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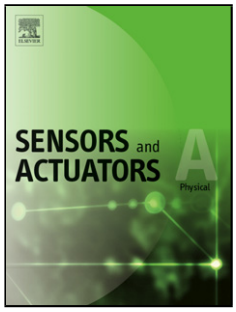

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Permittivity Extraction of Glucose Solutions Through Artificial Neural Networks and Non-invasive Microwave Glucose Sensing

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Highlights

- Accurate permittivity model for glucose/water solutions is vital for sensor simulations
- Appropriate RF sensor design is needed for achieving high sensitivity
- The small change in blood glucose levels is challenging to measure
- Challenges and sources of problems in glucose concentration measurement

Abstract:

An accurate low-cost method is presented for measuring the complex permittivity of glucose/water solutions. Moreover, a compact non-invasive RF/microwave sensor is presented for glucose sensing with the reasoning behind design parameters as well as simulation and measurement results. The complex permittivity values of aqueous solutions of glucose were measured with an in-house manufactured open-ended coaxial probe and the values were extracted from the measured complex reflection coefficients (S11) utilizing artificial neural networks. The obtained results were validated against a commercial probe. The values were fitted to the Debye relaxation model for ease of evaluation for a desired glucose concentration at a desired frequency. The proposed permittivity model in this paper is valid for glucose concentrations of up to 16 g/dl in the 0.3-15 GHz range. The model is useful for simulating and validating non-invasive RF glucose sensors.

Keywords: Blood glucose, non-invasive, RF sensor, permittivity, measurement

1. Introduction

Diabetes Mellitus (DM) is a disease associated with high blood glucose levels (BGL) affecting over 400 million people worldwide [1]. The normal glucose level in the blood ranges from 72 mg/dl to 108 mg/dl whereas patients with DM may experience levels as high as 400mg/dl. In this case, the glucose level needs to be regulated through medication or insulin shots to reduce the chance of long-term negative health effects [2]. The conventional measurement methods are invasive where an accurate BGL measurement can be taken at health clinics/hospitals. However, portable BGL

measurement devices are widely used by patients for convenience that allow for an instant reading, anytime and anywhere. This method requires a small drop of blood, which is usually obtained from a pricked fingertip, to be applied onto a test strip. The test strip is then inserted into the measurement device for a BGL reading. Depending on the severity of the disease, a patient may need to take up to 10 measurements a day, which causes discomfort. Furthermore, the blood contaminated consumables such as test strips and needles should be disposed of properly to avoid the spread of blood-related diseases. A non-invasive measurement device is highly desirable to avoid the discomfort and the aforementioned risks. There are various methods that researchers have been working on to measure BGL non-invasively [3-5]. One of the popular and promising methods is the Radio Frequency (RF)/microwave sensing where an RF sensor is used to measure the change in the dielectric properties of blood [6, 7].

Each biological tissue has its own set of electrical properties. Dielectric spectroscopy is deployed to investigate the complex permittivity of tissues and observe possible changes. The most common method is to use an open-ended coaxial probe, which is commercially available through several manufacturers. This method is useful for characterizing the dielectric properties of tissues but not applicable as a direct BGL measurement method as the measurement setup is bulky and measurement sensitivity does not provide the resolution needed for tracking the small changes in BGL. A more suitable way of investigating the dielectric properties of tissues is to use a resonant planar resonator for direct BGL measurements. These are easy to fabricate, cost-effective and they offer flexibility in the design. When a resonator comes in contact with a tissue, the radiated electromagnetic (EM) waves interact with it and the resonator's frequency response is affected by this [8]. By carefully examining these

changes, one can estimate the electrical characteristics of the tissue. Changing glucose level in the blood causes a variation in the dielectric properties of the blood. Therefore, this change can be measured to work out the glucose level. Human blood contains glucose, other necessary substances as well as water, which constitutes about 50% of its volume. Additionally, 92% of blood plasma is made up of water by volume [9]. For this reason, blood can be approximated by glucose/water solution as an initial step for the purpose of designing and validating a non-invasive RF sensor. Hence, an accurate model for the complex permittivity of aqueous solutions of glucose is essential. A model was proposed by the authors in [10,11], which was then extended in this work. Moreover, the reasoning behind the selection of design parameters e.g. resonator type, operation frequency, in RF glucose sensors is mostly overlooked and not elaborated on in the open literature. Thus, the fundamental parameters for RF glucose sensor design are explained in this paper along with an appropriate sensor design. The characterization of the dielectric properties of aqueous solutions of glucose, the parameters for the proposed permittivity model and the designed sensor with measured results are given and elaborated on in the following sections of this paper.

2. Debye complex permittivity model and measurement of aqueous solutions of glucose

Cole-Cole relaxation model, (1), is commonly used for modelling the complex permittivity of materials [12]:

$$\varepsilon^*(\omega) = \varepsilon' - j\varepsilon'' = \varepsilon_\infty + \frac{\varepsilon_s - \varepsilon_\infty}{1 + (j\omega\tau)^{1-\alpha}} + \frac{\sigma_s}{j\omega\varepsilon_0} \quad (1)$$

where ε' $\varepsilon^{'}$and ε'' are the dielectric constant and dielectric loss factor values of a material, respectively, ε_∞ is the permittivity at infinite frequency, ε_s is the static permittivity, ω is the angular frequency, τ is the relaxation time, σ_s is the static

conductance, ε_0 is the permittivity of free space, α is the exponent parameter. In case of $\alpha = 0$, the equation reduces to the Debye model. Furthermore, the term with the static conductance can be omitted for materials with low conductivity. These parameters are found in the published literature for many different materials and biological matter [13]. Aqueous solutions of glucose can also be modelled this way. For this purpose, measurements were taken with a coaxial probe and the permittivity values were extracted from the measured S11 values. These permittivity values were then fitted to the Debye model to obtain the parameters to be later used for sensor simulations.

2.1 The Proposed Open-Ended Coaxial Probe and the Permittivity Extraction Method

A compact low-cost probe was designed, simulated and manufactured. The main housing is made of brass where the copper center conductor is surrounded by a PTFE dielectric. The dimensions of the probe are shown in Fig. 1.

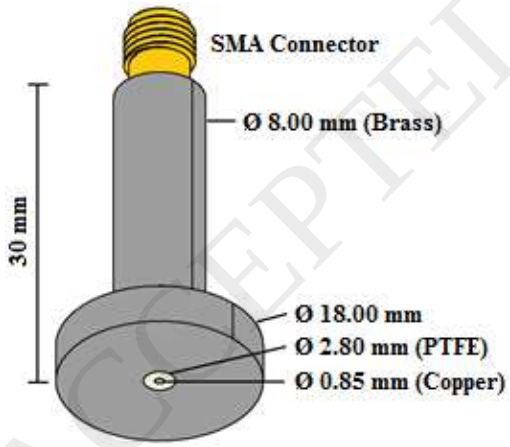


Fig. 1. Dimensions of the proposed open-ended coaxial probe

The dimensions were chosen based on similar probe designs in the open literature [14], which allows for measurements from about 500 MHz to 20 GHz range.

S-parameter measurements were taken on a Keysight N5227A PNA vector network analyzer (VNA). The extraction method published in [15, 25] was used to extract the permittivity values from the obtained S-parameters. First, a measurement was taken in air to calculate the phase shift introduced by the probe. Next, deionized water was measured at 25 °C to calculate the probe specific capacitance values. To validate the accuracy of the probe and the permittivity extraction process, liquids with very well-known dielectric properties were measured such as, ethanol, methanol, acetone and isopropyl alcohol. The extracted permittivity values were compared with the theoretical values computing using (1) with the parameters published in the literature. A deviation of about 30% was observed between the two. This could be due to measurement uncertainties and the simplicity of the calibration method.

To investigate the possibility of reducing the disagreement between the results using a heuristic approach, Artificial Neural Networks (ANN) were employed.

The following steps were applied to bring the confidence interval of the measurements to less than 3%:

1. The open-ended coaxial probe was modelled in CST Microwave Studio (MWS) software [16] and its physical parameters of the model were tweaked until simulation results and the actual measured S-parameter measurements (magnitude and phase) in air were in total agreement.

2.The model was simulated with the aforementioned liquids as well as other liquids with known dielectric properties.

3. A large dataset is required to appropriately train the ANNs in order to get accurate results. This was achieved by creating over ten digital synthetic liquid phantoms by arbitrarily assigning values to the variables in Debye equation (1) in addition to the known liquid phantoms. This allowed for generating a variety of

complex permittivity curves in the desired frequency range. The probe model was also simulated with these phantoms to obtain the S-parameters which substantially expanded the training dataset. This method allows for digitally measuring the probe's response for any liquid, hence, the dataset can be expanded as much as needed with variety of liquids which would otherwise be very hard or impossible to measure physically.

4. Complex permittivity values were extracted using the simulated S-parameters with the conventional method.

5. Complex permittivity values were separated into the real and imaginary parts.

6. Using the extracted and theoretical permittivity values, two feedforward ANNs were trained in MATLAB [17] using the Levenberg-Marquardt algorithm, one for the calculation of the real part and the other for the imaginary part. The optimum number of hidden nodes were found to be 11, less number of nodes resulted in large errors in the estimated permittivity values and more nodes resulted in over-training of the ANNs resulting in estimation errors if a liquid with very different permittivity characteristics was measured than that of the ANNs were trained with.

7. Finally, S-parameters are measured for any desired liquid, the permittivity values are extracted using the conventional method and the extracted values are fed into the trained ANNs for final permittivity values.

This method is especially useful as it can be used with in-house manufactured open-ended coaxial probes and any calibration/extraction method to achieve accurate results, without the need for sophisticated methods for calibration. Due to the large dataset used to train the ANNs, they are able to handle variations in S11 values. The structure of the ANNs is shown in Fig. 2.

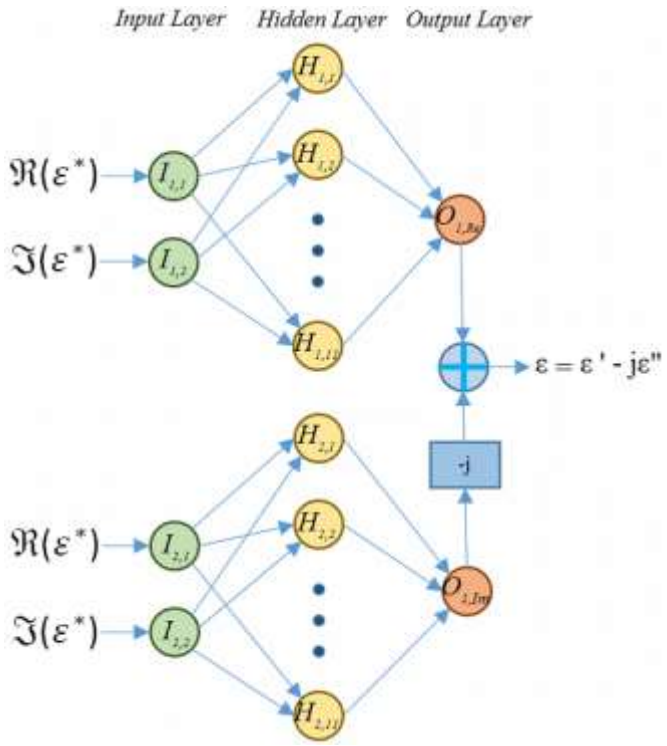


Fig. 2. Artificial Neural Network structure for permittivity extraction

Complex permittivity of aqueous solutions of glucose from 100 mg/dl to 500 mg/dl was measured in the 1-8 GHz band using the method explained and the measured data were published in [11].

2.2 Extended Proposed Debye Parameters for 0-16000 mg/dl Range in the 0.3-15 GHz Band

To validate the proposed model and extend it both in concentration and frequency ranges, concentrations from 1 g/dl to 16 g/dl were measured with a commercial dielectric probe (Speag DAK 3.5 [18]) on a Rohde & Schwarz ZVL13 VNA. The measured real and imaginary parts for the permittivity are shown in Fig. 3 and Fig. 4, respectively.

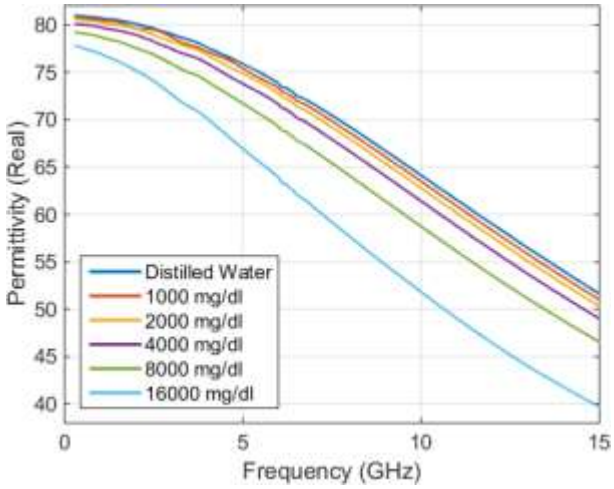


Fig. 3. Real part of the measured permittivity (0 to 16000 mg/dl)

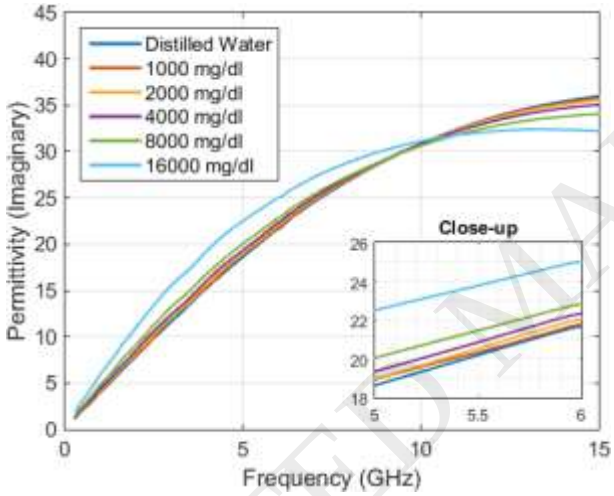


Fig. 4. Imaginary part of the measured permittivity (0 to 16000 mg/dl)

The trend reversal in the dielectric loss observed in Fig. 4 at about 10 GHz is associated with the orientation of the water and glucose molecules with the applied EM field.

The obtained results were fitted to the Debye model using 2nd order quadratic equations as follows:

$$\varepsilon_{\infty}(\chi) = a_n\chi^2 + b_n\chi + c_n \tag{2}$$

$$\varepsilon_s(\chi) = a_n\chi^2 + b_n\chi + c_n \tag{3}$$

$$\tau(\chi) = a_n\chi^2 + b_n\chi + c_n \tag{4}$$

where χ is the concentration of the glucose in mg/dl. The permittivity can be calculated in this range for any concentration value using (1) with the Debye parameters given in (2), (3) and (4) and the coefficients noted in Table 1.

	a_n	b_n	c_n
ε_∞	$-8.214x10^{-8}$	$2.148x10^{-3}$	8.722
ε_s	$2.318x10^{-9}$	$-2.793x10^{-4}$	81.015
$\tau\ (ps)$	$-8.370x10^{-9}$	$5.150x10^{-4}$	8.776

Table 1. Coefficients for the Proposed Debye Parameters

The previous proposed model and the extended model measured with the commercial probe were compared and the resulting error graph is shown in Fig. 5.

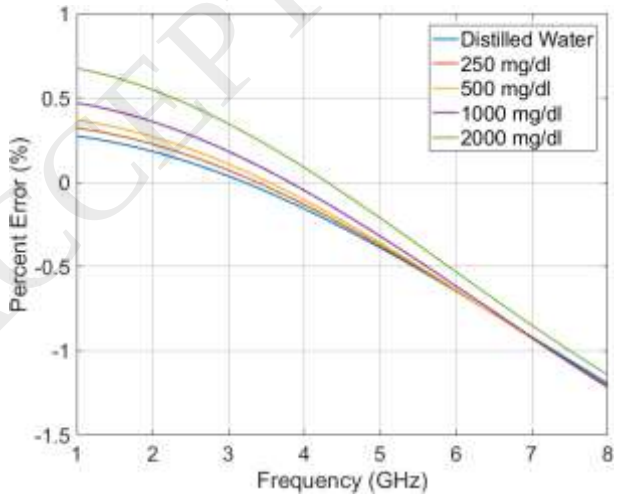


Fig. 5. Real part of the measured permittivity (0 to 16000 mg/dl)

3. Non-invasive RF Sensor Design

The parameters that need to be considered in non-invasive RF sensor design as well as the proposed compact sensor are explained in this section.

3.1 Preliminary Design Considerations

The fingertip is a popular site for measuring blood glucose due to having a good amount of fresh blood and homogeneity of the biological tissue layers present. However, this introduces a restraint in the sensor size as the fingertip is a small area. The sensor should be small enough to be covered by the fingertip when taking a measurement in order to constraint the EM fields inside the fingertip as much as possible. Otherwise, if the sensor is partially covered by the fingertip, different proportions of EM fields exist in the tissues as well as air [19]. This alters the sensor's frequency response making the measurements more prone to positioning errors. The fingertip can be modelled as four layers, namely, skin (1mm), fat (0.5mm), blood (5mm) and bone (4mm) layers [7] as shown in Fig. 6. The bone layer was added to mimic the structure of a fingertip.

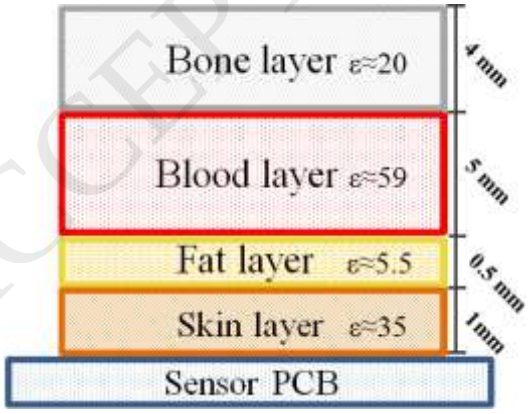


Fig. 6. The 4-layer fingertip model used for simulations

The size of the sensor and the penetration depth inside the tissues are defined by the frequency of operation of the sensor where the penetration depth is the predominant factor. To sense blood glucose, a sufficient amount of EM fields need to penetrate through skin and fat layers in the fingertip and reach the subcutaneous tissue where the blood capillaries exist. Biological tissues are lossy dielectric media where their conductivity value is greater than zero. This means that the EM fields are attenuated while propagating through the media.

The penetration depth is calculated by (5) and it is the distance where the RF power is reduced to $1/e$ $(e = 2.718)$ of its original value [20].

$$d_p = \frac{c}{2\pi f \sqrt{2\varepsilon' \left[\sqrt{1 + \left(\frac{\varepsilon''}{\varepsilon'}\right)^2} - 1\right]}} \tag{5}$$

where d_p is penetration depth in meters, f is frequency in Hertz, c is the speed of light in free space $(3x10^8 m/s)$. The penetration depth values for skin, fat and blood for 800MHz, 2400MHz and 4800MHz were calculated in MATLAB using (1) and (5) with the Cole-Cole parameters from [13] and are given in Table 2. The frequency points were chosen arbitrarily to demonstrate the trend of the changing penetration depth.

	Penetration depth (mm)		
	800 MHz	2400 MHz	4800 MHz
Skin	30.82	3.46	0.88
Fat	67.31	10.0	3.19
Blood	19.62	2.21	0.57

Table 2. Simulated Penetration Depth Values at Various Frequencies

This shows that a frequency too low results in a large penetration depth, causing the EM fields to propagate further than the layer of interest and a frequency too high

results in insufficient penetration. However, choosing a high frequency allows for sensor miniaturization. Hence, a trade-off must be made between penetration level and sensor size while selecting the frequency of operation.

Another attenuation mechanism is the intrinsic impedance mismatch between the layers shown in Fig. Each tissue has its own intrinsic impedance value given by (6) depending on its electrical parameters causing further attenuation.

$$\eta=\sqrt{\frac{j\omega\mu}{\sigma+j\omega\varepsilon}} \tag{6}$$

where;

$$\sigma = \omega\varepsilon''\varepsilon_0 \tag{7}$$

When an EM wave travels from a dielectric medium to another with a different permittivity value, part of the wave reflects back from the boundary due to the mismatch of the intrinsic impedance [21]. The reflection coefficient between two layers can be calculated using (11):

$$\Gamma=\frac{\eta_2-\eta_1}{\eta_2+\eta_1} \tag{8}$$

The reflection coefficient values were evaluated using (6), (7) and (8) in MATLAB and are given in Table 3.

	$\lvert\Gamma\rvert$		
	800 MHz	2400 MHz	4800 MHz
Skin-Fat boundary	0.441	0.445	0.449
Fat-Blood boundary	0.538	0.541	0.544

Table 3. Simulated Reflection Coefficient Values at Various Frequencies

It can be seen that the magnitude of the reflection coefficient does not vary much with the frequency. Assuming that the sensor impedance is matched to the skin's impedance at the desired frequency of operation and the finger is pressed firmly against the sensor, the EM fields will be mostly coupled to the skin and there will be about a 3 dB attenuation at each tissue boundary due to intrinsic impedance mismatch. This loss is for a single trip where multiple reflections are not taken into account and tissues are assumed to be aligned at the boundaries. A greater loss is expected in reality as the tissue boundaries are not perfectly aligned and the layers are not well defined since different biological layers are usually intertwined. In addition, blood is found in a complex network of capillaries together with the subcutaneous tissue. These factors create an uncertainty and present a challenge for the simulation and measurement of the glucose level.

3.2 The Proposed RF Sensor

A compact RF sensor was designed paying attention to the previously discussed parameters. The designed sensor is based on a one-port microwave resonator which acts as an antenna used for near-field radiation. Keeping the calculated penetration depth values in mind, the resonance frequency of the unloaded sensor was chosen to be 4.8 GHz, however, when the fingertip is placed on top of the sensor, the resonance frequency shifts down to about 3.25 GHz depending on the pressure applied [22]. The sensor was fabricated on a Rogers RO3006 laminate with a thickness of 32 mil and a dielectric constant of 6.5. The sensor has a main sensing area that resembles an interdigital capacitor for achieving high capacitance to maximize the electric field for increased sensitivity to permittivity change. The 50 Ω feed line is located at the back of the substrate as a coplanar waveguide and is connected to the resonator through a

plated via hole. This is to ensure that the fingertip does not come into contact with the feed line, possibly altering the sensor response. Other RF sensors found in the open literature such as [6,7,23,24] are large in size where the proposed resonator only occupies an area of 11 mm x 4 mm that can easily be fully covered by a fingertip. The layout of the designed sensor is shown in Fig. 7.

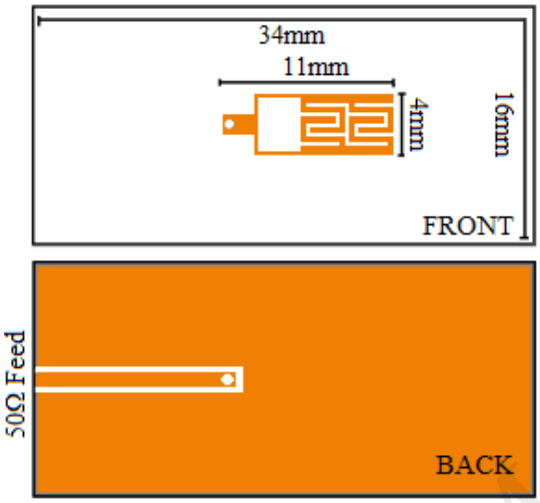


Fig. 7. Layout of the designed sensor

The sensor was simulated in CST MWS and measured in air for the unloaded response (no fingertip) using a VNA. It was also simulated with the 4-layer fingertip model and measured with an actual fingertip. The simulated and measured responses are shown in Fig. 8.

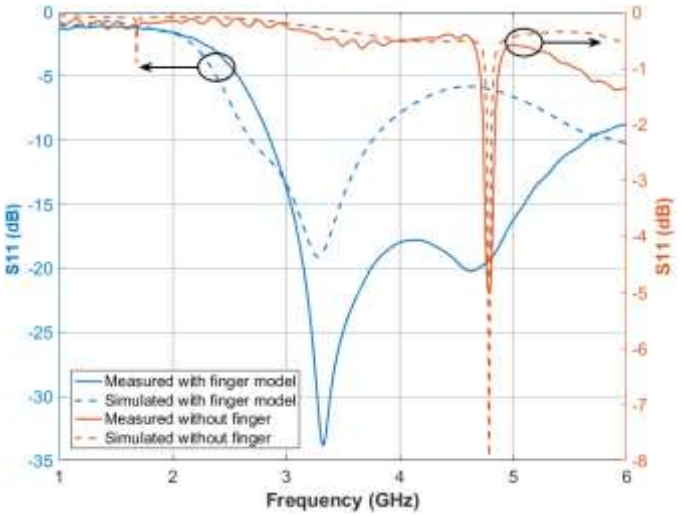


Fig. 8. Measured response of the sensor in air and with finger and simulated response of the sensor in air and with fingertip model

There is a good agreement between both when the sensor is unloaded. The simulated response with the fingertip model and the measured response with an actual finger show a resonant peak at the same frequency; however, it can be observed that the Q-factor of the sensor is lower in the measured case leading to a wideband resonance. This is due to the inaccuracies of the 4-layer fingertip model used in CST MWS and a more accurate model is difficult to achieve due to the complex nature of the tissues as explained previously. However, this model is a good starting point for simulations. Firstly, the sensor was simulated with only a glucose/water solution layer.. The resulting frequency shift is shown in Fig. 9.**Error! Reference source not found.** with a zoomed in section of the main resonance points. In this case, a frequency shift of 34 MHz was observed resulting in a deviation of 17 kHz/mg.dl^{-1}.

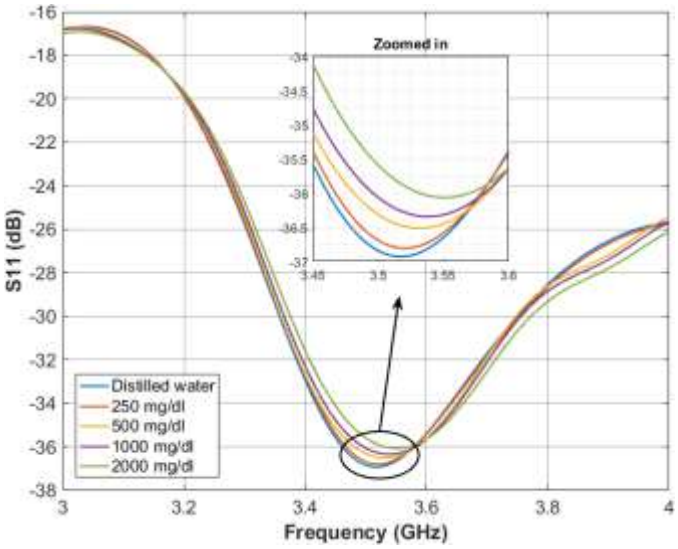


Fig. 9. Simulation results with 0mg/dl to 2000mg/dl glucose/water solution alone

Next, the sensor was tested with actual glucose/water solutions, where all measurements were performed at 25 °C. The sensor was inserted between two Perspex plates where the top plate had an opening above the sensing area. Liquid samples of 120 µl were placed in this opening to measure the frequency response of the sensor for the same concentration levels reported previously. The photograph of the sensor with the Perspex plates is shown in Fig. 10

Fig. 10. Sensor with the Perspex plates and sample opening

The obtained results are shown in Fig. 11.

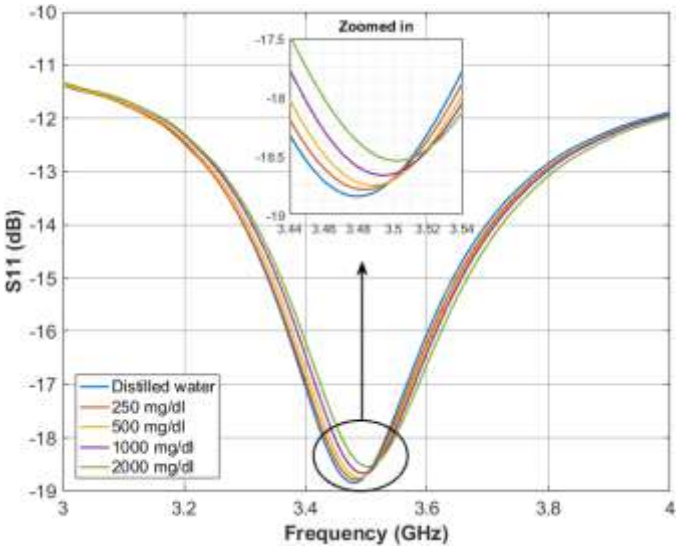


Fig. 11. Measurement results with 0mg/dl to 2000mg/dl glucose/water solution alone

A frequency shift of 32 MHz was observed between 0 mg/dl and 2000mg/dl range resulting in a deviation of 11 kHz/mg.dl^{-1}. The frequency shift is almost a linear function of the glucose concentration as shown in Fig. 12. Each sample was measured 10 times and the average frequency shift values were recorded along with the confidence interval. It can be observed that the measurement error is more likely with small concentration values.

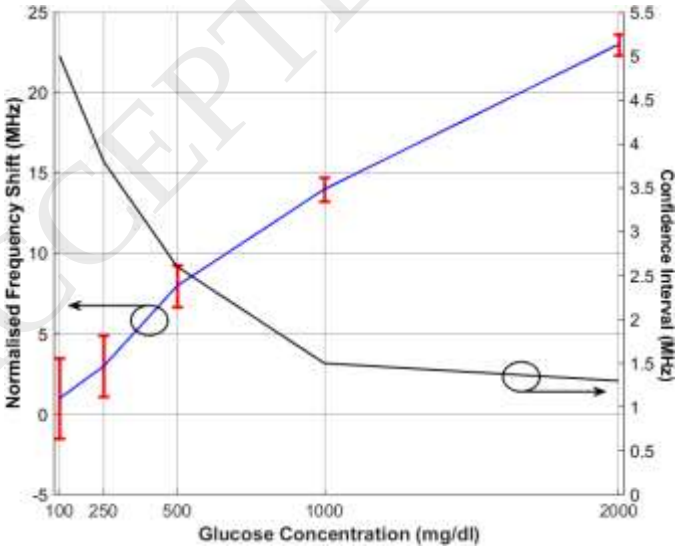


Fig. 12. Normalized frequency shift vs. glucose concentration and confidence interval

After this, the sensor was simulated with the 4-layer fingertip model to evaluate the effects of biological layers where the blood layer was replaced with the proposed glucose Debye model as an approximation to blood to test the sensor with 0 mg/dl (pure water) to 2000 mg/dl glucose solutions. The simulation results obtained are illustrated in Fig. 13 with a zoomed in section of the main resonance points. The resonance peak was observed at 3288 MHz for pure water and at 3292 MHz for 2000 mg/dl.

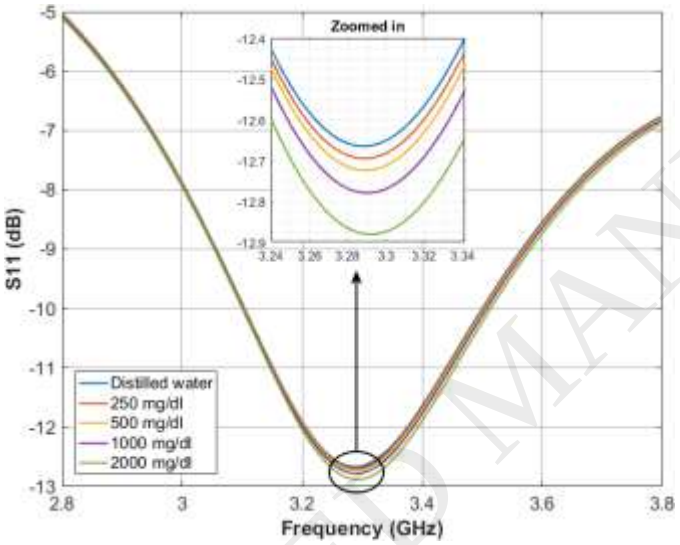


Fig. 13. Simulation results with 0 mg/dl to 2000 mg/dl glucose/water solution within the 4-layer fingertip model

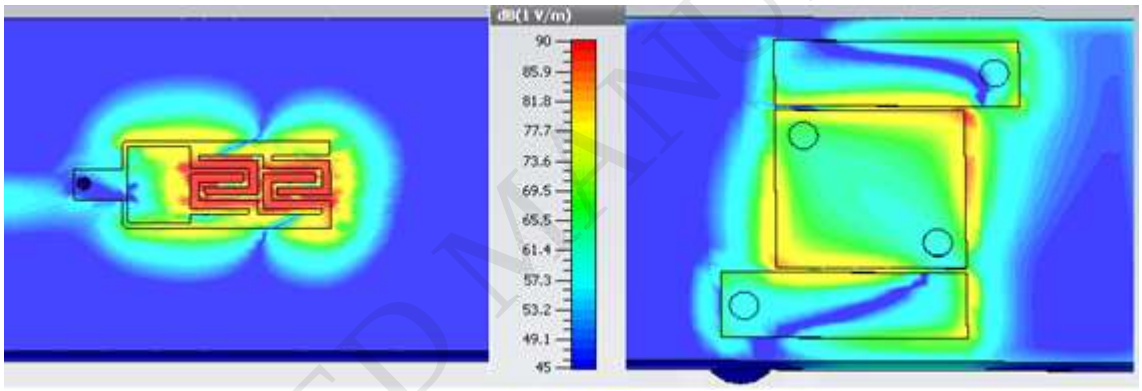
The evaluation of the Debye model proposed above for the mentioned concentration values results in:

$$\Delta\varepsilon = \varepsilon_{0\,mg/dl} - \varepsilon_{2000\,mg/dl} = 78.74 - 77.95 = 0.79 \quad (9)$$

This means that for this glucose range a permittivity change of only ~0.79 is expected. This is a very small change to resolve considering the lossy nature of the tissues surrounding the glucose/water layer and the attenuation mechanisms explained in the

previous section. The lack of sensitivity in the results shown above in Fig. 9. illustrates the difficulty. A frequency shift of only 4 MHz was observed for this concentration range. Moreover, 2000 mg/dl is an exaggerated value to demonstrate the effect of glucose; however, considering that the BGL is lower in a real-life situation, it is challenging to sense the variation. Assuming that the frequency shift caused is a linear function of the glucose concentration, the expected deviation is 2 kHz/mg.dl^{-1}.

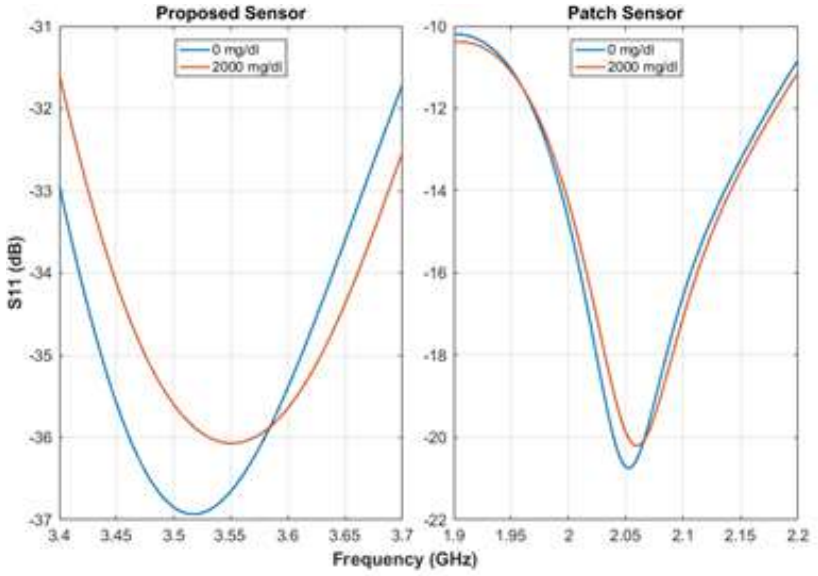
The sensor proposed in this study was compared with another sensor found in the open literature [7] to assess the difference in sensitivity. The electric field distribution was simulated in CST and is shown in Fig. 14.



a) b)

Fig. 14. Electric field distribution in the a) proposed sensor b) sensor from [7]

The proposed sensor's sensitivity compared to the sensor in [7] was expected to be higher due to stronger electric fields shown in Fig. 14. To observe this, both sensors were simulated with 0 mg/dl and 2000 mg/dl glucose/water simulations and the results are shown in Fig. 15.



a) b)

Fig. 15. Sensor responses of the a) proposed sensor b) sensor from [7]

As it can be seen from Fig. 15 where both graphs have the same 300 MHz span in the frequency axis, the proposed sensor is more sensitive than the sensor found in the open literature [7]. For the simulated glucose concentration range, the proposed sensor showed a 32 MHz frequency shift whereas the other sensor only showed 7 MHz shift. This demonstrates the importance of sensor design for achieving better sensitivity to glucose variations.

The sensitivity could be increased by using a sensor that is even more sensitive to the variation in the permittivity, by working at a higher frequency in the expense of reduced penetration depth or using an active circuit along with the sensor whose response would be amplified by the change in the sensor's capacitance, making it possible to observe smaller variation in the permittivity but also more prone to errors and inaccuracies.

Finally, an actual fingertip was placed on the sensor for a measurement after fasting for four hours and then repeated after consuming a drink containing 50 grams of

glucose. No frequency shift was observed. However, this was expected as the simulation results suggested that there would be minimal to no shift in the response. The photograph of the sensor mounted in a 3D printed enclosure is shown in Fig. 16.

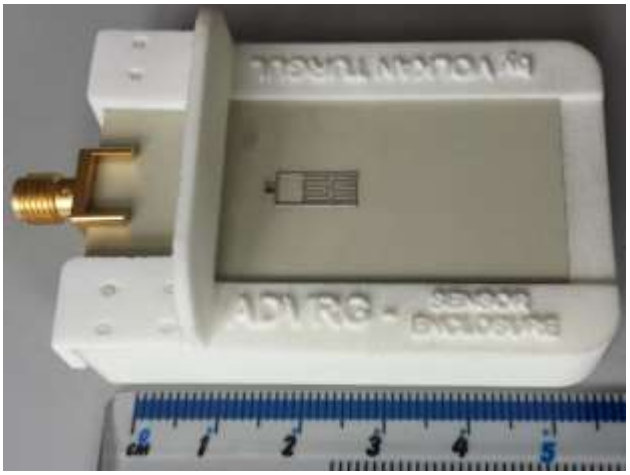


Fig. 16. Photograph of the fabricated sensor

4. Discussion

The following criteria should be considered carefully for a successful sensor design:

The sensitivity of the sensor to glucose highly depends on its structure i.e., the amount of electric field existing in the near field. The sensor should be as compact as possible to confine the radiated field in the measurement site. The difference in the dielectric constant for two different concentrations of glucose/water solutions increases as the frequency increases. Therefore, choosing a higher frequency of operation offers a greater measurement range increasing the measurement resolution and it also helps reduce the resonator size. However, the penetration depth decreases and the loss factor increases for the biological layers as the frequency increases. A good balance should be kept between these parameters to achieve sensitive glucose measurements.

5. Conclusion

Firstly, a low-cost open-ended coaxial probe was proposed for permittivity measurement of materials. The extracted permittivity values from the measured S-parameters were improved utilizing a heuristic approach that reduces the dependency of the measurement accuracy on the calibration process. Using the probe and the extraction method the complex permittivity values of aqueous solutions of glucose was first measured by the authors from 100 mg/dl to 500 mg/dl in the 1-8 GHz frequency band as reported in [10]. The values were fitted to the Debye model and relevant parameters were proposed. The work was later extended and validated by using a commercial dielectric probe. Concentrations up to 16000 mg/dl were measured in the 0.3 – 15 GHz frequency band. The values were fitted to the Debye model and the new parameters were proposed for this extended range. The two models were compared to evaluate the performance of the extraction algorithm and the error level was shown to be less than 3%. To the authors' best knowledge, there was no accurate model for aqueous solutions of glucose in the open literature previously. The proposed permittivity models are useful for simulating RF sensors in EM simulation software.

Secondly, a compact microwave sensor was proposed for glucose sensing elaborating on the selection of frequency of operation and loss mechanisms caused by the biological tissue layers. The sensor was simulated with the proposed models and measured with a fingertip as well as glucose/water solutions. It was observed that the presence of biological tissues decreases the measurement sensitivity. However, the sensor can measure glucose level when the solution is directly placed on the sensor. A good agreement between simulated and measured results was achieved.

The non-invasive measurement of glucose is a challenging subject, especially real measurements on biological measurement sites. Research has been ongoing in this area but most results reported in the open literature are inconsistent with no useful sensor responses when the sensors are used on a real body part for a measurement. Sensor structures and frequency of operation appear to be selected with no solid ground in most reported works. Paying attention to the explained design parameters, a better sensitivity to glucose solutions was achieved than the works referenced throughout this work. However, there is a great deal of work that needs to be carried out to obtain the sensitivity needed to measure glucose from a biological site. The measurements are also highly dependent on the fingertip positioning on the sensor as well as the pressure applied [22] onto the sensor. With the minimal frequency shift expected in the sensor's frequency response due to the variation of BGL, these factors have a much greater effect on the response. The authors continue to investigate ways of achieving better measurement sensitivity as well as mitigating the effects of these factors, awaiting publication.

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