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Towards an Optimized Tetrapolar Electrical Impedance Lithium Detection Probe For Bipolar Disorder: A Simulation Study

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Abstract— **Bipolar disorder is characterized as a manic-depressive syndrome with severe risks to the individual. Bipolar patients' therapy involves administration of lithium which has proven to be effective for mood stabilization. The therapeutic concentration window for lithium in blood plasma is typically between 0.6-1.5 mM and is of vital importance that concentrations do not exceed the 1.5mM as it can be toxic. Accurate monitoring of the concentration changes of Lithium in blood, down to levels of approximately 0.2mM is vital since toxicity levels are in close proximity to therapeutic levels. This paper aims to study the sensitivity of tetrapolar electrical impedance measurements when used to monitor changes in the conductivity of a solution/sample as in the case of changes in Lithium concentration in blood.**

I. INTRODUCTION

Bipolar disorder is classified as a neuropsychiatric disorder with intermittent manic and depressive episodes [1]. The disorder has also received a great deal of attention as it can also affect children leading to increased rates of suicide if left untreated [2]. Typical treatment for bipolar disorder involves the administration of Lithium salts in tablet forms. Long-term Lithium treatment however is not a risk-free process as it has a narrow therapeutic blood concentration window between 0.6-1.5mM. Increasing concentration to levels above 1.5mM are considered to be toxic for the body [3]. Closely monitoring the concentration levels of Lithium in patients undergoing treatment is of vital importance since toxicity levels are in close proximity with therapeutic levels within <0.2mM. Clinically established techniques in the measurement of blood lithium concentrations include flame emission photometry (FEP) and atomic absorption spectroscopy (AAS) [4, 5] which require a laboratory setting and are not suitable for home use. Other non-clinically established techniques include potentiometry via ion sensitive electrodes (ISE's) with high affinity to Lithium [6], as well as capillary electrophoresis [7]. ISE methods as well as electrophoretic techniques require the use of specific ion selective membranes or the application of high voltage signals (in the order of kV) for ion separation respectively. Protein molecules present in a physiological fluid can affect the sensitivity of ISE's towards a particular ion, thus samples may require additional filtration. It is therefore desirable to detect blood lithium using a highly sensitive sensing method that is not cumbersome; that does not employ high voltages; and that does not depend on highly variable, short-lived membranes. This paper aims to study the sensitivity of tetrapolar (4-electrode) electrical impedance measurements; ultimately used to detect changes in the concentration of Lithium in human blood plasma. This study is part of a larger project where optical spectroscopy provides the necessary specificity, without attaining the much desired 0.2mM concentration variation sensitivity. Electrical impedance measurements are typically performed through application of a small ac signal via a pair of current carrying (CC) electrodes and monitoring of the induced transfer signal via a separate pair termed pick up (PU) electrodes. Injected ac signals are typically in the range of µA-mA and additional sample filtration is not required; hence reducing the processing time. The measured induced signal is termed as the transfer signal and the extracted impedance is termed as the *"transfer impedance"*; which is dependent upon the electrode configuration used. The transfer impedance or changes in the transfer impedance recorded due to changes in the conductivity of the sample under test (SUT) are dependent upon the sensitivity of the particular electrode configuration [8]. This can be advantageous in this particular application as enhanced sensitivity towards changes in the concentration of Lithium in blood is vital.

II. MODELLING

A. Tetrapolar probe

The sensitivity of an electrode configuration used in impedance measurements is given by:

$$S = \frac{\vec{J_1} \cdot \vec{J_2}}{I^2} \qquad (1)$$

where, $\vec{J_1}$ is the current density (A/m^2) vector at a particular region of the volume (voxel) due to the signal injection dipole (CC pair) and $\vec{J_2}$, is the reciprocal current density (A/m^2) vector if the signal injection dipole was the other electrode pair (PU pair) [8]. I is the injected current and $(.)$ denotes the dot product. The sensitivity equation represents the signal transfer function from one dipole to the other which constitutes the basis for the total impedance being measured. The total transfer impedance would be a summation or a volume integral of the total sensitivity field multiplied by the resistivity of the volume conductor or, in case of a non-homogeneous volume, the resistivity of each sub region. The measured transfer impedance is therefore given by:

$$Z_{transf} = \iiint \rho . S \, dv \qquad (2)$$

where ρ is the resistivity (Ω.m) of the material. In case of changes in Lithium concentration in blood plasma it can be assumed that the resistivity/conductivity is changing uniformly throughout the sample therefore any subsequent change in transfer impedance is dependent upon the sensitivity of the electrode configuration. In a tetrapolar configuration the sensitivity in particular regions of the volume can be either positive, negative or zero.
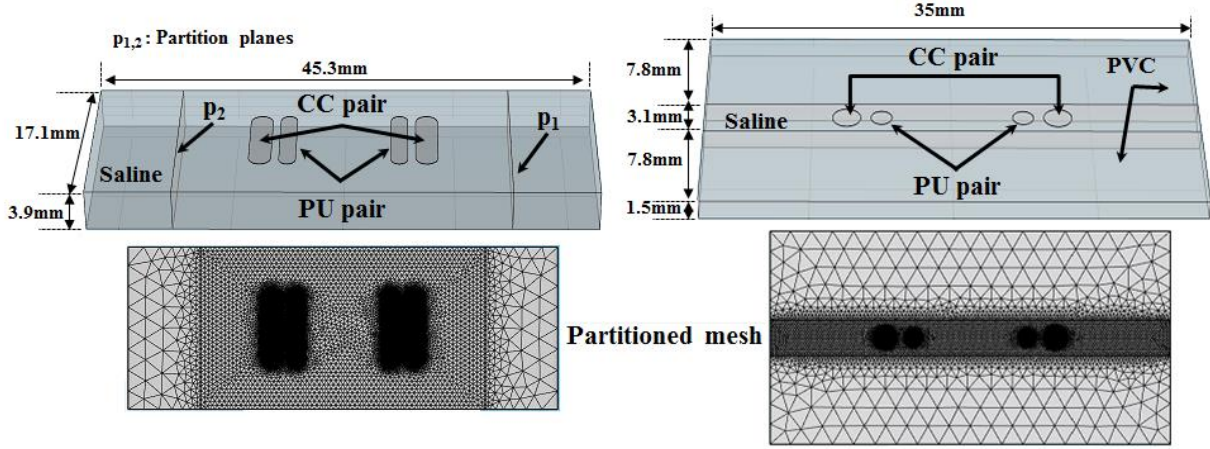
Fig. 1: (Left) Geometrical model of existing probe (Prb1) with four rectangular electrodes with smoothed corners. Planes p1 and p2 are partitioned with the emulated "saline" volume in order to produce a partitioned mesh. (Right) Geometrical configuration of new probe (Prb2) with reduced "saline" volume. Four circular electrodes of diameter and initial inter-electrode separation distances equal to that of Prb1 were used. Partitioned mesh was produced by assigning finer mesh geometry to the "saline" domain.

If a change in conductivity takes place at a region of negative sensitivity then the associate change in the measured transfer impedance would be of the opposite sign hence leading to erroneous interpretation of the nature of the change. Similarly conductivity changes in regions of zero sensitivity would result in unchanged measured impedance. It worth mentioning however, that in this particular study, conductivity changes at specific regions of the volume are not of interest, as changes of conductivity occur throughout the volume, but the overall sensitivity (S_{total}) of the electrode configuration as it is overall affected by negative and zero sensitivity regions.

1) Finite element models (FEM) for simulation

For the sensitivity field calculations, two coplanar tetrapolar configurations were simulated (Fig. 1) using Comsol multiphysics (Comsol, Inc., 5.1, 2015) in an isotropic volume of uniform conductivity; assigned to match the conductivity of physiological saline. The configuration shown in Fig.1 (Left) is a representation of an already existing fabricated probe (**Prb1**) with four rectangular electrodes with rounded corners. The emulated saline volume is approximately 3mL. CC electrodes are 8mm high, 2mm wide and 50µm thick while the PU electrodes are 8mm high, 1.5mm wide and 50µm thick. The separation distance between the PU electrodes is 10mm (between centers) and the edge-to-edge separation between the PU and CC electrodes is 0.7mm. Fig.1 (right) shows a new configuration (**Prb2**) with a saline volume of 162µL. As the current project moves towards the design of fluidic devices able to hold drop-like volumes of blood, this papers aims to study the effects of volume reduction in the sensitivity of tetrapolar impedance measurements. The initial CC pair and PU pair inter electrode distances and separations of **Prb2** were kept the same as in **Prb1**. CC and PU pairs in **Prb2** are 2mm and 1.5mm in diameter respectively. Sensitivity field simulations were performed using the AC/DC module provided by Comsol, solving for the electrical potential using a quasi-static solution of Maxwell's equations. CC and PU electrodes were assigned material properties (electrical conductivity and relative permittivity) of silver while the "saline" volume was initially assigned a conductivity of 1.65S/m (conductivity of physiological saline). For each electrode pair, a current terminal was assigned to one electrode, with a 1A boundary condition, while a ground terminal, of zero potential, was assigned to the other one.

B. Effect of volume reduction on S

Fig.2 shows the result of the simulation for both **Prb1** and **Prb2** after varying the conductivity of the saline volume. In each case the change in transfer impedance magnitude |**ΔZ**| from the initial baseline value (1.65 S/m) was calculated and the total sensitivity (S_{total})**.** The volume integral equation used for the calculation of (S_{total}) is shown in Fig.2 as well as the baseline values for the 1.65 S/m case (**Z$_{0prb1}$** and **Z$_{0prb2}$**). Fig. 3 shows a plot of the spatial sensitivity distribution across a slice in the middle of the volume, on the same color range.

$$S_{total} = \iiint_{saline} \frac{J_{x1}\cdot J_{x2} + J_{y1}\cdot J_{y2} + J_{z1}\cdot J_{z2}}{1[A]^2}\, dv$$
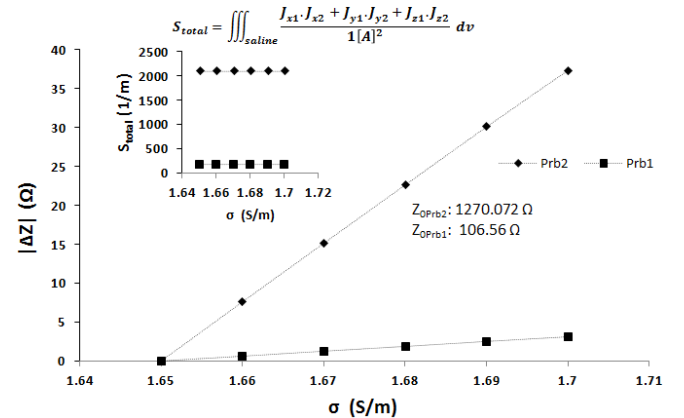
Z_{0Prb2}: 1270.072 Ω
Z_{0Prb1}: 106.56 Ω

Fig. 2: Simulated change in total sensitivity and associate change in measured transfer impedance magnitude for various conductivity values for **Prb1** and **Prb2**.

C. Effect of inter-electrode separation (PU)

Figs. 4-5 show the effect of varying the inter-electrode separations of the PU pair, upon the total sensitivity (S_{total}) and the associated change in the measured transfer impedance for **Prb2** only. Fig. 4, shows the change in total sensitivity and

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associated transfer impedance change for changes in the separation of the PU pair while keeping the CC pair at a constant separation (24.9mm). Finally in Fig.5, the change in total sensitivity and associated change in the measured transfer impedance magnitude is shown for changes in the conductivity of the "saline" volume for varying PU separation while keeping the separation between PU and CC constant.
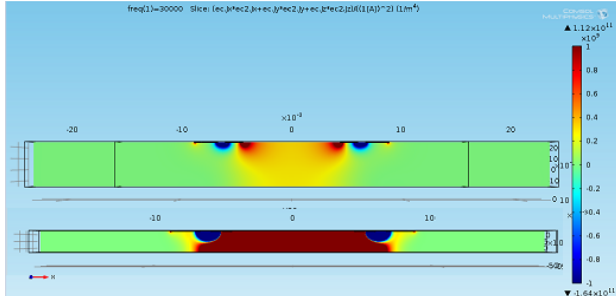

Fig.3: Simulated spatial sensitivity distribution for Prb1 (top) and Prb2 (bottom) indicating the regions of positive (red) and negative contributions (blue).
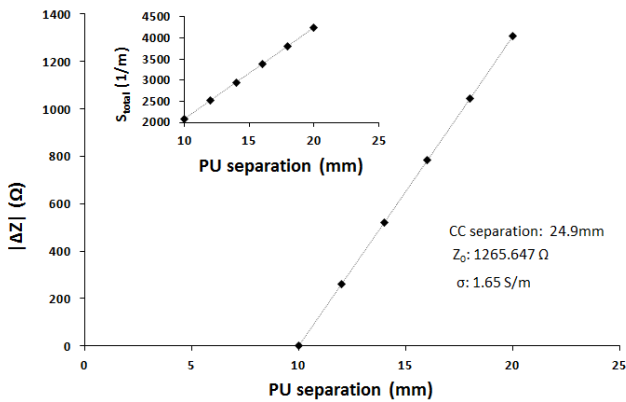

Fig. 4: Simulated change in transfer impedance magnitude for different PU pair separation and associated change in total sensitivity for **Prb2**.
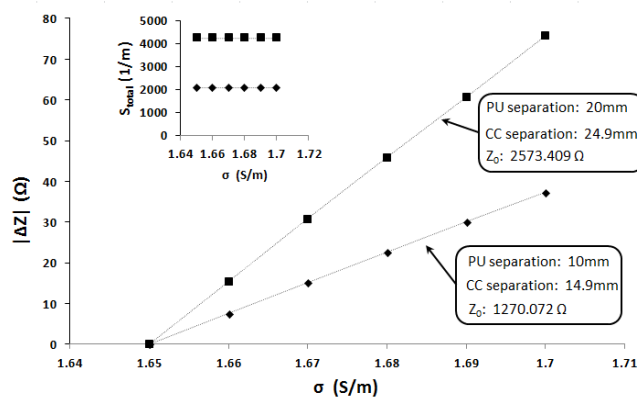

Fig. 5: Simulated change in transfer impedance magnitude for different PU and CC separation, while keeping the PU and CC separation constant, for various conductivities for **Prb2**. Associated change in total sensitivity (embedded plot)

III. DISCUSSION AND CONCLUSION

The effect of reduction in volume on the sensitivity of the probe is shown in Fig. 2 and3. The embedded plot in Fig.2

shows an over tenfold increase in the total sensitivity in the case of **Prb2.** The associated change in the measured transfer impedance, when the conductivity of the volume is increased, is proportional to the change in sensitivity, (as the conductivity is uniformly changed) as also shown in (2).

This change in total sensitivity is also reflected in Fig.3 in which the spatial sensitivity of **Prb2** appears to be more intense on the same color mapping. It is worth mentioning that the regions of negative sensitivity (blue regions) also appear more intense, which also indicates an enhanced negative effect, however there seems to be a much higher contribution of regions at the bottom of the volume in **Prb2** (red positive sensitivity regions) which may explain the overall total increase in sensitivity.The results shown in Fig.4-5 only concern **Prb2** as the aim is to move towards smaller volume dimensions. In Fig.4 it is observed that increasing the separation of the PU pair, there a proportional increase in total sensitivity, (Fig. 4 embedded plot) and an associated increase in the change in measured transfer impedance.

Finally in Fig.5, an almost doubled change in the measured impedance is observed which is also reflected in an equal change in the total sensitivity (embedded plot) after varying PU and CC separation. It is worth mentioning as well that the sensitivity is mostly affected by the PU pair separation rather than the CC pair separation in a co-planar electrode configuration as the total sensitivity is equal to the initial and final sensitivity in Fig.4 (embedded plot). The study therefore of the sensitivity distribution in tetrapolar electrical impedance measurements can serve as a powerful tool in increasing the probe resolution to small changes in the conductivity.

REFERENCES

[1] R. H. Belmaker, "Bipolar Disorder," *The New England Journal of Medicine,* vol. 351, pp. 476-486, 2004.

[2] N. Lofthouse and M. A. Fristad, "Bipolar disorders," in *Children's needs III: Development, prevention and intervention*, Washington, DC, National Association of School Psychologists, 2006, pp. 211-224.

[3] R. T. Timmer and J. M. Sands, "Lithium Intoxication," *J. Am. Soc. Nephrol.,* vol. 10, pp. 666-674, 1999.

[4] B. F. Rocks, R. A. Sherwood and C. Riley, "Direct Determination of Therapeutic Concentrations of Lithium in Serum by Flow-Injection Analysis with Atomic Absorption Spectroscopic Detection," *Clin. Chem.,* vol. 28, no. 3, pp. 440-443, 1982.

[5] J. K. Grime and T. J. Vickers, "Determination of Lithium in Microliter Samples of Blood Serum Using Flame Atomic Emission Spectrometry with a Tanatalum Filament Vaporiser," *Analytical Chemistry ,* vol. 47, no. 3, pp. 432-435, 1975.

[6] M. Novell, T. Guinovart, P. Blondeau, F. X. Rius and F. J. Andrate, "A paper-based potentiomtric cell for decentralised monitoring of Li levels in whole blood," *Lab Chip,* vol. 14, no. 7, pp. 1308-1314, 2014.

[7] E. Vrouwe, R. Luttge and A. van den Berg, "Direct measurement of lithium in whole blood using microchip capillary electrophoresis with integrated conductivity detection," *Electrophoresis,* vol. 25, pp. 1660-1667, 2004.

[8] S. Grimnes and O. Martinsen, "Sources of error in tetrapolar impedance measurements on biomaterials and other ionic conductors," *J. of Physics D : Applied Physics,* vol. 40, pp. 9-14, 2007.