A systematic approach for the accurate non-invasive estimation of blood glucose utilizing a novel light-tissue interaction adaptive modelling scheme

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Abstract. Diabetes is one of the biggest health challenges of the 21st century. The obesity epidemic, sedentary lifestyles and an ageing population mean prevalence of the condition is currently doubling every generation. Diabetes is associated with serious chronic ill health, disability and premature mortality. Long-term complications including heart disease, stroke, blindness, kidney disease and amputations, make the greatest contribution to the costs of diabetes care. Many of these long-term effects could be avoided with earlier, more effective monitoring and treatment. Currently, blood glucose can only be monitored through the use of invasive techniques. To date there is no widely accepted and readily available non-invasive monitoring technique to measure blood glucose despite the many attempts. This paper challenges one of the most difficult non-invasive monitoring techniques, that of blood glucose, and proposes a new novel approach that will enable the accurate, and calibration free estimation of glucose concentration in blood. This approach is based on spectroscopic techniques and a new adaptive modelling scheme. The theoretical implementation and the effectiveness of the adaptive modelling scheme for this application has been described and a detailed mathematical evaluation has been employed to prove that such a scheme has the capability of extracting accurately the concentration of glucose from a complex biological media.

1. Introduction

Diabetes mellitus is a disease characterized by persistent hyperglycaemia (high blood sugar levels). Since the first therapeutic use of insulin in 1921 diabetes has been a treatable, however chronic condition and the main risks to health are its characteristic long-term complications. These include cardiovascular disease, chronic renal failure, retinal damage which can lead to blindness, nerve damage, erectile dysfunction, to gangrene [1]. Around 1.9 million people in the UK and more than 194 million worldwide have been diagnosed with diabetes. Regular blood glucose testing, especially in Type 1 diabetics, is essential to keep adequate control of the glucose levels and to reduce the chance of long-term complications of the disease [2].

Currently, blood glucose can only be monitored through the use of invasive techniques. Most of these involve drawing blood through a small pinprick and placing a drop on a test strip. The glucose level in the blood is then measured using one of several ways available in the

market today. These measurements must be taken several times, up to half a dozen, a day by those with diabetes. The risk of infection and measurement inaccuracy are present with all of the invasive techniques. In addition, to the discomfort caused by the pinprick and the resultant bruising, many diabetics (especially children) do not check their glucose levels as often as recommended and as a result increase their chance of developing hyperglycaemia or diabetic coma.

Advances in technology have allowed the investigation of new techniques for assessing blood glucose in an attempt to find one that is non-invasive, accurate, continuous, easy to use, reproducible and inexpensive. Examples of techniques used for the non-invasive monitoring of blood glucose include fluid extraction from skin (or reverse iontophoresis), interstitial fluid harvesting, non-optical electromagnetic radiation (far infrared (FIR) spectroscopy, radio wave impedance), optical rotation of polarized light, thermal emission spectroscopy, and visible light and near infrared spectroscopy. All of these techniques [3][4] share advantages and disadvantages, as well as have limitations that preclude their routine application for non-invasive monitoring of blood glucose. The main problem experienced with prior attempts at blood glucose measurement is calibration. Because of varying amounts of protein, fats, and water in different people, a single, universal measurement scheme has not been developed yet. Interference in the absorption of these with the absorption of blood glucose has caused the most problems with prior research.

The actual measurement of blood glucose through absorption in the visible to low near infrared light region has the problems of interference through protein and fat absorption. Measurement in the near infrared region has the problems with interference from water [5][6]. Due to the strong interference in the visible and near-infrared bands as mentioned above, none of these optical techniques have currently shown much success when brought to clinical trials. Some of these techniques may also cause mild discomfort when applied to the skin. Also, some of them are designed as single use devices and consequently the expense of these disposables could impede frequent use of the monitor. Therefore, to date there is no widely accepted and readily available non-invasive monitoring technique to quantify blood glucose.

A key factor for the improvement of non-invasive techniques for objective monitoring of blood glucose lies in further understanding the mechanisms and processes that cause major problems in the measurement of blood glucose concentration [7]. There are a number of components, which absorb optical radiation at the same wavelengths as glucose. These components are present in much higher concentrations with greater absorption characteristics than glucose. Under normal conditions the concentrations of these components change at a much slower rates than glucose concentration (days against minutes); therefore, it is possible to calibrate an optical measurement system empirically to measure glucose concentration [8][9]. However, calibration must be done individually for each patient and repeated approximately once a week (after calibration, the precision degrades rapidly with time). Other situations that could also require recalibration include, use of medications that absorb the same wavelength; alterations in haemoglobin concentration or other proteins that absorb at the applied wavelength; alterations in body temperature; alterations in state of hydration or nutrition [5]. In addition, the calibration is invasive. These make the empirical calibration approach for photometric glucose measurement expensive, impractical and not truly non-invasive.

We believe we can develop a new novel non-invasive optical glucose sensor based on a non-empirical analytical technique called ***"adaptive modelling measurement"*** to overcome the calibration problems and to provide continuous and accurate measurements of blood glucose concentration in diabetic patients. The description of this technique and a mathematical evaluation demonstrating how this technique will allow the accurate estimation of blood glucose will be the subject of this paper.

2. Methods

In the methodology, the hypothesis of using a novel adaptive modelling scheme as a basis for the development of a complete system (hardware and software) for the estimation of blood glucose will be explained. A detailed mathematical approach demonstrating the theoretical extraction of blood glucose concentration (based on optical techniques) from a complex biological media will be employed.

2.1. Adaptive modelling measurement technique

Adaptive modelling measurement is a non-empirical analytical technique that will not require individual calibration and in theory it could be used to measure other blood chemical components, apart from glucose. Its implementation for the optical absorption spectroscopy non-invasive blood glucose concentration measurement is presented in **Figure 1**.

This adaptive modelling could be implemented by using either transmittance or reflectance photometric techniques applied to vascular tissue of diabetic patients. This is shown in **Figure 1** as *"Vascular tissue"*. Properties of interest of the *"Vascular tissue"* are represented numerically by a vector of parameters $X = \{x_1, x_2, x_3..x_n\}$. The emitted optical radiation wavelength and intensity $I_{E\lambda}$ should be selected in such a way so that alteration of any chosen property of the *"Vascular tissue"* will produce a change in the detected optical radiation $I_{D\lambda}$. One of the properties of the *"Vascular tissue"* will be **glucose concentration**, which is represented by one of the parameters in the vector X.

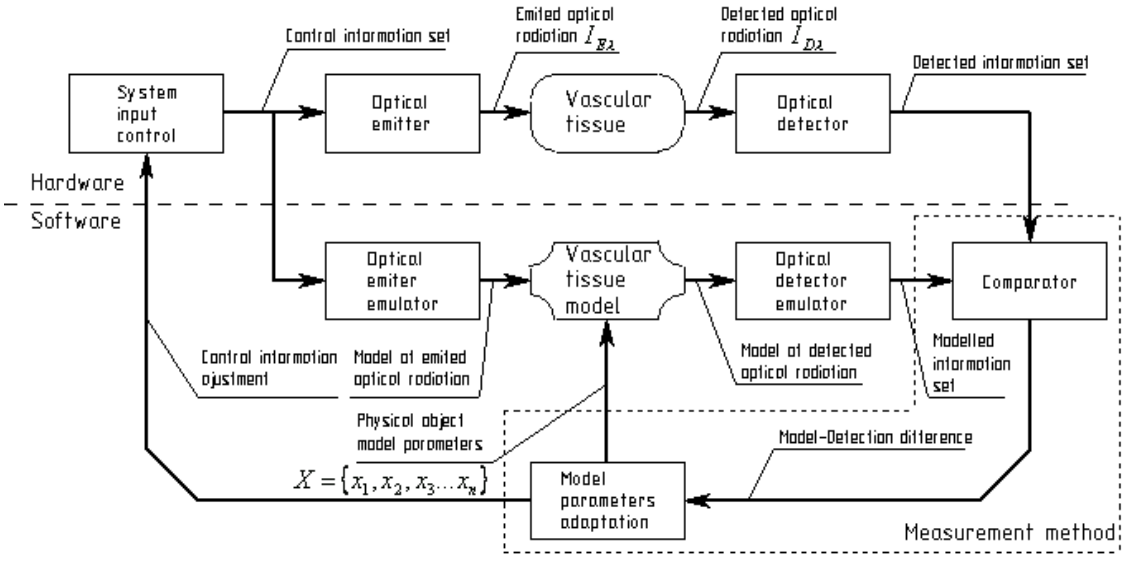

Figure 1. Adaptive modelling scheme for the optical absorption spectroscopy non-invasive blood glucose concentration evaluation.

The relationship between emitted and detected optical radiation will be established by a mathematical approximation of the *"Vascular tissue"* defined in **Figure 2** as *"Vascular tissue model"*. When the parameters in the vector x match the properties of the *"Vascular tissue"*, then the *"Model-detection difference"* will become small, and vector x could be accepted as a description of the real properties of the vascular tissue. Mathematically the existence of more than one vector x producing close "*Model-detection differences"* is possible. Therefore, the *"Optical emitter"* must emit radiation with a certain number of different intensities, wavelengths and in different geometrical positions in respect to the *"Optical detector"* depending on the *"Control information set"*. Thus, the correct vector x will be the one which produces the smallest *"Model-detection difference"* for a sufficiently large number of *"Control information sets"*.

Measurement of glucose concentration using an optical technique employing the adaptive modelling scheme can be represented by the two following nested loops (first nested into second):

1. The "Control information set" is fixed and consequently the "Detected information set" is also fixed. The "Vascular tissue model" takes initial predefined parameters and produces a "Modelled information set". The "Modelled information set" and the "Detected information set" are subtracted by the "Comparator" to find the "Model-detection difference". The "Model parameters adaptation" adjusts the parameters striving to decrease the "Model-detection difference" and passes them back to the "Vascular tissue model". The cycle is repeated until the best matching vector of parameters is found.

2. "Model parameters adaptation" changes the "Control information set" and repeats the first cycle. These repetitions occur until the vector of parameters x which works for all "Control information sets" is found. The information of the glucose concentration is then extracted from the vector of parameters.

This algorithmic blood glucose estimation procedure will allow continuous "auto-calibration" of the blood glucose measuring system, making it efficient without the need of individual calibration. This suggested technique is intended to overcome the empirical calibration problem of existing technologies as outlined above.

The above general description of the adaptive modelling scheme explains descriptively the system's principle of operation without any details whether such a system can form the basis of a working device. Therefore, the following sections are an attempt to analytically justify the feasibility of the adaptive modelling measurements for the non-invasive optical absorption blood spectroscopy. The process for glucose concentration evaluation is based on the measured light intensity values. This process will be explained and analysed in the following sections.

2.2. Signal Separation and Information Extraction (SSIE)

Figure 2 shows the radiation propagation through tissue, between emitter (light emitting diode) and photodetector (photodiode). Where λ is a monochromatic radiation wavelength, $I_{E\lambda}$ is an emitted radiation intensity, $I_{D\lambda}$ is a detected radiation intensity, and l is a relative emitter–detector position.

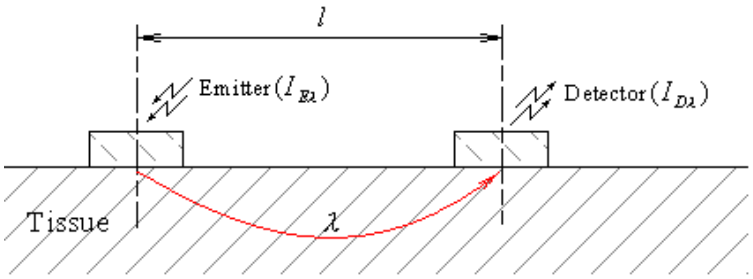

Figure 2: Tissue optic radiation back scattering model.

2.2.1. Signal separation

The purpose of this subsection is to identify which part of the optical radiation emitted on the biological media is lost either due to scattering or absorption [10][11]. To do that, let $I_{L\lambda}$ represent radiation intensity losses in tissue. Then for the wavelength λ:

$$I_{L\lambda} = I_{E\lambda} - I_{D\lambda} \quad (1)$$

Modern quantum theory of light postulates that intensity losses occur due to the different kinds of photons scattering and absorption [12][13]. Thus, if S_λ are the losses occurring due to the scattering and A_λ are the losses due to the absorption on light at wavelength λ, then the following sum can be stated as:

$$I_{L\lambda} = S_\lambda + A_\lambda \quad (2)$$

Suppose that there is an optical model describing the propagation of the light in the tissue [7][14]-[19]. This model (Figure 2) should provide sufficient approximation of the experimentally obtained light intensity, $I_{L\lambda}$ and should allow functional parameterization of the tissue properties and separation of the absorbed and scattered parts of the light intensity losses (like in Equation 2):

$$E_\lambda = F(P_\lambda, l, I_{E\lambda}) + G(H_\lambda, l, I_{E\lambda}) \quad (3)$$

Where E_λ is a model approximation for the radiation intensity losses in the tissue $I_{L\lambda}$; $F(P_\lambda, l, I_{E\lambda})$ is a approximating parameterized function for the radiation losses occurring due to the tissue scattering S_λ; and $G_\lambda(H_\lambda, l, I_{E\lambda})$ is the approximating parameterized function for the losses occurring due to the tissue radiation absorption A_λ. $P_\lambda = \{p_{1\lambda}, p_{2\lambda}, p_{3\lambda} \ldots p_{n\lambda}\}$, and $H_\lambda = \{h_{1\lambda}, h_{2\lambda}, h_{3\lambda} .. h_{m\lambda}\}$ are parameter vectors describing scattering and absorption properties of the tissue.

Suppose that the optical measuring device allows the measurement of light intensity losses $I_{L\lambda}$ at wavelength λ at k different geometric locations l_i. Then k sets of variables $(l, I_{E\lambda}, I_{L\lambda})$ can be obtained experimentally and substituted into Equation 3:

$$\begin{cases} E_{1\lambda} = F(P_\lambda, l_1, I_{E1\lambda}) + G(H_\lambda, l_1, I_{E1\lambda}) \\ E_{2\lambda} = F(P_\lambda, l_2, I_{E2\lambda}) + G(H_\lambda, l_2, I_{E2\lambda}) \\ \dots \\ E_{i\lambda} = F(P_\lambda, l_i, I_{Ei\lambda}) + G(H_\lambda, l_i, I_{Ei\lambda}) \\ \dots \\ E_{k\lambda} = F(P_\lambda, l_k, I_{Ek\lambda}) + G(H_\lambda, l_k, I_{Ek\lambda}) \end{cases} \approx \begin{cases} I_{L1\lambda} = S_{1\lambda} + A_{1\lambda} \\ I_{L2\lambda} = S_{2\lambda} + A_{2\lambda} \\ \dots \\ I_{Li\lambda} = S_{i\lambda} + A_{i\lambda} \\ \dots \\ I_{Lk\lambda} = S_{k\lambda} + A_{k\lambda} \end{cases} \quad 4$$

If the left system of equations approximates the right system, for the sufficiently high number k of the different experimentally measured variable sets $(l, I_{E\lambda}, I_{L\lambda})$ (Figure 2) then the following hypotheses can be stated for each line in Equation 4:

$$F(P_\lambda, l_i, I_{Ei\lambda}) \approx S_{i\lambda} \quad 5$$

$$G(H_\lambda, l_i, I_{Ei\lambda}) \approx A_{i\lambda} \quad 6$$

Equations 5 and 6 mean that the model E_λ in a set of Equations 4 that closely approximates scattered and absorbed parts of the light intensity loses in the tissue. Thus, this set of equations can be rewritten into the following form:

$$\begin{cases} 0 = F(P_\lambda, l_1, I_{E1\lambda}) + G(H_\lambda, l_1, I_{E1\lambda}) - I_{L1\lambda} \\ 0 = F(P_\lambda, l_2, I_{E2\lambda}) + G(H_\lambda, l_2, I_{E2\lambda}) - I_{L2\lambda} \\ \dots \\ 0 = F(P_\lambda, l_i, I_{Ei\lambda}) + G(H_\lambda, l_i, I_{Ei\lambda}) - I_{Li\lambda} \\ \dots \\ 0 = F(P_\lambda, l_k, I_{Ek\lambda}) + G(H_\lambda, l_k, I_{Ek\lambda}) - I_{Lk\lambda} \end{cases} \quad 7$$

“Approximately equal sign” has been intentionally substituted by the “equal sign”. This form corresponds to the ideal case of the “perfect optical tissue model”. Unknown variables in these equations are scalars of the tissue parameters vectors $P_\lambda = \{p_{1\lambda}, p_{2\lambda}, p_{3\lambda} \dots p_{n\lambda}\}$, and $H_\lambda = \{h_{1\lambda}, h_{2\lambda}, h_{3\lambda} .. h_{m\lambda}\}$, total number of those unknown variables is $m+n$. Thus, the number of equations k in the system of Equations 7 required to keep the system solvable is:

$$k = m + n \quad 8$$

This number determines the minimum amount of the optical emitter-detector combinations in the measuring device required to obtain the variable sets $(l, I_{E\lambda}, I_{L\lambda})$ *necessary* to build a solvable system of Equations 7.

The optical tissue model and relative emitter-detector geometrical positions must be chosen in such a way that the equations in the system will be independent (i.e. it must not be possible to cancel one of the equations by axiomatically allowed algebraic transformations). There will be cases when the system of equations has more than one solution. Thus, the model E_λ must

allow to eliminate all except one solution by cancelling, mathematically allowable although physiologically impossible, tissue parameters sets H_λ and E_λ.

Unlike an ideal case of the "perfect optical tissue model", substitution of the physically correct parameters sets H_λ and E_λ into model Equation 3 would result in a model approximation error Δ:

$$\left|I_{L\lambda} - E_\lambda\right| < \Delta \qquad 9$$

Practically this error should be less than some pre-required value, which is obtained empirically. This value reflects the required accuracy of the glucose concentration measurement results (e.g. 5%). Thus, each equation in the set of Equations 7 should be changed into model error inequality:

$$I_{Li\lambda} - F(P_\lambda, l_i, I_{Ei\lambda}) + G(H_\lambda, l_i, I_{Ei\lambda}) < \Delta_i \qquad 10$$

It may not be possible to solve such system of inequalities analytically and some adaptive algorithm may have to be used to numerically evaluate P_λ and H_λ tissue parameter vectors.

The number $m+n$ will depend on the particular optical tissue model. Selected variable sets $(l, I_{E\lambda}, I_{L\lambda})$ must not produce dependency in the system of Equations 7. Thus, the model should be constructed prior to the variable sets selection. Generally, a model of higher complexity should result in better measurements accuracy, although higher complexity would significantly increase the sensor's hardware and software requirements. Therefore, unnecessary accuracy should be avoided during optical tissue model design, keeping it as simple as measurement results would allow.

Assume that the mathematical and physiological correct set of parameters (P_λ, H_λ) describing tissue optical properties on wavelength λ is found, then those parameters would be the averaged values for all tissue light absorbing components, and they would not allow distinguishing between different components. To evaluate a particular tissue component such as glucose the concentration of more than one light wavelength is required.

2.2.2. Information extraction

Suppose that the tissue contains κ physical components which do absorb radiation at wavelength λ_1 [20][21]. Any other tissue components not included in those κ do not absorb at wavelength λ_1. One of those components is the glucose. Lets assume that there is a set of wavelengths $\{\lambda_2, \lambda_3, .. \lambda_j, .. \lambda_\kappa\}$, and for each component j the wavelength λ_j exists, on which that component absorbs light radiation. Any other component from those κ may or may not absorb on the wavelength λ_j. Thus, if the light intensity loss on wavelength λ_j is $A_{\lambda j}$ (Equation 6) then:

$$\begin{cases} A_{\lambda 1} = U_{1\lambda 1} + U_{2\lambda 1} + \ldots + U_{i\lambda 1} + \ldots + U_{\kappa\lambda 1} \\ A_{\lambda 2} = U_{1\lambda 2} + U_{2\lambda 2} + \ldots + U_{i\lambda 2} + \ldots + U_{\kappa\lambda 2} \\ \ldots \\ A_{\lambda j} = U_{1\lambda j} + U_{2\lambda j} + \ldots + U_{i\lambda j} + \ldots + U_{\kappa\lambda j} \\ \ldots. \\ A_{\lambda\kappa} = U_{1\lambda\kappa} + U_{2\lambda\kappa} + \ldots + U_{i\lambda\kappa} + \ldots + U_{\kappa\lambda\kappa} \end{cases} \quad 11$$

Where $U_{i\lambda j}$ is the part of the radiation intensity loss at wavelength λ_j, occurring due to the absorption by the tissue component i.

Practically, system of Equations 11 means that if there are $\kappa - 1$ components which absorb light on the same wavelengths as glucose, then the measuring device should be able to emit and measure light intensities on at least κ different wavelengths. Each wavelength must also have k physical channels for *Signal separation* modelling, in order to distinguish between absorbed and scattered parts of the light intensity losses.

The Beer-Lambert equation is a well known empirical law [12][22] relating light absorbance to absorbing component concentration in simple non-scattering samples. In its roots this equation is a solution of a linear integral of the light intensity losses occurring during light propagation along the straight line through the sample. The basic assumption, taken in the derivation of this integral is that for small parts of the sample mater, light intensity absorbed by the particular sample absorber is proportional to the absorber's concentration [23][24]. This assumption can be used even if the light does not propagate along straight lines, although the integral in this case will not be linear.

Another assumption used in conventional spectroscopy is that if there are two or more absorbing components in the material then the total sample's absorption will be the sum of absorptions of each component obtained separately [12]. This assumption is the classic case of the linear superposition principle and it has been used to construct the system of Equations 11. The optical tissue model used in the Signal separation process can be used to create another set of equations. One integral equation should be built for the each absorbing component i in the tissue, which would relate its concentration c_i [10], absorbed part of the light intensity $U_{i\lambda j}$ at wavelength λ_j and the emitted radiation intensity $I_{E\lambda j}$. To build such equations, absorption coefficients (not the same as Beer-Lambert law absorptivities, although they are related [21]) of the all κ tissue components on each wavelength λ_j are required:

$$U_{i\lambda j} = L(c_i, Y_{i\lambda j}, P_{\lambda j}, I_{E\lambda j}) \quad 12$$

where L is an integral equation; $P_\lambda = \{p_{1\lambda}, p_{2\lambda}, p_{3\lambda} \ldots p_{n\lambda}\}$ are parameters describing scattering property of tissue (obtained during the Signal separation process); and $Y_{i\lambda j} = \{y_{i\lambda j,1}, y_{i\lambda j,2} y_{i\lambda j,3} \ldots y_{i\lambda j,q}\}$ are absorption coefficients of each component i at wavelength λ_j (measured and preliminary programmed in to measuring system). Thus, system of Equations 11 can be combined with Equations 6 and rewritten into the following approximating form:

$$\begin{cases} G(H_{\lambda 1}, l_1, I_{E\lambda 1}) = L(c_1, Y_{1\lambda 1}, P_{\lambda 1}, I_{E\lambda 1}) + \ldots + L(c_i, Y_{i\lambda 1}, P_{\lambda 1}, I_{E\lambda 1}) + \ldots + L(c_k, Y_{k\lambda 1}, P_{\lambda 1}, I_{E\lambda 1}) \\ G(H_{\lambda 2}, l_2, I_{E\lambda 2}) = L(c_1, Y_{1\lambda 2}, P_{\lambda 2}, I_{E\lambda 2}) + \ldots + L(c_i, Y_{i\lambda 2}, P_{\lambda 2}, I_{E\lambda 2}) + \ldots + L(c_k, Y_{k\lambda 2}, P_{\lambda 2}, I_{E\lambda 2}) \\ \ldots \\ G(H_{\lambda i}, l_i, I_{E\lambda i}) = L(c_1, Y_{1\lambda i}, P_{\lambda i}, I_{E\lambda i}) + \ldots + L(c_i, Y_{i\lambda i}, P_{\lambda i}, I_{E\lambda i}) + \ldots + L(c_k, Y_{k\lambda i}, P_{\lambda i}, I_{E\lambda i}) \\ \ldots. \\ G(H_{\lambda k}, l_k, I_{E\lambda k}) = L(c_1, Y_{1\lambda k}, P_{\lambda k}, I_{E\lambda k}) + \ldots + L(c_i, Y_{i\lambda k}, P_{\lambda k}, I_{E\lambda k}) + \ldots + L(c_k, Y_{k\lambda k}, P_{\lambda k}, I_{E\lambda k}) \end{cases} \quad 13$$

The only unknown variables in this equations system are tissue components concentrations c_i. The number of the equations is equal to the number of the unknown variables, by construction. Thus, in theory, by solving this equations system, component concentrations c_i (including glucose) could be found analytically or by adaptation (numerically).

3. Conclusions and discussion

This paper challenges one of the most difficult non-invasive monitoring techniques, that of blood glucose, and proposes a new novel approach that will enable the accurate, and calibration free estimation of glucose concentration in blood. This approach is based on spectroscopic techniques and a new adaptive modelling scheme.

The theoretical implementation and the effectiveness of the adaptive modelling scheme for this application has been presented and a detailed mathematical approach has been employed to prove that such a scheme has the capability of extracting accurately the concentration of glucose from a complex biological media comprised of many light absorbing material such as tissue, venous and arterial blood, water, fat, bone, etc. The mathematical derivation shown above has demonstrated that the accuracy of the glucose concentration depends on the complexity of the model. The more the information in the model relating to others absorbers within the biological media the more accurate the concentration of glucose will be extracted.

This stage of the work paves the way and suggests the software and hardware specifications including the optical glucose sensor design. It also sheds light of what will be the minimum number of wavelengths used for the estimation of blood glucose of an accuracy that will be acceptable by the clinical experts.

Further developmental (software and hardware) and experimental (in vitro) stages are suggested to support the successful implantation of the proposed adaptive modelling scheme.

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