Analytical Model for Real Time, Noninvasive Estimation of Blood Glucose Level

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Abstract — **The paper presents an analytical model to estimate blood glucose level from measurements made non-invasively and in real time by an antenna strapped to a patient's wrist. Some promising success has been shown by the RIT ETA Lab research group that an antenna's resonant frequency can track, in real time, changes in glucose concentration. Based on an in-vitro study of blood samples of diabetic patients, the paper presents a modified Cole-Cole model that incorporates a factor to represent the change in glucose level. A calibration technique using the input impedance technique is discussed and the results show a good estimation as compared to the glucose meter readings. An alternate calibration methodology has been developed that is based on the shift in the antenna resonant frequency using an equivalent circuit model containing a shunt capacitor to represent the shift in resonant frequency with changing glucose levels. Work under progress is the optimization of the technique with a larger sample of patients.**

I. Introduction

With the rapid advances of medical technology, Radio Frequency (RF) techniques are becoming increasingly popular for a variety of applications such as non-invasive diagnosis, continuous monitoring of physiological data, communication between implanted devices, and communication to external devices. The RF Medical Applications include pacemakers, implantable cardioverter defibrillators, neuro-stimulators, implantable drug delivery systems, sensors and diagnostics. The noninvasive RF applications are Magnetic Resonance Imaging (MRI), RF Electrocardiogram (ECG), microwave imaging etc.

Another emerging RF technology is a class of noninvasive glucose monitoring techniques being aggressively pursued by researchers. The notable ones are interstitial fluid chemical analysis, breath chemical analysis, infrared spectroscopy, optical coherence tomography, Raman spectroscopy, thermal spectroscopy, ocular spectroscopy, ultrasound, fluorescence and impedance spectroscopy [1]. A recent release, the GlucoTrack, [2] uses ultrasound, electromagnetic and thermal techniques. Another noninvasive system of interest is the one by Google, which is a contact lens that measures the glucose level in tears [3]. The success of all the above methods is still to be seen.

The frequency and power allocations for the medical applications are regulated by Federal Communications Commission (FCC), and authorized by U.S Food and Drug Administration (FDA) [4]. The radiation limits for all the medical applications comply by FCC regulations defined in [5] and [6]. There are frequency allocations for each application for communication between implants or to a monitoring device as summarized in Table I.

Table I Frequency Allocation

Application	Frequency	Distance for communication
Inductive coupling	< 200kHz	< 1 foot
RF devices and medical Micro Power Networks	401MHz- 457 MHz	A few feet
Wireless Medical Telemetry	608 – 614 MHz, 1395 – 1400 MHz 1427 – 1432 MHz	several hundred feet
Medical Body Area Networks	2.36GHz – 2.4GHz	A few feet
Wi-Fi, Bluetooth Zigbee	2.4 GHz and 5.8 GHz	A few hundred feet
Ultra wideband	3GHz – 10.6 GHz	A few feet

The objective of the present work is to develop an analytical model to estimate blood glucose level from non-invasive measurements made in real time by an antenna strapped to a patient's wrist. Some promising success has been shown by the RIT ETA Lab research group that the antenna's resonant frequency can track, in real time, changes in glucose concentration An equivalent circuit model containing a shunt capacitor has been developed to represent the shift in resonant frequency with changing glucose levels from which the increase in glucose level is obtained. This is compared with the calibration developed earlier by our research group based on changes of the antenna's input impedance.

II. Effect of Glucose on Dielectric Properties of Blood

A. In-vitro measurements of blood samples

We, at the Rochester Institute of Technology, partnered with the State University of New York at Buffalo to perform an in-vitro study [7] on 10 patient volunteers with glucose levels ranging from normal (87 mg/dl) to (330 mg/dl). Using the Agilent 85070E dielectric probe and an Agilent 8720B network analyzer, we measured the dielectric permittivity and conductivity of the blood samples in a frequency range of 500MHz – 8GHz (Figure 1).

The Cole-Cole model (1), [8-10] offers an efficient and accurate representation of biological tissues over a wide range of frequencies. The complex permittivity $\varepsilon(\omega)$ is given

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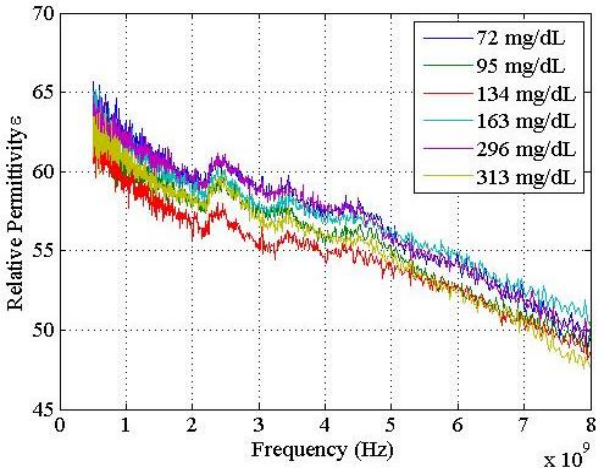
in (1) where ε_s and ε_∞ are the static and infinite frequency dielectric constants, $\Delta\varepsilon = \varepsilon_s - \varepsilon_\infty$, ω is the angular frequency and τ is the relaxation time constant. The exponent parameter α_n allows for the broadening of the dispersion.

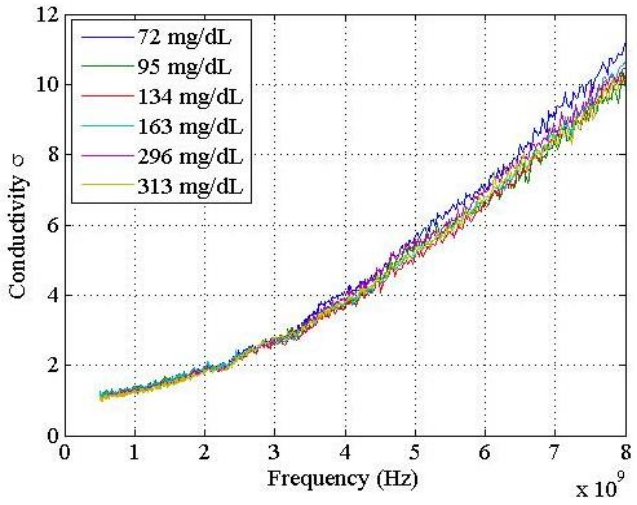
The model in (1) is modified to include the change in glucose level. This is done by curve fitting in-vitro measurements (figure 1), to obtain the parameters σ, $\Delta\varepsilon_1$ and α_1 and theses are given in Table II. The variation of $\Delta\varepsilon_1$ with changes in glucose level, Δg, is introduced into the Cole-Cole model and the modified expression is given by (2). The relative permittivity obtained using (2) is shown in Figure 2 for the same glucose levels corresponding to the in-vitro measurements,

$$\varepsilon(\omega) = \varepsilon_\infty + \frac{\Delta\varepsilon_1}{1+(j\omega\tau_1)^{(1-\alpha_1)}} + \frac{\Delta\varepsilon_2}{1+(j\omega\tau_2)^{(1-\alpha_2)}} + \frac{\sigma}{j\omega\varepsilon_0} \quad (1)$$

$$\varepsilon(\omega) = \varepsilon_\infty + \frac{\Delta\varepsilon_1 - 0.0462\Delta g}{1+(j\omega\tau_1)^{(1-\alpha_1)}} + \frac{\Delta\varepsilon_2}{1+(j\omega\tau_2)^{(1-\alpha_2)}} + \frac{\sigma}{j\omega\varepsilon_0} \quad (2)$$



(a) Dielectric Permittivity vs Frequency



(b) Dielectric Conductivity vs Frequency

Figure 1 In-vitro Measurements of dielectric permittivity and conductivity

Table II. Parameters for Cole-Cole and Modified Cole-Cole Model

Parameter	Cole-Cole Model	Modified Cole-Cole Model
σ	0.7	0.4
$\Delta\varepsilon_1$	56	56.875
α_1	0.1	0.064

$\varepsilon_\infty = 4$; $\Delta\varepsilon_2 = 5200$; $\alpha_2 = 0.1$; $\tau_1 = 8.38 \times 10^{-9}$ (s); $\tau_2 = 132.63 \times 10^{-9}$ (s). Δg is the change in glucose level with respect to initial reading.

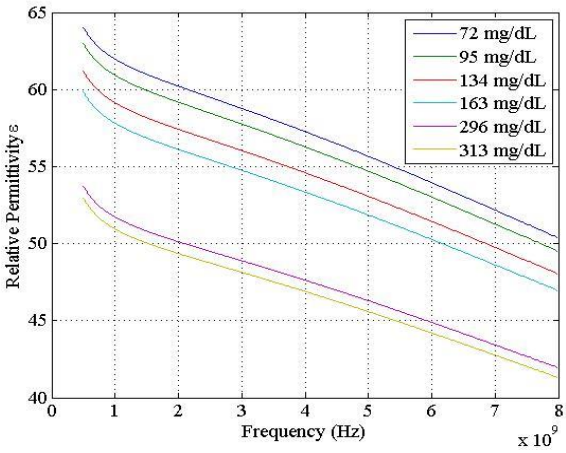
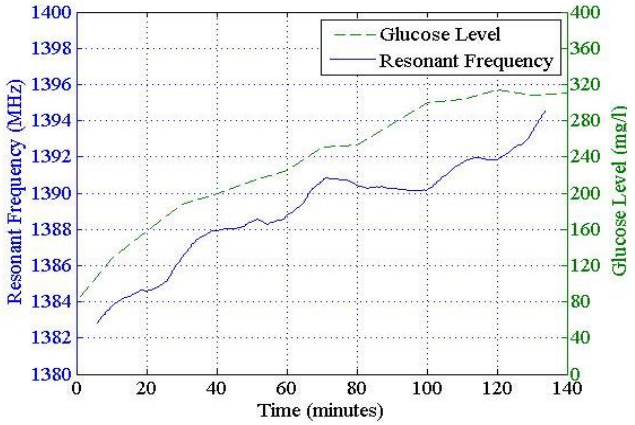


Figure 2 Modified Cole-Cole Model obtained by curve fitting in-vitro measurements

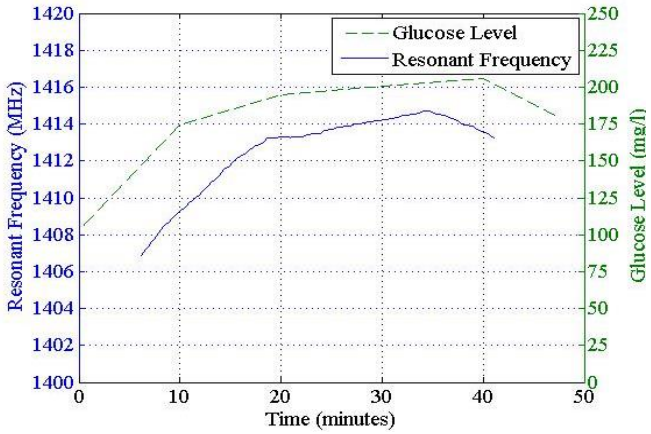
It is known that the permittivity of blood decreases with glucose level [11]. This behavior is seen for the set varying from 72mg/dl to 134 mg/dl and not for the higher glucose levels. Perhaps this may be the effect of other chemicals contained in blood such as sodium or potassium. More in-vitro studies will be done to clarify this. The technique presented in this paper, uses the antenna response that is based on the cumulative effect of tissue and blood composition of an individual human subject. While we make measurements in real time on an individual, it is reasonable to assume that the changes in the antenna's response are solely due to the rising glucose level. In conclusion, it shows that a calibration is necessary for each individual patient.

A. Input Impedance Method for Glucose Level Estimation

The technique utilizes a planar dipole to measure input impedance and resonant frequency. The antenna, strapped on the arm of a patient, is connected to a network analyzer automated to make measurements every 15 seconds, figure 1. The resonant frequency vs. time is shown in Figure 3, for a diabetic and a non-diabetic patient after a eating a meal. A traditional glucose meter was used to measure glucose levels every ten minutes. It is seen that the antenna successfully tracks changes in glucose level as stated in [7]. The solid line is the glucose level measured by a glucose meter and the dashed line is the resonant frequency of the antenna. It is seen that here is a significant difference in the range of blood glucose and resonant frequency between the diabetic and non-diabetic subjects. This validates our claim that a calibration, unique to each patient, is necessary.



(a) Diabetic Patient.



(b) Non-Diabetic Patient

Fig. 3 Relationship between Glucose Level and Resonant Frequency for Diabetic and Non-Diabetic Patients

An equivalent circuit model, shown in Fig. 4, is developed where the elements are dependent on glucose level. The final equation of the model is given in (3) [12].

$$Zin = \frac{(\omega(A_3\Delta g^{-1.45})(j(Z_a + A_1\Delta g^{-0.8}) - \omega Z_a(A_1\Delta g^{-0.8})(A_2\Delta g^{-1.8})))}{j\omega Z_a(A_1\Delta g^{-8})(A_3\Delta g^{-1.45}) + Z_a + A_1\Delta g^{-0.8} + \omega^2(A_3\Delta g^{-1.45})(A_2\Delta g^{-1.8})(Z_a + A_1\Delta g^{-0.8})} \quad (3)$$

Z_a is the input impedance at initial reading;
Δg is the change in glucose level with respect to initial reading.

From a second measurement of input impedance made on the same patient, using (3) the glucose level is estimated. Table III shows there is a good comparison using the calibration and that measured by a glucose meter.

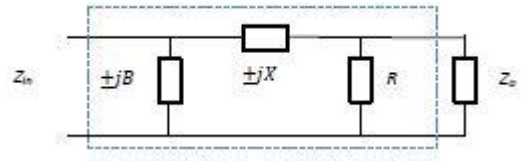


Fig. 4 Equivalent Circuit Model Representing Changing Input Impedance

Table III. Blood Glucose Estimate from Antenna Input Impedance

Time (min)	Δg (mg/dl) solved using (3)	Glucose Estimate (mg/dl)	Actual Glucose (mg/dl) from glucose meter
0		88	88
11	68	156	175
25	124	212	210
30	134	222	223
36	149	237	234
78	153	241	228
88	127	215	205

Za = 41.71 – j6.06 Ω

B. Resonant Frequency Method

The calibration using the input impedance method works well. However, the time period for gathering the data which extends from the initial glucose value to the highest value can get to be quite long. To address this issue, this work investigates another technique using shift in the antenna resonant frequency. The input impedance at two glucose levels (72mg/dl) and (330mg/dl) is illustrated in Figure 5. Resonant frequency is defined when, simultaneously, the imaginary part of the input impedance goes to zero and the real part becomes a maximum.

A typical resonant circuit contains capacitive and inductive elements. Since the dielectric permittivity is the key parameter that changes with glucose level, and is also seen to decrease with glucose levels, the capacitance would decrease and result in an increase of the resonant frequency. This behavior is consistent with the results in Figure 3 and Figure 5. An equivalent circuit to represent this behavior is shown in Figure 6.

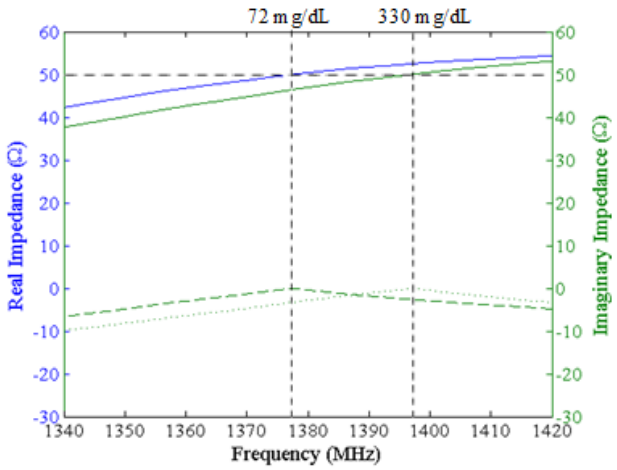


Fig. 5 Antenna Input Impedance with changing glucose level

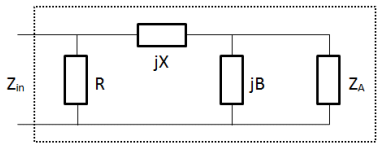


Fig. 6 Equivalent Circuit to Represent Changing Resonant Frequency

The parameters R, L and C are calculated which are dependent on glucose levels. The equations relating the parameters with glucose level are given in (4), (5) and (6). Based on these equations, input impedance, from Fig. 6, is calculated using equation (7) at every time instant. The resonance is defined as the imaginary part of the impedance equating to zero and hence at every step, a resonant frequency is obtained.

$$R = A_1 \Delta g^{B_1} \quad (4)$$

$$L = A_2 \Delta g^{B_2} \quad (5)$$

$$C = A_3 \Delta g^{B_3} \quad (6)$$

where $A_1 = 15425, A_2 = 1.0071, A_3 = 114.3$ and $B_1 = -0.484, B_2 = -0.342, B_3 = 0.101$

$$Zin = \frac{(Z_A A_1 \Delta g^{B_1} - \omega^2 A_1 \Delta g^{B_1} A_2 \Delta g^{B_2} A_3 \Delta g^{B_3} Z_A + j\omega A_1 \Delta g^{B_1} A_2 \Delta g^{B_2})}{(Z_A - \omega^2 A_2 \Delta g^{B_2} A_3 \Delta g^{B_3} Z_A - \omega^2 A_1 \Delta g^{B_1} A_2 \Delta g^{B_2} A_3 \Delta g^{B_3} + j(\omega A_2 \Delta g^{B_2} + \omega A_1 \Delta g^{B_1} A_3 \Delta g^{B_3} Z_A)} \quad (7)$$

The relationship between the change in resonant frequency and the change in glucose level is given in (8). Based on these equations, the change in glucose level is estimated. Table IV gives the comparison between actual glucose levels with estimated glucose levels. Fig. 7 gives the Clarke Error Grid analysis for the predicted results.

$$\Delta g = A_4 \Delta f^{B_4} \quad (8)$$

where $A_4 = 2.8622$ and $B_4 = 1.7411$

Table IV. Blood Glucose Estimate from Resonant Frequency

Time (min)	Δf (MHz)	Δg (mg/dl) solved using (7)	Glucose Estimate (mg/dl)	Actual Glucose (mg/dl) from glucose meter
0			89	89
30	7.3125	91	180	199
54	9.1875	136	225	229
82	10.125	161	250	260
90	10.875	182	271	272
106	12.1875	222	311	310
120	12.375	228	327	326

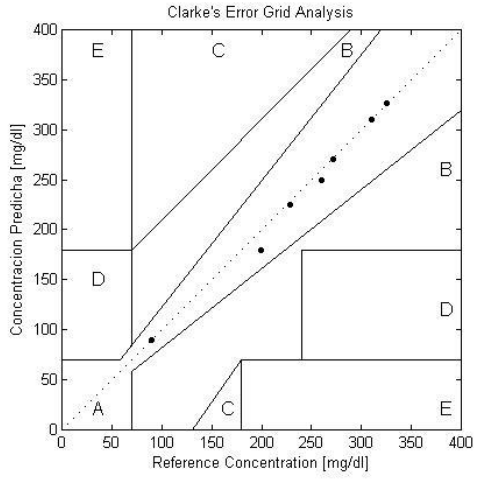


Fig. 7 Clarke Error Grid Analysis Results

III. Conclusion

Based on an in-vitro study of blood samples of diabetic patients, the paper presents a modified Cole-Cole model that incorporates a factor to represent the change in glucose level. A calibration technique using the antenna's input impedance is discussed and the results show good blood glucose estimation as compared to the glucose meter readings. An alternative calibration methodology has been developed that is based on the shift in the antenna resonant frequency. The estimated glucose level results based on resonant frequency technique shows good correlation with the actual glucose levels proven by the Clarke Error Grid analysis.

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