hierarchical structure based on fuzzy logic for monitoring the depth of anesthesia (DOA). The monitoring system was developed in two levels (Linkens D.A, Shieh J.S, Peacock J.E 1996). The first level was a self-organizing fuzzy learning algorithm. The FL system included heat rate and systolic arterial pressure as inputs variables. The authors developed the rule base of the system by using two different approaches. In the first, the rule base was developed from anesthetists' experience, resulting into seven rules. Self organizing learning obtained automatically six rules from training input-output data. In order to include all possible situations, a suitable trial protocol was designed with the help of anesthetists. The first level output is the FL interpretation of primary depth of anesthesia (PDOA). In order to decide the DOA with more confidence, when the first level decided that DOA is light, a second level was developed. Based on linguistic rules of Sweating, Lacrimation and Pupil response, and a scoring system, the second level was able of deciding the degree of lightness of DOA. Levels one and two were merged to produce the confidence DOA.

In order to test the system a linguistic model simulator was designed as an alternative to pharmacokinetic-pharmacodynamic model for propofol drug administration. The model was again build on two levels. The first level was concerned with induction stage. Three linguistic variables were assigned to propofol and fentanyl (high, medium and low). Three linguistic variables were assigned to systolic arterial pressure and heart rate. The second level was concerned with the maintenance stage. Supply of anesthetic agents were divided into three categories increase, constant and decrease for propofol and high, low and zero for the amount of fentanyl. Systolic

pressure was divided according to anesthetist experience in five ranges for change. The proposed model was tested in clinical and simulation conditions. The first level fuzzy model has shown similar results when applied with expert and self learned rules. The patient model was tested by simulating three clinical scenarios. The patient model was further developed as presented in 2004 by the same authors (Shieh J.S, Linkens D.A, Peacock J.E, 2004). The linguistic patient model was adapted with linguistic definitions for fentanyl time constant for the induction and maintenance stage. The model was clinically validated both off-line and on-line in ten (10) and seventeen (17) patients under general anesthesia in 2005 (Shieh J.S, Linkens D.A, Peacock J.E, 2005). The off-line validation was performed on data recorded from 10 surgical patients. Both rule base models worked similar. Deviation of the self organized rule base was within +/-15% to anesthetists decisions in drugs administration. Based on this the self organizing fuzzy model was used for on-line validation. Recovery times did not always agree between patient data and the model. For this reason rule base was adapted prior to testing it on-line. On line results have shown very low mean recovery time (7.8 min), when control was assigned to the model. However the final control of drug administration was always in the hands of anesthesiologist. The authors concluded that the systems' second level should incorporate clinical signs to guarantee the safety of the patient.

Nunes et al presented a simulation system replicating patients' undergoing general anesthesia, during routine intravenous anesthesia (Nunes C.S et al 2005). The proposed architecture includes three components. The first component is a fuzzy relational classifier. The classifier was trained with 2/3 of data gathered from surgical maintenance phase, the remaining 1/3 were used for testing purposes. The signals used for the training were Auditory Evoked Potentials (AEP), extracted from the EEG trace, with wavelet transforms. The AEP signals were clustered and the FLC specified the class membership of DOA. DOA was designed with five membership values, ranging from Awake to Deep. During the training phase, anesthesiologist opinion was the classification evaluation "golden standard". Testing showed that the system was able to classify all the samples. A second classifier was developed based on cardiovascular variables (change in Heart Rate, HR and Systolic Arterial Pressure, SAP), but the performance was inferior to the AEP classifier.

The second model is a patient model. The model utilizes propofol and Remifentalil infusions rates, and produce changes in HR, SAP and AEP features. Infusion rates

were feed into a three compartment Pharmacokinetic model, to determine plasma concentrations of drugs independently. An effect compartment, a hypothetical compartment describing the delay between plasma and effect concentrations, translated concentrations into effect concentrations, which were used as inputs to TSK fuzzy model. The TSK model was trained using ANFIS method. Each output variable was trained separately, resulting into three distinct TSK controllers, one for each model output. During training, TSK controllers for changes in HR and SAP, appear to smooth out the disturbances due to stimuli.

The third component is the surgical stimuli model. This is a Mamdani inference engine. The engine describes the small changes in HR and SAP due to the perceived stimulus. The knowledge base was developed from domain experts. The model failed to take into consideration the observed delay between stimulus and effect on cardiovascular variables.

The authors have tested the proposed model in a series of open loop simulations (Mahfouf M, Nunes C.S et al 2005). The AEP-FRC applied to maintenance phase, while during the induction phase a cardiovascular RFC was used instead. The model was described as performing adequately concerning the effects of stimulus to HR and SAP, while the administered drug concentrations were within range.

The model was also tested in closed-loop simulation. To perform this task an FRC system was developed for adjusting the drugs infusion rates. The infusion rates were adjusted according to DOA level, suggested by the proposed model. The infusion FRC suggested changes in Reminefantanil in two cases through linguistic rules, and propofol infusion rate during specific scenario. The fuzzy controller performing the adjustments to propofol, was trained in terms of tuning the scaling factors with the use of GAs. The system was capable of adjusting infusion rate of both administered drugs, during the simulated scenarios, taking into consideration the drugs synergism.

3.1.6 From theory to ICU clinical practice

While most of the suggested research that was described in the previous paragraphs has failed to impact outcomes, few have been commercially applied.

Proportional assist ventilation (PAV), suggested by Younes (Younes M 1992) is available by Tyco Carlsbad USA and as PPS by Siemens Draeger Medical, Germany

(Lellouche F, 2009). Neurally adjusted ventilatory assist (NAVA), suggested by Sinderby (Sinderby C et al 1999), has recently become available by Marquet Critical Care, Sweden (Lellouche F, 2009). Adaptive support ventilation (ASV), was based on the work of Otis (Otis AB, 1950) and Mead (Mead J 1960) suggesting that for a given minute ventilation there is an optimum respiration rate and tidal volume setting. This mode of ventilation is commercially available by Hamilton Medical, Switcherland (Lellouche F, 2009). SmartCare™, is the commercial name of NeoGanesh (Dojat M et al 1997). This is the only knowledge based intelligent system available in clinical use. It was built and commissioned in 2003 by Draeger Medical, Germany.

Current Regulatory framework does not require the evaluation of the outcome of a new mode of ventilation. As Branson (Branson RD 2005) comments "*Manufacturers need only to demonstrate engineering success in a lung model in order to obtain marketing approval through the Food and Drug Administration's 510(k) process; patient studies are not required.*".

In a recent study by Branson and Joahannigman (Branson RD, Joahannigman JA, 2004), the evidence on improving outcomes was categorized and published research was graded. Grading was performed on a scale of A to D as shown in the following table.

Table 3.1: Evidence level grades (taken from Branson RD, Joahannigman JA, 2004)

Evidence Level	Type of Study or Evidence	Evidence Grade
I	Randomized controlled trial with a statistically significant result	A
II	Randomized controlled trial (questions of validity or bias)	A
III	Observational study	B
IV	Studies with historical controls	B
V	Bench study, animal study, case report	C
(not applicable)	Expert opinion	D

In Branson's (Branson RD, Joahannigman JA, 2004), bibliographic grading of the evidence levels, only one study by Fernandez-Vivas M et al (Fernandez-Vivas M et al, 2003) of the PAV mode was graded with A. This reveals that there are insufficient data for providing evidence that new ventilation modes improve outcome.

4. Methodology

4.1 Methodology strategy

As presented in chapter 3, many authors have approached the problem of optimizing ventilation management utilizing different technologies and methods.

Section 3.2 identified the major differences and drawbacks of the suggested systems. In order to advance the research in this area, researchers have to provide answers in the following questions:

I. How can the developer reduce or even eliminate subjectivity from the systems architecture and decision making logic?
II. Which is the most suitable approach – technology for developing systems that optimize ventilation management process?
III. Which evaluation method is optimal for testing the developed systems in their preliminary stage?

Published research that utilizes experts' feedback in the development of the models architecture introduces subjectivity to the systems. Therefore it is crucial to implement a method that reduces the requirement of experts' feedback. Concerning the basic systems architecture, translated as input and output variables of the systems, most authors make choices based on previously published work, available respiratory physiology models and experts' feedback. Although experts' feedback should not be excluded from the designing stage, since "mimicking their logic" is the research target, the method should incorporate a system of reducing subjectivity. Statistical analysis has always been an excellent tool for pursuing this goal.

Decision trees, Fuzzy systems, computerized protocols and knowledge base systems have in common the need of experts' input to the system's logic. Although respiration physiology models are an attractive alternative, the need of coefficients is also a source of subjectivity and specificity. Hybrid models, on the other hand, are capable of optimizing their architecture and decision making process while eliminating or minimizing expert's feedback. However the performance of the hybrid systems is also a function of the size and quality of the available training sets.

Intelligent models show a large variation in their internal architecture. ANNs have been around for a long time and their efficiency has been exhibited in many medical applications. However ANNs suffer from the black box syndrome, where the developer is faced with a trained decision making engine which has no transparency

of its operating principles. Neural Networks driven fuzzy systems, improve the problem of transparency, but only in terms of input and output domain partitioning. Neuro-Fuzzy method overcomes the black box problem. It uses the strengths of ANN for producing transparent to the end user, fuzzy systems. Evolutionary algorithms applied on fuzzy logic have also gained their respect in the medical field. They also provide a means of optimizing systems architecture for a specific problem, while the end product of the optimization process is a comprehensive model.

Since there are no comparative studies on the appropriateness of intelligent models, applicable to the ventilation management process, one cannot make decisions on the optimum method. For this reason the presented research attempts a preliminary evaluation of the intelligent methods on the problem in hand.

It is clear that the optimum method for evaluating a medical system is the application of the system to laboratory animals, or on volunteered humans. However such an approach requires a system that has already passed a preliminary qualification test. In the last decades the evaluation of a system based on a model of physiology has gained acceptance. However the evaluation of a model based on another model (evaluation model) has obvious and hidden drawbacks. Some of the drawbacks are: (1) the tested model's performance depends highly on the efficiency of the evaluation model. (2) The tested system's architecture is constrained by the available variables of the evaluation model. (3) The generalizability of the tested model is confined by the specificity of the evaluation model.

Hybrid models are commonly tested against a sub set of the collected data. This approach evaluates the performance against unused data (data not used for training purposes), thus evaluates the models performance against clinical decisions. Real clinical decisions, and not expert scenarios, are considered the golden standard. It is obvious that modelling a human process can only be evaluated against clinical outcomes. Since the ultimate measure of clinical outcomes is patient's survival the use of clinical decisions that produced such an outcome is the suggested evaluation method. Although such a retrospective evaluation is considered sufficient, there are many limitations. The most important limitation is expressed very fluently by the Nobel laureate in Physics Nils Bohr: "**Prediction is very difficult, especially if it's about the future.**" (Univ. of Exeter). Decision making in uncharted areas is a major problem of models' efficiency. The problem is minimized by increasing the quantity and the quality of the available training sets. Increasing the data sets quantity during the training phase, allows the model to account for the common incidence

encountered in a particular problem. Thus the increased quantity decreases the model's specificity. However quality is concerned with accuracy of data and appropriateness for the task. In ventilation management, accuracy is an important issue. Furthermore models could not always distinguishing false and inaccurate measurements, as clinicians do. Additionally appropriateness is also important. Are the collected variables representative of the process? Is the process described by a single category or the process, as well as the collected data, has to be assigned to subcategories?

The following sections briefly describe the method chosen for the proposed research. The choice of the methods as well as the evaluation methods have been designed so as to overcome the stated problems.

4.2 Methodology overview

The methodology is presented in steps according to their logical and chronological order:

4.2.1 Identification of key variables to the problem

In an effort to decrease the number of models' variables (search space), a questionnaire was developed and circulated to ICU doctors for identifying the relative importance of respiration related physiology and ventilator settings variables. The questionnaire was prepared with the cooperation and assistance of ICU personnel of Agia Olga (Konstantinopoulio) General Hospital of Athens. Eighteen (18) ICU doctors of Ag. Olga, Thriasio and Nikaia general hospitals of Athens-Greece answered the questionnaire. Answers were collected, encoded and statistically analyzed. This process intended to reduce the problem's search space, namely the input and output variables participating in the models design.

4.2.2 Data collection

The set of variables identified in step 1 (section 4.2.1), were recorded during the patient data acquisition phase. Acquisition was performed automatically with the use of certified medical software, in two ICUs; namely the ICU of University Hospital of Heraklio-Crete (PAGNI) and the ICU of Navy Veteran's General Hospital of Athens

(NIMITS). Sufficient patients' data, for the purpose of preliminary evaluation of the models, were collected from eight ICU patients with different pathologies, all ventilated in control mode. The three pathologies utilized for the purpose of the research, namely COPD, ALI-ARDS and Normal lungs, are representative of lung mechanical properties for the common health related patient categories described in section 2.2.1. The utilization of two ICUs for the data collection was to establish a database that would include possible differences in strategies on ventilation management.

4.2.3 Database development

The recorded data (approximately 70h records) were classified by the ICU medical staff of PAGNI into three lung pathologies. The three categories were COPD, ALI-ARDS and Normal lungs. For each category a database was developed. The database included all the measured variables in time intervals of five (5) minutes. The total number of data sets in all categories was eight hundred and forty one (841). A second database was developed which included only the recorded data at time instances when ICU clinical staff applied changes to ventilator settings (29 records). Recorded data were randomly allocated into training (60%) and evaluation (40%) sets. Data sets were scaled in the range of zero to one, and a normalized database was formed.

4.2.4 Data Analysis

The recorded data were further analyzed using correlation, in an attempt to identify strong relationships between output variables (ventilator settings) and input data (physiology variables). This analysis was performed on the grounds of the following research question: "*Is the decision making of ICU clinicians on ventilator settings performed on a subset of measured variables? Does the subset vary between different lung pathologies? Could the analysis of real data including monitored variables and ventilator settings reveal clinicians decision making pattern?"*. The analysis revealed that a subset of input variables exhibited higher degrees of correlation with output data. The number and type of input data varies with lung pathology and ventilator setting.

4.2.5 Evaluation of data analysis

To confirm that the correlation analysis provided medical acceptable results, three clinical evaluators from different hospitals were asked to comment on our findings. The number of evaluators was restricted by the number of participating hospitals. Evaluators were working in PAGNI, NIMITS and Ag. Olga hospitals. Evaluators were asked to classify the correlation coefficients into one of three decisions: accepted, rejected or accepted under given conditions. Based on a voting process, the physiology variables that exhibited high correlation degrees with ventilator settings, and were accepted by the majority of evaluators were chosen for use in the development of the intelligent systems.

4.2.6 EVOFINE Toolbox development

Two Matlab® toolboxes were developed and tested for the optimization and learning of fuzzy systems. The first toolbox, named **EVOFINE** (**EV**olution **O**f **F**uzzy **IN**ference **E**ngines) evolved fuzzy systems assuming no prior knowledge, based only on available recorded patient data. The search for the optimum fuzzy system was performed simultaneously on fuzzy sets and fuzzy rules. Fuzzy Sets were allowed to change linguistic variables size and position within predefined limits, so as not to lose their linguistic meaning. The Rule Base was optimized both in rules' definition and rules' weight. The only preset variable was the number of rules and fuzzy sets. The Pittsburg approach was chosen as the appropriate evolutionary method (Cordon O, Herrera F, et al, 2001,).

The software tool was developed in Matlab version 7.1 (®Mathworks), in order to simplify user interface for training settings, as well as viewing of GA results. The software preformed the evolution of fuzzy inference engine, as well as storing experiment settings and results. Evolution was performed with a customized-modified version of the Sheffield University's GAs toolbox (Evolut. Comp. Research Group 1994).Several other features were incorporated into the developed software, such as choice of Scaling function, evolution using constant or variable mutation rates, choice of membership values type and user defined input and output variables.

4.2.7 FUN Toolbox development

The second toolbox was named **FUN** (**FU**zzy **N**eural). The software was also developed in Matlab version 7.1 (®Mathworks). A simplified user interface allowed the user to specify the fuzzy system setup as well as the Neural Network architecture. The toolbox develops the Rule Base of a Fuzzy system by substituting the rules with a NN, based on available input – output data sets.
Both toolboxes were designed and developed in a general context and not for the specific application.

4.2.8 Toolbox evaluation

The performance of the EVOFINE and FUN toolboxes was tested against non linear mathematical function and a dynamic control systems namely the cart balancing pole system. This evaluation was performed for determining the robustness of the proposed toolboxes. Both toolboxes were applied to build models of multi input – single output (MISO) functions namely the z=sin(x*y), and cart pole control systems. The performance was tested by means efficiently mapping the three dimensional non linear function and efficiently balancing the cart pole respectively, in predefined input and subsequently output domains in terms of root mean square error (rmse) and pole balancing time. This stage compared the performance of the two suggested approaches in developing intelligent fuzzy systems of non linear mathematical functions and dynamic systems, against ANN and ANFIS methods. Detailed analysis on the tests performed is presented in Appendix III.

4.2.9 Evaluation of systems architecture

We conducted small scale experiments to identify the appropriate GA, Fuzzy, neural network, FUN and ANFIS architecture. Criteria were the performance and the simplicity (translated as computation time) of the models.
The experiments performed on the proposed soft computing methods, were carried out in order to derive “rules of thumb” that would be latter applied on the development of the mechanical ventilation models. Although for ANN and ANFIS, the rules of thumb are known, such as relationship of data set size and NN complexity, this was not true for the new toolboxes; namely the EVOFINE and FUN. Based on the experiments the main characteristics of the systems such as RB

size, damping or constant mutation rates, defuzzification technique, were evaluated. Conclusion from the preliminary evaluation were used in the development of the ventilation models.

Furthermore the process of correlation analysis and evaluation resulted into simplified model's architectures in terms of input variables to each model. Reducing the number of input variables reduces systems complexity but also adapts the models to human perception of the process.

4.2.10 Mechanical ventilation advisory models

Development of the AI models was based on the results of sections 4.2.5 to 4.2.9. EVOFINE, FUN, ANFIS and ANN Matlab toolboxes were applied for the AI system models. Different models were developed for each pathology (COPD, ALI-ARDS & Normal), by utilizing the recorded patient training data. Models used the MISO architecture, where the inputs were the highly correlated physiology variables and output was one of the ventilator settings. For each category six (6) AI system models were developed, one for each ventilator setting, with the use of the four proposed methods.

4.2.11 Models' evaluation

The resulting AI systems were tested against evaluation data. Performance was measured in terms of root mean square error and absolute mean error between clinicians recorded actions and model's advice given as an error and as percentage error. Evaluation included also the development computation time. Computation time is not important in the development phase of a system, but is crucial during the maintenance phase when models have to be retrained with newly available data. Furthermore patient scenarios from the collected data were developed and presented to ICU clinicians. The purpose of this evaluation was to identify whether the difference between the developed models suggestions and the clinical applied decisions was clinically significant. The clinical decisions difference on the patient scenarios provided an upper medically acceptable limit of disagreement between clinicians; thus the upper acceptable limit of disagreement between the models decisions and applied clinical decisions on ventilator settings.

Clinicians presented with patient scenarios and were asked to advice on ventilation settings. The doctors' advice was then statistically analyzed. The outputs from the models were compared against the clinicians' advice for the same scenarios. The analysis was performed in order to investigate whether the models' disagreement with clinical decisions was within the range of clinical disagreement on scenarios. Finally we compared the four approaches performance and concluded on the appropriateness for research purposes.

4.3 Research Ethics

Ethical approval was obtained for all research phases which involved collecting human data. Prior to circulation the questionnaire was granted ethical approval for the methods, human resources and materials, by the ethical committee of the department of Medical Instrumentation Technology of the Technological Educational Institute (TEI) of Athens (www.teiath.gr). Due to lack of an appropriate dedicated institutional ethics committee in the Universities and the Technological Institutes in Greece, the department's ethics committee acts under exceptional circumstances. The duration from application to approval for acquiring ethical approval by the department's committee was less than a month.

For the collection of patient physiology data, the ethics committee of the University Hospital of Heraklio Crete (PAGNI) granted the approval (*www.**pagni**.gr*). We have fully complied with the ethics committees guidelines for these institutions. Patients' data were collected directly from digital outputs of medical equipment by using certified medical software and cabling. Data collected included basic demographics, relevant to our research and physiology variables and ventilator settings and not patient information that could reveal a patient's identity. Throughout the report patients are referred to with a numbering system.

5. Questionnaire Development & Evaluation

5.1 Questionnaire

A questionnaire (available in Appendix VI) was prepared and circulated to ICU doctors of three General Hospitals namely Konstantinoupolio (former Agia Olga) general hospital, Thriasio general hospital and Nikaia general hospital.

The purpose of the questionnaire was to collect data on ventilation related variables, in order to derive, with the use of statistics, the relative significance of patient physiology variables and ventilator settings, according to doctor's experience and expertise, on the process of Ventilation Management in controlled ventilated patients.

This would result in minimizing the research search space and so reduce the number of input and output variables for our models, and thus reducing complexity during the development process.

5.1.1 Development

Five groups of ventilation related variables have been identified with the assistance of the ICU clinician personnel of Konstadinoupolio (former Agia Olga) general hospital. For this purpose a series of three meetings were held at the hospital, together with an introductory presentation about the purpose of the research project. The variables were grouped according to the acquisition method, and the physiology principle they describe. The final grouping is described in table 5.1.

A questionnaire (available in Appendix IV) was prepared and circulated to ICUs doctors of three General Hospitals namely Agia Olga general hospital, Thriasio general hospital and Nikaia general hospital.

In order to promote understanding of the purpose of the research, the first page of the questionnaire described the research as well as the purpose of the questionnaire. A second page followed with completion and mailing guidelines.

Table 5.1: Variables' grouping.

Variables Groups	Variables
Patient Demographic Data	Patient's Age
	Patient's Height
	Patient's Weight
	Patient's Sex
Non Invasively acquired variables	Arterial Oxygen Saturation (SpO_2)
	End Tidal Capnography (E_TCO_2)
	Heart Rate (HR)
	Core Body Temperature
	Extremes Body Temperature
Blood Gases	Partial Pressure of Oxygen in Arterial blood (PaO_2)
	Partial Pressure of Carbon Dioxide in Arterial blood ($PaCO_2$)
	Hydrogen Ions Concentration in blood (pH)
	Concentration of HCO_3 in blood
	Oxygen Saturation of Central Vein blood (S_VCO2)
	Partial Pressure of Oxygen in Venous blood (PvO2)
	Partial Pressure of Carbon Dioxide in Venous blood (PvCO2)
	Oxygenation Index (PaO2 / F_IO_2)
Volume, Flow and airway pressures.	Expired Volume (V_e)
	Mean airway Pressure (P_{MEAN})
	Maximum-Peak Inspiratory airway Pressure (PIP)
	End-Inspiratory Pause Pressure ($P_{PLATEAU}$)
	Intrinsic PEEP (Auto PEEP)
Lung mechanics	Lung Compliance (C)
	Airway Resistance (R)
	Work of breathing (WOB)
Hemodynamic variables	Cardiac Output (CO)
	Mean Pulmonary Artery Pressure (MPAP)
	Variation of Systolic arterial pressure
	Central Venous Pressure (CVP)
	Pulmonary Capillaries Wedge Pressure (PCWP)
Ventilator Settings	Minute Ventilation (V_E)
	Tidal Volume (V_T)
	Respiration Rate (RR)
	Positive End Expiratory Pressure (PEEP)
	Fractional Inspired Oxygen (F_IO_2)
	Maximum allowed airway Pressure (P_{peak} or Pmax)
	Inspiration Time / Expiration Time ratio (I/E)
	Maximum Inspiratory Flow (F_{peak} or Fmax)
	Inspiratory Pause
	Inspiration Flow Pattern

The questionnaire was designed with closed questions, where answers were scored with an analog rating scale from 0 to 10. Zero (0) described a variable of small significance for the process of ventilation management, while ten (10) was used for a variable of high significance.

Five major categories of physiology variables were proposed. ICU clinicians were asked to classify their relative importance in ventilation management decision making. The categories are shown in the left column of table 5.1.

In total 26 physiology variables have been identified. These variables are utilized by ICU doctors during control ventilation management for estimating the adequacy of mechanical ventilation. In addition 4 variables were included in the questionnaire (patient's Age, Weight, Height and Sex), describing the initial phase of ventilator set up.

The above 26 variables summarized the doctor's feedback for the efficiency of the ventilation process. Doctors utilize the trends and values of these physiology variables in combination with patient's pathophysiology and pharmacology, to evaluate the adequacy of ventilation. If ventilation is judged as insufficient, then doctors induce changes to ventilator set up to improve patients' ventilation. For that purpose 10 variables (bottom of Table 5.1), which describe the most important settings of the ventilator apparatus, have been included to the questionnaire.

5.1.2 Coding

Coding is the process of formatting qualitative answers in a way that can be statistically analyzed. For the purpose of analyzing data, the responder's answers from the first two fields were coded as follows:

- Sex was coded as 1 for male and 2 for female responders.
- Patient age was coded into groups of 1 (18-35 years), 2 (36-45 years), 3 (46-55 years) and 4 (56-70 years).

The remaining fields were recorded into a spreadsheet format, for direct statistical analysis, since the numerical scale of the answers did not required any further processing.

5.2 Questionnaire Results

The questionnaire was designed to explore the importance of the variables in ventilator management. It was hypothesised that not all variables have the same significance in the ventilation process. This would allow to decrease the number of variables incorporated into the developed model, thus decreasing the search space and subsequently the number of monitored – recorded variables.

The questionnaire was circulated and answered by eighteen (18) intensivists of three general hospitals in Attica-Greece province; namely Thriassio - Elfesina general Hospital, Konstadinoupolio general hospital and state general hospital of Nikaia. Questionnaires were delivered by hand to the directors of the ICU, following an introductory conversation on the purpose of the research. The number of participating intensivists was dictated by the directors of the ICUs and the number of available personnel.

Thirty nine percent (39%) of responders were male. The responders between the ages of thirty six (36) to fifty five (55) accounted for the eighty eight percent (88%) of all the responders, while the mean working experience in ICU was 8.5 years (table 5.2)

Table 5.2: Responders statistics.

Hospital	**Number of respondents**	**% male**	**age groups %**	**Average ICU experience in years (SD)**
H1	4	25	1: 0 2: 50 3: 50 4: 0	4 (2,9)
H2	6	33	1: 0 2: 66,6 3: 33,3 4: 0	9,8 (6,6)
H3	8	50	1: 25 2: 25 3: 50 4: 0	9,8 (10,9)
Total (H1,H2,H3)	18	39	1: 11,1 2: 44,4 3: 44,4 4: 0	8,5 (8,35)

Question Three asked the doctors to rate the importance of basic patient characteristics on the initial ventilator settings. Answers revealed that a patient's weight is the most important factor (fig. 5.1 and table 5.3). This high score was anticipated since initial settings of tidal volume are set based on ml/Kg are reported

in most literature. Height was ranked as the second variable, which is related to the body mass index (BMI). Sex and age do not seem to have a significant role in ventilation. Lung's phenomenal age is defined by the mechanical properties rather than the actual patient's age, and sex is accounted for with the use of the weight variable; sex and weight are highly correlated variables.

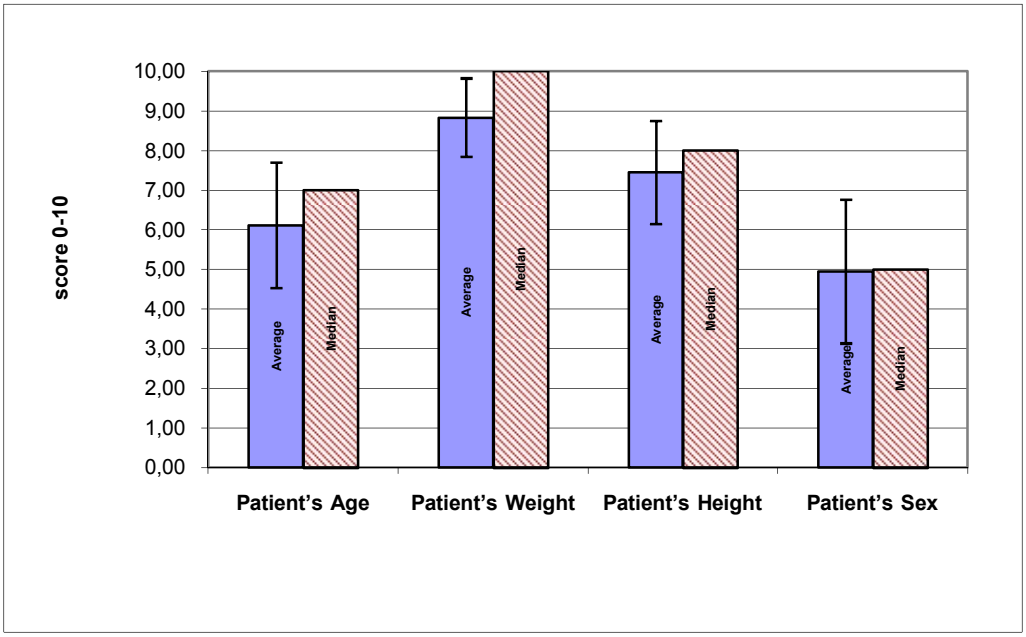

Figure 5.1: scoring of patient's characteristics; answers average (blue) & median (dashed red).

Table 5.3: scoring of patient's characteristics.

	Avg	Median	SD
Age	6,11	7,00	3,16
Weight	8,83	10,00	1,98
Height	7,44	8,00	2,59
Sex	4,94	5,00	3,62

Patient's weight (table 5.3) has shown a small SD value when examining the total of responders' answers. This presents a good agreement between responders.

All of the questionnaire variables were grouped into five (5) groups (Fig 5.2). Variable grouping was decided upon by the method of acquisition (invasive or non-invasive), the type of equipment (bedside monitor, ventilator, and blood gas analyzer) and the physiology system (respiration-lung and cardiac-circulation physiology) they monitor. Blood gases, acquired usually through arterial and/or venous sampling were identified based on their average value and the low SD among hospitals, as the most important group. Variables related with lung volume and

pressure measurements scored as the second best group. Lung mechanics, non-invasively monitored physiology variables and hemodynamic variables scored in a descending order. None of the groups was considered as irrelevant to the process of ventilation management. The worst group was ranked with a median value of 8. This outcome was anticipated since the grouping was designed with the assistance of intensivists.

Group scoring values were used for decisions on the number and type of variables that were included in our model. It was decided to only include variables from the four best scoring groups, namely in descending order blood gases, pressure-volume, lung mechanics and non-invasive variables. Hemodynamic variables were excluded based on their low scoring and on the need of catheterization prior to monitoring, which is not always available or applied. Oxygenation index (OI) is calculated directly from blood gases and ventilator settings (OI= PaO_2/FiO_2) and for this reason it was included as a candidate in our models.

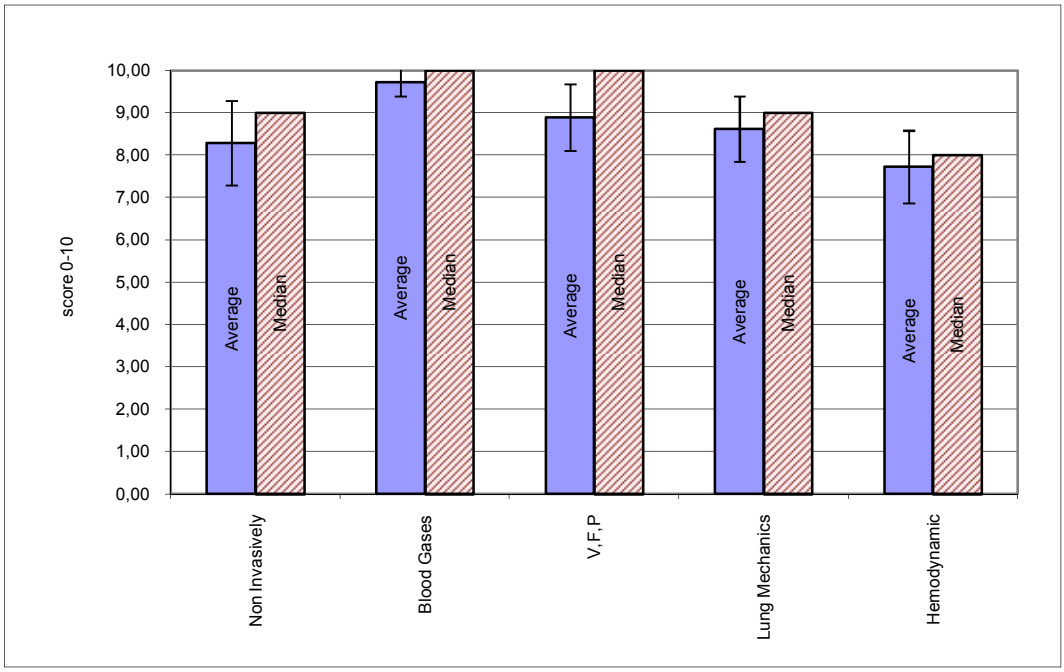

Figure 5.2: scoring of variables groups; answers average (blue) & median (dashed red).

Table 5.4: scoring of variables groups.

	Avg	Median	SD
Non Invasively	8,28	9,00	1,99
Blood Gases	9,72	10,00	0,67
Volume Flow pressure	8,89	10,00	1,57
Lung mechanics	8,61	9,00	1,54
Hemodynamic variables	7,72	8,00	1,71

Answers on specific variables for each group, were used for identifying the final group of model's variables.

Question five (5) asked the respondent to score the non-invasive monitored variables. The resulting scores, shown in Fig 5.3 and table 5.5, identify arterial oxygen saturation and heart rate as the most important candidate variables for our model. End Tidal Capnography has also exhibited a high ranking, slightly inferior to heart rate. Both SpO_2 and E_TCO_2 are related to adequacy of ventilation; however clinicians seem to value more the former. Core body temperature has scored higher than extremes body temperature. This is mainly due to core body temperature relationship to infections (fever), while extreme body temperature signifies thermal shock and circulation problems. There was a large variation among answers provided by different hospitals for the extreme temperature, however none of the hospitals ranked extreme temperature above five (average value).

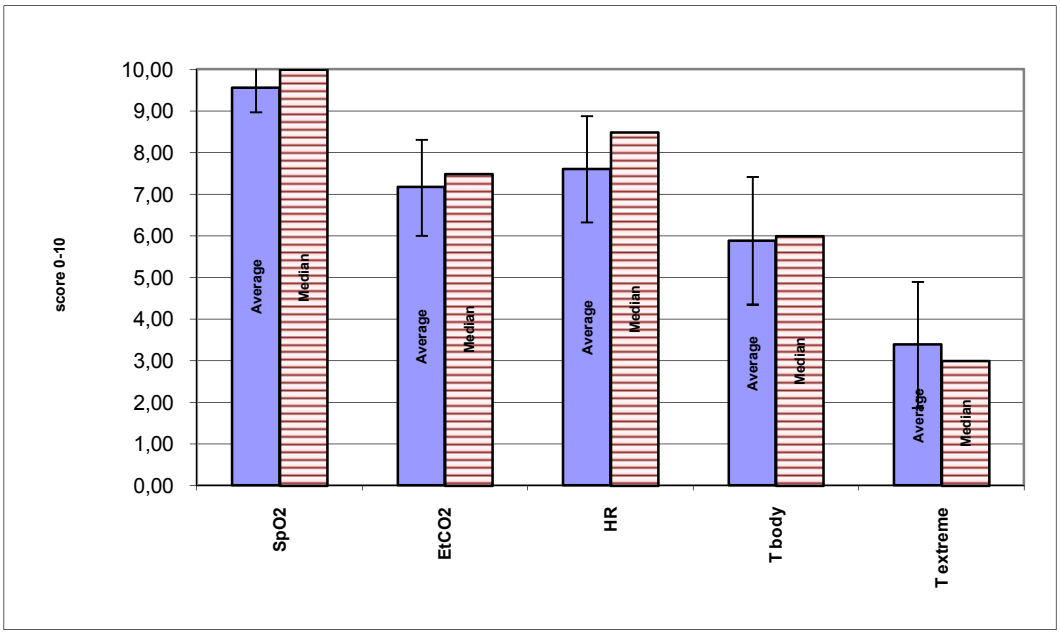

Figure 5.3: scoring of non-invasive variables; answers average (blue) & median (dashed red).

Table 5.5: scoring of non-invasive variables.

	Avg	Median	SD
SaO2	9,56	10,00	1,15
ETCO2	7,17	7,50	2,31
HR	7,61	8,50	2,55
Core Temperature	5,89	6,00	3,07
Extremes Temperature	3,39	3,00	3,03

Question six (6) was concerned with the ventilator related variables. Participants were asked to score volume, pressure and lung mechanics variables based on their importance in selecting appropriate ventilation settings. In figure 5.4 and table 5.6, the average and median scoring values from volume-pressure and lung mechanics groups are shown. Plateau and peak pressure as well as compliance and expired volume scored very high both in average and median scores. Compliance (C) exhibited a slightly higher variation than airway resistance (R). Mean pressure, airway resistance (R) and WOB scored above 8. Auto-PEEP at first glance exhibits a poor scoring. However this is attributed to an error in the produced photocopies of the questionnaire, where the scoring fields are not clearly printed for this variable. Most responders were confused with the scoring of the variable and left the specific field blank. This answer was coded with zero (0). Once the problem was identified, it was decided to exclude the specific variable from the analysis process. The variable was excluded on the following grounds: (1) introducing false measurements; (2) trapping air into the lungs could be indicated by the increased airway resistance and poor lung compliance as well by limited expired volume. However the misleading printout could be a source of bias concerning the variables participating in question six (6), in terms of possibly excluding an important variable. This does not reduce the importance of scoring of the other variables since each variable was scored independently from the others.

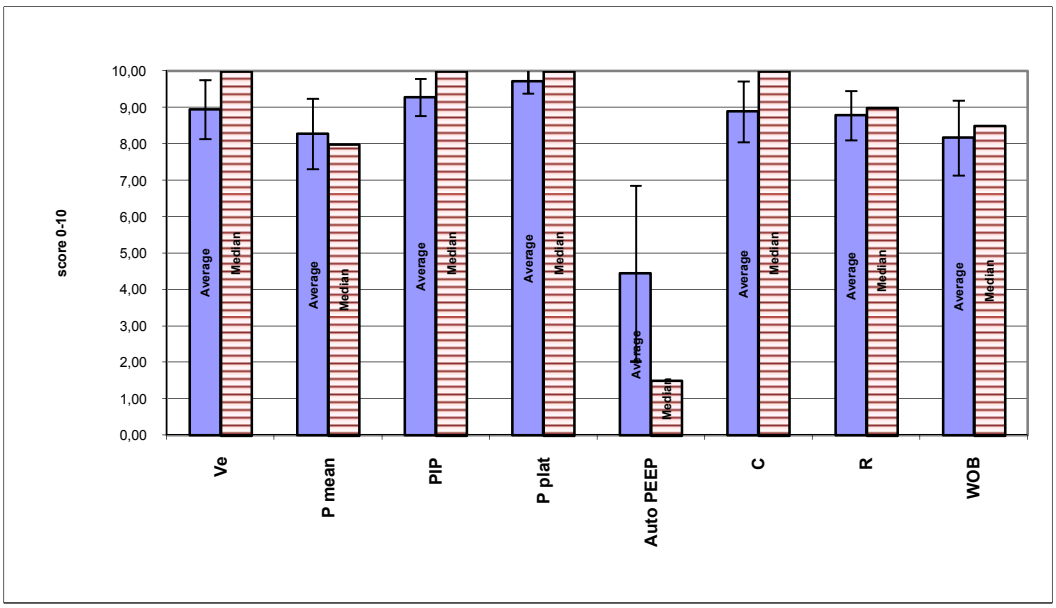

Figure 5.4: scoring of ventilation related variables answers; average (blue) & median (dashed red).

Table 5.6: scoring of ventilator variables.

	Avg	Median	SD
VE	8,94	10,00	1,63
P_{MEAN}	8,28	8,00	1,93
PIP	9,28	10,00	1,02
$P_{PLATEAU}$	9,72	10,00	0,67
Auto PEEP	4,44	1,50	4,83
C	8,89	10,00	1,68
R	8,78	9,00	1,35
WOB	8,17	8,50	2,07

Question seven (7), asked participants to score the variables measured invasively. Invasive measurements are performed either with the support of catheterization equipment, or with the acquirement of blood samples. The results of question 7 are presented graphically into two groups (fig. 5.5 & 5.6). The first group is the blood sample measurements (blood gases), and the second group is the catheterization measurements (blood pressure and cardiac output variables). Arterial blood gases have scored higher than venous measurements. HCO_3, has the lowest score among arterial gases; this is attributed to known close relationship to arterial CO_2 which provides sufficient information. In the second group on invasive variables, OI has exhibited the higher score. OI is not directly measured but rather calculated based on arterial oxygen concentrations and supplied oxygen concentration. Arterial, venous and pulmonary pressures scored lower. Variation of systolic pressure has scored higher than invasive blood pressure measurements. Variation of systolic pressure is closely related to changes in circulation induced by the mechanical ventilation.

Similarly CO could be constrained due to mechanical ventilation. However CO scoring was lower than arterial blood gases measurements and variation among hospitals was higher.

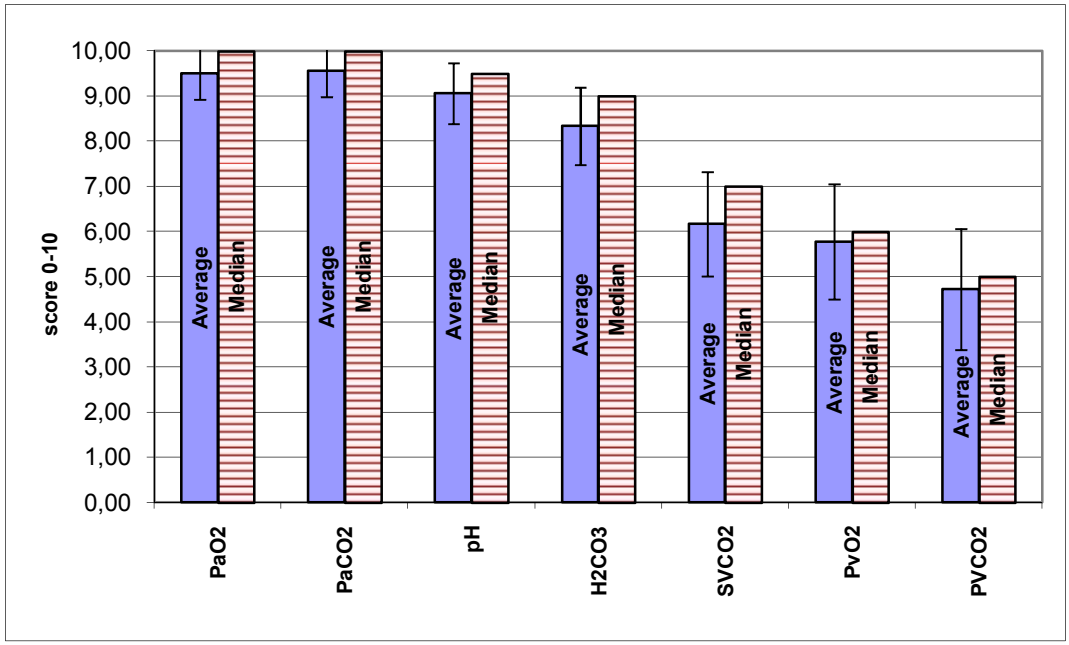

Figure 5.5: scoring of blood gases; average (blue) & median (dashed red).

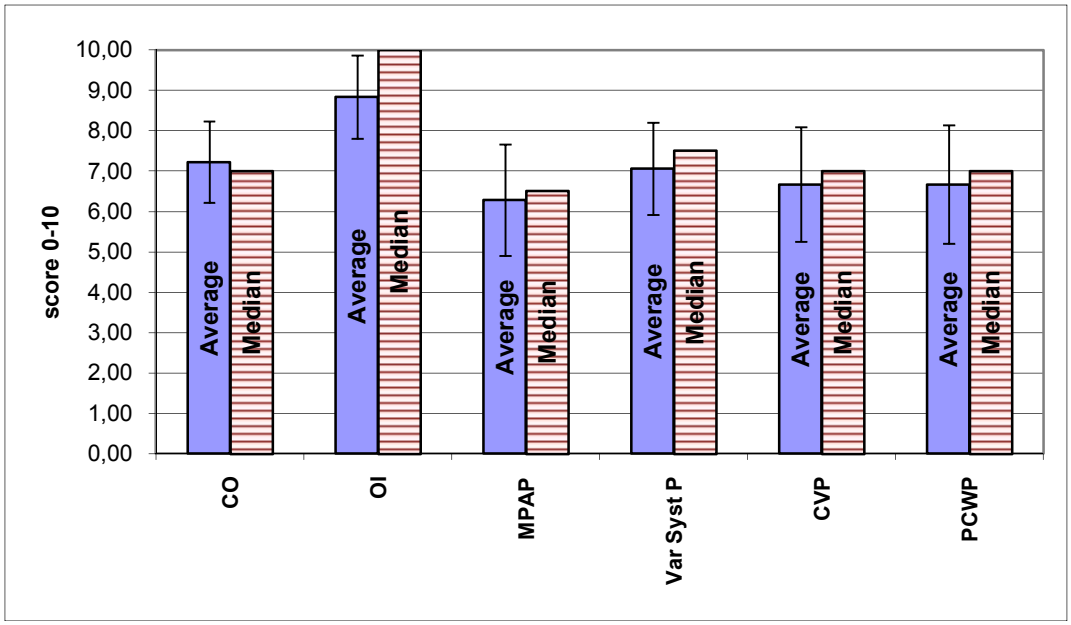

Figure 5.6: scoring hemodynamic variables; average (blue) & median (dashed red).

Table 5.7: scoring of invasive variables.

	Avg	Median	SD
PaO_2	9,50	10,00	1,15
$PaCO_2$	9,56	10,00	1,15
pH	9,06	9,50	1,35
HCO_3	8,33	9,00	1,71
S_VCO_2	6,17	7,00	2,31
PvO_2	5,78	6,00	2,56
$PVCO_2$	4,72	5,00	2,67
C.O.	7,22	7,00	2,02
OI	8,83	10,00	2,07
MPAP	6,28	6,50	2,76
Variation of Syst. Art.Pr	7,06	7,50	2,29
CVP	6,67	7,00	2,83
PCWP	6,67	7,00	2,93

The final question concerned with the importance of ventilator settings. Responders ranked FiO2 and maximum allowed pressure (Pmax) as the most important variables. V_T, RR, PEEP and minute ventilation (VE) were similarly ranked. However VE in control ventilation is the product of V_T times RR, and thus is sufficiently described by these variables. Inspiration over expiration time ratio (I/E), maximum flow and flow pattern were ranked slightly lower, but relatively high (median values of 9). Inspiratory pause, exhibited the lowest average and median value (3.4 and 0 respectively). This is due to the fact that all responders of the first hospital (H1) did not rank this field at all. Thus the median value was set to zero. This could indicate a bias in the questionnaire. However informal interviews followed the analysis of the questionnaire revealed that the specific variable is considered of small importance, relative to other variables, in the ventilation process.

Table 5.8: scoring of ventilator settings.

	Avg	Median	SD
VE	9,44	10,00	1,25
V_T	9,44	10,00	1,15
RR	9,17	10,00	1,72
PEEP	9,11	10,00	1,75
FIO2	9,56	10,00	1,04
PIP	9,50	10,00	0,71
(I/E	8,00	9,00	2,70
Peak Flow	8,17	9,00	2,46
Insp.Pause	3,39	0,00	4,02
Insp. Flow Pattern	8,00	9,00	2,70

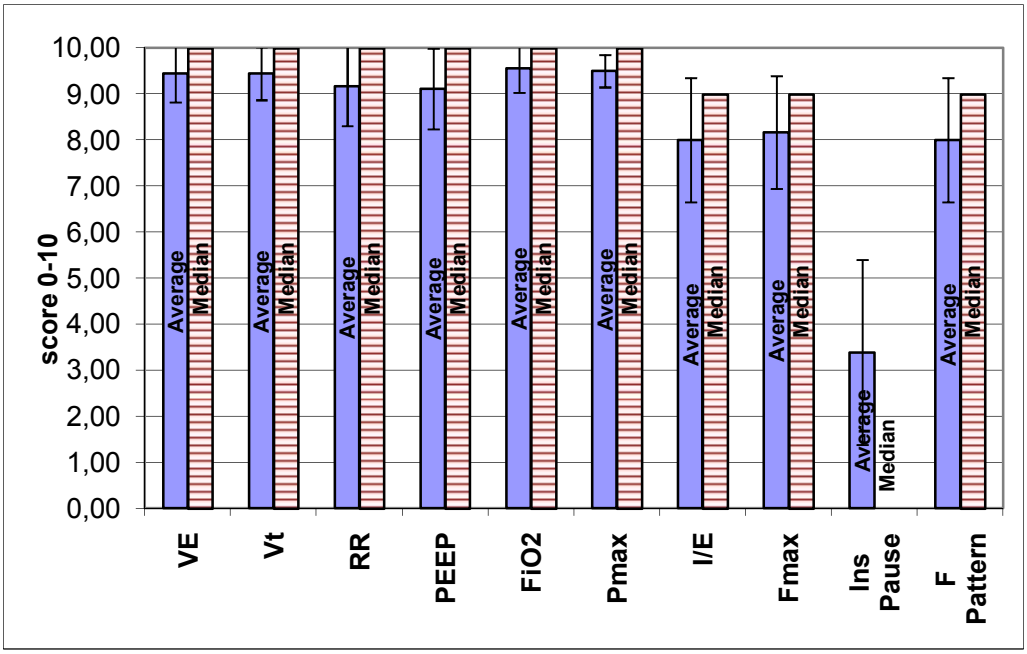

Figure 5.7: scoring ventilator settings; average (blue) & median (dashed red).

The aim of the questionnaire was to identify relative importance of physiology variables and ventilator settings in the ventilation management process. For this reason Average values, Mean values and Standard Deviation (SD), was calculated for each of the variables.

The final choice of variables was preformed based on those that exhibit the highest average and mean score. The scoring of variable groups was used for identifying the number of variables chosen from each group. Based on group scores, eleven (11) variables were included in our models, as well as one calculated variable; namely the oxygenation index (OI). The groups with the higher scores contributed with more variables to our model. This approach resulted into utilizing four (4) variables from the blood gases group, three (3) from the volume-pressure group, two (2) from the lung mechanics group and two (2) from the non-invasively acquired variables group. The decaying number of variables reflects the group's importance to the ventilation management process.

Six output ventilator settings were chosen as system's outputs (Table 5.9). Tidal volume (V_T), respiration rate (RR), Positive End Expiratory Pressure (PEEP), maximum inspiratory pressure (pressure limit –Pmax), maximum inspiration flow (Fmax) and Fractional Inspired Oxygen (FiO_2), were chosen. Although minute ventilation scored very high it was excluded from the development process since in control ventilation mode its value is given by the product of tidal volume multiplied by the respiration rate. Similarly flow pattern setting (F Pattern) was excluded on the

grounds that is not available in all commercial ventilator equipment. Inspiratory pause was excluded on the grounds that it was not answered by one hospital due to a photocopy error. Informal consultation on the I/E ratio has suggested the importance of the variable when auto-PEEP is present. However since the measured variable of auto-PEEP was excluded, as discussed earlier, the specific setting was not chosen for participating in the models.

The classification of the ventilation related variables resulted into a reduced set of physiology and ventilator variables. The reduction of the number of ventilation related variables simplifies the recording phase and reduces the complexity of the problem.

Table 5.9: selected variables.

Variable type	**Variable**	**Recording method & device**
Monitored	Arterial Oxygen Saturation (SpO_2)	Automatically Monitor/Central Station
	Heart Rate (HR)	
	Arterial Blood O_2 partial pressure (PaO_2)	Manually Patient's Chart
	Arterial Blood CO_2 partial pressure ($PaCO_2$)	
	Hydrogen Ion concentration (pH)	
	Concentration of HCO_3 in blood (HCO_3)	
	Oxygenation Index =PaO_2 / F_IO_2 (OI)	Calculated
	Maximum-peak airway pressure (PIP)	Automatically Ventilator
	End Inspiratory pause pressure (Pplateau)	
	Lung Compliance (C)	
	Airway Resistance (R)	
	Expired Volume (Ve)	
Ventilator Settings	Tidal Volume Settings (V_T)	
	Positive End Expiratory Pressure settings (PEEP)	
	Fractional Inspired Oxygen (F_IO_2)	
	Respiration Rate Settings (RR)	
	Inspiration flow limit (Fmax)	
	Airway pressure limit setting (Pmax)	

5.3 Patient Data

Peripheral University Hospital of Heraklio (PAGNI), Crete and Navy Veterans' hospital of the Ministry of Defence in Athens (NIMITS) were chosen as the appropriate settings for collecting ICU patient data. The choice was based on availability of medical devices that were equipped with digital outputs (RS232), for data acquisition. The ICUs were equipped with Siemens-Draeger ventilators, which have *medibus* serial interface enabled. Furthermore the ICUs were equipped with a central monitoring station, able to record patients' variables trends for the duration of patient's stay.

For the collection of patient physiology data, the ethics committee of the PAGNI and hospital granted the approval. Patients' data were collected directly from digital outputs of medical equipment by using certified medical software namely ®MedLink 4.0 by Nortis (Nortis), and ®VentView by Siemens-Draeger (Siemens-Draeger). Data collected included only physiology variables and ventilator settings excluding any other information that could reveal the patients' ID.

A typical software interface and data records snapshot screen is shown in figures 5.8 and 5.9 respectively.

While monitors could provide only with arithmetic values (Trends), ventilators could also provide flow, and pressure real time waveforms. Numerical data collection was chosen in seconds with a maximum period of 5 min. Real time flow and pressure waveforms were acquired from the ventilator devices at a sampling rate dictated by the medical apparatus, for future research. Blood gases data were collected manually directly from patient's bed side charts. Blood gases were collected at time intervals specified by clinicians. The physiology variables and ventilator settings recorded are shown in table 5.9.

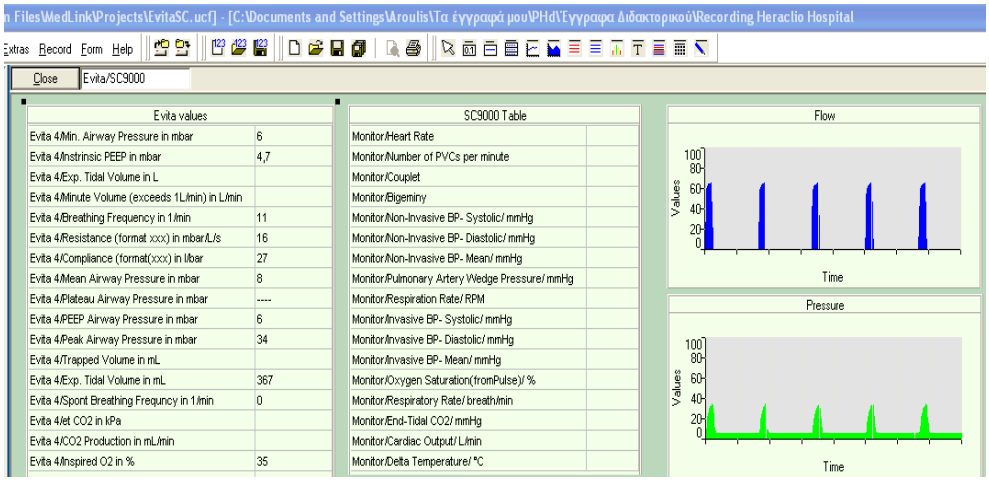

Figure 5.8: Data acquisition Software interface from Ventilator apparatus.

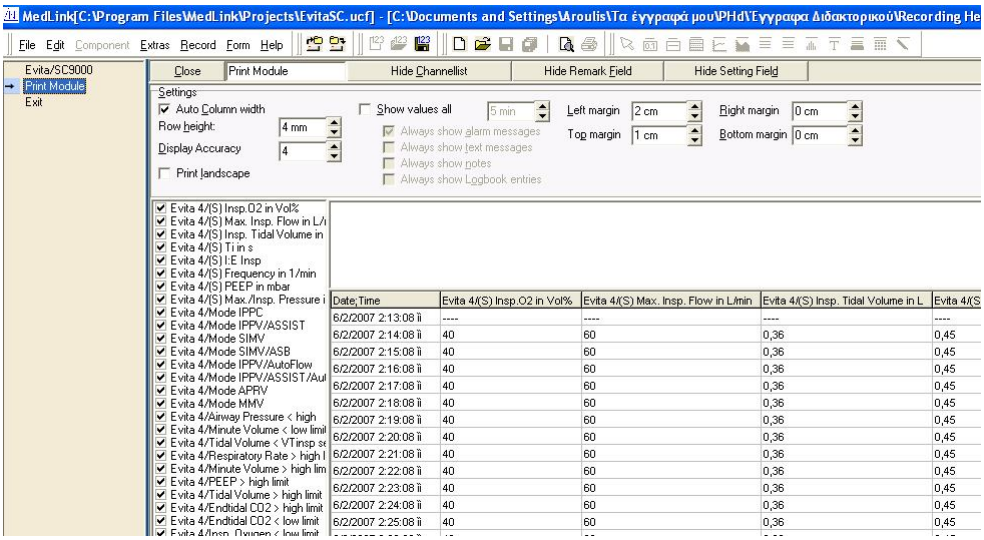

Figure 5.9: Software data records.

Approximately seventy hours of patients' data were collected from eight ICU patients with different pathologies, ventilated in control mode. The utilization of two ICUs for the data collection was to establish a database that would include possible differences in strategies on ventilation management.

Recorded patient data were extracted to Excel format (®Microsoft). Due to small variation between successive samples data were re-sampled at five (5) minute intervals. Table 5.10 presents the format of the database for COPD records of one hour and ten minutes (1h 10min) duration. The time points were changes were implemented to at least one of the ventilator settings were identified and used for the development of a second database that includes only the records at the point of change. Furthermore data sets were scaled into the range of zero (0) to one (1), and used for the development of a scaled data set which was named *normalized* set.

Table 5.10:COPD example Patients' database

Time h:min	Physiology Variables												Ventilator Settings					
	SpO2	PaO2	PaCO2	pH	O2 Index	Ve (ml)	PIP (mbar)	Plateau	C (l/bar)	R (mbar/L/s)	HR	HCO3	Vt ml/Kgr	RR (BPM)	PEEP(mbar)	FiO2	Max Insp P (mbar)	Max Flow (L/min)
0:00	99	69	70	7,4	115	351	49	40,9	22	27	86	44	3,36	27	2	0,6	84	80
0:05	99	69	70	7,4	115	350	48	39,5	23	26	86	44	3,36	27	2	0,6	84	80
0:10	99	69	70	7,4	115	345	47	38,1	24	24	85	44	3,36	27	2	0,6	84	80
0:15	99	67	73	7,39	112	354	47	38,5	23	24	86	45	3,36	27	2	0,6	84	80
0:20	94	71	69	7,42	203	369	36	26,5	28	18	63	44	4,53	21	6	0,35	76	60
0:25	94	71	69	7,42	203	365	36	26,8	27	18	63	44	4,53	21	6	0,35	76	60
0:30	94	71	69	7,42	203	349	36	27,5	25	18	62	44	4,53	21	6	0,35	76	60
0:35	94	71	69	7,42	203	319	37	29,2	23	18	62	44	4,53	21	6	0,35	76	60
0:40	94	71	69	7,42	203	283	36	28,2	23	18	61	44	4,53	21	6	0,35	76	60
0:45	95	71	69	7,42	203	342	37	28,2	26	18	63	44	4,53	21	6	0,35	76	60
0:50	94	71	69	7,42	203	357	36	27,2	26	18	61	44	4,53	21	6	0,35	76	60
0:55	94	76	73	7,4	217	312	33	24,5	25	14	62	46	4,53	21	6	0,35	76	60
1:00	95	76	73	7,4	217	355	34	24,5	28	14	59	46	4,53	21	6	0,35	76	60
1:05	94	76	73	7,4	217	305	33	24,5	25	14	60	46	4,53	21	6	0,35	76	60
1:10	94	76	73	7,4	217	355	32	22,5	28	14	59	46	4,53	21	6	0,35	76	60

As described in the methodology paragraphs, patients were classified into three major lung pathologies. The resulted database is described in table 5.11.

Patient 1 suffered from COPD and has been recorded for a prolonged period. The recordings were made into two successive days. Recording was interrupted on the first day (approximately after 17h) following clinical personnel request. The recording was continued on the second day after a 4h break in recording process. The recording time of the patients does not describe the full period that the patients were ventilated in control mode. The recording time was limited by changes in ventilation mode, shifting from control to assist ventilation and from medical procedures requiring the pause of bed side ventilation. Most of the recording were performed based on availability of patients ventilated in control mode, and were restricted by the available time in the ICU, as well as the availability of specialized personnel (technical personnel) to assist the initiation of the recording phase.

Table 5.11: Patient records overview.

Lung Pathology	Patient	Sex	Age	Weight (Kgr)	No of records (5min)	Time (h:min)	Applied changes No of records
COPD	1	M	48	75	455	37:55	16
	2	M	51	90	27	2:15	
	3	M	43	110	42	3:30	
ALI-ARDS	4	F	78	100	75	6:15	10
	5	F	66	70	55	4:35	
	6	M	59	80	59	4:55	
Normal lungs	7	F	55	50	108	9:00	3
	8	M	78	80	20	1:40	

Utilizing random generator software in Matlab we have randomly distributed patient records into training and evaluation sets for all categories. The training set accounted for the sixty percent (60%) of the available data while the evaluation set accounted for the forty percent (40%). Resulted data sets were scaled, forming the normalized database, and used to models with normalized input – output data. The random allocation of available data into training and evaluation sets results into participation of the same patients into both sets. However the time instances represented by the measured variables and the ventilator settings are different; thus the time specific patient needs are also different. The relatively small sample of patients for each category does not provide sufficient data for applying different patients for the evaluation and training sets. Additionally the use of specific patients for training the develop models would result in patient specific systems.

5.4 Correlation results

The use of the questionnaire simplified the data collection process by limiting the number of recorded variables. A research question was established and correlation analysis was used to support it. The research question is summarized in the following paragraph:

"*Is the decision making of ICU clinicians on ventilator settings performed on a subset of measured variables? Does the subset vary between different lung pathologies? Could the analysis of real data including monitored variables and ventilator settings reveal clinicians decision making pattern?"*.

The validity of the research question would result into further reduction of the problems search space, by incorporating into the intelligent models only the physiology variables that play an important role in the ventilation strategy for each pathology; and more specific the variables that exhibit high degree of relationship with specific ventilator settings for each lung category.

In order to investigate the validity of the question and to define the degrees of relationship between inputs (monitored physiology variables) and outputs (ventilator settings), correlation analysis and statistical significant tests on the analysis ($p<0.05$) were performed. The correlation analysis was performed on both the developed databases; for each lung pathology. The two databases were the 5 minute trends and the applied changes database.

Correlation and significance tests (Bland M, 1996), were performed between measured physiology variables and ventilator settings. The analysis was performed separately on each lung's pathology.

Correlation is measured by the correlation coefficient (C or *r*). When C is close to zero, the variables are uncorrelated. Absolute values of C close to 1, reveal a strong linear relationship between variables. The value of C was computed based on Pearson's linear correlation coefficient (Bland M, 1996).

For each correlation test, we have calculated the probability value (P-value <0.05). Small P-values support the hypothesis that correlation is nonzero.

Tables 5.12 to 5.13 present the correlation analysis of the recorded data for the three lung pathologies. Analysis was performed on both databases; namely the five minute records and the applied changes database. Absolute correlation coefficients below 0.5 presents a weak relationship between variables. Absolute correlation coefficients between 0.5 and 0.75 exhibit a strong relationship, while absolute coefficients above

0.75 describe a very strong relationship between variables. Strong and very strong relationships are identified in bold writing. Negative values of C reflect change in the variables in the opposite direction. The tidal volume is expressed in terms of volume per patient's weight (ml/Kg), in order to allow comparison between different patients.

We calculated correlation coefficients (C) and probability values (P) with the use of Matlab ™ statistics toolbox. We have defined a threshold of 0.5 for C. Variables that exhibited C above the threshold value *at least in one of the two databases* and coefficients were statistically acceptable ($P<0.05$), were used for calculating an average correlation coefficient (C_{avg}). The variables for which the C_{avg} was calculated they were chosen as candidate inputs to the intelligent systems.

The above process was not similar for the normal lungs category since the number of available data was very small in the applied changes database, as shown in table 5.11. In normal lungs category we have chosen as candidate inputs to our models the variables that exhibited C above the threshold value and P below the 0.05. In this category C_{avg} matches the C calculated for the five minute records database.

Although justification or rejection of degree and direction of correlation requires deep knowledge of human physiology and medical background, the following points attempt to identify and comment key findings:

- PEEP variable does not correlate with any of the recorded variables for Normal lungs. This is mainly attributed to the fact that small or zero PEEP is applied to these patients.
- SpO_2 does not relate strongly with any of the ventilator settings. SpO_2 values are maintained in stable margins (94-98%). Only under extreme respiration deficiency SpO_2 values fall below 90%. Thus SpO_2 seems to have a random variation around physiological values; thus does not correlate strongly with any of the ventilator settings (in the 5 min database, table 5.12). However the applied changes database correlation we observe that SpO_2 is highly correlated with a number of factors improving oxygenation (V_T, PEEP,FiO_2).
- OI is based on calculus is related to inspired oxygen concentration. Additionally the OI is relevant to variables that improve blood oxygenation. Such factors, accepted and supported by bibliography, are PEEP, minute ventilation (product of RR times V_T), and mean airway pressure (closely related to maximum pressure). These strong relationships are observed in all patient categories.

- Blood gases (PaO2, PaCO2, pH, HCO3), reflect the efficiency of ventilation. For normal lungs almost all settings (excluding PEEP), present a strong relationship with blood gases. For COPD and ALI-ARDS lungs this is not true. In these cases simple interventions (changes in volume and RR) do not have a significant effect. Increasing mean pressure and functional residual capacity (FRC) through PEEP, improves ventilation efficiency. On the other hand respiration is a major mechanism for eliminating CO_2, and changing pH & HCO_3 values. Based on this RR is related to changes in blood ions.
- Expired volume (Ve) is expected to have strong correlation with V_T, since patients are ventilated in control mode.
- Maximum recorded (PIP) and plateau pressures, are strongly related to applied PEEP and flow/pressure limits. The relationships are self explained since an elevated initial pressure at the lungs (PEEP) results to higher maximum pressure for a given volume, and flow rate regulates the amount of air delivered (for a specific time); thus maximum airway pressures.
- Static lung compliance (C), as measured by the medical equipment is calculated based on PEEP and Plateau values. Therefore correlation between pressure and flow settings is directly related to C calculation.
- Similarly static airway resistance is calculated based on PIP, Plateau and flow measurements. This relationship could be observed in COPD & ALI-ARDS categories.
- The difference in existence and degree of correlation between categories is attributed to the different strategies in ventilation.

Table 5.12: correlation coefficients and P values for all categories.

	vt ml/kgr		RR (BPM)		PEEP(mbar)		FiO2		Max Insp P (mbar)		Max Flow (L/min)		
	r	P	r	P	r	P	r	P	r	P	r	P	
SpO2	0.23	0.01	-0.10	0.26	-0.15	0.10	-0.14	0.13	0.18	0.04	-0.28	0.00	Normal Patients Correlation
PaO2	**0.92**	0.00	**-0.61**	0.00	-0.38	0.00	**-0.70**	0.00	**0.82**	0.00	**-0.72**	0.00	
PaCO2	**-0.93**	0.00	**0.85**	0.00	0.33	0.00	**0.89**	0.00	**-0.93**	0.00	0.30	0.00	
pH	**0.91**	0.00	**-0.79**	0.00	-0.33	0.00	**-0.84**	0.00	**0.89**	0.00	-0.37	0.00	
O2 Index	**1.00**	0.00	**-0.89**	0.00	-0.38	0.00	**-0.94**	0.00	**0.99**	0.00	-0.35	0.00	
Ve (ml)	**-0.59**	0.00	**0.82**	0.00	0.12	0.17	**0.78**	0.00	**-0.70**	0.00	-0.34	0.00	
PIP (mbar)	-0.32	0.00	0.03	0.74	-0.09	0.33	0.10	0.26	-0.21	0.02	**0.59**	0.00	
Plateau	0.02	0.82	-0.09	0.29	0.01	0.92	-0.08	0.38	0.05	0.56	0.14	0.13	
C (l/bar)	-0.43	0.00	**0.51**	0.00	0.20	0.03	**0.50**	0.00	-0.47	0.00	-0.08	0.38	
R (mbar/L/s)	-0.17	0.06	0.19	0.04	0.01	0.92	0.19	0.04	-0.18	0.04	-0.01	0.95	
HR	**0.52**	0.00	**-0.76**	0.00	0.03	0.72	**-0.72**	0.00	**0.64**	0.00	0.37	0.00	
HCO3	0.49	0.00	-0.46	0.00	-0.19	0.04	-0.48	0.00	0.49	0.00	-0.12	0.19	
SpO2	-0.41	0.00	**0.65**	0.00	**-0.51**	0.00	**0.55**	0.00	0.02	0.73	**0.57**	0.00	COPD Patients Correlation
PaO2	0.24	0.00	0.14	0.00	0.41	0.00	-0.11	0.01	**-0.68**	0.00	-0.10	0.02	
PaCO2	-0.06	0.14	-0.47	0.00	-0.23	0.00	-0.16	0.00	**0.86**	0.00	-0.17	0.00	
pH	-0.03	0.50	-0.01	0.85	-0.11	0.01	-0.05	0.24	0.32	0.00	-0.05	0.28	
O2 Index	**0.86**	0.00	-0.43	0.00	**0.84**	0.00	**-0.86**	0.00	-0.17	0.00	**-0.83**	0.00	
Ve (ml)	0.04	0.33	0.18	0.00	0.06	0.16	0.03	0.51	-0.33	0.00	0.06	0.21	
PIP (mbar)	**-0.57**	0.00	0.25	0.00	**-0.75**	0.00	**0.55**	0.00	**0.58**	0.00	**0.55**	0.00	
Plateau	**-0.57**	0.00	0.26	0.00	**-0.73**	0.00	**0.57**	0.00	0.42	0.00	**0.58**	0.00	
C (l/bar)	0.00	0.98	0.18	0.00	0.23	0.00	0.08	0.06	**-0.72**	0.00	0.09	0.05	
R (mbar/L/s)	-0.48	0.00	0.26	0.00	**-0.69**	0.00	**0.51**	0.00	0.45	0.00	**0.52**	0.00	
HR	-0.13	0.00	**0.52**	0.00	-0.17	0.00	0.33	0.00	-0.35	0.00	0.34	0.00	
HCO3	-0.06	0.19	-0.43	0.00	-0.21	0.00	-0.18	0.00	**0.84**	0.00	-0.19	0.00	
SpO2	**-0.51**	0.00	-0.34	0.00	-0.32	0.00	**-0.59**	0.00	**-0.49**	0.00	**0.32**	0.00	ALI-ARDS Patients Correlation
PaO2	-0.24	0.00	**0.70**	0.00	**-0.80**	0.00	**-0.57**	0.00	**0.75**	0.00	**-0.82**	0.00	
PaCO2	0.25	0.00	**0.91**	0.00	-0.33	0.00	-0.01	0.84	**0.93**	0.00	**-0.88**	0.00	
pH	0.15	0.03	**-0.70**	0.00	**0.67**	0.00	**0.52**	0.00	**-0.60**	0.00	**0.64**	0.00	
O2 Index	**-0.73**	0.00	0.02	0.73	**-0.92**	0.00	**-0.99**	0.00	0.03	0.73	-0.20	0.01	
Ve (ml)	**0.80**	0.00	-0.01	0.88	**0.90**	0.00	**0.96**	0.00	-0.08	0.27	0.29	0.00	
PIP (mbar)	**0.54**	0.00	-0.43	0.00	**0.92**	0.00	**0.78**	0.00	**-0.63**	0.00	**0.77**	0.00	
Plateau	0.40	0.00	-0.39	0.00	**0.88**	0.00	**0.73**	0.00	**-0.64**	0.00	**0.75**	0.00	
C (l/bar)	-0.16	0.03	0.44	0.00	-0.45	0.00	-0.25	0.00	**0.66**	0.00	**-0.68**	0.00	
R (mbar/L/s)	**0.64**	0.00	-0.22	0.00	**0.90**	0.00	**0.86**	0.00	-0.39	0.00	**0.56**	0.00	
HR	-0.28	0.00	**-0.50**	0.00	-0.25	0.00	-0.37	0.00	-0.37	0.00	0.34	0.00	
HCO3	**0.51**	0.00	**0.81**	0.00	0.05	0.49	0.39	0.00	**0.87**	0.00	**-0.77**	0.00	

Table 5.13: correlation coefficients and P values for all categories, for applied changes data set.

	vt ml/kgr		RR (BPM)		PEEP(mbar)		FiO2		Max Insp P (mbar)		Max Flow (L/min)		
	r	P	r	P	r	P	r	P	r	P	r	P	
SpO2	--		--		--		--		--		--		Normal Patients Correlation
PaO2	--		--		--		--		--		--		
PaCO2	--		--		--		--		--		--		
pH	--		--		--		--		--		--		
O2 Index	--		--		--		--		--		--		
Ve (ml)	--		--		--		--		--		--		
PIP (mbar)	--		--		--		--		--		--		
Plateau	--		--		--		--		--		--		
C (l/bar)	--		--		--		--		--		--		
R (mbar/L/s)	--		--		--		--		--		--		
HR	--		--		--		--		--		--		
HCO3	--		--		--		--		--		--		
SpO2	**-0.69**	0.00	**0.64**	0.01	**-0.59**	0.02	**0.73**	0.00	-0.13	0.64	**0.59**	0.02	COPD Patients Correlation
PaO2	0.21	0.44	0.23	0.39	0.47	0.07	-0.04	0.89	**-0.83**	0.00	-0.32	0.23	
PaCO2	-0.06	0.83	-0.40	0.12	-0.33	0.21	-0.17	0.52	**0.93**	0.00	0.16	0.56	
pH	0.02	0.93	-0.42	0.11	-0.24	0.38	-0.13	0.62	**0.68**	0.00	0.11	0.67	
O2 Index	**0.87**	0.00	**-0.50**	0.05	**0.84**	0.00	**-0.87**	0.00	-0.22	0.41	**-0.75**	0.00	
Ve (ml)	-0.03	0.90	0.19	0.48	0.07	0.81	0.10	0.70	-0.34	0.20	0.05	0.85	
PIP (mbar)	**-0.61**	0.01	0.28	0.30	**-0.86**	0.00	**0.56**	0.02	**0.59**	0.02	**0.82**	0.00	
Plateau	**-0.61**	0.01	0.23	0.40	**-0.85**	0.00	**0.57**	0.02	**0.63**	0.01	**0.75**	0.00	
C (l/bar)	0.02	0.93	0.38	0.15	0.39	0.13	0.13	0.63	**-0.97**	0.00	-0.21	0.43	
R (mbar/L/s)	**-0.51**	0.04	0.28	0.29	**-0.74**	0.00	**0.53**	0.04	**0.49**	0.05	**0.63**	0.01	
HR	-0.09	0.73	**0.58**	0.02	-0.07	0.80	0.36	0.17	-0.44	0.09	0.12	0.65	
HCO3	-0.04	0.87	-0.44	0.09	-0.33	0.21	-0.18	0.50	**0.93**	0.00	0.16	0.55	
SpO2	**-0.79**	0.02	-0.20	0.64	**-0.54**	0.17	**-0.77**	0.03	-0.41	0.31	0.18	0.68	ALI-ARDS Patients Correlation
PaO2	-0.28	0.50	**0.68**	0.06	**-0.52**	0.18	-0.27	0.51	**0.61**	0.11	**-0.57**	0.14	
PaCO2	-0.14	0.75	**0.92**	0.00	-0.42	0.30	-0.09	0.83	**0.88**	0.00	**-0.84**	0.01	
pH	**0.70**	0.05	**-0.60**	0.12	**0.83**	0.01	**0.69**	0.06	-0.37	0.37	0.43	0.29	
O2 Index	**-0.94**	0.00	0.04	0.92	**-0.90**	0.00	**-0.97**	0.00	-0.18	0.67	0.06	0.89	
Ve (ml)	**0.92**	0.00	-0.15	0.72	**0.77**	0.02	**0.88**	0.00	0.06	0.88	0.18	0.68	
PIP (mbar)	**0.69**	0.06	**-0.63**	0.09	**0.81**	0.02	**0.62**	0.10	**-0.67**	0.07	**0.81**	0.02	
Plateau	**0.74**	0.04	-0.34	0.40	**0.89**	0.00	**0.72**	0.05	**-0.50**	0.20	**0.58**	0.13	
C (l/bar)	-0.49	0.21	0.22	0.60	**-0.52**	0.19	**-0.50**	0.20	0.04	0.93	-0.09	0.83	
R (mbar/L/s)	0.45	0.26	-0.29	0.49	0.48	0.23	0.38	0.35	-0.48	0.23	**0.62**	0.10	
HR	-0.32	0.44	**-0.56**	0.15	-0.33	0.42	-0.41	0.31	-0.43	0.29	0.49	0.21	
HCO3	0.48	0.23	**0.71**	0.05	0.20	0.64	**0.53**	0.18	**0.85**	0.01	**-0.74**	0.04	

5.4.1 Evaluation of Correlation Results

Correlation results were presented to three experienced ICU doctors from PAGNI, NIMITS and Konstadinoupolio general hospital of Athens. Two of the doctors participated in the questionnaire development. The doctors were asked to evaluate the presented correlation coefficients. Presented coefficients were the average values of both databases results that exceeded the C threshold; namely the five minute trends and the applied changes databases. Evaluation was performed in terms of Accepting (**A**), Rejecting (**R**) or Accepting under given conditions (**Auc**) the existence and the direction of the relationship between input – physiological measured variables and the ventilator settings. Accepted under given conditions was introduced to the evaluation process following an informal conversation with intensivists, based on the grounds that for a given ventilation strategy and patient

pathology the relationship could be accepted. Evaluation was not concerned with the value of the relationship strength. Each variable was evaluated in isolation with the remaining correlated variables and ventilator settings. Evaluators' answers were used for identifying the input variables for each intelligent model. The choice was based on a majority voting of evaluators' answers. When the majority of evaluators accepted or accepted under given conditions the relationship between a measured variable and a ventilator setting, then this variable was incorporated into our model as input. Table 5.14 presents the evaluation results.

Evaluators' voting process rejected in normal category 8 out of 28 relationships (28%) between ventilator settings and monitored variables. Five of the relationships could be easily justified as rejected since there is no apparent cause and effect relationship between them; namely RR with Ve & C and FiO_2 with Ve, C & HR. However the relationship between FiO_2 and arterial CO_2 & pH was rejected mainly on the grounds of the direction of the relationship.

In the COPD category, voting rejected 9 out of 31 (29%) of correlation coefficients. Rejection included relationships such as FiO_2 with R, PIP, $P_{plateau}$. Rejection of the above correlation coefficients was anticipated, since there is no apparent relation between percentage of oxygen and lung mechanics. However the relationship between maximum pressure and oxygenation variables (PaO_2, pH, HCO_3), as well as lung mechanics indicators (C, R, $P_{plateau}$) was rejected although there are supporting evidence suggesting that changes in mean airway pressure (related to maximum allowed pressure) improve oxygenation and the fact that lung mechanics are important for regulating the maximum pressure allowed.

ARDS evaluation rejected 6 out of 20 (30%) coefficients. Rejection in ARDS was higher than the other categories. HCO_3 correlation was rejected for all ventilation settings (RR, Pmax, Fmax) although coefficients were high. Relationship of FiO_2 with Ve and $P_{plateau}$ was rejected since there is no mechanism explaining their relation. All evaluators rejected the relationship between pH and PEEP although there is an explanatory mechanism. PEEP is applied for improving oxygenation by changing FRC volume which supports the gas exchange between alveolar and venous gases. This should improve venous CO_2 levels; thus changing blood pH.

Table 5.14: Evaluators' scoring on correlation results.

	vt ml/kgr		RR (BPM)		PEEP(mbar)		FiO2		Max Insp P (mbar)		Max Flow (L/min)		
	r	Evl	r	Evl	r	Evl	r	Evl	r	Evl	r	Evl	
SpO2													Normal Patients
PaO2	0.92	3/3	-0.61	3/3			-0.70	3/3	0.82	3/3	-0.72	3/3	
PaCO2	-0.93	3/3	0.85	3/3			0.89	1/3	-0.93	3/3			
pH	0.91	2/3	-0.79	2/3			-0.84	1/3	0.89	3/3			
O2 Index	1.00	3/3	-0.89	3/3			-0.94	3/3	0.99	3/3			
Ve (ml)	-0.59	1/3	0.82	0/3			0.78	0/3	-0.70	2/3			
PIP (mbar)											0.59	2/3	
Plateau													
C (l/bar)			0.51	1/3			0.50	0/3					
R (mbar/L/s)													
HR	0.52	3/3	-0.76	3/3			-0.72	1/3	0.64	3/3			
HCO3													
SpO2	-0.55	3/3	0.64	3/3	-0.55	3/3	-0.64	3/3			-0.58	3/3	COPD Patients
PaO2									-0.75	1/3			
PaCO2									0.90	2/3			
pH									0.50	0/3			
O2 Index	0.87	2/3	-0.47	3/3	0.84	2/3	-0.87	3/3			-0.79	3/3	
Ve (ml)													
PIP (mbar)	-0.59	3/3			-0.81	2/3	0.56	1/3	0.59	2/3	0.68	3/3	
Plateau	-0.59	3/3			-0.79	2/3	0.57	1/3	0.52	1/3	0.66	2/3	
C (l/bar)									-0.84	1/3			
R (mbar/L/s)	-0.50	3/3			-0.71	2/3	0.52	1/3	0.47	1/3	0.58	3/3	
HR			0.55	2/3									
HCO3									0.89	0/3			
SpO2	-0.65	3/3					-0.68	3/3					ALI-ARDS Patients
PaO2													
PaCO2			0.91	3/3					0.90	2/3	-0.86	2/3	
pH					0.75	0/3							
O2 Index	-0.84	3/3			-0.91	3/3	-0.98	3/3					
Ve (ml)	0.86	3/3			0.84	3/3	0.92	1/3					
PIP (mbar)					0.86	3/3					0.79	3/3	
Plateau	0.57	3/3			0.89	3/3	0.72	1/3					
C (l/bar)													
R (mbar/L/s)													
HR													
HCO3			0.76	0/3					0.86	0/3	-0.75	0/3	

Evaluators rejected relationships not on the grounds of strength but on the grounds of medically accepted (based on experience and expertise) physiology mechanisms. Ve – RR rejection for normal category (r=0.82) and SpO_2 – V_T acceptance for COPD (r=-0.55) are typical examples.

The presentation of the correlation coefficients to the evaluators could be considered as a possible cause of bias. However the use of more than one evaluator and the majority voting process is expected to minimize the bias effect. Furthermore the purpose of this evaluation was to evaluate correlation findings; thus this would not be possible without informing the evaluators of the coefficients.

5.5 Models' Basic Architecture

The minimization of the search space accomplished with the correlation statistics and the evaluation of the relationships, provided as with the basic architecture of the FRBSs.

As stated in paragraph 5.4.1, physiology measured variables that were accepted by the majority of the evaluators were chosen to participate as input variables for the FRBSs.

We decided to develop individual models for each lung pathology in order to incorporate different ventilation strategies used in different pathologies. Due to the nature of the proposed FRBSs development method we anticipated that resulting models will be optimal, in the case of GAs, or trained, in the case of NN, ANFIS & FUN, for a given ventilation strategy. A separate FRBS was designed for a given ventilator setting. In this way we have simplified the structure of the FRBS, since for each ventilator setting, a different number and type of input variables participates.

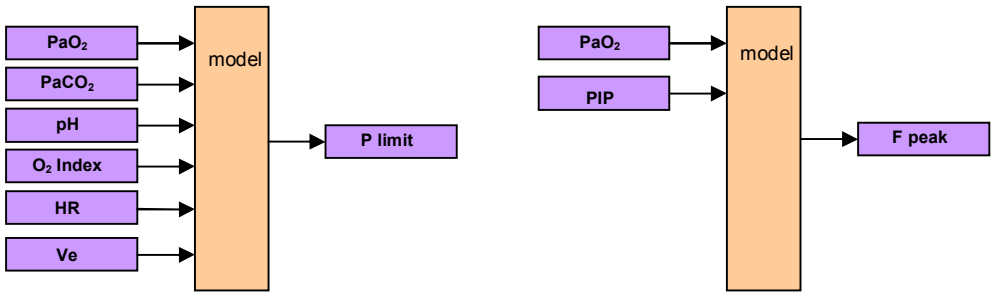

Figure 5.10: Plimit & Fpeak sample FRBSs architecture for Normal Lungs.

Based on evaluators' results and voting process we have concluded to seventeen (17) different architectures for the models. In total the number of models should have been eighteen (18). The maximum number of models is calculated by the product of the ventilator settings times the number of lung categories. However in the case of PEEP ventilator setting for the normal lung category, none of the measured physiology variables is correlated with the setting and thus there are no suggested inputs for the system. Table 5.15 presents the basic architecture of the proposed FRBSs.

Table 5.15:Models' input-output variables based on evaluators voting.

Input Variables	V_T	RR	PEEP	FiO_2	Pmax	Fmax	
SpO2							Normal Patients
PaO2	*	*		*	*	*	
PaCO2	*	*			*		
pH	*	*			*		
O2 Index	*	*		*	*		
Ve (ml)					*		
PIP (mbar)						*	
Plateau							
C (l/bar)							
R (mbar/L/s)							
HR	*	*			*		
HCO3							
SpO2	*	*	*	*		*	COPD Patients
PaO2							
PaCO2					*		
pH							
O2 Index	*	*	*	*		*	
Ve (ml)							
PIP (mbar)	*		*		*	*	
Plateau	*		*			*	
C (l/bar)							
R (mbar/L/s)	*		*			*	
HR		*					
HCO3							
SpO2	*			*			ALI-ARDS Patients
PaO2							
PaCO2		*			*	*	
pH							
O2 Index	*		*	*			
Ve (ml)	*		*				
PIP (mbar)			*			*	
Plateau	*		*				
C (l/bar)							
R (mbar/L/s)							
HR							
HCO3							

6. Evaluation of Models Performance on Patients' Database

6.1 Overview

Two custom toolboxes were developed, namely the EVOFINE and the FUN toolbox (Appendix II). The developed toolboxes were designed to model the decision making process for ventilation management. The architecture of the models was derived by the evaluated correlation coefficients, based on real physiology data, (section 5.5) and the experimental results of EVOFINE and FUN toolboxes against the mathematical function and the cart pole dynamic system (Appendix III.1 – III.2).

The models were trained with the use of the training set which accounted for sixty percent (60%) of the recorded patient data. The data set of the training set has been randomly selected from the patients' database of five minutes trends. Since the architecture of the models was different for each lung pathology category, namely Normal, COPD and ALI-ARDS, different models were developed and trained.

The resulted models were tested against the evaluation and the training set in terms of *rmse* (eq.II.1) and mean absolute error (*mae,* eq. 6.1a) as well as their percentage (eq. 6.1b & II.2) over the output variable range.

$$mae = \frac{1}{N}\sum_{i=1}^{N}\left|FRBSout(i) - dataout(i)\right| \qquad eq.\ 6.1a$$

$$\%\ mae = \frac{MAE}{abs\left[\max(data_{out}) - \min(data_{out})\right]} * 100 \qquad eq.\ 6.1b$$

Furthermore we have developed and trained Artificial Neural Network (ANN) and ANFIS models, similar to those described in Appendix III.3 & III.4, in order to test our models performance against established approaches in modelling complex systems.

Finally we have presented three ICU doctors with patient scenarios for the three lung categories and requested their clinical expertise on the appropriate ventilator settings. This test was performed so we statistically analyze the doctors' responses and compare them against our models performance. Comparison was performed in terms of the variation of doctors' suggestions against the mean absolute error of our models.

6.2 Models Architecture

The basic models' architecture was chosen based on the evaluation of the correlation coefficients, as it was presented in section 5.5. The basic architecture for each ventilator setting (output variable) is different for each lung's pathology, as pointed out during the correlation analysis of the physiology measured data against the ventilator settings.

Regardless of the development process the number and type of input variables is held constant for each lung pathology and ventilator setting. Additionally the range of the input and output variables is also maintained constant according to the analysis performed on the available data, presented in Appendix VII, table VII.1.

However the internal architecture of the models is described in the experiment setup of the EVOFINE and FUN toolboxes as well as the ANN and ANFIS methods. The choice of the final architecture of the models is based on the conclusions drawn by the trials performed against the mathematical and cart pole systems, as described in Appendix III.1 to III.5. Furthermore the final architecture is a compromise between conclusions drawn on trials, number of available training sets, and available computational resources.

Taking into consideration the experimental conclusions, described in section III.5.1, it was decided to evolve our EVOFINE models for 100 generations, utilizing damping mutation rates. The number of generations was decided based on the restriction applied due to computation time. It was decided to used Triangular and Trapezoid MFs for describing the variables' domains, and five MFs for each variable.

Due to practical considerations the RB of each model was limited so as the maximum number of rules did not exceed four hundred. The percentage of the rules used in comparison to the total number of rules that described each system was variable. The variation is caused by the different architectures of the models, namely the different number of input variables participating in each model. According to eq. II.7b, the *Full RB* that completely describes the FRBS depends on the number of FSs and the number of variables. Since the number of FSs was held constant and the number of outputs was limited to one for each model, the number of inputs was the decisive variable for the Total number of rules.

Performing the calculations for the model of the P_{max} of the Normal lung's category, based on the equations II.4b, II.7b and II.5 and table II.5 (Appendix II) we have:

Using eq. 3.4b $L_{FS\_Gaussian} = (Ni + No) * (N_{FS} * 2) = (6+1) * (5*2) = 70$

Using eq. 6.7b $N_{FullRB} = N_{FS}{}^{(N_i)} = 5^6 = 15625$

Using eq 6.5 $L_R = (Ni + No + 1) * N_R = (6+1+1) * 78125 = 625000$

Thus to completely describe the RB of the P_{max} of the Normal lung's category, we need 15625 rules and a chromosome length that completely describes the system, equal to the sum of the Fuzzy Sets ($L_{FS\_Gaussian}$) and Fuzzy Rules (L_R) chromosome (625070 elements). If we multiply this by the number of individuals in a given population (e.g. 100 individuals), then we require a large memory allocation for storing the structure of the chromosomes. Since the size of the chromosomes was exceeding our computational resources we have decided to incorporate sub-architectures of the *Full RB*.

Table 6.1: Architecture –setup of EVOFINE models.

	Model	No of Fuzzy Rules	Full RB (No FS^input para)	No of Input variables	% of Full RB	No FSs
ALI-ARDS	Vt	156	625	4	25	5
	RR	5	5	1	100	5
	FiO2	25	25	2	100	5
	Pmax	5	5	1	100	5
	Fmax	25	25	2	100	5
	PEEP	156	625	4	25	5
COPD	Vt	156	3125	5	5	5
	RR	125	125	3	100	5
	FiO2	25	25	2	100	5
	Pmax	25	25	2	100	5
	Fmax	156	3125	5	5	5
	PEEP	156	3125	5	5	5
Normal	Vt	156	3125	5	5	5
	RR	156	3125	5	5	5
	FiO2	25	25	2	100	5
	Pmax	391	15625	6	2,5	5
	Fmax	25	25	2	100	5
	PEEP	---	---	---	---	---

In table 6.1 we present the internal architecture of the EVOFINE evolved FRBSs. Percentage of the *Full RB* ranges from 2.5 to 100% depending on the number of input variables participating in each model. The rest of the characteristics are

constant throughout the models. Column one presents the number of rules used for each model, column three describes the number of input variables used for each model according to table 5.5, and columns two and four present the number of the *Full RB* that describes the system and the number of rules used as a percentage of the *Full RB* respectively. All models use the same GAs setup; 100 individuals, 100 generations, 0.7 damping mutation rate, 0.7 crossover rate, RWS.

As already stated (paragraph 5.5), the PEEP models for the Normal lungs category has not been developed, due to the fact that none of the input variables exhibited correlation with PEEP variable.

Similar to EVOFINE the basic architecture of the FUN models was the same, concerning the number and type of input variables for each ventilator setting, according to table 5.5. The setup of FUN for each model is presented in table 8.3. The FUN models architecture is closely related to the architecture of experiment 8, presented in section III.2, table III.7. The fuzzy setup common to all FUN models is the type of MFs and the number of FS for each input – output variable. The Triangular – Trapezoid MFs have exhibited better results compared to Gaussian MFs, for similar NN architectures as presented in the trials of table III.7. Based on the conclusions drawn from section III.5.1, we have maintained the number of FSs to a value of five (5), so as to avoid resembling an ANN by assigning to each arithmetic value a "dedicated" MF.

The ANN of FUN models is a feed-forward back propagation network (*newff*), with one hidden layer. Based on the NN architecture of experiment 8 in table III.7, we are using *tansig* and *logsig* transfer functions. The number of nodes in the input layer is variable, calculated by the number of input variables times the number of FSs assigned for each variable domain. Similarly the number of nodes for the output layer is equal to the number of FSs assigned to the output variable; this number is constant and equal to five (5) due to the constant number of FSs for all FUN models. The number of nodes in the hidden layer is variable and depends on the number of nodes of the input layers and consequently to the number of input variables and assigned FSs. The number of nodes must equal or exceed the nodes calculated by Kolmogorov's theorem and at the same time should remain less than the number of training sets for an epoch. According to table 5.11, the available training sets (60%) for each lung category is 314, 113 and 76 for the COPD, ALI-ARDS and Normal lungs category respectively. The number of nodes for the hidden layer (N_{H1}) is given by the following equation:

$$N_{H1} = N_{IN} * n \qquad \text{eq. 6.2a}$$

Where N_{H1} is the number of hidden layer 1 nodes, N_{IN} is the number of input layer nodes and n is a multiplier.

Based on *Kolmogorov's* theorem and the empirical assumption that the increased number of hidden nodes improves NN performance (to a limit, too many nodes leads to overtraining and lack of generalization) we have:

$$N_{H1} = N_{IN} * n \geq \left(N_{IN} * 2 + 1\right) \qquad \text{eq. 6.2b}$$

$$N_{IN} * n \geq \left(N_{IN} * 2 + 1\right) \Rightarrow n \geq \left(N_{IN} * 2 + 1\right) / N_{IN} \qquad \text{eq. 6.2c}$$

However due to the limitation of the available training set, we have:

$$N_{H1} = N_{IN} * n \leq N_{DS} \Rightarrow n \leq N_{DS} / N_{IN} \qquad \text{eq. 6.2d}$$

Where N_{DS} is the number of available data sets for each category.

Utilizing eq. 6.2d and 6.2c we have:

$$\left(N_{IN} * 2 + 1\right) / N_{IN} \leq n \leq N_{DS} / N_{IN} \qquad \text{eq. 6.2e}$$

$$n = N_{DS} / \left(N_{IN} * 2 + 1\right) \qquad \text{eq. 6.2f}$$

A multiplier (n) given by equation 6.2f, satisfies eq. 6.2e as long as the training set is approximately four times higher than the number of inputs to the NN. If this is not applicable then n is given by equation 6.2c, as exhibited in table 6.2 for the tidal volume and respiration rate model.

Applying the above equations (6.2c and 6.2d) to the number of N_{IN} for each model we get the architecture of table 6.2 in terms of hidden nodes. Based on table 6.2 calculations and table 5.5 basic architecture table 8.3 describes the FUN models architecture. All models share an equivalent NN architecture; namely traindx training function, tansig-logsig transfer function, newff NN type and 1000 training epochs.

Table 6.2: Calculation of FUN Hidden Layers nodes.

		NIN	NDS	NDS/NIN	(NIN*2+1)/NIN	(NIN*2+1)	n=NDS/(2*NIN+1)	NH1=round [round(n)*NIN]
COPD	**Vt**	25	314	12,56	2,040	51	6,157	154
	RR	15	314	20,93	2,067	31	10,129	152
	FiO2	10	314	31,40	2,100	21	14,952	150
	Pmax	10	314	31,40	2,100	21	14,952	150
	Fmax	25	314	12,56	2,040	51	6,157	154
	PEEP	25	314	12,56	2,040	51	6,157	154
ALI-ARDS	**Vt**	20	113	5,65	2,050	41	2,756	55
	RR	5	113	22,60	2,200	11	10,273	51
	FiO2	10	113	11,30	2,100	21	5,381	54
	Pmax	5	113	22,60	2,200	11	10,273	51
	Fmax	10	113	11,30	2,100	21	5,381	54
	PEEP	20	113	5,65	2,050	41	2,756	55
Normal	**Vt**	25	76	3,04	2,040	51	1,490	51
	RR	25	76	3,04	2,040	51	1,490	51
	FiO2	10	76	7,60	2,100	21	3,619	36
	Pmax	30	76	2,53	2,033	61	1,246	61
	Fmax	10	76	7,60	2,100	21	3,619	36
	PEEP	.....	.....	.....	.....	.....	.....	....

Table 6.3: Architecture –setup of FUN models based on calculations from table 6.2

	Model	**No FSs**	**No Inputs**	**Number of Nodes**		
				Input Layer	**Hidden Layer 1**	**Output Layer**
ALI-ARDS	Vt	5	4	20	55	5
	RR	5	1	5	51	5
	FiO2	5	2	10	54	5
	Pmax	5	1	5	51	5
	Fmax	5	2	10	54	5
	PEEP	5	4	20	55	5
COPD	Vt	5	5	25	154	5
	RR	5	3	15	152	5
	FiO2	5	2	10	150	5
	Pmax	5	2	10	150	5
	Fmax	5	5	25	154	5
	PEEP	5	5	25	154	5
Normal	Vt	5	5	25	51	5
	RR	5	5	25	51	5
	FiO2	5	2	10	36	5
	Pmax	5	6	30	61	5
	Fmax	5	2	10	36	5

Similar to the EVOFINE and FUN architectures the ANN basic architectures is given by the table 5.5. We have decided to test three different ANN models for the problem of modelling the ventilation management process. The first model which will be named for now on as *ANN Kolmogorov*, use equations 6.2a to 6.2f to calculate the number of the nodes in the hidden layer. The number of nodes is presented in table 6.4. The second model uses similar architecture as the *ANN Kolmogorov,* but it was trained with scaled input and output variables to the range of zero (0) to one (1). This model will be termed for this thesis as *ANN Normalized*. The third model was designed with an empirical architecture and will be termed as *ANN empirical*.

Table 6.4: Calculation of hidden layer node number for the ANN.

		N_{IN}	N_{DS}	N_{DS}/N_{IN}	$(N_{IN}*2+1)/N_{IN}$	$(N_{IN}*2+1)$	$n=N_{DS}/(2*N_{IN}+1)$	$N_{H1}=round$ $[round(n)*N_{IN}]$
COPD	**Vt**	5	314	62,80	2,200	11	28,545	143
	RR	3	314	104,67	2,333	7	44,857	135
	FiO2	2	314	157,00	2,500	5	62,800	126
	Pmax	2	314	157,00	2,500	5	62,800	126
	Fmax	5	314	62,80	2,200	11	28,545	143
	PEEP	5	314	62,80	2,200	11	28,545	143
ALI-ARDS	**Vt**	4	113	28,25	2,250	9	12,556	50
	RR	1	113	113,00	3,000	3	37,667	38
	FiO2	2	113	56,50	2,500	5	22,600	45
	Pmax	1	113	113,00	3,000	3	37,667	38
	Fmax	2	113	56,50	2,500	5	22,600	45
	PEEP	4	113	28,25	2,250	9	12,556	50
Normal	**Vt**	5	76	15,20	2,200	11	6,909	35
	RR	5	76	15,20	2,200	11	6,909	35
	FiO2	2	76	38,00	2,500	5	15,200	30
	Pmax	6	76	12,67	2,167	13	5,846	35
	Fmax	2	76	38,00	2,500	5	15,200	30
	PEEP	.....	.....	.....	.....	.....	.....	....

The *ANN Kolmogorov* is a feed-forward back propagation network (*newff*), with one hidden layer, based on the NN architecture of experiment 6 in table III.9. The

number of nodes in the input layer is variable, equal to the number of input variables. Similarly the number of nodes for the output layer is equal to the number of the output variables; this number is constant and equal to one (1). The number of nodes in the hidden layer is variable and depends on the number of nodes of the input layers and the available training sets as shown in table 6.4. The NN was trained for 1000 epochs.

The architecture of the *ANN Kolmogorov* for each category is presented in table 6.5.

Table 6.5: Architecture of ANN Kolmogorov & Normalized models for all categories.

	Model	No Inputs	Number of Nodes		
			Input Layer	Hidden Layer 1	Output Layer
COPD	Vt	5	5	143	1
	RR	3	3	135	1
	FiO2	2	2	126	1
	Pmax	2	2	126	1
	Fmax	5	5	143	1
	PEEP	5	5	143	1
ALI-ARDS	Vt	4	4	50	1
	RR	1	1	38	1
	FiO2	2	2	45	1
	Pmax	1	1	38	1
	Fmax	2	2	45	1
	PEEP	4	4	50	1
Normal	Vt	5	5	35	1
	RR	5	5	35	1
	FiO2	2	2	30	1
	Pmax	6	6	35	1
	Fmax	2	2	30	1
	PEEP	---	---	---	---

The architecture of the *ANN Normalized* was similar to the *ANN Kolmogorov* in terms of layers and number of nodes. The difference between the two models was that the *ANN Normalized* was trained with the normalized training set, which was the available training set scaled in the range from 0 to 1. The *ANN Normalized* uses *tansig* and *purelin* transfer functions. The choice of the transfer functions was based on trials that suggest that tansig and logsig functions at the output nodes do not perform adequately since available data are scaled in the 0 to 1 range.

The *ANN empirical* was designed based on the architecture of experiment 6 in table III.10, which exhibited the best performance in modelling the cart pole system. It has two hidden layers. The number of nodes in each layer is given by the following equations:

$$N_{H1} = round(\mathrm{N}_{DS}/2) \qquad \text{eq. 6.3a}$$

$$N_{H2} = round(N_{H1}/2) \qquad \text{eq. 6.3b}$$

The *ANN empirical* utilized the normalized training set for each category for training purposes. The NN was trained for 1000 epochs. The resulted architecture is described in table 6.6.

Table 6.6: Architecture of ANN empirical models for all categories.

	Model	No Inputs	Number of Nodes			
			Input Layer	Hidden Layer 1	Hidden Layer 2	Output Layer
COPD	Vt	5	5	157	78	1
	RR	3	3	157	78	1
	FiO2	2	2	157	78	1
	Pmax	2	2	157	78	1
	Fmax	5	5	157	78	1
	PEEP	5	5	157	78	1
ALI-ARDS	Vt	4	4	61	30	1
	RR	1	1	61	30	1
	FiO2	2	2	61	30	1
	Pmax	1	1	61	30	1
	Fmax	2	2	61	30	1
	PEEP	4	4	61	30	1
Normal	Vt	5	5	38	19	1
	RR	5	5	38	19	1
	FiO2	2	2	38	19	1
	Pmax	6	6	38	19	1
	Fmax	2	2	38	19	1
	PEEP	---	---	---	---	---

Similar to the EVOFINE, FUN and ANN architectures the ANFIS basic architecture is given by the table 5.5. Since the number of available training sets was relatively small and the ANFIS NN node number depends upon the number of model's inputs and FSs, we have kept the number of FSs small for all models, equal to 2 (table 6.8).

Table 6.7 : Comparison table for ANFIS architecture for the COPD models.

	Model	Fuzzy Setup				Evaluation Results	
		No of Fuzzy Rules	No of Input variables	No FSs	Input Type FSs	rmse	Comp. time (h:min:sec)
COPD	Vt	243	5	3	trimf	0,00095	0:05:08
	RR	27	3	3	trimf	0,03271	0:00:02
	FiO2	9	2	3	trimf	0,00124	0:00:01
	Pmax	9	2	3	trimf	0,03479	0:00:01
	Fmax	243	5	3	trimf	0,00000	0:05:08
	PEEP	243	5	3	trimf	0,00001	0:05:11
COPD	Vt	32	5	2	gausmf	0,00251	0:00:04
	RR	8	3	2	gausmf	0,03696	0:00:01
	FiO2	4	2	2	gausmf	0,00131	0:00:01
	Pmax	4	2	2	gausmf	0,04929	0:00:01
	Fmax	32	5	2	gausmf	0,00045	0:00:04
	PEEP	32	5	2	gausmf	0,00025	0:00:04

Table 6.8: Architecture of ANFIS models.

	Model	No of Fuzzy Rules	No of Input variables	No FSs
COPD	Vt	32	5	2
	RR	8	3	2
	FiO2	4	2	2
	Pmax	4	2	2
	Fmax	32	5	2
	PEEP	32	5	2
ALI-ARDS	Vt	16	4	2
	RR	2	1	2
	FiO2	4	2	2
	Pmax	2	1	2
	Fmax	4	2	2
	PEEP	16	4	2
Normal	Vt	32	5	2
	RR	32	5	2
	FiO2	4	2	2
	Pmax	64	6	2
	Fmax	4	2	2
	PEEP	---	---	---

Only two FSs were describing the variable's domain, and we decided to use Gaussian MFs (gausmf). The choice of Gaussian MFs was based on trials performed on available training data both on Triangular and Gaussian MFs. In table 6.7, we present trials for the COPD category, for both the Gaussian and the Triangular MFs type. The increased number of MFs for the Triangular type results in a larger number of rules for the fuzzy system. Furthermore the computation time increases with the ANFIS complexity. Even though as results suggest (table 6.7), the increased number of MFs leads to an improved performance, based on the experience from the ANFIS toolbox the number of adjusted variables exceeds the available training set. As it was discussed in ANN models architecture, the large number of NN nodes will lead to loss of model's generalizability. The ANFIS systems were trained for 5 epochs.

6.3 Training Process

The following sections present the training process of the developed models for the Ventilation management process.

6.3.1 Evolution of FRBS, for modelling the Ventilation Management Process.

Based on the architectures of table 6.1, an original population of 100 individual FRBS for each model was randomly developed. As it is described in Appendix II, the coding was performed with the use of two chromosomes. To each chromosome for each generation we have applied evolutionary mechanisms. The performance of the FRBS was tested against the available training data set. During the evolutionary process the best chromosomes of each generation were stored in spreadsheet format in user specified directory.

Figure 6.1 presents sample plots of the performance of the FRBS during the evolutionary process. Performance is measured in terms of *rmse %* as in eq. II.2 (Appendix II). The use of the percentage allows direct comparison between systems that utilize different units of measurement. The arithmetic value of the error of the best individual in the last generation is displayed at the top of each figure. The figures display the best (min error), the worst (max error) and the mean performance of all individuals in a given generation. Convergence of the mean plot to the minimum error suggests that most of the FRBSs have evolved architectures very similar among them or very similar in terms of performance.

Large deviations from the mean value, usually towards the opposite than the desired direction, are mainly attributed to the mutation process. However it is possible that crossover operation might result to an offspring with worst performance.

In most of the evolution process presented in figure 6.1, the convergence occurs at generations above twenty (20). In plots of figures 6.1, we observe two different patterns of convergence of minimum and maximum error. The first pattern is where minimum and maximum errors converge, (FiO_2 for COPD category). The second pattern is where there is no convergence of maximum error to the minimum, (V_T for ARDS). This observation is attributed to the complexity of the FRBS. When complexity is high, thus large number of input variables and RB, the high variable mutation rates at the last generations affect overall performance. On the other hand when architectures of FRBS are simple, high mutation rates do not affect the chromosomes performance.

While the rmse % is a good measure for comparing performances it is not easily translated to a numerical value for a given variable. For this reason we provide the reader with a measure of error for each variable in order to make reading of figures more comprehensive (Table 6.9).

Table 6.9: Indication of measure for the rmse %.

Variable	Min value	Max value	Range	Value of 0.1% rmse	Value of 0.5% rmse	Value of 1% rmse
VT (ml/Kgr)	2	12	10	0,01	0,05	0,1
RR (bpm)	5	30	25	0,025	0,125	0,25
FiO2	0,25	0,8	0,55	0,00055	0,00275	0,0055
Pmax (mbar)	40	90	50	0,05	0,25	0,5
Fmax (L/min)	15	80	65	0,065	0,325	0,65
PEEP (mbar)	0	15	15	0,015	0,075	0,15

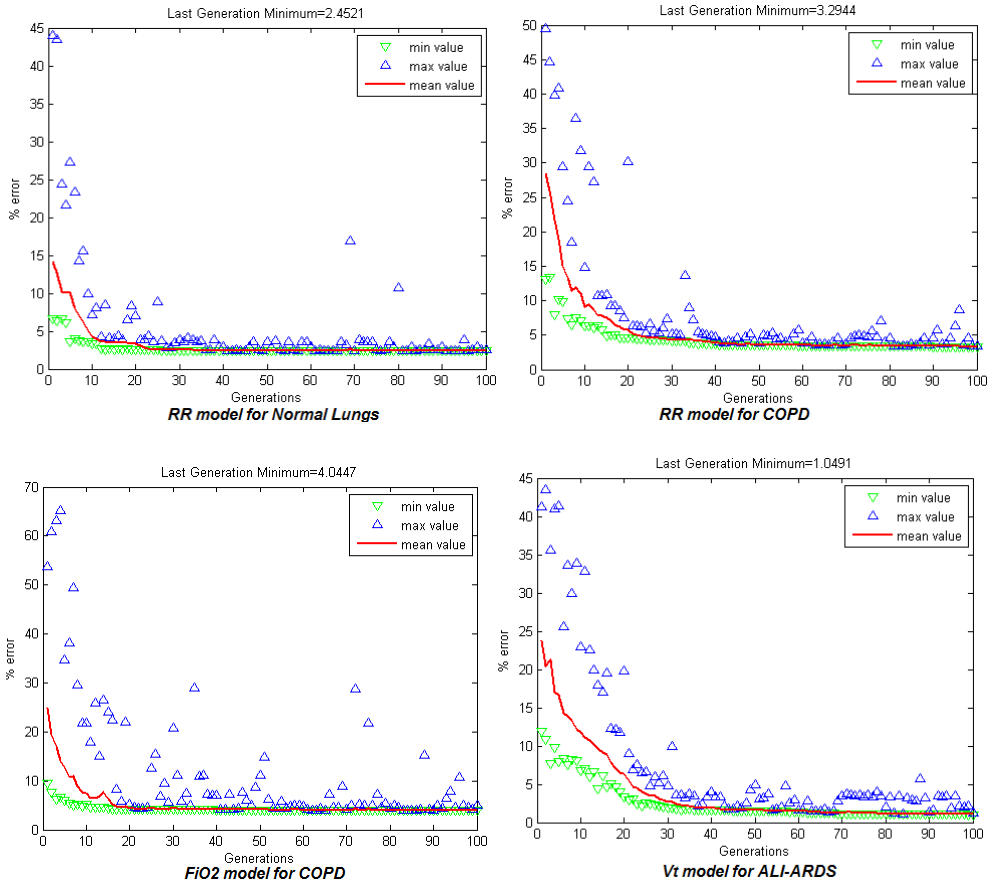

Figure 6.1: Graphical presentation of sample EVOFINE FRBSs evolution process.

6.3.2 Training Process of the FUN ANN

As presented in Appendix II FUN toolbox utilized ANN for substituting the RB of the FRBS. The main characteristic of the FUN ANN is that there is an increased number of inputs and outputs to the system, equal to the number of inputs – outputs multiplied by the number of the assigned MFs.

In order to understand the measure of the performance of the ANN developed for the FUN toolbox, one has to understand that the NN is trained to best map the membership degrees for the given number of MFs representing the input(s) and output(s) variables domain. Analytical, the training data set is automatically translated into membership degrees for each corresponding FS. If a SISO system is designed with five (5) MFs, then for each input and output value in the training set we get a corresponding five value array. Each value in the array is the membership degree to a given membership function.

The training process of the ANN uses the *mse* as a measure of the ANN performance. The measure of performance for the ANN is the error (mse) between the membership degrees for each membership function of the calculated ANN output and the membership degrees for each membership function for a given output value of the training set.

Since all input and output data are translated into membership degrees, ranging by default from zero (0) to one (1), there is no need to introduce normalized training data to the ANN.

Figure 6.2 presents sample plots of the training progress of the FUN ANN. NN were trained with the available training set for each category for 1000 epochs.

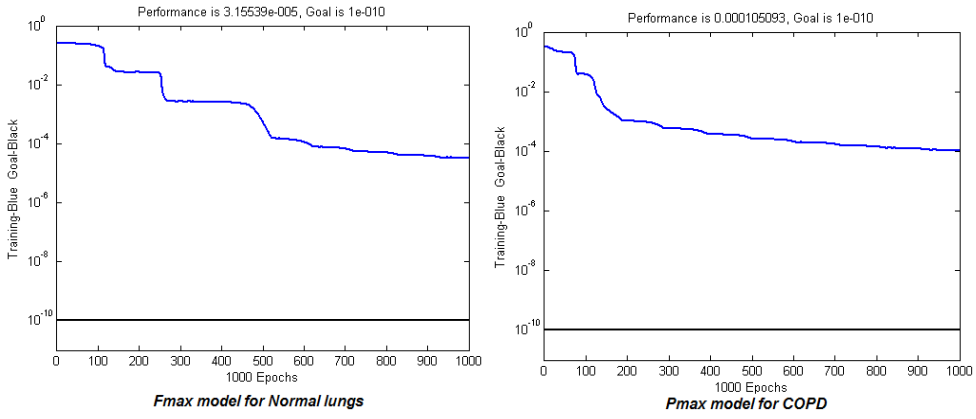

Figure 6.2: Graphical presentation of sample FUN ANN training process.

6.3.3Training Process of the ANN

Three different ANNs have been trained (tables 6.5 & 6.6). The training of the *ANN Kolmogorov* was performed with the available training data set for each category. However the *ANN Normalized* and *ANN empirical* were trained with the scaled training set. The difference in the use of the training sets is also related to the interpretation of the mse that the ANN measures performance.

In the case of the *ANN Kolmogorov*, the *mse* is in the same units of measurement as the models output if we calculate the square root of the performance value (*rmse*). Consider the performance of the ANN Kolmogorov for the Fmax in the COPD category set (table 6.12). The trained network achieved a performance of 30.47. Calculating the square root of this value we get an approximate *rmse* of 5.5 L/min. The use of the *rmse* gives us a more comprehensive approximation of the mean difference between the models output and the training set. In table 6.10 we provide the interpretation for some predefined values of *mse* in terms of *rmse* in order to make reading of figure 6.3 easier with the help of table 6.9.

Table 6.10: Presentation of rmse interpretation for given mse values.
(Valid for figure 6.5)

.

mse	10,00000	1,00000	0,50000	0,01000	0,00100	0,00010
rmse	3,162278	1	0,707107	0,1	0,031623	0,01

In figure 6.3 we observe mainly three “types” of training processes. The first type is a fast training of the ANN, which succeeds the goal performance before the maximum number of epochs available for the training. Example plots are the training of the FiO2 model for the Normal lungs category and the Pmax model for the ALI-ARDS category. In these cases the ANN could easily map the relationship between input variables and model’s output. This could be attributed to the appropriate architecture of the ANN, to the existing relationship between input and output variables and the sufficient representation of this relationship to the training set.

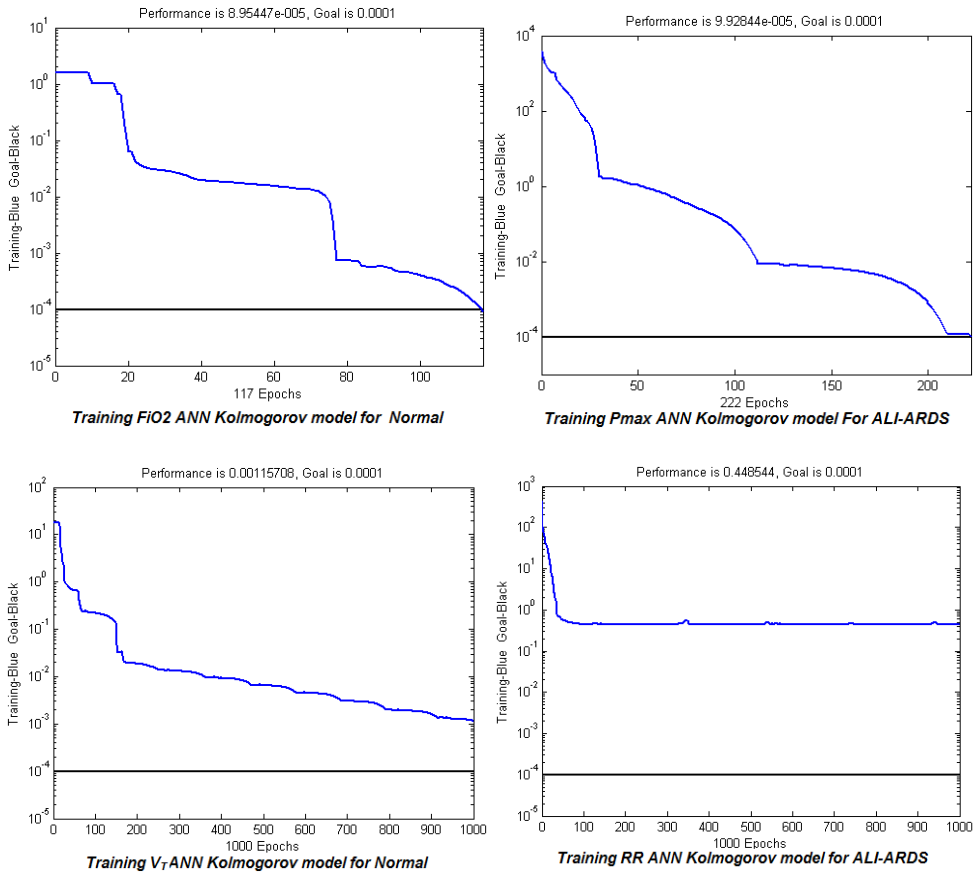

Figure 6.3: Graphical presentation of sample ANN Kolmogorov training process.

The second type is the training process which has constant improvement in performance but does not succeed in achieving the training goal. Example plot is the training of V_T model for the Normal category (fig. 6.3). Continuous improvement suggests that the target could be achieved if the ANN was allowed to be trained for more epochs. The relationship between input and output variables exist, but the type of relationship is more complicated and thus more training epochs or improved architectures of the NN should be implemented.

The third type is the training process where there is a fast improvement in ANN performance during the first few epochs, but the performance remains relative stable for the rest of the training process. Example plot are the training of the RR model for the ALI-ARDS category. Although in some cases performance is considered appropriate for the task, as in the training of RR for the Normal model (performance is mse=1.935, or rmse=1.39 bpm, table 6.11), the training process posses questions on the appropriateness of the ANN architecture, the number and type of input variables and the existence of a relationship between them, and the good representation of input and output variables to the training set.

The following paragraphs attempt to produce logical assumptions on the effect of each of the above factors in ANN performance:

- *ANN architecture*: ANNs were developed on an architecture that performed well during the tests on the cart pole system and the mathematical function. One could argue that although architecture performs well on a specific problem it does not guarantee good performance on modelling a different system. However the *ANN Kolmogorov* and the *ANN Normalized* have exactly the same architecture but utilize different training set; the *un*-normalized and the normalized set respectively. If the architecture was the underlying reason for their performance, then in both cases the ANN should exhibit the same problems during training. Examining the RR and Pmax results (table 6.11) for the Normal models, we observe that the *ANN Normalized* performed very well in comparison to the *ANN Kolmogorov*. Thus the draw backs observed in the training process could not be attributed to the architecture with certainty. In this case the improvement in performance could be attributed to the use of scaled input and output values which overcomes the problem of training NN with a large variation in inputs values.
- *Existing Relationship between inputs and outputs*: The type and number of inputs participating in each model was chosen based on correlation between available inputs and the output in question. If such a relationship was false, then the ANN tries to map a non existence relationship, leading to a poor performance during training. Similar to the logical assumptions of the previous paragraph, if the type and number of inputs to an ANN were not appropriate for the model, then in all cases the ANN should not be able to adequately map the relationship. However observing the training performance of the Fmax for the COPD category (table 6.12), we do not observe similar difficulties in training. This observation leads us to the logical assumption that the type and number of input variables were appropriately chosen for the models.
- *Training Set representative of the modelled system:* The training set was generated with the use of a randomization process from all the available – recorded data. Randomization process on each own should eliminate bias in choice among the available data. However since the randomization algorithms are pseudo-random generators it could be the case of introducing

bias in our training set. However since the same training sets were used in all ANN for the same lung categories, the same type of problematic training should occur in all the applied ANN. Since this is not backed up from the available training data, it should not be considered as an important factor for the training performance.

- *Number of input variables participating in the model:* In the case of RR and Fmax models for the ALI-ARDS, we have identified a single variable as input to the models (table 5.15). *ANN Kolmogorov* has exhibited very poor training process for these models as expected (table 6.13). However the use of the normalized training sets has shown that the problem of modelling a SISO system was overcome.
- *Scaled (Normalized) training sets*: We have implemented linear scaling of all the available input – output training sets. Data were linearly scaled in the domain of zero (0) to one (1), where zero was the minimum value and one was the maximum value of the scaled variable. *ANN Normalized* and *empirical* have used the normalized training set for their training process. The theoretical advantage of improving performance by reducing large variations in the input data when input data are presented to the NN, has been supported by the training performance of the "normalized" ANNs. The performance of training results of *ANN Kolmogorov* and *Normalized* which utilize similar architectures (tables 6.11 to 6.13), support the appropriateness of the scaled inputs.

6.3.4Training Process of the ANFIS

The ANFIS models were developed according to table 6.8 architecture. Models were trained for 5 epochs.

Overall performance of the training process is excellent (tables 6.11 to 6.13). However training performance of ANFIS models in Normal category suggests perfect mapping of the relationship between inputs and outputs. The underlying reason for this is the small number of data sets in Normal category (Table 5.11). The small number of sets and the complexity of the models could have result into overtraining of the system. However the architecture of the ANFIS is minimum in terms of FSs; two (2) FSs for each input variable. Since the number of FSs is minimum, the size of RB is also maintained as small as possible.

Table 6.11: Performance, Normal Category, Training Set.

Mean Error %	Fmax (L/min)	Pmax (mbar)	PEEP (mbar)	FiO2	RR (BPM)	Vt (ml/kgr)	EVOFINE	FUN Bisector	FUN Weighted Average	FUN Near Maxima	ANN Normalized	ANN **Kolmogorov**	ANN **empirical**	ANFIS
	0.04	1.33	X	0.00	0.25	0.08	**EVOFINE MAE**							
0,90	**0.06**	**2.66**	**X**	**0.00**	**0.99**	**0.81**	**EVOFINE MAE %**							
	0.07	1.48	X	0.00	0.61	0.09	**EVOFINE rMSE**							
	0.11	2.97	X	0.00	2.45	0.88	**EVOFINE rMSE %**							
	0:07:00	0:24:00	X	0:06:00	0:14:00	0:14:00	**Training Time**							
	3,17	3,69	X	0,02	1,39	0,75		**FUN MAE**						
5,94	**4,87**	**7,39**	**X**	**4,35**	**5,57**	**7,51**		**FUN MAE %**						
	3,42	3,86	X	0,02	1,42	0,75		**FUN rMSE**						
	5,27	7,72	X	4,39	5,68	7,52		**FUN rMSE %**						
	3,26	3,58	X	0,02	1,32	0,73			**FUN MAE**					
5,79	**5,02**	**7,16**	**X**	**4,24**	**5,29**	**7,23**			**FUN MAE %**					
	3,41	3,87	X	0,02	1,37	0,73			**FUN rMSE**					
	5,24	7,74	X	4,31	5,49	7,32			**FUN rMSE %**					
	0,45	0,05	X	0,00	0,57	0,27				**FUN MAE**				
1,32	**0,69**	**0,10**	**X**	**0,83**	**2,29**	**2,72**				**FUN MAE %**				
	1,09	0,05	X	0,01	1,50	0,72				**FUN rMSE**				
	1,68	0,11	X	1,95	6,01	7,22				**FUN rMSE %**				
	0:00:05	0:00:05	X	0:00:05	0:00:05	0:00:05				**Training Time**				
	0,35	9:42	X	0,00	0,15	0,08					**NN MAE**			
0,67	**0,54**	**19:25**	**X**	**0,62**	**0,62**	**0,76**					**NN MAE %**			
	0,65	11:31	X	0,01	0,25	0,10					**NN rMSE**			
	1,00	23:03	X	1,35	1,00	1,00					**NN rMSE %**			
	0:00:05	0:00:01	X	0:00:01	0:00:05	0:00:02					**Training Time**			
	2,95	3,17	X	0,00	1,06	0,02						**NN mae**		
3,17	**4,53**	**6,34**	**X**	**0,56**	**4,22**	**0,18**						**NN mae %**		
	4,37	3,98	X	0,01	1,39	0,03						**NN rMSE**		
	6,72	7,96	X	1,73	5,57	0,34						**NN rMSE %**		
	0:00:05	0:00:05	X	0:00:05	0:00:05	0:00:05						**Training Time**		
	0,06	1:08	X	0,00	0,02	0,01							**NN mae**	
0,08	**0,10**	**2:17**	**X**	**0,02**	**0,09**	**0,11**							**NN mae %**	
	0,09	1:12	X	0,00	0,03	0,02							**NN rMSE**	
	0,14	2:24	X	0,13	0,11	0,16							**NN rMSE %**	
	0:00:07	0:00:06	X	0:00:06	0:00:07	0:00:07							**Training Time**	
	0,09	0,00	X	0,00	0,00	0,00								ANFIS MAE
0,03	**0,13**	**0,00**	**X**	**0,00**	**0,00**	**0,00**								ANFIS MAE %
	0,02	0,00	X	0,00	0,00	0,00								ANFIS rMSE
	0,03	0,00	X	0,00	0,00	0,00								ANFIS rMSE %
	0:00:01	0:00:07	X	0:00:01	0:00:01	0:00:01								**Training Time**

Table 6.12: Performance, COPD Category, Training Set.

Mean Error %	Fmax (L/min)	Pmax (mbar)	PEEP (mbar)	FiO2	RR (BPM)	Vt (ml/kgr)	EVOFINE	Bisector	Weighted Average	Near Maxima	ANN Normalized	ANN **Kolmogorov**	ANN **empirical**	**ANFIS**
							EVOFINE MAE	**FUN MAE**	**FUN MAE**	**FUN MAE**	**NN MAE**	**NN mae**	**NN mae**	ANFIS MAE
							EVOFINE MAE %	**FUN MAE %**	**FUN MAE %**	**FUN MAE %**	**NN MAE %**	**NN mae %**	**NN mae %**	ANFIS MAE %
							EVOFINE rMSE	**FUN rMSE**	**FUN rMSE**	**FUN rMSE**	**NN rMSE**	**NN rMSE**	**NN rMSE**	ANFIS rMSE
							EVOFINE rMSE %	**FUN rMSE %**	**FUN rMSE %**	**FUN rMSE %**	**NN rMSE %**	**NN rMSE %**	**NN rMSE %**	ANFIS rMSE %
							Training Time	**Training Time**	**Training Time**	**Training Time**	**Training Time h:min:sec**	**Training Time**	**Training Time**	**Training Time**
	1.11	0.19	0.50	0.01	0.52	0.22								
1,94	**1.70**	**0.39**	**3.35**	**1.89**	**2.08**	**2.24**								
	2.79	0.65	0.55	0.02	0.82	0.38								
	4.29	1.29	3.63	4.05	3.29	3.82								
	0:32:00	0:10:00	0:32:00	0:10:00	0:29:00	0:35:00								
	3,95	1,54	0,98	0,02	0,58	**0,16**		**0,16**						
3,89	**6,07**	**3,08**	**6,54**	**3,79**	**2,32**	**1,55**		**1,55**						
	4,13	1,69	1,02	0,03	0,90	**0,20**		**0,20**						
	6,35	3,37	6,79	4,74	3,60	**2,03**		**2,03**						
	3,97	1,49	0,76	0,01	0,50	**0,16**			**0,16**					
3,40	**6,11**	**2,97**	**5,07**	**2,64**	**2,00**	**1,59**			**1,59**					
	4,16	1,67	0,78	0,02	0,77	**0,20**			**0,20**					
	6,41	3,33	5,19	4,19	3,07	**2,03**			**2,03**					
	0,91	0,10	0,18	0,03	0,60	**0,42**				**0,42**				
2,33	**1,40**	**0,20**	**1,20**	**4,62**	**2,39**	**4,19**				**4,19**				
	2,64	0,17	0,54	0,05	0,85	**0,54**				**0,54**				
	4,06	0,34	3,60	8,36	3,40	**5,42**				**5,42**				
	0:00:36	0:00:34	0:00:37	0:00:36	0:00:45	**0:00:40**				**0:00:40**				
	0,84	6:56	0,16	0,01	0,46	**0,10**					**0,10**			
1,24	**1,29**	**13:53**	**1,07**	**1,62**	**1,85**	**1,01**					**1,01**			
	1,54	19:49	0,24	0,02	0,67	**0,13**					**0,13**			
	2,37	15:39	1,62	3,51	2,69	**1,33**					**1,33**			
	0:00:15	0:00:15	0:00:15	0:00:15	0:00:15	**0:00:15**					**0:00:15**			
	3,51	0,19	0,05	0,01	0,51	**0,07**						**0,07**		
1,71	**5,39**	**0,38**	**0,34**	**1,36**	**2,03**	**0,74**						**0,74**		
	5,52	0,75	0,07	0,02	0,74	**0,10**						**0,10**		
	8,49	1,50	0,47	2,82	2,97	**1,01**						**1,01**		
	0:00:15	0:00:15	0:00:15	0:00:15	0:00:15	**0:00:15**						**0:00:15**		
	0,56	4:40	0,10	0,01	0,32	**0,06**							**0,06**	
0,86	**0,86**	**9:21**	**0,67**	**1,38**	**1,29**	**0,59**							**0,59**	
	1,17	6:54	0,15	0,02	0,55	**0,08**							**0,08**	
	1,80	13:48	0,97	3,09	2,20	**0,84**							**0,84**	
	0:00:50	0:00:50	0:00:50	0:00:50	0:00:50	**0:00:50**							**0:00:50**	
	0,01	0,38	0,00	0,01	0,43	**0,03**								**0,03**
0,83	**0,01**	**0,76**	**0,02**	**2,17**	**1,72**	**0,28**								**0,28**
	0,00	0,05	0,00	0,00	0,04	**0,00**								**0,00**
	0,00	0,10	0,00	0,24	0,15	**0,03**								**0,03**
	0:00:04	0:00:01	0:00:04	0:00:01	0:00:01	**0:00:04**								**0:00:04**

Table 6.13: Performance, ALI-ARDS Category, Training Set.

Mean Error %	Fmax (L/min)	Pmax (mbar)	PEEP (mbar)	FiO2	RR (BPM)	Vt (ml/kgr)	EVOFINE	Bisector	Weighted Average	Near Maxima	ANN Normalized	ANN **Kolmogorov**	ANN **empirical**	ANFIS
	0.84	1.72	0.19	0.00	0.95	0.07	**EVOFINE MAE**	**FUN MAE**	**FUN MAE**	**FUN MAE**	**NN MAE**	**NN mae**	**NN mae**	ANFIS MAE
1.85	**1.29**	**3.44**	**1.28**	**0.57**	**3.79**	**0.74**	**EVOFINE MAE %**	**FUN MAE %**	**FUN MAE %**	**FUN MAE %**	**NN MAE %**	**NN mae %**	**NN mae %**	ANFIS MAE %
	1.69	2.58	0.29	0.00	1.16	0.11	**EVOFINE rMSE**	**FUN rMSE**	**FUN rMSE**	**FUN rMSE**	**NN rMSE**	**NN rMSE**	**NN rMSE**	ANFIS rMSE
	2.61	5.17	1.89	1.15	4.64	1.05	**EVOFINE rMSE %**	**FUN rMSE %**	**FUN rMSE %**	**FUN rMSE %**	**NN rMSE %**	**NN rMSE %**	**NN rMSE %**	ANFIS rMSE %
	0:06:00	0:06:00	0:17:00	0:08:00	0:05:00	0:16:00	**Training Time**	**Training Time**	**Training Time**	**Training Time**	**Training Time**	**Training Time**	**Training Time**	**Training Time**
	3,88	1,76	1,03	0,02	1,48	0,66								
5,29	**5,97**	**3,52**	**6,89**	**2,86**	**5,94**	**6,58**								
	3,96	2,14	1,08	0,02	1,53	0,67								
	6,09	4,29	7,20	3,60	6,11	6,69								
	3,53	1,39	0,92	0,01	1,20	0,58								
4,54	**5,43**	**2,78**	**6,12**	**2,34**	**4,81**	**5,75**								
	3,65	1,90	0,99	0,02	1,27	0,59								
	5,62	3,79	6,60	2,89	5,09	5,91								
	0,66	2,56	1,90	0,03	0,71	1,52								
7,07	**1,02**	**5,11**	**12,66**	**5,57**	**2,84**	**15,23**								
	1,96	4,61	2,14	0,04	1,31	1,59								
	3,02	9,23	14,27	7,00	5,26	15,88								
	0:00:07	0:00:07	0:00:08	0:00:08	0:00:08	0:00:08								
	0,44	7:17	0,12	0,01	0,23	0,07								
0,77	**0,68**	**14:34**	**0,78**	**0,91**	**0,92**	**0,74**								
	0,65	11:07	0,20	0,01	0,67	0,10								
	1,00	22:15	1,31	1,36	2,68	1,00								
	0:00:05	0:00:03	0:00:10	0:00:03	0:00:08	0:00:04								
	0,82	0,00	0,14	0,01	0,30	0,02								
0,95	**1,26**	**0,01**	**0,94**	**2,11**	**1,21**	**0,17**								
	1,93	0,01	0,25	0,04	0,67	0,02								
	2,97	0,02	1,67	7,75	2,68	0,25								
	0:00:10	0:00:03	0:00:10	0:00:10	0:00:10	0:00:10								
	0,06	0:29	0,11	0,00	0,30	0,02								
0,38	**0,09**	**0:58**	**0,72**	**0,05**	**1,20**	**0,19**								
	0,17	1:11	0,18	0,00	0,67	0,03								
	0,25	2:22	1,19	0,18	2,68	0,29								
	0:00:10	0:00:02	0:00:10	0:00:10	0:00:04	0:00:10								
	0,24	0,67	0,07	0,00	1,14	0,00								
1,12	**0,36**	**1,34**	**0,44**	**0,03**	**4,55**	**0,00**								
	0,05	0,15	0,01	0,00	0,13	0,00								
	0,08	0,30	0,09	0,01	0,54	0,00								
	0:00:01	0:00:01	0:00:01	0:00:01	0:00:01	0:00:01								

6.4 Discussion on Final Architectures

FUN and ANN methods altered the original architectures of models only in terms of training the NN based on the available training sets. On the other hand EVOFINE and ANFIS resulted in FRBSs for each lung category that exhibited optimum performance for the available training sets. Since the architecture of the EVOFINE and ANFIS FRBS resembles original architectures only in terms of settings (size of RB, Number of MFs etc, as presented in tables 6.1 and 6.8) the following figures and tables present samples of the resulted MFs and surface graphs for each FRBS.

6.4.1 Presentation of Resulted Architectures for FiO2 model for the COPD category.

Utilizing as a vehicle the FiO_2 model for the COPD category the resulted architectures of all the modelling methods are presented. The FiO_2 model for the COPD category is chosen due to the simplicity in terms of number of input variables (according to table 6.1 only two input variables).

In order to provide some insight in the evolution process of the EVOFINE toolbox figure 6.4 and tables 6.14 and 6.15 describe the architecture of the evolved FRBSs of the FiO_2 model for the COPD category. FiO_2 COPD model evolution process is presented in figure 6.1 (bottom left). The performance of the last generation's best individual has improved by approximately 5% in respect to the best individual of the first generation (figure 6.1, bottom left). Figure 6.4 presents graphically the input and output variables fuzzy sets as well as the models response to changes, while tables 6.14 and 6.15 present the architectures of the best individual of the first generation and the best individual of the last generation respectively in terms of evolved fuzzy rules and numerical values of the fuzzy sets.

EVOFINE has altered the original architectures both in terms of position and size of FSs (figure 6.4 and bottom of table 6.14 and 6.15), as well as the size and the type of Fuzzy Rules (top table 6.14 and 6.15). The change in models' response is reflected in the surface mapping of the FRBSs output (figure 6.4 top right and bottom right). Trapezoid membership functions are described with four numbers (points), while triangular membership functions are described with three numbers (tables 6.14 & 6.15bottom).

The size of the RB is reduced to 23 by applying zero weights to 2 rules in the final generation (rule 8 & 14, top of table 6.15). However as stated in Appendix II, the EVOFINE toolbox does not safeguard against duplicate or conflicting rules. A detailed explanation of the EVOFINE algorithm is provided in Appendix II.

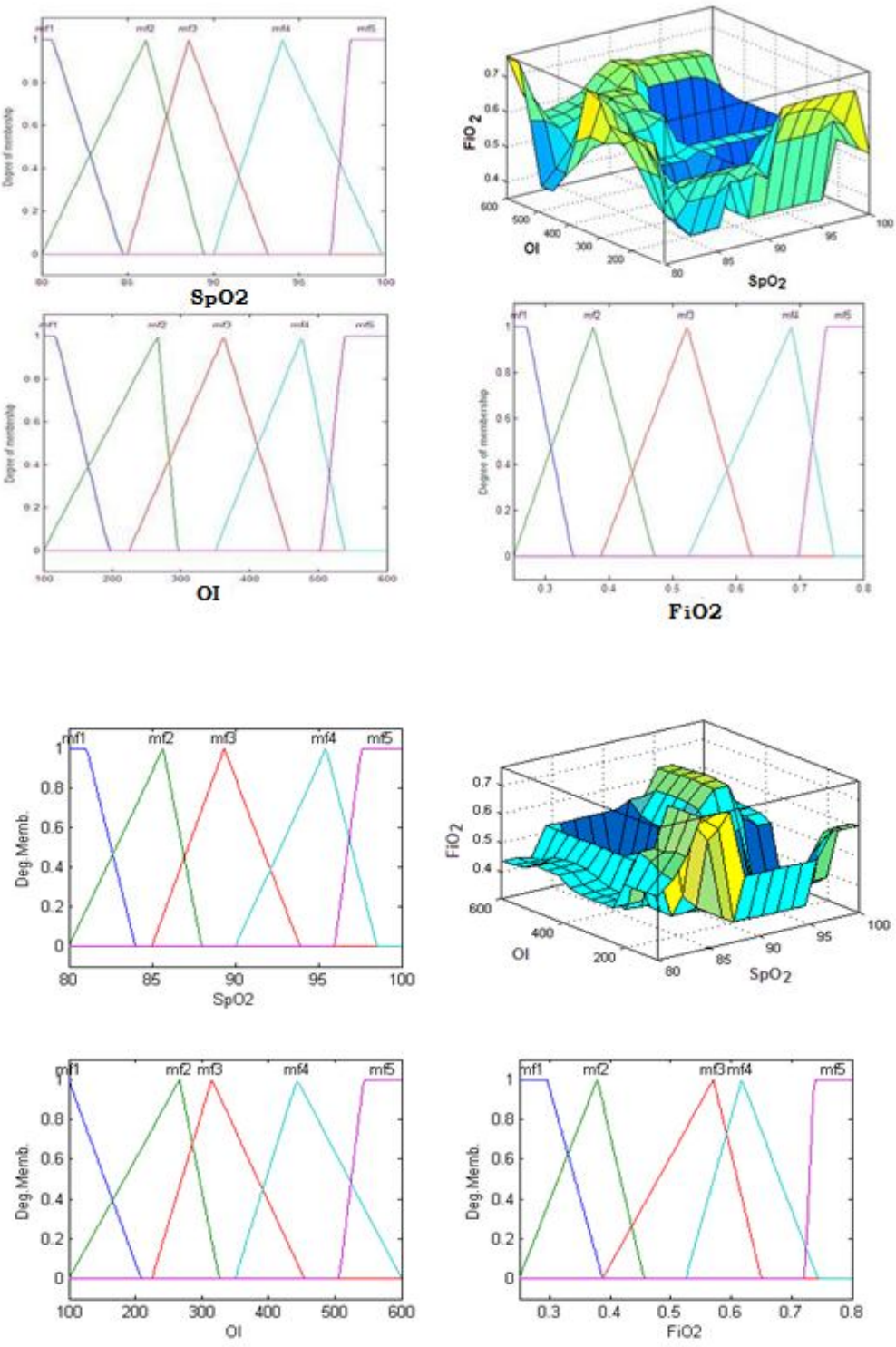

Figure 6.4: Graphical presentation of FiO_2 COPD EVOFINE FRBSs for the best individual of the first generation (top) and last generation (bottom).

Table 6.14: Rules (top) and Fuzzy Sets (bottom) of FiO_2 COPD EVOFINE FRBSs for the best individual of the first generation.

Rule	Inference Logic						Rule Weight
1	IF SpO2 is mf	1	AND OI is mf	3	THEN FiO2 is mf	5	1
2	IF SpO2 is mf	1	AND OI is mf	4	THEN FiO2 is mf	5	0,3
3	IF SpO2 is mf	1	AND OI is mf	2	THEN FiO2 is mf	5	1
4	IF SpO2 is mf	2	AND OI is mf	1	THEN FiO2 is mf	5	0,6
5	IF SpO2 is mf	2	AND OI is mf	4	THEN FiO2 is mf	4	0,9
6	IF SpO2 is mf	1	AND OI is mf	2	THEN FiO2 is mf	2	0,1
7	IF SpO2 is mf	4	AND OI is mf	4	THEN FiO2 is mf	2	0,5
8	IF SpO2 is mf	3	AND OI is mf	5	THEN FiO2 is mf	5	0,6
9	IF SpO2 is mf	1	AND OI is mf	5	THEN FiO2 is mf	5	0,6
10	IF SpO2 is mf	5	AND OI is mf	1	THEN FiO2 is mf	1	0
11	IF SpO2 is mf	2	AND OI is mf	2	THEN FiO2 is mf	2	0,5
12	IF SpO2 is mf	1	AND OI is mf	3	THEN FiO2 is mf	5	0,7
13	IF SpO2 is mf	4	AND OI is mf	1	THEN FiO2 is mf	5	1
14	IF SpO2 is mf	2	AND OI is mf	5	THEN FiO2 is mf	1	0,7
15	IF SpO2 is mf	2	AND OI is mf	2	THEN FiO2 is mf	1	0,5
16	IF SpO2 is mf	2	AND OI is mf	3	THEN FiO2 is mf	3	0,3
17	IF SpO2 is mf	4	AND OI is mf	2	THEN FiO2 is mf	2	0,3
18	IF SpO2 is mf	2	AND OI is mf	1	THEN FiO2 is mf	1	0,4
19	IF SpO2 is mf	1	AND OI is mf	4	THEN FiO2 is mf	2	0,8
20	IF SpO2 is mf	2	AND OI is mf	5	THEN FiO2 is mf	5	1
21	IF SpO2 is mf	1	AND OI is mf	2	THEN FiO2 is mf	5	0,3
22	IF SpO2 is mf	4	AND OI is mf	1	THEN FiO2 is mf	4	0,2
23	IF SpO2 is mf	3	AND OI is mf	5	THEN FiO2 is mf	4	1
24	IF SpO2 is mf	1	AND OI is mf	4	THEN FiO2 is mf	1	0,5
25	IF SpO2 is mf	4	AND OI is mf	5	THEN FiO2 is mf	4	1

Variable	Membership Function	Membership Functions Coding			
		point 1	point 2	point 3	point 4
SpO2	mf1	80,00	80,00	80,63	84,69
	mf2	80,00	86,09	89,43	
	mf3	85,00	88,56	93,16	
	mf4	90,00	94,01	99,81	
	mf5	96,86	97,99	100,00	100,00
OI	mf1	100,00	100,00	118,51	195,81
	mf2	100,00	266,44	295,36	
	mf3	225,00	362,64	457,92	
	mf4	350,00	476,62	538,04	
	mf5	504,38	537,54	600,00	600,00
FiO2	mf1	0,25	0,25	0,27	0,34
	mf2	0,25	0,38	0,47	
	mf3	0,39	0,52	0,62	
	mf4	0,53	0,69	0,75	
	mf5	0,70	0,74	0,80	0,80

Table 6.15: Rules (top) and Fuzzy Sets (bottom) of FiO_2 COPD EVOFINE FRBSs for the best individual of the last generation.

Rule	Inference Logic						Rule Weight
1	IF SpO2 is mf	1	AND OI is mf	3	THEN FiO2 is mf	3	0,5
2	IF SpO2 is mf	4	AND OI is mf	2	THEN FiO2 is mf	1	0,5
3	IF SpO2 is mf	4	AND OI is mf	2	THEN FiO2 is mf	2	0,7
4	IF SpO2 is mf	5	AND OI is mf	1	THEN FiO2 is mf	4	0,1
5	IF SpO2 is mf	1	AND OI is mf	1	THEN FiO2 is mf	3	0,3
6	IF SpO2 is mf	1	AND OI is mf	4	THEN FiO2 is mf	3	0,8
7	IF SpO2 is mf	3	AND OI is mf	2	THEN FiO2 is mf	1	0,1
8	IF SpO2 is mf	4	AND OI is mf	4	THEN FiO2 is mf	3	0
9	IF SpO2 is mf	1	AND OI is mf	3	THEN FiO2 is mf	1	0,8
10	IF SpO2 is mf	1	AND OI is mf	5	THEN FiO2 is mf	3	0,4
11	IF SpO2 is mf	1	AND OI is mf	5	THEN FiO2 is mf	2	0,8
12	IF SpO2 is mf	5	AND OI is mf	4	THEN FiO2 is mf	2	0,5
13	IF SpO2 is mf	4	AND OI is mf	4	THEN FiO2 is mf	4	1
14	IF SpO2 is mf	5	AND OI is mf	1	THEN FiO2 is mf	2	0
15	IF SpO2 is mf	4	AND OI is mf	2	THEN FiO2 is mf	1	0,1
16	IF SpO2 is mf	3	AND OI is mf	2	THEN FiO2 is mf	2	0,1
17	IF SpO2 is mf	1	AND OI is mf	4	THEN FiO2 is mf	2	0,6
18	IF SpO2 is mf	5	AND OI is mf	1	THEN FiO2 is mf	3	0,1
19	IF SpO2 is mf	5	AND OI is mf	4	THEN FiO2 is mf	4	0,9
20	IF SpO2 is mf	3	AND OI is mf	4	THEN FiO2 is mf	1	0,6
21	IF SpO2 is mf	5	AND OI is mf	1	THEN FiO2 is mf	4	0,9
22	IF SpO2 is mf	2	AND OI is mf	1	THEN FiO2 is mf	5	0,7
23	IF SpO2 is mf	5	AND OI is mf	3	THEN FiO2 is mf	1	0,6
24	IF SpO2 is mf	5	AND OI is mf	2	THEN FiO2 is mf	2	0,2
25	IF SpO2 is mf	4	AND OI is mf	4	THEN FiO2 is mf	5	0,7

Variable	Membership Function	Membership Functions Coding			
		point 1	point 2	point 3	point 4
SpO2	mf1	80,00	80,00	81,07	84,01
	mf2	80,00	85,68	87,98	
	mf3	85,00	89,34	93,91	
	mf4	90,00	95,47	98,53	
	mf5	95,98	97,60	100,00	100,00
OI	mf1	100,00	100,00	100,00	208,75
	mf2	100,00	266,67	326,24	
	mf3	225,00	314,65	454,22	
	mf4	350,00	442,71	600,00	
	mf5	506,53	543,03	600,00	600,00
FiO2	mf1	0,25	0,25	0,30	0,39
	mf2	0,25	0,38	0,46	
	mf3	0,39	0,57	0,65	
	mf4	0,53	0,62	0,74	
	mf5	0,72	0,74	0,80	0,80

Figure 6.5 and table 6.16 present in detail the resulted architecture of the FUN FiO_2 model for the COPD category; the basic architecture is provided in table 6.3. The FUN FiO_2 resulted model for the COPD category is displayed in figure 6.5. Ten input variables (membership degrees for each membership function mf) are the NN inputs. Similarly the five NNs' outputs are the membership degrees of the FiO_2 setting. For simplicity a subset of the node interconnections is presented in figure 6.5.

Table 6.16 presents all the node weights and biases for the resulted (trained) FiO_2 NN model for the COPD category.

As described in detail in Appendix II, the input variables of the available data set are transformed into degrees of membership for each membership function. The transformed values are feed into the network as inputs. The trained NN predicts the desired output values in terms of membership degrees for the output variable, which in this case is the FiO_2 ventilator setting for the COPD category. The NN substitutes the fuzzy rule decision making inference engine. However before suggesting appropriate ventilation settings a final step needs to be performed. Defuzzification of the NNs suggested membership degrees results into numerical suggestion.

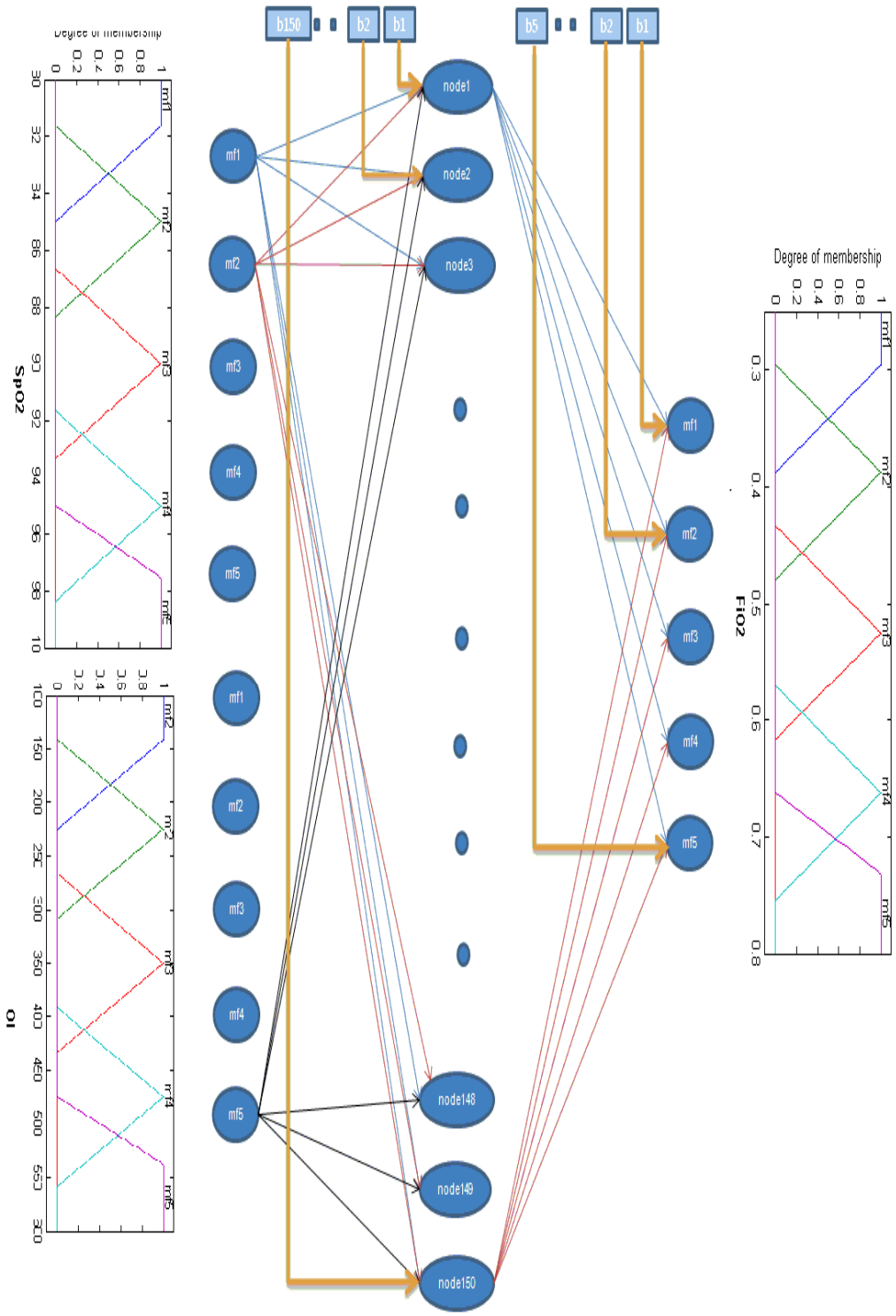

Figure 6.5: Architecture of FUN model for FiO2 COPD category.

Table 6.16: FiO_2 COPD FUN NN model's node weights and bias.

		Hidden Layer Node Weights										Output Layer Node Weights					
	Hidden Layer	SpO2					OI					FiO2					Output Layer
node No	Bias	mf1	mf2	mf3	mf4	mf5	mf1	mf2	mf3	mf4	mf5	mf1	mf2	mf3	mf4	mf5	Bias
1	-0,02	-1,14	1,85	1,19	-0,22	-0,76	2,05	1,32	-2,01	2,11	0,49	-0,02	-0,43	-0,33	0,06	-0,15	-2,83
2	-3,65	1,35	2,07	-1,29	-2,25	1,60	1,38	-0,28	-0,90	1,58	-0,68	0,04	0,31	0,01	-0,05	-0,23	1,33
3	2,98	-0,57	-0,62	-2,75	1,42	-0,31	-1,77	0,54	-0,43	2,75	0,06	-0,29	0,19	0,21	-0,34	-0,15	-0,12
4	-5,23	2,34	1,93	-2,31	-0,01	-0,30	2,00	0,58	0,55	1,44	-0,20	0,33	0,14	-0,24	-0,22	-0,14	1,30
5	-0,25	-0,93	-0,57	2,85	1,49	1,47	-1,52	2,29	-0,11	-0,29	-0,10	0,06	0,08	0,37	-0,33	0,34	-2,84
6	-5,80	1,71	0,56	2,11	0,41	-1,57	0,89	0,83	-1,44	1,57	2,24	0,12	-0,18	0,37	0,22	-0,35	
7	0,71	-1,71	-1,70	0,80	0,88	-1,61	1,70	0,55	2,23	-0,38	1,85	-0,45	0,13	0,41	-0,06	-0,19	
8	-3,57	1,37	0,88	-1,57	0,83	1,66	-1,90	0,28	-1,92	1,83	1,38	-0,30	-0,09	0,43	0,07	0,15	
9	-1,78	0,59	-1,62	0,52	1,05	-2,02	-1,02	0,93	0,81	-2,26	2,21	-0,01	0,15	0,19	0,07	0,35	
10	-0,38	-1,08	0,91	1,86	2,14	2,73	1,14	-0,20	-1,05	-0,66	-0,95	0,37	-0,44	0,16	0,20	0,25	
11	3,22	-2,36	0,57	-0,07	-2,58	2,60	0,79	-0,77	0,19	-0,67	0,05	0,01	-0,04	0,03	-0,19	0,39	
12	2,21	-0,31	1,17	-2,19	0,37	1,85	-0,35	-1,24	2,18	-2,24	0,33	-0,24	-0,01	0,02	-0,42	0,18	
13	2,95	-1,42	1,35	-2,25	-1,64	-0,02	-2,26	0,93	1,25	0,04	1,65	0,39	-0,23	0,29	0,08	-0,29	
14	-1,10	1,72	1,60	-1,75	1,10	1,68	-1,60	-1,80	-1,54	-0,58	-0,51	0,05	0,17	0,18	0,43	-0,21	
15	7,39	-1,50	1,46	-1,50	-1,33	-1,69	-0,36	-1,04	-1,90	-1,25	-1,92	-0,32	-0,09	-0,06	-0,20	-0,31	
16	-3,89	1,00	2,25	0,03	1,20	0,49	-0,78	-2,09	-1,55	1,80	1,73	-0,25	0,00	0,47	0,37	0,33	
17	0,30	0,03	-1,77	-2,17	0,10	-1,72	0,61	2,04	-2,28	0,54	0,74	0,44	-0,11	0,32	0,12	-0,31	
18	1,51	-0,32	1,87	-1,18	1,45	1,56	-1,57	1,62	0,63	-2,07	-1,44	-0,10	-0,12	-0,23	-0,01	-0,26	
19	4,92	-1,62	-0,26	0,71	-0,51	-1,84	1,26	1,46	-2,22	-1,21	-2,10	0,34	0,04	-0,09	-0,24	-0,10	
20	-2,52	1,87	-0,52	1,93	-1,80	0,35	2,09	-1,11	0,85	-2,07	0,07	0,10	0,09	-0,32	-0,20	0,36	
21	0,28	-2,80	-0,30	1,33	-0,20	1,29	-1,33	2,04	0,20	2,00	0,29	0,46	0,06	0,10	-0,29	0,37	
22	-0,30	-2,25	0,52	2,68	-0,89	-0,54	-0,78	1,94	1,25	0,01	1,32	0,16	0,25	-0,42	-0,06	-0,25	
23	-4,12	2,20	1,75	-0,84	-2,21	0,70	-0,09	0,38	1,96	-0,60	1,74	-0,05	0,17	-0,15	0,14	-0,08	
24	1,04	-1,99	-1,76	-1,45	1,22	0,83	1,66	1,72	1,17	-1,35	1,06	-0,06	0,12	-0,02	0,24	-0,15	
25	-1,22	1,79	1,17	-1,71	1,55	1,97	-0,79	-1,53	-1,08	-0,29	-1,82	-0,26	0,07	0,30	0,40	0,11	
26	-2,64	1,85	1,15	1,07	1,93	-1,79	-1,26	1,22	-1,36	-1,65	0,87	0,16	-0,09	0,44	0,30	0,20	
27	-1,20	1,23	-1,23	-1,87	1,24	1,60	-1,13	1,34	-2,01	1,58	-1,23	0,45	0,16	0,39	-0,36	0,07	
28	-2,55	0,97	1,86	1,47	-0,65	-0,38	1,99	-2,01	-1,28	-1,43	1,61	-0,33	0,16	-0,14	-0,20	0,38	
29	-2,79	1,06	-1,72	2,01	0,01	-1,55	1,99	-0,50	2,40	-0,12	-0,91	-0,38	0,21	-0,08	0,10	-0,39	
30	1,46	0,44	-1,80	-0,75	2,43	-1,05	-2,32	-0,69	-1,94	0,52	-0,73	-0,24	-0,18	-0,11	-0,12	0,16	
31	-1,67	-0,22	1,76	2,25	1,99	0,69	-1,83	-0,25	1,94	-1,02	0,36	-0,12	0,09	0,22	0,25	-0,01	
32	0,29	-1,73	2,02	2,07	-0,93	1,68	1,49	-1,19	-1,15	0,65	-0,90	0,28	-0,27	0,36	-0,13	-0,28	
33	1,91	-1,92	-0,60	-1,51	0,84	2,20	-0,02	-1,23	2,14	-1,72	0,64	0,01	-0,42	-0,22	-0,01	-0,02	
34	4,78	-1,18	-0,52	-1,76	0,60	-1,71	0,86	-1,14	-2,03	1,84	-1,95	0,13	0,05	0,10	0,05	-0,06	
35	-3,12	1,90	-1,23	-0,25	-2,36	0,76	-0,69	0,81	1,81	2,24	0,74	0,38	-0,19	0,16	-0,24	-0,10	
36	2,88	-0,67	2,26	0,65	-2,00	0,58	-0,39	1,43	-1,71	-1,66	-1,77	0,06	0,30	-0,30	-0,34	-0,36	
37	1,67	-1,32	-1,87	-1,70	0,24	1,14	1,84	1,31	1,02	-2,30	0,70	0,25	0,22	-0,35	-0,43	0,12	
38	0,48	0,54	-2,75	-1,43	0,70	-0,96	2,27	-0,57	-1,23	1,23	-1,32	0,05	-0,61	-0,05	0,19	-0,36	
39	0,77	-1,76	2,07	-2,49	0,12	0,40	1,86	1,76	-0,70	0,16	-0,70	-0,18	0,08	0,17	-0,45	0,26	
40	-2,06	1,93	-1,35	2,43	-2,00	0,93	-0,76	-0,39	-0,73	-0,09	1,94	0,19	0,19	0,48	-0,28	0,12	
41	-4,54	-0,29	1,52	1,50	2,29	-0,19	1,13	-0,12	1,21	2,18	1,98	0,24	0,19	0,05	-0,21	-0,12	
42	-0,56	1,69	1,98	-0,73	1,62	-0,17	0,87	-1,82	-2,39	-0,14	-1,33	0,26	0,01	-0,38	0,36	0,19	
43	-1,08	2,44	2,35	-1,81	-1,28	1,15	0,69	-1,10	-1,04	-0,71	-0,55	0,12	0,13	0,16	0,16	-0,17	
44	-1,75	-1,44	2,07	2,10	1,02	0,35	2,42	0,20	-1,73	0,02	0,92	-0,28	-0,15	0,36	0,20	-0,02	
45	-0,75	2,48	0,97	0,43	-1,76	0,70	-1,48	-1,97	-1,45	1,51	0,12	0,08	-0,18	0,00	-0,09	0,23	
46	0,53	0,52	-2,42	-0,88	-0,41	1,59	1,14	-1,96	0,03	-2,31	1,25	-0,14	0,28	0,56	0,14	-0,26	
47	-0,67	-0,97	1,41	1,63	0,70	1,26	1,97	0,33	-2,17	0,88	-2,02	0,21	-0,38	0,04	0,30	-0,23	
48	1,82	-1,72	0,41	1,85	1,39	-2,12	-2,41	1,49	-0,68	-0,07	-0,64	0,44	-0,07	-0,33	-0,18	-0,38	
49	2,16	-2,03	1,15	-0,38	1,58	1,35	-0,77	-1,99	-1,20	-1,82	1,47	-0,01	-0,04	-0,44	0,03	0,22	
50	1,60	-2,10	-1,58	0,56	0,71	2,33	-1,33	2,14	-0,60	-0,77	-0,96	-0,32	0,25	0,11	0,08	-0,27	
51	0,05	-1,38	-0,42	1,78	-1,38	1,02	1,33	-2,74	-0,13	1,63	1,13	0,22	-0,17	-0,20	-0,03	-0,22	
52	5,73	-1,64	-1,18	0,35	0,83	-1,97	-1,76	-1,81	-1,60	-1,82	0,59	-0,39	0,12	0,01	0,18	-0,19	
53	-3,10	1,71	0,75	1,83	-2,55	-0,38	0,67	1,97	-1,17	1,31	0,64	-0,25	0,07	-0,09	-0,11	0,23	
54	4,25	-0,43	-0,39	-1,61	-2,47	1,75	-0,20	-0,16	-1,92	0,57	-2,27	-0,25	-0,32	0,12	0,21	0,08	
55	0,40	0,52	1,35	-0,35	1,60	1,56	-1,77	-2,77	-0,78	-1,57	0,36	-0,29	-0,11	-0,35	-0,20	-0,01	
56	3,94	-0,97	1,09	-2,12	-0,19	0,11	-2,81	-1,18	1,34	-1,88	-0,01	-0,03	-0,24	-0,20	0,25	0,21	
57	1,05	2,68	-0,13	-0,01	-0,15	-0,81	-2,28	0,86	-2,43	-1,35	-0,78	0,51	-0,12	-0,52	-0,13	-0,12	
58	1,74	-1,36	-0,13	-0,29	-0,27	-1,92	2,44	1,70	-0,13	0,23	-2,57	-0,05	-0,04	-0,34	0,15	-0,34	
59	0,50	-1,25	-2,14	1,13	0,57	1,55	0,22	-0,49	2,28	-2,33	0,60	0,04	0,19	-0,18	-0,40	-0,15	
60	1,60	-1,88	-1,59	1,76	-2,23	0,43	1,53	0,47	1,48	-1,22	-0,93	0,12	0,30	-0,31	-0,15	-0,30	
61	-1,50	0,75	-1,87	-1,29	2,43	-0,13	1,45	1,42	-2,02	0,17	1,23	-0,16	-0,10	0,03	-0,15	-0,39	
62	-1,18	-1,52	1,62	0,02	1,88	-1,63	0,33	-1,83	1,95	1,68	0,64	-0,29	0,53	-0,20	0,39	-0,23	
63	-0,27	0,65	1,81	-1,72	-1,96	0,83	1,86	-1,41	-1,31	-0,75	1,55	-0,02	-0,03	-0,02	0,29	-0,24	
64	2,76	0,61	0,42	1,61	0,26	-1,90	-0,42	-2,22	-0,88	-2,64	-1,51	0,40	0,17	-0,26	0,00	0,31	
65	-0,18	1,84	1,52	-0,68	-0,89	-1,05	1,47	-1,91	-1,36	-1,09	2,12	-0,03	0,19	-0,43	0,28	0,22	
66	0,71	-1,72	1,36	-1,48	-1,95	-1,76	1,44	0,22	1,74	0,17	1,41	-0,12	-0,31	0,34	-0,09	-0,30	
67	-1,77	-1,84	1,23	-0,75	1,70	1,92	0,80	1,75	0,24	1,10	-2,08	-0,15	0,20	-0,19	-0,45	0,17	
68	3,08	-1,90	-2,54	1,86	-0,80	-1,54	-1,74	0,90	0,12	-0,66	0,69	-0,35	0,08	0,01	-0,20	-0,08	
69	0,44	1,70	1,97	-2,09	0,87	-1,54	-0,24	0,15	1,17	-2,01	-1,27	-0,12	0,24	-0,14	0,08	0,04	
70	-2,02	0,03	0,06	-0,63	-1,52	-0,44	2,29	1,35	2,18	-1,52	2,15	-0,27	-0,27	-0,12	0,38	-0,04	
71	-1,39	1,69	-0,93	-2,13	1,78	-1,69	1,18	1,05	2,08	-0,64	0,26	0,25	0,23	-0,28	-0,01	0,19	
72	0,07	-0,88	1,39	-2,75	2,47	-0,01	0,43	0,70	-0,43	-1,80	0,92	-0,08	0,26	0,28	0,08	-0,37	
73	-2,53	2,07	-2,07	1,69	-0,31	1,39	2,12	0,29	-1,35	-0,11	1,30	0,15	-0,22	0,14	0,33	0,34	

74	-1,52	0,79	1,01	0,70	1,78	-0,98	-1,40	2,31	1,79	-2,14	-0,62	-0,02	-0,27	-0,58	0,03	0,06
75	0,70	0,28	0,38	-1,72	-0,33	0,93	1,39	-1,61	2,26	-2,69	-0,29	0,14	-0,20	0,37	0,12	-0,04
76	2,84	0,53	-0,20	-1,38	-1,95	2,04	-1,99	-1,82	-1,39	1,16	-0,70	0,38	-0,32	0,17	0,39	0,20
77	-2,18	1,20	2,36	2,21	0,71	-0,62	0,70	-1,20	0,63	0,81	-2,36	-0,34	0,34	-0,04	0,11	0,09
78	-0,22	2,71	-1,46	-0,05	0,54	-2,46	0,31	2,19	-0,58	-0,60	0,14	0,24	0,00	-0,34	0,19	0,36
79	-3,00	2,04	-1,09	1,78	-1,43	0,45	1,61	1,15	2,29	0,41	-1,07	-0,30	-0,01	0,23	-0,14	-0,03
80	-3,60	1,46	-0,08	2,27	-0,86	2,00	2,18	-0,90	1,91	-0,50	0,16	-0,09	-0,43	0,14	-0,01	0,21
81	2,75	0,47	-1,03	0,91	0,33	-1,00	-3,02	-1,35	1,91	-0,77	-1,93	-0,01	0,54	-0,46	-0,50	0,21
82	-2,81	-1,09	0,38	-1,81	-0,46	1,87	1,89	-0,71	1,63	1,78	1,83	-0,24	-0,28	-0,21	0,47	-0,07
83	-1,80	-0,34	0,14	-2,08	1,77	1,67	1,09	2,19	-1,15	-1,43	1,29	0,07	-0,06	-0,01	-0,20	0,29
84	2,17	-1,21	-2,58	1,02	-0,18	-0,03	-0,75	1,72	-1,15	0,88	-2,55	0,12	0,18	-0,33	0,09	0,21
85	-0,36	0,06	0,91	-1,17	1,71	-0,80	-2,99	0,09	0,23	2,42	1,01	-0,12	-0,63	-0,13	-0,05	0,24
86	1,35	-0,61	1,37	1,23	-2,23	-0,78	-0,64	-1,33	1,28	-2,62	1,13	-0,24	0,10	-0,36	-0,01	-0,37
87	-3,37	1,00	1,78	-0,18	-0,63	1,61	0,55	-1,18	-0,19	3,19	1,51	0,21	0,42	-0,25	0,44	-0,27
88	3,52	1,59	-1,99	1,07	-1,47	-1,81	-0,60	-1,70	-1,95	-0,28	0,97	-0,09	-0,01	-0,26	-0,13	-0,08
89	2,29	0,79	1,20	0,91	-2,43	-0,19	-1,91	-1,13	-2,18	1,61	-0,04	0,53	-0,40	-0,29	0,19	0,09
90	3,15	-1,86	0,36	-0,99	2,12	-0,70	-2,32	-0,23	-1,82	-1,86	-0,17	0,23	0,12	0,27	-0,34	0,18
91	0,52	-2,28	-0,60	-1,54	1,06	1,33	-0,65	1,25	-1,31	2,20	-1,41	0,00	-0,28	-0,08	0,27	-0,25
92	2,50	2,58	0,88	-0,82	-2,53	0,59	0,24	-0,91	-1,04	-0,59	-1,92	0,05	0,35	-0,35	0,26	0,12
93	-0,85	1,36	1,84	0,38	2,51	-0,42	-0,44	1,35	-2,39	-1,31	-0,18	0,33	0,07	-0,12	0,14	-0,22
94	0,24	-1,65	-1,46	0,76	1,05	-2,02	1,16	-1,06	1,38	-1,68	1,91	0,34	0,08	-0,18	0,27	0,20
95	-0,58	-0,83	1,04	-0,46	-2,42	-1,37	1,91	1,66	-1,70	1,37	0,50	-0,14	0,30	0,29	-0,16	0,07
96	-1,57	-1,16	-1,67	1,88	1,00	-1,58	1,67	-0,91	-0,40	2,43	0,55	0,33	0,04	0,27	-0,05	0,35
97	1,86	1,55	0,18	-1,76	0,25	-2,36	-2,30	-0,94	0,98	0,85	1,45	-0,31	0,10	0,06	-0,30	0,26
98	-3,03	-0,37	2,50	2,50	-1,47	-1,79	0,42	-0,05	0,88	1,43	0,53	-0,24	0,41	0,35	0,10	-0,35
99	1,84	-0,98	-1,78	-1,36	0,14	-2,54	-0,57	1,38	0,02	2,13	-1,36	-0,01	0,26	0,19	0,16	-0,20
100	1,44	-2,20	-1,86	0,35	0,32	0,93	1,88	-1,05	0,79	-1,83	-1,84	0,05	0,00	0,16	0,13	-0,24
101	-2,39	-2,01	0,34	1,34	-0,22	0,75	1,06	2,26	-0,08	2,10	-2,10	-0,26	-0,07	0,24	-0,06	-0,04
102	3,52	-0,10	2,06	-1,88	-1,51	0,06	-0,81	-1,41	-1,24	-1,98	-1,74	-0,12	0,20	-0,37	-0,30	-0,38
103	0,66	-1,31	-1,68	-2,09	0,57	0,21	-0,72	2,06	-2,14	0,96	1,30	0,39	0,30	-0,27	0,21	-0,36
104	-0,72	0,50	1,57	1,98	-1,30	-1,84	0,47	0,98	2,05	0,69	-1,95	0,25	-0,07	0,24	0,27	-0,12
105	4,18	1,95	-1,69	-1,21	-1,92	-1,05	0,91	-1,77	0,78	-1,83	-0,59	0,03	-0,12	-0,25	0,04	-0,31
106	3,35	-1,73	1,35	0,46	-1,29	-2,46	-1,86	-0,08	-2,29	-0,30	-0,67	0,39	0,51	-0,06	-0,04	0,05
107	0,05	1,78	-0,20	-0,88	1,56	0,67	-2,06	-1,74	2,12	1,15	-1,22	0,50	-0,30	0,13	0,17	0,29
108	-2,50	1,71	1,38	2,13	0,67	1,67	1,36	-1,82	0,53	-1,56	1,09	0,13	-0,46	-0,19	0,03	0,04
109	3,12	-0,67	1,50	-1,27	-0,62	-1,62	-0,73	-2,18	-1,74	1,18	-2,01	-0,17	0,06	0,03	0,18	0,13
110	-4,06	0,51	1,40	1,31	1,16	2,02	2,32	1,46	1,56	-0,61	-1,08	0,03	0,11	0,00	0,14	-0,20
111	-0,82	1,87	-1,82	0,44	-1,76	2,08	1,04	1,56	0,38	1,38	-1,18	-0,33	0,05	-0,32	-0,27	0,25
112	-0,60	-0,79	1,03	-0,80	1,87	-1,48	2,15	1,33	-2,08	-1,14	-1,15	-0,02	0,01	0,05	0,19	-0,09
113	-0,50	0,13	0,04	2,65	-2,06	1,00	1,24	1,30	0,97	0,05	-2,21	0,31	-0,25	0,02	-0,04	0,30
114	-1,06	0,17	-1,49	2,02	2,25	2,06	1,48	0,22	0,35	-0,98	-1,55	0,21	-0,20	0,19	-0,47	0,20
115	-1,05	-1,39	-2,06	-1,68	-0,07	2,14	0,49	-0,56	1,41	-0,79	2,12	0,06	0,17	0,13	0,36	0,26
116	-1,58	1,65	-0,50	-2,37	-0,12	2,02	2,31	-0,02	0,65	0,22	1,66	-0,16	0,18	0,20	0,37	0,26
117	-1,49	0,18	-1,06	0,97	-0,46	0,97	2,32	1,32	2,30	1,18	-2,09	-0,03	0,15	0,14	0,21	-0,25
118	-3,15	-2,15	-2,00	1,71	0,28	2,26	0,97	1,21	0,88	1,32	-0,49	-0,39	-0,48	0,00	0,03	0,24
119	-1,27	-2,21	1,68	0,14	0,18	-1,53	-0,26	1,62	-1,90	-0,03	2,25	0,00	-0,36	-0,31	0,02	0,10
120	0,65	-2,98	-1,51	-1,34	1,64	-0,15	-0,55	-0,78	1,23	1,41	-1,07	0,35	-0,12	-0,13	0,24	0,25
121	-4,64	-0,40	1,78	1,65	2,43	-1,90	0,55	1,13	-0,13	1,90	-0,66	0,18	0,16	0,22	0,27	0,37
122	4,24	1,61	-1,49	-0,94	0,91	-2,26	-2,22	-0,79	1,45	-1,14	-0,47	0,25	-0,21	0,02	0,14	0,08
123	-1,20	-0,64	1,13	1,99	0,18	0,42	2,31	-0,05	-2,43	-1,85	-1,17	-0,01	0,42	0,45	0,44	-0,26
124	2,95	2,55	1,11	-0,37	-1,57	-2,10	0,41	-0,48	-2,14	0,75	-1,04	-0,25	-0,37	-0,36	0,12	0,36
125	1,03	-1,07	-0,75	-1,42	1,89	-0,64	-2,53	-1,96	1,83	-0,12	-0,03	-0,39	0,02	-0,18	-0,31	-0,11
126	3,17	2,39	-2,23	-0,39	-1,47	-0,63	-1,52	-1,65	0,06	1,57	0,68	0,16	-0,23	-0,12	-0,32	0,03
127	2,41	-1,83	1,25	-2,09	-0,92	-0,39	-1,41	0,29	-2,48	-1,37	0,96	-0,07	0,22	-0,15	0,17	0,11
128	0,75	1,10	0,23	-1,47	-2,35	2,03	0,13	0,40	-1,57	1,57	1,79	0,03	0,08	-0,14	0,14	0,16
129	-0,72	-2,29	-0,97	2,06	-0,04	-1,24	-0,76	-0,57	-1,32	0,68	2,51	-0,08	-0,05	-0,17	0,41	-0,15
130	-1,81	1,30	-2,05	1,19	-0,60	0,41	0,10	2,23	0,33	2,13	1,93	-0,05	-0,10	0,12	0,23	-0,39
131	-0,91	-0,09	0,47	-2,10	-0,87	-2,02	1,90	-1,87	-0,18	1,20	1,82	0,24	-0,04	0,45	0,42	0,28
132	-1,35	-1,15	-1,68	-1,50	2,47	-2,19	0,42	-0,26	0,84	0,73	1,63	0,18	-0,09	-0,08	-0,28	-0,13
133	1,70	-2,24	-2,62	0,61	-0,25	0,06	-0,30	-0,94	-0,45	-2,34	1,54	-0,30	-0,13	0,17	-0,01	-0,02
134	2,48	2,06	0,16	1,86	1,40	-0,92	-2,04	-1,83	-1,55	0,33	-0,77	0,21	-0,14	-0,32	-0,02	-0,26
135	2,05	0,93	-1,93	-1,81	1,31	2,06	-1,78	-0,87	-0,65	1,58	0,80	-0,07	0,09	-0,24	-0,38	-0,11
136	0,26	-1,37	0,22	-1,73	0,71	0,65	-2,02	-1,02	2,64	-1,71	-0,84	0,47	0,00	-0,36	0,24	-0,14
137	0,58	-1,34	-0,70	-0,91	-0,81	0,14	-1,33	-1,68	-2,16	2,47	1,47	0,03	0,12	-0,31	-0,09	0,02
138	0,47	2,73	0,87	2,16	-2,22	0,40	-0,24	-1,53	-0,35	0,81	0,37	0,01	-0,34	0,04	-0,06	-0,02
139	-0,97	1,83	-0,71	0,97	1,22	-1,86	1,62	-0,95	1,75	2,23	-0,34	0,10	0,31	0,14	-0,08	0,35
140	-1,14	-0,37	1,81	-2,15	2,93	-0,05	-1,26	-0,12	-1,64	0,02	-0,76	0,06	0,32	-0,11	-0,44	-0,06
141	-2,75	-1,30	-1,89	-1,93	-0,89	0,45	0,55	1,88	1,54	2,06	0,94	-0,34	0,10	-0,15	0,05	0,30
142	-1,95	0,80	-2,14	-0,49	1,75	1,14	2,05	2,11	0,48	1,28	0,99	0,03	-0,25	0,21	-0,31	-0,15
143	0,40	-0,43	0,50	2,20	-2,04	-1,71	0,53	-1,12	0,81	-1,93	-1,76	0,03	0,36	-0,16	0,20	-0,04
144	2,51	1,22	1,73	-0,04	-1,11	-1,51	-2,51	1,65	-1,38	1,33	0,42	-0,10	-0,04	0,40	-0,04	-0,28
145	-1,69	-2,56	0,34	-0,55	-0,61	-0,22	-0,22	2,81	-0,69	1,80	-1,45	0,10	0,10	-0,44	0,28	0,25
146	1,44	1,11	2,00	0,27	-1,58	-1,82	1,24	-1,83	0,59	2,14	-0,89	-0,04	-0,23	-0,49	0,07	0,05
147	-1,88	0,12	0,45	2,14	2,12	1,49	1,27	1,62	1,39	-1,33	-1,26	-0,23	0,07	0,31	-0,44	-0,05
148	1,73	1,42	0,31	0,21	-2,47	2,11	0,14	0,50	1,34	0,07	-2,55	0,26	-0,04	-0,42	0,29	0,39
149	0,59	0,75	-1,04	0,38	2,42	1,57	-1,25	0,50	-1,26	2,57	-1,11	-0,17	-0,32	-0,42	-0,17	-0,35
150	-0,29	-0,67	-2,04	1,85	0,81	-1,28	-0,80	-2,28	-0,85	1,96	-0,76	0,04	-0,26	-0,26	0,43	0,16

The final architectures of the trained NN of Kolmogorov, Normalized and Empirical models for the FiO2 ventilator setting for the COPD category are presented in tables 6.17 to 6.19. Tables 6.17 to 6.19 present the resulted weights and biases for the Kolmogorov's, Normalized and Empirical models respectively. In table 6.19, the weights of the second hidden layer are not given due to increased number of data (weights are described by a matrix of 157 X 79 elements)

Figures 6.6 to 6.8, present the trained NNs architectures. The NNs are not described in detailed, in terms of interconnections and detailed node number. The transfer functions used are provided in table 6.5. NNs of figure 6.6 and 6.7 have the same architecture, 126 nodes in the hidden layer, however due to different training set the resulted weights and biases are different (tables 6.17 and 6.19). Empirical NN architecture (figure 6.8) is different. It uses two hidden nodes with 157 and 79 nodes respectively.

Table 6.17: FiO_2 COPD NN Kolmogorov's node weights and bias.

Node No	Hidden Layer Bias	Hiden Layer Node Weights		Output Layer Bias	Output layer Node Weights
		SpO2	OI		FiO2
1	-101,47	0,53	0,19	0.4914	0,12
2	-172,27	1,95	-0,15		0,21
3	135,90	-1,60	0,17		-0,10
4	311,26	-3,01	-0,06		-0,94
5	-151,12	1,08	0,19		0,98
6	311,62	-3,03	-0,06		-0,92
7	197,82	-2,21	0,14		-0,90
8	-11,01	0,35	-0,20		-0,77
9	295,44	-3,06	0,03		-0,38
10	310,52	-3,02	-0,05		0,42
11	-145,15	1,03	0,18		-0,75
12	125,30	-0,81	-0,19		0,02
13	58,61	-0,85	0,19		-0,81
14	-166,03	1,92	-0,15		0,39
15	261,29	-2,37	-0,13		-0,45
16	-307,10	3,13	-0,02		-0,08
17	-241,71	2,14	0,14		0,29
18	252,77	-2,27	-0,13		-0,93
19	-301,33	3,12	-0,02		0,79
20	122,92	-0,81	-0,19		0,93
21	17,23	-0,45	0,19		-0,61
22	-310,19	3,13	-0,02		-0,69
23	-237,42	2,10	0,13		-0,56
24	-252,71	2,74	-0,09		0,11
25	-275,11	2,57	0,10		0,78
26	250,00	-2,27	-0,13		-0,36
27	112,90	-1,43	0,17		-0,10
28	-140,71	1,03	0,19		-0,09
29	302,29	-2,96	-0,06		0,18
30	-139,97	1,71	-0,16		0,43
31	-153,81	1,17	0,16		0,43
32	-181,37	1,48	0,16		-0,49
33	287,53	-2,76	-0,09		-0,77
34	16,74	-0,48	0,19		-0,78
35	55,86	-0,88	0,19		-0,77
36	-304,13	3,13	-0,02		-0,30
37	273,40	-2,59	-0,10		0,45
38	228,70	-2,05	-0,16		-0,24
39	-305,05	3,06	0,05		0,41
40	116,46	-0,80	-0,20		-0,28
41	269,11	-2,58	-0,16		-0,97
42	-152,07	1,85	-0,16		-0,67
43	-184,11	1,57	0,22		0,73
44	216,43	-2,46	0,12		0,12
45	280,88	-2,74	-0,11		-0,93
46	244,20	-2,27	-0,16		-0,67
47	-246,12	2,27	0,10		-0,66
48	-231,05	2,60	-0,13		-0,81
49	-256,11	2,42	0,14		0,51
50	55,69	-0,18	-0,22		-0,51
51	303,22	-3,08	-0,03		0,52
52	-237,84	2,68	-0,10		0,08
53	269,45	-2,57	-0,07		0,89
54	232,30	-2,14	-0,15		0,98
55	-290,88	2,88	0,04		-0,91
56	283,60	-2,76	-0,01		0,96
57	44,56	-0,83	0,18		-0,36
58	-228,76	2,61	-0,11		-0,09
59	273,80	-2,67	-0,12		0,43
60	140,82	-1,12	-0,19		0,87
61	-277,77	2,73	0,10		0,10
62	-269,80	2,95	-0,11		-0,76
63	238,86	-2,25	-0,14		0,05
64	164,37	-1,39	-0,17		0,12
65	255,32	-2,46	-0,14		-0,62
66	153,36	-1,92	0,16		-0,38
67	-222,08	2,05	0,15		0,92
68	-119,56	1,58	-0,21		0,88
69	-207,60	1,90	0,16		-0,56

70	285,70	-3,09	0,03	0,61
71	-202,02	2,39	-0,14	-0,46
72	213,52	-2,49	0,15	0,62
73	-35,80	-0,03	0,19	-0,17
74	222,58	-2,58	0,12	0,24
75	-173,11	1,52	0,17	0,10
76	223,64	-2,10	-0,14	0,03
77	-106,38	1,47	-0,21	-0,96
78	270,42	-2,69	-0,10	-0,14
79	-254,70	2,88	-0,06	-0,96
80	53,07	-0,99	0,14	-0,95
81	276,83	-2,78	-0,09	-0,05
82	244,64	-2,80	0,08	0,05
83	-238,13	2,30	0,14	0,91
84	-278,86	2,82	0,08	0,55
85	62,03	-0,33	-0,19	-0,68
86	-58,44	1,04	-0,19	0,24
87	-35,44	-0,06	0,23	0,49
88	-253,81	2,89	-0,07	-0,69
89	227,12	-2,66	0,10	0,17
90	213,62	-2,03	-0,15	0,86
91	262,05	-2,62	-0,11	-0,06
92	161,58	-2,08	0,12	0,56
93	-160,37	1,43	0,18	0,24
94	-161,37	1,44	0,17	-0,91
95	256,48	-2,92	0,08	-0,84
96	52,35	-0,26	-0,19	-0,06
97	258,00	-2,59	-0,11	-0,15
98	272,66	-2,78	-0,08	0,98
99	285,25	-3,13	0,02	0,09
100	-119,64	1,00	0,20	0,89
101	-212,45	2,57	-0,09	-0,78
102	-280,66	2,91	0,06	-0,66
103	-96,68	1,46	-0,17	-0,26
104	140,31	-1,89	0,15	0,37
105	20,24	0,28	-0,20	0,96
106	-281,62	2,94	0,07	-0,90
107	-256,09	2,60	0,11	-0,82
108	234,36	-2,77	0,09	-0,84
109	272,98	-3,07	0,04	0,36
110	285,61	-3,03	-0,07	0,83
111	227,81	-2,26	-0,14	-0,86
112	261,70	-3,00	0,06	0,18
113	208,70	-2,55	0,12	-0,55
114	65,91	-1,18	0,18	0,95
115	173,90	-2,23	0,14	-0,20
116	234,96	-2,79	0,09	0,03
117	12,09	-0,64	0,19	0,02
118	187,00	-1,80	-0,16	0,19
119	-189,41	2,39	-0,12	-0,26
120	258,74	-2,67	-0,10	-0,78
121	-264,54	2,75	0,09	0,22
122	-230,66	2,33	0,13	0,06
123	-228,38	2,75	-0,09	0,02
124	-238,26	2,84	-0,07	-0,72
125	243,75	-2,88	0,08	-0,36
126	135,73	-1,24	-0,18	0,02

Table 6.18: FiO_2 COPD NN Normalized model's node weights and bias.

Node No	Hidden Layer Bias	Hiden Layer Node Weights		Output Layer Bias	Output layer Node Weights
		SpO2	OI		FiO2
1	20,58	-26,87	87,97	-0,02	0,10
2	-65,14	56,04	44,13		0,12
3	30,29	-38,05	77,45		-0,47
4	-33,27	1,87	97,27		-0,10
5	57,58	-39,68	-75,47		0,01
6	-49,14	25,68	88,83		0,35
7	57,85	-41,18	-73,55		0,16
8	0,78	-4,89	97,01		-0,19
9	-54,51	35,90	79,88		-0,10
10	48,21	-56,34	43,15		0,04
11	-58,46	44,47	68,84		-0,32
12	-57,54	62,35	-12,43		-0,19
13	23,59	-33,58	82,26		-0,09
14	38,25	-48,67	61,58		-0,29
15	55,27	-61,71	18,48		-0,09
16	-3,72	11,23	-95,75		-0,24
17	-60,01	62,67	7,67		-0,13
18	46,27	-25,88	-88,68		-0,02
19	54,27	-40,04	-75,00		0,39
20	38,84	-15,28	-94,38		-0,28
21	-40,82	18,47	92,97		0,40
22	-51,79	36,88	78,81		0,17
23	-60,09	60,73	25,16		0,06
24	35,60	-48,55	61,82		-0,24
25	53,39	-41,32	-73,35		0,31
26	59,11	-55,98	-44,26		0,13
27	52,58	-40,69	-74,18		-0,10
28	9,17	-21,52	91,43		0,39
29	-31,50	45,86	-66,55		0,19
30	6,94	-19,46	92,53		0,25
31	-41,65	55,35	-46,15		-0,25
32	57,98	-58,24	-36,55		0,14
33	56,94	-62,01	-16,08		-0,23
34	20,58	-36,02	79,75		-0,34
35	-57,12	60,56	26,11		0,08
36	0,83	11,82	-95,58		-0,27
37	50,55	-61,99	15,63		0,21
38	20,00	-36,48	79,24		-0,42
39	39,80	-55,46	45,81		-0,06
40	49,16	-40,44	-74,52		-0,08
41	-44,26	59,17	-32,94		0,09
42	41,60	-57,46	39,50		-0,04
43	-28,78	46,62	-65,27		0,05
44	-27,11	7,03	96,67		0,27
45	-40,25	56,98	-41,09		0,04
46	-37,09	54,79	-47,82		0,33
47	53,18	-53,89	-50,28		0,18
48	-40,01	57,36	-39,79		-0,02
49	11,64	-30,36	85,20		-0,43
50	22,14	-41,79	72,68		0,20
51	-50,93	62,74	3,28		0,36
52	-52,71	61,12	22,50		0,26
53	-32,76	18,74	92,91		0,23
54	44,56	-61,36	21,48		0,23
55	-21,84	3,55	97,13		-0,18
56	-48,79	62,87	-1,25		-0,34
57	20,94	-42,64	71,63		0,34
58	5,36	-25,86	88,69		0,06
59	-50,86	61,26	21,85		0,01
60	-48,16	48,88	61,21		-0,24
61	45,44	-43,50	-70,27		-0,21
62	-46,18	62,70	-6,97		-0,05
63	49,81	-55,95	-44,34		0,00
64	-41,63	61,05	-23,20		-0,01
65	47,21	-62,86	-2,86		-0,23
66	3,32	18,06	-93,21		0,28
67	-37,51	31,71	84,02		0,10
68	16,62	1,94	-97,26		-0,11
69	43,57	-43,66	-69,97		0,16
70	25,86	-50,23	58,50		-0,06
71	45,36	-48,91	-61,20		0,32
72	34,88	-58,02	37,42		0,01
73	-14,79	-6,00	96,86		-0,43
74	14,44	6,71	-96,75		-0,11
75	-30,25	55,05	-46,96		0,01
76	-35,38	31,95	83,80		0,12
77	46,54	-57,36	-39,81		0,03
78	-38,91	61,46	-20,39		-0,37
79	-36,77	35,48	80,26		0,46
80	39,86	-41,87	-72,59		-0,01
81	-12,09	39,46	-75,72		-0,20
82	-42,53	48,56	61,78		-0,28
83	-15,91	-7,98	96,51		-0,06
84	-40,93	46,12	66,12		0,02

85	0,98	26,40	-88,31	0,35
86	27,11	-54,75	47,80	-0,25
87	42,94	-53,06	-52,20	-0,23
88	35,40	-37,32	-78,34	-0,34
89	17,72	-9,91	-96,09	0,05
90	-41,26	62,78	4,80	-0,05
91	2,53	26,32	-88,37	-0,08
92	-39,17	46,67	65,19	0,11
93	39,56	-48,13	-62,59	0,50
94	33,20	-36,00	-79,77	0,02
95	20,68	-51,21	56,43	0,02
96	-41,89	58,78	34,54	0,46
97	-40,90	61,95	16,49	0,06
98	41,41	-59,25	-32,48	0,17
99	35,29	-62,21	14,01	-0,09
100	40,64	-61,06	-23,09	0,31
101	-23,81	23,41	90,32	0,11
102	-36,65	46,65	65,22	-0,29
103	8,47	-41,52	73,07	-0,39
104	-7,50	40,75	-74,10	-0,02
105	0,99	-34,17	81,68	0,00
106	-34,76	62,61	-8,68	-0,11
107	-1,03	-32,57	83,24	0,13
108	-30,08	36,73	78,97	-0,05
109	-6,46	1,32	97,29	-0,01
110	-15,52	14,32	94,75	0,02
111	9,77	-44,80	68,26	0,14
112	37,87	-58,46	-35,75	0,07
113	4,18	30,72	-84,90	-0,08
114	-7,42	4,26	97,08	0,18
115	28,99	1,16	-97,29	0,06
116	36,15	-54,69	-47,98	0,12
117	-7,32	-28,30	86,89	-0,24
118	-5,19	2,70	97,22	-0,27
119	-35,30	54,34	48,91	0,15
120	-6,61	43,89	-69,66	0,28
121	-30,08	42,90	71,13	-0,41
122	-21,75	-12,68	95,31	-0,15
123	-33,91	62,38	12,05	-0,47
124	27,28	-61,43	20,62	-0,09
125	-13,91	17,51	93,46	0,01
126	-15,66	20,52	91,98	-0,25

Table 6.19: FiO_2 COPD NN Empirical model's node weights and bias.

Node No	Hidden Layer 1 Bias	Hiden Layer 1 Node Weights		Hidden Layer 2 Bias	Hidden Layer 2 Node Weights	Output Layer Bias	Output layer Node Weights
		SpO2	OI				FiO2
1	51,39	-58,84	59,18	1,44	Matrix 157 X 79	-0.0020	-0,42
2	51,86	-59,44	57,72	-1,40			0,18
3	-22,73	30,23	-98,03	1,37			0,21
4	-50,04	20,11	104,07	1,32			0,38
5	-38,55	47,68	-79,70	-1,29			-0,43
6	-67,77	70,03	-6,73	-1,25			-0,08
7	-37,52	47,09	-80,53	-1,22			0,28
8	-56,12	63,92	-44,81	1,19			-0,25
9	68,10	-70,16	1,52	-1,14			-0,18
10	-41,94	52,09	-72,78	1,11			-0,40
11	71,18	-65,42	-39,28	1,07			0,04
12	-18,27	27,44	-99,97	-1,03			-0,27
13	-38,14	49,06	-77,67	0,98			-0,44
14	-63,68	46,59	81,22	-0,96			0,08
15	41,78	-53,01	71,17	0,92			-0,33
16	69,59	-62,33	-49,88	-0,87			-0,53
17	63,59	-47,75	-79,58	0,85			-0,41
18	49,62	-24,24	-101,93	0,82			0,39
19	-69,40	66,16	36,18	0,77			0,18
20	40,76	-53,11	70,99	-0,74			-0,49
21	-52,24	63,20	-47,20	-0,69			0,51
22	-62,86	48,54	78,43	0,66			0,42
23	68,12	-62,80	-48,45	-0,63			-0,20
24	-68,26	65,42	39,27	0,59			0,02
25	-60,32	68,93	-20,29	0,55			-0,10
26	-63,50	51,80	73,27	0,52			0,00
27	-35,15	49,22	-77,42	0,48			0,09
28	-62,99	70,06	-5,90	-0,45			0,29
29	66,88	-68,05	-26,47	0,41			0,22
30	37,22	-10,02	-107,51	0,37			-0,01
31	64,70	-69,97	-8,21	0,33			-0,16
32	32,49	-47,69	79,68	-0,29			0,37
33	59,60	-46,99	-80,67	-0,26			0,27
34	5,96	-18,72	104,69	-0,22			0,11
35	-26,00	41,72	-87,34	0,19			0,58
36	-60,57	50,27	75,75	0,15			-0,05
37	-42,77	58,39	-60,24	-0,11			-0,24
38	52,27	-35,76	-93,47	0,08			0,15
39	-58,84	48,12	79,05	0,03			0,34
40	59,76	-50,46	-75,45	0,00			0,20
41	59,99	-70,05	6,32	0,03			0,59
42	62,90	-69,61	-13,61	0,07			-0,30
43	58,30	-48,84	-77,97	-0,11			-0,01
44	11,69	-28,15	99,50	0,15			0,29
45	-44,64	25,95	100,92	0,19			0,37
46	-10,65	-1,08	108,61	-0,23			0,33
47	31,25	-6,95	-108,08	0,26			0,54
48	-54,60	68,67	-22,31	0,30			-0,06
49	-4,73	21,30	-103,50	0,34			0,30
50	24,57	-43,75	84,93	0,37			-0,28
51	62,04	-64,05	-44,35	0,41			0,31
52	-57,72	51,91	73,07	-0,44			-0,38
53	5,60	9,67	-107,59	-0,48			0,17
54	54,50	-46,23	-81,71	-0,52			-0,25
55	15,81	-35,58	93,62	0,56			0,43
56	26,14	-46,74	81,02	-0,59			-0,38
57	60,58	-68,07	-26,39	-0,63			-0,36
58	-1,09	-16,70	105,50	-0,66			-0,23
59	-14,97	35,65	-93,56	0,70			0,16
60	4,98	12,44	-106,90	0,74			0,07
61	-52,05	68,86	-20,91	0,78			-0,51
62	-0,88	-18,05	104,97	-0,81			0,47
63	-58,18	59,38	57,89	0,85			-0,09
64	-54,78	51,40	73,94	-0,89			0,21
65	48,72	-40,11	-89,12	-0,92			0,27
66	-30,19	52,90	-71,37	-0,95			0,20
67	-26,42	6,53	108,15	1,00			0,33
68	50,65	-68,94	20,27	1,04			-0,36
69	45,50	-36,11	-93,15	1,08			-0,51
70	48,87	-68,27	25,07	1,10			-0,52
71	40,59	-28,76	-99,08	-1,14			-0,39
72	44,19	-65,67	38,25	-1,18			-0,10
73	46,96	-67,58	29,22	-1,21			-0,15
74	39,14	-62,28	50,03	1,25			0,01
75	-53,09	70,15	-2,41	1,29			0,24
76	56,05	-68,68	-22,26	1,33			-0,35
77	54,99	-59,23	-58,24	-1,37			0,26
78	-37,75	26,76	100,41	-1,41			0,35
79	-3,56	-19,42	104,38	-1,44			0,2645711

80	-9,81	-12,00	107,02
81	-55,44	66,65	33,95
82	40,95	-64,99	40,96
83	23,42	-50,06	76,11
84	49,81	-50,43	-75,55
85	9,05	14,41	-106,31
86	54,31	-66,67	-33,86
87	-0,29	26,18	-100,78
88	-47,08	46,69	81,09
89	-21,82	49,84	-76,47
90	44,27	-42,22	-86,76
91	45,89	-45,65	-82,47
92	17,16	-45,82	82,26
93	-40,31	66,24	-35,83
94	50,84	-58,24	-60,59
95	37,34	-64,50	42,78
96	-14,42	43,92	-84,70
97	-8,97	-17,81	105,07
98	-16,13	46,18	-81,79
99	-46,51	50,54	75,34
100	37,22	-33,88	-95,12
101	-50,70	68,04	26,58
102	-43,46	45,74	82,37
103	8,45	-39,30	89,98
104	50,28	-66,37	-35,24
105	49,12	-60,60	-54,76
106	-30,86	61,42	-52,53
107	-38,01	66,79	-33,30
108	49,02	-62,88	-48,22
109	17,11	-49,61	76,82
110	4,20	26,92	-100,31
111	19,85	-52,68	71,75
112	7,52	23,59	-102,30
113	20,93	-13,40	-106,62
114	-15,70	49,33	-77,25
115	-12,61	2,45	108,56
116	1,04	32,11	-96,59
117	-37,89	68,05	-26,48
118	-42,63	70,04	-6,52
119	-26,76	-1,46	108,60
120	40,16	-69,45	15,54
121	-33,23	65,72	-38,07
122	11,07	-2,50	-108,55
123	-40,31	69,73	-12,06
124	44,72	-69,40	-16,07
125	17,31	15,28	-106,02
126	-1,16	-34,48	94,60
127	-8,28	-26,63	100,49
128	-37,77	69,21	-17,92
129	-11,06	-23,91	102,12
130	40,45	-52,55	-71,97
131	30,32	-34,00	-95,02
132	42,15	-57,84	-61,50
133	-43,33	62,56	49,18
134	-16,49	54,38	-68,64
135	26,36	-29,02	-98,90
136	32,04	-67,13	31,60
137	-36,86	48,26	78,85
138	12,67	24,41	-101,84
139	-40,53	57,73	61,75
140	-3,89	43,30	-85,48
141	40,90	-60,18	-55,85
142	-24,80	63,02	-47,75
143	-12,85	52,87	-71,41
144	28,81	-36,37	-92,89
145	-8,55	-30,98	97,47
146	32,86	-44,42	-84,09
147	-22,54	62,14	-50,45
148	36,72	-53,25	-70,73
149	7,46	-5,85	-108,25
150	-9,98	-30,64	97,72
151	37,03	-55,60	-66,25
152	34,09	-49,49	-77,00
153	3,26	-45,66	82,48
154	-22,45	-16,98	105,39
155	-32,78	48,21	78,93
156	22,34	17,67	-105,12
157	-33,45	69,95	-8,48

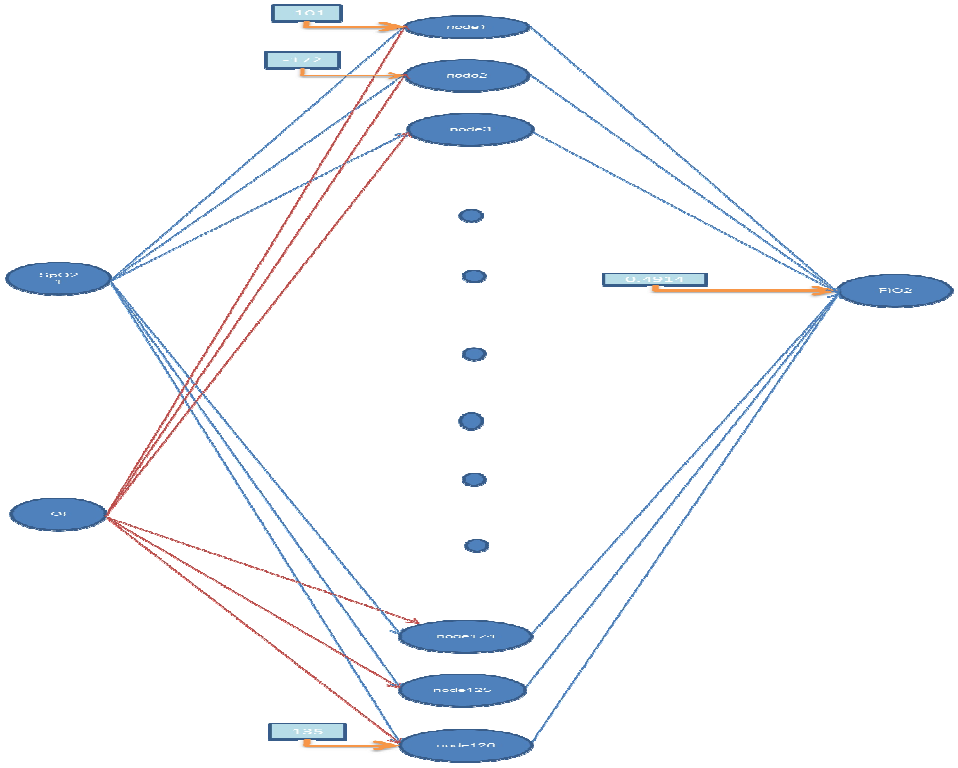

Figure 6.6: FiO_2 COPD NN Kolmogorov's architecture.

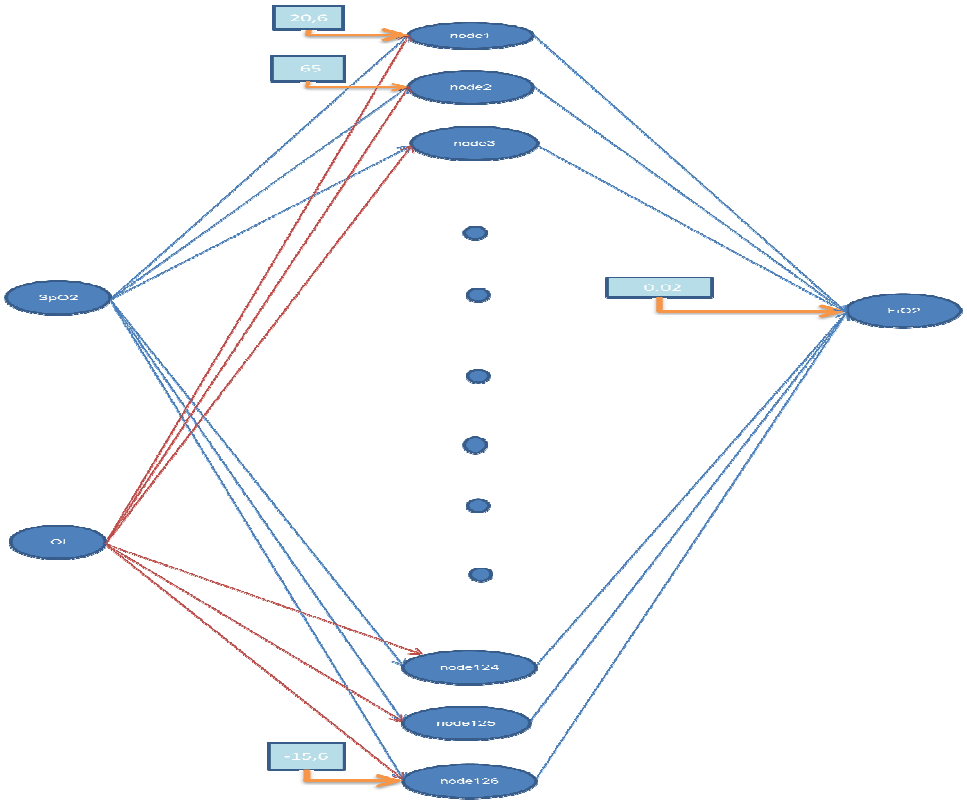

Figure 6.7: FiO_2 COPD NN Normalized architecture.

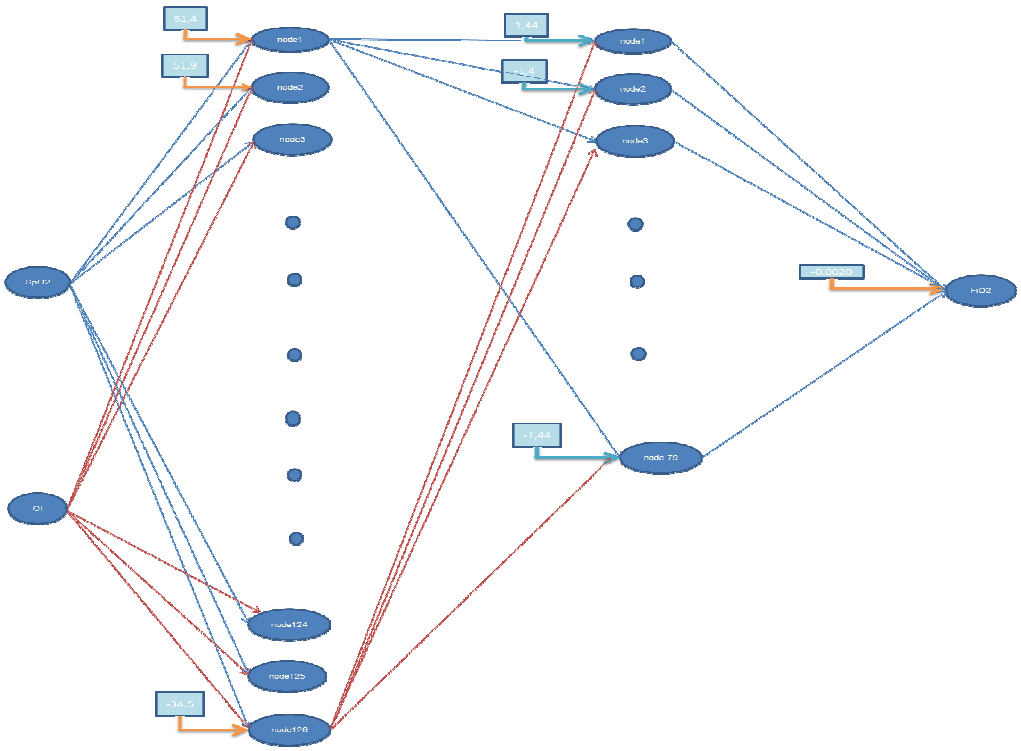

Figure 6.8: FiO_2 COPD NN Empirical architecture.

The resulted architecture of FiO2 model for the COPD category is provided in figure 6.9 and table 6.20.

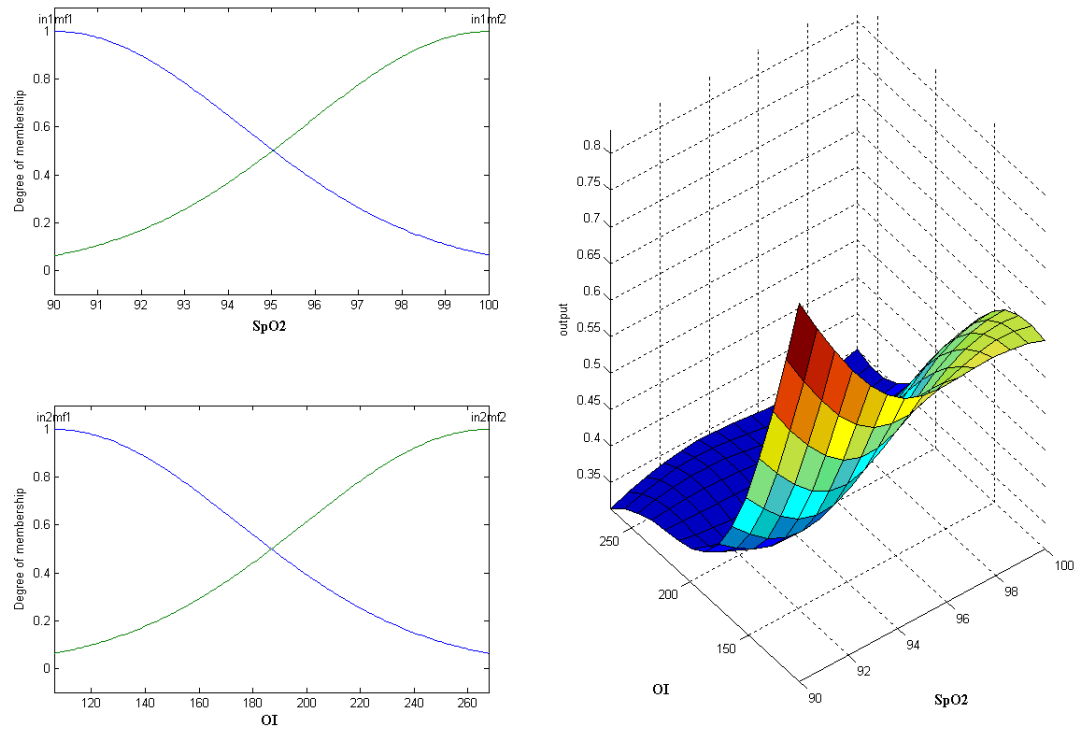

Figure 6.9: ANFIS FiO2 model for COPD category, resulted input fuzzy sets and systems' response surface mapping.

Table 6.20: Inference Engine for ANFIS FiO2 model for the COPD category.

Rule	Inference Logic									Rule Weight
						FiO_2= a*SpO_2 +b*OI + c				
						a	b	c		
1	IF SpO2 is mf	1	AND OI is mf	1	THEN FiO2 is	-0.08	-0.01	8.91		1
2	IF SpO2 is mf	1	AND OI is mf	2	THEN FiO2 is	0.03	-0.003	-0.92		1
3	IF SpO2 is mf	2	AND OI is mf	1	THEN FiO2 is	-0.03	0.002	3.45		1
4	IF SpO2 is mf	2	AND OI is mf	2	THEN FiO2 is	0.02	0.002	-2.09		1

As it is described in Appendix IV, the Matlab (® Mathworks) ANFIS toolbox generates fuzzy inference engines of TSK type. The output of the ANFIS models is described by a mathematical function (as shown in table 6.20 for the FiO_2 ventilator setting). The coefficients (a,b,c) applied to the function differ among different rules applied for a given input data set. Additionally the Matlab ANFIS toolbox adapts FSs not to a predefined domain but rather on the domain described by the training data set.

6.4.2 Discussion on EVOFINE and ANFIS resulted Architectures

In general sample resulted architectures shown in figures 6.10 to 6.19, present a smoother surface mapping for the ANFIS FRBSs compared to EVOFINE FRBSs. However the surface mapping of ANFIS is based on a sub-domain compared to EVOFINE mapping. This is attributed to the predefined domain used by EVOFINE, while ANFIS adapted domains to the range of input variables.

A closer look at the mapping reveals that EVOFINE FRBSs always calculate output values, within the predefined limits. In contrast ANFIS FRBSs produce in several models, outputs which are outside the limits defined by the training sets, and in several cases the magnitude of the model's output is potentially harmful to the patient. The following list presents the ANFIS FRBSs potentially problematic calculated outputs:

- Pmax model the COPD category (fig. 6.10): suggests for a given numerical value of inputs, negative values for the Pmax ventilator setting.
- PEEP model for COPD category (fig. 6.11), suggests for a given numerical combination of SpO_2, PIP and Pplateau inputs, negative PEEP values.

- Fmax model for COPD category (fig. 6.12), suggests negative maximum gas flow for a numerical combination of SpO_2 and R inputs.
- V_T model for ALI-ARDS category (fig. 6.13), suggests delivery of negative volumes for a numerical combination of OI, SpO_2 and Ve inputs.
- PEEP model for ALI-ARDS category (fig. 6.14), suggests extremely high values and additionally negative values of PEEP for a numerical combination of input values.
- Fmax model for ALI-ARDS category (fig.6.15), suggest negative gas flow values for most of the surface mapping.

The failure of the above ANFIS models to adequately map the surface area, could be attributed to lack of available data representing in whole of the inputs and outputs domain.

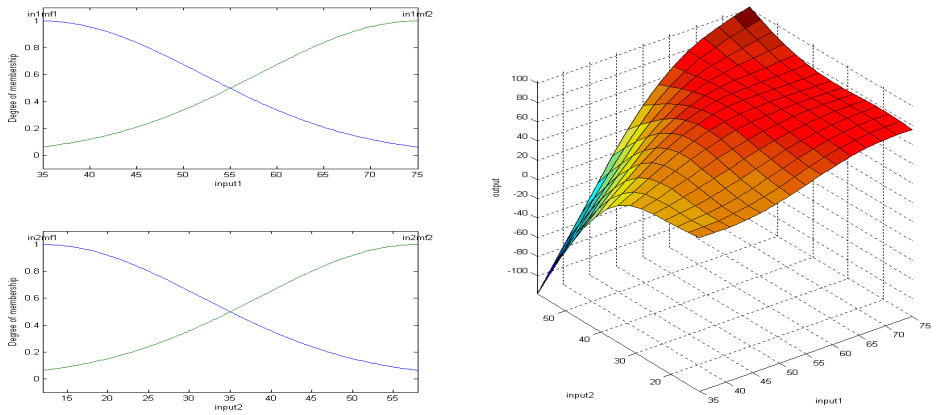

Figure 6.10: Resulted ANFIS FRBS architecture for the Pmax for the COPD Category.

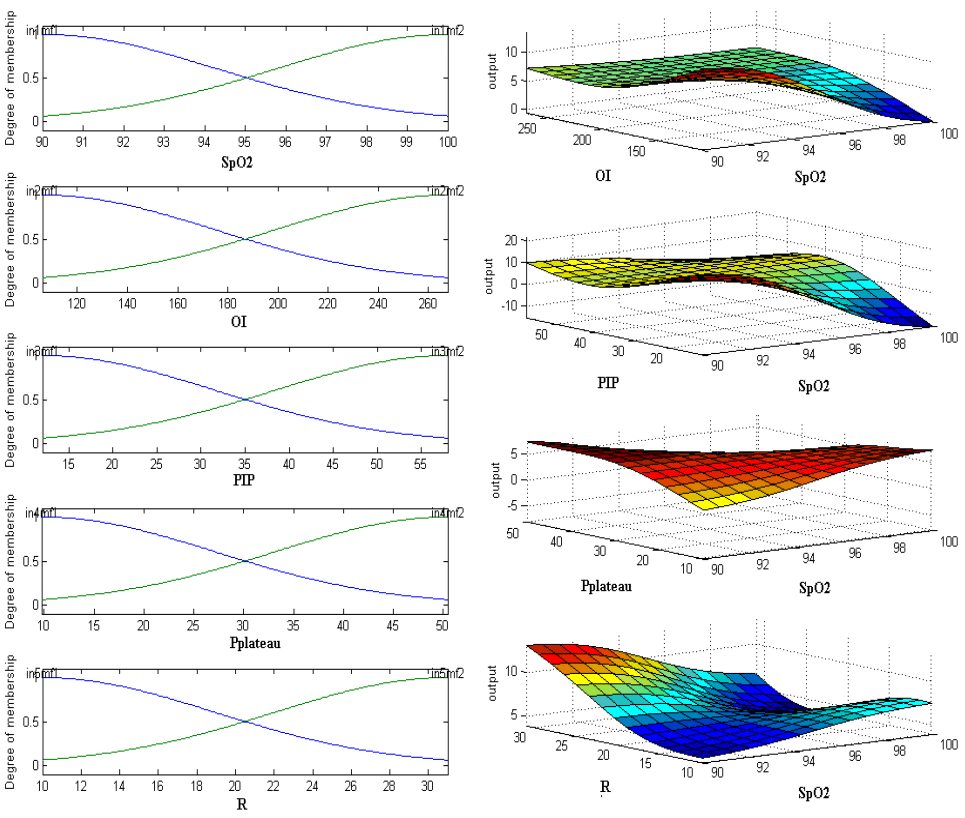

Figure 6.11: Resulted ANFIS FRBS architecture for the PEEP for the COPD Category.

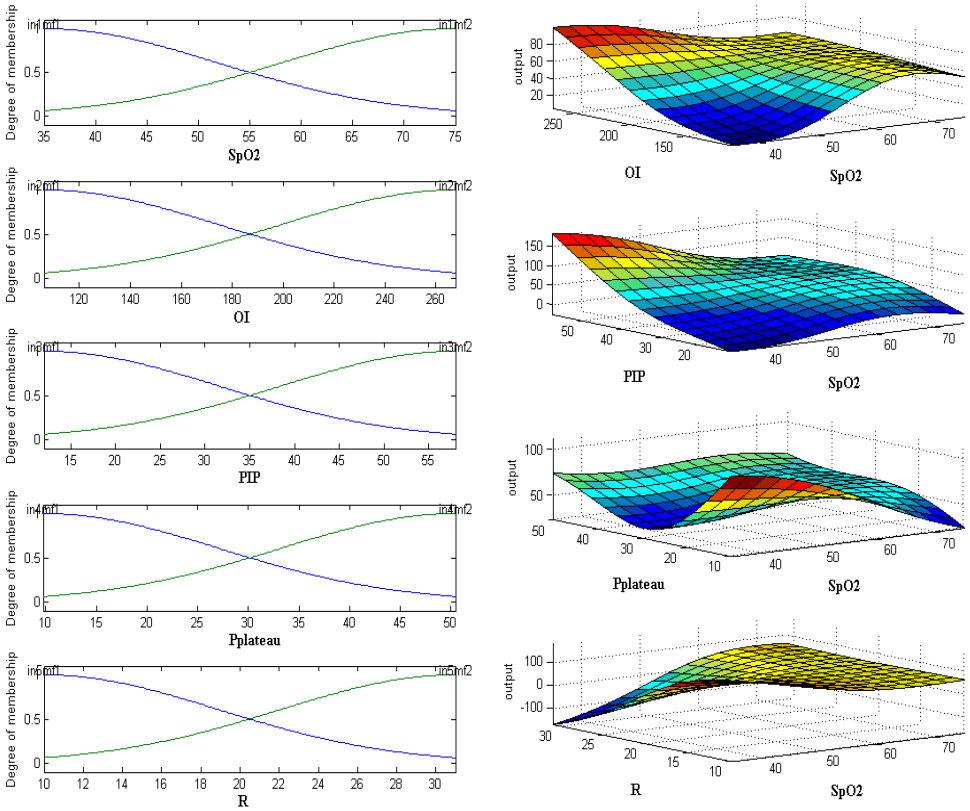

Figure 6.12: Resulted ANFIS FRBS architecture for the Fmax for the COPD Category.

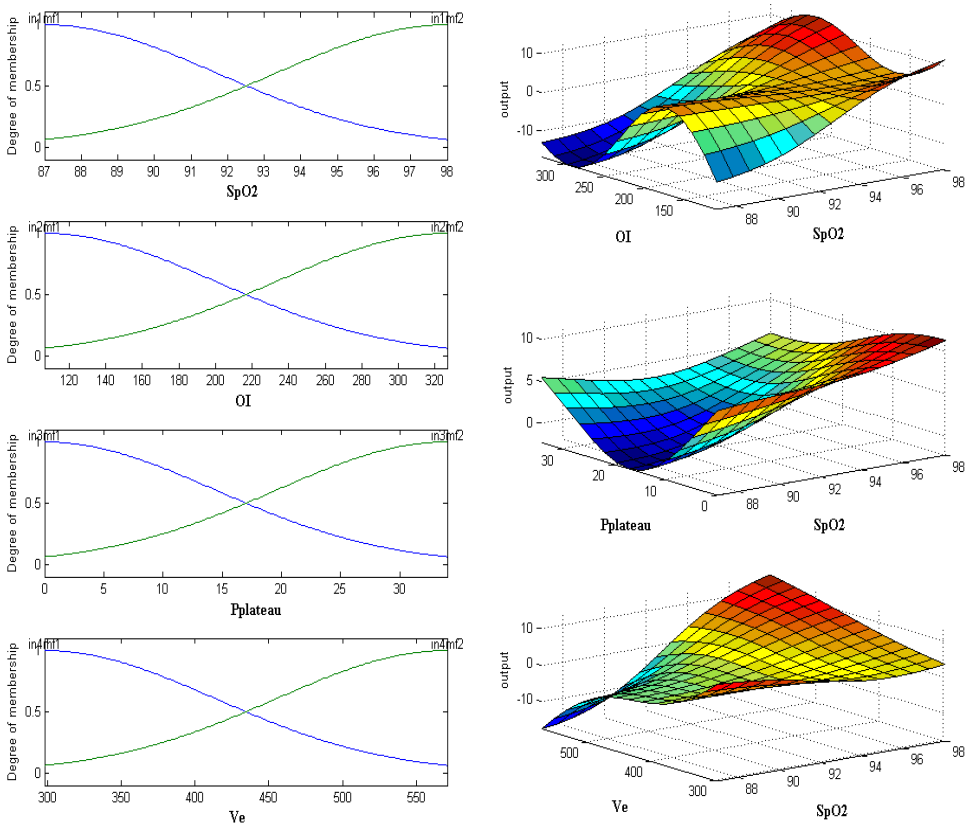

Figure 6.13: Resulted ANFIS FRBS architecture for the V_T for the ALI-ARDS Category.

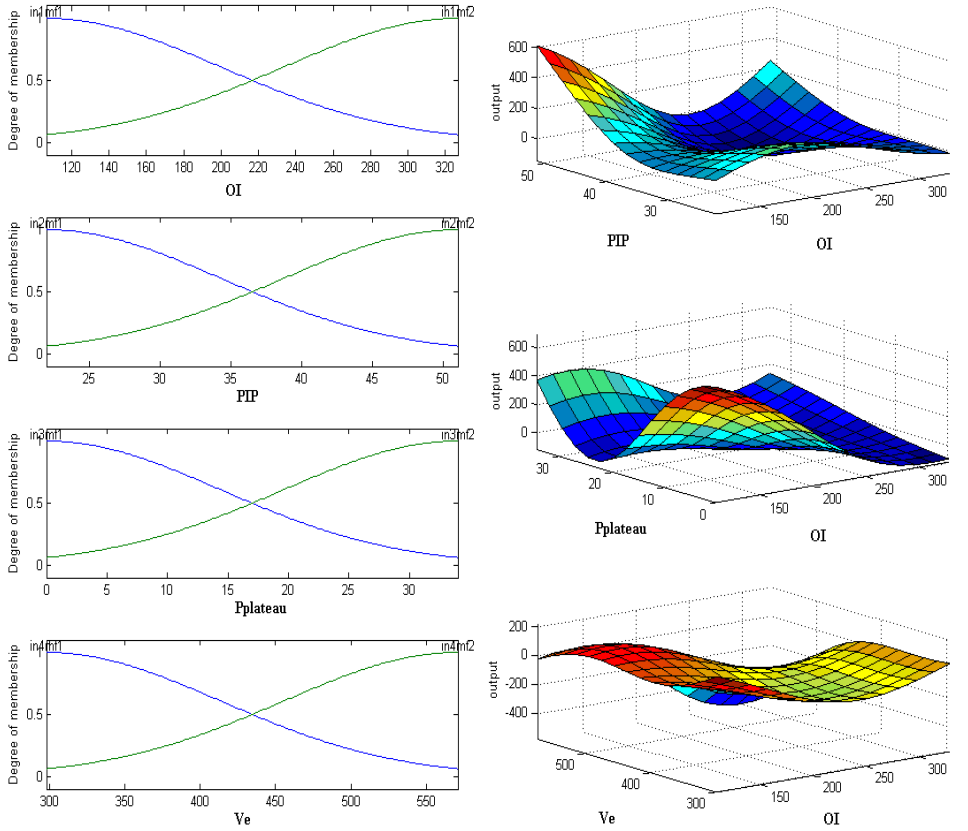

Figure 6.14: Resulted ANFIS FRBS architecture for the PEEP for the ALI-ARDS Category.

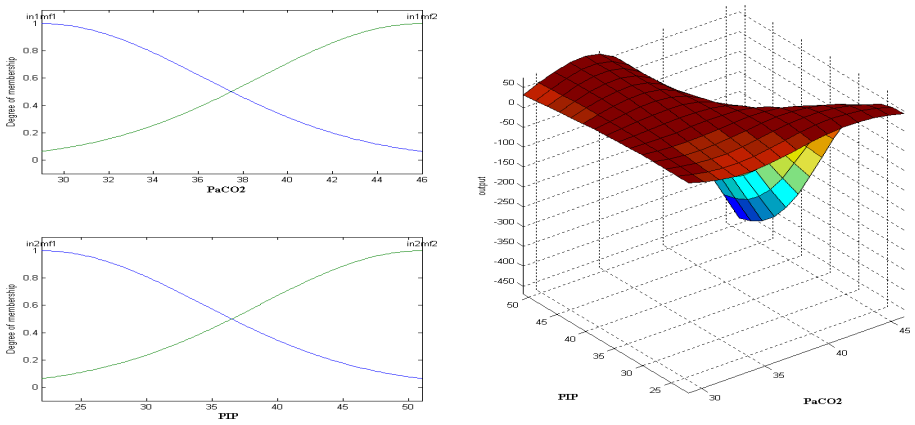

Figure 6.15: Resulted ANFIS FRBS architecture for the Fmax for the ALI-ARDS Category.

EVOFINE models (fig. 6.16 to 6.19) suffer from flat response. The flat response of the model is attributed to a simplification of the full architecture in terms of *full* RB. It is clear that when the *full* RB was applied, the surface mapping did not exhibit flat areas. However the *full* RB was used only in simple models, where the number of participating input variables was small. Furthermore the flat response of EVOFINE models could be attributed to non-representation of the specific area to the training data set. Example surface plots are:

- V_T model for Normal Category (fig. 6.16). The models utilized only 5% of the *full* RB architecture. Flat areas suggest no response thus any rules dictating the response of the model.
- FiO_2 model for Normal Category (fig. 6.17). In this case the full RB was applied (25 rules). There are no flat areas in the surface mapping of the resulted model.
- P*max* model for the Normal Category (fig. 6.18). In this case we observe that for a given combination of inputs (HR and PaO_2 or OI and PaO_2), the systems output is constant. One could argue that the specific inputs were not appropriately chosen for the model. However since the rules applied to this model represent only 2.5% of the full RB, it is expected that the system will remain "unconscious" for a given combination of inputs variables. If the choice of inputs was incorrect, then in all the models developed (ANN, FUN and ANFIS) for the same ventilator setting, response should be constant. Thus one could not attribute the constant response to the choice of input variables.

- PEEP model for ALI-ARDS category (fig. 6.19). In this case a subset (25%) of the *full* RB (625 Rules) was used for the development of the model and subsequently some rules do not apply.

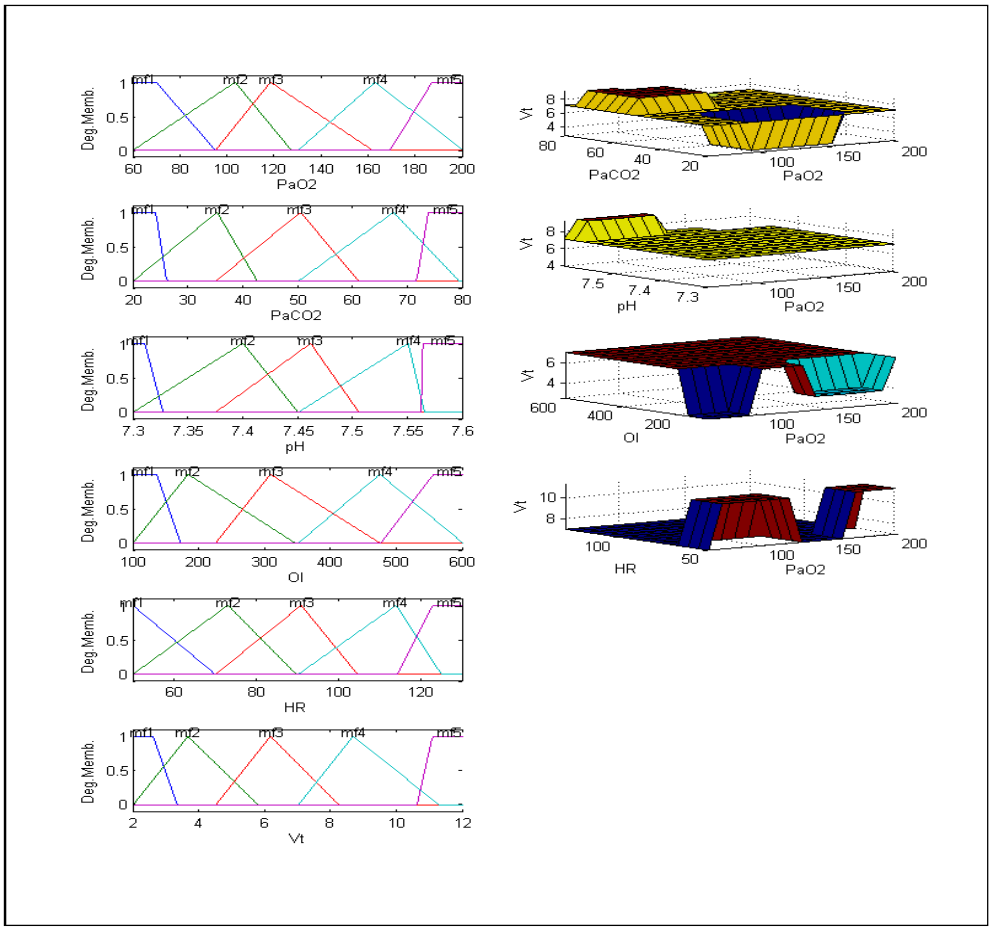

Figure 6.16: Resulted EVOFINE FRBS architecture for the V_T for the Normal Category.

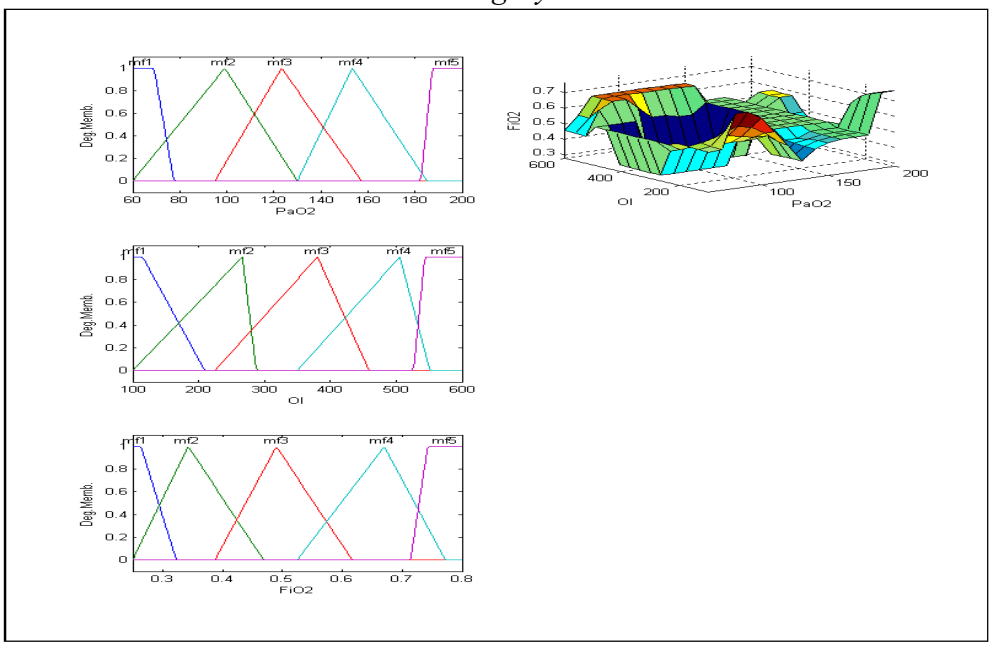

Figure 6.17: Resulted EVOFINE FRBS architecture for the FiO_2 for the Normal Category.

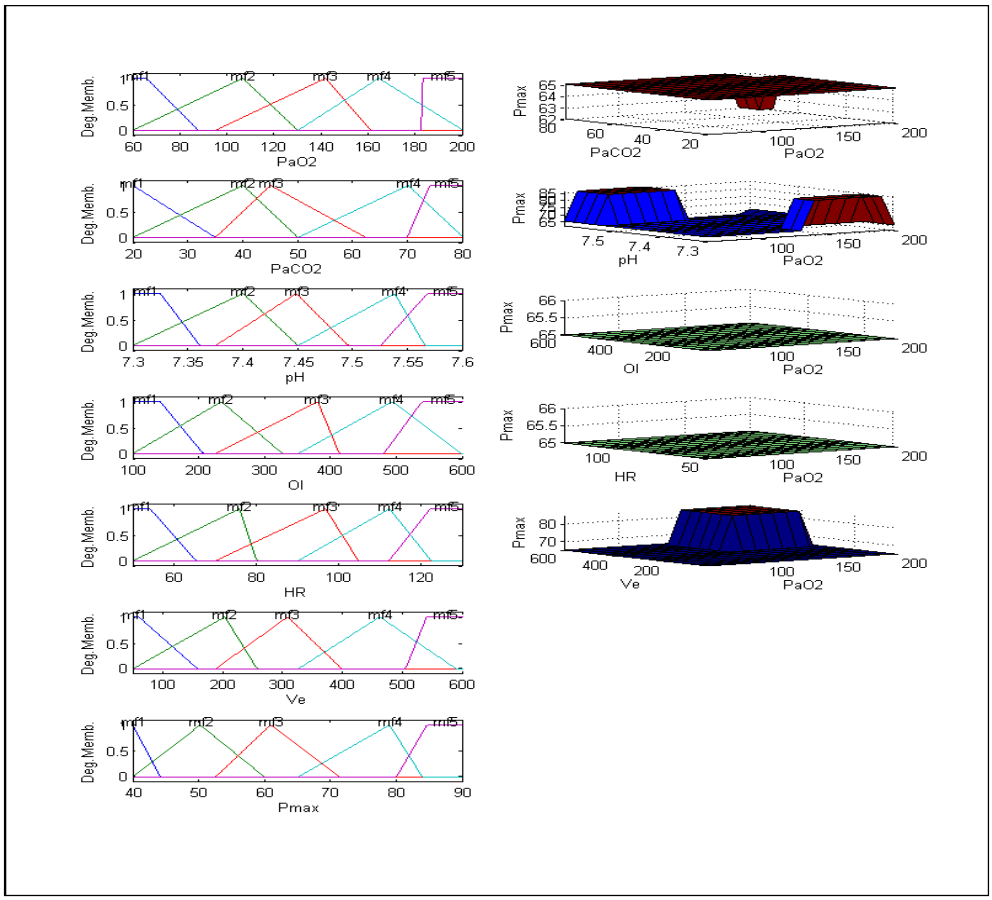

Figure 6.18: Resulted EVOFINE FRBS architecture for the Pmax for the Normal Category.

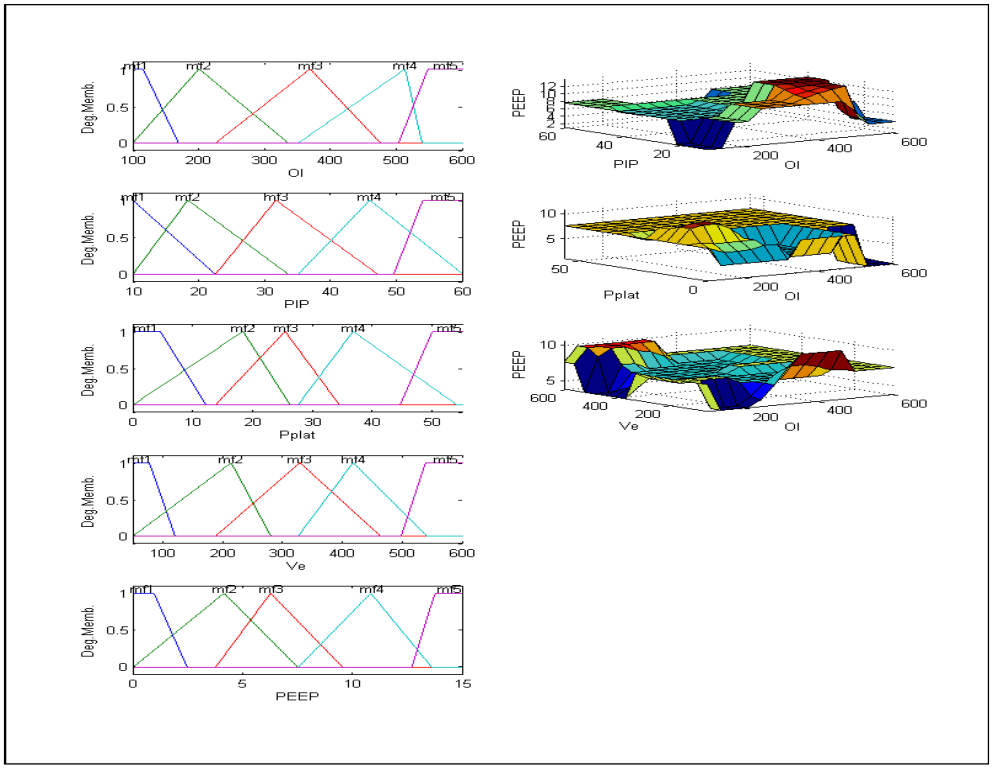

Figure 6.19: Resulted EVOFINE FRBS architecture for the PEEP for the ALI_ARDS Category.

6.5 Models Performance

The developed models performance was measured against the evaluation set. The performance was measured both in terms of mean absolute error (*mae*) and root mean square error (*rmse*), as described by equations 6.1 and II.1 (Appendix II) respectively. While the *mae* gives us a direct and comprehensive measure of the mean error between the model's output and the expected (data set) value, the use of the *rmse* provides us with a good comparison measurement between the training and the evaluation process.

The EVOFINE FRBSs, FUN, ANFIS and the ANN *Kolmogorov* models were tested against the *un*-normalized data sets. ANN *Normalized* and *empirical* models were tested against the normalized data sets. The difference in the type of the training sets reflects the difference in the training process. The *un*-normalized and the normalized sets are different representations of the recorded variables.

The model's performance is numerically presented in tables 6.21 to 6.23 and graphically in figures 6.20 to 6.22.

Comparison between different output variables could only be done with the use of percentage representations of errors (mae % and rmse %). The mean *mae* provides us with a measure of the overall performance of the toolbox for a specific lung category and data set.

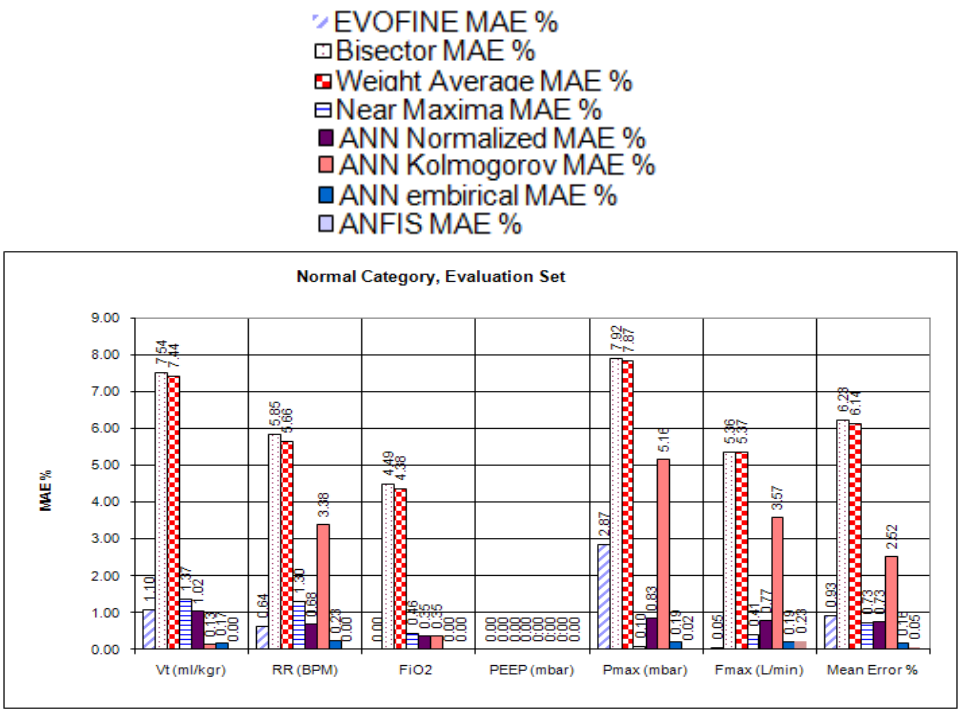

Figure 6.20: Performance, Normal Category, Evaluation set.

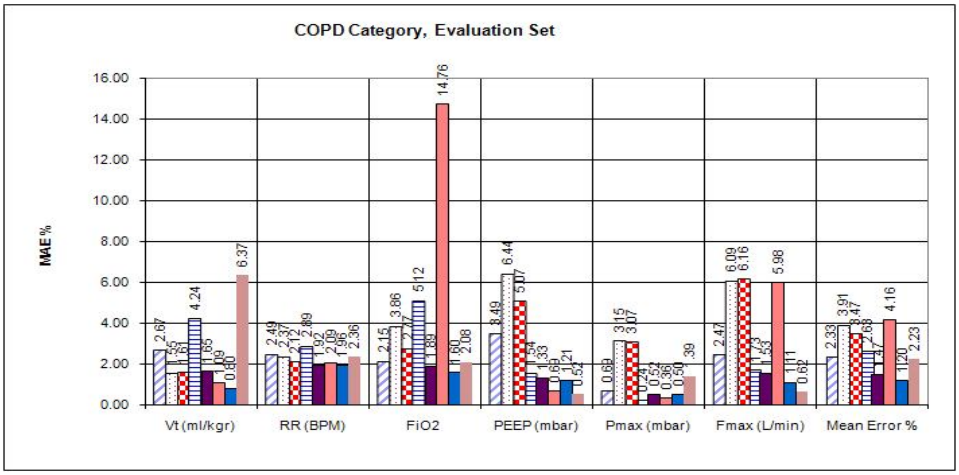

Figure 6.21: Performance, COPD Category, Evaluation set.

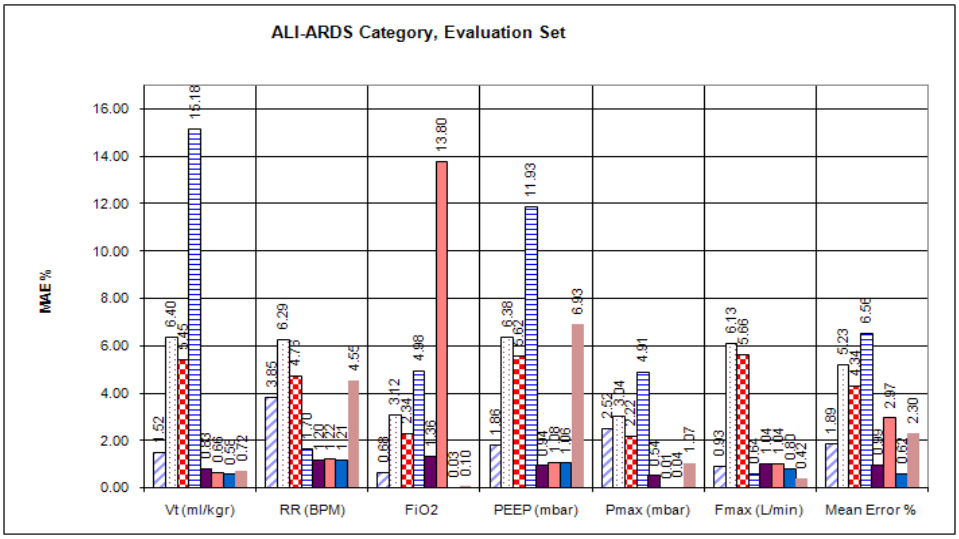

Figure 6.22: Performance, ALI-ARDS Category, Evaluation set.

Table 6.21: Performance, Normal Category, Evaluation Set.

Mean Error %	Fmax (L/min)	Pmax (mbar)	PEEP (mbar)	FiO2	RR (BPM)	Vt (ml/kgr)	EVOFINE	Bisector	Weighted Average	Near Maxima	ANN Normalized	ANN **Kolmogorov**	ANN **empirical**	**ANFIS**
	0.03	1.44	X	0.00	0.16	0.11	**EVOFINE MAE**	**FUN MAE**	**FUN MAE**	**FUN MAE**	**NN mae**	**NN mae**	**NN mae**	ANFIS MAE
0,93	**0.05**	**2.87**	**X**	**0.00**	**0.64**	**1.10**	**EVOFINE MAE %**	**FUN MAE %**	**FUN MAE %**	**FUN MAE %**	**NN mae %**	**NN mae %**	**NN mae %**	ANFIS MAE %
	0.07	1.52	X	0.00	0.41	0.17	**EVOFINE rMSE**	**FUN rMSE**	**FUN rMSE**	**FUN rMSE**	**NN rMSE**	**NN rMSE**	**NN rMSE**	ANFIS rMSE
	0.10	3.04	X	0.00	1.64	1.72	**EVOFINE rMSE %**	**FUN rMSE %**	**FUN rMSE %**	**FUN rMSE %**	**NN rMSE %**	**NN rMSE %**	**NN rMSE %**	ANFIS rMSE %
	3,49	3,96	X	0,02	1,46	0,75								
6,23	**5,36**	**7,92**	**X**	**4,49**	**5,85**	**7,54**								
	3,61	4,06	X	0,02	4,48	0,76								
	5,56	8,11	X	4,52	5,90	7,55								
	3,49	3,93	X	0,02	1,41	0,74								
6,14	**5,37**	**7,87**	**X**	**4,38**	**5,66**	**7,44**								
	3,56	4,09	X	0,02	1,44	0,75								
	5,48	8,18	X	4,42	5,75	7,48								
	0,27	0,05	X	0,00	0,33	0,14								
0,73	**0,41**	**0,10**	**X**	**0,46**	**1,30**	**1,37**								
	0,83	0,05	X	0,01	1,14	0,50								
	1,28	0,10	X	1,32	4,54	4,99								
	0,50	0,42	X	0,00	0,17	0,10								
0,73	**0,77**	**0,83**	**X**	**0,35**	**0,68**	**1,02**								
	0,72	0,46	X	0,00	0,28	0,21								
	1,10	0,92	X	0,89	1,10	2,15								
	2,32	2,58	X	0,00	0,85	0,01								
2,52	**3,57**	**5,16**	**X**	**0,35**	**3,38**	**0,13**								
	3,24	3,15	X	0,00	1,06	0,03								
	4,99	6,31	X	0,36	4,25	0,27								
	0,12	0,09	X	0,00	0,06	0,02								
0,16	**0,19**	**0,19**	**X**	**0,00**	**0,23**	**0,17**								
	0,21	0,28	X	0,00	0,17	0,04								
	0,32	0,56	X	0,01	0,67	0,36								
	0,15	0,01	X	0,00	0,00	0,00								
0,05	**0,23**	**0,02**	**X**	**0,00**	**0,00**	**0,00**								
	0,03	0,01	X	0,00	0,00	0,00								
	0,05	0,02	X	0,00	0,00	0,00								

Table 6.22: Performance, COPD Category, Evaluation Set.

Mean Error %	Fmax (L/min)	Pmax (mbar)	PEEP (mbar)	FiO2	RR (BPM)	Vt (ml/kgr)	EVOFINE	Bisector	Weighted Average	Near Maxima	ANN Normalized	ANN **Kolmogorov**	ANN **empirical**	ANFIS
							EVOFINE MAE	**FUN MAE**	**FUN MAE**	**FUN MAE**	**NN mae**	**NN mae**	**NN mae**	ANFIS MAE
							EVOFINE MAE %	**FUN MAE %**	**FUN MAE %**	**FUN MAE %**	**NN mae %**	**NN mae %**	**NN mae %**	ANFIS MAE %
							EVOFINE rMSE	**FUN rMSE**	**FUN rMSE**	**FUN rMSE**	**NN rMSE**	**NN rMSE**	**NN rMSE**	ANFIS rMSE
							EVOFINE rMSE %	**FUN rMSE %**	**FUN rMSE %**	**FUN rMSE %**	**NN rMSE %**	**NN rMSE %**	**NN rMSE %**	ANFIS rMSE %
	1.61	0.35	0.52	0.01	0.62	0.27								
2.33	**2.47**	**0.69**	**3.49**	**2.15**	**2.49**	**2.67**								
	4.61	1.86	0.73	0.03	0.96	0.55								
	7.09	3.72	4.85	5.78	3.82	5.48								
	3,96	1,57	0,97	0,02	0,59	0,16		0,16	0,16	0,42	0,16	0,11	0,08	0,64
3,91	**6,09**	**3,15**	**6,44**	**3,86**	**2,37**	**1,55**		**1,55**	**1,61**	**4,24**	**1,65**	**1,09**	**0,80**	**6,37**
	4,10	1,77	1,01	0,03	0,91	0,20		0,20	0,20	0,56	0,54	0,19	0,12	0,40
	6,31	3,54	6,75	5,41	3,63	2,01		2,01	2,03	5,63	5,37	1,92	1,24	3,96
	4,00	1,54	0,76	0,02	0,53	0,16								
3,47	**6,16**	**3,07**	**5,07**	**2,77**	**2,12**	**1,61**								
	4,18	1,79	0,79	0,03	0,80	0,20								
	6,43	3,57	5,26	4,71	3,19	2,03								
	1,13	0,12	0,23	0,03	0,72	0,42								
2,63	**1,73**	**0,24**	**1,54**	**5,12**	**2,89**	**4,24**								
	2,91	0,25	0,71	0,05	1,07	0,56								
	4,47	0,49	4,71	9,46	0,27	5,63								
	1,00	0,26	4:47	0,01	0,48	0,16								
1,47	**1,53**	**0,52**	**7:56**	**1,89**	**1,92**	**1,65**								
	1,83	0,58	7:40	0,03	0,70	0,54								
	2,82	1,15	3:09	4,95	2,81	5,37								
	3,89	0,18	0,10	0,08	0,52	0,11								
4,16	**5,98**	**0,36**	**0,69**	**14,76**	**2,09**	**1,09**								
	6,09	0,68	0,21	0,45	0,75	0,19								
	9,37	1,37	1,41	81,56	3,00	1,92								
	0,72	0,25	4:21	0,01	0,49	0,08								
1,20	**1,11**	**0,50**	**5:02**	**1,60**	**1,96**	**0,80**								
	1,26	0,51	10:43	0,02	1,06	0,12								
	1,94	1,02	23:33	3,84	4,22	1,24								
	0,41	0,70	0,08	0,01	0,59	0,64								
2,23	**0,62**	**1,39**	**0,52**	**2,08**	**2,36**	**6,37**								
	0,30	0,07	0,03	0,00	0,11	0,40								
	0,46	0,13	0,17	0,30	0,44	3,96								

Table 6.23: Performance, ALI-ARDS Category, Evaluation Set.

Mean Error %	Fmax (L/min)	Pmax (mbar)	PEEP (mbar)	FiO2	RR (BPM)	Vt (ml/kgr)	EVOFINE	Bisector	Weighted Average	Near Maxima	ANN Normalized	ANN **Kolmogorov**	ANN **empirical**	**ANFIS**
							EVOFINE MAE	**FUN MAE**	**FUN MAE**	**FUN MAE**	**NN MAE**	**NN mae**	**NN mae**	**ANFIS MAE**
							EVOFINE MAE %	**FUN MAE %**	**FUN MAE %**	**FUN MAE %**	**NN MAE %**	**NN mae %**	**NN mae %**	**ANFIS MAE %**
							EVOFINE rMSE	**FUN rMSE**	**FUN rMSE**	**FUN rMSE**	**NN rMSE**	**NN rMSE**	**NN rMSE**	**ANFIS rMSE**
							EVOFINE rMSE %	**FUN rMSE %**	**FUN rMSE %**	**FUN rMSE %**	**NN rMSE %**	**NN rMSE %**	**NN rMSE %**	**ANFIS rMSE %**
							0.15	0,64	0,55	1,52	0,08	0,07	0,06	0,07
							0.96	1,57	1,19	0,43	0,30	0,30	0,30	1,14
							0.28	0,96	0,84	1,79	3:23	0,16	3:49	1,04
							1.26	1,52	1,11	2,46	0,27	0,00	0,02	0,54
							0.60	3,98	3,68	0,42	0,68	0,67	0,52	0,27
1.89							**0.93**	**6,13**	**5,66**	**0,64**	**1,04**	**1,04**	**0,80**	**0,42**
							1.24	4,03	3,78	1,19	1,36	1,46	0,88	0,07
							1.91	6,20	5,81	1,53	2,09	2,24	1,36	0,10
							0.00	0,02	0,01	0,03	0,01	0,08	0,00	0,00
							0.68	**3,12**	**2,34**	**4,98**	**1,36**	**13,80**	**0,03**	**0,10**
							0.01	0,02	0,01	0,04	0,02	0,38	0,01	0,00
							2.05	3,59	2,65	6,45	3,78	69,62	1,82	0,06
							0.96	1,57	1,19	0,43	0,30	0,30	0,30	1,14
							3.85	**6,29**	**4,76**	**1,70**	**1,20**	**1,22**	**1,21**	**4,55**
							1.22	1,61	1,25	0,95	0,71	0,71	0,71	0,17
							4.88	6,43	5,01	3,80	2,82	2,83	2,82	0,67
							0.15	0,64	0,55	1,52	0,08	0,07	0,06	0,07
							1.52	**6,40**	**5,45**	**15,18**	**0,83**	**0,66**	**0,58**	**0,72**
							0.37	0,66	0,57	1,61	0,12	0,13	0,13	0,03
							3.68	6,58	5,67	15,10	1,16	1,29	1,34	0,26
5,23														
4,34														
6,56														
0,99														
2,97														
0,62														
2,30														

6.6 Intelligent Models Advice against Clinician Recommendations

The graphical and numerical representation of the mean errors provides us with information about the overall performance of the developed models. In order to present more accurately the performance of the models in the following figures the graphical representation of the suggested output value (blue dashed line) and the relevant clinical decision (red solid line) for the evaluation data is presented.

Clinical decisions made on ventilator settings occur at variable time intervals, depending on physiology status of the patient and on personnel availability. The intelligent models derive with suggestions in each data set presented to the model. The proposed models do not account for the temporal changes of the data set. The data sets present patient health status in 5 minute intervals, as it has already been discussed (section 5.3). The models output exhibits in most of the cases a variation around clinical decisions. This is attributed to the fact that models respond to changes in the physiology recorded values.

Observing figures 6.23 to 6.39, as a general rule there no directionality of the models' output against clinicians' choices. The models' outputs follow in general the variation of clinicians' choices.

Important observations in EVOFINE models performance against evaluation sets are as follows:

- Fig. 6.23, Tidal volume (ALI-ARDS), shows a peak value in the opposite direction of clinicians' suggestions.
- Fig. 6.24, Tidal volume (COPD), shows large deviations from the suggested clinical decisions.
- Fig. 6.30, FiO_2 (COPD), in one occasion, the suggestion is in the opposite direction to clinician's advice.
- Fig. 6.34, Pmax (Normal) has a slightly elevated out in comparison to clinicians advice.
- Fig. 6.36, Fmax (COPD) is producing in three occasion's very low advice on ventilation flow.
- Fig. 6.39, PEEP (COPD), is constantly suggesting larger PEEP values

Important observations in FUN models performance against evaluation sets are as follows:

- Fig. 6.23, modelling the V_T for ARDS category performance is poor the advices of the FUN model were implemented in the opposite direction to clinicians' decisions.
- Bisector and Weighted Average techniques were constantly producing large errors, with mean errors for each category above 3% (fig. 6.25). It seems that most of the cases the trained ANN fires more than one membership degrees for each element in the data set, leading to a shift of the produced output. Since the NOM technique ignores the less important membership functions, this feature is not present in the simulation results of NOM FUN models.

Important observations in ANN models performance against evaluation sets are as follows:

- In the simulation of the *ANN Kolmogorov* models, the Fmax for COPD (fig. 6.36) and the Pmax for the Normal category (fig. 6.34), the models' output was constant. The characteristics of the model, such as architecture, number and type of input variable, do not provide us with an obvious reason for the constant response of the model. If the number and type of input variables was incorrectly chosen for the model, then the same deterioration in performance should occur also to the other ANN models. Since this is not the case, one could only assume that the type of ANN could not efficiently map the specific variable.
- ANNs with only one input as in Pmax model for ALI-ARDS (fig. 6.32), have inadequate architectures. However the performance of the trained ANN in such simplified architectures was better than other methods such as FUN; FUN was expected to have better performance in such SISO architectures due to translation of crisp values to N membership degrees prior to NN training.
- ANN Models' suggestions are very responsive to physiology variables changes. Output in most cases constantly fluctuates around clinical decisions, suggesting slight changes for improving ventilation.

Important observations in ANFIS models performance against evaluation sets are as follows:

- ANFIS in general follows very closely clinical decisions. However in the case of PEEP model for ALI-ARDS category (fig. 6.38) suggestions could be hazardous to the patient.
- Tidal Volume ANFIS model in COPD model (fig. 6.24), suggest negative volume. This is clinically impossible.

The key observations from the models' suggestions against the clinical advice are summarized to the following paragraphs:

- In general EVOFINE, NN and ANFIS models have closely mapped clinical decision making pattern. However the models seem to be more responsive to variations of the physiology variables than the clinicians' recommendations. This is shown as fluctuations of the models' suggestions around clinical decisions (e.g. fig. 6.27).
- FUN models' performance depends highly on the defuzzification method. In many of the evaluated FUN models there is a directionality of the suggested settings (e.g. fig. 6.25).
- In several cases, such as VT, RR, FiO2 and PEEP models for COPD category (figs 6.24, 6.27, 6.30 and 6.39 respectively) some models agree on different settings than the clinical advice. This suggests that the models have mapped in a similar way a given input – output relationship, described by the data set. The difference between the clinician and the models' suggestions could be attributed to disagreement between models and clinicians or to the no availability of a clinician at the specific time, represented by the data set. The second assumption highlights the importance of the application of the evaluated models to the ventilation management process since the models are continuously available, adopting the ventilation strategy to physiology changes.
- Although ANFIS models map closely clinical suggestions, in several cases they produce advice potentially hazardous to the patient (fig. 6.38 and 6.24). This problem has also been discussed in section 6.4.2, through the observation of the ANFIS surface mapping of the systems' response.

Additionally since the details of the ANNs decision making process has not been explored (through rule extraction techniques), the same problem could potentially apply to some of the ANN models. Thus prior to clinical application of the evaluated models it is important to apply safeguarding algorithms against excess model's advice.

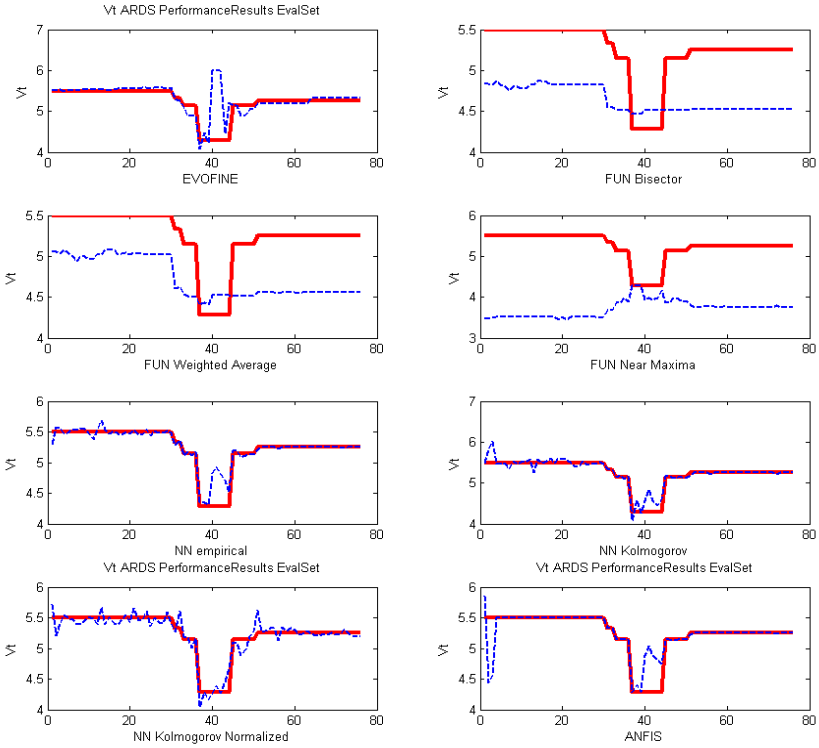

Figure 6.23: Model's Output (blue dashed) vs. clinical decisions (red solid), for Tidal Volume in ALI-ARDS lung category.

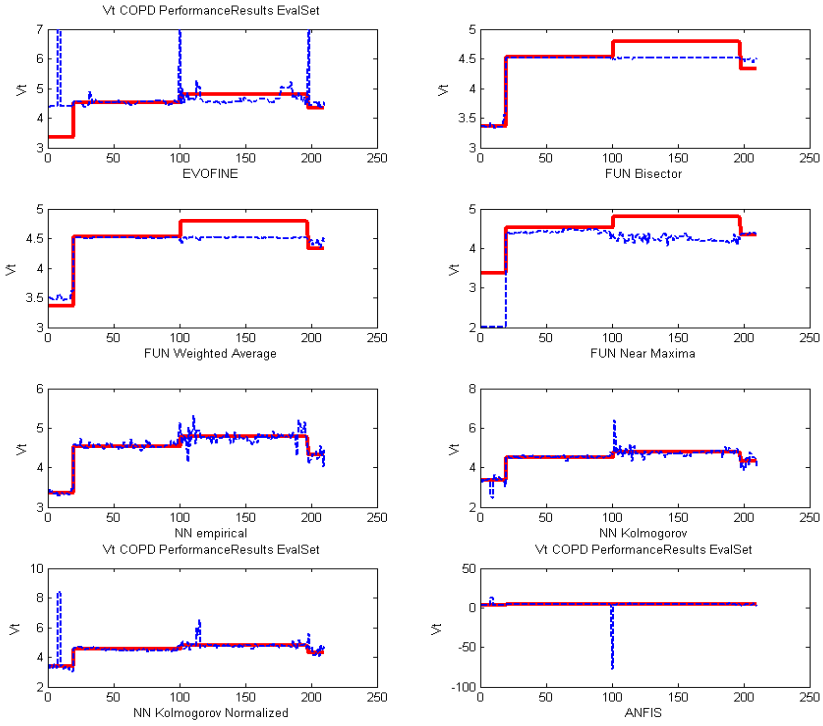

Figure 6.24: Model's Output (blue dashed) vs. clinical decisions (red solid), for Tidal Volume in COPD lung category.

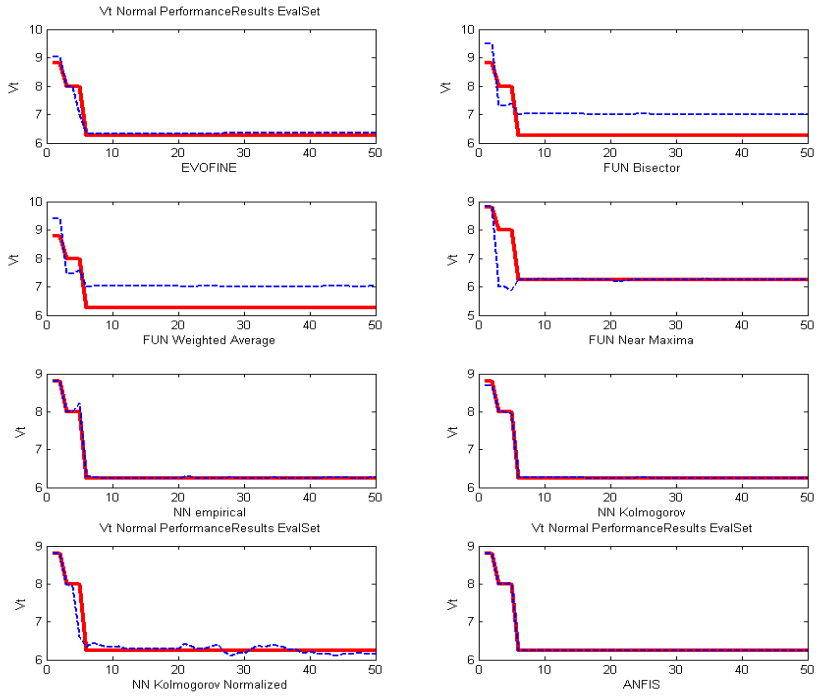

Figure 6.25: Model's Output (blue dashed) vs. clinical decisions (red solid), for Tidal Volume in Normal lung category.

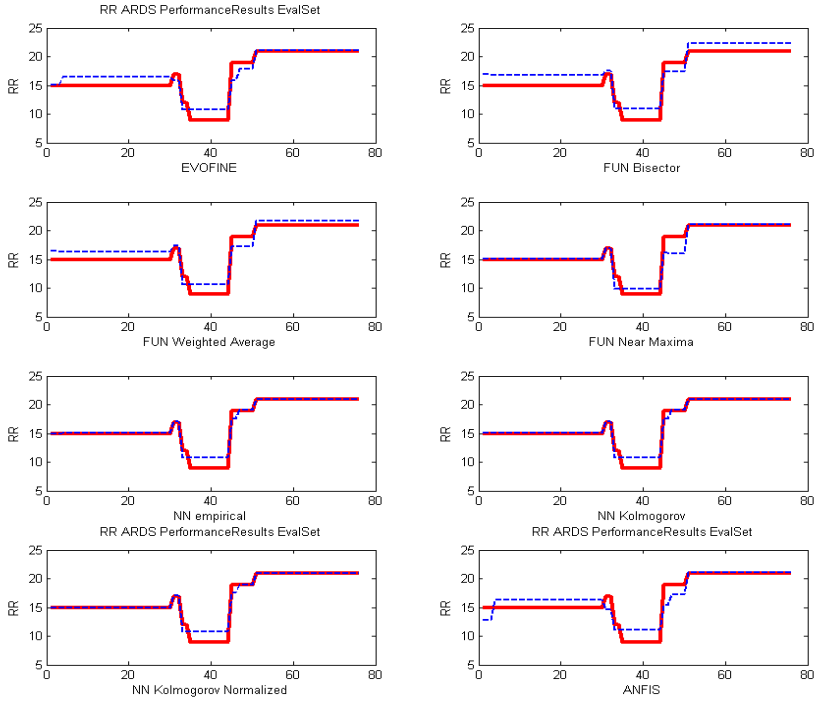

Figure 6.26: Model's Output (blue dashed) vs. clinical decisions (red solid), RR in ALI-ARDS lung category.

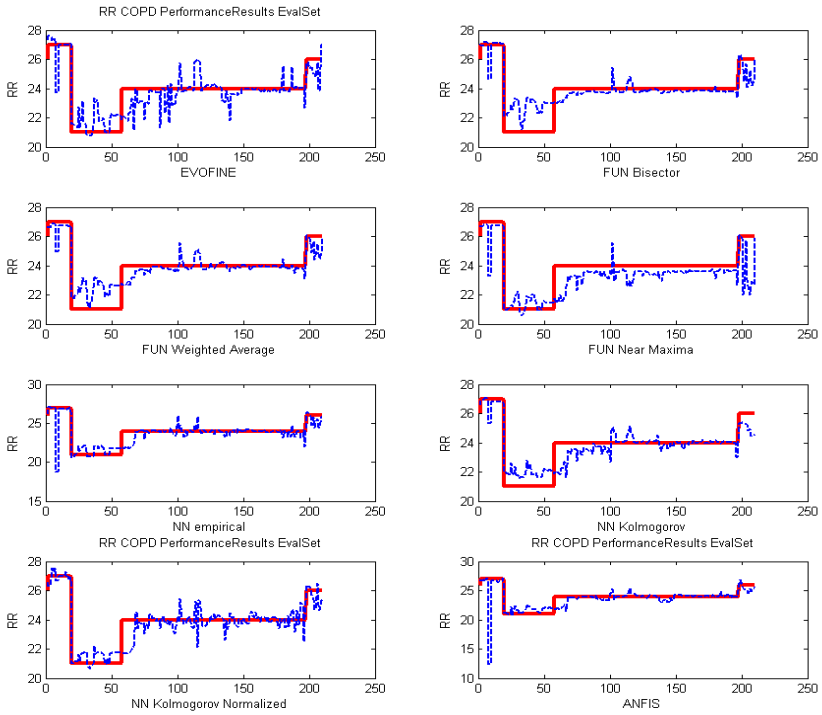

Figure 6.27: Model's Output (blue dashed) vs. clinical decisions (red solid), RR in COPD lung category.

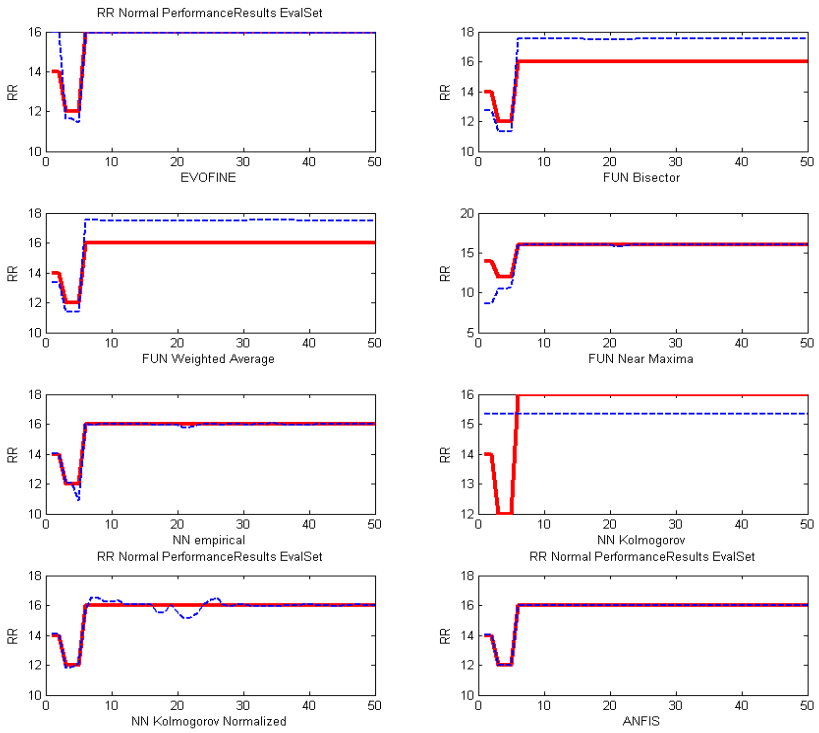

Figure 6.28: Model's Output (blue dashed) vs. clinical decisions (red solid), RR in Normal lung category.

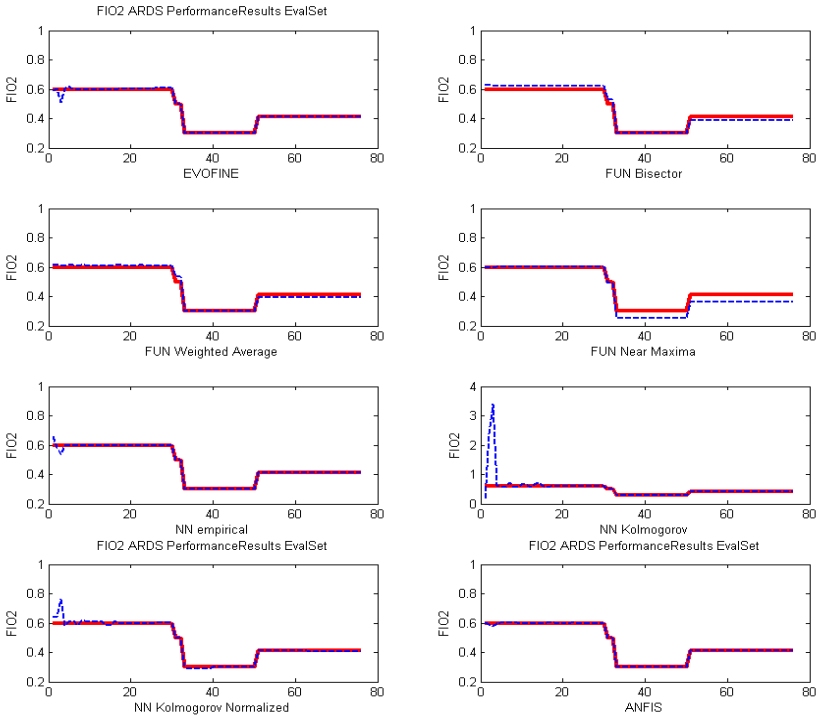

Figure 6.29: Model's Output (blue dashed) vs. clinical decisions (red solid), FiO_2 in ALI-ARDS lung category.

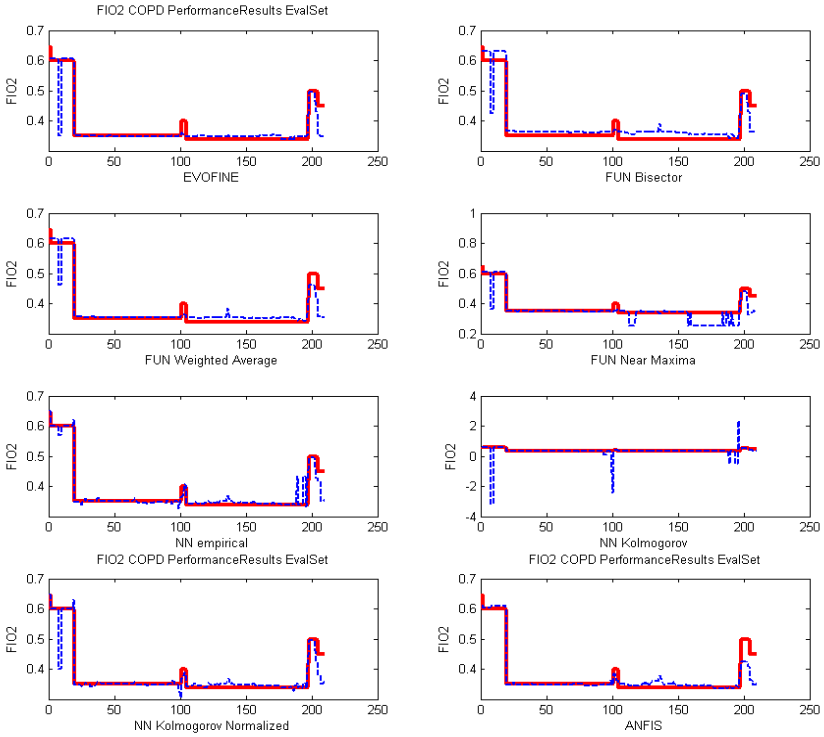

Figure 6.30: Model's Output (blue dashed) vs. clinical decisions (red solid), FiO_2 in COPD lung category

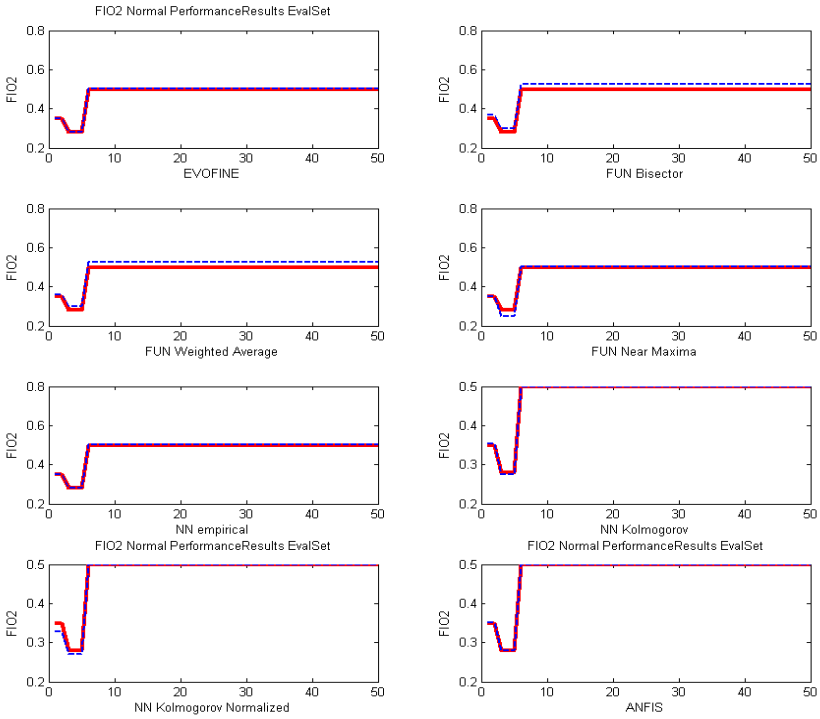

Figure 6.31: Model's Output (blue dashed) vs. clinical decisions (red solid), FiO_2 in Normal lung category .

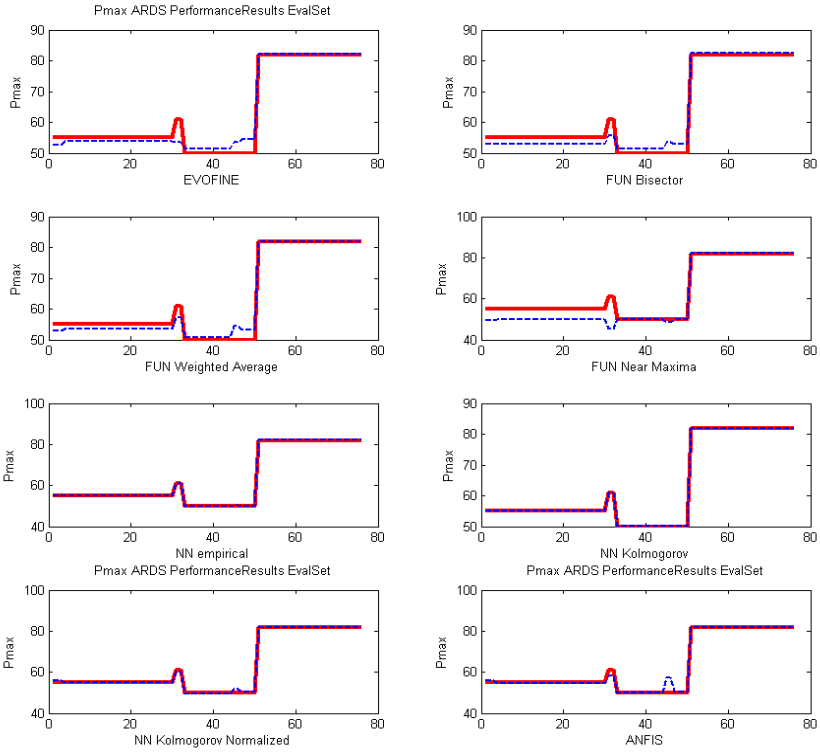

Figure 6.32: Model's Output (blue dashed) vs. clinical decisions (red solid), Pmax in ALI-ARDS lung category.

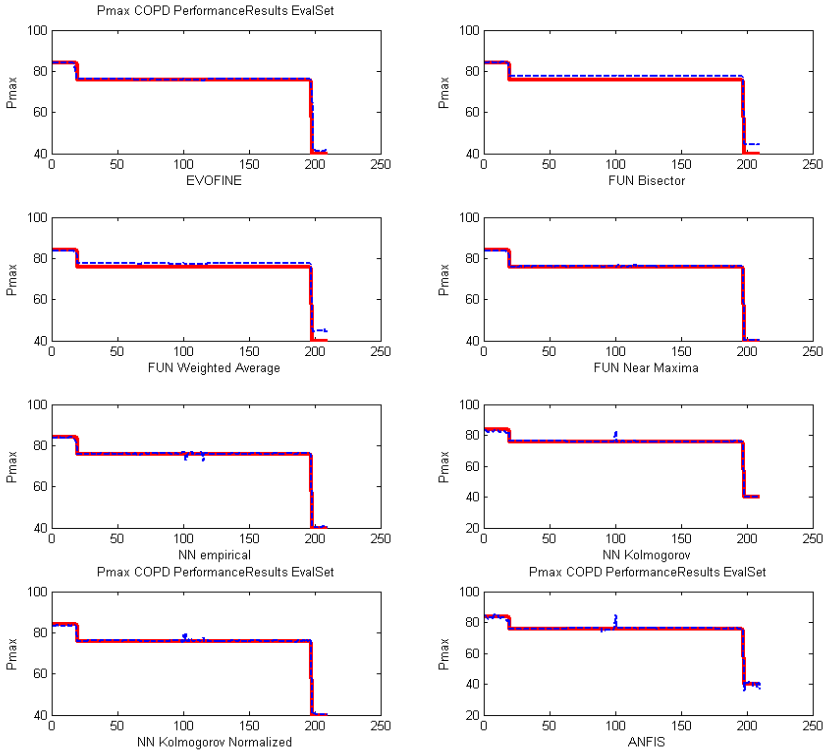

Figure 6.33: Model's Output (blue dashed) vs. clinical decisions (red solid), Pmax in COPD lung category.

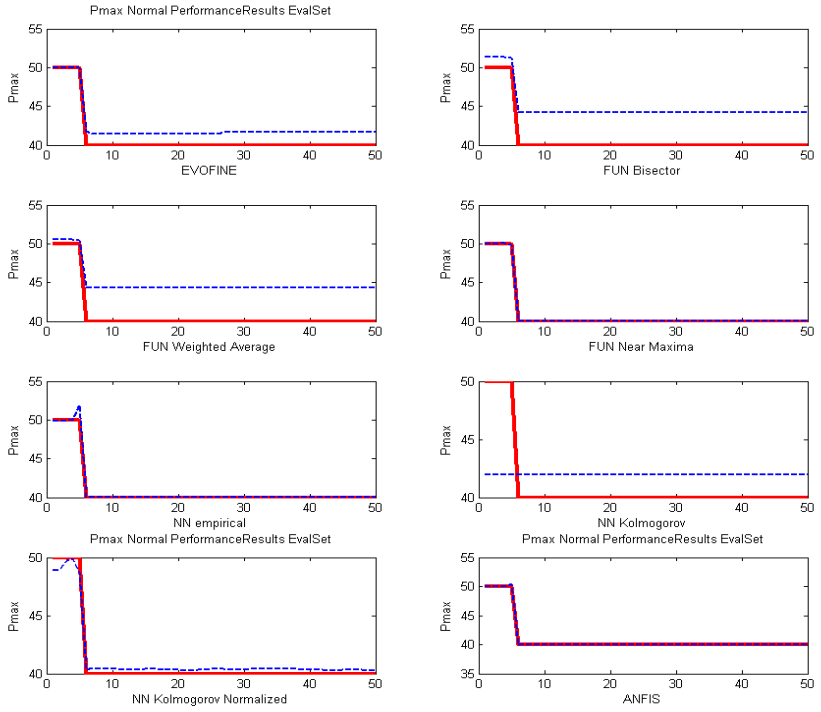

Figure 6.34: Model's Output (blue dashed) vs. clinical decisions (red solid), Pmax in Normal lung category.

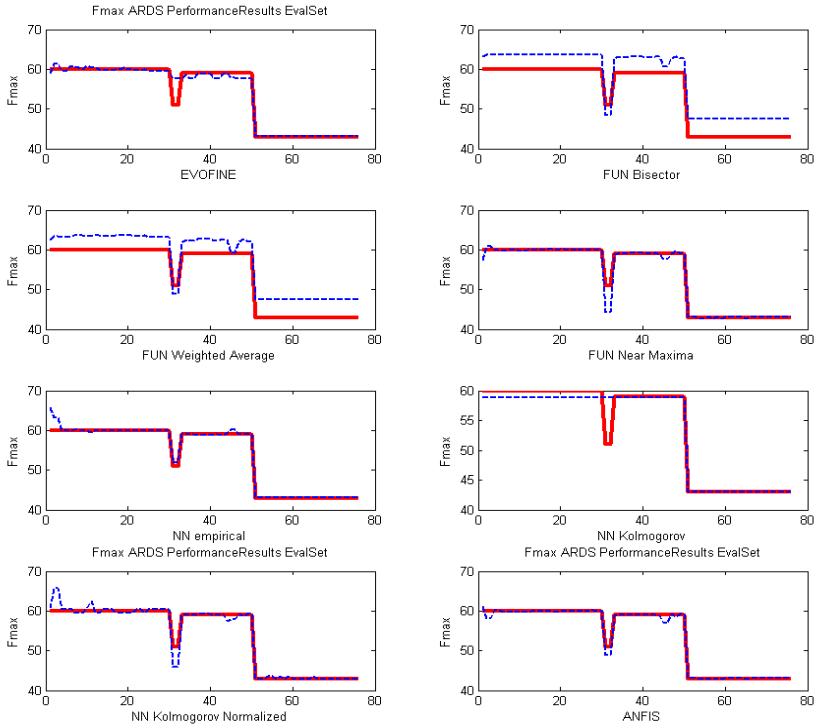

Figure 6.35: Model's Output (blue dashed) vs. clinical decisions (red solid), Fmax in ALI-ARDS lung category.

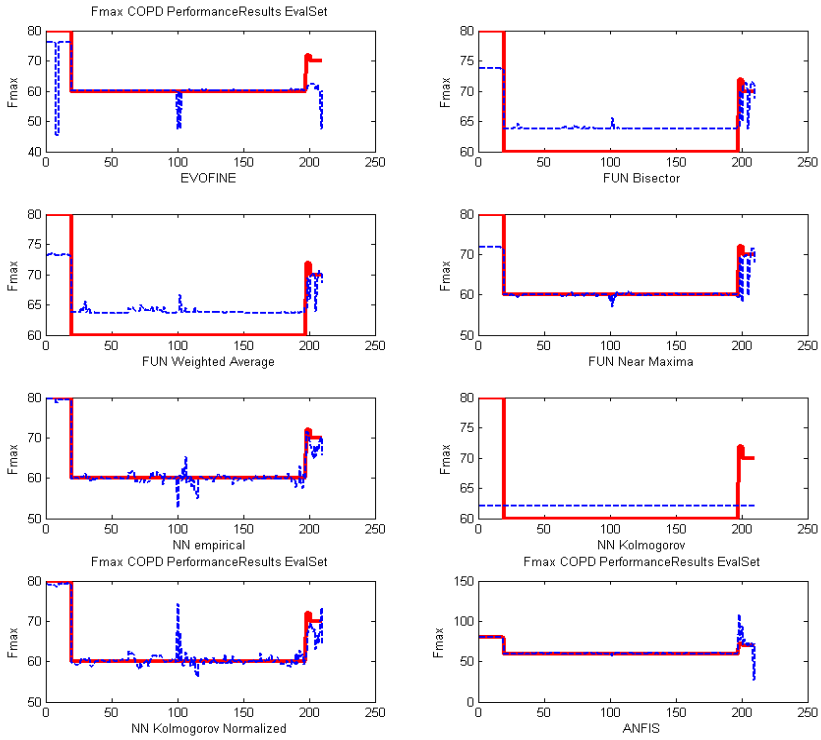

Figure 6.36: Model's Output (blue dashed) vs. clinical decisions (red solid), Fmax in COPD lung category.

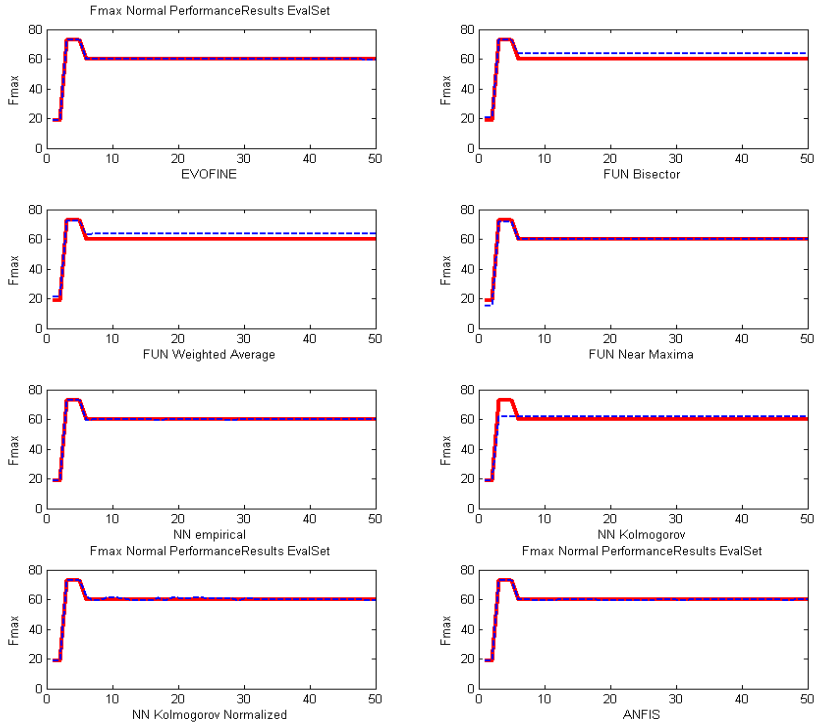

Figure 6.37: Model's Output (blue dashed) vs. clinical decisions (red solid), Fmax in Normal lung category.

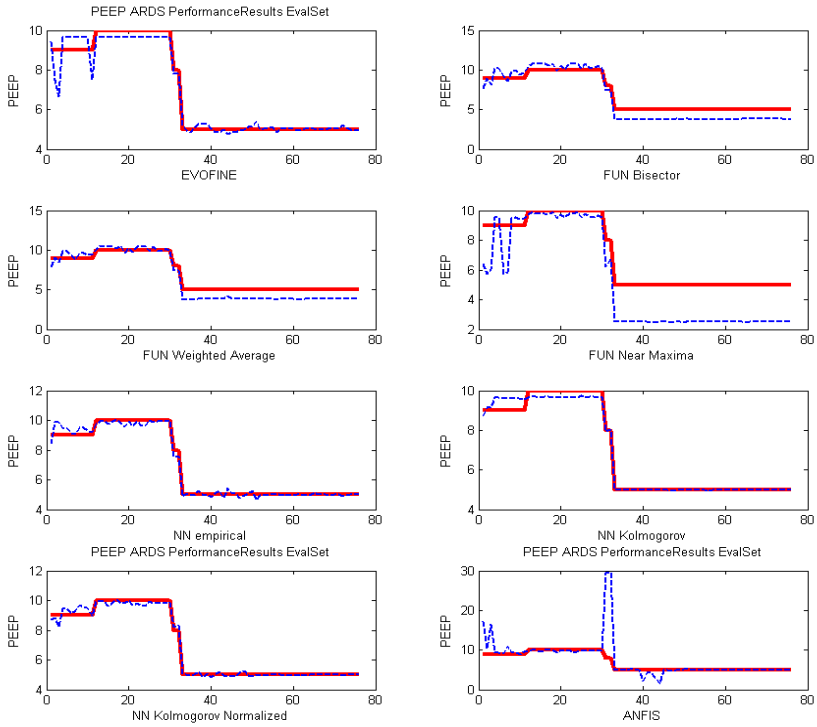

Figure 6.38: Model's Output (blue dashed) vs. clinical decisions (red solid), PEEP in ALI-ARDS lung category.

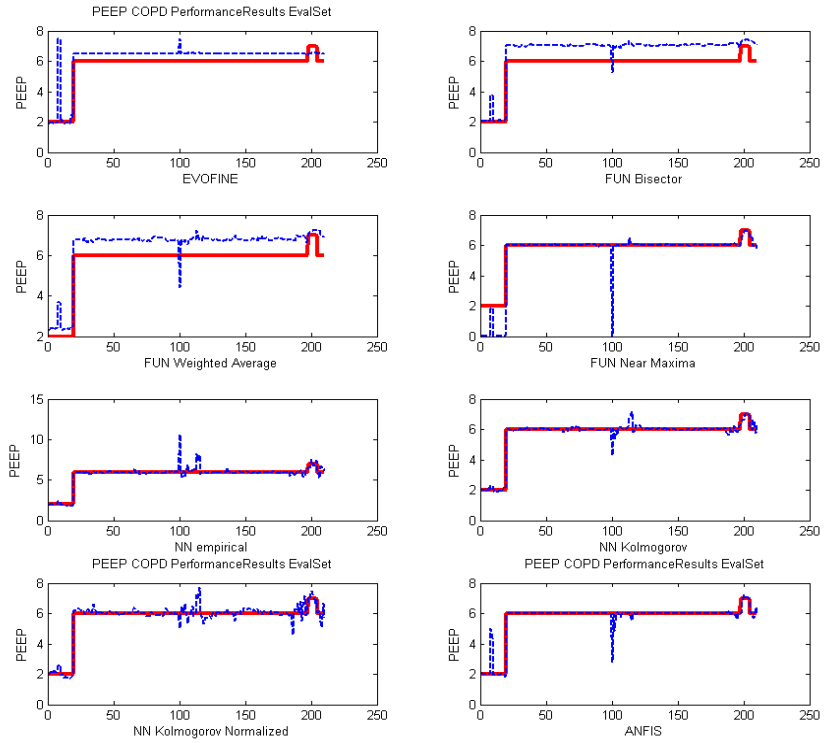

Figure 6.39: Model's Output (blue dashed) vs. clinical decisions (red solid), PEEP in COPD lung category.

6.7 Patient Scenarios

The evaluation of the developed models with the use of the evaluation sets, gives us the accuracy of predictions of the models against real data. However the recorded data represent choices made by ICU clinicians based on their expertise and experience and could not be considered as the only solution to a medical decision making process.

In order to examine whether the intelligent models suggestions are within the experts disagreement span, patient scenarios were developed. The scenarios were developed from the available recorded data and thus they reflect real patient cases. ICU doctors were provided with the basic lung pathology, Normal lungs, ALI-ARDS or COPD, with the demographic data related to ventilation settings and the time variations of the physiology variables similar to the inputs of our developed models. Doctors were asked to advice on the appropriate ventilation settings, similar to the outputs of our models. An example COPD patient scenario is presented in table 6.24.

The scenarios were circulated to three ICU doctors of the NIMITS hospital. Each doctor made their decisions independently in order to avoid bias. The answers were statistically analyzed and are presented in table 6.25.

As results in table 6.25 suggest and as we anticipated, clinical decisions exhibit variation among peers. This is mainly attributed to the differences in doctor's experience and expertise, to the different approaches in ventilation management, to the lack of direct interaction with the patient and the lack of prescribed medications in the presented scenarios.

The collected responses were analyzed based on the *range* of clinical decisions, and the standard deviation (SD) of answers as described by equations 6.3 and 6.4.

$$range = X_{\max} - X_{\min} \qquad \text{eq. 6.3a}$$

$$\%range = \left(X_{\max} - X_{\min}\right) * 100 / \left(MAX_{value} - MIN_{value}\right) \qquad \text{eq. 6.3b}$$

$$SD = \sqrt{\sum_{i=1}^{n} \left(X_i - \overline{X}\right) / (n-1)} \qquad \text{eq. 6.4}$$

Where: n is the available number of data, $\overline{X}$ *is the mean value and* MAX_{value}, MIN_{value} *is the ventilator settings maximum and minimum values in the recorded data as given in table AV.1.*

The largest range in decisions is observed in Pmax and Fmax ventilator settings in all lung categories. The smallest range is observed in FiO_2 settings. The use of % *range* allows direct comparison between different ventilator settings. Although in numerical terms FiO2 range was small, expressed as a percentage displays large variations in Normal and ALI-ARDS lung categories. In both cases in scenario 1, doctors have suggested settings with 18% difference between them.

Table 6.24: COPD example of patient scenario.

Sex	Male	**Height**	1,75 m	**Weight**	75Kgr	**Age**	48					
Time	SpO2	PaO2	PaCO2	pH	O2 Index	PIP (mbar)	Plateau (mbar)	C (l/bar)	R (mbar/L/s)	HR	HCO3	Ve
15:30	94	71	69	7,4	203	36	0	26	18	61	44	354
16:00	94	71	69	7,4	203	37	0	23	18	62	44	346
16:30	94	71	69	7,4	203	35	0	26	17	62	44	369
17:00	94	76	73	7,4	217	33	0	25	14	62	46	334
18:00	92	76	73	7,4	217	35	0	28	16	71	46	351
18:30	90	76	73	7,4	217	34	0	23	22	71	46	348
19:00	94	76	73	7,4	217	37	0	26	19	65	46	351
19:30	95	76	73	7,4	217	36	0	28	17	62	46	353
20:00	95	76	73	7,4	217	36	0	26	19	58	46	324
20:30	94	76	73	7,4	217	36	0	28	17	60	46	330
21:00	93	76	73	7,4	217	37	0	22	18	64	45	340
21:30	93	76	73	7,4	217	36	0	26	17	64	45	340
22:00	93	76	73	7,4	217	35	0	28	17	64	45	360
22:30	94	76	73	7,4	217	35	0	26	17	65	45	341
23:00	94	76	73	7,4	217	38	0	27	19	64	45	362
23:30	94	76	73	7,4	217	36	0	26	17	62	45	359
0:00	94	76	73	7,4	217	36	0	26	17	63	45	360
0:05	95	76	73	7,4	217	36	0	30	18	61	45	365
0:10	94	76	73	7,4	217	35	0	30	18	61	45	353

Please Advice on the Appropriate Ventilation Settings

Vt (ml/kgr)	**RR (BPM)**	**PEEP (mbar)**	**FiO2**	**Max Insp P (mbar)**	**Max Flow (L/min)**

Tidal Volume and RR exhibited small differences in the range of 5 to 10% with the exception of RR in Scenario 2 for ALI-ARDS and Normal lung category. However a numeric value of 1 ml/Kg for the tidal volume is translated as a difference of 75 ml for a patient of 75 Kg.

Doctors' answers and analysis supports the argument that clinical decisions for the ventilation management process show large variations. Thus a measure of performance of a model should not only be the performance of the model against available data, but also in terms of providing results that are within the range of clinicians' advice.

Mwan values	ARDS mean values	ALI-ARDS		COPD mean values	COPD				Normal mean values	Normal			
		2	1		4	3	2	1		2	1	or	
		7,00	7,00		6,67	6,11	5,45	6,67		7,00	7,00	1	Vt (ml/Kg r)
		8,00	7,00		6,67	6,11	5,91	7,33		8,00	7,00	2	
		8,00	7,50		7,73	6,67	5,45	6,67		8,00	7,50	3	
0,73	0,75	1,00	0,50	0,69	1,07	0,56	0,45	0,67	0,75	1,00	0,50		Range
7,29	7,50	10,00	5,00	6,86	10,67	5,56	4,55	6,67	7,50	10,00	5,00		% Range
0,42	0,43	0,58	0,29	0,40	0,62	0,32	0,26	0,38	0,43	0,58	0,29		SD
		20,00	16,00		12,00	14,00	12,00	14,00		20,00	16,00	1	RR (bpm)
		16,00	16,00		14,00	12,00	12,00	14,00		16,00	16,00	2	
		18,00	16,00		12,00	12,00	14,00	16,00		16,00	16,00	3	
2,00	2,00	4,00	0,00	2,00	2,00	2,00	2,00	2,00	2,00	4,00	0,00		Range
8,00	8,00	16,00	0,00	8,00	8,00	8,00	8,00	8,00	8,00	16,00	0,00		% Range
1,10	1,00	2,00	0,00	1,15	1,15	1,15	1,15	1,15	1,15	2,31	0,00		SD
		0,40	0,60		0,40	0,40	0,50	0,50		0,40	0,60	1	FiO2
		0,40	0,60		0,40	0,40	0,50	0,50		0,40	0,60	2	
		0,40	0,50		0,40	0,40	0,50	0,50		0,40	0,50	3	
0,03	0,05	0,00	0,10	0,00	0,00	0,00	0,00	0,00	0,05	0,00	0,10		Range
6,06	9,09	0,00	18,18	0,00	0,00	0,00	0,00	0,00	9,09	0,00	18,18		% Range
0,02	0,03	0,00	0,06	0,00	0,00	0,00	0,00	0,00	0,03	0,00	0,06		SD
		10,00	6,00		6,00	6,00	8,00	8,00		10,00	6,00	1	PEEP (mbar)
		8,00	6,00		6,00	8,00	7,00	7,00		8,00	6,00	2	
		8,00	6,00		6,00	8,00	7,00	6,00		8,00	6,00	3	
1,08	1,00	2,00	0,00	1,25	0,00	2,00	1,00	2,00	1,00	2,00	0,00		Range
7,22	6,67	13,33	0,00	8,33	0,00	13,33	6,67	13,33	6,67	13,33	0,00		% Range
0,61	0,58	1,15	0,00	0,68	0,00	1,15	0,58	1,00	0,58	1,15	0,00		SD
		40,00	50,00		50,00	40,00	60,00	50,00		40,00	50,00	1	Pmax (mbar)
		45,00	45,00		50,00	50,00	60,00	50,00		45,00	45,00	2	
		45,00	40,00		55,00	55,00	55,00	50,00		45,00	40,00	3	
7,08	7,50	5,00	10,00	6,25	5,00	15,00	5,00	0,00	7,50	5,00	10,00		Range
14,17	15,00	10,00	20,00	12,50	10,00	30,00	10,00	0,00	15,00	10,00	20,00		% Range
3,75	3,94	2,89	5,00	3,35	2,89	7,64	2,89	0,00	3,94	2,89	5,00		SD
		50,00	50,00		60,00	60,00	60,00	60,00		50,00	50,00	1	Fmax (L/min)
		60,00	60,00		65,00	60,00	60,00	65,00		60,00	60,00	2	
		50,00	50,00		60,00	60,00	65,00	70,00		50,00	50,00	3	
8,33	10,00	10,00	10,00	5,00	5,00	0,00	5,00	10,00	10,00	10,00	10,00		Range
12,82	15,38	15,38	15,38	7,69	7,69	0,00	7,69	15,38	15,38	15,38	15,38		% Range
4,75	5,77	5,77	5,77	2,69	2,89	0,00	2,89	5,00	5,77	5,77	5,77		SD

Table 6.25: ICU doctors responses to patient scenarios and statistical analysis.

6.8 Models' suggestions and Peers' disagreement

The performance of the models' suggestions against clinical decisions has been presented and discussed in section 6.6. However as discussed in the previous section (6.7), the models' suggestions have also to be evaluated against clinical disagreement. Since there is not a single solution to the problem of ventilation management, one has to examine whether the models' suggestions are within clinical disagreement.

For this reason the models' suggestions were statistically evaluated against the SD of clinical disagreement on patient scenarios. The analysis was performed to identify the percentage of models' suggestions which was within the peer disagreement range; peer disagreement is described by the SD of clinical decisions on patient scenarios which is presented in table 6.25.

Tables 6.26a, 6.26b and 6.26c, present the statistical analysis of the models' suggestions against clinical disagreement. The following tables present for each lung pathology (1st column), for each modelled ventilator setting (2nd column) the model's (3rd column) suggestions outside the clinical SD as a percentage of the total suggestions (4th column). Column five provides the number of suggestions that were outside the clinical SD. The last column presents the total number of suggestions made by the tested models, which is equal to the number of the evaluation sets.

The results of tables 6.26a, 6.26b and 6.26c are also presented graphically in figures 6.40 to 6.43 for each modeling method and for all developed models (ventilator settings for all lung pathologies).

EVOFINE, NN Normalized, NN empirical and ANFIS methods have succeeded in having less than 10% (above 90% success) of their suggestions outside clinical SD in 9, 9, 12 and 10 respectively out of the 17 evaluated models. However the models were 100% successful (0% suggestions outside clinical SD) in few cases. ANFIS, NN empirical, NN Kolmogorov and EVOFINE provided all suggestions within clinical SD in 4, 4, 4 and 3 models respectively.

Although FUN method was the worst among soft computing methods evaluated in terms of mean error between model's suggestions and clinical decisions, the FUN NM models succeeded in having less than 10% (above 90% success) of their suggestions outside clinical SD in 8 out of the 17 evaluated models.

The evidence as described in tables 6.26a to 6.26c and figures 6.40 to 6.43, do not support that there is a ventilator setting more difficult to be modeled than the others. It can be seen (figures 6.40 to 6.43) that were a method has failed to provide suggestions within the clinical SD, another has succeeded. Examples are the EVOFINE and NN Kolmogorov and Normalized models for the Pmax setting of the Normal category which have failed to give suggestions within the SD, while for the same setting NN empirical, FUN NM and ANFIS have succeeded. However the only cases were the results suggest a difficulty in modeling by all methods, is the FiO_2 setting for the COPD lung category. All methods used for modelling the processes have failed; 100% of suggestions outside the clinical SD. However this is not attributed to the complexity of the modeled process but rather on the fact that clinician SD was zero, meaning there was no variation among peers (table 6.25).

Although the results from tables 6.26a to 6.26c provide us with sufficient information on the overall performance of the methods, it is clinically important to examine whether there are suggestions potentially harmful to the patient. For this reason figures 6.44 to 6.60 present the scatter diagrams of clinical decisions vs. models' suggestions. The blue dashed lines represent the clinical SD, thus models suggestions confined in the dash lines are acceptable.

There are several cases where the error of the suggested settings is sufficiently high to pose a hazard to the patient. Example diagrams presenting such situations are the following:

- In figure 6.60 we observe that ANFIS suggests few but very high PEEP values which are not clinically acceptable.
- In figure 6.57 we observe that ANFIS suggests very high flow rates, while EVOFINE is suggesting low flow rates. While in the case of ANFIS the suggestions are not clinically acceptable, the EVOFINE suggestions require further clinical evaluation.
- In figure 6.51 the NN Kolmogorov suggests FiO_2 settings not only clinically unacceptable but outside the variable domain. In the same figure we observe that all models are constantly providing suggestions of smaller FiO_2 values.
- In figure 6.48, ANFIS model suggest very low values of RR. Although all models provide several answers outside the clinical SD, the difference in numerical value is not significant.

- Several suggested tidal volume (V_T) settings for EVOFINE and NN Normalized models (figure 6.45), are higher than the clinical decisions. ANFIS model in the same figure suggests tidal volume settings which are hazardous to the patient.
- Similarly in figure 6.59, we observe that FUN NM model suggest zero PEEP values, while EVOFINE suggests very high values of PEEP, potentially hazardous to the patient.

As discussed in sections 6.4.2 and 6.6, and shown in the above paragraphs, models could suggest values outside the clinical SD and in several occasions outside the clinically acceptable limits. Thus it is crucial for a clinical decision support system to safeguard against excessive advice.

Table 6.26a: Models' suggestions outside peer disagreement (peer SD), for V_T and FiO_2 ventilator settings.

Category	Variable	Model	% of suggestions outside clinical SD	Number of suggestions outside clinical SD	Total No of suggestions
ARDS	Vt	EVOFINE	11,84	9	76
		FUN BIS	96,05	73	
		FUN WA	96,05	73	
		FUN NM	94,74	72	
		NN emb	6,58	5	
		NN Kolm	10,53	8	
		NN Norm	9,21	7	
		ANFIS	10,53	8	
COPD		EVOFINE	40,95	86	210
		FUN BIS	46,19	97	
		FUN WA	47,14	99	
		FUN NM	55,71	117	
		NN emb	7,62	16	
		NN Kolm	13,81	29	
		NN Norm	13,81	29	
		ANFIS	18,10	38	
Normal		EVOFINE	6,00	3	50
		FUN BIS	100,00	50	
		FUN WA	100,00	50	
		FUN NM	6,00	3	
		NN emb	2,00	1	
		NN Kolm	0,00	0	
		NN Norm	2,00	1	
		ANFIS	0,00	0	

Category	Variable	Model	% of suggestions outside clinical SD	Number of suggestions outside clinical SD	Total No of suggestions
ARDS	FIO2	EVOFINE	2,63	2	76
		FUN BIS	76,32	58	
		FUN WA	38,16	29	
		FUN NM	57,89	44	
		NN emb	3,95	3	
		NN Kolm	19,74	15	
		NN Norm	9,21	7	
		ANFIS	1,32	1	
COPD		EVOFINE	100,00	210	210
		FUN BIS	100,00	210	
		FUN WA	100,00	210	
		FUN NM	100,00	210	
		NN emb	100,00	210	
		NN Kolm	100,00	210	
		NN Norm	100,00	210	
		ANFIS	100,00	210	
Normal		EVOFINE	0,00	0	50
		FUN BIS	100,00	50	
		FUN WA	96,00	48	
		FUN NM	6,00	3	
		NN emb	0,00	0	
		NN Kolm	0,00	0	
		NN Norm	4,00	2	
		ANFIS	0,00	0	

Table 6.26b: Models' suggestions outside peer disagreement (peer SD), for RR and Pmax ventilator settings.

Category	Variable	Model	% of suggestions outside clinical SD	Number of suggestions outside clinical SD	Total No of suggestions
ARDS	**RR**	EVOFINE	61,84	47	76
		FUN BIS	97,37	74	
		FUN WA	97,37	74	
		FUN NM	23,68	18	
		NN emb	18,42	14	
		NN Kolm	18,42	14	
		NN Norm	18,42	14	
		ANFIS	65,79	50	
COPD		EVOFINE	36,67	77	210
		FUN BIS	29,05	61	
		FUN WA	29,05	61	
		FUN NM	33,33	70	
		NN emb	27,62	58	
		NN Kolm	40,95	86	
		NN Norm	30,00	63	
		ANFIS	30,00	63	
Normal		EVOFINE	6,00	3	50
		FUN BIS	100,00	50	
		FUN WA	100,00	50	
		FUN NM	10,00	5	
		NN emb	2,00	1	
		NN Kolm	100,00	50	
		NN Norm	6,00	3	
		ANFIS	0,00	0	

Category	Variable	Model	% of suggestions outside clinical SD	Number of suggestions outside clinical SD	Total No of suggestions
ARDS	**Pmax**	EVOFINE	65,79	50	76
		FUN BIS	100,00	76	
		FUN WA	65,79	50	
		FUN NM	44,74	34	
		NN emb	0,00	0	
		NN Kolm	0,00	0	
		NN Norm	25,00	19	
		ANFIS	50,00	38	
COPD		EVOFINE	8,57	18	210
		FUN BIS	95,71	201	
		FUN WA	95,71	201	
		FUN NM	11,90	25	
		NN emb	18,57	39	
		NN Kolm	9,52	20	
		NN Norm	22,86	48	
		ANFIS	25,24	53	
Normal		EVOFINE	90,00	45	50
		FUN BIS	100,00	50	
		FUN WA	100,00	50	
		FUN NM	0,00	0	
		NN emb	2,00	1	
		NN Kolm	100,00	50	
		NN Norm	98,00	49	
		ANFIS	2,00	1	

Table 6.26c: Models' suggestions outside peer disagreement (peer SD), for Fmax and PEEP ventilator settings.

Category	Variable	Model	% of suggestions outside clinical SD	Number of suggestions outside clinical SD	Total No of suggestions
ARDS	**Fmax**	EVOFINE	2,63	2	76
		FUN BIS	97,37	74	
		FUN WA	97,37	74	
		FUN NM	3,95	3	
		NN emb	3,95	3	
		NN Kolm	2,63	2	
		NN Norm	6,58	5	
		ANFIS	5,26	4	
COPD		EVOFINE	16,19	34	210
		FUN BIS	95,71	201	
		FUN WA	95,71	201	
		FUN NM	12,38	26	
		NN emb	10,48	22	
		NN Kolm	100,00	210	
		NN Norm	13,81	29	
		ANFIS	5,71	12	
Normal		EVOFINE	0,00	0	50
		FUN BIS	90,00	45	
		FUN WA	94,00	47	
		FUN NM	4,00	2	
		NN emb	0,00	0	
		NN Kolm	6,00	3	
		NN Norm	2,00	1	
		ANFIS	0,00	0	

Category	Variable	Model	% of suggestions outside clinical SD	Number of suggestions outside clinical SD	Total No of suggestions
ARDS	**PEEP**	EVOFINE	0,00	0	76
		FUN BIS	0,00	0	
		FUN WA	0,00	0	
		FUN NM	5,26	4	
		NN emb	0,00	0	
		NN Kolm	0,00	0	
		NN Norm	0,00	0	
		ANFIS	6,58	5	
COPD		EVOFINE	1,43	3	210
		FUN BIS	1,90	4	
		FUN WA	1,43	3	
		FUN NM	8,57	18	
		NN emb	1,90	4	
		NN Kolm	0,48	1	
		NN Norm	0,95	2	
		ANFIS	1,43	3	

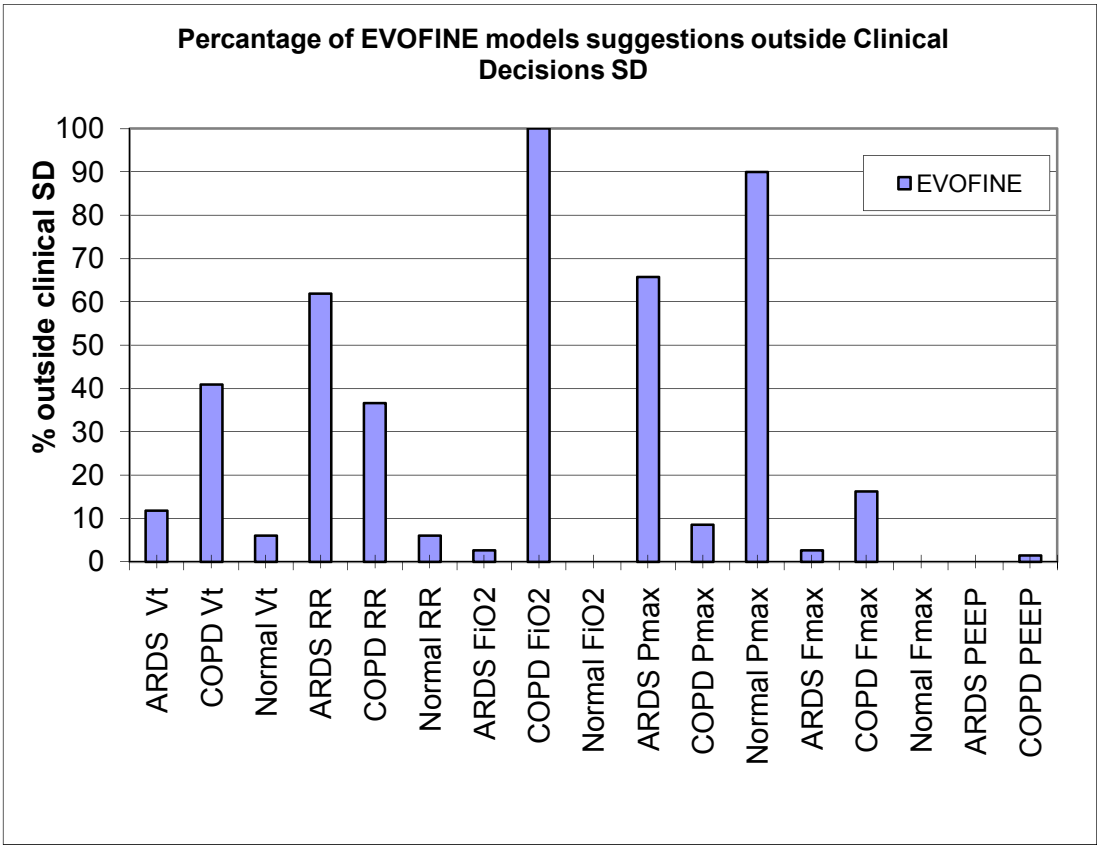

Figure 6.40: Percentage of EVOFINE suggestions outside SD of peer disagreement.

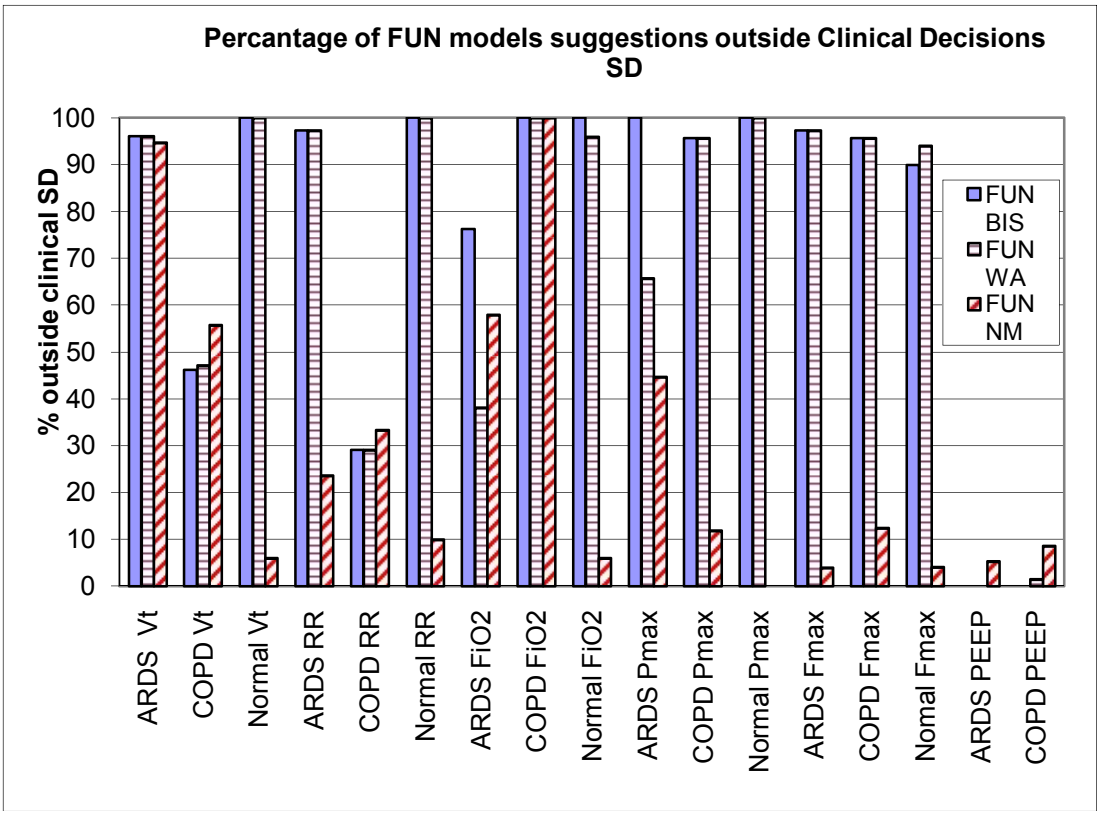

Figure 6.41: Percentage of FUN suggestions outside SD of peer disagreement.

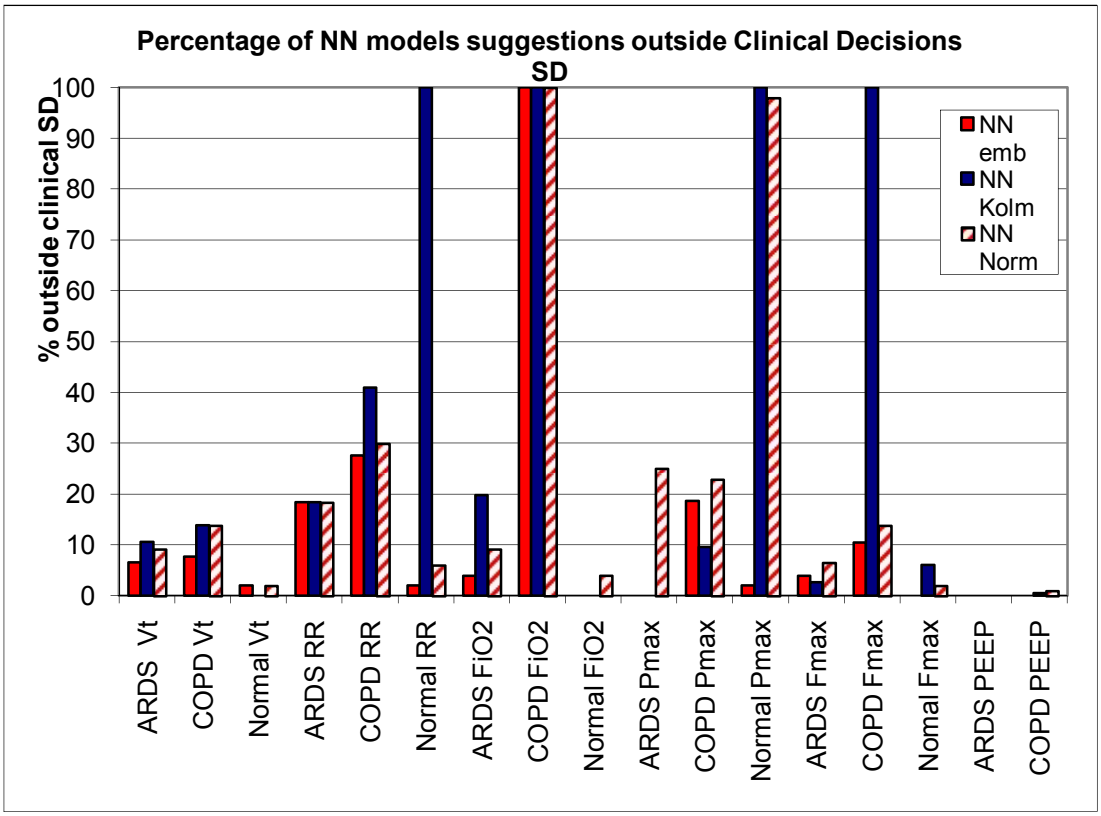

Figure 6.42: Percentage of NNs suggestions outside SD of peer disagreement.

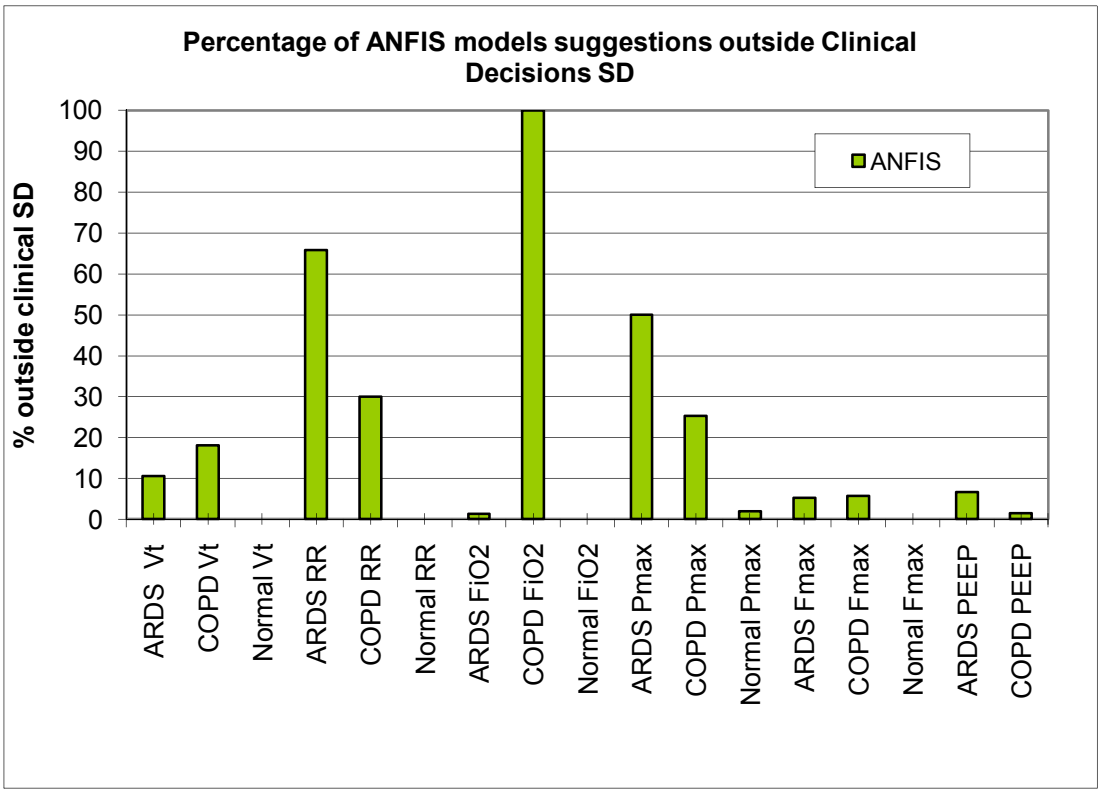

Figure 6.43: Percentage of NNs suggestions outside SD of peer disagreement.

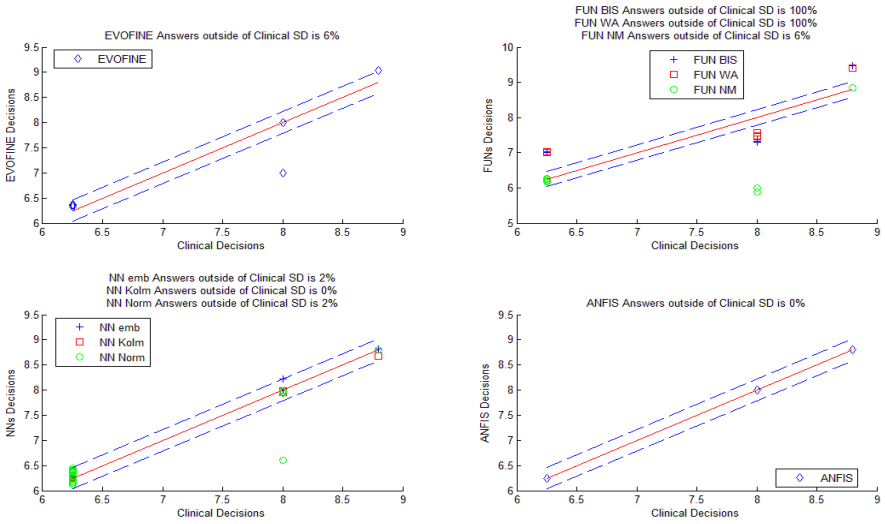

Figure 6.44: Scatter diagram of models' vs. clinical decisions for V_T Normal

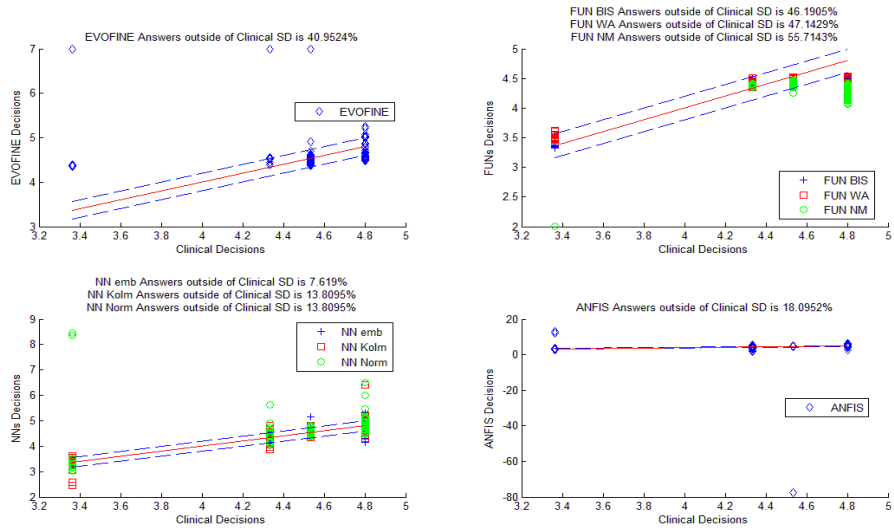

Figure 6.45: Scatter diagram of models' vs. clinical decisions for V_T COPD

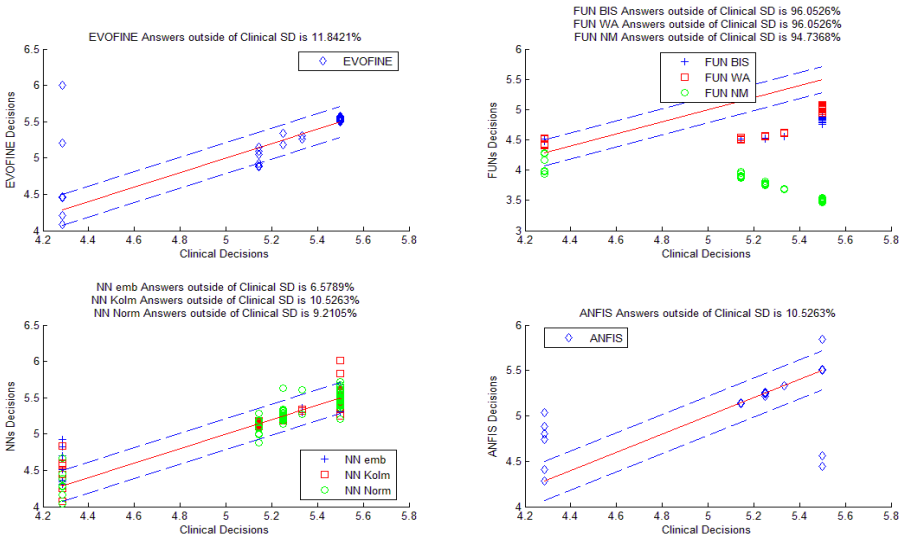

Figure 6.46: Scatter diagram of models' vs. clinical decisions for V_T ARDS

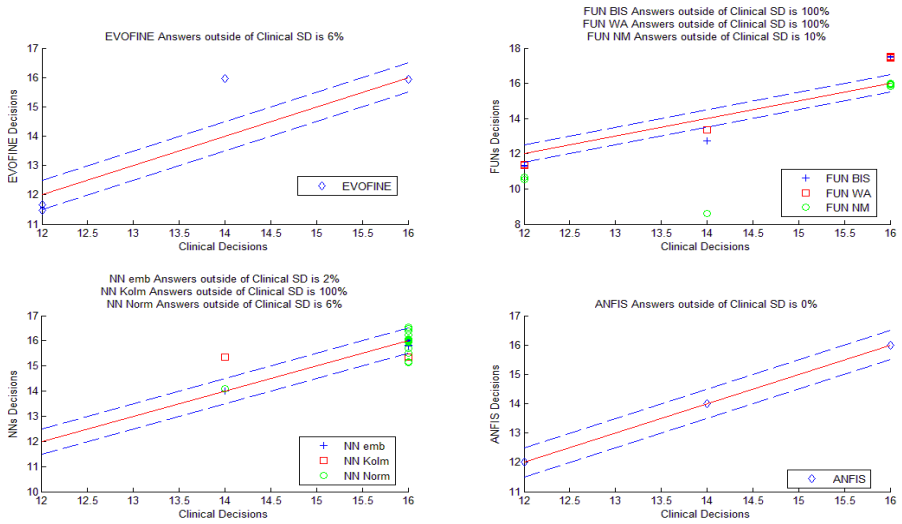

Figure 6.47: Scatter diagram of models' vs. clinical decisions for RR Normal

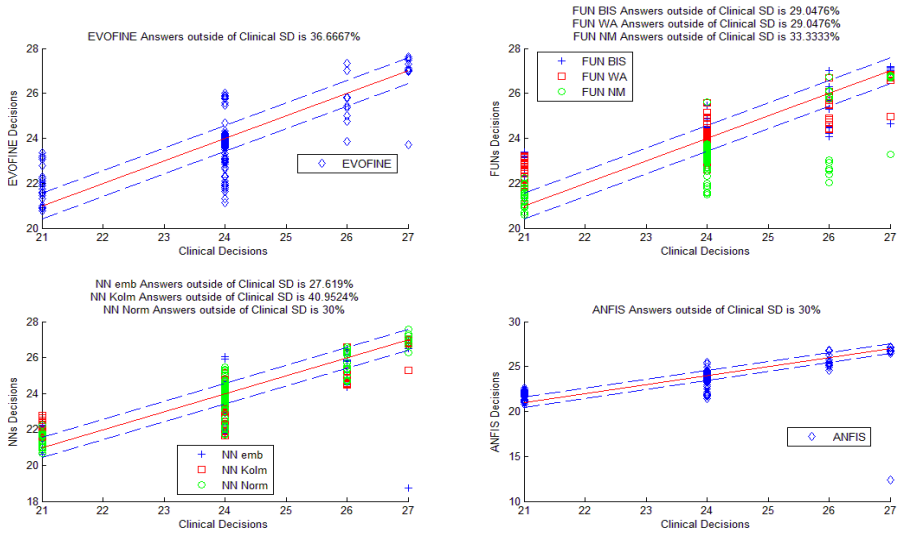

Figure 6.48: Scatter diagram of models' vs. clinical decisions for RR COPD

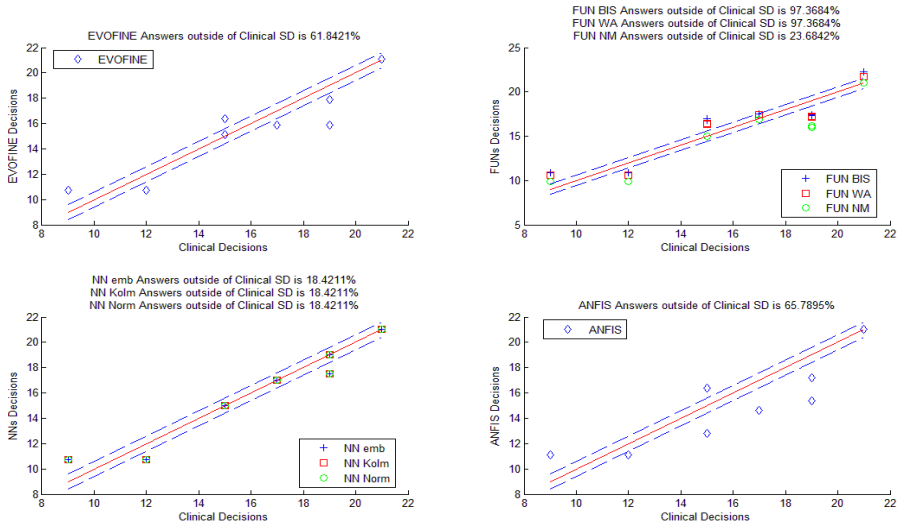

Figure 6.49: Scatter diagram of models' vs. clinical decisions for RR ARDS

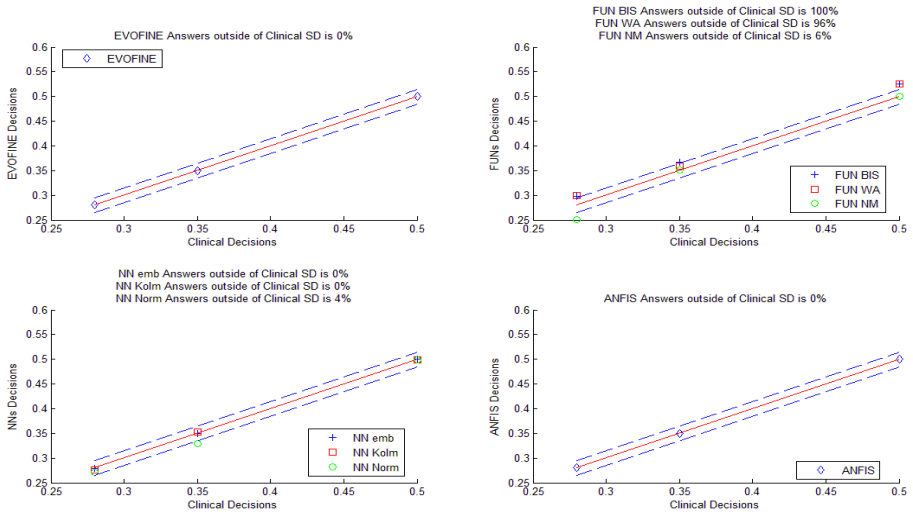

Figure 6.50: Scatter diagram of models' vs. clinical decisions for FiO_2 Normal

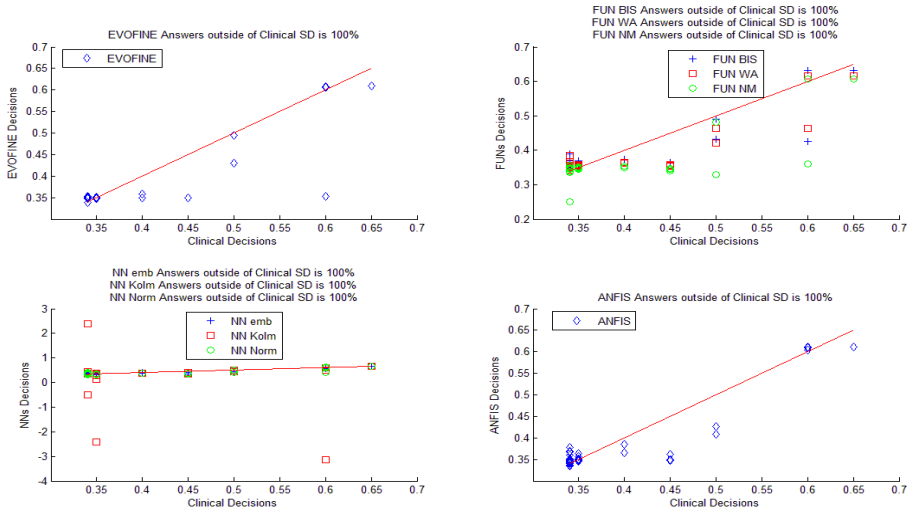

Figure 6.51: Scatter diagram of models' vs. clinical decisions for FiO_2 COPD

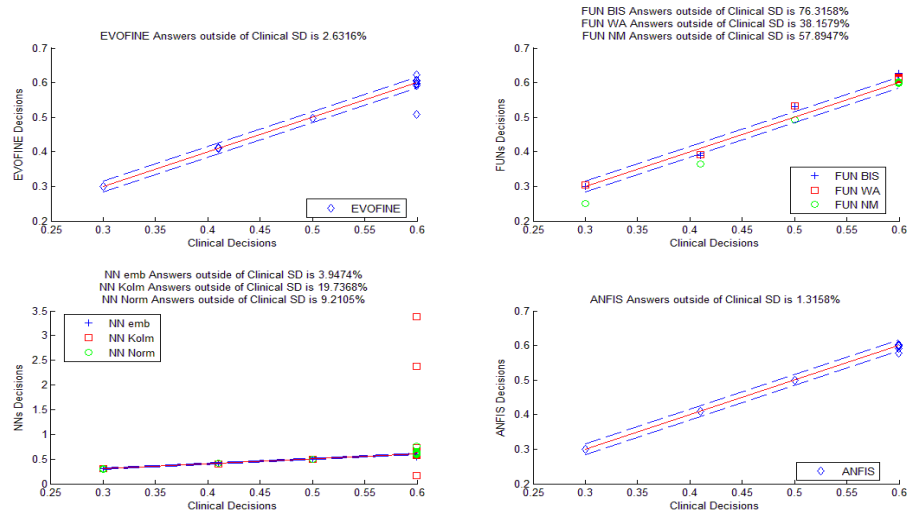

Figure 6.52: Scatter diagram of models' vs. clinical decisions for FiO_2 ARDS

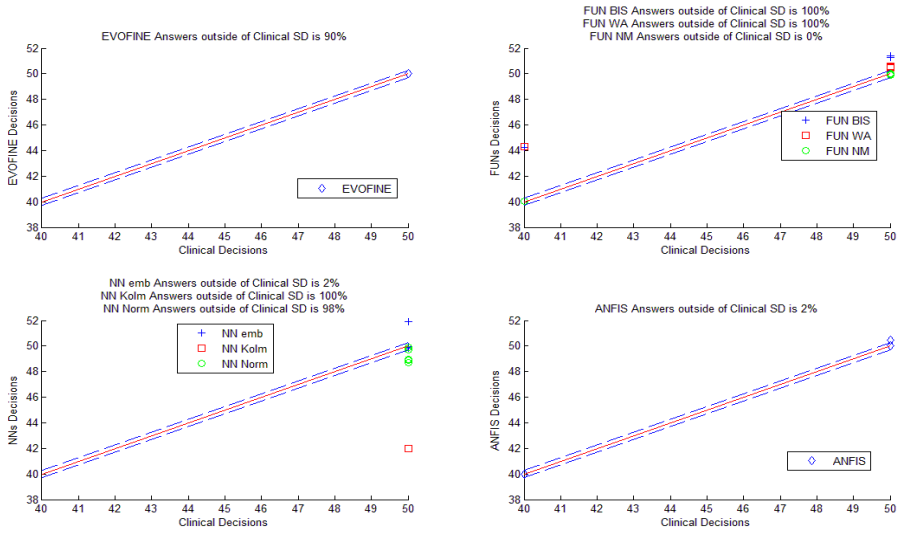

Figure 6.53: Scatter diagram of models' vs. clinical decisions for Pmax Normal

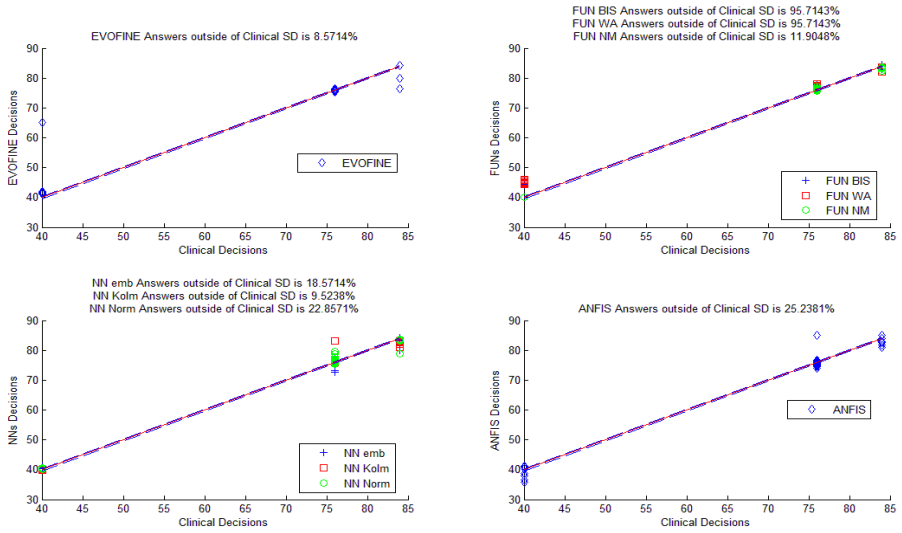

Figure 6.54: Scatter diagram of models' vs. clinical decisions for Pmax COPD

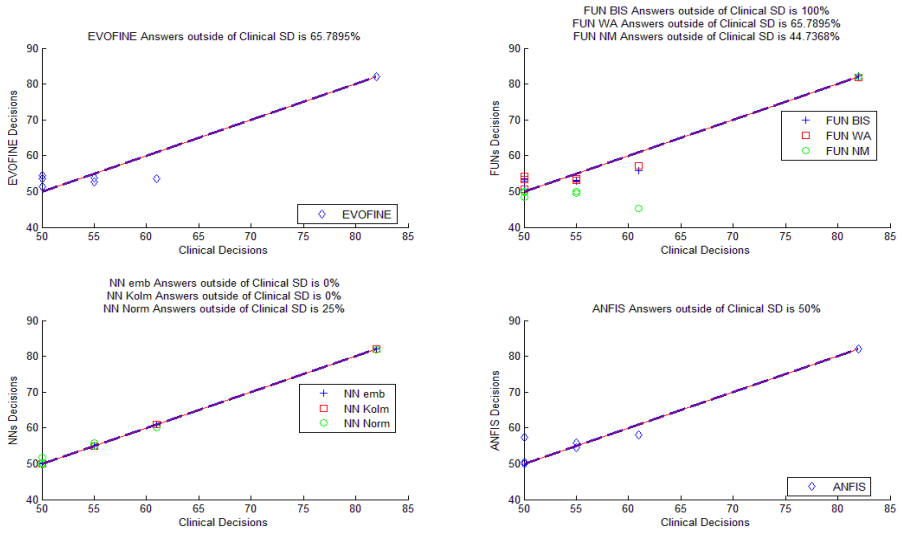

Figure 6.55: Scatter diagram of models' vs. clinical decisions for Pmax ARDS

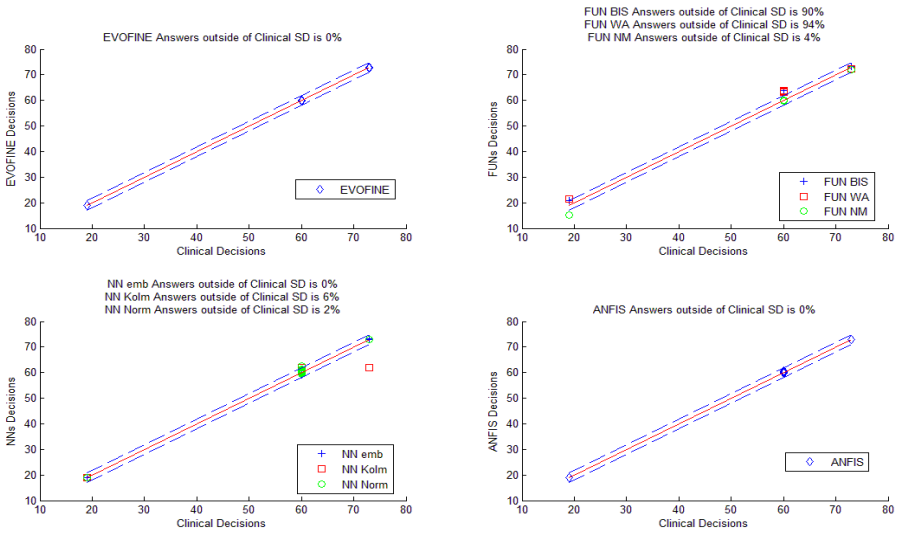

Figure 6.56: Scatter diagram of models' vs. clinical decisions for Fmax Normal

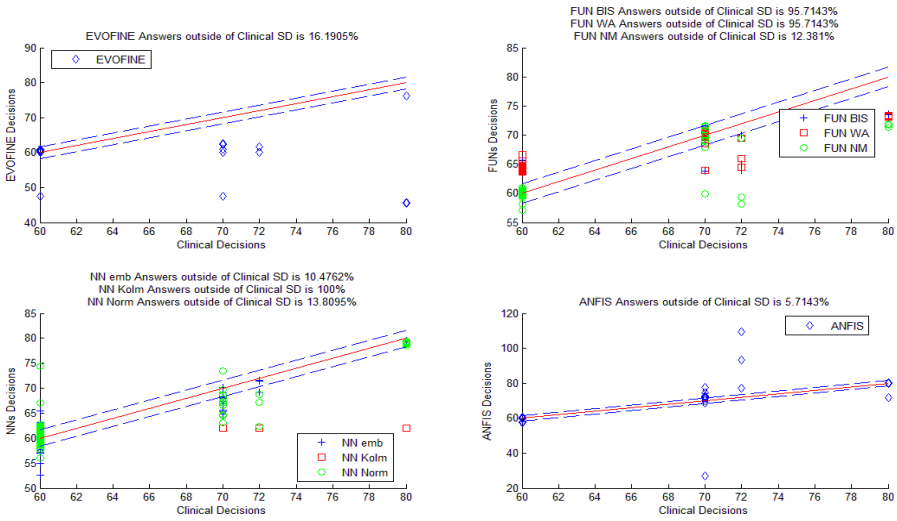

Figure 6.57: Scatter diagram of models' vs. clinical decisions for Fmax COPD

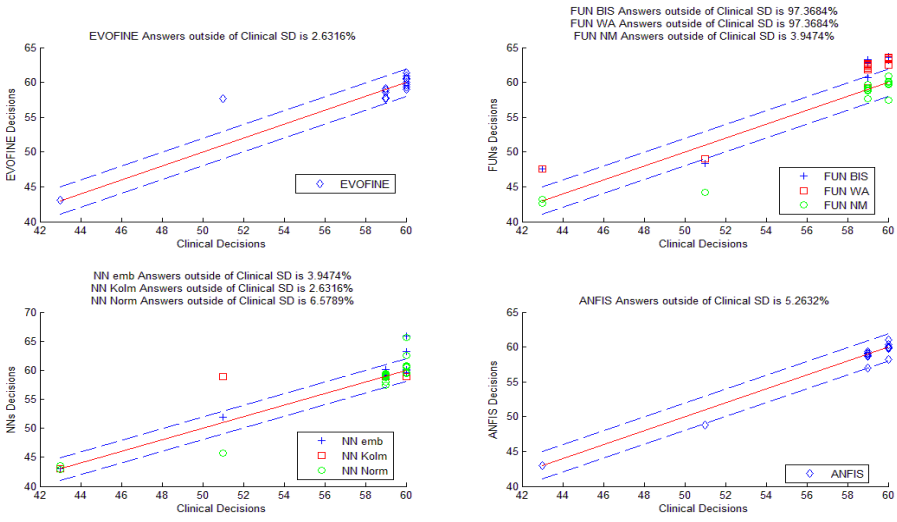

Figure 6.58: Scatter diagram of models' vs. clinical decisions for Fmax ARDS

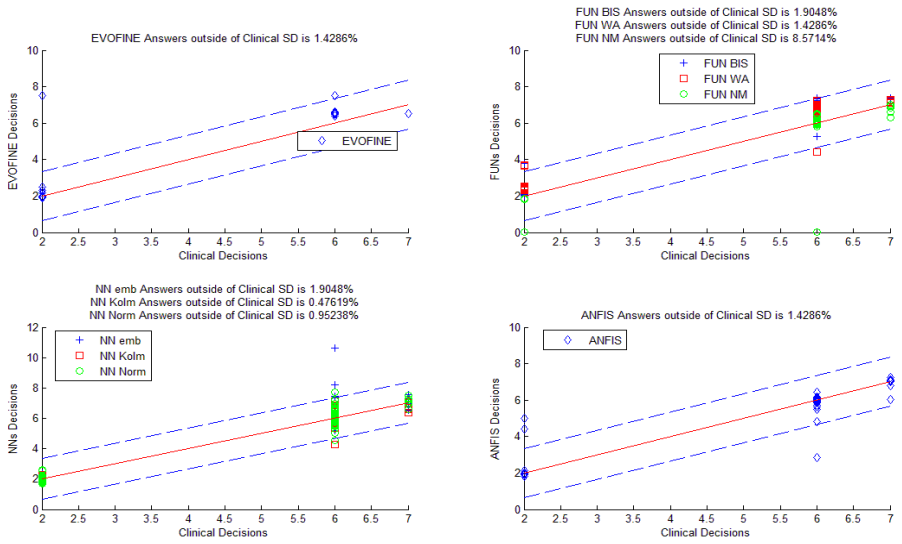

Figure 6.59: Scatter diagram of models' vs. clinical decisions for PEEP COPD

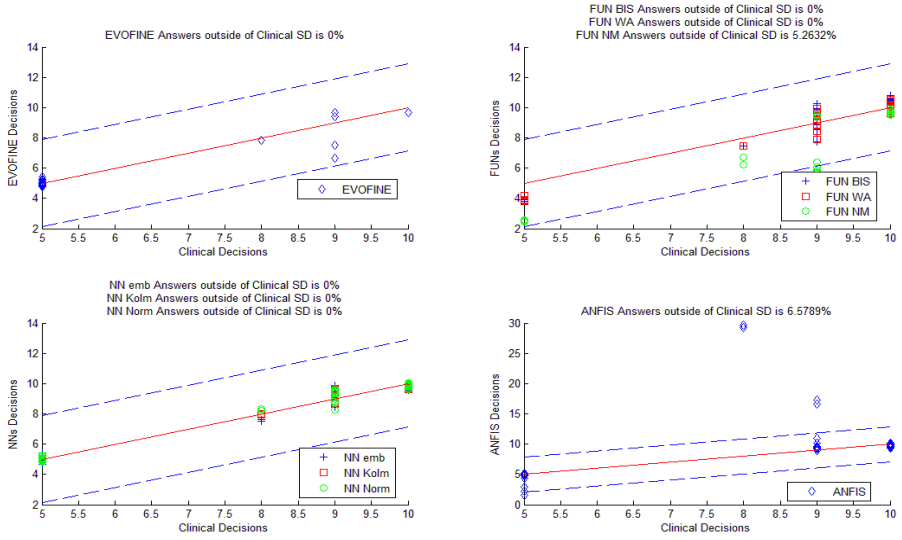

Figure 6.60: Scatter diagram of models' vs. clinical decisions for PEEP ARDS

7. Discussion

7.1 Discussion key subjects

The presented results in chapter 6 of the models performance will be discussed taking the following key points into consideration:

- Discussion on methods for limiting the number of input variables to the models.
- Choice of methods for developing the models.
- Toolboxes' efficiency in developing models.
- Evaluation of models against available data sets.
- Comparison of models performance.
- Comparison of models performance against clinical scenarios.
- Comparison of the presented approach to other authors.

7.1.1 Discussion on methodology for limiting input variables

The problem of limiting the number of input variables to the models was addressed with the use of basic statistical analysis.

The identification of important physiology variables and ventilator settings was performed with the use of a developed questionnaire. The questionnaire was circulated to three general hospitals in Athens, Greece and responses were collected from eighteen (18) ICU doctors. The results were statistically analysed and variables that scored high were chosen for recording.

Following the recording phase of real patient data, patients were classified with the assistance of an experienced ICU clinician, into three major categories related to the ventilation management process. The three categories were the ALI-ARDS, the COPD and the Normal lungs category.

Collected data were re-sampled into five (5) minute trends and they were analyzed in terms of correlation coefficients. This analysis was performed to further reduce the number of inputs for our models from the set resulting from the questionnaire, and thus simplify the architecture, reduce training time and produce more accurate results.

There are alternative methods for addressing the problem of models architecture and limitation of the problem's search space. We present some of them in the following paragraphs as well as the arguments for not introducing them in our research:

- *One should collect the total of available data and create models as close to human decision making with all the available data*: As a general argument this approach could be implemented. But a question is raised, which patient related data would form a good representation of clinicians' decision making process. Should all measured variables be incorporated to our models? If so should the drug administration process be also recorded? Should patient's case mix (present of multiple illness), and followed by a specific relevant importance to ventilation management be incorporated? Doctor/ patient interaction, translated from verbal or acoustic – sensory inputs from the patients should be properly encoded and introduced to the research? The list of possible candidates to the model is far too big for the purpose of the current research. Furthermore the resulting models would require considerable processing power for training and evaluation purposes. In contrast we decided to elicit from unstructured conversations and related bibliography, the most important variables that could be numerically recorded. Then we identified the most important according to ICU clinicians experience and expertise, and finally we mathematically calculated and evaluated by experts the relationship between the recorded data and the ventilator settings, based on the assumption that each ventilator setting is chosen with a subset of the available data.
- *Expert ICU doctors should be involved in the choice and evaluation process of the available data:* A major drawback of relying on individuals for eliciting expert knowledge is that results are highly biased from their theoretical and empirical background. Although this problem could be overcome by increasing the number of clinical participation into the research, the following practical problems arise: First the active participation of many ICU doctors from different hospitals requires motivation and dedication for the purpose of the research, and second one has to elicit a golden standard from multiple clinical decision making patterns. Since conflict in decision making process among clinical personnel exists, such a task is highly difficult and time consuming. For this reason it was decided to elicit the experts

experience and expertise with the use of statistical tools that would minimize the individuals' bias in our research. However since experts knowledge in the field should not be ignored, we have incorporated their knowledge in every step of the method, but rather than relying on few experts we decided to evaluate their opinion with statistical methods. During the development of the questionnaire the ICU staff of Ag. Olga general hospital provided the basic variables. The responders to the questionnaire suggested the importance of the physiology variables and their responses were analyzed. In this way it was managed to minimize individual biases in the final results. Furthermore clinicians from three different hospitals evaluated the strength of the relationships that were derived from the collected data, based on the correlation analysis between physiology variables and ventilator settings. Thus experts participated in every step of the research but their opinion was counterbalanced with the use of statistical analysis.

- *Limiting the number of variables into the models could be performed with methods that exclude human bias:* It is true that one could implement Principal Components Analysis, GAs or another well established method for identifying relationships between physiology data and ventilator settings. However one could not exclude experts' opinion on the resulted relationships. For this reason at some point ICU doctors should evaluate results concerning the strength and the existence of relationships. The specific argument requires further investigation in future research, since it is possible that different techniques would provide us with different relationships between input and output data. However since ICU doctors evaluated the correlation results, and based on their majority voting the input variables were chosen for our models, the possibility of utilizing input data irrelevant to our research was minimized.

7.1.2 Artificial Intelligent Methods for model development

It was decided to develop the models with methods that allow development without the feedback from experts, based on available data sets. In this way it was anticipated that the resulted models would elicit and incorporate both the experience and the expertise of the medical staff. ICU doctors were consciously excluded from the

design and architecture of the models since eliciting information from experts in complex systems is a difficult and time consuming task and also a source of bias to the research.

Two main AI methods are established in modelling complex systems, namely Fuzzy Logic and Artificial Neural Networks. Although Fuzzy Systems have proven their efficiency in modelling complex systems they require expert's feedback during the development and tuning phase. Alternatively one could incorporate other AI methods that provide the capability to FRBSs to adapt, tune or train for a specific task.

We have decided to evaluate the use of GAs and ANN in evolving and training FRBS, and at the same time apply ANN to model the ventilation management process. The following paragraphs briefly discuss the methods we have used and the limitations of each method:

- *ANFIS method*: ANFIS has been successfully tested in relevant medical applications (Kwok H.F. 2003). However the ANFIS toolbox of Matlab (® Mathworks) has the following limitations: It can only implement Sugeno type FRBS, the number of output variables is limited to one and the number of rules is dictated by the available input(s) membership functions. Although these features are limitations in terms of design flexibility, ANFIS method has the advantage of optimizing FRBS structure both in terms of RB and FSs.
- *Evolution of FRBS with the use of GAs (EVOFINE toolbox)*: EVOFINE toolbox utilizes GAs for evolving FRBSs based on their performance against an available training data set. One of the main draw backs of the method is the use of a subset of the RB due to increased complexity and limited computational resources. However as we have exhibited in experimental trials, a subset of the RB could adequately map a complex system. Furthermore the computation time for evolving complex FRBSs is higher than the other methods. The advantage of the EVOFINE toolbox is that it evolves both the RB and tunes the FSs of the FRBSs assuming no prior knowledge on the architecture.
- *ANN driven FL (FUN toolbox)*: FUN toolbox substitutes the RB of the FRBSs with an ANN. One of the drawbacks of FUN toolbox is the use of predefined FSs in terms of number, position and shape. Due to the design of the FUN toolbox, the ANN adapts to model a given training set consisting of

membership degrees for each input – output values. Thus the ANN output is numerical values of membership degrees. We have shown that different defuzzification methods provide us with different performance for the same ANN trained model.

- *ANNs*: ANNs are widely used in modelling complex systems in a variety of medical and non-medical applications. We have shown that the use of normalized training sets advance the ANN performance when the input domains have a large magnitude variation among input – output variables. The main drawback of ANNs is that the resulting model is a "black box" for the evaluator and the developer. The elicitation of NN's operating principles requires the application of rules extraction methods.

The following paragraphs discuss other relevant AI methods as alternatives to those used in our research:

- *Chromosome Coding techniques*: Apart from the main coding approaches such as Pittsburgh, Michigan and Iterative approaches, there are several other approaches disseminated to the research community (Jamei M. 2004). All of them exhibit positive and negative features as discussed in the Appendix IV. However our approach was different. The RB and the FSs were coded into two separate chromosomes utilizing different coding; integer and real coding respectively. The FRBS was fully customizable from the EVOFINE toolbox allowing the user to perform trials with different architectures in a simple and straight forward manner. Additionally the coding of two separate chromosomes is translated as autonomous evolution of each chromosome. Thus possible deterioration of the architecture of one chromosome might be counter balanced by the improvement of the other. However the opposite is also true; improvement in one chromosome could be counter balanced by deterioration of the other. The best FRBSs from each generation are stored for the user, so it is possible to go back in time and examine the system's performance. We have incorporated rule weights into the coding, so the evolution process optimizes the structure and the weight of each rule, so incorporating rule minimization when weights are zero (0). We have adapted the Sheffield's' GA toolbox in order to exchange only complete rules during crossover. We have introduced damping mutation rates and experimentally

exhibited that they perform faster, resulting in better individuals and decreased computation time. Additionally it is planned for the future to advance the EVOFINE toolbox in such way to search for the optimum combination of RB and FSs chromosomes, rather than treating each pair as a single FRBS. The performance of our approach is backed up by experimental data on non linear mathematical function and the cart pole system (Appendix III).

- *Elicitation of the RB of an FRBS*: Several methods have been proposed for the automatic elicitation of the RB of a FRBS (Liu F. 2006. Jamei M. 2004, Wang L.X, Mendel J.M, 1992, Chen C.L, Chen Y.M, 1993). In our approach we have used the well established GAs method as well as the NN driven FRBS. While the first optimizes randomly constructed RBs, and the quality of the final outcome is partially attributed to this randomization and on the processing power available (number of individuals', chromosomes' length and training generations), the NN driven FRBSs method has the advantage of developing a model for the total number of rules for a FRBS, at least representative for the rules dictated by the available training sets. Furthermore our FUN toolbox allows the development of Mamdani type NN driven FRBSs.
- *FRBS vs. ANN*: Theoretically both methods could equally map a complex search space (Bukley JJ et al 1993). However there is no evidence of their comparative performance in applications on modelling medical support systems for highly complex tasks such as the ventilation management process. Even though they have been applied in similar problems, the quality, quantity and type of data sets was not the same, leading to expected differences in the outcomes. For this reason we decided to test both architectures against a given problem. Results, as it is discussed further in the next sections, suggest that performance is highly affected by the setup details of each method rather than the method on each own.

7.2 Models' Performance

7.2.1 EVOFINE models' performance

Chapter 6 presented the performance of the developed models against the clinical decisions of domain experts. The FRBSs were evolved for 100 generations. Evolved FRBSs have been tested against the training and evaluation sets, in terms of *mae* and *rmse*, and their equivalent percentage in the range of the available variables, which was also the input and output domain of the model's variables.

The number of input variables and consequently the RB as a percentage of the total rules describing the system does not seem to have a profound effect on the performance of the models. With the help of the table 5.15, we observe that the RR model for Normal, ALI-ARDS and COPD categories have 5,1 and 3 inputs respectively and the corresponding percentage of the full RB is 5, 100 and 100% (table 6.1). Although the Normal RR model used the less complex architecture in terms of RB, its performance is superior to the other categories. Figure 7.1 presents the overall (mean) performance of the models for each patient category. The results suggest that Normal category was modelled more accurately than the other two. This could not be attributed to the simplicity and small number of the available data. Although RR in Normal category was modelled with a 5 % of the full RB, as opposed to 100% for COPD & ARDS, the corresponding number of rules was higher than the other two categories; 156, 125 and 5 rules for Normal, COPD and ARDS respectively. The increased number of rules seems to have resulted into a more accurate mapping of input – output relationships.

An important drawback of the use of GAs is the increased computational time. Figure 7.2, presents the training time for a hundred generations (100) and a hundred individuals (100). COPD was the slowest among the models mainly due to the large number of available data sets. Additionally, the number of input variables to a model, and as a result the size of the RB, affected the computation time. Pmax model for the Normal category used 6 inputs and 391 rules. As shown in figure 7.2, it has the slowest training time among other categories. Although training time is not crucial for the initial training, it becomes crucial during systems maintenance, due to retraining when new data sets are available.

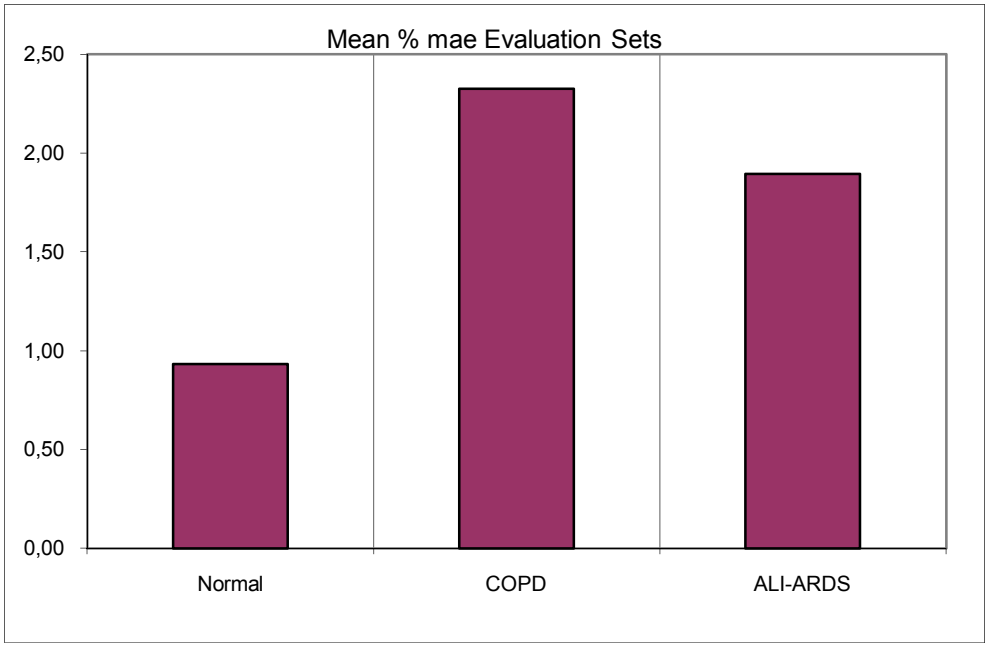

Figure 7.1:Mean % mae of EVOFINE models.

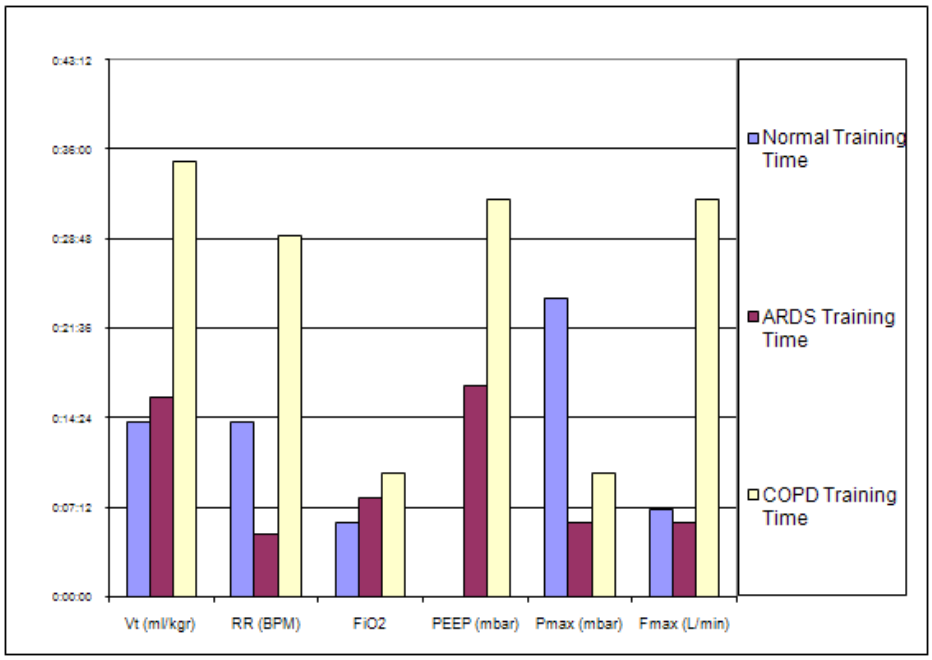

Figure 7.2:Training time of EVOFINE models; y axis is time hours:min:sec

As theory of GAs and results from the experiments carried out for the mathematical function (table III.1, Appendix III), the performance of an evolved FRBS is expected to improve with increased number of evolution generations. One could re-run the experiments for a larger number of generations in order to develop more efficient models in expense of computation time. Figure 7.3 shows the evolution of RR for the ALI-ARDS category for 100 (top) and 500 (bottom) generations. Computation time

is approximately 6 and 26 minutes respectively, while performance has improved from 4.64 to 4.15 % *rmse*.

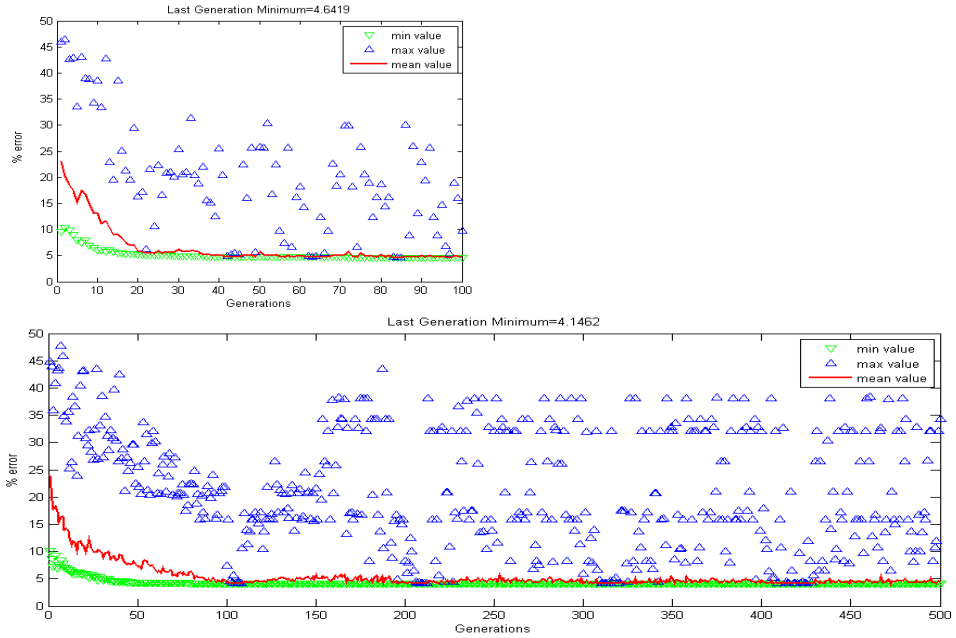

Figure 7.3: Evolution of RR (ALI-ARDS) for 100 (top) and 500 (bottom) generations.

We were tempted, mainly because of the results of the ANN models that used the normalized training set, to examine the performance of an evolved FRBS with the use of normalized training sets. We have carried out two experiments. The evolution process of the FRBSs with the use of un-normalized and the normalized training sets is presented in figure 7.4 for two models. Results are not supporting that the performance is further improved, in reality it deteriorates, and for this reason we did not evolved the models with the use of the normalized training sets.

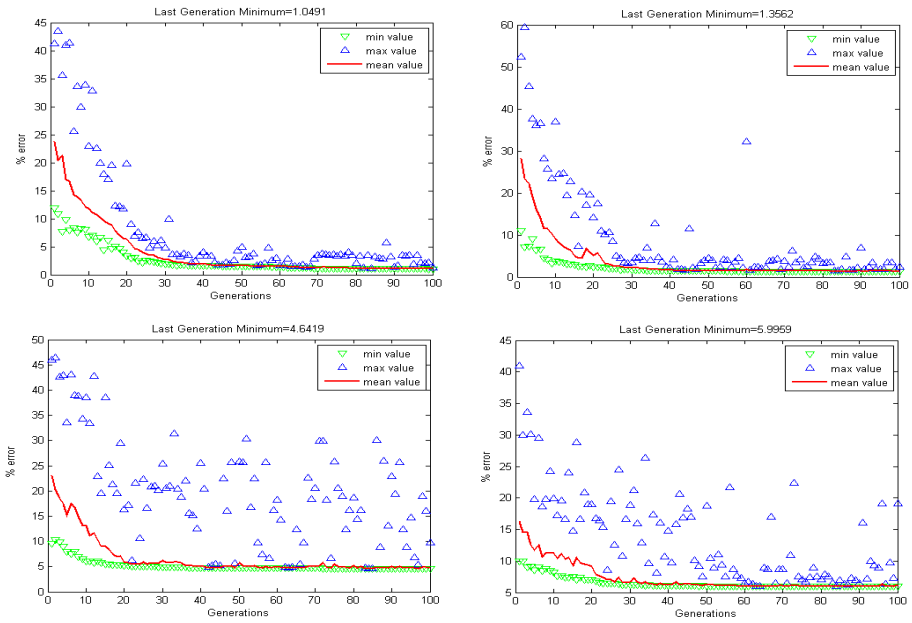

Figure 7.4: (left) V_T (top) and RR (bottom) model for ARDS category with the use of the un-normalized training set (right) V_T (top) and RR (bottom) model for ARDS with normalized training set.

Evaluation of EVOFINE's models against clinical disagreement (section 6.8) has shown that 9 out of 17 evolved FRBS (approximately 53% of the models) were producing suggestions within clinical SD for more than 90% of the cases. Additionally 4 of the 17 evolved models produced advice within clinical SD for all the presented data sets.

In terms of clinical decisions potentially hazardous to the patient we have identified three cases which require further evaluation in the future. These are the models of PEEP for COPD (fig. 6.59), the tidal volume for COPD (fig. 6.45) and the Fmax for COPD category (fig. 6.57).

7.2.2 FUN models' performance

The ANN of FUN models was trained for 1000 epochs with the translated, fuzzified, data sets. The output produced during the simulation of the FUN models was the degree of memberships for the output linguistic variables.

Since defuzzification process is important in terms of produced crisp output values, we decided to explore different defuzzification techniques. Bisector, Weighted Average and Near (Smallest) of Maxima (NOM or SOM) were introduced to the model as defuzzification methods. While the first two produce a crisp output based on the output linguistic variables which are fired by the Inference Engine logic, the SOM takes into consideration the prevailed linguistic variable. Although techniques such as Center (middle) of Maxima could also been used for this purpose, they tend to produce constant outputs for symmetrical linguistic functions. On the other hand the SOM technique is affected not only by the specific linguistic variable but also by the degree of membership, as exhibited in the following figure.

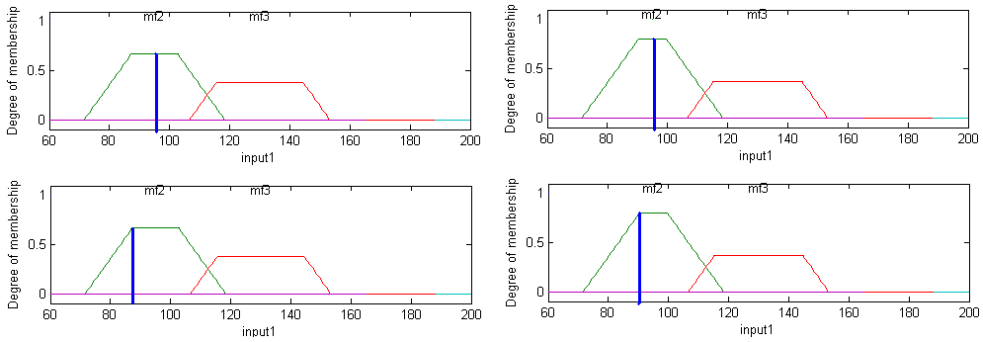

Figure 7.5: Near of Maxima or Smaller of Maxima SOM (bottom) defuzzification technique vs. Middle of Maxima MOM (top).

The developed FUN models were tested against the evaluation set. Figure 7.6 presents the mean % mae of the models for all the patient categories.

The defuzzification technique of SOM (NOM) has in general produced more accurate results.

The computation time for the training of the FUN toolbox (fig. 7.7), was a fraction of the computation time of the EVOFINE toolbox. COPD required more time for the training again due to the large data set available.

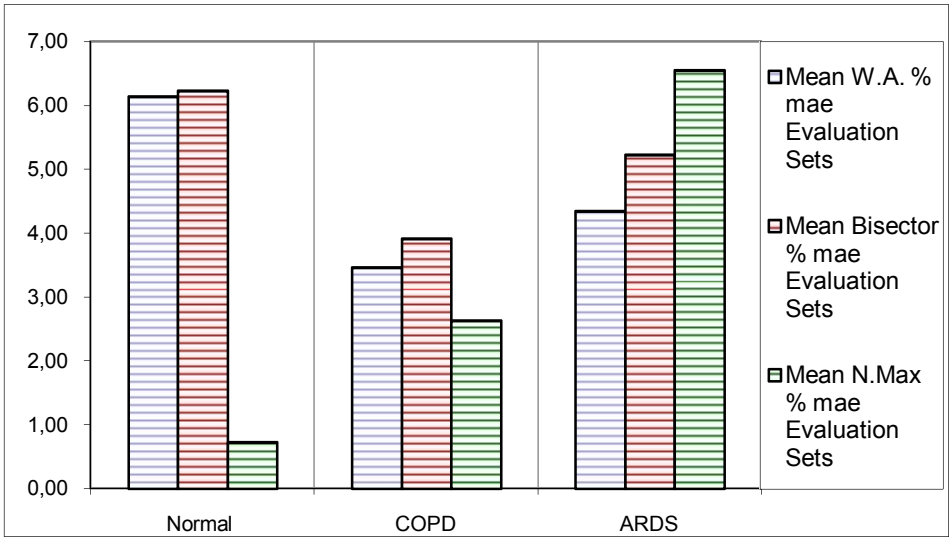

Figure 7.6: Mean % mae of FUN models.

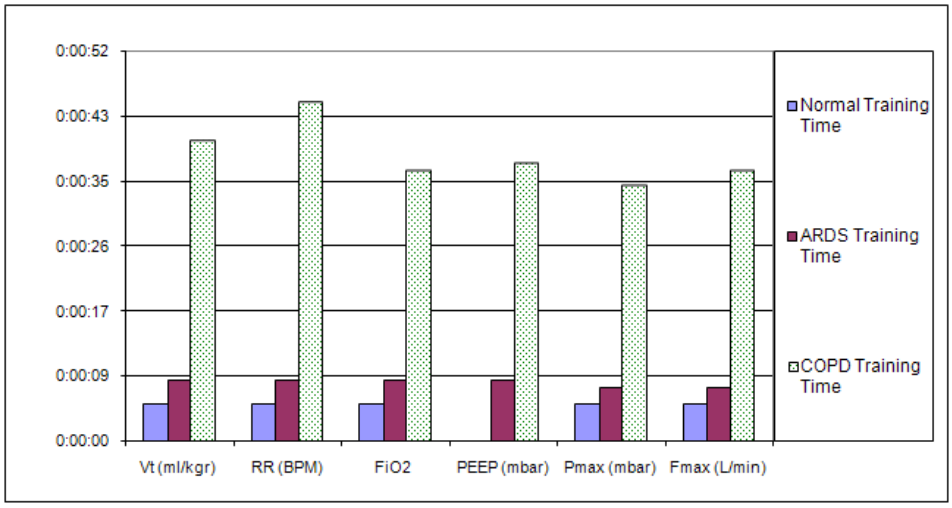

Figure 7.7:Training Time for FUN models.

Additionally to the mean performance of the FUN models against clinical decisions, the performance of the models in terms of clinically acceptable was evaluated in section 6.8.

FUN models utilizing the NM defuzzification method have provided suggestions within clinical SD in 8 out of the 17 developed models (47% of the developed FUN models). The FUN models utilizing BIS and WA defuzzification techniques failed to produce advices within clinical SD. Only 11% of the developed models provided suggestions that were above 90% within the clinical SD.

FUN models' exhibited a tendency to provide smaller numerical values than the clinical decisions (fig. 6.41 to 6.60). The magnitude of disagreement between clinical advice and models' suggestions requires further investigation in the future.

7.2.3 ANN models' performance

We developed and tested three ANN models. The *ANN Kolmogorov* models utilize the architectures of table 6.5 and fig. 6.6, and they were tested with the five (5) minute data sets. The *ANN Normalized* has exactly the same architecture as the *ANN Kolmogorov* but it was trained with the scaled data sets. The *ANN empirical* used double hidden layer architecture and it was also tested with the scaled data set (table 6.6 and fig. 6.8). All NNs were trained for 1000 epochs.

Since the recorded physiology variables have different domains, pH for example ranges from 7.3 to 7.6 while OI ranges from 100 to 600, it was expected that an ANN utilizing the recorded training set could not adequately map the solution. This assumption is experimentally verified. The *ANN Kolmogorov* exhibited the worst performance among the trained ANN in the majority of the simulations. In cases where the *ANN Kolmogorov* model performed similar to the other ANN the input variables that participated in the model exhibited similar domains.

As the number of inputs to an ANN model increases, so does the complexity of the model. However the increased number of variables, assuming that the ANN architecture is adequate and the data set appropriate, should increase the accuracy of predictions

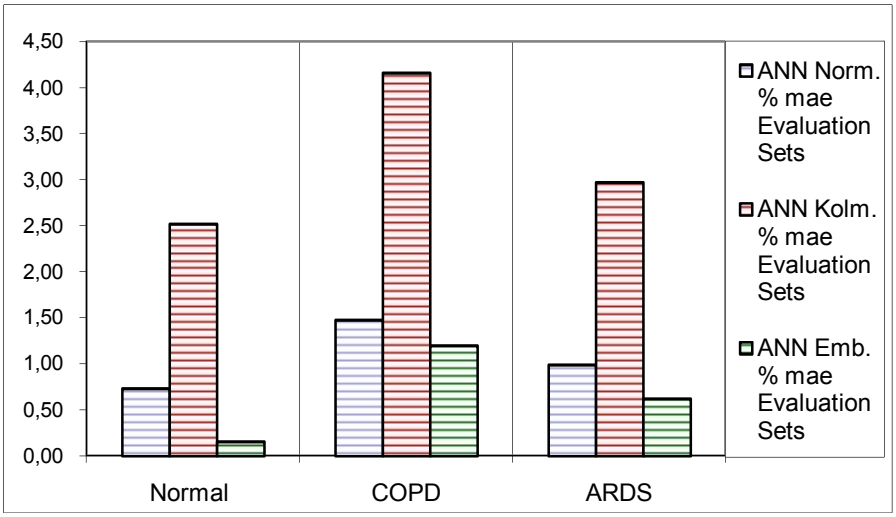

Figure 7.8:Mean % mae of ANN models.

The *ANN empirical* performed better in all patient categories (fig. 7.8). This is mainly attributed to the use of two hidden layers. The use of scaled inputs (normalized training sets), has improved the performance of the ANNs. However

due to the increased architecture of the double hidden layer ANN, the computation time has been increased (fig. 7.9). Computation time depends on the number of trainings sets for each category, and the achievement of the training goal prior to the predefined number of epochs (e.g. training of *ANN Kolmogorov* Pmax for ARDS category fig. 6.3 and *ANN Kolmogorov* RR for ARDS).

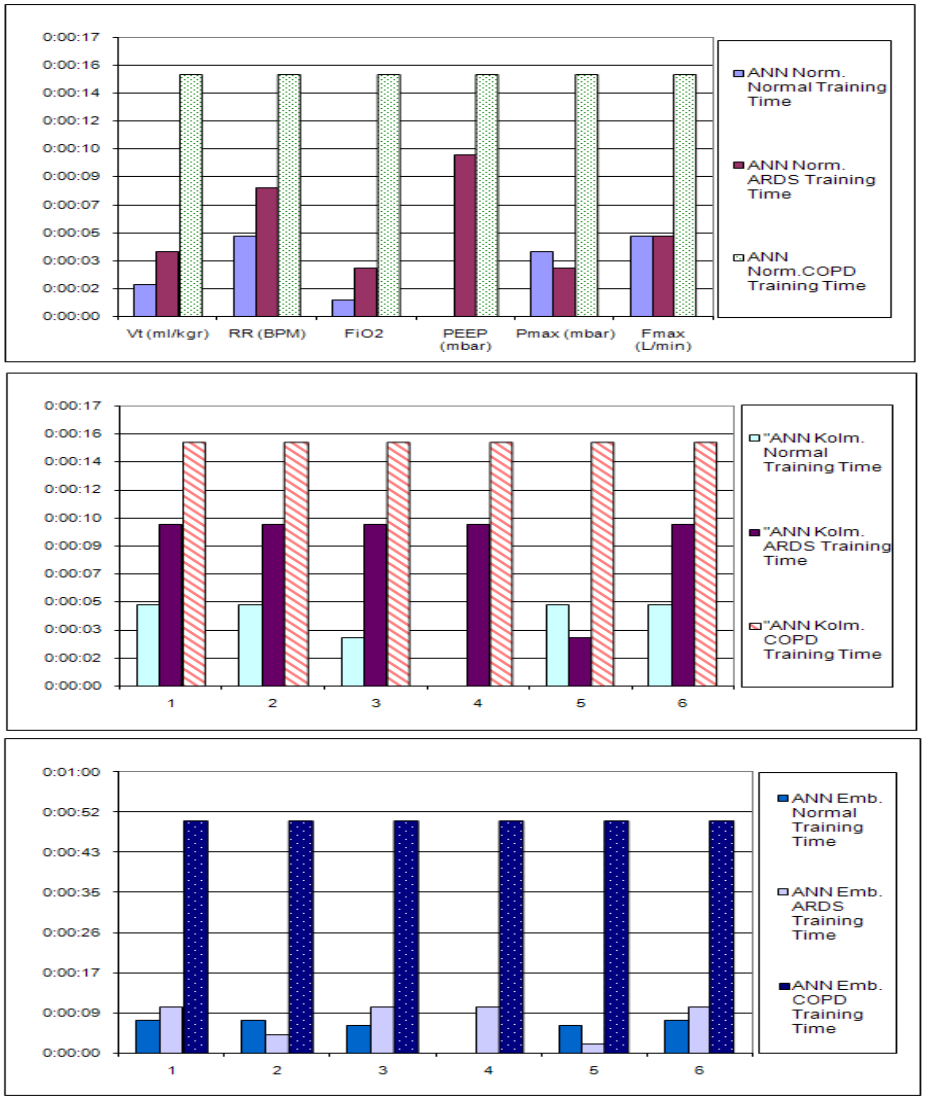

Figure 7.9: Computation time of ANN models. Top ANN Kolmogorov, middle ANN normalized, bottom ANN empirical.

Section 6.8 presents the evaluation of NNs' models against the clinical disagreement. Both of the NN empirical and Normalized were 100% successful (0% suggestions outside clinical SD) in 4 out of 17 developed models (23,5% of the trained models). However the models were above 90% successful in 9, 8 and 12 out of the 17 developed models for the Normalized, Kolmogorov and Empirical NN respectively (53%, 47% and 70,6% of the developed models). In terms of models' suggestions

within clinical SD, NN empirical were the best models among all evaluated methods. Although NN empirical suggested in several cases settings outside the clinical deviation (fig. 6.40 to 6.60), there were no suggestions identified as hazardous to the patient. However this is not true for the other two trained NNs. NN Kolmogorov suggested FiO2 settings outside the variables range (fig. 6.51, COPD category), while NN Normalized suggested tidal volume settings close to double the clinical decision (fig. 6.45, COPD category).

7.2.4 ANFIS models' performance

ANFIS models were trained for 5 epochs based on the architectures of table 6.7. ANFIS models' performance was numerically shown in tables 6.21 to 6.23 and graphically presented in figures 6.23 to 6.39. In this section we present the summary of the ANFIS models in terms of mean % mae and computational time.

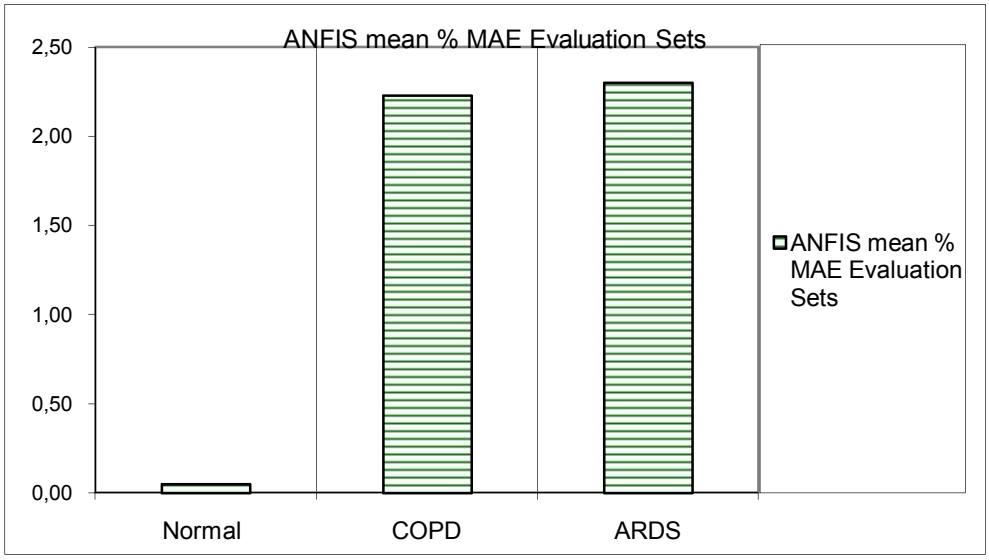

Figure 7.10:mean % mae of ANFIS models

The evaluation of the ANFIS resulting FRBSs against evaluation data sets reveals that, as expected, Normal lungs category was the easiest to model, similar to the other methods applied.

Although the evaluation results suggest that in almost all models the ANFIS method adequately maps the relationship between input(s) and output variables, the surface graphing presented in figures 6.10 to 6.15, reveals that under a given set of input values some of the models could suggest clinically unacceptable outputs. The cases where the ANFIS models could potentially result into clinically unacceptable suggestions are identified and described in section 6.4 and 6.8. The existence of such suggestions by the ANFIS models is attributed to the available data sets. The available data do not cover all possible arithmetic combinations that provide us with the surface mapping of a controllers output.

Figure 7.11 describes the mean % mae of all the models in each category both for the evaluation and the training set. As it was already discussed the Normal category was more efficiently mapped compared to COPD and ARDS category, due to the small

number of available data, which might have caused loss of generalizability of the ANFIS models.

The small number of epochs used for training the ANFIS models has resulted into small computational times (fig. 7.11). ANFIS has outperformed all other methods in terms of computation time and could only be compared to FUN models.

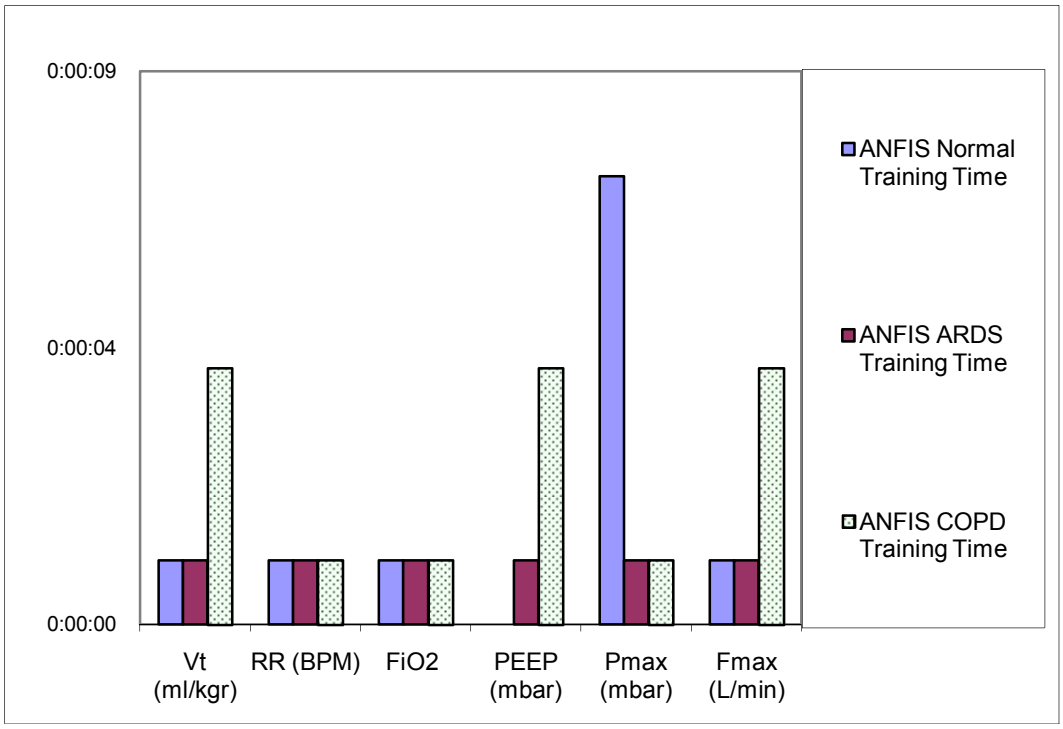

Figure 7.11: Computation time for ANFIS models.

Evaluation of the ANFIS method against clinical disagreement (section 6.8) has revealed that 10 out of 17 (59%) ANFIS models were providing answers within clinical SD above 90% of their suggestions. Additionally 4 out of 17 (23,5%) ANFIS models were 100% successful in terms of providing all suggestions within clinical SD.

Although mean performance of ANFIS against clinical SD was the second best among all methods, in several occasions the suggestions were identified as hazardous to the patient. ANFIS models provided hazardous suggestions in PEEP settings for ARDS (fig. 6.60), in Fmax settings for COPD (fig. 6.57), in RR settings for COPD (fig. 6.48), and in tidal volume for COPD (fig. 6.45).

7.3 Methods Comparison

The AI methods were compared in terms of performance and in terms of computation time. Furthermore the results were evaluated against to the responses of ICU doctors to the clinical scenarios.

Figure 7.12 presents the mean absolute error expressed as a percentage (% *mae*) of all the methods applied in the different lung pathologies.

As it is suggested by the previous sections COPD category was the most difficult to model, since the overall performance of most models was degraded in comparison to the other categories.

The *ANN empirical* that utilized double hidden layer architecture and the normalized training set exhibits superior performance over the other methods in most patient categories.

While ANFIS, EVOFINE and *ANN Normalized* models compete for the second best, the mean performance of the models against all categories and sets (fig. 7.12), suggests that the *ANN Normalized* has exhibited a slightly better performance in the evaluation data sets. Thus the use of ANN trained with the normalized training set have been shown to perform better than the other AI methods. However the GA evolved FRBSs maintain their generalizability when they are applied to the evaluation set. Similarly the *ANN empirical and Normalized* maintain their performance when applied to evaluation set with small deterioration. ANN *Kolmogorov* and ANFIS on the other hand deteriorate their performance when they are simulated against the evaluation set (figs 7.12 & 7.13 and tables 7.11 to 7.13 and 7.14 to 7.16). Although ANFIS did not excel in terms of performance, this is mainly attributed to the simplicity of the models architecture as described in table 6.8. The restriction on FS participating for each input, and consequently on the RB of the fuzzy system is dictated by the small size of the training set. To achieve good generalization toward unseen data, the size of training data set should be at least as big as the number of modifiable variable in ANFIS. The number of modifiable variables is given by the "premise" modifiable variables plus the "consequent" modifiable variables, as described in Appendix IV (IV.4.4). FUN models exhibit the worst performance, even against the *ANN Kolmogorov* model. The only case where the FUN models perform better than the *ANN Kolmogorov* is the NOM FUN model for the Normal category.

The training process of the EVOFINE models required more computational resources and computational time (fig. 7.15). This is an important drawback of the use of GAs, since the development of the models is restricted by the computational resources. As stated in early paragraphs the training of all models was not matched. Models that trained ANN were allowed to run for one thousand of epochs (1000) while the EVOFINE models were evolved for one hundred generations (100), and ANFIS models for five (5) epochs. The evolution process of the models for longer generation is expected to produce more efficient models. The ANFIS development process is the most efficient one, among the tested methods in terms of computational time.

Computation time is not as important in the training phase of a decision support system, but rather during the maintenance phase were generated systems have to be re-trained when new datasets are available.

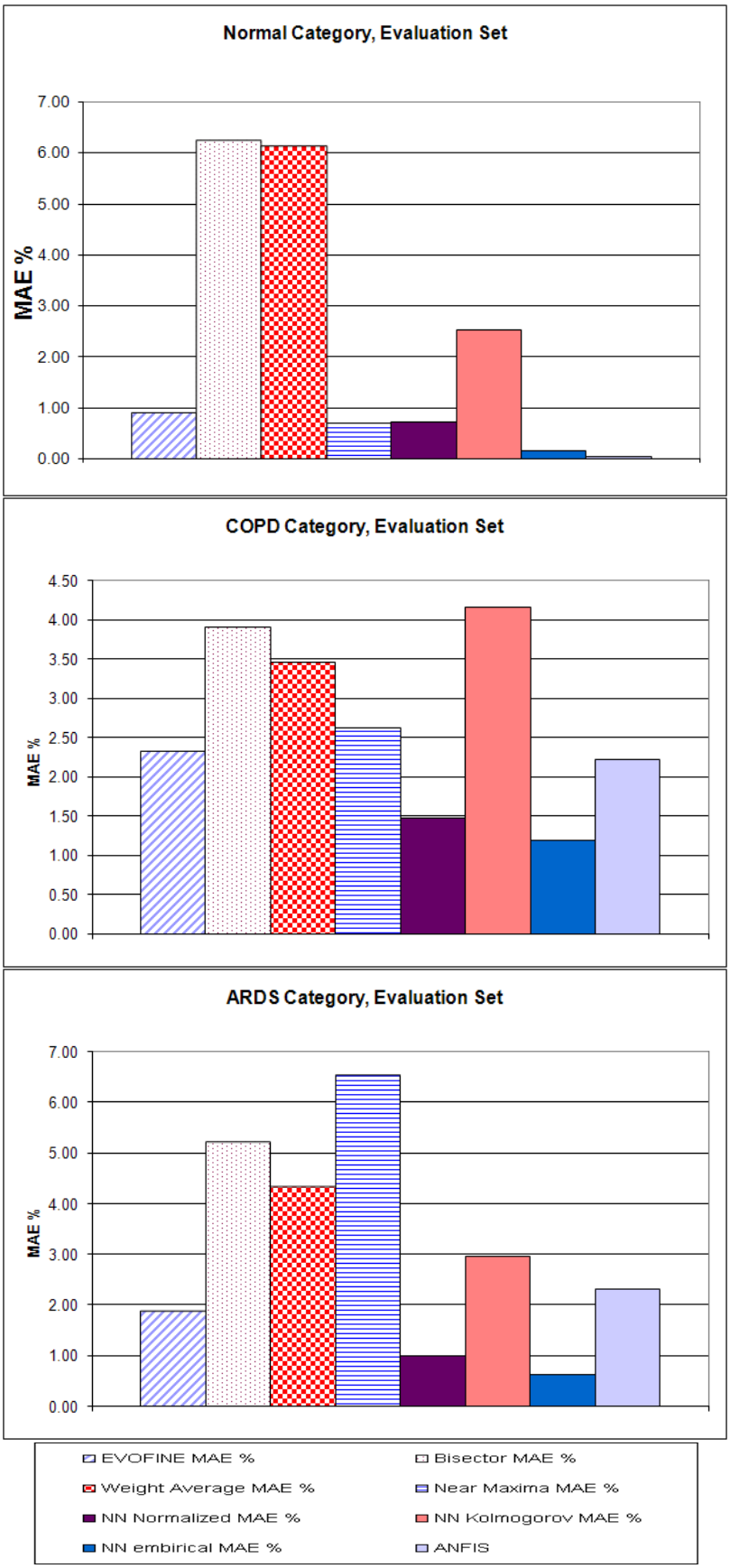

Figure 7.12:Mean % mae of models tested against the evaluation set.

Figure 7.13:Mean % mae of models tested against the training set.

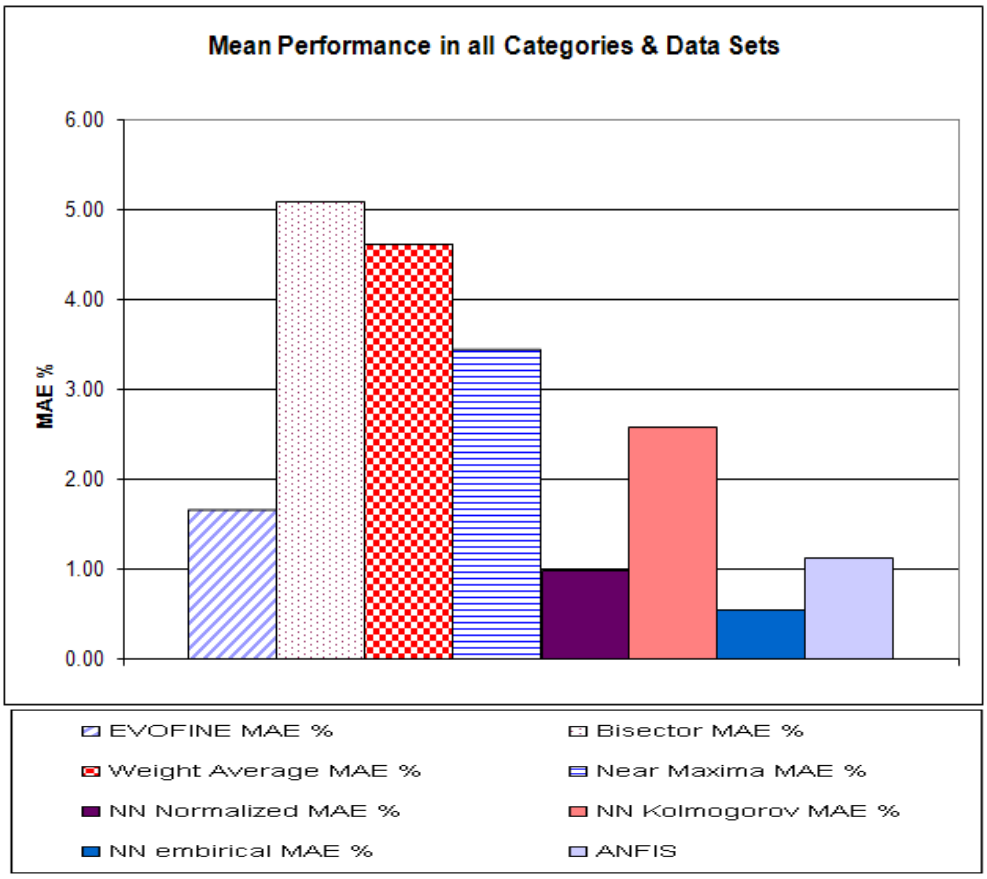

Figure 7.14:Mean % mae of models in all categories and in all data sets.

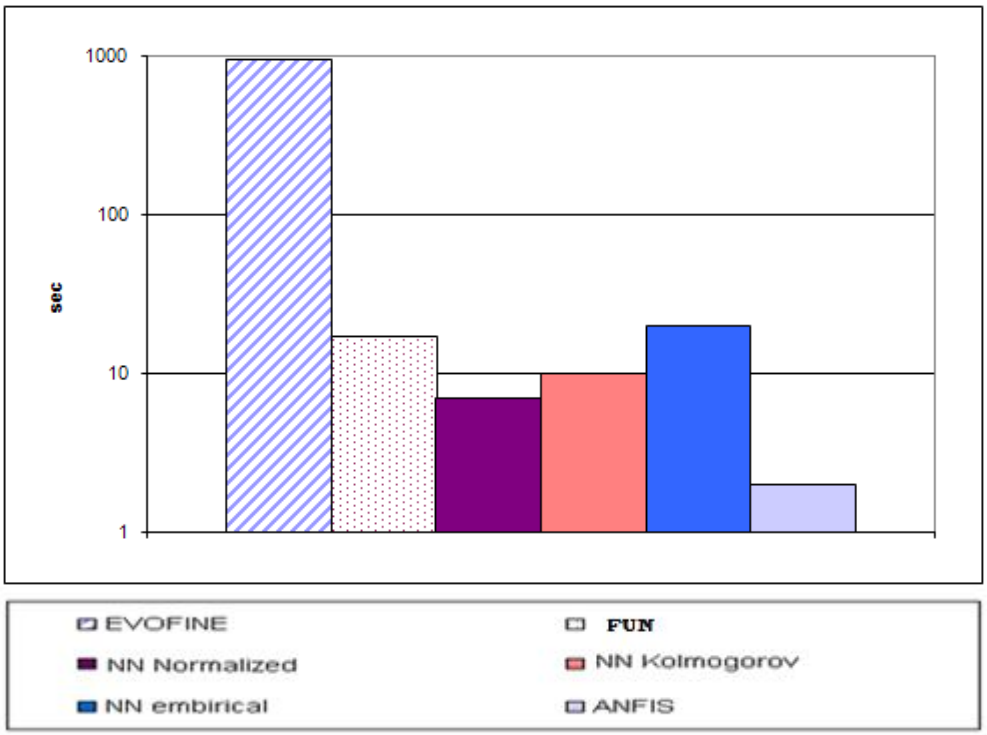

Figure 7.15: mean models' training time in seconds for all categories and in all data sets.

Addressing the initial research question, whether the ventilation management process could adequately modelled, it was found that examining the resulting models only by comparing their performance against "unseen" data sets is insufficient. As it was suggested early in the research, the complex task of ventilating ICU patients does not have a unique solution. The clinicians' ventilation strategy is based on their expertise and experience, as well as the available physiology measurements. If the process of ventilation management was well defined then there would have been no need of specialized ICU personnel, and doctors could be substituted by nurses with suitable guidelines.

Although comparing medical decisions to the models output is a straight forward method of evaluating performance, the performance of models in terms of agreement to a single clinical decision is not on its own an absolute measure of performance. Of equal significance is to investigate whether models' suggestions are not exceeding medical disagreement. For this reason the performance of the models was evaluated in terms of identifying whether the produced suggestions were within the range of medical decision making (Table 7.1).

An important aspect of evaluation of Clinical Decision Support Systems is the potential of providing suggestions hazardous to the patient. For this reason in section 6.8 the performance of the models' suggestions was evaluated in terms of potential hazardous suggestions to the patient. As it is shown in table 7.1, NN empirical models were 70.6% successful in providing suggestions above 90% within the clinical SD. Similarly the second best method was ANFIS with 59%, followed by EVOFINE and NN Normalized with 53% success. However ANFIS models were providing all suggestions within the clinical SD in 23.5% of the developed models, similar to EVOFINE and ANNs models.

Although table 7.1 suggests that ANFIS, EVOFINE and ANNs have a similar performance, it is important to point out that none of the NN empirical models was identified to provide suggestions potentially harmful to the patient. Although the same is true for FUN models, there is tendency to suggest lower values than clinical decisions which requires further investigation. ANFIS and NN Kolmogorov suggest in several occasions settings hazardous to the patient.

Table 7.1: Comparison of Models' performance in terms of providing suggestions within clinical SD.

Modelling method	Percentage of Models that provided suggestions within clinical SD in excess of 90% of suggestions	Percentage of Models that provided suggestions within clinical SD in all suggestions	Percentage of models that produced potentially hazardous advices
EVOFINE	53%	11.8%	17.6%
FUN BIS	11%	5.8%	Lower suggestions to clinician, requiring further investigation.
FUN WA	11%	5.8%	
FUN NM	47%	23.5%	
NN Empirical	**70.6%**	23.5%	**0%**
NN Normalized	53%	23.5%	5.8%
NN Kolmogorov	47%	23.5%	5.8%
ANFIS	59%	23.5%	23.5%

7.4 Comparison to other authors

As it is already stated in the chapter 3, several authors have published their work in the area of modelling respiration physiology and/or ventilation management. This section presents the methods and results of similar approaches (summary table is located at Appendix V, Table V.1), and presented work is discussed in comparison to other authors.

It is obvious from the fitness function used by authors, that comparing different models in terms of performance is difficult. The method commonly used for measuring performance is the comparison between the models output and a "gold" standard. However the gold standard is not always the clinical decisions, but often the response of a simulator (e.g. Kwok H.F, 2004). Our approach was the direct numerical comparison in terms of mean error between clinical suggestions and model's suggestions. The clinical decisions were considered the reference point since their adjustments maintained patients in breathing comfort. Furthermore the use of different hospitals for the recording and development of the data base should eliminate possible biases in terms of ventilation strategy.

Although direct comparison is difficult, we observe that benchmarking of models for the same author (e.g. Liu F, 2006), suggest that ANN perform very well. The models proposed by Liu et al (Liu F, 2006), performs with *rmse* of 1.13 to 7.39 for the FiO_2. Additionally we can calculate Kwok (Kwok H.F, 2003) *rmse* by calculating the root of the *mse* reported. Kwok's performance in terms of *rmse* exhibits minimum 2.56 and maximum 9.32 values (for changes in FiO_2). Similarly our models for ARDS, COPD and Normal lungs have performed with minimum 0.00, in all three cases and a maximum *rmse* 0.38, 0.45 & 0.02 respectively. The superiority in performance could be attributed to the architecture and to the increased number of recorded hours. Our models are pathology specific, and the number and type of participating variables is deducted from the data sets.

The number of ventilation settings adjusted by the authors' models' varies. Most of the models are concerned with a single output (dominating variable is the FiO_2), with a maximum of five output variables (Tehrani TF 2008, Jandre F.C, 2004). Our approach has modelled six ventilator settings. The development of individual models for each variable reduced the problems complexity.

Important in the development of the models is the database. Most of the authors incorporate into the data sets real patient data. Patient data are introduced either as row recordings (e.g. Schaublin J, 1996, Chen A.H, 2007), or as patient scenarios (e.g. Wang A, 2006). Furthermore, authors either process scenarios directly or through a respiratory model (e.g. Kwok H.F, 2004). The use of simulators introduces possible errors to the process. Errors could be caused by the inaccurate response of the patient's model or the insufficient representation of a specific patient by the model. Additionally, the holistic modelling of the ventilation management process requires modelling of different patient types. Authors in their effort to overcome the non specificity of their models have performed model fitting prior to application (Allerod C et al, 2008). We have incorporated three common pathologies into our models, however other authors have introduced different patient categories such as post-operative (Martinoni E.P, 2004), pneumonia (Kwok H.F, 2004), infants (Sun Y, 1994, Laubscher T.P, 1994), and animal studies (Chapman F.W, 1985, Jandre F.C, 2004), Fuzzy systems, ANFIS and ANN, are the three most common approaches, in recent publications, for modelling ventilation management. The appropriateness of the latter two is based on their ability to develop trained systems directly from available data. However it is common for authors to approach the problem by implementing classical feedback controllers (Chapman F.W, 1985, Tehrani F, 2005). The drawback of such systems is the need of a target value. The target value has to be representative of the patient's health status and the ventilation process. However a single variable could only be an estimate of the appropriateness of the ventilation settings. Furthermore the target value could not be set on normal ranges since it is usually pathology and patient specific; permissive hypercapnia is an example. Thus expert knowledge is required not only in the development phase but also during application.
In our research we have modelled the ventilation process of sedated, thus passive patients, ventilated in control mode. Several authors have modelled weaning (e.g. Chen A.H, 2007), BIPAP (Liu F, 2006) and Pressure Support ventilation (e.g. Dojat M, 2000).
Published work in the field mainly suffers from subjective decisions on the models architecture and/or decision making process. Subjectivity is introduced in the following phases of development:

- Identification of system's inputs and outputs. The decision of physiology variables and ventilator settings is based on experts' feedback, available

mathematical models and relevant published research. Unfortunately none of the presented papers provides a systematic unbiased method for selecting the variables appropriate for the task. Experts' knowledge is biased by experience and expertise, which exhibits a large variation among individuals and hospital settings. Mathematical models are biased from their inability to holistically model respiration physiology for all patient categories.

- Decision making engine. Knowledge based engines, and fuzzy rule systems (Tzavaras A 2005, Schaubin J 1996, Bouadma L 2005, Rutledge GW 1993, Kwok HF 2004, Shahasvar N 1995) depend on experts feedback, published knowledge and available protocols for designing the decision making engine. As discussed above, experts' introduce bias to the development process. Protocols are not universally accepted by clinicians. On the other hand the use of self adopting – learning tools such as neuro-fuzzy and ANN (Chen AH 2007, Liu F 2006, Kwok HF 2003, Wang A 2006), overcomes the problem of external feedback on decision making process. Unfortunately the published work that makes use of such technologies suffers from subjective decisions on the variables participating in the models (as discussed above). Alternatively authors use mathematical models for designing the DSS (Martinoni EP 2004, Laubscher TP 1994). Mathematical models are constrained from the available knowledge on respiration physiology.

Finally there is a difference in what the authors actually model. Modelling the respiration physiology does not provide us with a model of the process. Modelling the process is more often applied by a combination of knowledge base systems and inference engines (Shahsavar N, 1995 Shahsavar N, 1989, Betal S.Y, 2005). In our research we claim to have modelled the ventilation management process without incorporating knowledge base and qualitative representations. The process was modelled in two steps. First the identification of the models architecture (input-output variables) for a given pathology, based on analysis of clinicians' induced changes to ventilation settings, and second the development of models, trained with real patient data. Our attempt was to develop systems that incorporate experience, expertise and strategy.

8. Conclusions

8.1 Evaluation findings

The models' were preliminary evaluated against the evaluation data set. Models' suggestions were compared in terms of error against the clinical decisions. Evaluation has shown that ANNs utilizing the normalized - scaled recorded data performed better. The second best methods were the ANFIS and the Genetic Evolution of FRBSs. However the EVOFINE toolbox evolved FRBSs for one hundred generations (100) while the ANNs were trained with one thousand epochs (1000), mainly due to restriction of GAs computation time. Results on the mathematical function tests and on a single ventilation variable suggest that the evolution of FRBSs for more generations would produce more efficient FRBSs and probably more competitive results to the ANNs. Additionally ANFIS FRBS were developed with a simple architecture in terms of FSs, limiting their performance. The use of simple ANFIS FRBSs architectures was dictated by the small size of the training set. The FUN models performed worse than the ANFIS, ANN and the GA-FRBSs. Although we investigated the effect of different defuzzification techniques, none of them was competitive to the other AI methods.

One of the important findings of the research was that although the soft computing methods present different advantages and disadvantages in modelling ventilation management process the choice of a method is equally important to the adaptation of the systems architecture to the specific needs of a given problem.

The models' output was also evaluated against the clinical decisions made on real patient scenarios. The comparison was made between the models' suggestions and the clinical disagreement, expressed by the SD (tables 6.25 and 6.26a to 6.26c). As presented in section 7.3, table 7.1, NN empirical model was the most efficient model both in terms of suggesting settings within the clinical SD (at least 90% of the produced suggestions) in 70.6% of the developed models, but also in terms of not producing potentially hazardous suggestions for the patient. EVOFINE, NN Normalized and ANFIS have performed similarly; all three methods were capable of providing above the 90% of their suggestions, within the clinical SD in 53%, 53% and 59% of the developed models respectively. However ANFIS models under a given set of input values could result to suggestions that are potentially dangerous to

the patient in 23% of the developed models. The same hazard was identified for EVOFINE and NN Normalized models but for a significantly lower percentage (17.6% and 5.8% respectively). Many of the FUN models were producing lower ventilator settings than the clinicians' decisions. The deviation from clinical decisions was not identified as an obvious hazard and requires further clinical evaluation.

Since the identification of the appropriate models' architecture is an empirical search, tests have been performed to establish empirical guidelines. Tests were performed on the cart pole problem and on the mathematical function. The architectures with the optimum performance to the previously mentioned benchmarking problems were adapted to the ventilation management process modelling. Important findings of these experiments include: The use of damping mutation rates in developing FRBSs with GAs perform better than constant mutation rates; FRBS can be adequately modelled with a subset of the full RB; There is a balancing point for the number of FS describing its variable domain so as the system does not become deterministic but also there are sufficient FSs for partitioning the variables domain; In NN driven FL systems the defuzzification method plays an important role in the decision making performance of the model; We have developed an empirical algorithm for ensuring that the ANN nodes do not exceed the available training sets, for avoiding overtraining of the ANN, but at the same time the number of nodes satisfy Kolmogorov's theorem in order to adequately map the relationship between input and output variables; Complex ANFIS models require large training sets. To overcome this problem when training sets are limited, one has to reduce the FRBS complexity in expense to the models performance.

However since the architecture of a model is problem specific it could be the case that other architectures could perform better. This is also an important aspect that requires further investigation in future work.

8.2 Future work

Although it was attempted to approach the process of ventilation management methodologically there are suggestions for undertaking future work.

The research was concerned with ICU patients ventilated in control mode. However in order to holistically approach the ventilation management process, one should

consider assist modes and weaning process. Additionally in an automated process of ventilation management, the model should be able to identify lung pathology and automatically categorize the patient in one of the categories, and thus apply the appropriate model. Preliminary research has been carried out in this field, could be found in one of our publications (Tzavaras A, 2008).

Increasing the available data sets will potentially result into a more complete database. Additionally the large number of available data sets would allow the future researcher to increase the complexity of the models architecture, resulting into improved models' performance. This is an important issue in the case of ANN and ANFIS methods.

Limitation of the input variables to the models could also be performed with techniques such as Principal Component Analysis and Genetic Algorithms. Undertaking such a task would allow comparison of results against correlation analysis, and could possibly suggest different models' architectures.

Patients could be classified into sub-categories rather than the major three we have suggested. This would make models more pathology specific and potentially more accurate in their decision making process.

The developed models suggest ventilator settings based on a physiology variables data set which describes a specific time instance. However future research could incorporate temporal reasoning for adapting ventilator settings based on physiology trend analysis.

Alternative AI algorithms could be applied on the same problem. As Liu and Kwok (Liu F 2006, Kwok 2003) have shown other methods could be used for modelling the ventilation process. Alternatively other techniques could be used for the evolution of the FRBSs (Jamei M.et al 2004).

Furthermore an advanced GA for developing the FRBSs was suggested, based on EVOFINE toolbox. The proposed algorithm evolves independently the FSs and the RBs and assigns the performance to the FRBS according to the best combination of the available RBs in a generation with the available FSs. According to this method, the best mating pairs will be assigned with better fitness scores and thus the best FRBSs, which are described by the most appropriate combinations of RB and FSs, will have higher probability to advance to the next generation.

Resulted models could be evaluated by ICU clinicians. Examination of the systems decision making process could exclude potentially dangerous suggestions by the

models, allowing the models to be tested in the ICU setting. Although this is relatively straightforward to inference engines (GA-FRBS and ANFIS), the same is not true for models based on ANN (ANN and NN driven FRBS). In the case of ANN it is important to establish a methodology for allowing clinicians to understand its' decision making process.

8.3 Contribution of research

The presented approach has contributed in the field of IDSS applied in ventilation management in the following ways:

- Real patient physiology and ventilator settings data were collected and categorized in three lung pathologies. The produced database will be available for the research community.
- Statistical analysis of experts' opinion and evaluation of the collected data has suggested different architectures for three basic lung pathologies and six ventilator settings models. The proposed architectures could be used by other authors for evaluating different soft computing methods.
- Different soft computing methods were applied and evaluated in ventilation management. The performance as well as the advantages and disadvantages of each method for their application in ventilation management have been identified.
- The proposed approach to our best knowledge describes more holistically ventilation management compared to published work in the following ways:
  - It models the process rather than the physiology, developing intelligent models which embed the experience & expertise of the ICU personnel.
  - It is concerned with the decision making of multiple ventilation settings.
  - It categorizes patients into different lung pathologies for developing models.
  - It does not rely on pre-developed models for simulating human physiology but rather on real patient data.
  - It investigates the appropriateness of different AI methods, as opposed to a single method, for the task and compares their performance.

- The results are not compared only between the models but also against clinical suggestions on real patient scenarios.

- A new method for coding FRBS in chromosomes was suggested and evaluated. Results suggest that the proposed method evolves efficient FRBS assuming no prior knowledge of the architecture. The developed Matlab toolbox (EVOFINE), was not designed for the specific task and thus it can be applied to other modelling problems.
- Research has shown that computation time of evolving FRBSs could be reduced without compromising performance. Experiment results have shown that one can overcome the problem of increased computational resources efficiently by evolving FRBSs with a subset of the total rules describing the system. Additionally utilizing damping mutation rates evolve faster FRBSs to an optimum solution, thus saving computation time.

8.4 Final conclusions

Concluding on our initial research question and research findings, we summarize the following:

- The complexity of the ventilation management problem was significantly reduced with the application of statistical tools. ICU personnel feedback analysis has resulted into simplified models architectures for three lung pathologies.
- The ventilation management process could be adequately modelled with the synergetic utilization of AI techniques. Results suggest that the majority of the NNs, EVOFINE and ANFIS models were producing advice within the clinicians' disagreement.
- The appropriate AI method for the task is, by performance order, the ANN empirical, the ANFIS and the genetically evolved FRBSs, followed by NN driven FRBS. Evaluation against clinical recommendations has shown that ANNs performed better; mean average error as percentage of the best three techniques was 0.16%, 1.29% & 0.62 for ANN empirical, 0.05%, 2.23% & 2.30% for ANFIS and 0.93%, 2.33% & 1.89% for EVOFINE in Normal, COPD and ALI-ARDS categories respectively. Additionally evaluation

against clinical disagreement has shown that 70.6% of the NN empirical models were performing in 90% of their suggestions within clinical SD, while the percentages were 53%, 53% and 59% for the EVOFINE, ANFIS and NN Normalized models respectively. Additionally the NN empirical was not producing hazardous advices, while EVOFINE, ANFIS and NN Normalized were shown to produce potentially hazardous advice in 17.6%, 23% and 5.8% of the developed models. Thus it is suggested that models should be safeguarded against "excessive" produced advice.

- The main drawback of the ANN is that their input – output relationship is a black box. However it is possible and important prior to clinical evaluation to extract the NNs decision making logic with rule extraction techniques. GAs evolved FRBS require intense computational resources for competing with ANN. However the resulting model is transparent to the user. ANFIS requires a high number of training sets for delivering optimal results. In our research we were forced to utilize a very basic fuzzy architecture (only two FSs for each variable), due to lack of large amount of training sets. FUN models performance relies mainly on the defuzzification technique. The FUN performance in modelling ventilation management was the worst among soft computing techniques and for this reason it is not suggested as a vehicle for future research.
- The choice of architecture of the applied AI is equally important to the choice of the soft computing technique. It could be the case that the developed models could improve their performance by adapting different architectures. However the choice of the appropriate architecture is a complex problem on its own, and is usually problem specific.

To our best knowledge and efforts we have approached the ventilation management process holistically. We have shown the benefits and drawbacks of different intelligent decision support methods, and we have suggested future research approaches to the ventilation management process.

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Appendix I: Ventilation monitored variables and clinical targets

I.1 Blood Gases and pH

Blood gases and pH measurements are important in ventilated patients for the evaluation of oxygenation, ventilation and acid-base balance. Measurements could be performed on arterial and venous blood, directly with invasive measurements or indirectly with non-invasive measurements.

Partial pressure of oxygen in arterial and venous blood (PaO_2 and PvO_2), partial pressure of venous carbon dioxide ($PaCO_2$ and $PvCO_2$), and hydrogen ion concentrations (pH), are commonly measured in ICU. Invasive measurements are performed by directly sampling arterial or venous blood. Laboratory instrumentation is used for measuring the above variables. The advantage of this technique is accuracy of measurements. However for invasive measurements, patients are usually catheterized and there is a time gap between sampling and reporting on measurements. The normal adult values for blood gases are given in table I.1.

Table I.1: Physiological values for blood gases (Marieb E.N. 1995).

Variable (mm Hg)	Normal Value
PaO2	104
PvO2	40
PaCO2	40
PvCO2	45

Other technologies have been developed for providing a good estimation of blood gases utilizing non invasive measurements. Pulse oximetry (SaO_2) and end tidal capnography (E_TCO_2), are commonly used.

Pulse oximetry use light absorbance in two wavelengths to measure the concentration of oxygenated hemoglobin as a percentage of the total hemoglobin, giving a good indication of patient's oxygenation. The relationship between PaO_2 and oxygen saturation of hemoglobin is described by a sigmoid curved, named oxyhemoglobin dissociation curve (Fig I.1). The affinity of hemoglobin for oxygen

increases with higher PO_2. Unfortunately this is not the only factor affecting the affinity of hemoglobin. The molecule environment, changes the affinity. The change is graphically described by a shift to the left or right of the dissociation curve. Shifts to the right caused by acidosis, hypercarbia, hyperthermia and diphosphoglycerate (DPG), decrease the affinity. Shifts to the left caused by alkalosis, hypocarbia, hypothermia, decreased DPG and COHb increase hemoglobin affinity (Moyle J.T.B. 1994). Thus a reading of oxygen saturation is not clinically reliable concerning oxygenation, unless other factors are known.

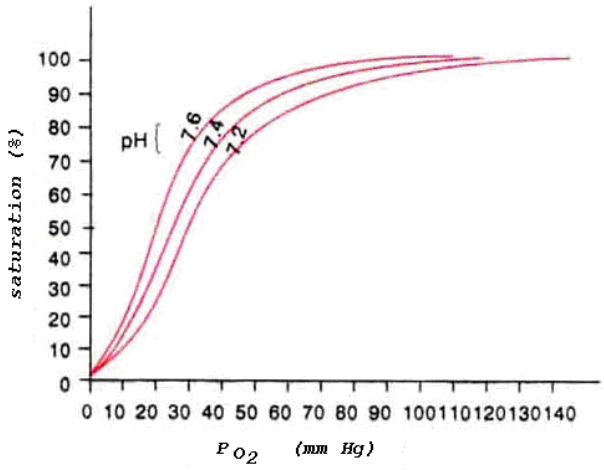


Figure I.1: Oxyhemoglobin dissociation curve. Shift caused by pH changes.

End tidal capnography, measures the concentration of carbon dioxide at the end of the expiration phase directly on the expired gases (main stream capnography), or by suctioning a sample of the expired gases (side stream). Measurement utilizes infrared light, where carbon dioxide exhibits absorbance peak. E_TCO_2 provides an estimation of alveolar P_{CO2} (P_ACO_2). Under normal ventilation-perfusion ratio (V/Q), the P_ACO_2 approximates $PaCO_2$. The difference between arterial and end tidal carbon dioxide pressures is usually smaller than 5 mmHg.

However both methods have limitations. Pulsed oximetry has accuracy of +/-4%, and measurements assume that carbohemoglobin (COHb) and methehemoglobin (metHb) concentrations are low. Furthermore vascular dyes affect the accuracy of readings, and low arterial pressures contribute in false measurements. When the V/Q ratio changes, usually due to changes in dead space, E_TCO_2, may be less than arterial. Presence of other gases that exhibit similar absorption peaks to infrared

light, such as N_2O used in anesthesia and humidity decrease the accuracy of the method.

Trancutaneous PO_2 and PCO_2 ($PtcO_2$ & $PtcCO_2$), utilize polarographic and Severinghaus electrodes respectively to measure blood gases. Electrodes are attached to patient's skin and heated to 44^o C. Measured gases are different than actual blood gases. In adults $PtcO_2$ is less than PaO_2, and $PtcCO_2$ is higher than $PaCO_2$. To overcome this problem manufacturers incorporate a correction factor, so that the displayed values are approximating the real values. Due to increased local skin temperature frequent changes in electrode position are necessary.

Since the driving force of gas exchange between alveolar gases and pulmonary arteries is the difference of partial pressures, one can improve oxygenation by changing alveolar concentrations. In atmospheric air and for normal breathing subjects the pressure gradient P_AO_2-PvO_2 is 64 mmHg, while for P_ACO_2-$PvCO_2$ is -5 mmHg. The mathematical relationship describing O2 partial pressure in alveoli is described in equation I.1 (Hess D.R., Kacmarek R.M. 2002).

$$P_AO_2 = FiO_2 * (Pb - P_{H2O}) - (PaCO_2 * (FiO_2 + (1 - FiO_2) / R) \qquad \text{eq. I.1}$$

Where:

FiO2 : inspired O_2 fraction.

P_{H2O} : water vapor pressure (47mmHg at 37o C)

R : respiratory quotient (CO_2 production / CO_2 consumption)

Pb : barometric pressure

The alveolar oxygen tension depends mainly on concentration of inspired oxygen. Increasing FiO_2 raises the driving force for diffusion of O_2 to blood through the lung membrane. However use of FiO_2 above 0.6 should be limited to short time due to oxygen toxicity. A simple method for calculating desired FiO_2 is given by the following formula (Pilbeam S.P. 1986):

$$(known)(PaO_2 / FiO_2) = (desired)(PaO_2 / FiO_2) \qquad \text{eq I.2}$$

Clinicians try to maintain blood gases close to normal levels (normal range of $PaCO_2$ is 35-45 mm Hg, and PaO_2 is 80-100 mmHg). In order to evaluate adequacy of

patient's oxygenation they use oxygen-tension indices (Hess D.R., Kacmarek R.M. 2002). The following indices are commonly used:

- Oxygenation Index (**OI**): is defined by the ratio of PaO_2/FiO_2. It is easy to use since there is no need for alveolar tension calculation. When the ratio is below 200 indicates ARDS, and ratio of 200 to 300 indicates lung injury.
- Respiratory Index (**RI**): is given by dividing the gradient $P_{(A-a)}O_2$ by PaO_2. Changes in $PaCO_2$ will not affect the nominator since its value is included in alveolar tension calculation.

$PaCO_2$ as described by equation I.3 is determined by tissue CO_2 production ($\overset{o}{V}_{CO_2}$), minute ventilation ($\overset{o}{V}_E$), and dead space/ tidal volume ratio (V_D/V_T). Dead space is the portion of minute ventilation that does not participate in gas exchange. Normal value of V_D/V_T ratio is between 0.2 and 0.4. Pulmonary embolism, mechanical ventilation, and hypo perfusion are the main causes of ratio increase.

$$PaCO_2 = (\overset{o}{V}_{CO_2} * 0.863) / (\overset{o}{V}_E * [1 - V_D / V_T]) \qquad \text{eq I.3}$$

In order to maintain a normal $PaCO_2$ when dead space or CO_2 production increases, clinicians have to increase minute ventilation. If the level of minute ventilation is very high, at levels which might result in ventilation injuries, then $PaCO_2$ is allowed to increase. This is termed as permissive hypercapnia. When alveolar ventilation decreases, $PaCO_2$ elimination is maintained stable; at higher levels of $PaCO_2$ (Hickling K.G, 1998). Reduction of minute ventilation is counter balanced by the reduction of dead space and increased cerebral blood flow.

Supra-atmospheric pressure at end expiration, referred to as PEEP, improves oxygenation by: preventing alveolar collapse, increasing functional residual capacity (FRC), and by decreasing intrapulmonary shunt. Excessive increase of PEEP may increase perfusion to well ventilated areas.

Measurement of hydrogen ion concentrations are made invasively and expressed as pH. Hydrogen ion is used as an indicator of the acid-base balance in blood. Acid base balance is expressed by Henderson-Hasselbalch equation (Hess D.R., Kacmarek R.M. 2002) :

$$pH = 6.1 + \log[HCO_3^-]/(0.03 * Paco_2) \qquad \text{eq I.4}$$

Respiration is the main mechanism for disposing bicarbonate acid; disposal rate is 10 times higher than kidneys (West J.B, 2004). Changes in the numerator of eq I.4 are metabolic acid-base disturbances, while changes in the denominator are respiratory related. If $PaCO_2$ increases then pH falls. The opposite is true when $PaCO_2$ decreases. Target pH value in ventilated patients is 7.35 to 7.45, if there is deviation below or above this level, we have acidosis and alkalosis respectively. Changes in pH can be compensated by changes in minute ventilation. Hyperventilation could decrease pH values, while hypoventilation will lead to increasing pH values. If renal and cardiovascular functions are adequate, pH values as low as 7.20 can be tolerated. However respiratory alkalosis should be avoided.

I.2 Lung Mechanics and Work of breathing

Respiratory passageway resistance (R), lung Compliance (C) and Elasticity (E) and alveolar surface tension, are factors that influence flow and volume delivery to the lungs. Resistance to ventilation is due to the anatomical structure of the conductive airways, the tissue resistance of the lungs and adjacent structures. Resistance is defined as the change in pressure for a given flow (eq. I.6), and is usually expressed in cm H_2O / (L/sec). In normal individuals the Resistance is about 0.6 to 2.4 cm H_2O / (L/sec). Lung Compliance is a measure of the change in lung volume that occurs with a change in intrapulmonary pressure and is measured in L/ cm H_2O (eq. I.5), and describes the stretchability of the lungs and chest wall (Ganong W.F. 1975). Elastance (E) and Conductance (G) are the reciprocals of C and R respectively, but are less commonly used (Pilbeam S.P. 1986).

$C = \Delta V / \Delta P$ eq. I.5

$R = \Delta P / \Delta F$ eq. I.6

$E = 1/C$ eq. I.7

$G = 1/R$ eq. I.8

Respiratory system static compliance (C_{RS}), it is the usual method for measuring respiratory system compliance. C_{RS} is a good indicator of system's compliance since dynamic compliance (eq I.5) is approximately linear except at the extremes of volume. C_{RS} is defined as the change in volume at end inspiration (V_T) over the end inspiratory pressure ($P_{plateau}$), minus total PEEP:

$$C_{RS} = V_T / (P_{plateau} - {}_{total}PEEP) \qquad \text{eq I.9}$$

Measurements of C_{RS} require a passive patient, thus control ventilation. C_{RS} is used to adjust ventilation strategy, either by changing the drug administration strategy (e.g. administration of bronchodilating drugs), or changing the minute ventilation. Reduced C_{RS} is often an indication of hyperinflation, suggesting lower volume delivery. PEEP values that maximize C_{RS}, allow for maximum oxygen transport with the lowest dead space (Shapiro R.S., Kacmarek R.M., 1998).

C_{RS} is actually the sum of chest wall (C_{CW}) and lung compliances (C_L) (eq I.10). Ventilation tubing compliance should be measured and subtracted from C_{RS}.

$$1/C_{RS} = 1/C_L + 1/C_{CW} \qquad \text{eq I.10}$$

Respiratory system resistance (R_{RS}) is the sum of lung (R_L) and chest wall (R_{CW}) resistance. R_L is further divided into resistance airway (R_{aw}) and tissue resistance (R_{LT}). R_{CW} and R_{LT} have a small contribution to overall resistance. Thus clinical measurements focus on R_{aw}.

Resistance varies with respiration phase, lung volume and flow rate. Increased tidal volume expands airway diameter, thus decreasing resistance. At low flow rates resistance is linear, while at high flow rates turbulence and pressure friction losses increase, resulting in an exponential flow pattern.

Inspiratory resistance (R_I), is calculated with different methods. Usually clinicians monitor the maximal resistance which is given by the eq I.11.

$$R_I = (PIP - P_{plateau}) / \overset{o}{V}_I \qquad \text{eq I.11}$$

Where: PIP, is Peak Inspiratory Pressure and $\overset{o}{V}_I$ *is inspiratory flow.*

In patients with ARDS an increase in R_{RS} is observed at high volumes or high PEEP levels. When we measure R_{RS} we include the endotracheal tube resistance (R_{ET}). R_{ET} should be subtracted for precise measurements of R_{RS}.

Expiratory resistance (R_E), exceeds R_I, showing large deviations in subjects with airflow obstruction. Increased R_E may suggest problems in the expiratory circuit (valve or water condensation). Insufficient expiration time could lead to auto-PEEP.

The simplest method to calculate R_E is by the passive exhalation time constant method. The time constant, in analogy to electronics, determines the rate of change in the volume of a lung that is passively inflated or deflated, as shown in the following formula:

$$V(t) = V_T * e^{-t/\tau} \qquad \text{eq I.12}$$

For the respiratory physiology the time constant (τ) is given by the product of resistance and compliance. Thus once we have determined the compliance, we can utilize the time taken to passively exhale volume at a level close to 63% of V_T to derive expiratory resistance as shown in eq I.13.

$$R_E = \tau / C_{RS} \qquad \text{eq I.13}$$

Assessment of patient's breathing workload is useful in determining the adequacy of ventilation support, improving patient-ventilator interactions in assist ventilation, and predicting ventilator dependence.

The work of respiratory muscles is assessed by the mechanical work of breathing and the oxygen cost of breathing. The ratio of these two is the mechanical efficiency of the respiratory muscles.

Work of breathing (WOB) is the work in joule (J), required to move 1L of gas through a pressure gradient of 10 cm H_2O. In healthy adults, the work of breathing is approximately 0.5J/L.

The inspiratory work of breathing during controlled ventilation is derived by the integral of the airway pressure versus volume (eq $I.14_a$). The work is performed by the apparatus. When compliance, resistance and flow are constant, mean airway pressure is a good approximation of work (eq $I.14_b$).

$$W = \int_0^{TI} P * \overset{o}{V} dt \qquad \text{eq I.14}_a$$

$$\bar{P}_{insp} = R_{RS} * V_T / T_I + 1/2 * V_T / C_{RS} + P_{ex} \qquad \text{eq I.14}_b$$

Where :

T_I : inspiration time

P_{ex} : Expiratory pressure (total PEEP)

During spontaneous breathing, the work is performed by respiration muscles. The work of the lung W_L, can be measured if an estimation of pleural pressure (P_{es}) is available, using the following formula (Sasson C.S.H., Mahutte C.K., 1998):

$$W_L = \int_0^{T_I} (P - P_{es}) * \overset{o}{V} dt \qquad \text{eq I.15}$$

When a patient is ventilated in assisted mode, inspiratory work is calculated by the difference between ventilator work and assisted work.

PEEP is an important determinant of WOB in spontaneous breathing. This is due to the fact that it places a threshold load to respiratory muscles, and also an elastic load due to hyperinflation. WOB has shown to increase from a mean of 0.48J/L without PEEP, to 1.7J/L with PEEP.

Given minute ventilation can be achieved through a wide combination of ventilation frequency and tidal volumes. The optimal frequency is the one that minimizes the WOB (Sasson C.S.H., Mahutte C.K., 1998).

During a patient's ventilation, WOB imposed by the endotrachial tubing (ET) is substantial. Flow resistance both in inspiration and expiration imposes work amounting to 70-80% of the total work. During mechanical ventilation PEEP has two different effects. It might increase WOB due to thoracic over distension, or it could decrease it due to improved lung compliance, decreased airway resistance, and prevention of alveoli collapse.

WOB is affected by ventilator settings. Trigger sensitivity is closely related to a patient's efforts to breath. Also the type of trigger imposes different WOB to the patient. Pressure trigger WOB is greater than flow trigger. Similarly PEEP increases the muscle effort to trigger a breath.

Once the inspiration is triggered, flow demand and ventilator capability to deliver affect WOB. In Pressure Support Ventilation (PSV), the larger the pressure gradient

the higher the flow delivered to the patient. When the delivered flow exactly matches patient's demand, then no assistance is given to muscles work. Once the flow exceeds the demand, patient WOB is decreased. However increase of flow beyond a level, may cause resistance to inspiration by the patient and result in patient-ventilator asynchrony.

Ventilation mode play also important role. When a patient is under sedation or paralysis, WOB is zero. During SIMV the WOB is defined by the percentage of assistance. If assistance accounts for greater than 60% of total ventilation, then WOB is reduced to 50%.

Oxygen cost of breathing (V_{O2}resp), "is the difference between the resting total body oxygen consumption ($\dot{V}_{O_2}$), and the total body consumption when breathing is altered" formula (Sasson C.S.H., Mahutte C.K., 1998). Measurement of $\dot{V}_{O_2}$ is made by measuring oxygen concentrations in inhaled and exhaled volume (eq I.16).

$$\dot{V}_{O_2} = FiO_2 * \dot{V}_I - FiO_2 * \dot{V}_E \qquad \text{eq I.16}$$

In healthy individuals V_{O2}resp is between 0.25 and 2.5 ml/L of ventilation, which is approximately 5% of total body oxygen consumption. Patients with COPD, $\dot{V}_{O_2}$ resp is larger and strongly influenced by body weight.

I.3 Volume, Pressure, Flow and respiration rate.

A typical flow-pressure curve of volume controlled ventilation is shown in figure I.2. Constant flow is delivered to the patient during inspiration phase. Since flow is a constant volume varies linearly. End of inspiration time is triggered when a patient has received a specific volume. Airway pressure reaches its peak value (PIP), at the end of inspiration phase. A pause follows inspiration where there is no flow of gases to and from the lungs. During this phase, pressure drops to a plateau value, mainly due to redistribution of lung volume to other un-inflated areas. Expiration phase is performed by allowing the patient to exhale to atmospheric or PEEP pressure. In the example of figure I.2, exhalation is performed on supra-atmospheric level.

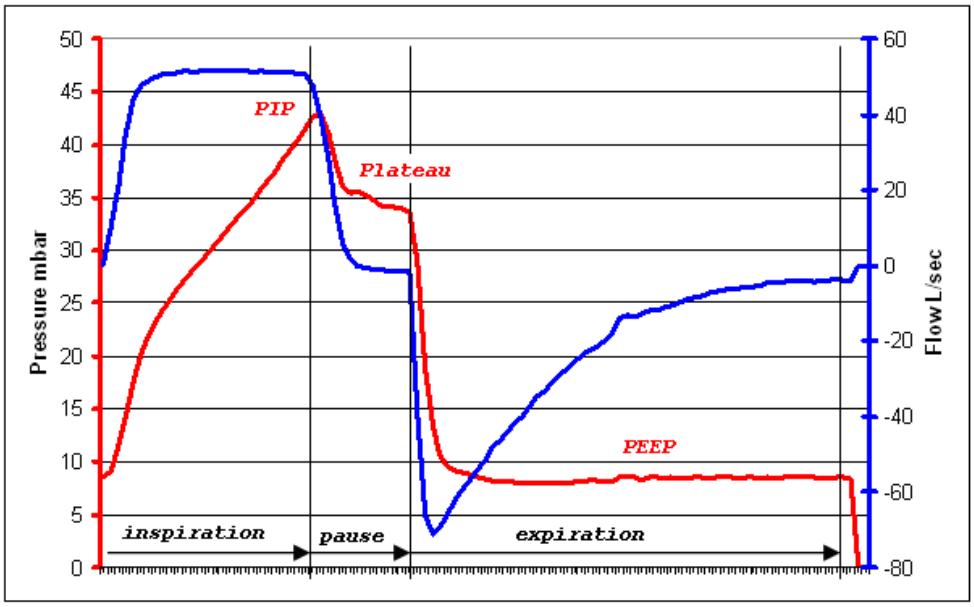


Figure I.2: Pressure & flow curves, recorded from ICU patient.

During initiation of mechanical ventilation, ICU clinicians are concerned with appropriate ventilator settings. Initial settings and physiology variables are monitored closely in the first few hours in order to take corrective actions.

General guidelines for initiation phase include:

- Initial tidal volume (V_T), may vary from 4 to 12 ml/Kg, depending on lung mechanical properties and patho-physiology. Normal lungs may be ventilated with V_T between 10-12 ml/Kg, while individuals with a chronic or obstructive disease may require lower volumes, 4-8 ml/Kg.
- Setting of pressure level is partially determined by desired V_T. Sufficiently high maximum pressure should be chosen, to enable volume delivery. Plateau pressure should not exceed 30 cm H_2O.
- However both V_T and Peak settings should be set so as to prevent lung injuries. Pressure limit usually exceeds peak by 5 to 10 cm H_2O. Similarly a low pressure limit is established a few cm H_2O below peak to act as an indication of significant circuit leaks.
- Respiration rate (RR), is usually set between 8 to 15 breaths per minute (BPM). In the presence of obstructive disease, low rates between 8-10 BPM are chosen. Normal pulmonary mechanics are ventilated with RR of 8-12 BPM.

- At the initiation phase, patients are ventilated with a FiO_2 of 1 (100% O_2). Due to oxygen toxicity, the FiO_2 level should drop below 0.6, within a few hours from initiation. PEEP is initially set around 5 cm H_2O, to increase FRC, unless cardiovascular instability is present.
- Descending flow pattern improves V_T distribution in comparison to constant flow. Peak flow should be adequate to insure inspiration time of 1 sec.

The equation of motion for the respiratory system formula (Sasson C.S.H., Mahutte C.K., 1998), describes the airway opening pressure (P_{ao}) required to drive gas into the lungs.

$$P_{ao} = \overset{o}{V} * R_{RS} + V(t) / C_{RS} + P_{ex} \qquad \text{eq I.17}$$

During controlled ventilation P_{ao} reflects the mechanical properties of the respiratory system. For a given flow and V_T, changes in compliance and resistance are reflected on PIP. Plateau pressure ($P_{plateau}$) is equal to alveolar pressure since there is no flow. $P_{plateau}$ is the pressure needed to inflate lungs with a specific V_T above end expiration pressure (P_{ex}).

Mean airway pressure ($_{mean}P_{ao}$), is the P_{ao} averaged over the entire respiratory cycle. Its value is important since it is correlated with arterial oxygenation and venous return.

Valuable information is also derived from the pressure curve shape. In constant flow ventilation, the initial rapid increase in P_{ao} indicates the pressure needed to overcome resistance. Increases in magnitude of the initial rise in P_{ao}, suggest increased resistance. The following linear increase indicates the pressure to overcome compliance. Changes in the shape of the second portion are related to changes in C_{RS}.

During assisted ventilation the pressure curve provides information on the patient's effort.

Flow trace profile remains constant during flow controlled ventilation. However this change during pressure controlled ventilation is heavily influenced by lung mechanics. In pressure controlled ventilation the driving force of airflow into the lungs is the difference in pressures between airways and alveolar pressure. As these pressures become equal, flow drop to zero. The flow curve shape is a decelerating ramp. Changes in the deceleration slope suggest changes in mechanical properties. If a time limit is reached before the flow becomes zero, an increase in respiration

duration is suggested causing an increase in V_T. Inspiration time (T_I) could be altered using the formula (Hess D.R., Kacmarek R.M. 2002):

$$T_I = (V_T)/(0.5)(\overset{o}{V}_{pk} + \overset{o}{V}f) \qquad \text{eq I.18}$$

where:

V_{pk} : is the peak flow (L/min)

Vf :is the end inspiration flow (L/min)

Persistence of end expiratory flow may indicate auto-PEEP. Auto-PEEP reflects the amount of air trapped in lungs above preset PEEP. Auto-PEEP usually suggests dynamic hyperinflation of the lungs; could be dangerous for the patient since it increases the risk of barotraumas, and WOB.

Managing a zero end inspiration flow, could be also succeeded by increasing peak flow, as follows (Hess D.R., Kacmarek R.M. 2002):

$$\overset{o}{V}_{pk} = [V_T - (0.5) * (\overset{o}{V}f * T_I)]/[0.5 * T_I] \qquad \text{eq I.19}$$

Inspiration and expiration time relationship is an important consideration in mechanical ventilation. Usually the relationship is expressed as I/E ratio. Ratios that increase inspiration time (e.g. 1/1, 2/1), increase mean airway pressure, with positive results to oxygenation and decreased cardiac output. Short expiration times are not sufficient for exhaling total tidal volume, thus leading to auto-PEEP. Usually I/E ratios of 1/2 are used for adult ventilation.

Advanced monitoring includes flow-volume and pressure-volume loops. Flow-volume loops display flow (Y axis) as a function of volume X (axis). During passive ventilation inspiration flow shape is dictated by the ventilator (in flow control) and lung mechanics (in pressure control). Exhalation shape provides information on airflow obstruction. Pressure-volume loops display volume as a function of pressure. The slope of the curves is the lung-chest compliance. P-V loops are used for determining appropriate PEEP levels. However measurements are made with sedated patients and identification of the correct PEEP level might require curve fitting mathematics.

I.4 Cardiovascular variables

Respiration physiology could not adequately describe tissue oxygenation without considering blood circulation. The integrated system of cardio respiratory unit includes ventricles, atriums, and arterial, venous and peripheral blood circulation.

During mechanical ventilation clinicians monitor hemodynamic variables, invasively through catheters. Central venous pressure (CVP), pulmonary artery pressure (PAP), pulmonary capillary wedge pressure (PCWP) and cardiac output (CO), are commonly monitored. CVP is monitored with the use of a catheter located in the superior vena cava (right atrium RA). CVP reflects the performance of right atrium (RA), thus the blood supplied to the right ventricle (RV).

Pulmonary pressures are monitored with a balloon tip catheter, capable of inflating and blocking blood circulation. Elevated PAP may indicate left-right shunt, left ventricular (LV) failure, mitral stenosis or pulmonary hypertension.

Cardiac Output (CO) is commonly measured with the thermo-dilution method, where a cold solution (bolus) is ejected into the RA, changing blood temperature. The changes in temperature are measured downstream and are used for computing CO. CO is normalized to patient's size by dividing it by body surface area (BSA). The ratio is called cardiac index (CI). Stroke volume is calculated by dividing the CO with the heart rate.

The mechanisms of heart – lungs interactions are many. One could find a good description and literature survey in chapter 14 of the Marini & Slutsky book (Pinsky M.R., 1998). This paragraph will attempt to briefly describe the cardio-effects of positive pressure ventilation.

Heart pump compensates for lung deficiencies by changing CO. When individuals breathe lung volumes below 10 ml/Kg, the heart rate increases. The opposite is true when lung volumes exceed 15 ml/Kg. This inspiration associated cardio acceleration is termed sinus arrhythmia (Pinsky M.R., 1998).

Pulmonary vascular resistance is modified by mechanical ventilation. Reduction of pulmonary vascular resistance is succeeded by increasing P_AO_2, re-expanding collapsed alveoli, reversing acute respiratory acidosis, or decreasing central sympathetic tone. Changes in lung volume cause changes in airways and extra-

alveolar vessels diameters. Decreasing volume leads to increasing vascular pulmonary resistance. If RV volume increases due to increased pulmonary vascular resistance, then ventricular interdependence will cause LV diastolic compliance to increase.

Mechanical ventilation may affect hemodynamic operation. During positive ventilation pleural pressure (P_{pl}) increases during inspiration and decreases during expiration; reversed function compared to spontaneous breathing (Hess D.R., Kacmarek R.M. 2002). Pleural changes affect CVP. Increased P_{pl} causes a decrease in venous blood return. Clinicians monitor changes in CVP to evaluate ventilation. A large decrease in CVP suggests high WOB, while a large increase suggests high lung compliance relative to chest compliance. PEEP and mean airway pressure affect CVP. The degree to which the changes in lung pressure are transmitted to P_{pl} is related to the lung and chest compliance. The change in P_{pl} (ΔP_{pl}) is described in eq I.20

$$\Delta P_{pl} / P_{aw} = C_L /(C_L + C_W) \qquad \text{eq I.20}$$

Appendix II: Custom Toolboxes

II.1 EVOFINE & FUN Matlab toolboxes

We have designed and developed two custom Matlab (®Mathworks) toolboxes, namely EVOFINE and FUN.

The EVOFINE toolbox (**EV**olution **O**f **F**uzzy **IN**ference **E**ngines) is capable of evolving FRBS with the use of available training data. FUN toolbox (**FU**zzy **N**eural) applies ANN for developing a trained RB of the FRBS based on available training data.

In the following paragraphs we describe in detail the architecture of the toolboxes. Both architectures were designed as general purpose tools and not specific for our research, allowing future researchers to utilize them in similar research areas. Both toolboxes were evaluated for their performance prior to their application in our research. Evaluation was performed by developing FRBS for modelling a multi input single output (MISO) systems. Two approaches were used for evaluation. The first was to test performance against non linear mathematical function, and the second was to test performance against a benchmarking control problem namely the cart pole balancing dynamic system.

II.2 Fuzzy System and Genetic algorithm

We have designed and developed a Matlab (Mathworks ®) toolbox for automatically generating FRBS from available input(s) – output(s) data in Excel (®Microsoft) format. The toolbox utilizes a modified version of the University of Sheffield's GAs toolbox (Evolutionary Computation Research Group, 1994) for Matlab.

Genetic Algorithms were chosen as the appropriate method for identifying the optimum structure of the fuzzy system, where no prior knowledge of the Knowledge Base (KB) was assumed. The system's fuzzy inference engine is based on Mamdani architecture, and the centroid method was chosen as the appropriate defuzzification method.

The EVOFINE toolbox allows the user to define fuzzy systems' variables in addition to the GAs settings, as shown in figure II.1.

User defined FRBS characteristics:

- Number of Inputs.
- Number of Outputs.
- Number of Fuzzy Rules.
- Number of Fuzzy Sets (membership functions) for input-output.
- Type of membership functions (Trapezoid-Triangular or Sigmoid-Gaussian).
- Domain of each input-output variable.

User defined GA settings:

- Number of Generations.
- Number of Individuals in each generation.
- Mutation type could be either constant or variable (damping).
- Mutation Rate.
- Crossover Rate.
- Use of scaling function as described in Goldberg (Goldberg D.E, 1989).
- GAs selection type, either Roulette Wheel Selection (RWS) or Stochastic Universal Sampling (SUS).

EVOFINE codes FRBS into two chromosomes. The first chromosome codes the membership functions in real format. The coding process depends on the selected membership function type. The second chromosome describes the fuzzy rules and rule weights. The coding process is described in detail in paragraph II.2.1. The chromosome pair (Fuzzy Sets & Rules) defines the KB of the FRBS. Each individual pair of the population is evaluated against the available data training set. The fitness function (error) of the GAs is described by equations II.1 & II.2, and describes the root mean square error (*rmse*) as a percentage scaled over the output range. While the mean square error (*mse*) provides a measure of model's error against available data (Achiche S et al ,2004; Bowerman B.L), the *rmse* returns the error to the same units as the data. The representation of *rmse* as a percentage scaled over the variables range, allow us to compare the error between variables of different domains and units. The GAs target is to evolve individuals which minimize the error, thus best describe the system.

$$rmse = \sqrt{\frac{1}{N}\sum_{i=1}^{N}\left[\left(FRBS_{out(i)} - data_{out(i)}\right)^2\right]} \qquad eqII.1$$

$$\%error = \frac{mse}{abs\left[\max(data_{out}) - \min(data_{out})\right]} * 100 \quad eq\ II.2$$

Where N: is the number of available training data.

Figure II.1 describes the EVOFINE setup screens. The top window is the main menu. The main menu allows the user to define basic setup; store and test develop systems and observe the evolution process (fitness value and generation number). GA setup menu (fig. II.1, bottom left) is used for controlling the GAs process in terms of number of individuals in each generation, number of generations the algorithm will run and GA evolutionary variables. Fuzzy Setup (fig. II.1, bottom right), prompts the user to define basic fuzzy architecture such as number of rules and fuzzy sets for each variable, as well as correspond input variables to spreadsheet columns.

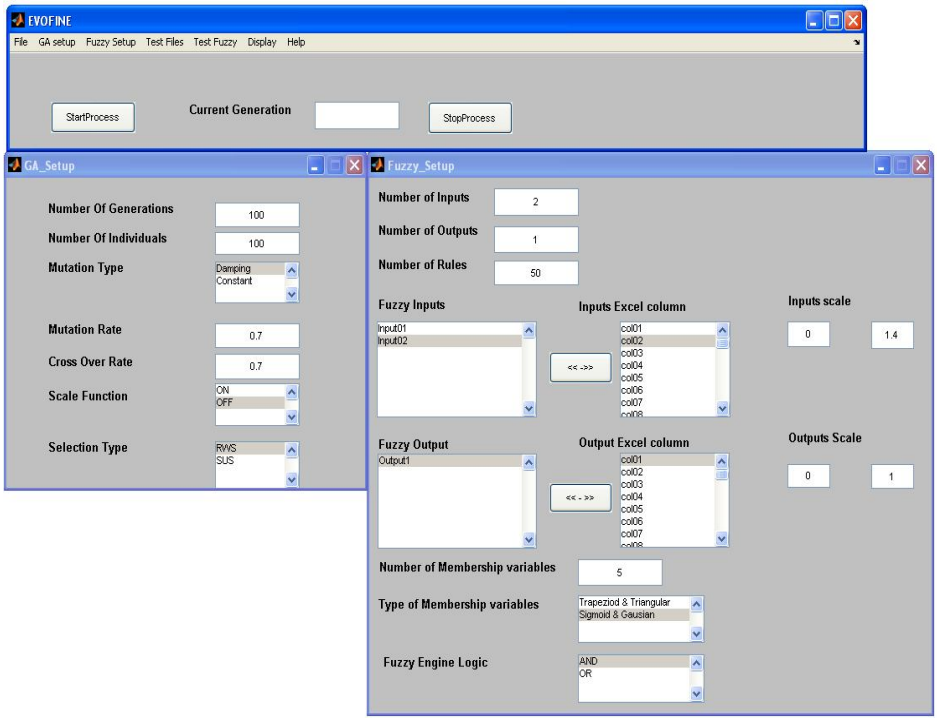


Figure II.1: Snap shot of EVOFINE toolbox.

The method validation was based on the ability of EVOFINE to evolve FRBS that describe mathematical relationships, based on a defined input – output set, following a similar method to Achiche (Achiche S et al 2004), and model systems such as the cart pole system.

We have tested the systems performance against multi inputs – single output systems (MISO), utilizing the mathematical equation of z=sin(x*y) and the inverse cart pole system.

II.2.1 Fuzzy Sets and Rules Coding.

The chromosome coding was based on Pittsburg approach, where the fuzzy set - fuzzy rules pair described the system's inference engine for each individual in the population.

The Pittsburgh approach was chosen, because it evolves the entire fuzzy system, dealing efficiently with the competition – cooperation problem of the RB set. However the evolution of full FRBSs is penalized by the increased computational time. The Michigan approach was not adopted on the grounds that each individual represents a single rule. Since rules compete it is difficult to identify a credit policy that promotes cooperation of rules. On the other hand the Michigan approach requires less computational resources. Similarly the iterative rule learning, utilizes an incremental rule base policy which can lead to sub-optimal FRBSs (Pena-Reyes C.A, 1999; Carse B., Fogarty T.C, 1996). Finally symbiotic evolution (Jamei M, 2004), is merging Pittsburgh and Michigan algorithms by randomly combining individual rules from a given population to form FRBSs. Each resulted FRBSs is evaluated and a fitness score is assigned to each participating rule. Although this approach combines the advantages of the Michigan & Pittsburg algorithms, it requires safeguarding algorithms against loss of overlapping of the Membership Functions (MFs)similarity of MFs participating in the solution and also non-participation of MFs. Due to its increased complexity, symbiotic evolution is computationally intense.

The coding of the FRBS is performed by generating two chromosomes. The first chromosome is in real format and describes the position and shape of the membership functions. The second chromosome is in integer format and describes the fuzzy rules as well as the weight of each rule.

The coding process of five (5) Trapezoid–Triangular shaped and Sigmoid-Gaussian membership functions is graphically described in figure II.2 and II.3 respectively.

The coding between the different types of membership functions differs in the number of elements required to describe the membership functions. While Trapezoid and Triangular membership functions need 4 and 3 elements respectively, Sigmoid

and Gaussian functions require only 2 elements. Gaussian functions are described by the center position (c) and the spread (σ) of the function as in equation II.3 (Matlab, ®Mathworks, gaussmf help files). The resulting fuzzy set chromosome is of variable length depending on type and number of input(s)-output(s) variables.

$$f(x,c,\sigma) = e^{-(x-c)^2/2\sigma^2} \qquad \textit{eq. II.3}$$

The only limitation applied in the development and coding process of the fuzzy set chromosomes is that membership functions should overlap. To secure this limitation membership functions are allowed to vary in shape and position within specified limits, adapted automatically to the number of fuzzy sets and inputs range.

The length of the FS chromosome (L_{FS}) depends on the number of FSs (N_{FS}), on the number of input (N_i) and output (N_o) variables and on the type of fuzzy sets. Equation II.4a is used for calculating the L_{FS} for Trapezoid-Triangular membership functions, and eq. II.4b is used for calculating the L_{FS} of Sigmoid-Gaussian membership functions.

Rule coding into chromosome is performed according to *Pittsburg* approach. Each chromosome represents the user defined number of rules (N_R). The length (L_R) of the rule chromosome is given by equation II.5, where N_i is the number of input variables, and N_o is the number of output variables.

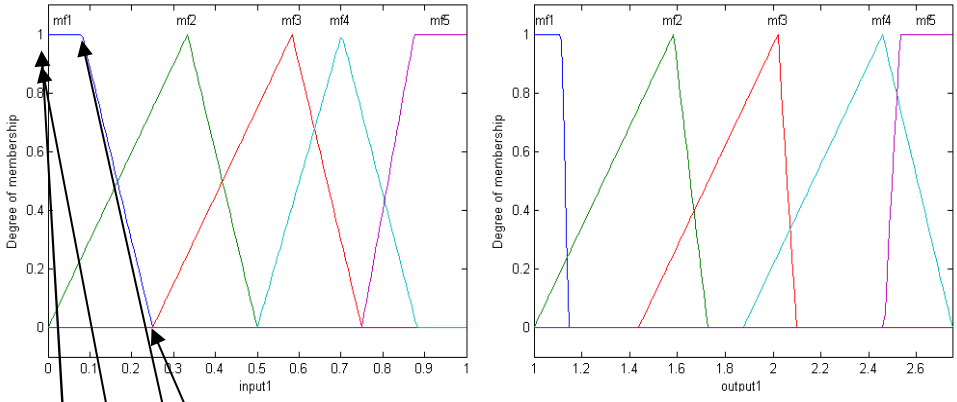
$$L_{FS\_Triang} = (N_i + N_o) * (4 * 2 + (N_{FS} - 2) * 3) \qquad \textit{eq. II.4a}$$

$$L_{FS\_Gaussian} = (N_i + N_o) * (N_{FS} * 2) \qquad \textit{eq. II.4b}$$

$$L_R = (N_i + N_o + 1) * N_R \qquad \textit{eq. II.5}$$

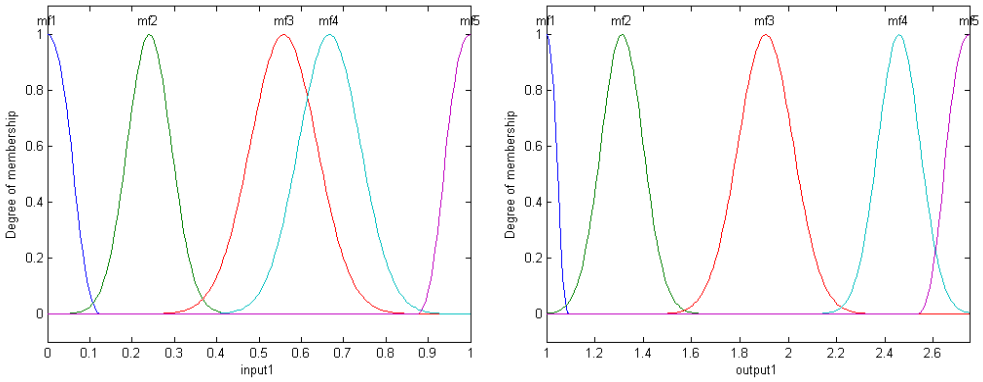
A coding example of a SISO FRBS with four (4) rules is given in tables II.1 & II.2. Where *W* is the weight of each rule (Table II.1).

The GA was designed to evolve systems with small number of rules, since it incorporates rule minimization by enabling variable weight of rules from zero (0) to one (1).



Input									output							
mf1				mf2			.	.	.	.	.	.	mf5			
0.0	0.0	0.08	0.25	0.0	0.33	0.5	.	.		.	.	.	2.46	2.53	2.75	2.75

Figure II.2: Trapezoid–Triangular membership functions coding.



input								output					
mf1		mf2		..	..	..	..	.	.	.	.	mf4	mf5
0,00004	0.12	0.05	0.24	.	.	.	.		.	.	.	0.087	2.458	2.538	2.748

Figure II.3: Sigmoid-Gaussian membership functions coding.

Table II.1: Rule description

1. If (input1 is mf4) then (output1 is mf5) (0.3)
2. If (input1 is mf4) then (output1 is mf4) (0.8)
3. If (input1 is mf1) then (output1 is mf1) (0.9)
4. If (input1 is mf5) then (output1 is mf4) (0.2)

Table II.2: coding of table II.1.

Rule 1			Rule 2			Rule 3			Rule 4		
In1	Out1	W/10	In1	Out1	W/10	In1	Out1	W/10	In1	Out1	W/10
4	5	3	4	4	8	1	1	9	5	4	2

II.2.2 Variable Mutation Rates.

The role of the mutation operation in GAs is to explore possible solutions that are not described by a given population. Although mutation is considered a secondary operation, it is very important in the exploration of large and complex search spaces. This feature becomes more important when we generate FRBS with subsets of RBs. Evolution of such systems is useful when the number of fuzzy sets and input-output variables increases substantially. Such systems have very large RB which dramatically increases a system's complexity, and thus computational time.

Our toolbox gives the user the ability of applying variable mutation rates based on equation II.6, graphically described for 100 generations in fig. II.4.

$$MUTrate = UserDefine\ dMUTrate * abs(\sin(x)/x) \qquad eq.\ II.6$$

Where: User Defined MUTrate is the initial mutation rate defined by the user.

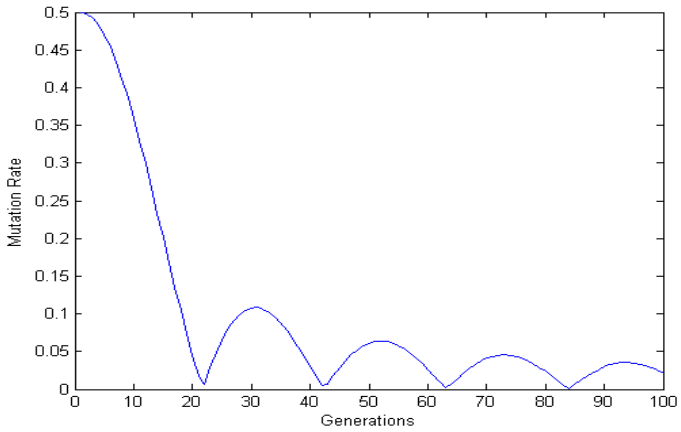


Figure II.4: Example of variable mutation rates, for UserDefinedMUTrate=0.5.

Whitely and Hanson (Whitely D, Hanson T, 1989) have suggested an adaptive mutation technique based on the homogeneity of the solution populations. The algorithm increases mutation rate when homogeneity is high. The proposed approach results in high mutation rates towards the end of the evolution process where individuals have converged to an optimum solution.

Pham and Karaboga (Pham D.T., Karaboga D., 1997), suggested three different strategies for variable mutation rates. The first strategy gradually increases the mutation rate when the performance has not improved for a predefined number of generations. The mutation rate is returned to a minimum probability when the best individual in a population improves its performance. The main drawback of this strategy is that high mutation rates towards the end of evolution steps might lead to deterioration in

individuals' performance rather than improving it. The second strategy applies higher mutation rates to poor solutions. The third strategy applies mutation probabilities to digits rather to chromosomes. It initially applies higher probabilities to most significant digits and then as performance is improved the focus is shifted to the least significant ones. This approach assumes a binary like coding of the chromosomes. The authors have shown that all three variable mutation strategies outperformed the constant mutation rate algorithm in the design of a fuzzy controller.

Our hypothesis is that damped cyclic mutation rate will allow the GA to explore the search space more efficiently particularly in the initial generations where the high mutation rates permit increased sampling of the solution space and the lower rates encourage convergence and better performance of the resulting FRBS.

II.2.3 Evolution algorithm.

The Sheffield University GA toolbox was adapted to the needs of FRBS evolution process. The modifications were performed by developing our own bespoke double point crossover functions. Crossover functions were written to enable the exchange of whole membership function(s), for the fuzzy sets chromosome and the whole of rule(s) for the rule chromosome, instead of parts (Figure II.5).The evolution process is described by the flow diagram of figure II.6. Evaluation of each individual FRBS in the population is performed by generating the FRBS, described by the individual fuzzy sets and rules, and applying it to the available training data. The fuzzy sets chromosome and the rules chromosome are assigned with a fitness value equal to the percentage error described in eq. II.2.

Rule 1			Rule 2			Rule 3			Rule 4		
In1	Out1	W/10	In1	Out1	W/10	In1	Out1	W/10	In1	Out1	W/10
4	5	3	4	4	8	1	1	9	5	4	2
4	5	3	4	3	2	2	2	0	5	4	2

Crossover

Rule 1			Rule 2			Rule 3			Rule 4		
In1	Out1	W/10	In1	Out1	W/10	In1	Out1	W/10	In1	Out1	W/10
4	5	3	4	3	2	2	2	0	5	4	2
4	5	3	4	4	8	1	1	9	5	4	2

Figure II.5: Graphical example of Rules Crossover.

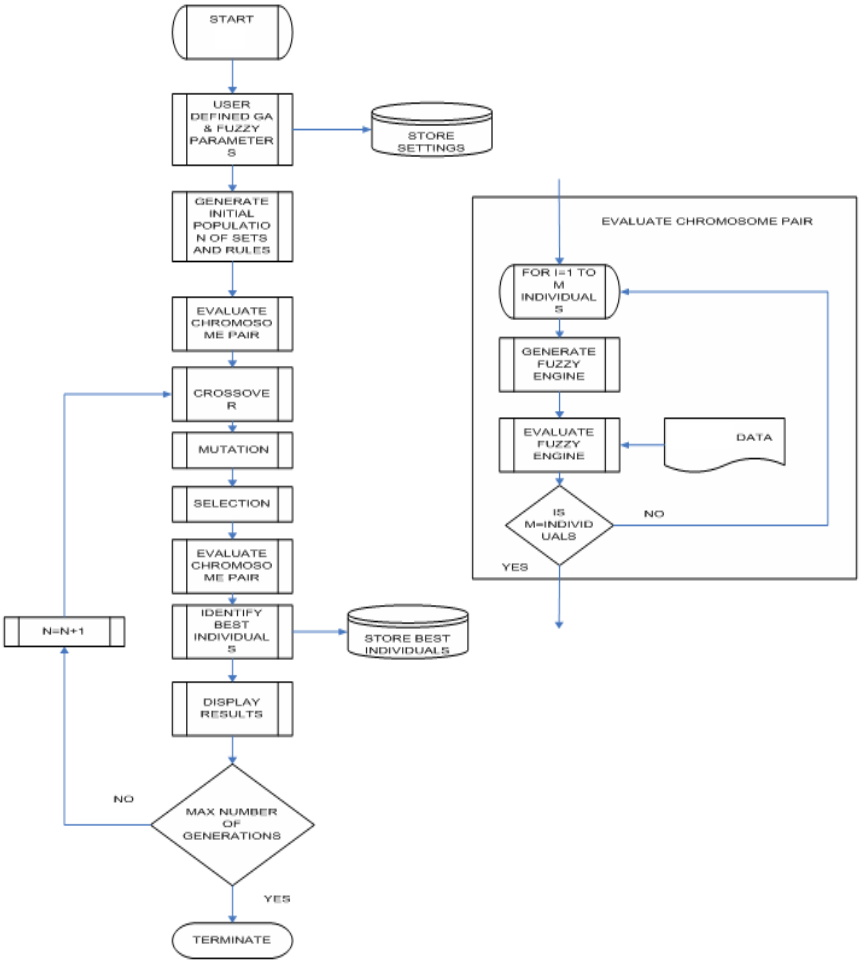


Figure II.6: Flow diagram of the EVOFINE software.

Analytically the GA algorithm initialized random individuals for both chromosomes. Each individual is described by the two chromosomes. In order to evaluate the proposed fuzzy system for each individual, a fuzzy system is generated based on an individual's sets and rules. The toolbox does not safeguard against duplicate or conflicting rules, since evolution process is expected not to favor chromosomes with such features. The input data are fed into this fuzzy system, and output crisp values are stored. The arithmetic values of the outputs are used for deriving the percentage (%) performance of eq II.2. The fuzzy system is then destroyed and a new one for the next individual is created and evaluated. This process is repeated until all individuals are evaluated. All individuals are now assigned with a fitness function, representative of their performance against the available data base. Scaling function is optionally activated by the user.

The GA targets to minimize fitness (small error between fuzzy system's output and database). Once all individuals are assigned with a fitness function, parent selection

is performed. The selection algorithm is user defined (RWS, SUS), but most commonly used is the roulette wheel selection method. The lowest fitness value (small error) individuals have a higher probability of advancing in the next generation.

The new generation is subject to crossover and mutation mechanisms. The crossover performed by the software is a double point crossover for each of the chromosomes. Each chromosome is subject to the same mechanisms as if it was independent of the other. This approach is justified by the following reasons. First a crossover between fuzzy sets and rules could not be performed due to the different structure of chromosomes; the first is composed of real numbers, while the second consists of integer numbers. Second, crossover and mutation is performed to each chromosome independently, thus it is possible to alter shape and position of FS without affecting the RB and vice versa. Furthermore we suggest in future research to build an algorithm that identifies the best combination between evolved FS and RB chromosomes by assigning pair's fitness. Mutation is performed according to a user defined probability. The number selected by the user is the probability of a chromosome's element to mutate. The user interface permits constant mutation rates and damping mutation rates. Damping mutation rates are not constant, but are decaying sinusoidal, based on the equation II.6. Since mutation rates of negative value are without meaning, we calculate the absolute sinusoidal damping. Negative mutation rates represent a negative probability of change; such probability is equivalent to zero probability.

The new population after crossover and mutation mechanisms is ready to be evaluated in terms of fitness to the training data set. To maintain the size of the original population, the new individuals are reinserted into the old population. Replacement of individuals in the old population is based on fitness. Old individuals with low fitness values are replaced by the fittest of the new population.

II.2.4 Evolution and Computation resources

The computational time of the GA algorithm depends on chromosomes' length, and thus on the number of rules, number of fuzzy sets and number of input – output variables, the number of individuals in each generation and the size of the training set.

The following calculation example provides some insight of the problem's complexity when dealing with the full systems' architecture as described by the questionnaire analysis.

A complete system's representation as it was described from the questionnaire results includes twelve (12) input variables and six (6) output variables. Assuming we have multiple MISO systems, where all 12 inputs are used for inferring a single output variable, the possible combination of rules (search space of RB), which will be termed from now on as *Total Rules,* of a system is given from the product of the number of membership variables (eq.II.7a). However in order to fully develop a functional system we need a subset of the *Total Rules* (search space), by avoiding conflicting rules. The subset will be termed *Full RB*. The calculation of *Full RB* is given by equation II.7b.

$$N_{TotalRules} = N_{FS}^{(N_i+N_o)} \quad eq.\ II.7a^*$$

$$N_{FullRB} = N_{FS}^{(N_i)} \quad \text{eq.II.7b}^*$$

**Assuming all input-output variables have the same number of FS for MISO system.*

To clarify the difference between *Total Rules* and *Full RB*, consider a simple fuzzy system with one input and one output. Each domain is partitioned by 2 membership functions, named "low" and "high". The *Total Rules* (search space) could be given by all possible combinations (2^2 , eq.II.7a):

1. IF input is low THEN output is low
2. IF input is low THEN output is high
3. IF input is high THEN output is low
4. IF input is high THEN output is high

However it is not possible to have conflicting rules such in the case of 1&2 and 3&4. Although the above system could be described by only two (2) rules, the *Full RB* (2^1 , eq. II.7b), we do not know from the beginning which two of the four are the appropriate ones.

If we examine three scenarios of different EVOFINE architectures we can see the exponential growth of the systems complexity and thus the huge amount of computational resources necessary for the algorithmic optimization of such a system. The three scenarios are presented in the following table:

Table II.3: EVOFINE architecture scenarios.

	Scenario 1	Scenario 2	Scenario 3
Number of Input Variables	12	12	3
Number of Output Variables	1	1	1
Number of FS describing inputs-outputs domains	5	3	5
Type of FS (Trapezoid-Triang or Sigmoid – Gaussian)	Trapezoid-Triang	Trapezoid-Triang	Trapezoid-Triang
Number of Rules	Full RB	Full RB	Full RB
Number of Individuals in each Generation	100	100	100

The number of *Total Rules* ($N_{TotalRules}$) of an FRBS describing all possible rules is calculated by the number of FS raised in the power of the sum of input and output variables. Equation II.7a is applied when we have equal number of FSs for all inputs and outputs; otherwise it is the product of all the FSs of the FRBS. The number of *Full RB*, represents the maximum number of rules which do not conflict with each other (eq. II.7b). This means that for a given combination of input membership functions we infer a single output membership function.

Using equations II.4a, II.5 & II.7 we can calculate the length of the FS and RB chromosomes respectively:

Table II.4: Chromosome Lengths

	Scenario 1	Scenario 2	Scenario 3
L_{FS}	221	143	68
$N_{TotalRules}$ (RB search space)	$5^{13} \approx 1.2*10^9$	$3^{13} \approx 1.5*10^6$	$5^4=625$
N_{FullRB}	$5^{12} \sim = \approx 244*10^6$	$3^{12} \sim = \approx 531*10^3$	$5^3=125$
L_R	$(12+1+1)*N_{FullRB} \approx 3416*10^6$	$(12+1+1)* N_{FullRB} \approx 7434*10^3$	$(3+1+1)* N_{FullRB} \approx 625$

The total length of both chromosomes is the sum of FS and RB chromosomes ($L_T=L_{FS}+L_R$). The total length represents the array in which the individuals FRBS architecture is stored for the GA process. This length is further multiplied by the number of individuals in each generation to provide us with the amount of memory that should be available only for storing chromosomes architectures.

It is obvious from inspecting the size of the resulted chromosomes that we need vast computational resources for exploring such huge spaces in the case of scenarios 1 and 2. Furthermore the number of individuals in each generation should increase as the chromosomes' complexity increases in order to efficiently explore the problems' search space. However the simplification of scenario 3, provide us with a feasible solution in terms of computation time and resources.

Since computational resources for testing such a huge rule base were not available, one could either experiment with the full architecture but generating a subset of rules, or could experiment with subsets of the architecture or utilize both simplifications. The method for identifying the optimum sub architecture was described in previous paragraphs, in terms of reducing the input-output number of variables, and is experimentally analyzed in Appendix III, in terms of finding the optimum sub architecture for the EVOFINE algorithm.

Although the theoretical analysis suggests a huge number of rules, it is not always necessary to incorporate the *Full RB* for describing the system. This is due to combinations of linguistic variables which are not feasible in reality. For example it is not possible for a patient to have all the monitored variables within physiological limits and require maximum ventilation. This means that one can realistically describe the system with fewer rules, similar to human perception.

II.3 Neural Network Driven Fuzzy Reasoning System

We have designed and developed a Matlab (®Mathworks) toolbox for implementing NN driven FRBS, based on the work of Tagaki and Hayashi (Tagaki H, Hayashi I, 1992) and Wang and Mendel(Wang L.X, Mendel J.M, 1992).

The toolbox is capable of developing FRBS where the RB is substituted by a NN. This method provides a trained FRBS based on an available data set in spreadsheet format. The architecture of this method is described in Appendix IV.

The following FRBS characteristics are user defined:

- Number of Inputs.
- Number of Outputs.
- Number of Fuzzy Sets (membership functions) for input-output.
- Type of membership functions (Trapezoid-Triangular or Sigmoid-Gaussian).
- Domain of each input-output variable.

Additionally the following NN settings are user defined:

- Number of NN layers.
- Type of transfer functions in each layer.
- Number of Nodes in each layer.
- Type of training method.
- Type of NN.

- Type of error back propagation (e.g. mse).
- Number of training epochs.
- Target training error.

Although the proposed architecture it is essentially an artificial neural network, it exhibits the following characteristics:

1. It describes a cause and effect relationship providing some transparency to the black box feature of the NN.
2. It utilizes NN technology for processing not the mathematical notation of a variable but rather the transformation of the variable to the fuzzy domain, providing the NN with the equivalent but not the same information.
3. The transformation of the variable to the fuzzy domain encodes input data to the range from 0 to 1, this minimizes the difference in NN response due to differences in absolute magnitude of the inputs.
4. The use of fuzzification and de-fuzzification processes permits the system to efficiently deal with inaccurate and imprecise measurements of the input-output training data.

II.3.1 FUN toolbox

The FUN (**FU**zzy **N**eural) toolbox consists of a graphic user interface (GUI, fig. II.7) capable of retrieving training sets in spreadsheet format, defining NN and FRBS architecture, train NN driven FRBS, storing setup and resulted-trained NN, testing and displaying stored NN driven FRBS.

The method of developing NN driven FRBS is described by the fig. II.8. The toolbox translates input and output training data into membership degrees (μ_n, where n is the number of FSs for each input-output domain), with the use of Matlab Fuzzy toolbox. The resulted matrix of membership degrees is stored in memory for utilizing during the training process.

The user defines the NN architecture. The number of input nodes (input layer) is automatically assigned with a number of nodes equal to the sum of the input(s) membership functions. The number of layers and the number of nodes in each layer are both user defined. However the number of nodes in the last (output layer) should match the number of the summed output(s) membership functions.

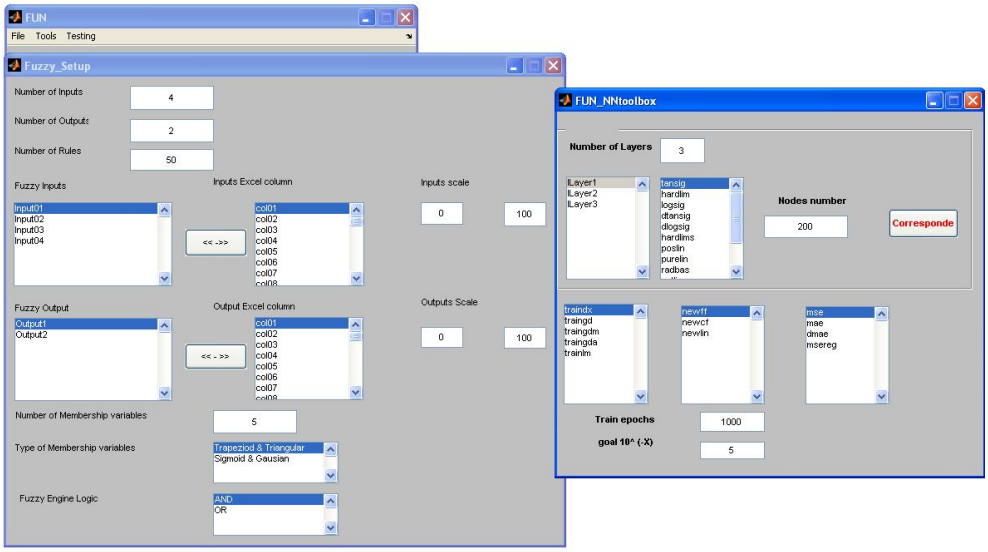


Figure II.7: Graphical User Interface of FUN.

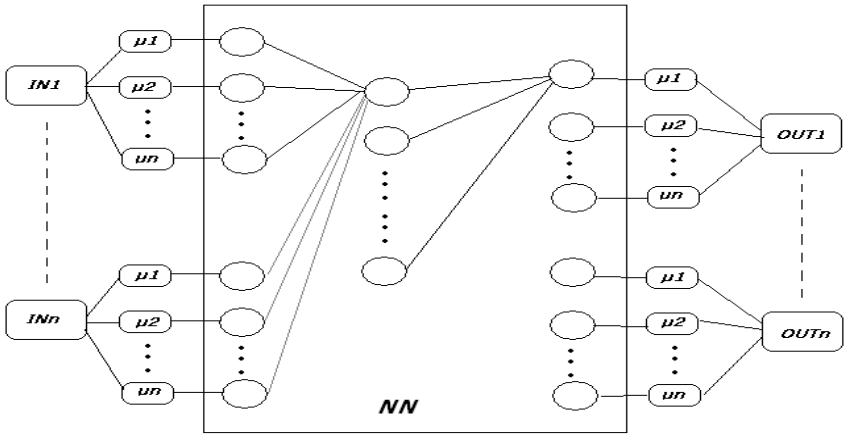


Figure II.8: NN driven FRBS architecture.

In the example of fig. II.9, the architecture of the NN driven FRBS for a system with 2 inputs and 1 output is presented. The number of FSs describing the inputs-output domain is defined to five (5) by the user. The software automatically assigns the fuzzy sets by evenly partitioning the domain space for each input – output variable. The user defined number of layers in this example is 3. The number of nodes to the input layer is automatically assigned to equal the sum of inputs fuzzy sets, thus equal to 10 in our example. The number of hidden nodes is defined by the user to 6, while the number of output layer nodes is equal to the output(s) fuzzy sets, in our case 5. For simplicity the interconnection of all nodes is not given in figure II.9.

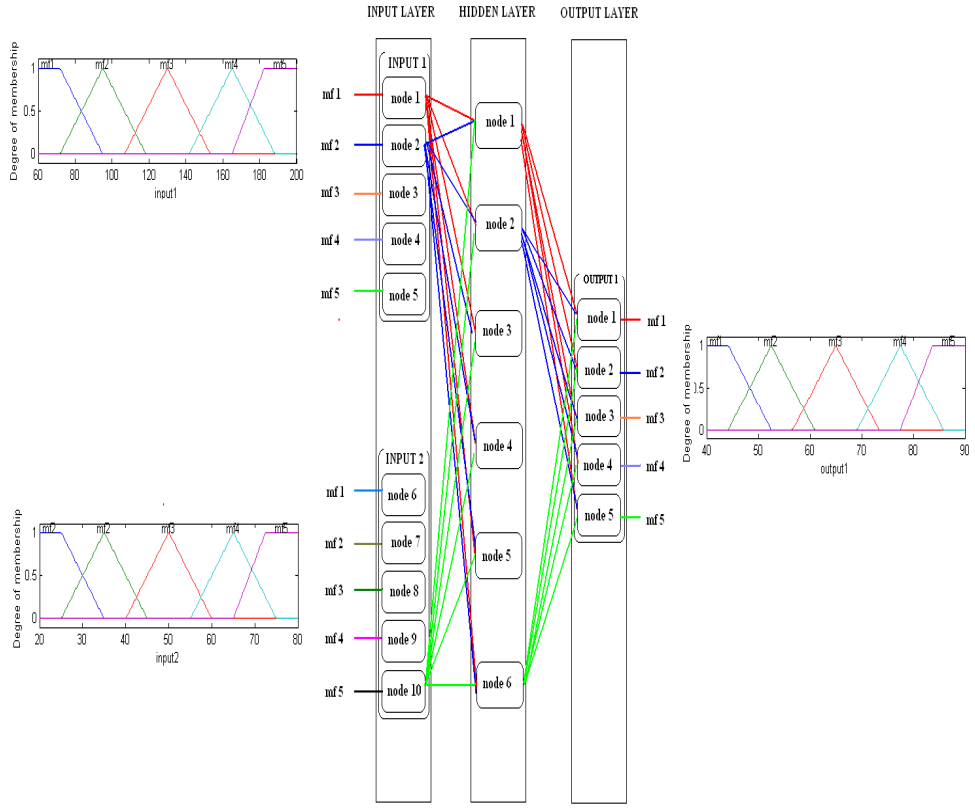


Figure II.9: Example architecture of NN driven FRBS.

The NN training is performed by introducing the membership degrees for each membership function for a given crisp input-output training set. The NN targets to adjust the nodes weights and biases in order to minimize the output error, translated as fit the output membership degrees as close to the membership degrees of the output training set. Table II.5, presents an example of translating an input – output training set to NN training data, for the example of fig. II.9.

Table II.5: Example of training data for the NN architecture of fig. 6.9

	Crisp value	Membership degree mf1	Membership degree mf2	Membership degree mf3	Membership degree mf4	Membership degree mf5
INPUT 1	**180**	0	0	0	0.35	0.9
INPUT 2	**30**	0.5	0.5	0	0	0
OUTPUT 1	**78**	0	0	0	0.8	0.1

The NN training is performed with the use of the Matlab 7.1 NN. The user defines one of the following NN functions shown in table II.6. Details on each functions' is provided in the NN help file of Matlab software.

Table II.6: FUN User defined NN functions.

Function group	Function name	Description
Network User Functions	*newff*	Create a feed-forward back propagation network
	newcf	Create a cascade-forward back propagation network
	newlin	Create a linear layer
NN training functions	*traindx*	Gradient descent with momentum & adaptive lr back propagation
	traingd	Gradient descent back propagation
	traingdm	Gradient descent with momentum back propagation
	traingda	Gradient descent with adaptive lr back propagation
	trainlm	Levenberg-Marquardt back propagation
NN performance functions	*mse*	Mean squared error performance function
	mae	Mean absolute error performance function
	dmae	Mean absolute error performance derivative function
	msereg	Mean squared error w/reg performance function

Similarly the user can define in each layer the transfer functions, as shown in table II.7.

Table II.7: FUN transfer functions.

	Function name	**Description**
Transfer functions	*tansig*	Hyperbolic tangent sigmoid transfer function
	hardlim	Hard limit transfer function
	logsig	Log sigmoid transfer function
	hardlims	Symmetric Hard limit transfer function
	poslin	Positive linear transfer function
	purelin	Linear transfer function
	radbas	Radial basis transfer function
	satlin	Saturating linear transfer function
	satlins	Symmetric saturating linear transfer function
	tribas	triangular basis transfer function
	softmax	Softmax transfer function

The GUI provides the user with flexibility in defining both NN and FRBS architecture, allowing FUN application in a wide range of research problems rather than been specific to our research.

The flow diagram of the NN driven FRBS toolbox, is provided in fig.II.10.

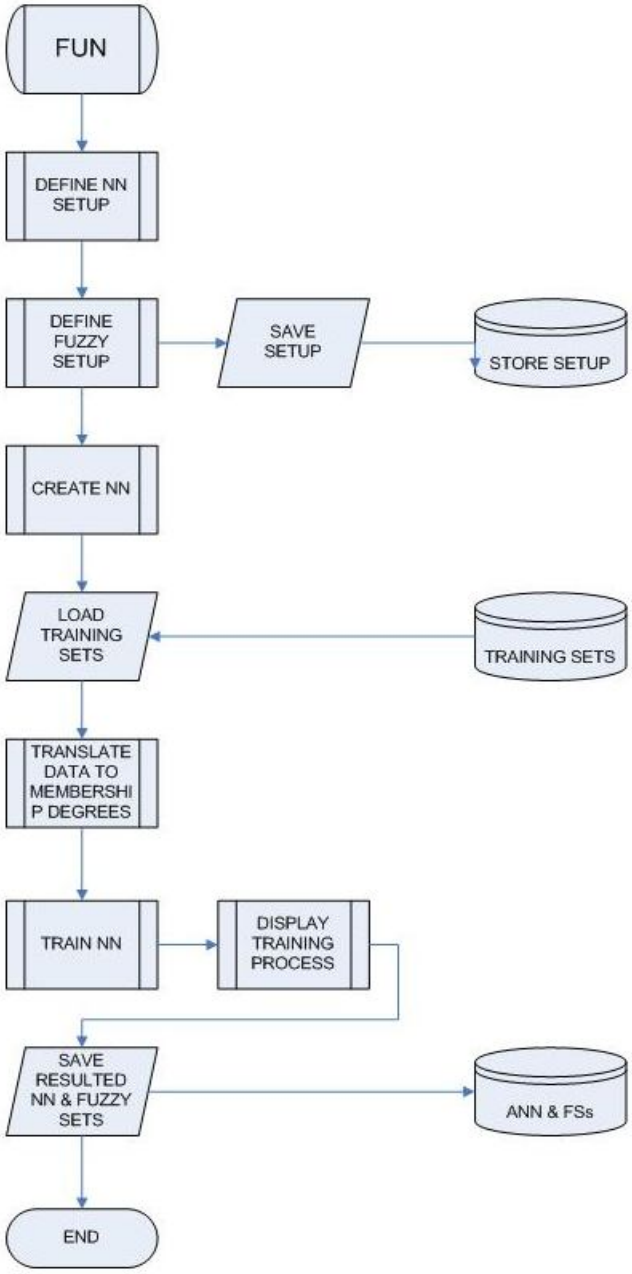


Figure II.10: FUN toolbox flow diagram.

Appendix III: Evaluation - comparison of EVOFINE, FUN, ANN and ANFIS.

III.1 EVOFINE evaluation

As described in section II.2.1, EVOFINE codes the FRBS with two chromosomes. The first chromosome codes the membership functions in real format. The second chromosome described fuzzy rules and rule weights. The chromosome pair (Fuzzy Sets & Rules) thus defines the FRBS. Each individual pair of the population is evaluated against the available data training set. The fitness function (error) of the GAs is described by equations II.1 & II.2, and describes the root mean square error as a percentage scaled over the output range. The GAs target is to evolve individuals which minimize the error, thus best describe the system in hand.

The EVOFINE toolbox was tested against both a theoretical mathematical function and a control scenario. A non linear MISO function, described by equation III.1 and figure III.1, was chosen as the modelled mathematical function. The function was chosen on the grounds of previously applied in similar research (Achiche S, 2004).

$$z = \sin(x * y) \qquad \textit{eq. III.1}$$

Where: 0<x<1.6 and 0<y<1.4

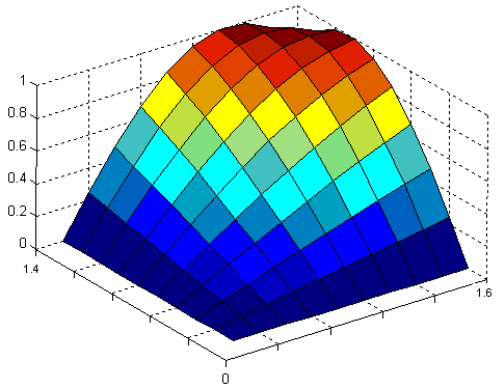


*Figure III.1: Graphical representation of function z=sin(x*y).*

Eighteen experiments were carried out for the mathematical function. The experiments settings are presented in table III.1. The experiments differ in the mutation type, which were either constant or variable, the shape and number of the membership functions which were either Trapezoid-Triangular (TRIANG), or

Sigmoid-Gaussian (GAUS), and the number of fuzzy rules. Experiments one to fourteen (1-14), were carried out for identifying the optimum EVOFINE setup. FRBSs architectures that performed well in these experiments were allowed to evolve for a larger number of generations in experiments fifteen to eighteen (15-18).

The size of the search space for the Rule Base (RB) of a fuzzy system is dictated by the number of input and output variables, and the number of the linguistic variables for each input-output variable. Assuming equal number of fuzzy sets for all input and output variables, then the number of possible rules is given by the equation II.7a. Total Rules, is the size of the search space for the RB of the FRBS. However when developing a FRBS, it is not advised to have conflicting rules in terms of equivalent *premise* (IF) but alternative *consequent* (THEN). Therefore the number of rules (RB) is described by equation II.7b in section II.2.4

Experiments 1 to 6, examine the effect of the RB size, utilizing a constant mutation rate. Figure III.2, describes the performance of the resulted FRBS (y axis), against the size of the RB expressed as percentage of the Total Rules (x axis). The % rmse of experiments 1 to 6 is described with blue crosses, while the displayed graph is the curve fitting. Curve fitting suggests that for a 2 input – 1 output FRBS system, as the one described by eq. III.1, the best performance is achieved when the number of rules equals the RB as it is expressed by eq. II.7b. However it is clear that one can utilize sub architectures in terms of rules number without significant compromising the FRBS performance. Especially in real world systems, some *premise* combinations do not exist, thus there is no need for a rule describing such combinations.

Table III.1: EVOFINE experiment's setup for the mathematical function.

Fuzzy Setup						GA Setup							Performance		
Experiment No	RB	% Total Rules	No FSs	Type FSs	Engine Logic	No Generations	No Individuals	Mut Type	Mut Rate	Cross Rate	Scaling	Selection type	rmse	% rmse	Computation time (h:min)
1	5	4.00	5	S,Z & Gauss	AND	100	100	const	0.01	0.7	OFF	RWS	0.1374	13.74	0:19
2	13	10.40	5	S,Z & Gauss	AND	100	100	const	0.01	0.7	OFF	RWS	0.1017	10.17	0:19
3	19	15.20	5	S,Z & Gauss	AND	100	100	const	0.01	0.7	OFF	RWS	0.1061	10.61	0:19
4	25	20.00	5	S,Z & Gauss	AND	100	100	const	0.01	0.7	OFF	RWS	0.1076	10.76	0:19
5	50	40.00	5	S,Z & Gauss	AND	100	100	const	0.01	0.7	OFF	RWS	0.1308	13.08	0:20
6	75	60.00	5	S,Z & Gauss	AND	100	100	const	0.01	0.7	OFF	RWS	0.1627	16.27	0:20
7	49	14.29	7	S,Z & Gauss	AND	100	100	const	0.01	0.7	OFF	RWS	0.1312	13.12	0:22
8	9	33.33	3	S,Z & Gauss	AND	100	100	const	0.01	0.7	OFF	RWS	0.1812	18.12	0:17
9	13	10.40	5	Triang & Trap	AND	100	100	const	0.01	0.7	OFF	RWS	0.1252	12.52	0:19
10	25	20.00	5	S,Z & Gauss	AND	100	100	damp	1.0	0.7	OFF	RWS	0.0852	8.52	0:19
11	25	20.00	5	S,Z & Gauss	AND	100	100	damp	0.9	0.7	OFF	RWS	0.0761	7.61	0:19
12	25	20.00	5	S,Z & Gauss	AND	100	100	damp	0.7	0.7	OFF	RWS	0.0807	8.07	0:19
13	25	20.00	5	S,Z & Gauss	AND	100	100	damp	0.5	0.7	OFF	RWS	0.0813	8.13	0:19
14	25	20.00	5	S,Z & Gauss	AND	100	100	damp	0.3	0.7	OFF	RWS	0.1134	11.34	0:19
15	25	20.00	5	S,Z & Gauss	AND	1000	100	damp	0.7	0.7	OFF	RWS	0.0638	6.38	3:03
16	25	20.00	5	S,Z & Gauss	AND	1000	100	const	0.01	0.7	OFF	RWS	0.0776	7.76	3:09
17	25	20.00	5	Triang & Trap	AND	1000	100	damp	0.7	0.7	OFF	RWS	0.0431	4.31	3:03
18	25	20.00	5	Triang & Trap	AND	1000	100	const	0.01	0.7	OFF	RWS	0.0777	7.77	3:09

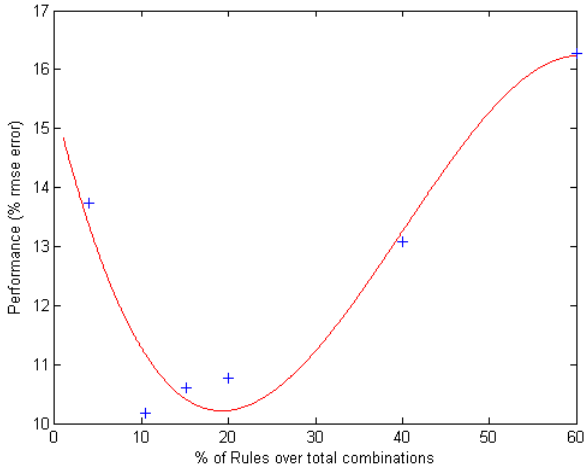


Figure III.2: effect of number of fuzzy rules in the performance of the resulted FRBS.

While maintaining the experiment 4 architecture we have carried a set of experiments (10 to 14), with variable mutation rates. Results suggest, fig. III.3, that initial damping mutation rates in the range of 0.5 to 0.9 outperform the constant mutation rates FRBSs. Curve fitting performed on the results, suggests that the optimum results are accomplished when damping mutation is initiated with values in the range of 0.7 to 0.8. The % rmse of experiments 10 to 14 is described with blue crosses, while the displayed graph is the curve fitting.

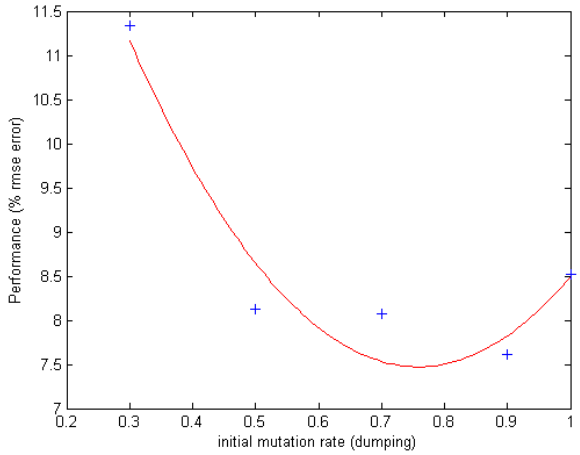


Figure III.3: effect of initial damping mutation rate in the performance of the resulted FRBS.

Similarly we have examined the effect of the number of FSs, while maintaining the rules number equal to the RB (eq. II.7b), to the FRBS performance (experiments 4, 7

and 8). Results presented in fig. III.4, show a variation in performance based on the FSs number. It is clear that large number of FSs results into complex search spaces, making the search of an optimal solution more difficult. On the other hand the use of small FSs numbers results in a simplification of the problem in hand.

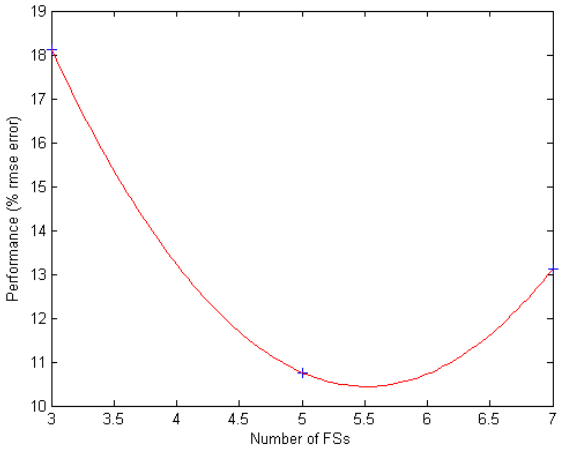


Figure III.4: effect of number of fuzzy sets in the performance of the resulted FRBS.

Examining the performance of experiment 18 in figure III.5 bottom, we observe that mean performance (solid red line) converge faster to the best solution. Damping mutation rates avoid premature convergence to a single solution (fig III.5, top). Convergence of mean and minimum error for experiment 18 occurs well before generation 50, while for experiment 17, where damping mutation is used, convergence occurs above generation 200. A close inspection of experiment 17 results (fig. III.5 top) reveals that mean values deviate periodically from minimum errors, at a rate equivalent to damping mutation rate. Early convergence to the best individual reduces the optimization power of the genetic algorithm, since most of the available chromosomes are similar. However damping mutation rates allows for the coexistence of a sufficient number of chromosomes with different architectures; thus exploring the search space more efficiently.

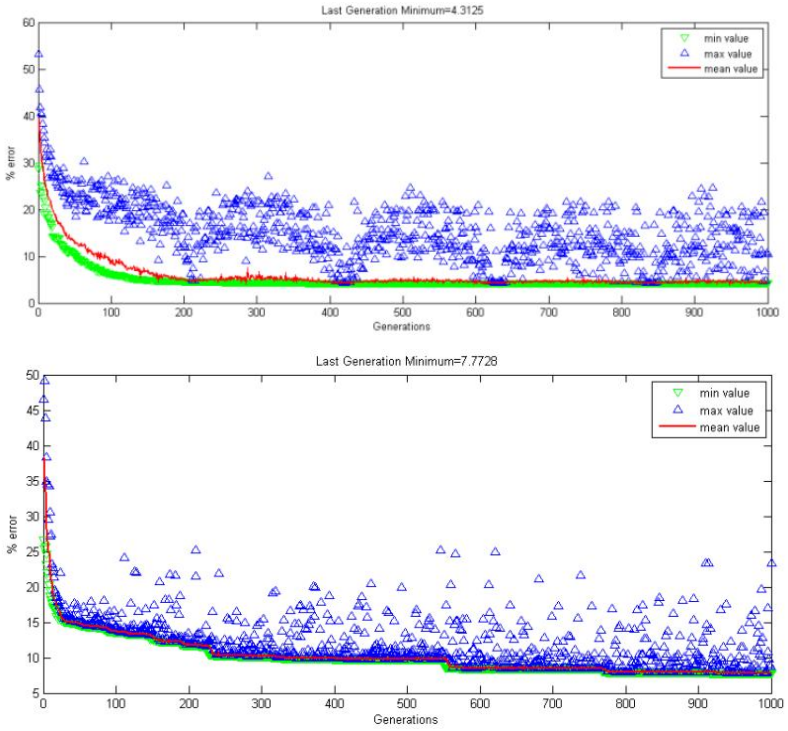


Figure III.5: Performance of evolved FRBSs, for eq. III.3.

(Top) damping mutation rate, experiment 17.
(Bottom) constant mutation rate, experiment 18.

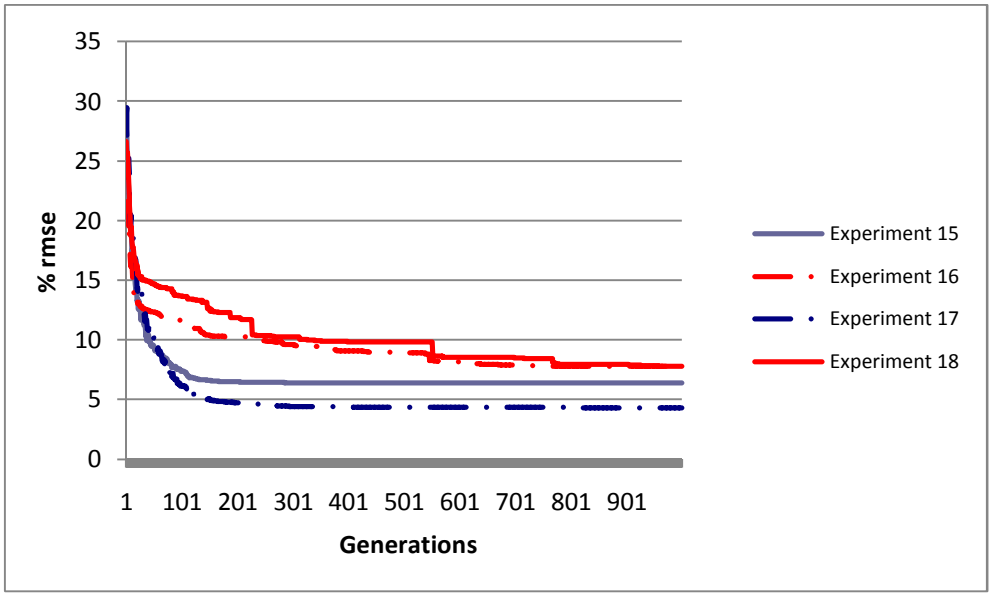


Figure III.6: minimum fitness values (error) of FRBS with different mutation types and membership functions for MISO system (z=sin[xy]).

Figure III.6, presents the results of automatic generation of FRBS, for experiments 15 to 18. Results are presented in terms of minimum error of the best individual in each generation. It is clear that experiments with damping mutation rates result faster

to a better solution. Figure III.5, describes graphically the output of the resulted FRBS for the experiments 17 to 18, against the available data set in terms of minimum, mean and maximum error. Figure III.7 presents the surface mapping of the mathematical function z=sin(xy). Experiment 17, which utilized damping mutation and resulted in a better solution according to table III.1, exhibits higher resemblance to the mathematical expression mapping of figure III.1.

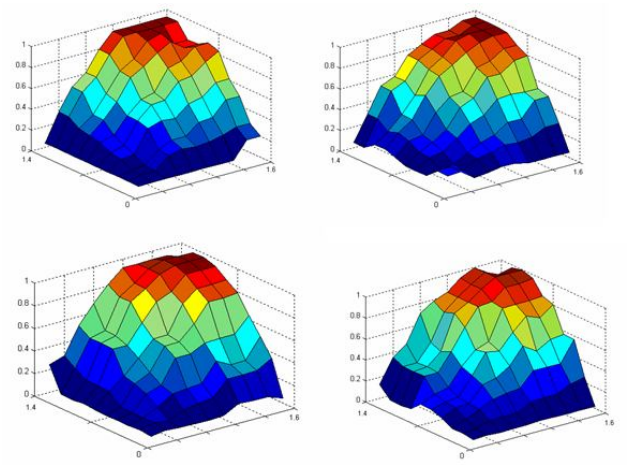


Figure III.7: Graphical representation of FRBS output for modelling MISO system (z=sin[xy]):

Top left: experiment 15, Top right: experiment 16

Bottom left: experiment 17, Bottom right: experiment 18.

The inverted pendulum, also known as the cart pole balancing problem, is a standard benchmark problem from the field of control theory. The pole balancing problem requires a closed loop feedback control system. The controller calculates the desired force amplitude and direction, applied to the cart, for moving the cart in the horizontal axis in order to maintain the pole in the upright position. The pole is free to move about the horizontal axis of the pivot (fig. III.8).

In order to implement the controller one has to develop a model of the cart pole system. The differential equations of motion required for predicting the movement of a frictionless cart pole system, could be found in the work of other authors such as Fogarty et al and Kandel et al (Fogarty T.C, 1994; Kandel A, 1993). The applied model's system variables, as well as the system's constrains are presented in table III.2

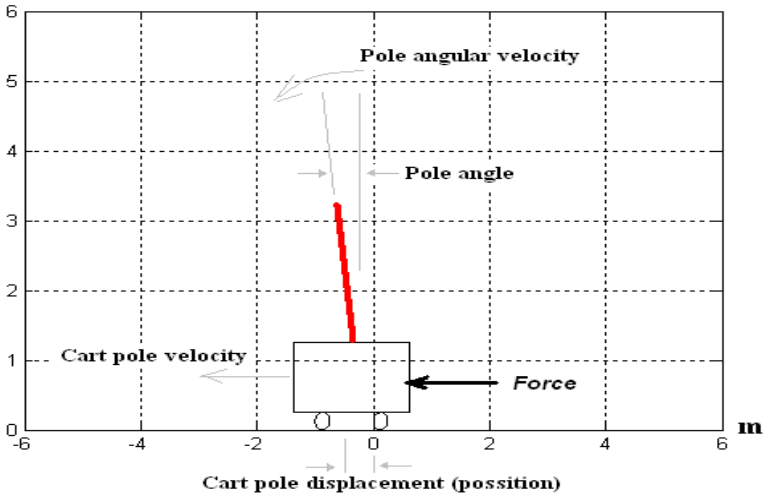


Figure III.8: Graphical simulation of cart pole dynamic system.

Table III.2: System variables & constrains

Symbol	Name & Description	Constrains
θ	Pole angle (rad)	$-0.52 \le \theta \le 0.52$
$\dot{\theta}$	Pole velocity (rad/sec)	
$\ddot{\theta}$	Pole acceleration (rad/sec^2)	
x	Cart position, as a relative offset from the middle (m)	$-1.5 \le x \le 1.5$
$\dot{x}$	Cart velocity (m/sec)	
$\ddot{x}$	Cart acceleration (m/sec^2)	
g	Gravitational acceleration = 9.81 (m/sec^2)	
m_c	Cart mass = 1.2 Kgr	
m_p	Pole mass = 0.1 Kgr	
l	half pole length, the distance from the pivot to the center of mass = 0.5m	
F	The magnitude of the applied force (N)	
τ	Simulation integration step dt= 0.02 sec	

A feedback linearization controller was implemented based on the work of Callinan (Callinan T, 2003), in order to produce training data for the EVOFINE toolbox. The Callinan controller was tested for various initial cart position and pole angle values, in order to test its performance. The controller was capable of maintaining the pole angle in the range of +/-0.0005^o and the cart position in the range of +/-0.0001m, in 9 to 12 sec, depending on initial angle and position. The performance results are presented in fig. III.9. The tests described in figure III.9, include 20 different setups. The controller was initialized at 20 distinct positions in the range of -0.5m to +0.5m

from the centre position. The range of distance was linearly spaced. Additionally for left (to centre) and right (to centre) positions, the initial pole angles were initialized at 10 pole angles in the range of -15 to + 15 degrees. Table III.3 describes the Callinan controller tests setup.

Table III.3: Callinan testing setup

Experiment	***Initial pole position (m)***	***Initial pole angle (rad)***
1	-0,500	*-0,262*
2	-0,447	-0,204
3	-0,395	-0,145
4	-0,342	-0,087
5	-0,289	-0,029
6	-0,237	0,029
7	-0,184	0,087
8	-0,132	0,145
9	-0,079	0,204
10	-0,026	0,262
11	0,026	-0,262
12	0,079	-0,204
13	0,132	-0,145
14	0,184	-0,087
15	0,237	-0,029
16	0,289	0,029
17	0,342	0,087
18	0,395	0,145
19	0,447	0,204
20	0,500	0,262

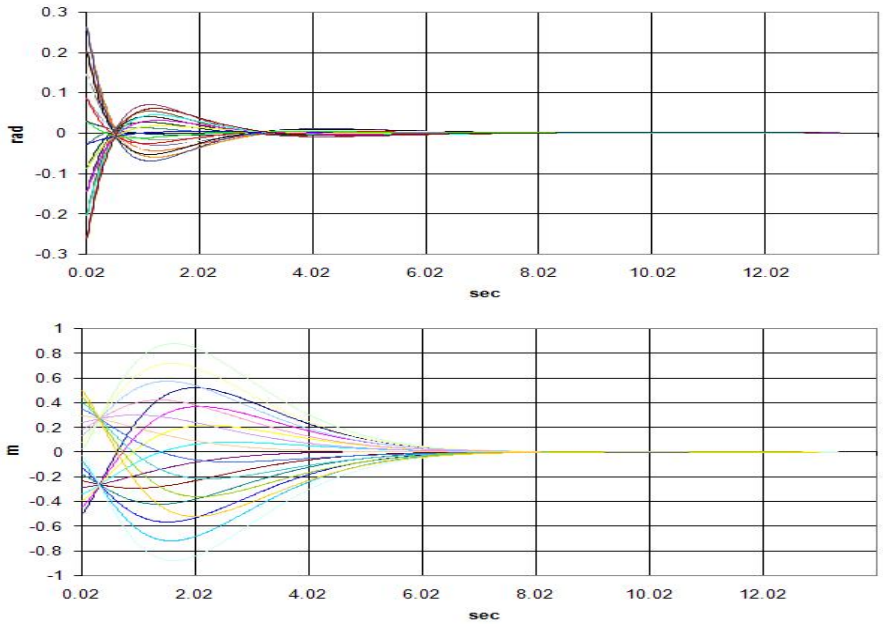


Figure III.9: Feedback linearization controller performance. (top angle, bottom position).

The controller data generation system is described in fig. III.10. The system consists of two random generators producing initial values *(-0.15<θ<0.15 rad, -0.55<x<0.55 m*) for the cart pole controller. Based on these initial values the closed loop controller was allowed to stabilize the cart pole system for a small number of steps (0.4 sec). Then the process was repeated with new random initial values until a large amount of training data was collected (10000 data sets). The controller's applied force, the pole's angle and angular velocity as well as the cart's position and velocity were recorded.

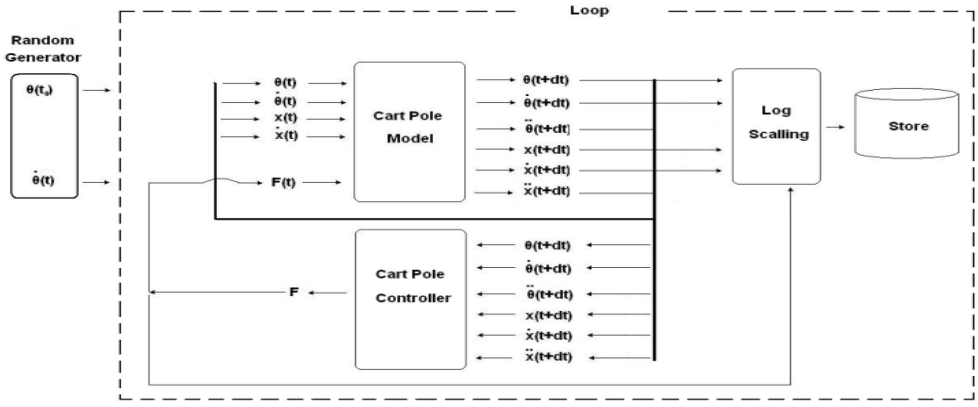


Figure III.10: Block diagram for training data generation based on the feedback linearization controller.

The generated data set was used as a training set for designing Proportional - Derivative (PD *like*) controllers for stabilizing the pole angle (θ). Angle (θ) and angle's derivative (dθ/dt) were the inputs to our models, while the required force for stabilizing the pole was the model's output. The range of the variables in the data set is presented in table III.4.

Table III.4: PD data base

Number of available training data	***10000***	
	max	***min***
Pole angle (rad)	*0.157*	*-0.157*
Pole angular velocity (rad/sec)	*1.3*	*-1.3*
The magnitude of the applied force (N)	*58.06*	*-58.06*

The recorded data were logarithmically scaled according to the pseudo-code presented below:

```
if value>=0
       value = value +1
       Scaled_value = log10(value)
elseif value<0
       value = value-1
       Scaled_value = -log10(abs(value))
End
```

The available training set was used for developing a FRBS cart pole controller, with the use of the EVOFINE toolbox. The FRBS architecture was based on the architectures that performed best on the experiments performed on the mathematical function. The FRBS was allowed to evolve for 100 and 1000 generations, utilizing damped mutation rates. The experiment setup is the same as in experiment 12 in table III.1. Figure III.11, presents the evolution process of experiment 1 and 3 (table III.5), of the FRBS in terms of worst, mean and best performance in each generation.

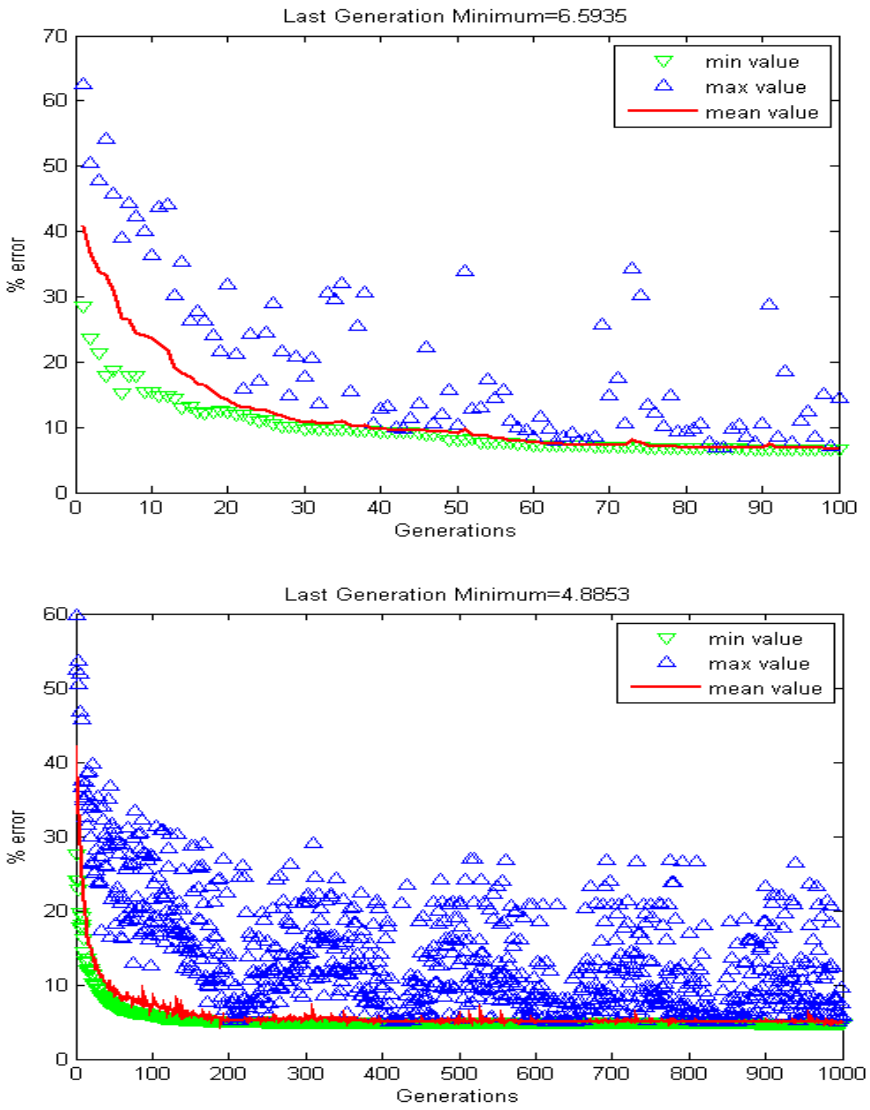


Figure III.11: Evolution process for FRBS cart pole controller. Experiment 1 (top), experiment 3 (bottom).

Figure III.12, presents, as an example, the evolved architecture of the FRBS for cart pole experiment 3. The membership functions for the input – output domains have been adapted in terms of shape and position through the evolution process. However overlapping is ensured by the EVOFINE algorithm. The surface mapping describes the behavior of the resulted FRBS in terms of RB, as presented in table III.6. As we have stated, although EVOFINE does not directly target in rule minimization, the incorporation of rules weight into the RB chromosome allows doing so. This is observed in table III.6, where rule 4 has zero weight and thus does not participate in the inference engine.

Table III.5: Cart pole EVOFINE experiments

Fuzzy Setup						GA Setup							Performance		
Experiment No	RB	%Total Rules	No FSs	Type FSs	Engine Logic	No Generations	No Individuals	Mut Type	Mut Rate	Cross Rate	Scaling	Selection type	rmse	% rmse	Computation time (h:min:sec)
1	25	20	5	S,Z & Gauss	AND	100	100	damp	0.7	0.7	OFF	RWS	0.2346	6.59	02:35:00
2	25	20	5	Triang & Trapez	AND	100	100	damp	0.7	0.7	OFF	RWS	0.2400	6.75	02:26:00
3	25	20	5	S,Z & Gauss	AND	1000	100	damp	0.7	0.7	OFF	RWS	0.1739	4.88	26:45:00
4	25	20	5	Triang & Trapez	AND	1000	100	damp	0.7	0.7	OFF	RWS	0.1323	2.90	24:46:00

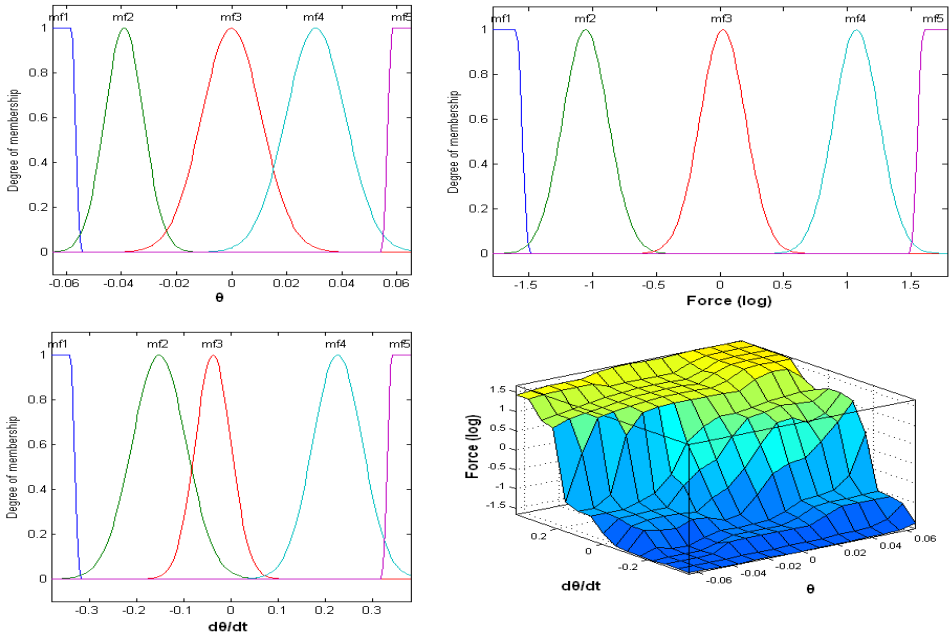


Figure III.12: Example of evolved architecture of EVOFINE FRBS, experiment 3.

Table III.6: Evolved Rule Base, EVOFINE cart pole experiment 3.

IF θerror is *MFx* **AND** dθerror is *MFx* **THEN** F is *MFx* (Weight)				
Rule	**θerror MF**	**dθerror MF**	**F MF**	**Rule Weight**
1	4	5	5	1.0
2	3	1	1	1.0
3	4	1	1	0.3
4	3	3	4	0.0
5	3	4	5	1.0
6	5	3	4	0.2
7	4	2	2	0.2
8	2	5	4	0.1
9	2	2	1	0.4
10	5	5	5	1.0
11	3	3	3	0.1
12	1	2	1	0.2
13	2	1	1	1.0
14	4	4	5	0.2
15	2	5	5	1.0
16	2	3	2	0.8
17	4	3	4	0.6
18	2	5	5	0.8
19	4	3	4	0.6
20	2	5	5	0.8
21	3	2	2	0.2
22	5	3	5	0.2
23	4	3	4	0.3
24	3	2	1	1.0
25	3	4	4	0.5

Once the models were developed they were evaluated against the cart pole mathematical model. The cart pole system was initialized for pole angles in the range of $-9^o < \theta < 9^o$ degrees, and all models were allowed a maximum of 20 sec to balance the pole. The initial values of pole angles were arbitrary chosen and were held constant for the tests performed for all models.

The application of the evolved FRBS revealed controllers evolved for a large number of generations were capable of balancing the pole in less than 2 seconds (Fig. III.13). However balance was achieved in angles very close to zero but not zero. Overshooting was not present in any of the tests carried out in experiment 3. On the other hand FRBS evolved for fewer generations were not stabilizing the pole, but rather fluctuating around vertical position in small angles (Fig. III.14).

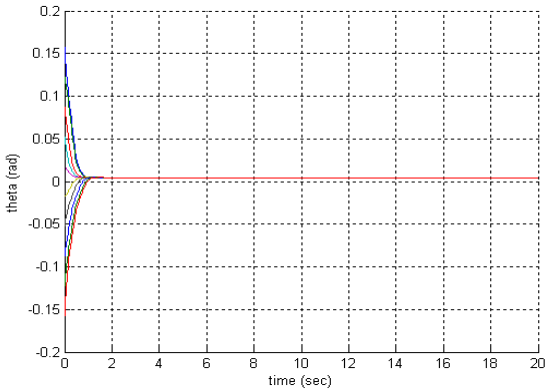


Figure III.13: EVOFINE, cart pole controller performance; balances pole, experiment 3.

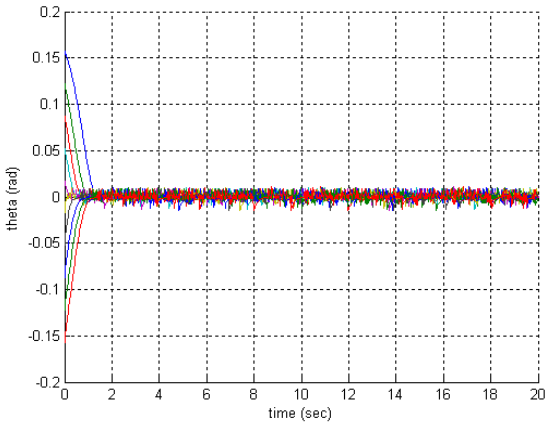


Figure III.14: EVOFINE, cart pole controller performance; fluctuating pole, experiment 2.

Experiments on modelling non linear MISO function, exhibited very similar performance in terms of final outcome. It is however clear that when damping mutation rates were applied the FRBS evolve faster an optimum solution.

The advantage of identifying faster an optimum solution lies in the required computation time. Experimental results, described in figure III.5, reveal that damping mutation rates achieve very good performance after 100 generations.

Experiments on modelling a dynamic system, namely the cart pole system, resulted in better performance than the feedback linearization controller base on the work of Callinan (Callinan T, 2003). However the Callinan controller was concerned with angle and position stabilization, which is a more complex task than angle stabilization. Although comparing the EVOFINE results with the algorithm used to generate the

training data has obvious shortcomings the advantages of the approach have been demonstrated.

We conclude that preliminary results support the efficiency of the EVOFINE toolbox and the initial hypothesis that variable-damping mutation rates explore more efficiently the search space.

Since the available variables during the EVOFINE setup process are many, namely five (5) for the fuzzy system setup and seven (7) for the GA setup, the problem of detecting the optimum architecture is a search problem in a complex space. However since the search space is problem specific, which in our experiments is a mathematical function and a dynamic system, we have run tests for identifying the important features that affect FRBS efficiency in modelling systems.

In summary the conclusions from the experiments performed on the EVOFINE toolbox are as follows:

- *Damping mutation rates find an optimum solution faster.*
- *A moderate number of Fuzzy Sets (FSs), describing each variable domain, is adequate for an efficient FRBS. Increasing the number of FS results in a deterministic model rather than a fuzzy system.*
- *Optimum performance is achieved when the number of rules equals the number of rules describing the system (FullRB, eq. 6.7b). A subset of the RB is sufficient for evolving FRBS with adequate performance. This is attributed to the fact that most systems have a number of rules that could not be applied in reality.*
- *Increasing the number of FS is automatically translated to increased number of rules describing the full RB of the system. Thus increasing the FS without increasing the number of rules participating in the FRBS, automatically suggests a smaller percentage of rules in terms of the rules search space; deteriorating the performance*
- *The application of FSs with Trapezoid & Triangular MFs Membership Functions (MFs), has exhibited better performance than the use of S-Z & Gaussian MFs. This assumption could be attributed to the coding and evolution process. Since the trapezoid-triangular MFs are coded with the use of three elements, mutation function is likely to drastically change the membership functions shape by changing only one element. However in the case of Gaussian functions, a change in a single element alters only the center or the width of the MF, maintaining the shape constant*

- *Computation complexity increases with the increase of the following factors: size of training set, size of RB, number of FS, use of Triangular FSs, number of individuals and number of generations. The size of the RB is proportional to the size of the FR chromosome. The number of FS is related to the number of rules that describe the system. Triangular MFs require three elements for describing the function, while Gaussian requires only two. Thus the FS chromosome of Triangular MFs is larger. Comparison of experiments 1 and 6 (Table III.1) reveals that an increase of RB from 5 to 75 increases computation time by 1 minute. On the other hand the increase of FS to 7 (experiment 7, table III.1) increase computation time by 2-3 minutes. The use of different MFs (experiments 16 and 18) shows that there is no important effect in computation time. The increase in computing intensity due to the number of individuals and generations is self explanatory. Observation of experiments on the mathematical function and the cart pole system reveals that evolution for 100 generation is approximately 19 minutes and $2^{1/2}$ hours respectively. The systems architecture is similar in terms of number of inputs and output variables as well as FS. The difference in computation time is attributed to the size of the training set (100 data sets for mathematical function and 10000 for cart pole). Similarly the computation time for 1000 generation exceeds 24 hours for the cart pole system, while for the mathematical function is approximately 3 hours. Computation time is one the most important restrictions of evolving complex FRBSs.*

III.2 FUN evaluation

In a similar manner to the EVOFINE evaluation the FUN toolbox was tested against non linear mathematical function (eq. III.1) and the cart pole dynamic control system (Fig. III.8). Performance was measured in terms of *rmse* and % *rmse* as previously described by equations II.1 & II.2 respectively. Computation time was record in order to allow comparison between FUN and other methods.

Due to the flexibility of FUN toolbox, the identification of an optimum architecture for the development of NN driven FRBS is a search for a solution in a complex space. Instead of investigating all possible combinations of FRBS and NN architectures, we have run a series of tests on the mathematical function (eq. III.1) in order to identify key features that deteriorate or improve the FUN performance. Experimental setup is presented in table III.7. All experiments presented utilize the *bisector* defuzzification method.

In experiments 1 to 7, we investigate the effect of the type and combination of transfer functions. Since NN output is a membership function ranging from 0 to 1, we were expecting that output membership functions that perform within this range would be more efficient. Example functions are the *logsig* and *poslin* transfer functions.

Experiment 8 differs in the type of transfer functions and type of fuzzy membership functions. The NN architecture is straight forward. It is a feed-forward back propagation network, with three layers. The number of nodes in the hidden layer was kept small in order for the NN to maintain its generalizability during the training process. The results suggest that the use of triangular MFs and the combination of *tansig-logsig* transfer functions performs well. Examining the percentage rmse in table III.7, it is observed that experiment 8 results in 5.98 % rmse, while the use of alternative transfer functions results into % rmse in the range of 7.62 to 55.71% rmse. Performance of this NN-FRBS architecture scores slightly higher to the best of EVOFINE experiments, evolved for 1000 generations. However computation time of the system's training is measured in seconds as compared to hours of the EVOFINE method. This architecture was our reference architecture for comparing changes in performance of the NN driven FRBS due to changes in the NN and/or FRBS characteristics.

Experiments 9 & 10, take up a similar architecture to experiment 8. However the number of MFs increases (Fig. III.15). Both architectures outperform the previous one. The increase of FSs from 5 to 20 slightly improves performance; % rmse of 5.98 and 5.19 respectively. However this architecture develops deterministic NN very similar to normal NN. Since "*each*" arithmetic value in the input domain tends to have a "dedicated" MF, the partitioning of the input space lose its fuzziness and thus loose the fuzzy properties.

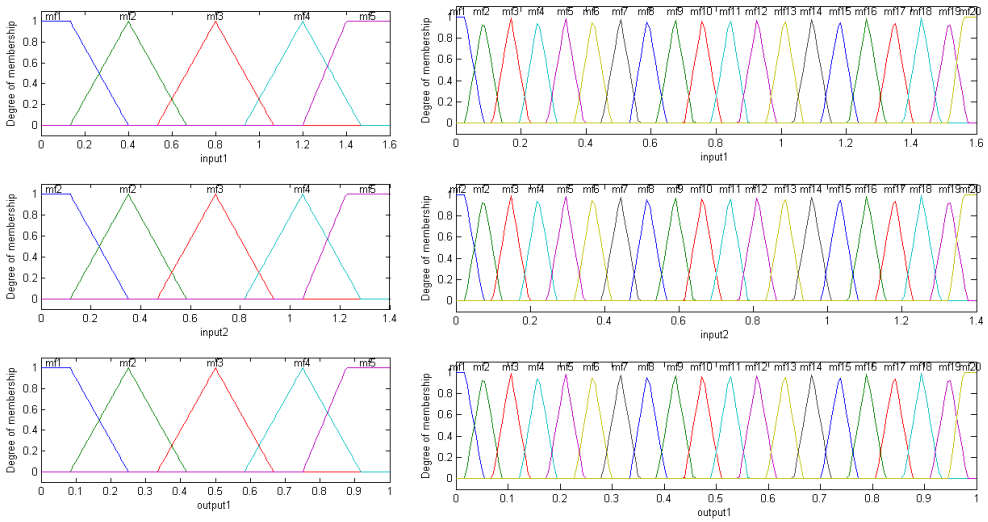


Figure III.15: Membership Functions (MFs); (left) experiment 8, (right) experiment 10.

Table III.7:Mathematical model, FUN Experiments Settings

Fuzzy Setup					NN setup									Performance		
Experiment No	**Number of MFs**	**Number of Inputs**	**Number of Outputs**	**MFs type**	**Number of Layers**	**Nodes Input** Layer/Hidden Layer 1/…/Output Layer	**Transfer Functions**			**Training epochs**	**NN training function**	**Type of NN**	**NN performance functions**	**rmse**	**% rmse**	**Computation time (h:m:sec)**
1	5	2	1	Sig-Gaussian	3	10/50/5	logsig	tansig		1000	traindx	newff	mse	0.0762	7.62	0:00:07
2	5	2	1	Sig-Gaussian	3	10/50/5	logsig	logsig		1000	traindx	newff	mse	0.2223	22.23	0:00:07
3	5	2	1	Sig-Gaussian	3	10/50/5	tansig	tansig		1000	traindx	newff	mse	0.1432	14.32	0:00:08
4	5	2	1	Sig-Gaussian	3	10/50/5	logsig	poslin		1000	traindx	newff	mse	0.5456	54.56	0:00:07
5	5	2	1	Sig-Gaussian	3	10/50/5	poslin	poslin		1000	traindx	newff	mse	0.5571	55.71	0:00:07
6	5	2	1	Sig-Gaussian	3	10/50/5	logsig	satlin		1000	traindx	newff	mse	0.4845	48.45	0:00:07
7	5	2	1	Sig-Gaussian	3	10/50/5	poslin	satlin		1000	traindx	newff	mse	0.2717	27.17	0:00:07
8	5	2	1	Trapez-Triang	3	10/50/5	tansig	logsig		1000	traindx	newff	mse	0.0598	5.98	0:00:08

18	17	16	15	14	13	12	11	10	9
5	5	5	5	5	5	5	5	20	10
2	2	2	2	2	2	2	2	2	2
1	1	1	1	1	1	1	1	1	1
Trapez-Triang	Trapez-Triang	Trapez-Triang	Trapez-Triang	Trapez-Triang	Trapez-Triang	Trapez-Triang	Trapez-Triang	Trapez-Triang	Trapez-Triang
3	3	3	4	4	3	3	3	3	3
10/50/5	10/50/5	10/50/5	10/500/100/5	10/500/100/5	10/50/5	10/2000/5	10/200/5	40/50/20	20/50/10
tansig	tansig	tansig	logsig	tansig	tansig	tansig	tansig	tansig	tansig
logsig	logsig	logsig	tansig	logsig	logsig	logsig	logsig	logsig	logsig
			logsig	logsig					
1000	1000	1000	3000	3000	3000	1000	1000	1000	1000
traindx	traingda	traingd	traindx	traindx	traindx	traindx	traindx	traindx	traindx
newff	newff	newff	newff	newff	newff	newff	newff	newff	newff
msereg	mse	mse	mse	mse	mse	mse	mse	mse	mse
0.074	0.061	0.263	0.059	0.0594	0.0591	0.0595	0.0596	0.0519	0.0527
7.74	6.10	26.30	5.90	5.94	5.91	5.95	5.96	5.19	5.27
0:00:07	0:00:07	0:00:07	0:03:55	0:03:27	0:00:17	0:00:57	0:00:15	0:00:10	0:00:09

19	20	21
5	10	5
2	2	2
1	1	1
Trapez-Triang	Trapez-Triang	Trapez-Triang
3	4	4
10/50/5	20/2000/200/10	10/50/10/5
tansig	tansig	tansig
logsig	tansig	tansig
	logsig	logsig
1000	3000	1000
traindx	traindx	traindx
newlin	newff	newff
mse	mse	mse
0.078	0.0257	0.0518
7.80	2.57	5.18
0:00:06	0:22:09	0:00:10

Experiments 11 to 12 examine the effect of increasing the number of hidden layer's nodes. The number of nodes increases to 200 and 2000 respectively. The effect of increased node number is not very profound (Fig. III.16).

The following figures present samples of the performance of the training process based on the NN output being a degree of membership. This is translated as having a value in the range of 0 to 1. Thus as shown in the experiment 8 training process (fig. III.16 left), the mse (Performance) of 0.0072 is the mse of all output membership degrees for the total of the training set. Performance axis (Y) is logarithmically scaled, while X axis presents the number of experiment epochs.

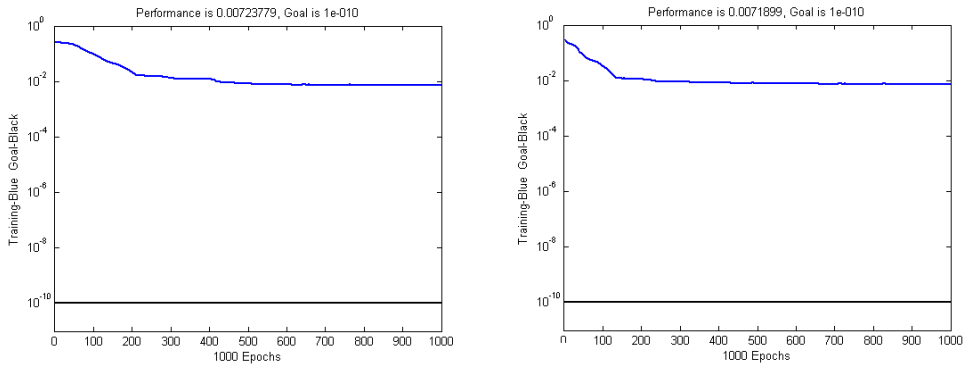


Figure III.16: Training performance; (left) experiment 8, (right) experiment 12.

Using experiment 8 architecture training process was carried out for more epochs (experiment 13). Results of experiment 13 suggest that although performance increases the rate of increase is lower (Fig. III.17).

Experiments 14 & 15 examine the effect of increased number of layers and nodes. Although compared to our reference architecture (experiment 8) the performance is slightly improved, this is achieved at the expense of the computational time; time increases from 8 seconds in experiment 8 to 3 to 4 minutes approximately for experiments 14 & 15.

Experiments 16 to 19 test the utilization of different types of NN, training functions and performance functions. The results suggest that compared to our reference architecture the performance deteriorates in each case.

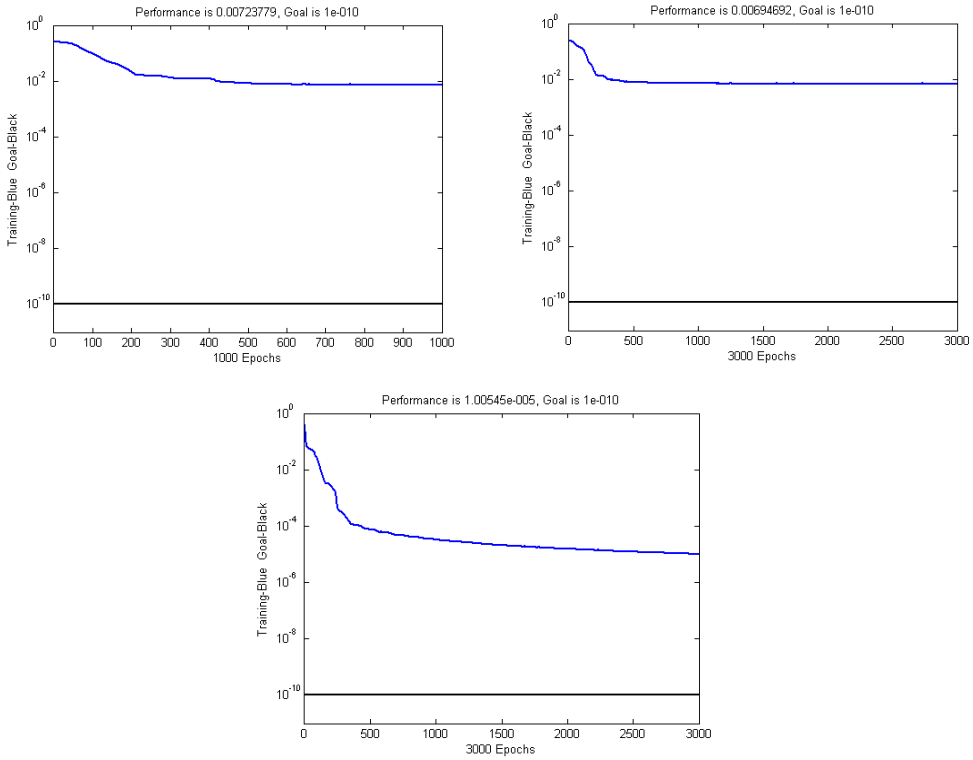


Figure III.17: Training performance. (top left) experiment 8, (top right) experiment 13, (bottom) experiment 20.

Experiment (20) has proven to be the more efficient architecture. We have incorporated all the features that shown an improvement in performance in all the previous tests. The number of layers and nodes as well as the number of MF and training epochs was increased. However although performance was improved, the computational time increased by 165 times. Another disadvantage of this architecture is that due to increased number of nodes, compared to the size of available training data (100 data sets), the NN is bound to lose its genera ability. Figure III.17 (bottom), presents the training process of the experiment 20. The slope of improving the NN performance is quite steep, showing that if the NN was allowed to train for more epochs the performance would have been improved. Figure III.18 presents the generated surface of the resulted NN driven FRBS. Comparing the original surface mapping of fig. III.1 to the presented graphs we observe how closely the NN driven FRBS of experiment 20 resembles the graphical representation of the mathematical function

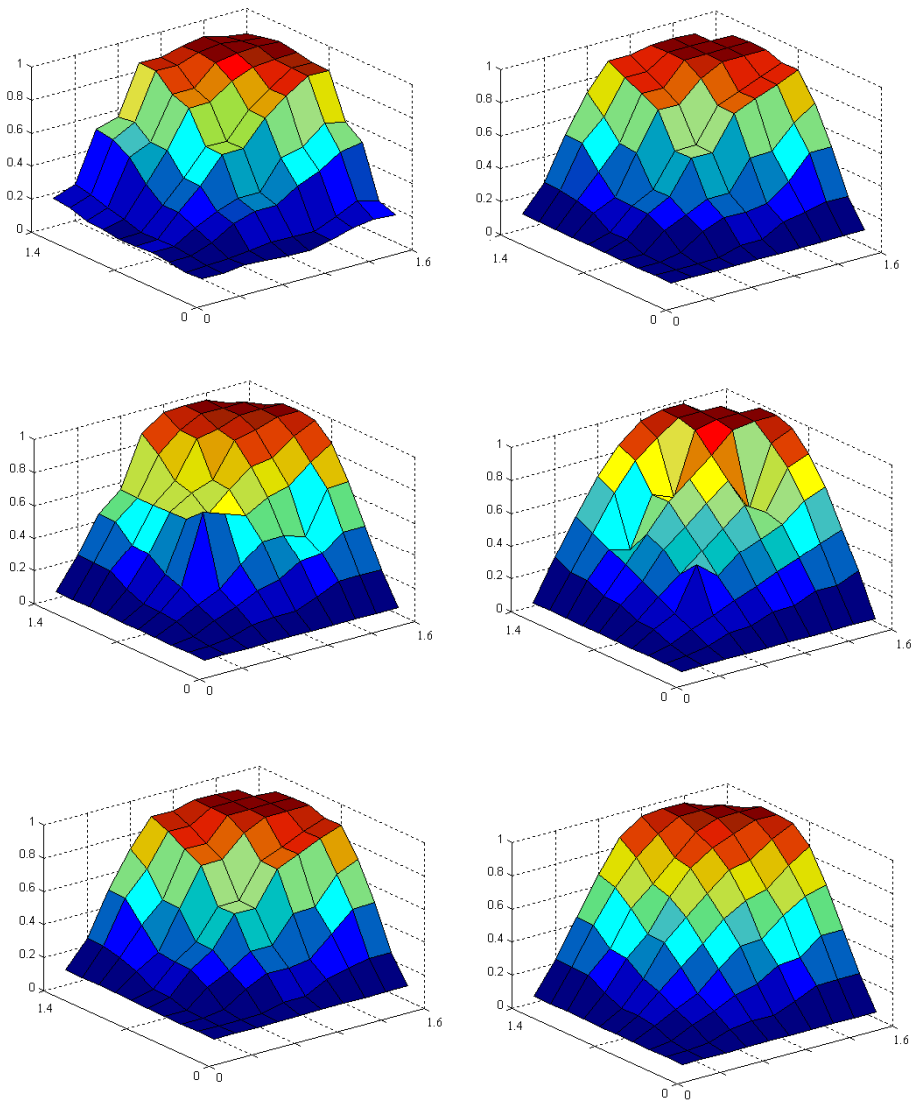


*Figure III.18: Surface mapping of FUN performance for z=sin(x*y);*

(top left) experiment 1, (top right) experiment 8, (middle left) experiment 10, (middle right) experiment 11, (bottom left) experiment 12, (bottom right) experiment 20.

Although the experiments with NN architectures for a large number of hidden layer nodes (2000 hidden layer 1 and 200 hidden layer 2) exhibited very good performance, most of the experiments were criticized in terms of loss of the ANN generalizability. It is known as a rule of thumb that the number of neurons in the middle layer should not exceed the number of data sets in an epoch so as the neural network does not memorize the input set.

Based on the above rule and taking into consideration the *Kolmogorov's* theorem as reformulated by Spencher's version of the representation theorem (Kurkova V. 1992), which states that a three layer ANN can map any real vector of dimension (M) to any

other real vector (N), when the middle layer has (2M+1) neurons, we decided to utilize NN architectures which have less hidden nodes than the total number of data sets for an epoch, which in our case they were 100, and middle layer node number exceeded the calculated number of Kolmogorov's theorem. Kurkova (Kurkova V. 1992) presents the approximation architecture of a NN with two hidden layers, where the first layer contains N*M*(M+1) nodes and the second hidden layer contains $M^2*(M+1)^N$ nodes. Experiments number 8 and 21 architectures have demonstrated good performance. The resulted surface mapping of the function is shown in the following figure.

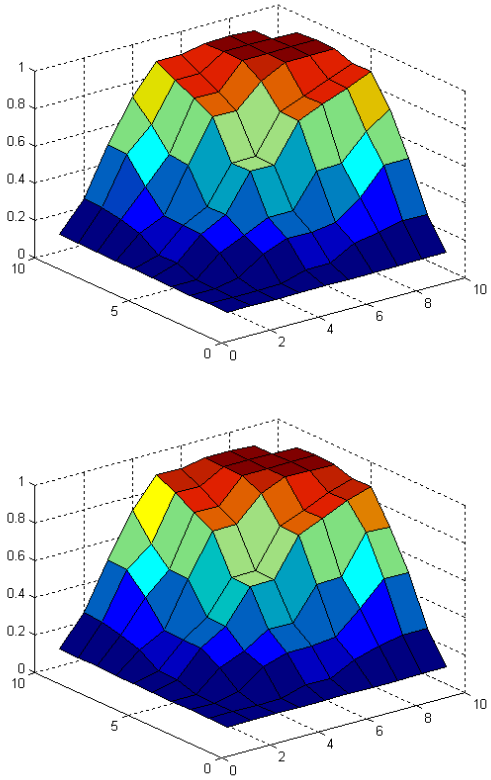


*Figure III.19: Surface mapping of FUN performance for z=sin(x*y); (left) experiment 8, (right) experiment 21.*

Similar architectures to experiments 8 and 21 were used for training NN-FRBS for the cart pole problem. As in EVOFINE evaluation we used the resulted NN-FRBS for balancing the cart pole system with initial angles in the range of -9^o to 9^o. The number of nodes in the hidden layers satisfies *Kolmogorov's* theorem, and does not exceed half the number of data sets available (data sets number is 10000).

The architecture of the developed NN-FRBS is described in table III.8. FUN 1 architecture is graphically displayed in fig. III.20. Performance was measured while FUN utilized the Bisector (BIS) defuzzification.

Table III.8: FUN tested architectures for the cart pole system.

Fuzzy Setup					NN setup							Performance		
Experiment No	**Number of MFs**	**Number of Inputs**	**Number of Outputs**	**MFs type**	**Number of Layers**	**Nodes Input Layer/Hidden Layer 1/.../Output Layer**	**Transfer unctioFns**	**Training epochs**	**NN training function**	**Type of NN**	**NN performance functions**	**rmse**	**% rmse/%mae**	**Computation time (h:min:sec)**
1	5	2	1	Sig-Gaussian	3	10/25/5	Tansig/logsig	1000	traindx	newff	mse	0.4970	13.96	00:01:48
2	5	2	1	Trian-Trapez	3	10/25/5	Tansig/logsig	1000	traindx	newff	mse	0.1640	4.61	00:01:42
3	5	2	1	Trian-Trapez	3	10/500/5	Tansig/logsig	1000	traindx	newff	mse	0.1568	4.41	00:31:14
4	10	2	1	Trian-Trapez	3	20/500/10	Tansig/logsig	1000	traindx	newff	mse	0.2066	5.80	00:34:23
5	5	2	1	Trian-Trapez	4	10/25/12/5	Tansig/tansig/logsig	1000	traindx	newff	mse	0.1447	4.91	00:02:20

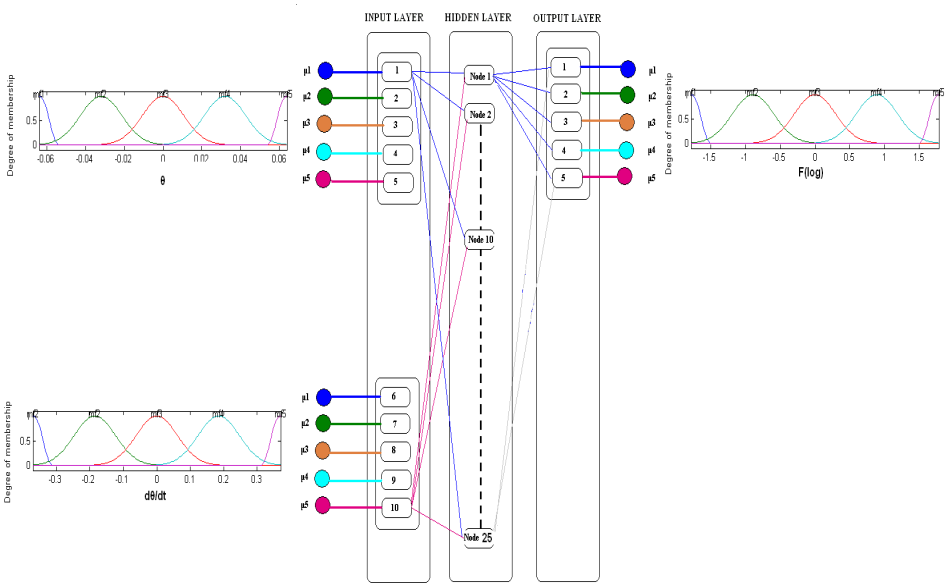


Figure III.20: Graphical representation of FUN 1 architecture.

Due to the method of training, FUN performance relies heavily on the defuzzification method. Since the ANN that substitutes the RB of the FRBS outputs the degrees of membership for the output membership functions, the appropriate action of the system is dictated by the defuzzification method. Figure III.21 presents the FUN experiment 3 performance on stabilizing the cart pole system for different defuzzification methods. It is clear that the defuzzification method affects the systems performance. However the choice of the appropriate defuzzification method is problem specific.

In the case of the cart pole system, defuzzification methods such as SOM and LOM failed to balance the cart pole system at least in one case (theta exceeded +/- 0.52 rad limit). This could be attributed to the dependence on a single prevailing output membership function rather than "*average*" values. Similarly MOM did not succeeded in balancing the pole. However MOM was fluctuating around zero angles, in directions relevant to the initial theta. BIS and CEN methods, were balancing the pole by fluctuating around zero theta. Fluctuations were less intense in the case of BIS defuzzification method.

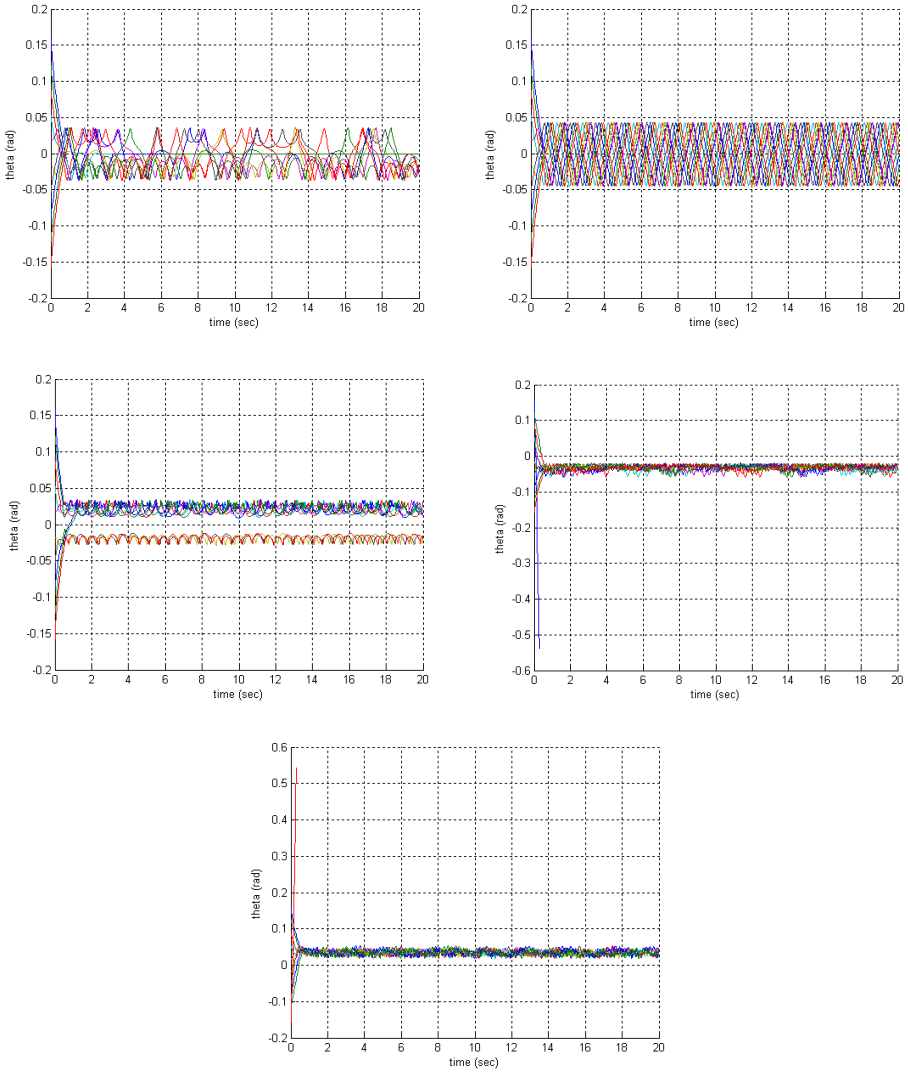


Figure III.21: Cart Pole results of FUN 3 architecture.

Utilization of different defuzzification methods. Starting from top left Bisector (BIS), Centroid (CEN), Mean of Maxima (MOM), Largest of Maxima (LOM), Smallest of Maxima (SOM).

III.3 ANN Evaluation

In a similar manner to the tests performed on the EVOFINE and FUN toolbox, Artificial Neural Networks (ANNs) were tested against the non linear mathematical relationship of eq. III.1, and the cart pole system.

The tests performed on the EVOFINE and FUN toolboxes were carried out for two main reasons. The first was to verify their operation, and the second was to identify optimal architectures – experiment setup for utilizing them latter in our research.

However the evaluation of the ANN was performed to allow a direct comparison between the suggested Artificial Intelligence Technologies and a well established method.

The architecture of the evaluated NN is fairly simple. It is a hetero-associative feed forward back propagation neural network with one or two hidden layers (Fig. III.22). The number of hidden nodes for experiments (Table III.9) was limited by the number of training sets available in each training experiment and on the number of inputs, in order to satisfy *Kolmogorov's* theorem (Kurkova V. 1992). The number of nodes to the input and output layers are defined by the problem.

Table III.9: ANN architectures for the z=sin(xy) function.

NN setup									Performance		
Experiment No	Number of Layers	Nodes Input Layer/Hidden Layer 1/.../Output Layer	Transfer Functions		Training epochs	NN training function	Type of NN	NN performance functions	rmse	% rmse	Computation time (h:min:sec)
1	3	2/10/1	logsig	purline	1000	traindx	newff	mse	0.098	6.98	0:00:25
2	3	2/40/1	logsig	purline	1000	traindx	newff	mse	0.0695	6.95	0:00:40
3	3	2/40/1	tansig	tansig	1000	traindx	newff	mse	0.0732	7.32	0:00:40
4	3	2/40/1	logsig	poslin	1000	traindx	newff	mse	0.0984	9.84	0:00:40
5	3	2/40/1	logsig	logsig	1000	traindx	newff	mse	0.0477	4.77	0:00:40
6	3	2/40/1	tansig	logsig	1000	traindx	newff	mse	0.0294	2.94	0:00:40

Table III.9, describes the settings of the experiments carried out for modelling the non linear mathematical function of eq. III.1. The different experiment settings focus on the appropriateness of the transfer functions and the number of hidden nodes for the problem in hand. Columns *rmse* and % *rmse* present the root mean square error of the ANN against the available data set. Figure III.23, presents the surface mapping

of the non linear function based on the ANN performance. The training set included 100 data sets. ANN architectures introduced a maximum number of 40 hidden nodes, avoiding over-training of the ANN.

Results from table III.9, and graphical representations (fig. III.23) suggest that the ANN architecture of experiment 6 is optimal for the problem in hand. If we closely observe graphical surface mapping of experiments 1 to 3, we can see that hidden layer transfer functions result to negative values of the output variable, while the output domain is from zero (0) to one (1).

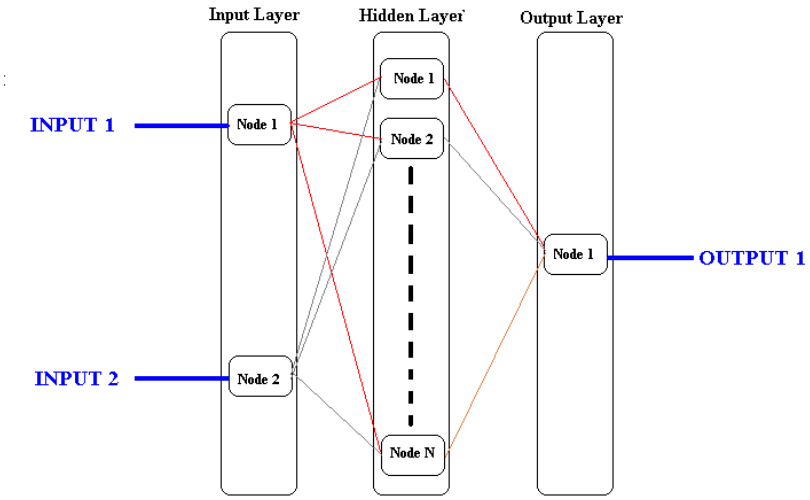


Figure III.22:Basic Architecture of the ANN.

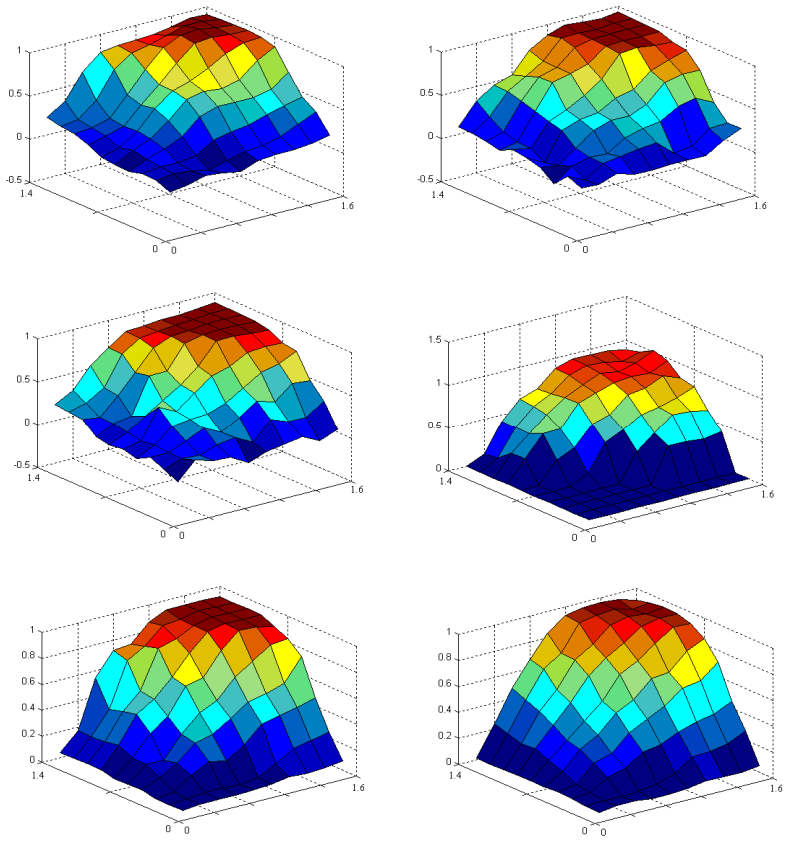


*Figure III.23: Surface mapping of ANN performance for z=sin(x*y);*

(top left) experiment 1, (top right) experiment 2, (middle left) experiment 3, (middle right) experiment 4, (bottom left) experiment 5, (bottom right) experiment 6.

Similar architectures to experiment 6, were trained with the available data set for the cart pole system. Table III.10 presents the experiment settings. The number of nodes as well as the number of hidden layers was allowed to increase due to the larger data set available (10,000 data sets).

Experiments 5 to 7, utilize a two hidden nodes architecture. The number of nodes in the second hidden layer is the half (rounded) the number of nodes in the first hidden layer. Results suggest that increasing the number of hidden nodes does not provide us with an optimum solution. Figure III.24 presents graphically the change in performance related to the change in the number of hidden nodes. A relatively small number of hidden nodes provide better results (improved generalization), however as the number of nodes decreases further performance deteriorates (possible under training).

Table III.10: ANN architectures for the cart pole system.

NN setup										Performance		
Experiment No	Number of Layers	Nodes Input Layer/Hidden Layer 1/.../Output Layer	Transfer Functions			Training epochs	NN training function	Type of NN	NN performance functions	rmse	% rmse	Computation time (h:min:sec)
1	3	2/200/1	tansig	logsig		1000	traindx	newff	mse	0.2308	6.52	0:11:34
2	3	2/40/1	tansig	logsig		1000	traindx	newff	mse	0.1163	3.28	0:02:13
3	3	2/25/1	tansig	logsig		1000	traindx	newff	mse	0.0492	1.39	0:01:24
4	3	2/10/1	tansig	logsig		1000	traindx	newff	mse	0.0821	2.32	0:00:35
5	4	2/40/20/1	tansig	tansig	logsig	1000	traindx	newff	mse	0.0524	1.48	0:03:34
6	4	2/25/13/1	tansig	tansig	logsig	1000	traindx	newff	mse	0.0315	0.89	0:02:09
7	4	2/10/5/1	tansig	tansig	logsig	1000	traindx	newff	mse	0.0521	1.47	0:00:49

Architectures with higher complexity (Table III.10, experiments 5 to 7), provide us with better results in expense of computation time.

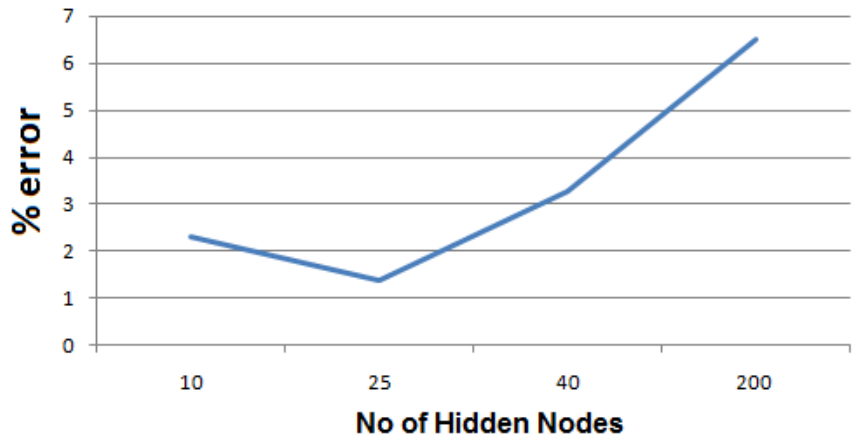


Figure III.24: Effect of hidden node number to ANN performance.

Figure III.25, presents the cart pole stabilization process for initial thetas ranging from -9^{o} to $+9^{o}$. Experiments with optimum performance (Table III.10, experiments 3 and 6), in terms of *rmse* have successfully balanced the pole at zero angles in less than two seconds. Only in a few cases of experiment 3 testing stabilization was achieved in over 2 seconds.

Experiments that exhibited poor performance (1 and 2), could not successfully balance the pole at zero angles for all the initial angles. Experiments 4, 5 and 7, have balanced the cart pole systems in less than four (4) seconds but in angles slightly greater than zero.

Balancing the pole at angles other than zero, describes the stabilization (no significant fluctuation) of the pole at angles close to zero while moving the cart to a specific direction for maintaining this angle. This is valid for our experiments since the evaluation was concerned only with the pole stabilization and not with the cart position. However such a stabilization is not effective since it appears at non zero angles.

Experiment 1, appears to stabilize at non zero angles the poles, depending on initial angle. If initially the pole tipped to the right, then stabilization appeared at none zero right angles. This is supported by the rmse percentage results of the experiment 1 (% rmse=6.52, table III.10).

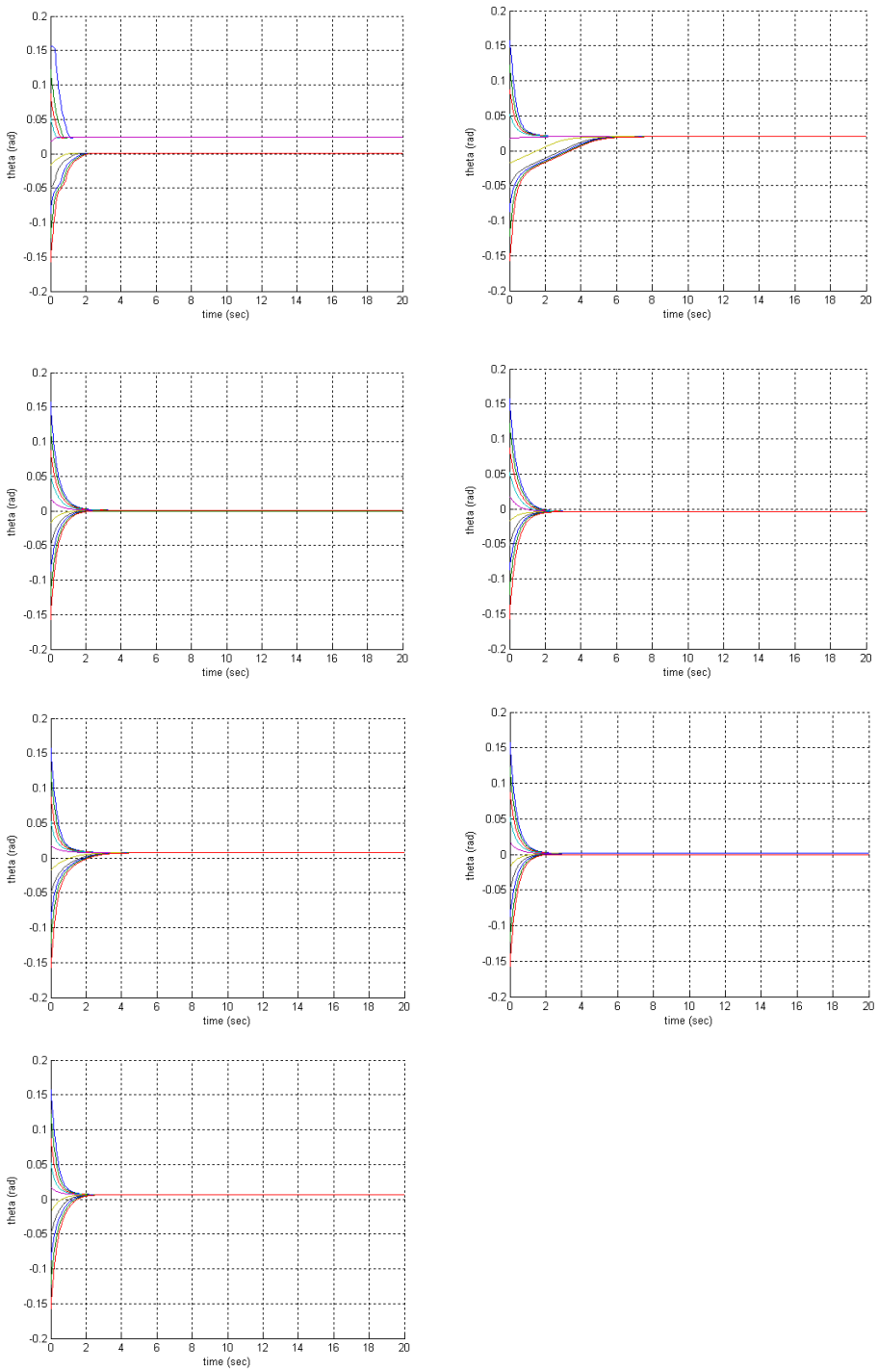


Figure III.25: ANN performance for the cart pole system;

Experiment 1 (top left), Experiment 2 (top right), Experiment 3 (raw 2 left), Experiment 4 (raw 2 right), Experiment 5 (raw 3 left), Experiment 6 (raw 3 right), Experiment 7 (bottom left).

Experiment 2, seems to deteriorate in performance for a specific direction of initial pole angles. Although performance deteriorates, balancing is achieved at the same angle direction but at longer stabilization time.

The best stabilization results were achieved with ANNs that performed best in table III.10; namely experiment 6 and experiment 3. This is in line with the conclusions drawn from figure III.25. The architectures of experiments 6 and 3 incorporate a hidden layer(s) architecture that involves sufficiently small number of nodes for achieving improved generalization and avoiding over training of the NN.

Table III.11: re-runs of ANNs tests.

NN setup								Performance
Re-runs of Experiment	Number of Layers	Nodes Input Layer/Hidden Layer 1/.../Output Layer	Transfer Functions		Training epochs	NN training function	Type of NN	NN performance functions	rmse
1	3	2/10/1	tansig	purline	1000	traindx	newff	mse	0.11289824
2	3	2/10/1	tansig	purline	1000	traindx	newff	mse	0.11401877
3	3	2/10/1	tansig	purline	1000	traindx	newff	mse	0.11404354
4	3	2/10/1	tansig	purline	1000	traindx	newff	mse	0.11393725
5	3	2/10/1	tansig	purline	1000	traindx	newff	mse	0.11448196

NN training was performed only once for each architecture. This could introduce bias to the results since different initialization weights could result into improved performance. For this reason the training and evaluation similar architectures to the experiment 4 (table III.10), was re-runned for five times for the mathematical function. Results of the tests are presented in table III.11. Results of rmse performance suggest that (with accuracy for the second decimal point) performance was similar. The difference was not sufficiently high; expressed as % rmse the

difference between worst and best performance was approximately 0.4%. The experiment suggests that there could be a bias in performance due to single experiment, although this is not significant.

III.4 ANFIS Evaluation

Similar to the previous evaluations ANFIS method was tested against the non linear mathematical function of eq. III.1 and the cart pole system.

We have developed and tested several architectures of ANFIS models against the mathematical function. The architectures as well as the models' performance are described in table III.12. Performance is measured in terms of *rmse* and % *rmse* as described by equations II.1 & II.2 respectively. Figure III.26 presents the resulted mapping of the mathematical function for each of the performed tests.

Experiments 1 to 4 examine the performance of the models with different types of membership functions. Experiment 1, utilizing triangular membership functions, performs better. Experiments utilizing linear output MFs type perform better than experiments utilizing constant MFs type; comparison of experiment 1 to experiment 5.

Table III.12: ANFIS mathematical function test architectures.

Fuzzy Setup					ANFIS Setup		Performance		
Test No	Fuzzy Rules	No FSs	Output MF type	Input MF type	No epochs	Train FIS Optim. Method	rmse	% rmse	Computation time (h:min:sec)
1	9	3	linear	trimf	5	hybrid	0.000182	0.018	0:00:01
2	9	3	linear	trapmf	5	hybrid	0.001744	0.174	0:00:01
3	9	3	linear	gausmf	5	hybrid	0.000509	0.051	0:00:01
4	9	3	linear	gaus2mf	5	hybrid	0.001514	0.151	0:00:01
5	9	3	constant	trimf	5	hybrid	0.002573	0.257	0:00:01
6	25	5	linear	trimf	5	hybrid	0.000010	0.001	0:00:01
7	49	7	linear	trimf	5	hybrid	0.000000	0.000	0:00:01
8	49	7	linear	gausmf	5	hybrid	0.000000	0.000	0:00:01

Increasing the number of MFs for each variable enhances models performance as witnessed in experiments 6 to 8. However the use of increased MFs has several drawbacks. First it requires a large number of training sets for implementing adequate training of the ANFIS-NN without compromising the NN generalizability; since the heart of the ANFIS algorithm is an ANN and the number of nodes is

dictated by the number of input-output variables and variable's FSs, a sufficiently large training set is needed, larger than the resulting node number. Second the increase of MFs leads to a deterministic fuzzy model. Finally the increased number of MFs results in a large number of fuzzy rules. The complexity of the fuzzy model increases with the number of input variables and the number of MFs for each variable. This is demonstrated in the number of rules for the experiments 7 and 1. Although experiment 7 outperforms the experiment 1, the number of rules is increased from nine (9) to forty nine (49).

Similarly when observing the surface mapping of the mathematical function (fig. III.26), it can be noticed that experiments 1 and 6 map the function with sufficient accuracy. Although experiments 7 and 8 demonstrate a better performance in terms of *rmse*, surface mapping deviates from the original mathematical function of figure III.1.

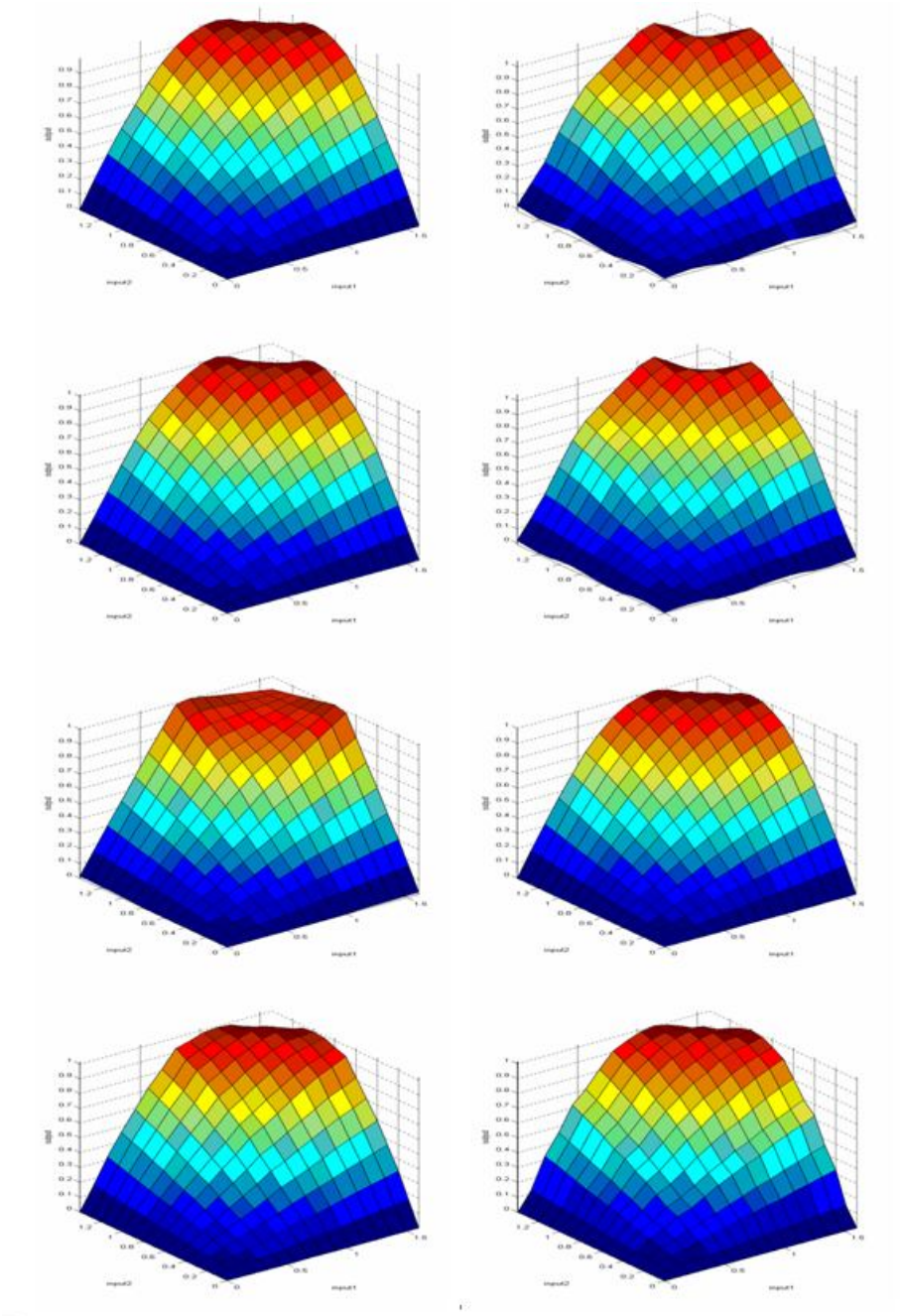


*Figure III.26.: surface mapping of ANFIS performance for z=sin(x*y); (top left) experiment 1,(top right) experiment 2, (raw 2 left) experiment 3, (raw 2 right) experiment 4, (raw 3 left) experiment 5, (raw 3 right) experiment 6, (bottom left) experiment 7, (bottom right) experiment 8.*

For modelling the cart pole system we have used the architectures of experiments 1 and 6. In a similar manner to the evaluation of the other methods we have used the available training sets for training and developing a *PDlike* cart pole controller. The angle and angle derivative were the system's inputs, while the output is the force applied to the cart.

Table III.13 describes the models architecture and figure III.27 presents the models performance on managing to balance the cart pole system.

Table III.13: Cart pole ANFIS models architecture.

Fuzzy Setup					ANFIS Setup		Performance		
Test No	Fuzzy Rules	No FSs	Output MF type	Input MF type	No epochs	Train FIS Optim. Method	rmse	% rmse	Computation time (h:min:sec)
1	9	3	linear	trimf	5	hybrid	0.0620	1.75	0:00:04
2	25	5	linear	trimf	5	hybrid	0.0204	0.58	0:00:16
3	49	7	linear	gaussmf	5	hybrid	0.0141	0.40	0:00:55
4	49	7	linear	trimf	5	hybrid	0.0125	0.35	0:00:55

The ANFIS models managed to balance the cart pole system in all occasions. Experiment 1 architecture was the slowest among ANFIS models. It required 8 seconds approximately for balancing the pole.

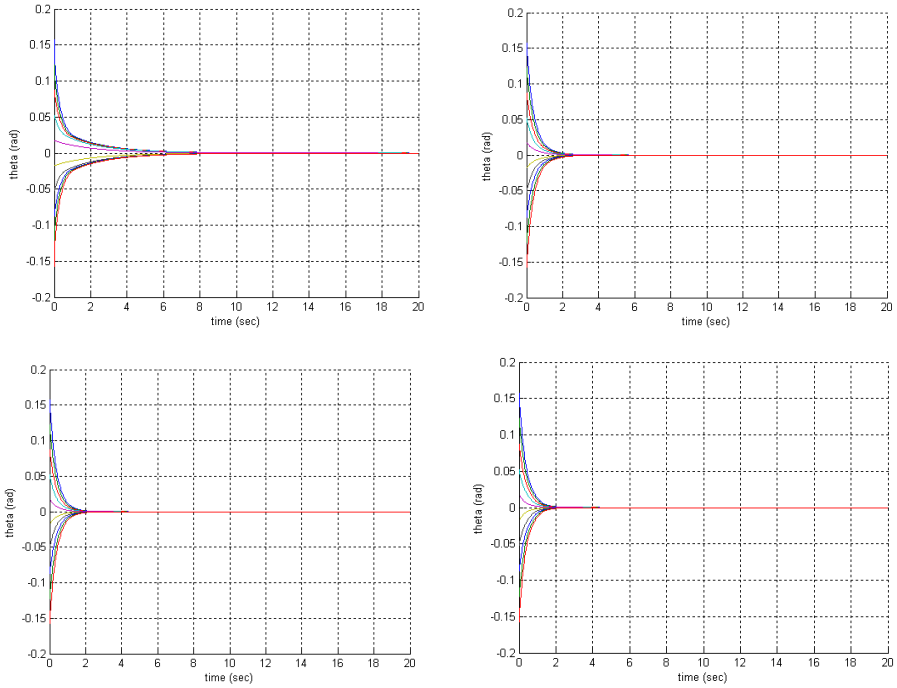


Figure III.27 : ANFIS cart pole models performance;
(top left) ANFIS model 1, (bottom right) ANFIS model 4.

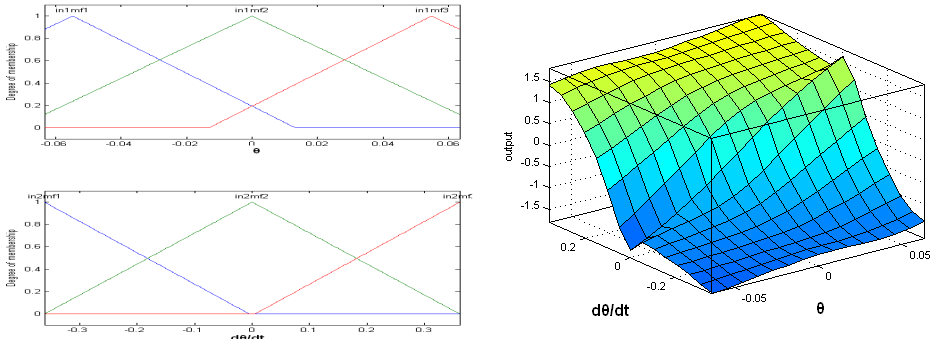


Figure III.28 : ANFIS experiment 1, resulted FRBS architecture.

Results of cart pole ANFIS controllers (fig. III.27) suggest that minimal FS and RB, (experiment 1, table III.13) require longer time for stabilizing the pole. The use of triangular MFs rather than Gaussian MFs, provides better performance in terms of rmse (table III.13, experiments 3 & 4). However during the application of the developed models on the cart pole simulation model, there was no significant difference in stabilization time.

As the complexity of the ANFIS model increases so does the computation time. Increasing the number of FSs for each input variable from 3 to 7, and subsequently increasing the RB, increases computation time by a factor of 13.75. In a simple ANFIS system with 2 inputs the change is not dramatic. However in more complex system this could be interpreted in computation times of hours instead of seconds.

III.5 Benchmarking against other authors and comparison of different applied methods

Although direct comparison against the work of other authors who utilized the same mathematical functions (Achiche S, 2004) for testing the efficiency of their genetic algorithm is not feasible due to the utilization of different performance criteria, we can draw assumptions on the models' performance based on the cart model performance; which is widely used as a benchmarking experiment.

Yi and Yubazaki (Yi J, Yubazaki N, 2000), suggested a fuzzy controller based on the dynamically connected single input rule modules (SIRM). Although the pole stabilization was assigned with higher priority than the cart position, the controller stabilized the cart-pole within 9.0 sec, for higher initial pole angles than our

experiments. Our controllers' performance was better, but our proposed controllers were concerned only with the pole stabilization, irrespectively to the cart position.

Magdalena (Magdalena L, 1997), applied an evolution algorithm for modifying the scaling function of each input or output variable. The evolved fuzzy controller was tested against the cart pole system. The fuzzy controller was capable of stabilizing the cart during the 60 sec experiment duration, but stabilizing times were graphically presented above the 10 seconds.

Belarbi et al (Belarbi K, 2005), suggested an evolution method for Mamdani FRBS rule minimization. Although the application of their controller to the cart pole system did not yield impressive results (stabilization above 9 sec), the resulted RB was very compact, with only five rules.

Gurocak (Gurokak H.B, 1999), applied genetic algorithms for tuning the RB of a fuzzy controller by shifting the peak fuzzy sets locations. Authors have applied their method for tuning a nine (9) rule PD-like fuzzy controller, and applied it to the cart pole system. The resulted FRBS balanced faster the pole than the un-tuned fuzzy controller, minimizing the overshoot. Balancing was achieved approximately in 1.5 sec. However the proposed method could be applied to final design stages, since it requires the existence of an initial rule base.

It is important to point out, that due to the adopted method of our research, the efficiency of the resulted cart pole controllers depends on efficiency of the controller used to generate the training set. The performance of the developed controllers is expected to improve with the use of a more advanced cart pole controller for generating data sets.

III.5.1 Discussion on methods efficiency

Modelling a complex system is usually a balance between performance and computational resources. In the experiments that we have carried out on the mathematical function, ANFIS modelling method has outperformed the other methods both in terms of performance and computation time (table III.14). However the modelling of dynamic systems is a more difficult task and performance against an available evaluation set does not always guarantee efficient operation under real tests. To overcome this obstacle developed models were tested against a simulation of the cart pole system rather than on an evaluation set.

The method adapted by the FUN toolbox has shown that although performance against the evaluation set was close to EVOFINE models, none of the developed *PDlike* controllers was capable of balancing the pole. Furthermore the performance of the FUN controllers was variable, depending on the defuzzification method (fig. III.21). Since the ANN structure used in the FUN toolbox was trained with input – output membership degrees, the defuzzification method is responsible for translating the ANN output to a crisp value, and thus the applied force to the cart system. We have tested five (5) of the most common defuzzification techniques namely the Bisector (BIS), the Centroid (CEN), the Mean Of Maxima (MOM), the Largest Of Maxima (LOM) and the Smallest Of Maxima (SOM).

EVOFINE toolbox has evolved optimal cart pole controller after one thousand generations, in the expense of computation time, over 24 hours on an Intel Quad PC. Although the performance in terms of *rmse* was not competitive to the ANN and ANFIS controllers' performance, the EVOFINE model was capable of balancing the pole in shorter time. However the balance was achieved in angles slightly higher than the zero angles (fig. III.13).

ANN and ANFIS *PDlike* controllers were capable of balancing the pole relatively fast (fig. III.25 & III.27), in a very similar form. However the ANFIS performance was superior to the ANN controller (table III.14). Additionally the computational time of ANFIS was less than half the time required for the ANN to be trained.

Table III.14: Comparison of different methods.

Z=sin(x*y)				
Method	Experiment No	Performance % *rmse*		*approximate computational time h:min:sec*
EVOFINE	17 (Table III.1)	4.31		03:03:00
FUN	20 (Table III.8)	2.57		00:22:09
ANN	6 (Table III.10)	2.94		00:00:40
ANFIS	6,7,8 (Table III.12)	0.00		00:00:01
Cart Pole Controller				
Method	Experiment No	Performance % *rmse*	*Balancing time (sec)*	*approximate computational time h:min:sec*
EVOFINE	4 (Table III.5)	2.90	~=2	24:46:00
FUN	3 (Table III.9)	4.41	---	00:31:14
ANN	6 (Table III.11)	0.89	~=2	00:02:09
ANFIS	4 (Table III.13)	0.35	~=2	00:00:55

All the above tests were performed with Matlab 7.1, on an Intel Quad PC.

Numerical results presented in table III.14, suggest that the optimum method for modelling the test systems is the ANFIS method. However prior to adopting this conclusion one should consider the following factors:

- EVOFINE similar to ANFIS methods result into comprehensive models, with transparent architecture to the end user. This is not true for FUN and ANN models, which suffer from the "black box" syndrome.
- EVOFINE, due to computational restrictions, was tested with suboptimal architectures, while ANFIS utilized optimal architectures. The RB of the EVOFINE FRBSs was a percentage of the total rules.
- EVOFINE incorporates rule weight; thus introduces rules minimization in the evolution process of the FRBSs. This could result into less complex and more readable FRBS. ANFIS does not have this feature, thus the complexity of the resulted FRBS depends on the number of participating inputs-outputs and the number of FSs describing each variable domain.
- ANFIS develops FRBSs with the use of ANN method. Thus all the applied limitations of ANN apply to ANFIS developed FRBS. The architecture in terms of input-output variables and FSs is restricted by the number of available training sets. If the number of data is sufficiently high for a given system, then a large number of FSs could apply to the FRBS. However this is not always the case as it will be exhibited in a latter chapter, during the application of ANFIS to the ventilation management process.
- ANFIS method as applied with the Matlab 7.1 toolbox results into TSK fuzzy systems. However EVOFINE and FUN toolboxes develop Mamdani and Mamdani "like" systems respectively. Mamdani FSs on the systems "premise" part of the inference engine allow flexibility both in terms of shape and number of FSs as well as defuzzification method.
- FUN and EVOFINE computation intensity could be counter balanced with the use of cluster computer systems.
- Results of all cart pole controllers capable of balancing the cart pole systems (EVOFINE, ANFIS and ANNs), exhibited zero overshoot.

As it has been shown in the experiments performed for each method the model's internal architecture is very important for the efficiency of a model. The

identification of an appropriate model's architecture for each method and for a given problem is a balance between designer's experience and expertise and computational resources. However the problem of finding the appropriate model's architecture for specific problems it is on its own, a problem of optimization.

Appendix IV: Artificial Intelligence Methods

IV.1 Fuzzy Rule Based Systems (FRBSs)

Fuzzy Rule Based Systems (FRBSs) constitute an extension to classical rule based systems. Classical rule based systems are utilizing classical set theory, where an element is represented in binary logic, assigned with values of true (0) or false (1), interpreted as belonging or not belonging to a set. FRBSs are build on the foundations of fuzzy set theory, were an object is not assigned with a crisp value but a membership value to a set.

Fuzzy Logic (FL) has its roots in the concept of three valued logic, where a variable could be assigned to three distinct logic levels: true, false and indeterminate. The concept of many valued logic was developed by mathematicians in the early 30s (Vitez T.S et al 1996). Fuzzy Sets (FSs) were introduced by Lofti A. Zadeh in 1965 (Cox E. 1994,). According to the FSs theory, an element could be assigned with any value between 0 and 1, to a specific set. Since the interval [0, 1] has infinite numbers, infinite degrees of membership to a set are possible. Thus a membership function maps every element of the universal set (often called universe of discourse), to an interval [0, 1], where 0 means no membership, and 1 complete membership.

FL is viewed as an extension of the classic logic systems, providing us with a framework for dealing with the problem of knowledge representation in uncertainty and imprecision. Its importance arises from the fact that it can mimic human reasoning, which is approximate in nature.

Knowledge representation is performed with the use of linguistic variables. A linguistic variable has values of words instead of numbers. Each value refers to a membership function. A membership function assigns to a numerical variable the degree to which it fits to a linguistic variable.

In figure IV.1, an example of FRBS is given to simplify the introduction of the underlying theory. The system is composed from two input variables and one output variable, which is described as Multi Input-Single Output (MISO) system. It functions as a minute volume ventilation controller which utilizes two patient physiology variables, Oxygen Saturation in arterial blood (SpO_2) and End Tidal Capnography (E_TCO_2), for determining the appropriate minute ventilation (V_E).

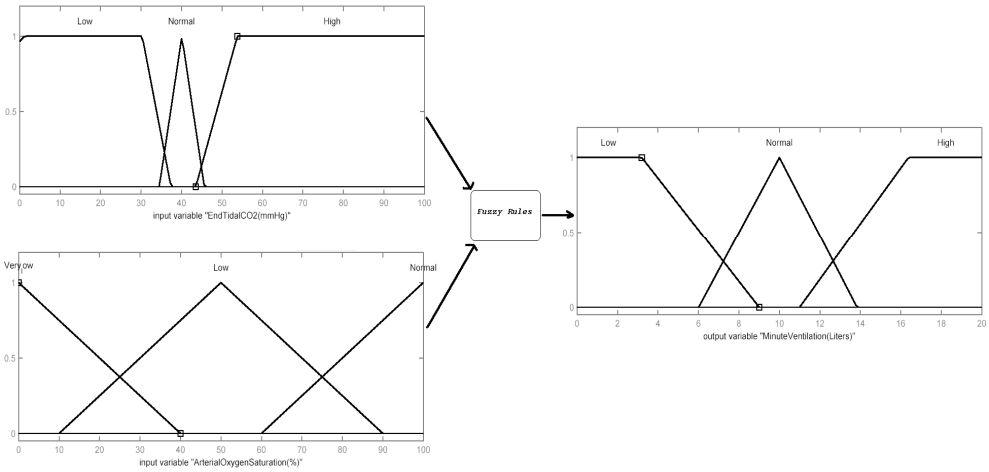


Figure IV.1: FRBS for patient ventilation control.

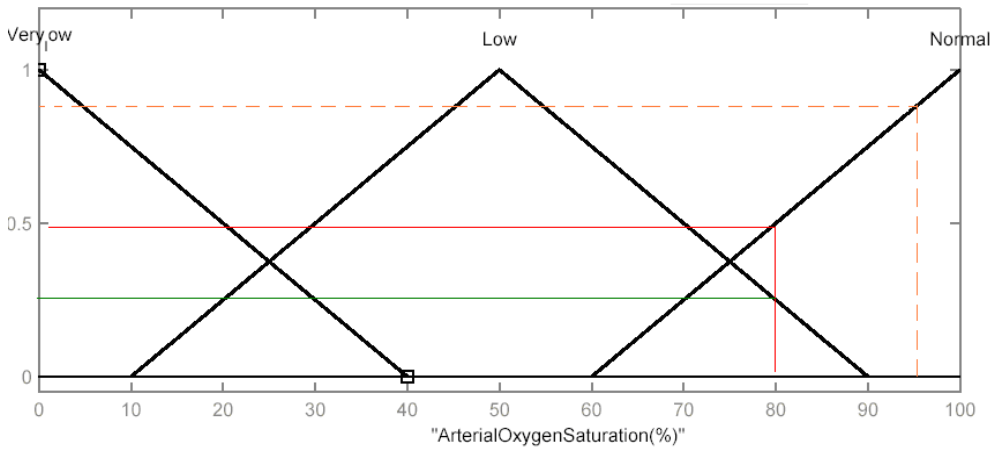


Figure IV.2: Crisp to Fuzzy.

The fuzzy space (universe of discourse) is composed of multiple overlapping linguistic variables. The universe of discourse for the SpO_2 variable is 0 to 100%. The fuzzy sets describing the universe of discourse overlap to some extent. The choice of the shape, number, position and size of fuzzy sets for a particular variable is problem specific. Traditionally the above characteristics of the fuzzy sets are identified with the assistance of experts on the field. In the above example we have developed three linguistic variables of triangular and trapezoid shape, namely "Very Low", "Low" and "Normal" Oxygen Saturation. The membership functions most commonly used in control theory are triangular, trapezoidal, Gaussian and sigmoid Z & S functions.

A crisp reading of patients Saturation is interpreted as membership degree to the fuzzy sets which compose the fuzzy space. A reading of 95%, (Figure IV.2) is

assigned with a 0.9 degree of membership only to the fuzzy set described by linguistic variable "Normal". If the reading is 80%, then the crisp value belongs to two fuzzy sets, "Normal" and "Low" but with different membership degrees, 0.5 and 0.3 respectively. The process of assigning membership degrees to crisp values is called *fuzzification*.

The mathematical representation of membership (μ) to a set (A), is given by equation IV.1, and is interpreted as the degree of membership of an element (x) in fuzzy set (A).

$$\mu_A(x) \in [0,1] \quad \text{eq. IV.1}$$

The total of linguistic terms and membership functions of a FRBS forms the Data Base (DB) of the system. DB might also include scaling factors used to transform between the universe of discourse, where fuzzy sets are defined, to the domain of the system variables.

Operations on fuzzy sets such as Union, Intersection & Complement are a generalization of operations of Classical Sets (Ross T.J, 1995). Fuzzy operations are mathematically described in the following equations:

Union	$\mu_{A \cup B}(x) = x_A(x) \vee x_B(x) = \max(x_A(x), x_B(x))$	eq IV.2
Intersection	$\mu_{A \cap B}(x) = x_A(x) \wedge x_B(x) = \min(x_A(x), x_B(x))$	eq IV.3
Complement	$\mu_{\bar{A}}(x) = 1 - \mu_A(x)$	eq IV.4

The logic of how the system responds to inputs, is formed as a collection of linguistic rules joined by the also operator. Linguistic rules are in the format of "IF *premise* THEN *consequent*".

The total of rules forms the Rule Base (RB) of the system. The form of rules expresses an inference, knowing the fact (*premise*) we can infer a conclusion (*consequent*). Based on this property the rule base of a system is commonly named Inference System. This form of knowledge representation expresses human empirical knowledge in a similar way to human communication. RB could be derived either by expert knowledge on the problem, or with the help of other methods such as Neural Networks (Nguyen H.T et al, 2003), Genetic Algorithms (Cordon O et al, 2001), and Wang and Mendel's method (Wang L.X, Mendel J.M, 1992).

Several methods have been developed for designing inference systems, widely known by their primary authors' names. Mamdani, Takagi-Sugeno-Kang (TSK),

Larsen and Tsukamoto, are the three more widely used methods. The first two methods are commonly applied, and are briefly described in the next paragraphs.
Mamdani in 1975 (Mamdani E.H, Assilian S, 1975), proposed fuzzy rules in the form of:

IF x_1 is A_1 AND x2 is A_2 AND …. THEN y_1 is B_1 AND y_2 is B_2 ….

Where A_i and B_i are fuzzy sets, and x_i and y_i are inputs and outputs respectively. The above rules are expressed in mathematical terms by the following equation:

$$R(x,y) = \bigvee_{i=1}^{n} (A_i(x) \wedge B_i(y) \quad \text{eq. IV.5}$$

Takagi-Sugeno-Kang (TSK) model rules are given in the form of:

IF x_1 is A_1 AND x2 is A_2 AND …. THEN $f_i(x_1,x_2,….x_k)$

Where $f_1,f_2,..f_n$ are functions, thus the model produces real valued function:

$$R(x) = \frac{A_1(x)f_1(x) + A_2(x)f_1(x) + ...}{A_1(x) + A_2(x) + ...} \quad \text{eq IV.6}$$

In order to fully describe the operation of the example Mamdani FRBS (fig. IV.1), we need to identify nine (9) rules, out of the 27 possible rules (Total number of potential rules). The total number of rules is calculated by the product of the fuzzy sets utilized by our system. In the case of our example the product is calculated utilizing 3 fuzzy sets for input S_pO_2, 3 sets for input E_TCO_2, and 3 sets for output V_E, a total of 3x3x3=27. As the number of inputs-outputs to a system and fuzzy sets increase the complexity of the RB increases. However it is not always necessary to incorporate the maximum number of rules to a system in order to model its operation, since some input - output combinations may not be true for the specific system. For the example FRBS of figure IV.1, for simplicity, we have empirically developed basic rules following Mamdani method. The four rules that describe the operation of our system are the following:

```
Fuzzy Rules
1. IF OxygenSaturation is Normal and Capnography is Normal THEN Ventilation is Normal
2. IF OxygenSaturation is Low and Capnography is High THEN Ventilation is High
3. IF OxygenSaturation is VeryLow and Capnography is High THEN Ventilation is High
4. IF OxygenSaturation is Normal and Capnography is Low THEN Ventilation is Low
```

An advantage of FRBSs is that rules are evaluated in parallel. When a rule is valid, participate in the problem solution, we say it is fired (activated). The application of RB is best understood with the graphical representation of an "instance" of the systems performance. In the example of figure IV.3, inputs have crisp values of Oxygen Saturation =83%, End Tidal CO_2=45 mmHg. The crisp values correspond to two linguistic variables for each input, firing two fuzzy rules (rule 1 & 2).

Based on Mamdani implication method and equations IV.2 & IV.3 the aggregated output for the rules will be given by the following relationship:

$$\mu_{NORMAL}(y) = \min[\mu_{NORMAL}(83), \mu_{NORMAL}(45)]$$
$$\mu_{HIGH}(y) = \min[\mu_{LOW}(83), \mu_{HIGH}(45)]$$
$$\mu(y) = \max[\mu_{NORMAL}(y), \mu_{HIGH}(y)]$$

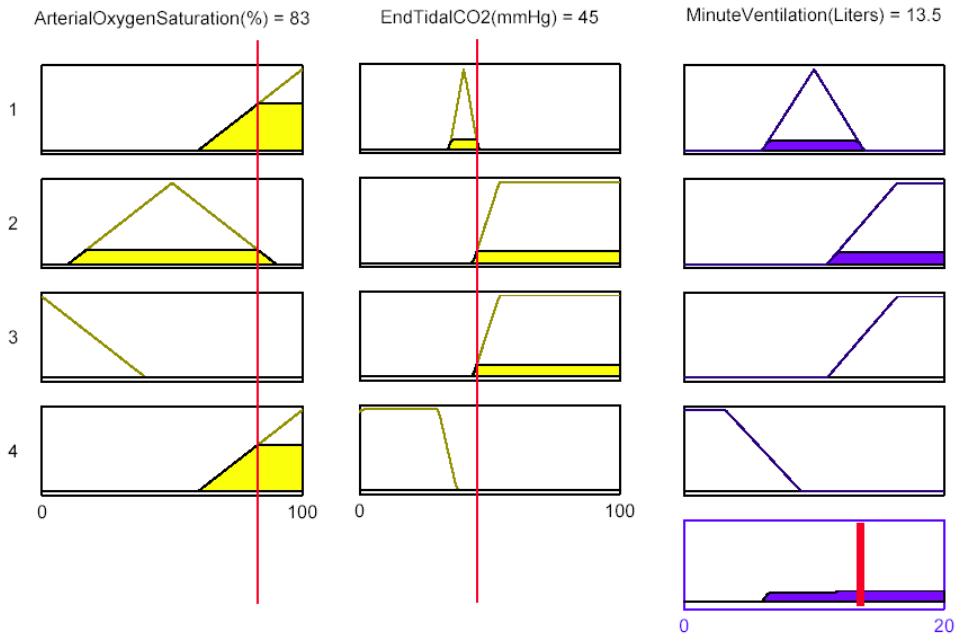


Figure IV.3: Graphical Inference Representation of example.

In inference systems such as Mamdani, where a fuzzy output is produced, it is common to translate the fuzzy output to crisp values. This process is called *defuzzification*. Defuzzification produces a crisp value that best reflects the FRBS operation. Methods such as Bisector, High-center of area, Max criterion, First of maxima (or smallest of maxima SOM) and middle of maxima (MOM), are described in the bibliography. Figure IV.4 gives the graphical representation of some the

prevailed methods. However the dominant method of defuzzification is the Center of Gravity (Centroid) method (Cox E, 1994). According to this method the crisp output is computed by identifying the center of area of the region of the system's output. This is graphically represented in the example of figure IV.3 (bottom, right side), computing of a crisp value for the ventilation rate of 13.5 L/min.

Bisector provides with similar results to centroid method and identifies the point at which the output area is divided into two equal areas.

Weighted average method is formed by weighting each membership function in the output by its respective maximum membership value.

Center of sums (COS) is similar to the weighted average method, but in contrast the weights are the areas of the membership functions instead of the membership values.

Middle of Maxima (*MOM*) identifies the mean of the maximum output functions. Similarly first (Smaller) (*SOM*) of maxima and last (Larger) of maxima (*LOM*) identify the minimum and the maximum value of the domain with maximized membership degree.

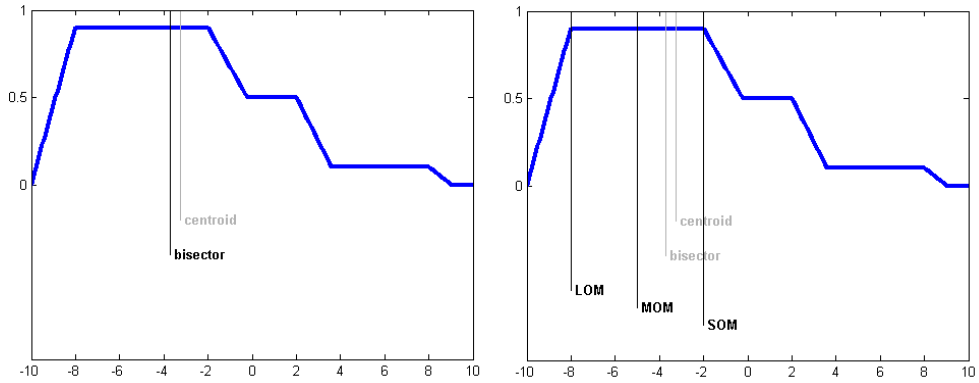


Figure IV.4: Graphical Representation of defuzzification methods. Left Centroid & bisector, Right Larger of Maximum (LOM), Middle of Maximum (MOM) and Smaller of Maximum (SOM).

Fuzzy Logic demonstrates several advantages over other methods. It can easily model complex systems, by introducing a development method similar to human communication; experts' knowledge is encoded directly in a form very similar to their decision making process; the RB of a FRBS is evaluated in parallel, thus all decision determinants are considered in the solution of a problem; FL model's uncertainty and imprecision in complex models where understanding is limited and/or judgmental; the fuzzy system could be developed with the input of experts, or

based on available input –output data with the synergism of other artificial intelligence methods.

IV.1.1 Fuzzy Logic Applications in Medicine

An initial query in the National Library of Medicine & the National Institutes of Health (NCBI, 2006), using the keywords "fuzzy *AND* medical", resulted in 457 articles of theory and application of Fuzzy Logic in the medical field. Figure IV.5 shows the number of relevant publications over the years 1995 to 2006.

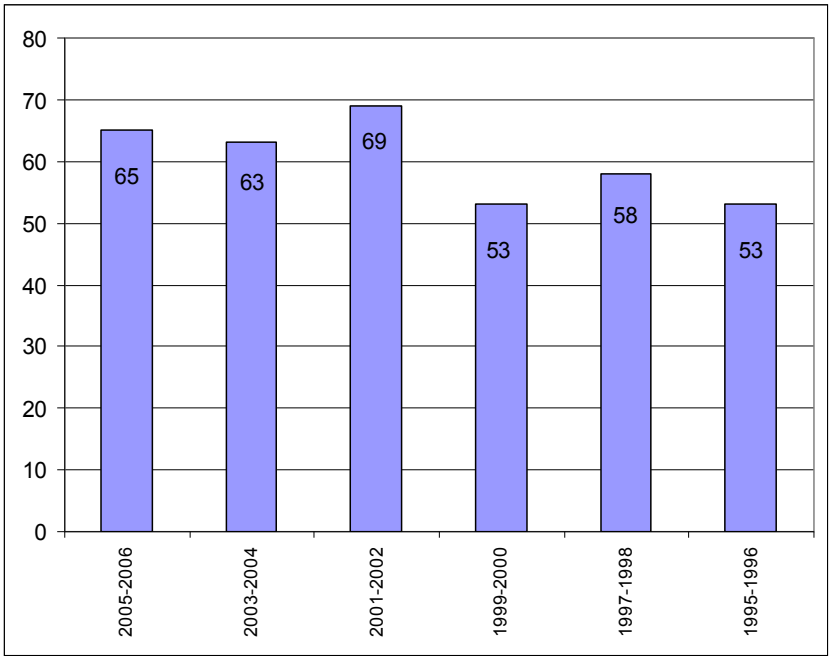


Figure IV.5: Articles containing the keywords "fuzzy AND medical", in NCBI query.

A more detailed literature survey by F. Steimann (Steimann F, 2001) reveals the main applications of fuzzy sets in the medical field. Figure IV.6, taken from Steinmann article, classifies published work into three major categories: classification, inference and control.

T. S. Vitez et al (Vitez T.S et al, 1996), categorizes medical applications of FL, very similar to Steimann publication, into the following categories: Pattern recognizers, Controllers and Expert systems.

Linkens (Linkens D.A et al, 1999), analyse further and categorize applications of fuzzy logic into: open – advisory control systems, closed loop adaptive and non-adaptive

systems, fuzzy unsupervised clustering, fuzzy supervised classification, and fuzzy modelling and identification.

Furthermore Linkens classifies applications of fuzzy logic according to medical discipline, and quotes relevant published work for each discipline. Linkens classifies published work into the following categories:

Table IV.1: FL categories

Invasive Medicine	**Regionally Defined Medical Disciplines**	**Neuromedicine**	**Image and Signal Processing (monitoring and control)**	**Laboratory**	**Basic Science**	**HealthCare**
Surgery	Dental	Psychology	Radiation medicine	Control	Medical information	Healthcare environment
Orthopaedics		Psychiatry	Radiology	Analysis of data	Anatomy	Healthcare organizations
Anaesthesia			Signal processing		Pathology	
Artificial Organs					Forensic medicine	
					Genetics	
					Pharmacology	
					Biochemistry	

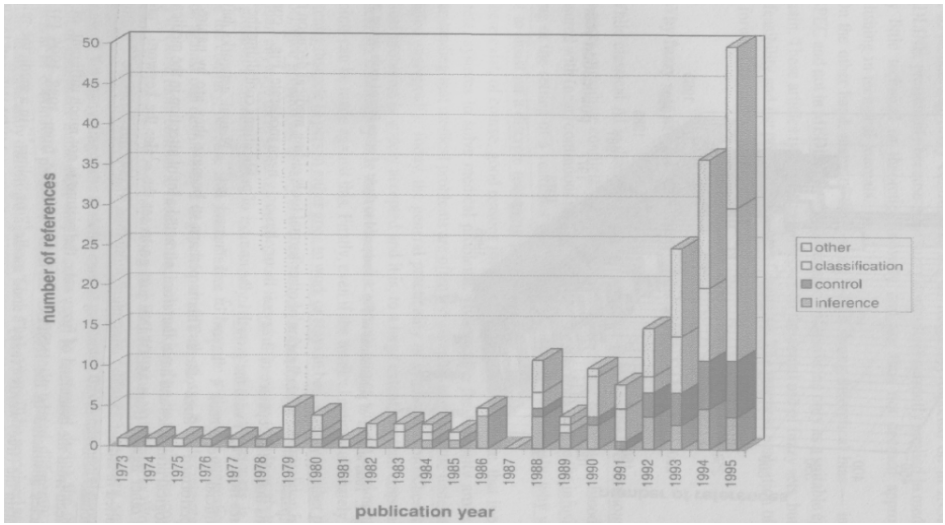


Figure IV.6: Published work on fuzzy – medical, according to publication year and category. Figure is taken from Steimann F, 2001.

IV.2 Genetic Algorithms (GAs)

Genetic Algorithms (GAs) is a subclass of Evolutionary Computation (EC) methods. Evolutionary Algorithms (EA) are search and optimization methods that emulate natural evolution based on three fundamental processes: Mutation, Recombination and Selection.

There are several types of EAs. The most profound are GAs, Genetic programming, Evolutionary programming and Evolution strategies.

GAs were first proposed by Holland (Holland J.H, 1962 & 1978), as search algorithms that evolve possible solutions through search in complex spaces.

GAs have been both theoretically and empirically proven to provide valid approaches to search problems (Cordon O et al, 2001). Since natural selection is the original concept of the development of GAs, the same terminology is adapted for the needs of describing GAs process. Terms as Chromosomes, Genes, Locus, Fitness, Genotypes and Phenotypes are utilized to describe the structural elements and algorithmic operations (Goldberg D.E, 1989).

The archetypal of a Genetic Algorithm proceeds in five steps. The developer has to represent genetic candidate solutions into chromosomes (often represented as binary strings) and to develop a method of assessing the acceptability of each solution (often referred to as fitness). The second step involves the random generation of an initial population (1st generation) of candidate solutions. The population is subject to genetic operations such as reproduction, crossover and mutation. Steps three to five are repeated for a specific number of generations or until a good solution to the problem have been achieved.

During reproduction a subset of strings (known as the mating pool), are copied according to their fitness (usually called objective function, a measure of string's "fitness" to the problem). The higher fitness is "translated" as higher probability of advancing to the next generation. Reproduction could be achieved by algorithms such as roulette wheel selection (Goldberg D.E, 1989), were the higher the fitness of a string, the larger the surface it occupies on the wheel. Spinning the wheel will result in selecting with higher probability, the strings with higher (or lower depending on nature of the problem) objective values.

Crossover is performed on the resulting population (following reproduction operation). Crossover is considered the most important operator. During this operation string segments of parent chromosomes are uniformly exchanged, producing offspring's of solutions that have demonstrated maximum fitness to the search problem. The number of parent chromosomes that undergo crossover operation, is dictated by the crossover probability.

Mutation is a secondary GA operation, which provides a means of searching unexplored solutions to a search problem. It also inhibits fast convergence to sub-optimal solutions (Cordon O et al, 2001). The probability of altering a bit of a chromosome is defined by the mutation rate. "As a rule of thumb", mutation probability per bit is chosen approximately as 0.001 (Goldberg D.E, 1989).

Evolutionary methods exhibit several advantages over other search and optimization techniques. There is no need for previews and expert knowledge; there is parallel search of the problem space leading to efficient exploration and exploitation of the search space and search solutions respectively; fast convergence to local optima is avoided (Pena-Reyes C.A, Sipper M, 2000).

IV.2.1 GAs Medical Applications

An initial query in the National Library of Medicine & the National Institutes of Health (NCBI, 2006), using the keywords "genetic algorithms medical", resulted in 562 relative articles.

Pena-Reyes and Sipper (Pena-Reyes C.A, Sipper M, 2000), in their survey of evolutionary computation in medicine, categorized the application of EAs according to medical task, in the following categories:

- Data mining: is the process of identifying patterns and regularities through available data. Two major approaches exist; supervised and unsupervised. The following two are the most popular applications: Diagnosis, papers found use EA to solve a wide range of diagnostic problems, Prognosis, papers found use EA to interpret and predict future patient condition.
- Medical Imaging and signal processing: Identify information hidden in medical images and temporal signals, or filter information through a noise signal - image.

- Planning and scheduling: involves the ontological distribution of resources among tasks, subject to constrains. EA used in planning and scheduling to solve problems such as allocation of hospital resources, treatment and surgery planning.

In their work, they have further categorized the evolutionary technique of Genetic Algorithms into classes according to the representation of the genome:

- Unidimensional, binary genome: This is the most widely used representation. Fifty one (51) articles were referenced for this class.
- Multidimensional genome: In medical images, matrices suggest genomes of many dimensions. Six (6), articles were referenced for this class.
- Real-valued genome: In variable optimization problems this representation is applied due to high precision. Seven (7), articles were referenced for this class.
- Rule-encoding genome: Rules are directly encoded to the genome. Two (2), articles were referenced for this class.
- Indexed representation: Genome is encoded using alphabet indexes. One (1), article was referenced for this class.

IV.3 Genetic - Fuzzy Systems (GFS)

One of main drawbacks of Fuzzy Systems is that they are not able to learn. Development of the Knowledge Base (RB and DB), is performed traditionally with the input from experts on the problem, or with the aid of other methods.
Wang and Mendel (Wang L.X, Mendel J.M, 1992), proposed a data driven RB generation process. It utilizes a training input-output data set to produce candidate linguistic rule sets; an importance degree is assigned to each rule; finally the RB of the system is composed from the rules with the higher importance degree from each set.
Another approach is the Self Organizing fuzzy logic controller (SOFLC), proposed by Porky and Mamdani (Chen C.L, Chen Y.M, 1993). The SOFLC is capable of generating and modifying control rules, based on an evaluation of systems performance. It utilizes the error between the expected output and the actual systems

output, as well as the corresponding error change, for replacing or correcting fuzzy rules. If at a specific instance the performance is poor then according to strategy, the correction is performed few samples back in time. This strategy is called delay-in-reward.

Artificial Neural Networks (ANNs or often described as NNs), have been extensively used in fuzzy systems (Tsoukalas L.H, Uhrig R.E., 1997). Neural Networks can be used in determining membership functions. During the first stage a NN is used for classification or clustering of domain data, and during the second stage, fuzzification is used for assigning fuzzy membership values to clusters. Tagaki and Hayashi (Tagaki H, Hayashi I, 1992) suggested a NN Driven Fuzzy reasoning method. According to this strategy a NN is trained from a set of input – output data, not based on their crisp values but rather on the degree of membership to predefined input – output fuzzy sets. The method could be presented, similar to TSK rules, by the following function:

$$\text{If } (x1,x2) \text{ is } A^S \text{ then } y^S = NN_S(x1,x2) \quad \text{eq IV.7}$$

Jang & Gulley developed a toolbox for Matlab®, named Adaptive network based fuzzy inference system (ANFIS), which is appropriate for learning fuzzy systems (Jang J.S, Gulley N, 1995). ANFIS is based on gradient descent optimization with feed forward NN, for learning single output TSK systems. ANFIS constructs a fuzzy inference system (FIS) whose membership function variables are tuned (adjusted) using either a back propagation algorithm alone, or in combination with a least squares type of method. A detailed description of ANFIS and NN Driven Fuzzy is provided in latter section (IV.4).

The use of GAs in the development of FRBS is encountered on a wide range of application (Sanchez E et al 1997 & Cordon O, Gomide F et al 2004). The usefulness of synergism of the two methods lies in the advantages of each method. GAs are well known for their ability to explore complex spaces for suitable solutions, incorporating a priori knowledge, while Fuzzy Systems present the Knowledge Base in terms familiar to the human communication, modelling efficiently imprecision and uncertainty.

GAs are used for optimizing existing FRBS, and learning KB, although the boundaries between the two approaches are not always clear. Applying GAs for

optimization results in a faster search and requires less computational resources, but it does not explore the total search space. In contrast applying GAs for learning – developing the FRBS will likely lead to optimal solutions but the process duration is increasing with the complexity of the FRBS.

Applications of GFSs are mainly focused on the following, briefly described, categories.

IV.3.1 Tuning the membership functions

As Herrera (Herrera F et al, 1995), has suggested the use of GAs can improve performance of an existing FRBS, by tuning the fuzzy sets based on training data. The process usually utilizes a mean square error (*mse*), between FRBS output and training set as a fitness function. An existing KB is considered as a perquisite for the tuning process. Tuning of FSs might involve tuning of shape, size, position, number, or a combination of the above. Important in all GFS is the encoding procedure of the desired element into a chromosome (long string). Encoding could be performed with Binary, Integer or Real values. Both the type of chromosome and the underlying logic of encoding are important.

Herrera and Lozano (Herrera F et al, 1995), encoded all Fuzzy Sets of a rule into a string Cr_i and combined all strings to form a chromosome $C=(Cr_1,Cr_2,..Cr_n)$. The string Cr_i was a representation of trapezoidal membership functions, in terms of both position and size. The coding utilized real valued genes to reduce search space size. The method was verified by numerical examples.

Gurocak (Gurokak H.B, 1999), propose a tuning process of shifting FSs. In order to avoid FSs moving throughout the domain, thus losing linguistic meaning, he constrained the movement of the sets. In coding the FS he used a binary code indicating the location of each FS. Gurocak concluded that the performance of tuning process depends on the quality of the original KB, thus this method could be used in final design stages.

Wong (Wong C.C, Her S.M, 1999) suggested a method of reducing the number of FS in order to reduce the complexity of the Fuzzy system. Encoding was performed by translating triangular shaped membership functions into strings. The combination of strings (chromosome) is the definition of Fuzzy rules. Population was initialized with different lengths of string combinations. GAs were applied to identify the optimum

set of strings. The application of the method to the inverted pendulum system showed that redundant rules were excluded from the optimum solution.

IV.3.2 Tuning the scaling functions

Fuzzy systems use scaling functions for normalizing the universe of discourse (of input and output variables). GAs are applied for adapting the scaled universe so as to better map the variable range. Changes of scaling functions result in change of controller sensitivity, shift of the working range and change in the shape of membership functions.

Magdalena (Magdalena L, 1997), proposed and tested a GAFS, on the cart pole example, capable of evolving the scaling functions, the membership functions and the control rules. In the proposed system each rule was binary encoded into two strings, the first described the input linguistic terms, while the second the output linguistic terms.

Cordon et al (Cordon O, Herrara F, Magdalena L, Villar P, 2001), developed a GAFS, in which all KB variables, naming scaling factors, membership functions and RB were evolved. In the genetic method a scaling function with two sensibility variables was used. The fuzzy system was encoded into chromosomes which were composed from three parts. The first part encoded the number of labels; the second part encoded the sensibility variables; and the third part encoded the working ranges. RB was generated by a simple Wang and Mendel's rule generation method. Authors concluded that good results were obtained from three applications of the proposed GAFS.

IV.3.3 Tuning – optimizing the RB

Assuming an initial FRBS has evolved its KB, it is possible to optimize with the aid of GAs the performance of the system by optimizing the performance of FRBS, or reducing its complexity by minimizing the number of rules. Chin and Qi (Chin T.C, Qi X.M, 1998), proposed a GA method for selecting an optimized subset of rules. The RB was encoded into a binary string, where the first bit indicates whether the rule is fired, and the consequent three bits represent the rule value. The proposed method

utilized two performance indicators, the minimum time-weighted integral of square errors and the combined index of overshoot and rise time. Chin and Qi concluded based on the inverted pendulum example, that the resulted reduced RB was superior over the total RB.

Roychowhury et al (Roychowhury A et al, 2005), suggested a RB refining method of a fuzzy logic controller (FLC) which modelled the decision making process of doctors diagnosing Pneumonia and Jaundice. A GA was applied only to the RB, keeping FS unaltered. The resulted FRBS was tested against pre-categorized patient data, concluding that the optimized FLC is effective for diagnosing a disease based on symptoms, in the absence of a doctor.

IV.3.4 Genetic Learning of the FRBS

The idea of optimization of fuzzy systems is not clearly distinctive from the concept of learning. As a general description we can define learning approaches as the methods which change complex data structures, which control the systems behavior.

There are mainly three different learning approaches for GFSs: *Michigan, Pittsburg* and *Iterative* These different methods approach the problem of cooperation versus competition (Cordon O, Herrera F, Hoffmann F, Magdalena L, 2001), by evolving populations in different ways. Cooperation vs. competition is used to describe the search of a GA to find through competition of population members the best cooperation between chromosome elements.

In the Michigan approach, which was originally introduced by Holland and Reitman in the 70s (Holland J.H, Reitman J.S, 1978), each chromosome represents a fuzzy rule. Therefore the population of chromosomes encodes the RB of the system. According to the survival of the fittest, rules with good performance survive. The system maintains the population with credit assignment mechanisms. Thus the Michigan approach is actually evolving the RB by competition of the rules. A GA based on Michigan approach is the Classifier System (CS).

In the Pittsburgh approach, introduced by Smith in the 80s (Smith S.F, 1980), each chromosome represents a population of RBs, instead of an individual rule. Thus each string expresses the system's behavior. Crossover and mutation mechanisms generate new RBs. Chromosomes could be of fixed or variable length. Since the output obtained from a fuzzy system is a cooperative action of fired rules, the

Pittsburgh approach addresses this feature adequately compared to the Michigan approach. The drawback of the approach is that GA has to search very large spaces, which makes it hard and slow to find optimal solutions.

The Iterative approach, search for an optimum solution is based on a two step process. In the first stage similar to Michigan approach, each chromosome represents a fuzzy rule. In contrast to Michigan method only the fittest of the population survives, to form part of the problem solution. Each rule that survives is added to the final set of rules. The sets are benchmarked against training data. During this second stage the process examines the cooperation of fuzzy rules, by utilizing Penalizing mechanisms. Iterative mechanism search the problem space at two different levels, through competitions of individual rules and with the cooperation of the fittest rules, thus most adequately address the problem of cooperation vs. competition.

The learning process involves the following steps: coding of elements into chromosomes; initialization of a population; introduction of chromosomes to the fuzzy system; evaluation of the performance of the chromosome against available data; evolution mechanisms such as crossover and mutation for the generation of new populations.

These three approaches are used for learning the FS, the RB and the KB of a fuzzy system. Practical issues arise from the adaptation of each approach such as different chromosomes coding techniques, computation power and usefulness on on-line systems.

Jamei et al (Jamei M et al, 2004), exploit the ability of Symbiotic Evolution (SE) to elicit Mamdani FRBSs. Each rule is coded into a chromosome utilizing Gaussian MFs. The algorithm randomly selects and combines a number (N_R) of rule chromosomes constructing a number (N_{FIS}) of FRBSs. Each resulted FRBS is evaluated and an average fitness value is assigned to each participating chromosome. The authors have coded MFs in binary format, and the MFs standard deviation was chosen from a predefined set of values in order to avoid very wide or very narrow MFs. The proposed algorithm safeguards against identical FSs by measuring the similarity among FSs. When similarity measure exceeds a predefined threshold, FSs are replaced. Furthermore authors have applied a post processing fine tuning technique for the Gaussian MFs in order to enhance FRBS performance. The suggested method was applied to the design of an active control suspension system with promising results.

An excellent example of Genetic learning of KB based on Pittsburgh approach is described by Carse et al (Carse B et al, 1996). They proposed a Pittsburgh-style classifier, in which encoding of rules is real numbered and the representation is similar to Michigan classifiers. Real valued encoding is employed, argued on the basis of faster and higher precision representation. The system learns both FS and RB simultaneously. Chromosomes are designed to encode both the FS and rules, allowing the simultaneous evolution of the KB. The authors favorably compared the performance of their proposed algorithm against classical Michigan and Pittsburg learning approaches, in specific system's instances of operation.

Lim and Willie, (Lim M.H, Willie N.G, 2003) implemented an iterative genetic fuzzy method for the automated generation of fuzzy rules, assuming a predefined set of linguistic values. RB was coded as a string, and the number of rules in a given chromosome became a constrain for the learning process. The entire space for a problem is described by RBs with different number of rules (n). The authors divided the space into subspaces according to the number of rules. The GA started from the chromosomes of length equal to half of the maximum number of rules that fully describe the fuzzy engine. If the evolution of the "middle" length rules exhibited performance better than a threshold (fitness value), the GA continued evolving chromosomes of rules with reduced length by one. If the evolution of middle length chromosomes did not result in an acceptable solution, the GA proceeded with chromosome lengths increased by one. Due to the coding of the chromosome, a special crossover operator was chosen, named position assigned crossover. The GA was used to evolve rules for an industrial application. The resulted RB was made up from ten (10) rules. The genetic-fuzzy engine was compared against an expert fuzzy system with seventeen (17) rules. The authors concluded that both systems exhibited desirable performance, but the genetically evolved fuzzy engine gave a faster response.

Belarbi (Belarbi K et al, 2005), proposed a GA algorithm for rule base reduction of a Mamdani fuzzy logic controller. The chromosome proposed in this work was composed by two sub-chromosomes. The first contains the triangular shaped fuzzy sets triplets that identify size and position of the FS, and the second contains the binary weights. The presentation of the chromosome is described in the following string:

Chromosome=([a_1,b_1,c_1, a_2,b_2,c_2,...a_n,b_n,c_n], [$w_{11},w_{12},...w_{1m}$], ...[$w_{n1},w_{n2},...w_{nm}$])

Where a_1,b_1,c_1 are the triplets of triangular FS_1, and $w_{11},w_{12},\ldots w_{1m}$ are the weights of Rule 1.

The optimization process was safeguarded against the search for a fuzzy system with zero rules. Performance criteria focused on exploring the chromosome with the minimum number of rules producing results of a given stability. Results on the example of pole and cart system showed that reduced RB fuzzy system exhibited good robustness properties.

IV.4 Synergism of Fuzzy and Neural Methods.

Fuzzy and neural systems have a complementary nature of characteristics. Dealing with uncertainty and inaccuracy is one the strengths of fuzzy logic while its weakness, the ability to learn, is the strong point of neural networks.

Buckley et al (Buckley J.J, Hayashi Y, Czogala E, 1993) have proven that feed forward neural nets can approximate fuzzy expert systems and vice versa. Authors have shown that both methods can approximate each other to any prescribed number of decimal places, concluding that "if a continuous process is controllable, then it can be controlled by some fuzzy controller" (Buckley J.J, Hayashi Y, Czogala E, 1993).

IV.4.1 Neural Networks

Neural networks consist of interconnected information processing units called artificial neurons (Figure IV.7). The structure of a neuron consists of external inputs (X1,X2,..Xn), synapses, dendrites, a soma and an axon, which transmits output to other neurons (Picton P, 2000).

Inputs are modified by weights (Wij), representing the synaptic junctions. Each synaptic output is an input to the soma called dendritic input. Each dendritic input is a transformed version of the external input. The mathematical relation usually applied for producing dendritic inputs is given in equation IV.8.

$$d_{ij} = W_{ij} * x_i \qquad \text{eq. IV.8}$$

The neuron produces an output when the aggregated activity of all dendritic inputs exceeds a threshold value (T). The aggregated activity is often computed as the summation of dendritic inputs (eq. IV.9).

$$I_j = \sum_{i=1}^{n} d_{ij} \qquad \text{eq. IV.9}$$

The neural output is performed with the activation or transfer function. Activation function varies with the type of neuron we choose to use. Perceptron for example uses the activation function of eq. IV.10, and produces binary output in terms of activation occurrence or not. Usually threshold (T), is a negative bias value.

$$Y_j = sign[\sum_{i=1}^{n} Wij * X_i + T_j] \qquad \text{eq. IV.10}$$

During neural network training an external input set and corresponding output set is utilized for adjusting weights and threshold values. The use of training input – output sets is named supervised training and is the prevailing method. Other methods such as graded learning, unsupervised learning and competitive learning have found application in neural networks development.

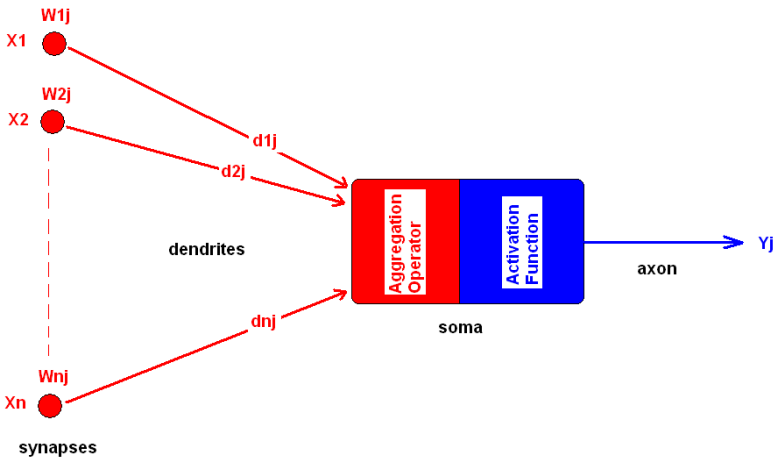


Figure IV.7: Schematic representation of a neuron.

IV.4.2 Synergism of Neural Nets and Fuzzy Systems

Neural networks and fuzzy systems are applied in synergism, by using two different approaches. The first is embedding fuzzy methods in neural networks described as fuzzification of neural systems (fuzzy-neural computing), and the second is introduction of neural networks to fuzzy systems, described as neuronal enhancements of fuzzy systems (Tsoukalas L.H, Uhrig R.E., 1997).

Fuzzy-neural computing is associated with the introduction of fuzzy approaches into neurons. The fuzzication is applied by substituting parts or total of neuron crisp operators with fuzzy ones.

Fuzzification could be applied to external inputs, where the input vectors are defined over the unit hypercube $[0,1]^n$. Inputs are fuzzy signals membership functions, thus the neuron could be considered as the representation of a linguistic variable. Similarly the output (Y) could be associated with a membership to some linguistic value.

Fuzzification of neurons could also be applied to synapses. The synaptic operator is substituted by min, max and more generally T and S norms operators. A logical OR (max) fuzzy synaptic operator is described in equation IV.11.

$$dij = W_{ij} \wedge x_i \qquad \text{eq. IV.11}$$

Fuzzification could also be performed on the aggregation operator. An aggregation function could be designed to select maximum or minimum dendritic inputs to a soma, as in equations IV.12 & IV.13, or bounded by a graded membership over the unit interval ($u \in [0,1]$), as in equation 2.34.

$$I_j = \bigvee_{i=1}^{n} dij \qquad \text{eq. IV.12}$$

$$I_j = \bigwedge_{i=1}^{n} dij \qquad \text{eq. IV.13}$$

$$I_j = \sum_{i=1}^{n} \mu_{dij}(u)/u \qquad \text{eq. IV.14}$$

Where $\wedge$ & $\vee$ is min and max respectively.

With the use of different types of fuzzy operators, in different parts of neurons we have neurons with different properties.

The second type of synergism is to introduce neural methods in fuzzy systems, neural network driven fuzzy reasoning is an example of such synergism. Cascading neural networks and fuzzy systems, not necessary in this order, is a hybrid combination of both methods. When numerical measurements provide much detail, then a NN may process information prior to feeding it into a fuzzy system in order to improve response time. Such systems accept measured inputs as inputs to a NN, and NN produce outputs which are feed as inputs to a fuzzy system (Fig. IV.8).

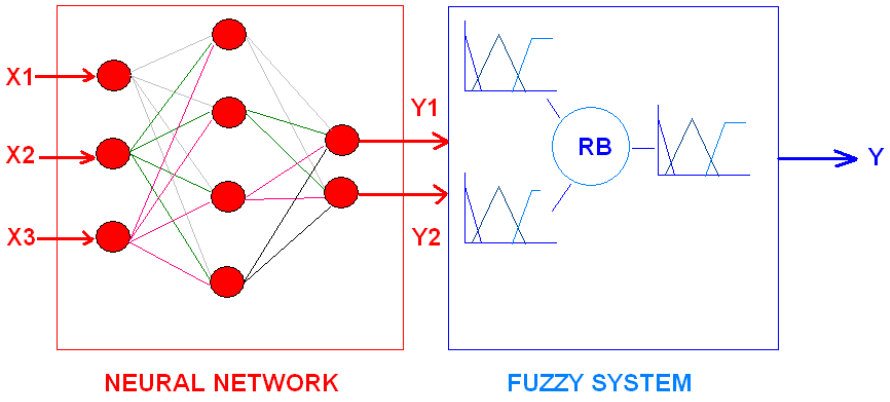


Figure IV.8: Cascaded systems.

Most commonly applied is the use of NN for identifying membership functions. NN have proven performance in clustering – classification problems, and are successfully implemented for clustering input – output domain data for fuzzy systems.

Takagi and Hayashi (Tagaki H, Hayashi I, 1992), proposed a neural network driven fuzzy reasoning (NDF) for TSK fuzzy systems, known as T-H method. NDF constructs inference rules from the learning function of neural networks. The architecture is designed on two NN. The first a back propagation NN represents fuzzy sets (IF part), while the second represents a relationship between input and output data of each rule (THEN part). NDF uses training data to obtain optimal membership functions and inference rules, but is unable to adapt – change rules in different environment. In the T-H method the TSK rules are replaced by a NN as shown in equation IV.15.

$$\text{IF } (X_1,..X_n) \text{ is } A^s \text{ THEN } y^s=NN_s(X_1,..X_n) \qquad \text{eq. IV.15.}$$

Where:
X: is the vector of inputs
NN_s: is a NN that determines output y^s
s: is the s^{th} rule
A^s: is the membership function of s^{th} rule.

Hayashi et al (Hayashi I et al, 1992), proposed a new version of NDF, capable of adjusting inference rules in responses to environment, thus capable of learning (NDFL). The inference rules structure is described by the equation IV.16.

$$\text{IF } (X_1,..X_n) \text{ is } A^s \text{ THEN } y^s=W_{s0}{}^k+W_{s1}{}^k*X_1,+..+W_{sn}{}^k*X_n \qquad \text{eq. IV.16}$$

Where:
W: are coefficients adjusted by pattern search method.

The pattern search method first explores the coefficients that point to the right direction for optimization, and second moving the coefficients to the pre-diagnosed direction for identifying the optimal solution.

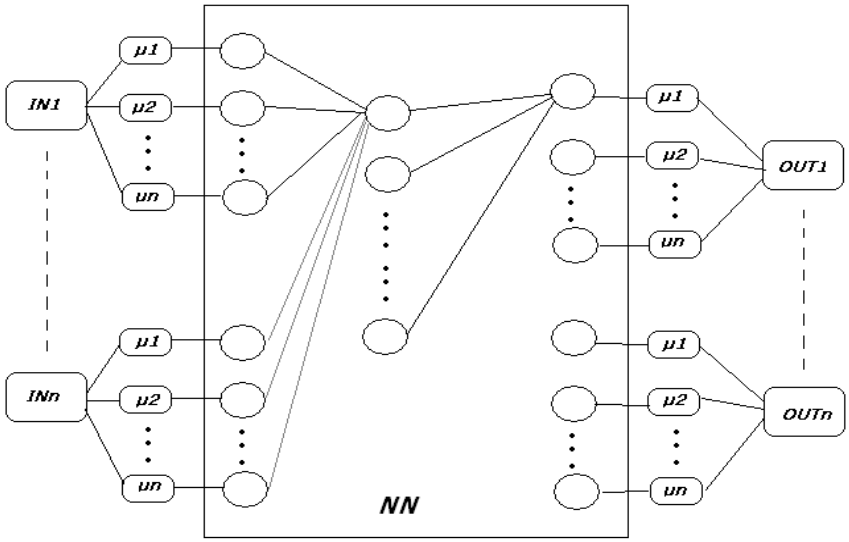


Figure IV.9: Architecture of the neural-fuzzy network proposed by XZ Wang et al.

Wang et al proposed a neural fuzzy network for RB generation (Wang X.Z et al 1997). The Input and Output variable domains are assigned to Linguistic Variables. Then, the Input–Output data sets are translated into membership degrees (μ_n), and they are being concurrently processed by the NN (Fig. IV.9). The NN outputs are membership degrees for the output variables. Although the proposed architecture it is essentially a neural net, it exhibits the following characteristics: first it describes a cause and effect relationship providing transparency to the black box feature of the NN, second it utilizes NN technology for processing not the mathematical notation of a variable but rather the transformation of the variable to the fuzzy domain, providing NN with equivalent but not the same information, third the transformation of the variable to the fuzzy domain encodes input data to the range from 0 to 1, this minimizes the difference in NN response due to differences in absolute magnitude of the inputs, fourth the use of fuzzification and de-fuzzification processes permits the system to efficiently deal with inaccurate and imprecise measurements of the input-output training data. The performance of the system depends heavily on the defuzzification technique.

Adaptive network fuzzy inference systems (ANFIS), was originally proposed by Jang (Jang J.S.R, 1993). ANFIS is actually a neural representation of TSK fuzzy systems capable of learning through training data.

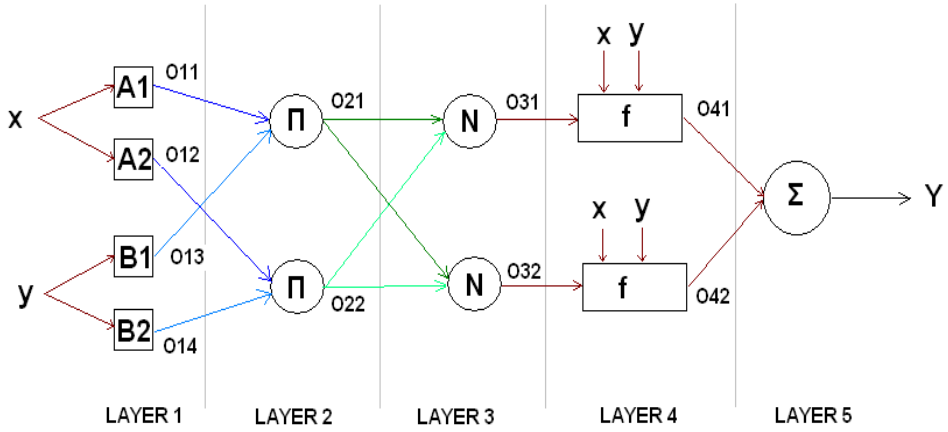


Figure IV.10: ANFIS architecture for 2 input variables and two rules.

Consider a two (2) inputs and two (2) rules TSK fuzzy system described by the following rules:

IF x is A1 and y is B1 THEN Y=f1(x,y) ($f1=w_{11}+w_{12}*x+w_{13}*y$)

IF x is A2 and y is B2 THEN Y=f2(x,y) ($f2=w_{21}+w_{22}*x+w_{23}*y$)

The above system's output is given by the following equation (Nguyen H.T et al 2003):

$$Y = \frac{A1(x)B1(y)f1(x,y) + A2(x)B2(y)f2(x,y)}{A1(x)B1(y) + A2(x)B2(y)} \qquad \text{eq. IV.17}$$

The above fuzzy system could be described by the neural network shown in fig. IV.10. The first layer of the system produces outputs, which are actually the membership functions for each input for the linguistic variables describing input domain data.

Thus we have, as an example for the first output:

$$O11 = \mu A(x) = A1(x) \qquad \text{eq. IV.18}$$

If the linguistic variable is of sigmoid shape then we can describe A1 as follows:

$$A1(x) = \frac{1}{1 + e^{b1(x-a1)}} \qquad \text{eq. IV.19}$$

Where a1 and b1 are the variables describing the membership function shape.

The output of the second system calculates the firing strength of each rule via multiplication or min operator. For example the first output of layer 2, is given by:

$$O21 = \mu A(x)\mu B(y) = A1(x)B1(y) \qquad \text{eq. IV.20}$$

The 3rd layer is actually a normalization function, were the strength of each rule is measured against the strength of the sum of all rules. For the first output of layer 3 we have:

$$O31 = \frac{O21}{O21 + O22} \qquad \text{eq. IV.21}$$

The fourth layer is utilizing the TSK functions and produces the first output as follows:

$$O41 = O31 f1 = \frac{O21}{O21 + O22} f1 = \frac{O21}{O21 + O22}(w_{11} + w_{12} * x + w_{13} * y) =$$
$$= \frac{A1(x)B1(y)}{A1(x)B1(y) + A2(x)B2(y)}(w_{11} + w_{12} * x + w_{13} * y) \qquad \text{eq. IV.22}$$

The final systems output is given by the summation of Y=O41+O42 and is equivalent to equation IV.23.

The learning of ANFIS system is similar to NN training but rather than optimizing weights, it adjusts a_i, b_i variables for optimizing fuzzy sets. Based on training data the ANFIS calculates the error between the output Y and the expected output O and adjusts variables for minimizing it, by the following equation:

$$Error = \frac{1}{2}(O - Y)^2 \qquad \text{eq. IV.23}$$

The presented ANFIS network is a functional equivalent to Sugeno fuzzy model. A Mamdani fuzzy system could be similarly constructed, however the resulted ANFIS is much more complicated (Jang JSR et al, 1995).

In ANFIS models development the number of input variables and FS partitioning of each variable dictates the complexity of the NN. An example will be provided for clarifying the above statement: an ANFIS with 2 inputs and 3 gaussian MFs for each input has 12 premise modifiable variables (calculated in the following way: 2(inputs)*3(MFs)*2(variables describing Gaussian shape). For the same system the consequent modifiable variables are 27 (calculated in the following way: 3(MFs)^2(inputs)*3). Thus in total 39 modifiable variables. If the same system had 5 MFs instead of 3 then the total of modifiable variables would have been 95. This imposes a limitation on the complexity of an ANFIS system based on the size of the available training set. If for example the available data set was 50 sets of data, then

the latter architecture could not apply, because modifiable variables exceed the number of data sets.

Appendix V: Table of published research work on ventilation management

Table V.1: List of selected published research on mechanical ventilation support systems.

	Author, Year of publication.	Method used.	Model development - tested	Physiology variables, input Variables to the system.	Controlled Variables, system's outputs.	Pathology for which the model is developed.	Database	Method for measuring performance.	Fitness measure, eg. *rmse*.	Fitness value.
2007	Chen A.H, 2007	ANN	Conjugate Gradient Method	Age, Days Intubation,Days estimating, HR, Psys, Spec. Vol. of blood, Na, K, PIP, Index quick breath, Cough, MV, X-ray, Capacity of Urine	Weaning predictions	Ventilated patinets	121 data sets of real patient data	Prediction of weaning vs successful weaning	Sensitivity & Accuracy	Sensitivity 0.79 Accuracy 0.73
			Levenberg-Marquarft							Sensitivity 0.80 Accuracy 0.63
			One-step-Secant							Sensitivity 0.83 Accuracy 0.74
2007	Tzavaras A, 2007	Neural Network Driven FL	FUN	SpO2, C,R, PIP, Pplat	VT,RR	4 COPD patients	43 hours	Difference between clinical sugestion & system advice	mse	VT 0.22 ml/Kgr RR 1.21 BPM
2006	Liu F, 2006	Neuro - Fuzzy System	Hebb-Rule-Deduct	SaO2, FiO2, RR, PEEP	FiO2	BIPAP patients	1h sampling, 408 data sets	System's suggestions vs Recorded Patient Data	rmse	1.13
			POPFNN							7.39
			RSPOP							7.35
			EFuNN							2.52
			DENFIS							2.11
			ANFIS							1.61
2006	Wang A, 2006	Neuro - Fuzzy System	ANFIS	Weight, PEEP, PIP, RR	Tidal Volume (VT)	Patient Data & SOPAVent simulation	5 patients (7 +1 senarios)	Model's output in terms of PaO2 & PaCO2 vs real measurements	Graphical presentation of advice vs measurements	No numerical values
2005	Tzavaras A, 2005	Fuzzy Logic	FRBS	SpO2, ETCO2, R,C, Temp, CO, Body Surface Area (BSA)	VT , RR	Simulation	Physiology Variables, calculated	Direction of suggested change	Graphical presentation of produced advice	No numerical values
2005	Bouadma L, 2005	Knowledge base	Computer driven system (CDS), embedded in ventilator	VT,RR, ETCO2	Pressure Support (PS), to keep patient into a comfort zone	ICU patients	42 ICU patients (9 excluded)	Weaning success	Weaning success / failure	25/7
2005	Spahija J, 2005	electrical diaphragm activity	servo control target adjustment of Pressure Support	electrical diaphragm activity	PS	healthy	11 healthy, rest & excersise	Comparison between assisted and normal breathing diap. El. Activity	mean values of diap.el.activity	In all cases was maintained bellow maximum target
2005	Betal S.Y, 2005	Fuzzy template & knowledge base	Fuzzy trend template fitting	SaO2, tcpO2, tcpCO2, RR, TI,TE, PIP ,PEEP, Pmean, FiO2.	Qualitative category	infants	7 neonates (124h)	Comparisons of changes suggested by the system vs	Agreement (%) between system's recommendations	Ventilation 91%

			knowledge base management advisor	3 qualitative variables	Icalibration tcp, suctioning, blood sampling, blood sampling & ventilation change (fuzzy), enter blood gas results, possible water trap, alert, insufficient oxygenation/ventilation			clinician's suggestions	and clinicians	Oxygenation 94%
2004	Kwok H.F, 2004	Neuro - Fuzzy System	ANFIS	Use SOPAVENT simulator (models inputs)	FiO2 for target PaO2	Septic and non-septic ventilated patients	ICU patients data 1999-2001	Model's output against patient specific model	mse	0.75kPa
			Linear regression						mse	2.06kPa
2004	Martinoni E.P, 2004	physiology model	model controller vs fuzzy controller (Schaublin, 1996)	eFECO2	VT, RR calculated for set point eFECO2	Surgery	16 patients	Difference between set point and measured	Mean Rise Time (sec) model for 1%vol change in target	144
									Mean Deviation from set point (vol%)	0.00
2004	Tehrani F, 2004	dual controller	mathematical & decision tree	SpO2, PetCO2, R,C	VT,RR for target PaCO2	COPD & ARDS Simulation & animal studies	Computer model of humman respiration	Time for stabilizing arterial gases to normal	Time	<25sec
			PID controller	FiO2	SpO2		6 Yorkshire pigs	SD of PetCO2 & SpO2	SD	1.78mmHg & +/- 1.76%
2004	Kwok H.F, 2004 (IEEE Trans. Inf. Tech. in Biomedicine) & Mahfouf M, "Intelligent systems in modelling and decision support in bioengineering"	FRBS & mathematical model	SIVA (Sheffield Intelligent Ventilator Advisor), Expert RB & RB tunned with perceptron learning rules, Two levels.	PaO2 & FiO2 (current & previous), PEEP	FiO2/ PEEP, for target PaO2 & PaCO2	ARDS, Pneumonia, septicaemia, BiPAP ventilation	4 clinical senarios, pneumonia patient simulated with SOPAVENT	Difference between target blood gases and simulated blood gases	Graphical representation and numerical data, commenent against ICU senarios	Fitness of output against SOPAVENT simulation (discussion)
				PaCO2 (current & previous),pH,Pinsp,RR	Pinsp/RR , for target PaO2 & PaCO2					
2004	Jandre F.C, 2004	feedback controller	PI controller PETCO2	VT,R,Tinsp, E, PETCO2	VT,RR, I/E time	6 piglets premedicated	Controlled CMV for 3x20 minutes in each piglet	Time for achieving Elastance & PETCO2 targets	time, mean & SD, Overshoot	PETCO2 53 +/- 22s, 3 +/-1 mmHg
			gradient descent PEEP	R,E,PEEP	PEEP					PEEP 235 +/- 182s, 6.5 +/- 1cmH2O
2003	Kwok H.F, 2003	Neuro - Fuzzy System	ANFIS	PaO2, FiO2, PEEP	changes in FiO2 for target PaO2	Senarios, based on 3 real patient data with shunt	71 Clinical senarios using SOPAVent model, 568 data sets	systems advice vs clinicians advice	mse	6.99
			Multilayer perceptron (MPL)							6.59
			FAVeM							86.97
			RBN-MB							54.86
2000	Dojat M, 2000	Feeddback controller	NeoGanesh	RR,VT, PETCO2	PS, for target RR,VT, PETCO2	Patient receiving PSV (acute respiratory failure)	10 patients	Proposed controller vs PSV	Time spent in acceptable ventilation vs standard PSV	Standard PSV 66+/- 24%, auto PSV 93+/- 8%
1996	Schaublin J, 1996	Fuzzy Logic	FRBS	(end tidal CO2 fraction)FECO2	VT , RR for target ETCO2	Surgery	30 Patients	systems control vs clinicians control	(Fuzzy-Manual %vol) Mean eFECO2	0.02
									Rise Time sec (Fuzzy-Manual)	(313-3392)=-79

1995	Shahsavar N, 1995 Shahsavar N, 1989	object oriented Knowled ge base	(KUSIVAR) Variable description s, transformat ion tables, expert rules & mathematic al models	40 variables, tranformed to symbolic based on classical set theory	Advice (not defined)	Left Ventricular failure, pulmonary edema, ARDS, Asthma, COPD, Flail chest, Extrapulmon ary VF (awake & sedated)	Not availiabl e	Not availiable	Not availiabl e	Not availiab le
			VentEX	Example of variables demographics, blood pressure, temp, X-ray results				Evaluatio n of Knowled ge Base, Interactio n of experts & simulator		Passed clinical tests, inferen ce adjuste d by clinicia ns
			VentEX Initiation model		Initiate or not ventilation		37 ICU patients	Validatio n of initial phase	Compari son between advice and real data	78% agreem ent
			VentEX treatment model		Minute Volume, RR, FiO2, PEEP		12 ICU patients, 1300h, 51 forms	Validatin g treatment	Compari son between simulator and 2 physisian s results, against expert (gold standard)	VentE X (%) diagree mnet MV:4.5 , RR:4.5, FiO2:1 1.1,PE EP:15.6 Physici ans' mean diagree ment (%) MV: 15.9, RR:4.5, FiO2:7. 3, PEEP:8 .9
								Validatin g weaninin g		VentE X disagre emnet 22.2%, Physici ans disagre emnet mean 24.45%
1994	Sun Y, 1994	Fuzzy Logic	FRBS	SaO2, (Error SaO2 & Delta SaO2)	FiO2	Infant ICU, no intracardiac shunt or vasoactive pressor medication	Infant patient data, 6h from each			
1994	Laubscher T.P, 1994	mathema tical model	mathematic al model	Test breaths data: RC, Dead Space, CO2 production	Ventilation start up values for: VT,RR	random selection, inclusion criteria hemodynami c & respiratory stability	25 ICU patients & 17 ICU children	Comparis on of controller & actual breathing patterns	two-tailed t-test	33/39 patients , differen ce was betwee n +/- 50% of mean
1993	Rutledge G.W, 1993	qualitati ve & quantitat ive computa tion	belief network	qualitative & semi qualitative inputs (eg Pneumonia)	Probability distributions of physiology parametrs for mathematical model	retrospective, surgical ICU patients	real clinical senarios	In another paper		
			mathematic al model (VentPlan)	Ventilator Settings	physiology variables & predicted ventilator settings		10 patients SpO2, HR, Pmean, CVP, PAP, Temp, blood gases, CO	Comparis on of model predictio ns against measured blood gases	correlati on, Average error, Standard Error	PaO2, PaCO2: corr 0.77/0. 61, Av.E 17.6/4. 8, SE 23.5/6. 3mmH g

			plan evaluator	Ventilator settings	Evaluation of Ventilator settings VT, FiO2, RR		335h, 10 patients	Direction of suggested change	Disagreed/Total changes	2/55 FiO2, 7/29 VT
1985	Chapman F.W, 1985	Feeddback controller	PI controller	FETCO2	VE (minute ventilation) for target FETCO2	five anesthetized dogs	5 dogs	Response of controller to induced step changes	Deviation from setpoint	FETCO2+/- 0.1%
									Time for returning FETCO2	<30sec

Appendix VI: Questionnaire

The questionnaire was originally written in Greek language and is translated for the purpose of the PhD thesis.

Athens…/…/2005

Dear Sir/Madame,

The department of Information & Measurement in Medicine of the City University London, in cooperation with the department of Medical Instrumentation Technology of the Technological Educational Institution of Athens, is performing a PhD research project, titled:

«Multivariable Ventilator Advisory System»

The purpose of the study is to design and test an Artificial Intelligence system that will acquire ventilation related patient variables and will produce advice on the desired ventilator settings for the ventilation management procedure.
We would appreciate your contribution, in the evaluation of the I.C.U. patient physiology variables and the ventilator settings, for C.M.V. (Continuous Mandatory Ventilation) ventilation mode, concerning their relative importance, according to your experience and expertise, in ventilation management process.
According to our ethical commitment, responder's identity will be disclosed from the produced results.

Thank you in advance for your cooperation.

Yours sincerely

Aris Tzavaras

Guidelines.

1. With the current questionnaire we target in collecting statistical information based on the expertise & experience of the I.C.U. doctors concerning the importance of the Ventilation related variables.
2. The answered questionnaire is returned to the **City University London, dep. Information & Measurement in Medicine**, **attention to Dr. P.Weller**, **without completing the sender's data**, in order to preserve the anonymity of the responder.
3. All questions (except the demographic ones), refer to **C.M.V.** (also known as I.P.P.V.) ventilation mode, of I.C.U. patients.
4. Please provide a single answer for each question field.
5. Answers ranking follows the scaling from 0 to 10, where 0 stands for Not significant and 10 for high significance.

Questionnaire

1. Please complete the following demographic data:

   Sex Male ☐ Female ☐

   Age Group 25-35 ☐ 36-45 ☐ 46-55 ☐ 56-70 ☐

2. Years of working experience in I.C.U, following Speciality training.

   Years ☐

3. Please classify the following patient characteristics according to their significance for deciding ventilator settings, in the starting phase of mechanical ventilation :

		Not Significant 0	1	2	3	4	5	6	7	8	9	**Very Significant** 10
1	**Patient's Age**	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐
2	**Patient's Weight**	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐
3	**Patient's Height**	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐
4	**Patient's Sex**	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐

4. Please classify the following variable groups, according to their significance in ventilation management process:

		Not Significant 0	1	2	3	4	5	6	7	8	9	**Very Significant** 10
5	**Non Invasively acquired variables (S_PO_2, E_TCO_2, HR, Temperature)**	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐
6	**Blood Gases (Pa_{O2}, Pa_{CO2} etc.)**	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐
7	**Measurements of Inspired, Expired Volumes, Flow and airway pressures.**	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐

8	**Measurements of Lung mechanics (Compliance & Resistance).**	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐
9	**Measurements of hemodynamic variables (Venous & Arterial pressures, C.O.etc).**	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐

5. Please classify the following variables according to their significance in ventilation management process:

		Not Significant 0	1	2	3	4	5	6	7	8	9	**Very Significant** 10
10	**Arterial Oxygen Saturation (S_aO_2)**	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐
11	**End Tidal Capnography (E_TCO_2)**	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐
12	**Heart Rate (HR)**	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐
13	**Core Body Temperature**	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐
14	**Extremes Body Temperature**	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐

6. Please classify the following variables, acquired directly or calculated from the ventilator, according to their significance in ventilation management process:

		Not Significant 0	1	2	3	4	5	6	7	8	9	**Very Significant** 10
15	**Expired Volume (V_E)**	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐
16	**Mean airway Pressure (P_{MEAN})**	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐
17	**Maximum-Peak airway Pressure (PIP)**	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐
18	**End-Inspiratory**	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐

	Pause Pressure ($P_{PLATEAU}$)											
19	**Intrinsic PEEP (Auto PEEP)**											
20	**Lung Compliance**	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐
21	**Airway Resistance**	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐
22	**Work of breathing (W)**	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐

7. Please classify the following variables acquired invasively, according to their significance in ventilation management process:

		Not Significant 0	1	2	3	4	5	6	7	8	9	**Very Significant** 10
23	**Partial Pressure of Oxygen in Arterial blood (PaO_2)**	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐
24	**Partial Pressure of Carbon Dioxide in Arterial blood ($PaCO_2$)**	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐
25	**Hydrogen Ions Concentration in blood (pH)**	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐
26	**Concentration of H_2CO_3 in blood**	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐
27	**Oxygen Saturation of Central Vein blood (S_VCO_2)**	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐
28	**Partial Pressure of Oxygen in Venous blood (P_vO_2)**	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐
29	**Partial Pressure of Carbon Dioxide in Venous blood (P_VCO_2)**	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐

30	**Cardiac Output (C.O.)**	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐
31	**Oxygenation Index (PaO_2 / F_IO2**	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐
32	**Mean Pulmonary Artery Pressure (MPAP)**	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐
33	**Variation of Systolic arterial pressure**	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐
34	**Central Venous Pressure (CVP)**	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐
35	**Pulmonary Capillaries Wedge Pressure (PCWP)**	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐

8. Please classify the following ventilator settings according to their significance in the ventilation management process:

		Not Significant 0	1	2	3	4	5	6	7	8	9	**Very Significant** 10
36	**Minute Ventilation (V_E)**	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐
37	**Tidal Volume (V_T)**	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐
38	**Respiration Rate (RR)**	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐
39	**Positive End Expiratory Pressure (PEEP)**	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐
40	**Fractional Inspired Oxygen (F_IO_2)**	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐
41	**Maximum-Peak airway Pressure (PIP)**	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐
42	**Inspiration Time /**	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐

	Expiration Time (I/E)											
43	**Maximum Inspiratory Flow (Peak Flow)**	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐
44	**Inspiratory Pause**											
45	**Inspiration Flow Pattern**	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐

Thank you for your cooperation

Appendix VII: Collected Data Range

Table VII.1: Table of input – output data domain values.

		Input Parametrs												Output Variables					
		SpO2	PaO2	PaCO2	pH	O2 Index	Ve (ml)	PIP (mbar)	Plateau	C (l/bar)	R (mbar/L/s)	HR	HCO3	Vt ml/kgr	RR (BPM)	PEEP(mbar)	FiO2	P peak (mbar)	F peak (L/min)
		1	2	3	4	5	6	7	8	9	10	11	12	1	2	3	4	5	6
ARDS Evaluation sets	**max**	97	100	46	7,5	323	572	48	31	65	24	92	24	5,5	21	10	0,6	82	60
	min	87	64	29	7,32	107	290	22	0	12	12	56	17	4,29	9	5	0,3	50	43
ARDS Training Sets	**max**	98	100	46	7,5	327	571	51	34	146	23	94	24	5,5	21	10	0,5	82	60
	min	87	64	29	7,32	107	298	22	0	8	9	54	17	4,29	9	5	0,3	50	43
COPD Evaluation Stes	**max**	100	97	75	7,46	268	602	51	43,2	61	35	123	46	4,8	27	7	0,65	84	80
	min	91	65,3	35	7,32	106	54	12	16	6	10	56	23	3,36	21	2	0,34	40	60
COPD Training Sets	**max**	100	97	75	7,46	268	602	51	55	61	35	123	46	4,8	27	7	0,65	84	80
	min	91	65,3	35	7,32	106	54	12	16	6	9,8	56	23	3,36	21	2	0,34	40	60
Normal Evaluation Stes	**max**	100	194	35	7,51	554	505	32	19	68	17	99	23,4	8,8	16	12	0,5	50	73
	min	92	105	25	7,42	211	384	17	14	36	12	63	7,44	6,25	12	5	0,28	40	19
Normal Training Sets	**max**	100	194	40	7,51	554	487	34	19	66	17	98	26	8,8	16	6	0,5	50	73
	min	96	105	25	7,41	211	370	16	14	36	11	63	7,44	6,25	12	5	0,28	40	19
Maximum & Minimum in all databases	**max**	100	194	75	7,51	554	602	51	55	146	35	123	46	8,8	27	12	0,65	84	80
	min	87	64	25	7,32	106	54	12	0	6	9	54	7,44	3,36	9	2	0,28	40	19
Used limits	**max**	**100**	**200**	**80**	**7,6**	**600**	**600**	**60**	**55**	**146**	**40**	**130**	**50**	**12**	**30**	**15**	**0,8**	**90**	**80**
	min	**80**	**60**	**20**	**7,3**	**100**	**50**	**10**	**0**	**6**	**5**	**50**	**7**	**2**	**5**	**0**	**0,25**	**40**	**15**

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