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A Method for Rapid, Reliable, and Low-Volume Measurement of Lithium in Blood for use in Bipolar Disorder Treatment Management

M. Qassem, L. Constantinou, I. F. Triantis, M. Hickey, E, Palazidou, and P. A. Kyriacou, *Senior Member, IEEE*

***Abstract*— *Goal:* Lithium preparations are considered the most reliable mood stabilizers for patients with Bipolar Disorder (BD), and are the most effective at reducing the risk of suicide. However, maintaining blood lithium concentration within the narrow therapeutic range of 0.4-1.2 mEq is crucial but extremely difficult. The aim of this work is to develop a personal lithium blood level analyzer using a novel method of combined optical and electrical impedance spectroscopy to test micro volumes of spiked samples of human blood.**

***Results:* Impedance measurements alone showed a limit of detection of less than 0.1 mEq within the therapeutic range, whereas optical measurements could verify the presence of lithium and provide a degree of lithium content. Optical specificity to lithium was further verified in qualitative assessment of lithium spiked blood samples with varying concentrations of sodium. Moreover, analysis of multiple linear regression yielded a prediction model of R2 = 0.322716 and RMSEP =0.223602 for optical measurements only using feature wavelengths, which were found to appear at minima 560 and 605 nm. Combined with impedance measurements, prediction of lithium concentration in samples with unknown lithium content was significantly increased to R2 = 0.876438, and RMSEP = 0.513554.**

***Conclusion:* The combination of optical and impedance modalities for determinations of blood lithium resulted in significant improvement to the sensitivity and accuracy of measurement.**

***Significance:* Results are complementary of the proposed opto-impedance method, and future work will now focus on the technical development of an integrated and miniaturized system for measurement of lithium levels in blood with a high level of accuracy and sensitivity.**

***Index Terms*—Mental Health, Electrical Impedance, Bipolar Disorder, Spectrophotometry, Personal Monitoring.**

I. Introduction

BIPOLAR Disorder (BD) is a lifelong and complex psychiatric syndrome characterized by alternating episodes of mania and depression that can vary in duration and time of occurrence [1], [2]. People with BD experience recurrent and severe swings between elevated mood and depression. The result is serious impairment of functioning in personal, social and work life and the quality of life of a Bipolar person in general. BP is also associated with higher mortality through suicide [3] as well as poor physical health [4]. The importance of good illness control with safe prescribing, that is acceptable to patients, cannot be overestimated. Long term management of Bipolar patients involves regular taking of mood-stabilizing preparations such as lithium, which after 60 years, remains the most effective therapy for controlling acute mania, preventing relapses and reducing the risk of suicide [5]–[7].

Long-term lithium treatment entails a considerable risk to the patient if not closely monitored, as the use of the drug must be controlled within a narrow therapeutic window of 0.6-1.0 mEq in serum (blood). Blood lithium levels above 1.5 mEq are considered toxic [8], and in many cases, lithium levels can increase above this limit, leading to serious consequences such as renal failure, seizures, coma and even death [9]. Toxicity can occur suddenly as a result of an overdose, drug interactions or dehydration [9].

Bipolar patients on lithium medication are required to attend regular clinic visits to undergo frequent blood tests. In practice, the number of patients that conform with this requirement currently falls below set standards, and high rates of treatment non-adherence exists [10]. This is partly due to the frequency of blood tests resulting in patients evading treatment. Because of this, the availability of a personal monitor would benefit Bipolar patients by reducing the need for frequent clinical visits, empowering them through involvement in the management of their illness, as well as improving adherence with effective monitoring by facilitating early detection of shifting of lithium concentrations outside the therapeutic range.

Methods for measuring lithium concentration in serum or plasma require high sensitivity to changes of <0.1 mM as toxicity levels are close to therapeutic levels. At present, the standard measurements of blood lithium concentration are performed via flame emission photometry (FEP) and atomic absorption spectroscopy (AAS) [11], [12]. Although both techniques provide the necessary accuracy and sensitivity of measurement, they are cumbersome and elaborate laboratory methods that cannot be translated into point of care devices for

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M. Qassem is with the Research Centre for Biomedical Engineering at City, University of London, Northampton square, London EC1V 0HB (correspondence e-mail: meha.qassem.1@city.ac.uk).

personal monitoring.

A handful of attempts to address the demand for personal monitoring of lithium have been reported, mainly through electrochemical methodologies such as Ion Selective Electrode (ISE) [13], [14] and electrophoresis [15], [16]. Some success has been achieved with these, but nevertheless, issues exist which relate to interference with other ions present in the sample [17], drifting of electrode-electrolyte interface impedance [18] and need for sample filtration [19]. Spectrophotometric [20] and spectrofluorimetric [21], [22] optical techniques have also been explored but these have focused on replacing current laboratory methods or used oral fluids as the testing media [23]. The latter have been linked to serum lithium levels, but are not standardized or clinically accepted as alternatives to serum levels.

This work proposes the combination of optical and electrical impedance spectroscopy methods for measuring blood lithium concentrations. Optical spectroscopy techniques can offer a high degree of selectivity, whereas previous experimentation [24] has shown that electrical impedance spectroscopy can offer a high degree of sensitivity to changes in ionic concentrations. Hence, it is hypothesized that the combination of the two methods would provide an enhanced degree of sensitivity and specificity to changes in lithium concentration in blood.

II. MATERIALS AND METHODS

A. Preparation of blood samples

Following ethical approval, a standard solution of 60 mEq Li_2CO_3 in deionized water was prepared, and subsequently, this was diluted further to make a set of solutions with the following concentrations: 12, 18, 24, 30, 36, 42, 48, 54 mEq.

Frozen mixed pool blood plasma from healthy individuals was obtained from a reliable provider (TCS biosciences Ltd, Buckingham, UK). Samples of human plasma that have been spiked with lithium were prepared by mixing 1 mL from each reagent of Li_2CO_3 prepared earlier i.e. 18, 24, 30, 36, 42, 48, 54 and 60 mEq with 29 mL of blood plasma, thus giving 8 samples of 30 mL, with lithium concentrations ranging between 0.4-2.0 mEq. To check for repeatability of measurement, another set of samples were prepared in the same way using a different batch of blood plasma, as well as an additional set of samples spiked with unknown lithium concentrations in plasma. The latter were used to validate measurements.

B. Reference flame photometry measurements

A flame photometer (M410 Sherwood Scientific Ltd, Cambridge, UK) was used to measure the concentration of dissolved lithium in the plasma samples. Measurements of concentration are displayed in parts per million (ppm, 1mmol/L of Li^+ is 6.93 ppm). Initially the instrument was left to warm up with the flame alight, and distilled water was aspirated for approximately 30 minutes. A standard solution provided by the manufacturer (containing 1.5 mM of Li^+) was at first aspirated for 20 seconds and the instrument ppm reading was set to 10.4 (corresponding to 1.5 mM). Successive measurements of known and unknown lithium concentrations from the prepared plasma samples were recorded, then used to extrapolate molar lithium concentration.

C. Optical measurements of blood lithium

The following reagents were prepared: 0.1 M of NaOH, 0.25 M of Na_2CO_3, 90 % $(CH_3)_2SO$ and 1 mM of Quinizarin in $(CH_3)_2SO$.

An amount of 500 µL from spiked samples of plasma were pipetted into a test tube, then were diluted with water to make up to 1 mL. An amount of 50 µL from diluted plasma was mixed with 100 µL of 0.1 M NaOH, 10 µL of 0.25 M Na_2CO_3, 40 µL of water, 2.15 mL of 90 % $(CH_3)_2SO$ and 50 µL of 1mM of Quinizarin in $(CH_3)_2SO$. Prior to testing, all samples were kept in a thermostatic bath at 25º for 30 mins.

Data was acquired using a dual beam spectrophotometer (Model: Lambda 1050, PerkinElmer Corp, Waltham, MA) with the Traycell (Helma GmbH & Co, Mulheim, Germany), which only requires 4-5 µL of sample volume for analysis.

The instrument was setup to acquire spectra between 450-700 nm at increments of 1 nm, with a response time of 0.2 secs and two running cycles for each sample. Slit width of the detector was fixed at 2 nm, and both reference and sample attenuators were kept at 100 %. Data pre-treatment, Partial Least Squares (PLS) and Multiple Linear Regression (MLR) analysis were performed using the Matlab® software (Mathworks Inc, Novi, MI), and the PLS-toolbox (Eigenvector Research Inc, Manson, WA) Matlab® add-on. Pre-processing methods which were applied to acquired spectra include baseline correction using the Whittaker filter, and Savitsky-Golay algorithms for both smoothing and second derivatives.

Since sodium fluctuations are the most likely to influence measurement, additional tests were performed to study the influence of sodium ion variation in blood. For this, four blood samples that had been spiked with lithium at 0.6, 1.0, 1.2 and 1.8 mmol/L of Li^+ were selected and from each of these, four additional samples were prepared by mixing 0.33 mL of deionized water, or 30, 45, or 60 mEq Na_2CO_3 with 9.78 mL of lithium spiked blood plasma. This provided a set of 16 samples with increased sodium concentration of 0, 1, 1.5 and 2.0 mmol/L.

D. Tetrapolar electrical impedance measurements of blood lithium

Tetrapolar electrical impedance measurements typically involve the injection of a low amplitude ac current into the sample under test (SUT) through a pair of current carrying (CC) electrodes and a separate pick up (PU) electrode pair used to monitor the resulting voltage. The relationship between the injected current and the measured voltage allows for the calculation of impedance. Since lithium is present in blood in its ionic form, the tetrapolar (4-electrode) probe contacting the sample will detect changes to Li concentration as changes to the electrical conductivity/impedivity of blood. Therefore, variations in the recorded voltage can directly translate to blood lithium concentration changes. A more detailed explanation of the method can be found in [24], where the sensitivity of the method to changes in lithium concentration in human blood

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plasma was tested and benchmarked. The probe presented in this paper consists of a co-planar 4-electrode arrangement shown in Fig 1. It was designed methodically using COMSOL FEM simulations prior to its fabrication to determine its sensitivity to changes in the conductivity of the SUT. Its electrode array geometry was thus optimized for enhanced resolution in small sample volumes (160µL). This design exhibited a significant improvement relative to a previous, larger (3mL) probe designed and tested by the authors and presented in [24].

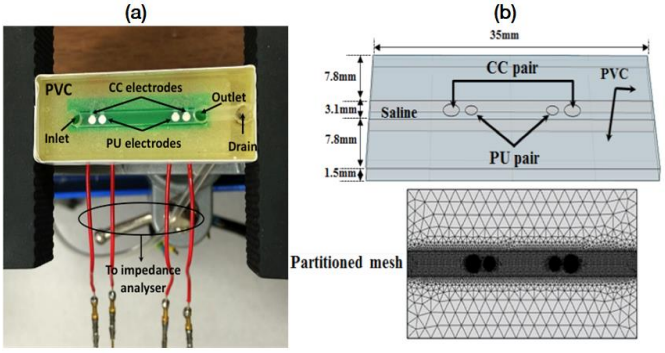

Fig 1. (a) The fabricated 160µL tetrapolar impedance probe (b) COMSOL model and geometrical configuration of the probe. Partitioned mesh was produced by assigning finer mesh geometry to the "SUT" domain.

The new probe features a tenfold increase in the total sensitivity, corresponding to a tenfold increase in the measured impedance change for specific Li concentration variations. Hence, with appropriately designed instrumentation for tetrapolar impedance measurements, the new probe has the potential to measure very small Li concentration variations.

Electrical impedance measurements using human plasma solutions spiked with lithium carbonate (Li_2CO_3) at different concentrations were performed using the Agilent 4294A precision impedance analyzer in a frequency bandwidth from 30 kHz to 300 kHz. Each measurement acquired 201 points throughout the bandwidth for both magnitude and phase of the sample's impedance and average respective values were calculated from these points. The measurements were repeated 5 times for each sample for statistical analysis. An initial baseline reference measurement using a plasma only solution was taken, and results are reported as the mean change in impedance magnitude and phase relative to that reference value.

E. Combination of optical and electrical impedance spectroscopy measurements

Overall, analysis of each prepared sample was carried out using both optical and impedance modalities (on two separate platforms), and data collected was used to assess each modality separately, and in combination, by using regression techniques to test the accuracy and sensitivity of lithium calibration and prediction in blood. Fig 2 provides a diagrammatic illustration of the measurement process.

III. RESULTS AND DISCUSSIONS

Samples of blood plasma, which were prepared to give lithium contents of 0.4-2.0 mEq in the order of 0.2 mEq, were first verified through FEP measurements, and are listed here in Table I. Linear regression was performed on FEP readings against set concentrations, where a positive correlation of R2 = 0.882 was found between both sets (Fig 3). FEP values were also used to extrapolate molar values of lithium in prepared blood samples, the result of which is summarized in Table I. It is assumed that the differences between set and measured Li^+ levels exist because samples were comprised of two sets prepared from different batches of blood which differ in homogeneity and lithium baseline. A paired t-test showed that extrapolated Li^+ concentrations were statistically significantly different from set values ($p = 0.0016$). Since FEP measurements are considered the standard in measuring lithium, the remainder of analysis was performed using values extrapolated from flame photometer readings.

A. Optical Spec. results

Preprocessed spectral data of spiked samples of blood plasma are shown in Fig 4. These feature prominent minima bands around 605 nm and 560 nm. Once again, results include data

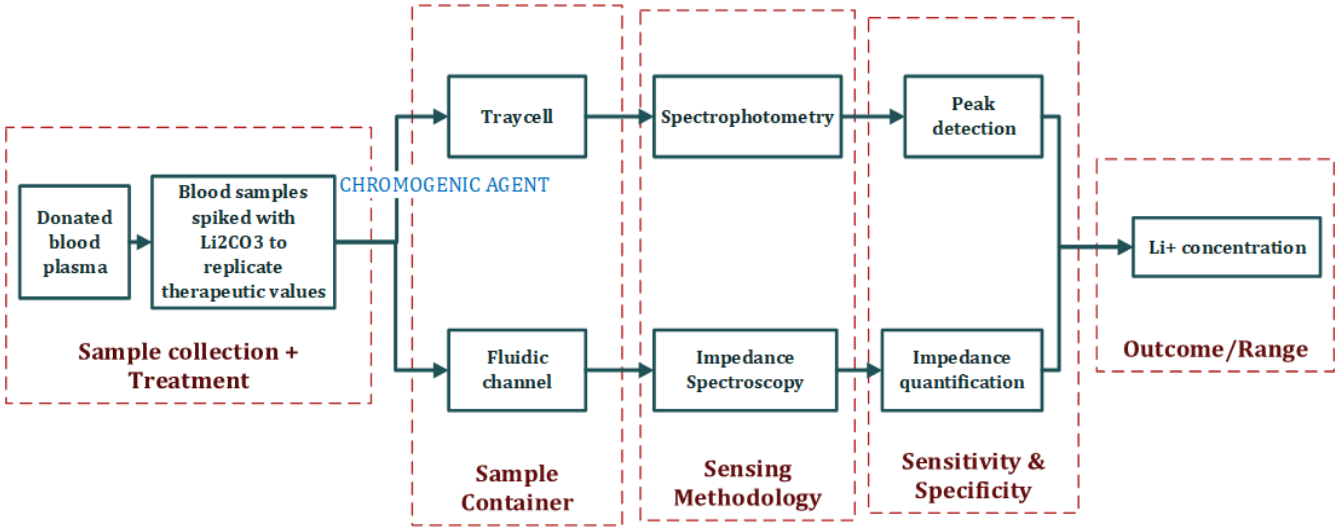

Fig 2. Process diagram of combined optical and electrical impedance method used to analyze lithium spiked samples of human blood.

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from two sets of lithium spiked samples of blood (plasma) prepared from different batches. Thus, baseline correction was performed on raw data from the two sets separately prior to performing additional preprocessing treatments of Savitsky-Golay second derivative and smoothing, peak shift correction (using minima at 605 nm as a reference point) and area normalization (range selected: 530-650nm). A general trend is evident where minima values, and in turn absorbance, around the bands of 605 and 560 nm varied in correspondence with lithium concentrations, thereby increasing with higher blood lithium contents. However, results also indicate a lack of sensitivity, particularly when measurements from different blood batches are considered.

TABLE I
FEP MEASUREMENTS OF LITHIUM CONCENTRATIONS IN HUMAN BLOOD (PLASMA)

Li^+ (mM) = FEP (ppm)/6.6941
Baseline of FEP (ppm) = 10.4/6.6941 = 1.4983 Li^+(mmol/L)

Conc (mEq)	FEP (ppm)	Li^+ (mM)
2.00	12.90	1.86
1.80	10.70	1.54
1.40	8.40	1.21
1.60	8.60	1.24
1.20	6.70	.97
1.00	6.40	.92
.80	6.80	.98
.60	5.20	.75
.40	3.60	.52
.00	.50	.07
.00	.60	.09
.60	3.40	.49
.80	4.20	.61
1.00	4.55	.66
1.20	5.50	.79
1.40	6.90	.99
1.60	7.60	1.10
1.80	8.70	1.25
2.00	9.50	1.37
2.00	12.90	1.86

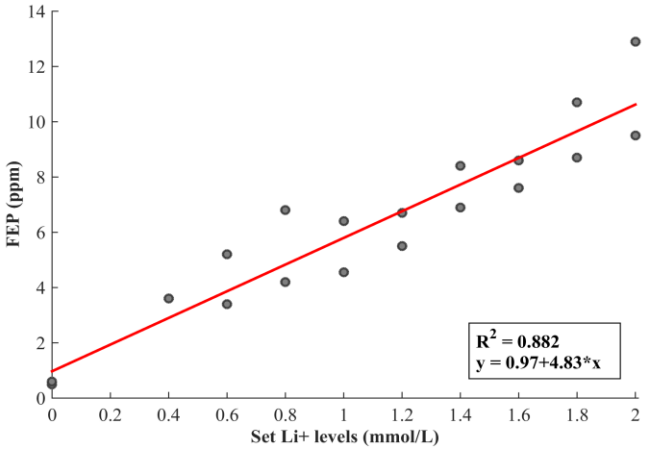

Fig 3. Calibration curve of FEP measurements of Li^+ concentration in spiked samples of human blood (plasma).

This is particularly evident when assessing the relationship between acquired spectra and lithium levels in plasma samples through Multiple Linear Regression (MLR), using full range data of pre-treated spectra between 530-650 nm. Spectral data were used as calibration data input whilst lithium concentrations obtained through FEP measurements were used as the dependent variable. Prior to producing the model, mean-centering and leave-one-out cross validation was applied, which ensured that the performance of the model is optimized. The results of regression (inset of Fig 4) yielded an R2 value of 1 but a significantly lower cross-validated R2 value of 0.5514.

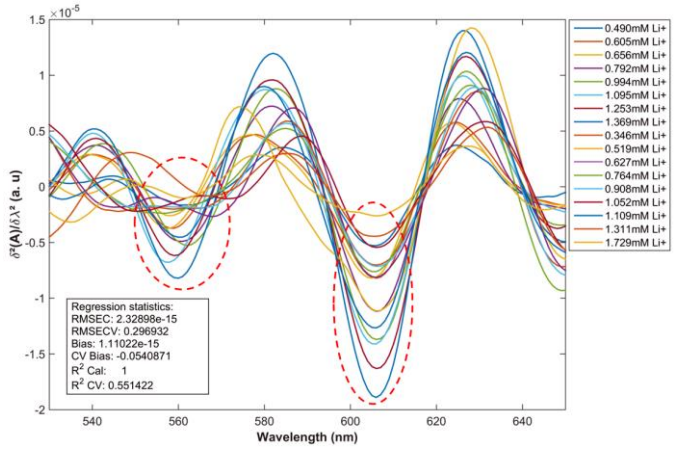

Fig 4. Second derivative spectra of therapeutic concentrations of lithium in blood in the range 530-650 nm after undergoing pre-treatment of baseline and peak shift corrections, Savistky-Golay filtering and normalization. Prominent bands found at 605 nm and 560 (circled).

This reduction is assumed to relate to differences in baseline and homogeneity between the two sets of blood samples, which although minimized through pre-processing, remain to decrease the accuracy of measurement. Similarly, the Root Mean Square Error (RMSE) of calibration (RMSEC: 2.32898e-15) was also found to be higher in cross-validation RMSE (RMSECV = 0.296932).

In addition to quantitative determinations of blood lithium levels, the degree of specificity to lithium using the proposed method was also investigated. Spectral measurements were collected from lithium spiked blood samples that had been mixed with Na_2CO_3, and underwent processing of baseline correction, Savitsky-Golay smoothing and area normalization. The resulting graphs are illustrated in Fig 5, showing four sets of measurements from four selected lithium spiked blood samples whose sodium contents were varied by specified amounts. An averaged spectrum of the respective lithium spiked blood (plasma) was used as a blank and subtracted from the graphs shown in Fig 5.

Looking at Fig 5, it is evident that a peak shift existed between the band relating to lithium absorption and that belonging to the sodium ion. Although actual bands are seen to vary between measurements, being located around 605-625nm for lithium and between 580-600nm for sodium, each set of spectral data clearly exhibited a difference of ≈20nm between the absorption bands of the two ions of interest, thereby indicating the possibility of high selectivity to lithium in blood with this method.

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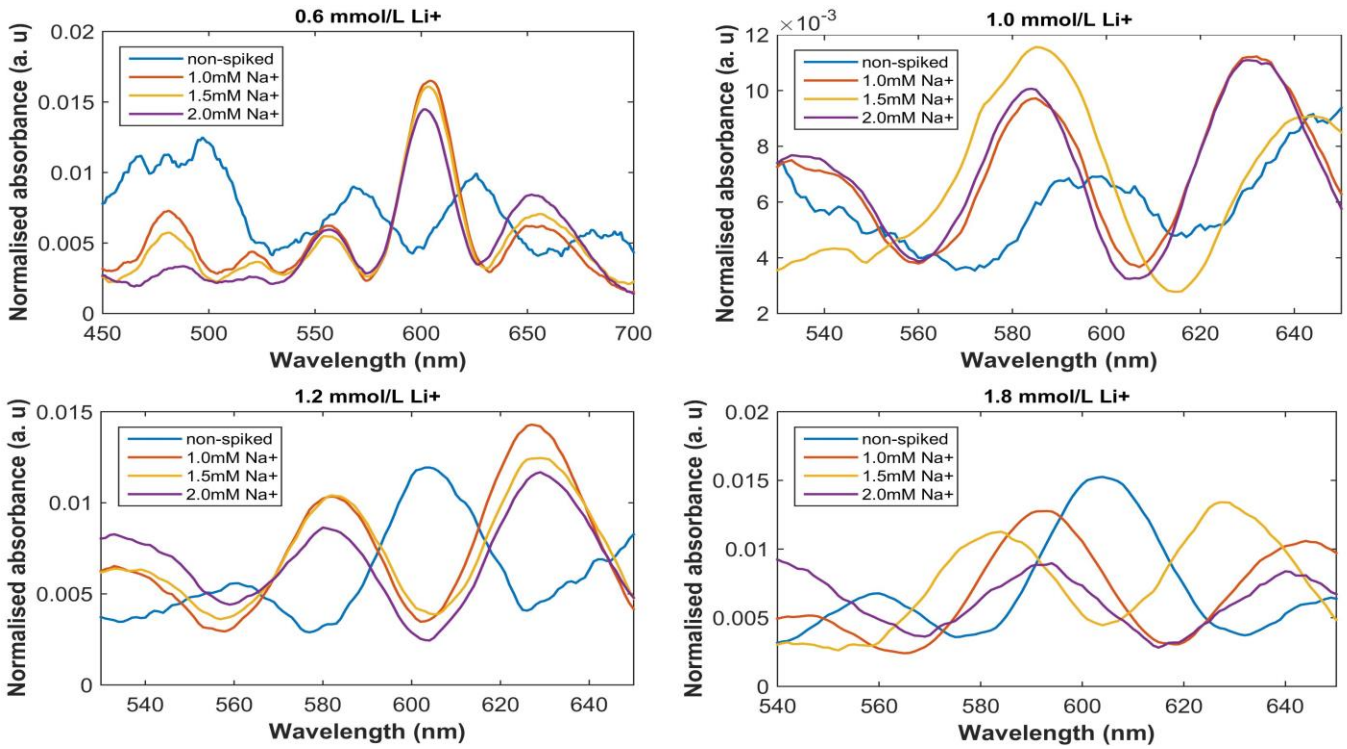

Fig 5. Preprocessed absorption spectra of a set of lithium spiked blood solutions (0.6, 1.0, 1.2, and 1.8 mmol/L Li^+ whose sodium concentrations were altered by 0, 1.0, 1.5, and 2.0 mmol/L Na+ for qualitative assessment of the effects of changes in sodium concentrations in spiked lithium samples.

As mentioned earlier, spectrophotometric measurements showed two minima bands around 560 and 605 nm that related to the presence of lithium in blood samples. To eliminate the need for broad range spectral data for diffuse visible spectroscopy, which can complicate the implementation of this method into a simple and personal monitoring device, optical wavelengths which expressed the highest regression coefficients were selected and used as input into dual wavelength optical analysis. These were obtained by extracting minima values around the selected regions from full range spectra. Linear regression analysis was then performed to test the possibility of calibration and prediction accuracy of lithium in blood using dual wavelength measurement. Validations were carried out by testing samples with unknown blood lithium concentrations. The descriptive statistics summarized in Table III provide an overview of the mean and standard deviation of the samples used in this analysis.

Table IV summarizes the prediction statistics and the performance of the regression analysis with selected feature wavelengths. Low performance for both calibration (R2 = 0.2972) and prediction of lithium (R2 = 0.322716) was observed using the dual wavelength method, as well as higher estimation of calibration error (RMSEC = 0.3036). The measured versus predicted blood lithium levels and error of estimation resulting from the regression are illustrated in Fig 6.

For further comparison of the optical method in relation to

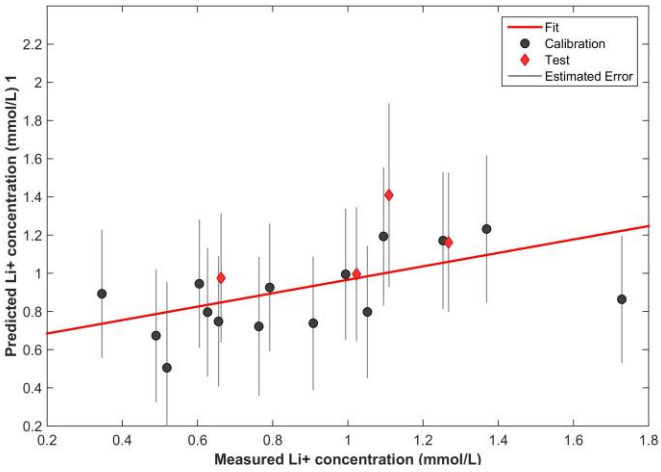

Fig 6. Measured versus predicted concentration of lithium ion in blood (plasma) using dual wavelength optical measurements only.

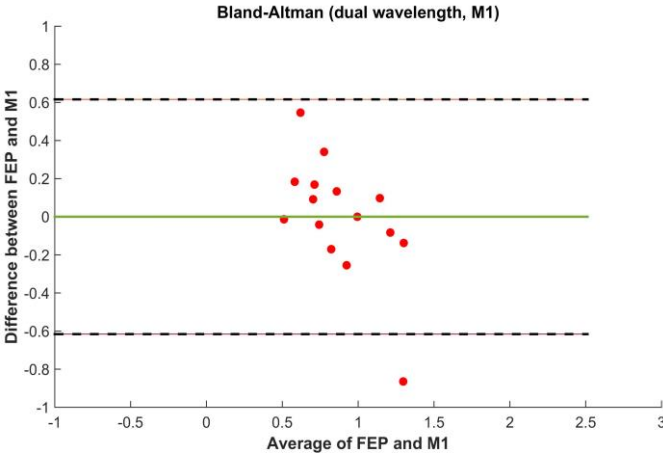

Fig 7. Bland Altman plot showing the difference against the average of dual wavelength method and standard FEP measurements of blood lithium concentration. Broken line (----) indicates the limits of agreement

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reference FEP measurements, agreement analysis was performed using the Bland Altman method. The resulting plot is shown here in Fig 7. General agreement is evident between optical and reference FEP measurements. Though a single variable is present outside the confidence limit and the magnitude of variation i.e. the confidence limits, are evidently large (-0.6 to 0.6 mmol/L) in relation to the required sensitivity for discriminating blood lithium levels within the therapeutic range.

B. Impedance Spec. results

Electrical impedance measurements of blood plasma only and blood plasma with dissolved Li_2CO_3 are shown in Table II and Fig. 8. A reduction in the mean impedance magnitude is observed from the plasma only solution with increasing Li_2CO_3 concentration (Table II). The calculated t-values reflect the difference in mean impedance magnitude between samples with the null hypothesis that there is no significant difference between them. Fig. 8(top) shows a plot of the change in the mean impedance magnitude (absolute change) with increasing Li^+ concentration. There is no significant change in the observed impedance phase as shown in Fig. 8(bottom). This, however, is expected as blood plasma contains only protein molecules, water and ions and thus can be considered as a conductive solution with the absence of any reactive species. Cell membranes can be considered as reactive species as they behave like tiny imperfect capacitors due to their bilayer structure and blood plasma is free of any cell-like structures.

TABLE II
ELECTRICAL IMPEDANCE MEASUREMENTS OF BLOOD PLASMA ONLY AND BLOOD PLASMA WITH DISSOLVED Li_2CO_3. MEAN VALUES FOR A BANDWIDTH BETWEEN 30 KHZ AND 300 KHZ.

Concentration (mM)*	$\|Z\| \pm$ SE (Ω)**	$\|t\|^{***}$	$\varphi(Z) \pm$ SE (deg.) **
Plasma only	3225.33 ± 1.66	-------	-5.44 ± 0.01
0.49	3210.87 ± 0.89	17.10	-5.49 ± 0.01
0.61	3200.72 ± 2.39	8.88	-5.52 ± 0.01
0.66	3178.52 ± 1.13	18.74	-5.48 ± 0.01
0.79	3167.04 ± 3.04	7.91	-5.47 ± 0.01
0.99	3154.34 ± 3.62	6.01	-5.44 ± 0.01
1.10	3148.58 ± 2.25	3.02	-5.43 ± 0.01
1.37	3145.40 ± 0.77	2.98	-5.43 ± 0.01
1.86	3140.41 ± 1.47	6.69	-5.42 ± 0.01

* Li^+ concentration ** Mean *** $t_{[0.05]}=1.86$ ($df=N1+N2-2$), $N1=N2=5$

Hence changes to the concentration of dissolved species would be reflected to changes in the impedance magnitude (due to change in the ionic content) and not to the phase (due to absence of any reactive species). Measured results indicate the suitability of the method to detect changes in the concentration of Lithium in blood plasma to <0.1mM. Error bars show the standard error in the reading taken from five individual measurements of the same solution.

C. Opto-impedance Spec. results

As mentioned earlier, electrical impedance measurements of spiked blood samples were capable of rapid and very accurate i.e. in the order of 0.1 mEq, determinations of conductivity in relation to changes in concentration of lithium ions. For the same sets of samples, spectrophotometric measurements showed two minima bands around 560 and 605 nm which related to the presence of lithium in blood samples, but with a lower degree of accuracy for predicting lithium concentration (around 55%), and even lower when considering selected feature wavelengths alone. Thus, optical measurements provide sufficient specificity for detecting lithium, whilst the method of electrical impedance offers exceptional accuracy in conductivity variations, but lacks specificity to a single element. For this reason, it is believed that the integration of optical and impedance measurement can provide an improved method for lithium determinations in blood.

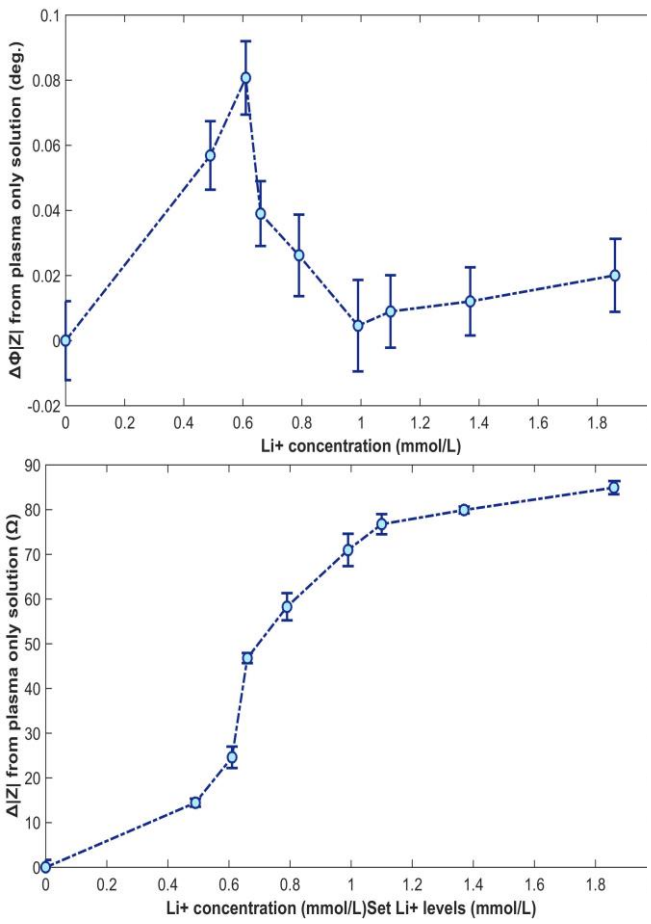

Fig 8. Results of changes in impedance (top) and phase (bottom) in relation to blood lithium concentrations.

TABLE III
DESCRIPTIVE STATISTICS OF REFERENCE FEP READ AND PROCESSED DATA OF EI AND FEATURE WAVELENGTHS OF OPTICAL MEASUREMENTS

	No of samples	**Min**	**Max**	**Mean**	**Std. Deviation**
FEP	15	0.3458	1.7289	0.8798	0.3749
Wavelength_1	15	-0.0070	0.0730	0.0290	0.0238
Wavelength_2	15	-0.0144	0.1439	0.0467	0.0404
Impedance	15	14.4555	96.6063	52.1171	27.3521

TABLE IV
COMPARISON OF PREDICTION ABILITY OF BLOOD LITHIUM LEVELS WITH MLR ANALYSIS USING FEATURE OPTICAL WAVELENGTHS, AND COMBINED OPTO-IMPEDANCE MEASUREMENTS.

	Calibration		Cross-validation		Prediction	
	Dual λ	**Opto-Impedance**	**Dual λ**	**Opto-Impedance**	**Dual λ**	**Opto-Impedance**
RMSE	0.303625	0.107321	0.334277	0.151728	0.223602	0.513554
Bias	0	1.11022e-16	-0.0118774	-0.00338763	0.119889	0.425177
R^2	0.297209	0.912195	0.17172	0.824603	0.322716	0.876438

Using the data acquired from the optical wavelengths which expressed the highest regression coefficients, together with measurements of electrical impedance, linear regression analysis was performed to test the possibility of calibration and prediction accuracy of lithium in blood using opto-impedance measurement. The descriptive statistics summarized in Table III provide an overview of the mean and standard deviation of the samples used in the analysis i.e. the two feature wavelengths from optical measurements and impedance data.

Similar to the previous analysis, mean centering and cross-validation through the leave-one-out were performed on the data prior to regression. Input data were also normalized to a length of 1 to account for differences between optical and impedance measurement. The precision and accuracy of the regression analysis was evaluated by using a set of samples with unknown lithium content as input for validation. These were prepared as described in Section 2(a).

Table IV summarizes the prediction statistics and the performance of the regression analysis with combined optical and impedance measurements. In this case, the addition of impedance measurements had a significant influence on improving the calibration and prediction of lithium levels in the blood samples. Compared to optical measurements alone, opto-impedance analysis had good performance for both calibration (R2 = 0.9122) and cross-validation (R2 = 0.824603), and the concentration of lithium in blood samples can be predicted with an accuracy of R2 = 0.8764, although its prediction error (RMSEP = .5136) was higher compared to that of the dual wavelength method (RMSEP = 0.2236). The measured versus predicted blood lithium levels and error of estimation resulting from regression of opto-impedance measurements are illustrated in Fig 9.

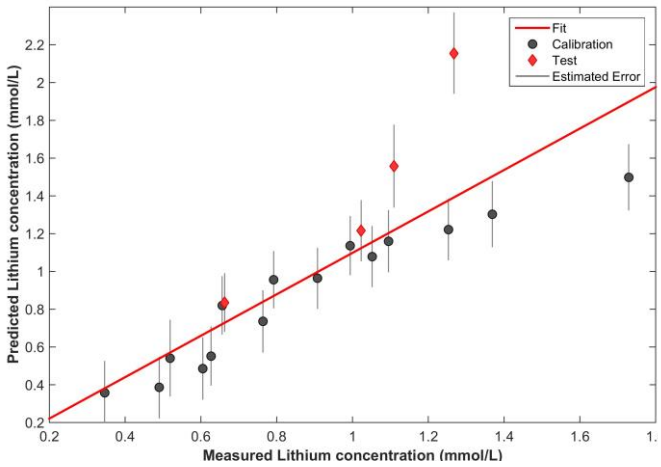

Fig 9. Measured versus predicted concentration of lithium ion in blood (plasma) using improved opto-impedance method.

In addition, Bland Altman analysis of agreement between opto-impedance and standard FEP measurements showed closer agreement between the two methods (Fig 10) in comparison to optical measurements alone, shown earlier in Fig 7. A reduction in the magnitude of variation is also evident, this time ranging between -0.2-0.2 mmol/L, which is sufficient to discriminate lithium levels within its therapeutic range, and similar to Fig 7, a single outlier is observed, though the magnitude of variation is less.

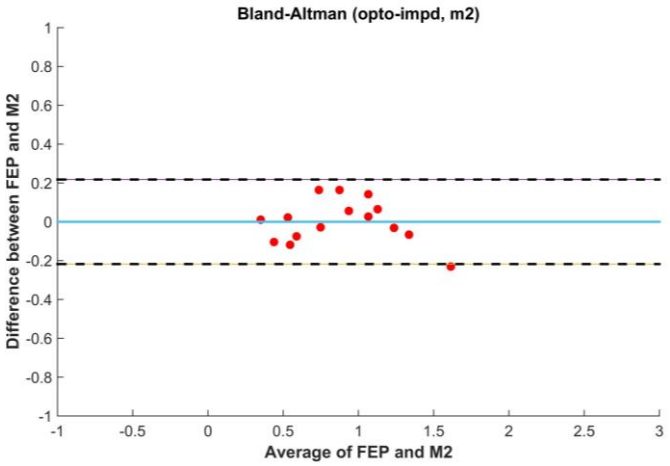

Fig 10. Bland Altman plot showing the difference against the average of opto-impedance and standard FEP measurements of blood lithium concentration. Broken line (----) indicates the limits of agreement.

IV. Conclusions

A combined method of spectrophotometric and electrical impedance measurement on blood plasma containing lithium levels in the therapeutic range normally found in Bipolar patients being treated with lithium medication was investigated. Using each method separately, it was found that electrical impedance is capable of highly accurate conductivity measurement, which can detect changes in lithium

concentration in the order 0.1mmol/L, whereas optical measurements were able to verify the presence of lithium in blood samples and provide some degree of lithium content. Specificity to lithium was further verified in qualitative assessment of lithium spiked blood samples with varying concentrations of sodium.

Results of multiple linear regression performed once using only feature wavelengths of optical measurements and again using the proposed combination method, showed significant improvement in both calibration and prediction with opto-impedance measurement, as well as reduced error of calibration and cross validation. Using blood (plasma) samples with unknown lithium content, the opto-impedance method provided considerably better prediction of lithium content and reduced error of measurement between samples.

In conclusion, combined optical and electrical impedance analysis can be most complementary particularly in this case, providing the benefit of both specificity and accuracy to lithium blood content. Future work will focus on further technical development of an integrated and miniaturized system suitable for personal monitoring of blood lithium levels in Bipolar patients.

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