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Multilayered Implantable Antenna Biosensor for Continuous Glucose Monitoring: Design and Analysis

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Abstract—This article reports a multilayer implantable biosensor for a continuous glucose monitoring system, tested on rats to determine the relationship between intravenous glucose level and resonance frequency of implant antenna sensor. An implantable antenna sensor with the volume 330.9 mm^3 is tested in three rats as an animal model. This antenna biosensor operates in the Medical Implant Communication Service frequency band (402–405 MHz) with the simulated and measured maximum gains of -13.33 and -21.1 dB, respectively. The specific absorption rate obtained is within the standard limits. An oral glucose tolerance test is proposed to obtain the variation in blood glucose level in the animal's body during measurement. The resonance frequency shift and the corresponding blood glucose level are observed at a regular interval of 30 minutes. A frequency shift of 4.94 kHz per mg/dL is observed. Also, the results related to the reflection coefficient and the factors affecting sensor performance are discussed. The biosensor performance is validated using the proposed simple linear regression model.

1. INTRODUCTION

Around 463 million adults are suffering from one of the most severe chronic diseases known as diabetes, and almost 760 billion USD is spent on its treatment worldwide which is 10% of global health expenditure [1]. In addition, diabetes increases other risks related to kidney, heart, and wound healing capability [2, 3]. Therefore, developing a low-cost sensor for continuous glucose monitoring (CGM) is crucial in the present scenario. The design of low-cost implantable glucose sensors has attracted much research interest in implantable medical devices (IMD) to make the monitoring system less painful for the patients and cost-effective for the designers. Typically, a traditional small-size IMD for CGM is composed of an antenna, a microcontroller, a battery, and sensors.

In the last few years, various approaches have experimentally demonstrated low-cost and effective solutions for CGM. Some recent studies have revealed the application of implantable antenna biosensors for CGM. In [4], for instance, an LC tank passive resonator with a volume of 16 mm^3 was proposed and tested in vitro with a sensitivity of 150 kHz per mg/dL for glucose concentration. A split ring resonator-based biosensor for glucose sensing was developed and tested in [5]. The shift in the resonance frequency concerning glucose, distilled water, and NaCl with a sensitivity of 0.107 MHz/mgml^{-1} was also demonstrated. In [6], an antenna-based glucose sensor, operating at 10 GHz, was designed using silicon carbide (SiC) bio-compatible material and tested in vitro in synthetic blood fluid (SBF) and pig blood. The sensor indicated frequency shifts of 97 kHz and 67 kHz for SBF and pig blood, respectively. Surgical protocol for sensor implant in rats was reported in [7] and [8]. In [7], an *in-vivo* experiment using rats was carried out to test the dual-band implantable antenna in medical implant communication service (MICS) and industrial, scientific, and medical radio (ISM) bands and discussed factors affecting

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sensor performance. In [8], two implantable antennas with volumes of 204 mm^3 and 399 mm^3 were surgically implanted and investigated in MICS (402–405 MHz) for long-term operation. Furthermore, in [9], 362 mm^3 and 127 mm^3 antennas were also tested in rats to explore the impact of the live tissue on the antenna performance.

The design considerations of implantable antennas for CGM include: minimizing the operating structure, the frequency of operation, confined specific absorption rate, increase in bandwidth, biocompatibility, and tuning insensitivity [10]. Previously reported antennas have been designed to operate in MICS [7, 8], MedRedio [11, 12], and ISM bands [3, 7, 9, 12–14]. To achieve a miniaturized implantable antenna, various antenna structures have been studied, such as planer inverted-F antenna (PIFA) [12], multi-layer PIFA with the high dielectric constant substrate [7–9, 11, 14], and the usage of magneto-dielectric material [13]. Some of these antenna prototypes provide miniaturization. However, they do not consider other requirements of implantable antenna for CGM, such as operating frequency and specific absorption rate (SAR). For an implantable antenna, the medical device radio communication service (401–406 MHz) frequency band, which includes the MICS band, is preferred over high frequencies. This is because the human tissue absorbs more energy at high frequencies, resulting in an increased specific absorption rate. In addition, propagating electromagnetic energy through the human body is challenging due to its inhomogeneous, lossy and dispersive environment. Therefore, the MedRadio band is primarily used in IMDs. Various testing approaches have been reported for an implantable antenna sensor. Noninvasive testing was done in [2, 5, 15, 16], and minimally invasive testing was reported [4, 17]. In [3, 6–9, 11, 13, 14, 18], invasive testing technique was demonstrated. A synthetic blood fluid with various glucose levels was used in [6]; a skin-mimicking gel and tissue model was used [14, 18]; a tissue phantom tissue was used in [3, 13]; and rat as a model animal was used [7–9]. The Invasive or *in-vivo* method is considered more reliable as it is less affected by external parameters such as sweat, environmental moisture, temperature, and dust particles.

In this article, a multilayer miniaturized implantable antenna biosensor for CGM is proposed. The designed biosensor is implanted in subcutaneous tissue surrounded by capillary blood or interstitial fluid (IF), which contains physiological information about the person's blood glucose level. The electrical properties of IF vary according to the blood glucose level [17, 19]. These fluctuations can be recorded remotely by observing the shift in the resonance frequency of the implant antenna. Testing implantable antenna biosensor for time-varying glucose levels in the subject's body (rat) using oral glucose tolerance test (OGTT) is performed. This article aims to design and test an implantable antenna capable of sensing glucose variation. Developing and testing a small-size low-cost IMD capable of continuous glucose monitoring is possible with this approach.

This article is organized as follows. Section 2 presents the proposed antenna sensor design and surgical implant protocol. Section 3 reports *in-vivo* measurements and outcomes of the glucose testing. The results are analyzed and discussed in Section 4. Finally, a future outlook is presented, and the paper is concluded in Section 5.

2. METHODOLOGY

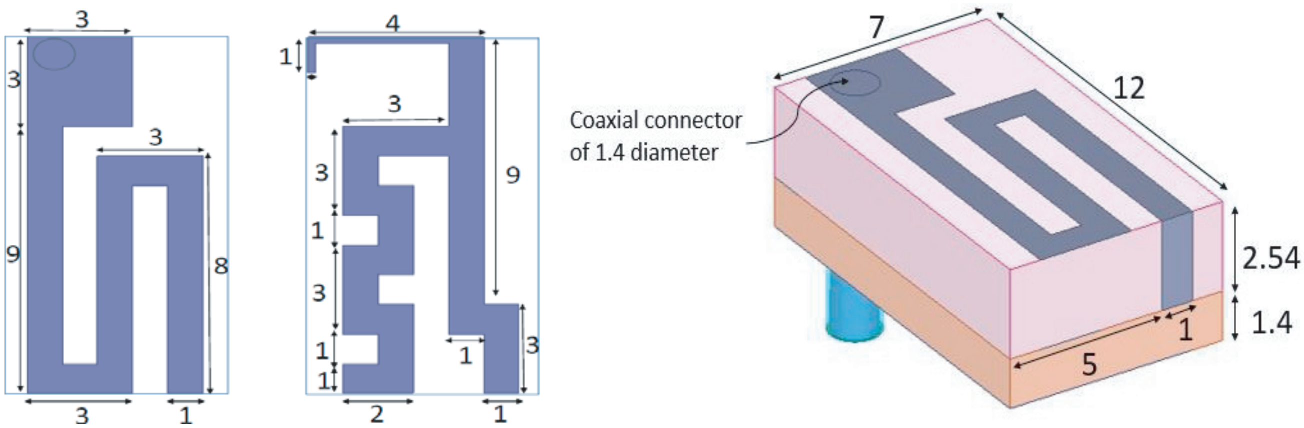
2.1. Implantable Antenna

A multilayer meandered implantable antenna sensor is designed for glucose sensing applications in the MICS band as illustrated in Fig. 1. High dielectric constant substrate and shorting of the plane are used to minimize the structure size.

The design consists of a meandered patch at two layers connected by shorting plane. These two patches lie on different substrates, i.e., a top layer is made of Rogers RT Duroid 610LM ($\varepsilon r = 10.2$) and a bottom layer with FR-4 Epoxy ($\varepsilon r = 4.4$) of thickness 2.54 and 1.4 mm, respectively. The simulation setup in the phantom model and fabricated antenna sensor is shown in Fig. 2.

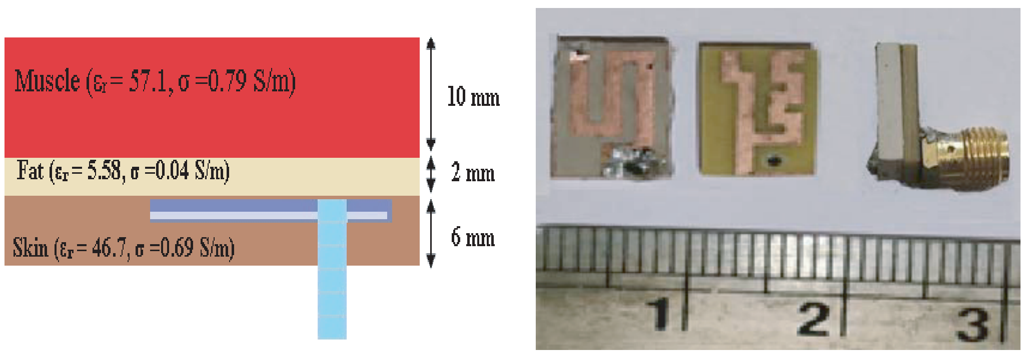
2.2. Experimental Protocol

Three healthy male rat subjects with standard glucose tolerance have been considered in this study. All three subjects were tested for blood glucose using the tail puncture method in the morning after overnight fasting (> 10 Hours). Subsequently, each subject was provided with the calculated oral glucose



(a) (b) (c)

Figure 1. Proposed sensor design. (a) Upper conductor layer. (b) Lower conductor layer. (c) Cross section.



(a) (b)

Figure 2. (a) Simulation setup in phantom model. (b) Fabricated prototype.

load (2 gm/kg) to observe the glucose absorption rate. After two days, the proposed surgical protocol was implemented. Fig. 3 presents an experimental protocol, which has been proposed to evaluate the response for glucose variation using OGTT. This protocol considers various factors such as the animal model selection, implant site, surgical plan of action, observations, measurements, and post-surgery procedure.

2.2.1. Selection of Animal Model

Our experiments have been conducted using rats, which have been long used as typical animal models [7]. Six months old three Wistar rats were selected, each with an average weight of 446 grams. To observe the effect of surgical procedure variation, the experiment was repeated on three different subjects with serial numbers I-1, I-2, and I-3. The animals with normal OGTT were selected to maintain relative uniformity in the blood glucose variation to be measured. Each animal was tested for glucose level by tail puncture method using a blood glucose meter (Accu-Check Active-model GB, Roche) after fasting overnight. The subcutaneous portion of the abdominal area was selected for the implant due to a high density of blood vessels.

2.2.2. Implant Procedure

Each animal was then anesthetized with isoflurane, an inhalation anesthetic. An opening with length ($L + 5$ mm) was made in the animal's abdominal area, and the sterile antenna sensor was implanted

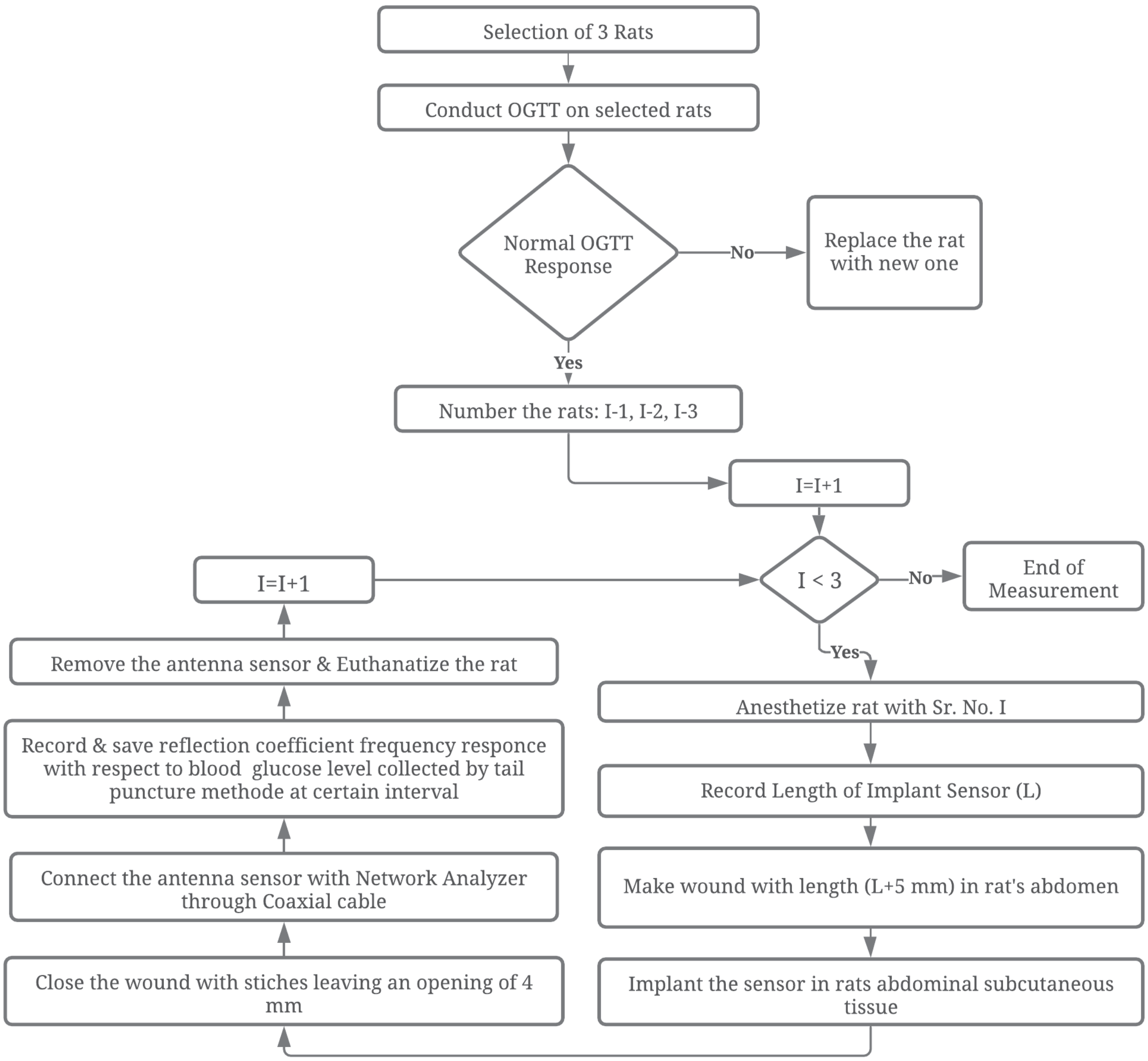


Figure 3. Proposed protocol for testing of implantable biosensor for CGM using OGTT in the rat as a model animal.

in subcutaneous tissue. After implantation, suturing of the wound was accomplished by using a silk suture with a 4 mm opening for a coaxial connector to come out of the skin.

2.2.3. The Testing and Measurement

After the surgical procedure, the coaxial connector was connected with KEYSIGHT FieldFox RF Analyser N99131. The resonance frequency response shift depending on the variation in the blood glucose demonstrated by the antenna was recorded. At the same time, the blood sample was collected by using the tail puncture method and tested for a glucose level.

After completing measurements, the animal was euthanized in a CO_2 chamber before its removal. The total time required from surgical implant to euthanize animals took a maximum of three hours each.

In vivo experiment was carried out in compliance with the legitimate necessities regarding care and handling of lab animals.

Due to the nonidentical internal tissue properties of each animal, the resonance frequency response of the biosensor is slightly different for each case. Glucose is the only component of interstitial fluid having reasonable change over other components like salt, minerals, fatty acids, calcium, etc. The proposed protocol helps to reduce the effects of other external parameters like implant procedural difference, air gap, etc.

3. IN VIVO MEASUREMENT

The proposed protocol was implemented for implantable antenna sensors. Fig. 4(a) explains the same surgical site with antenna sensor implanted in the subject. The experimental setup is shown in Fig. 4(b). The measurements were carried out in three different animal models. The *in vivo* experiment on the animal is conducted in parallel with OGTT, as shown in Fig. 4(c). OGTT results in a brisk hike in blood glucose levels, helping to record significant variations of the antenna sensor's blood glucose levels and respective resonance frequency shifts. The typical OGTT results of three different subjects are observed. The blood glucose level increases due to the use of Isoflurane during implant. This effect is kept in the OGTT plot after implant, as shown in Fig. 5. Measurements in three different animals are denoted by Animal I-1, I-2, and I-3, respectively.

(a) (b) (c)

Figure 4. (a) A sensor implanted in animal. (b) Experimental setup. (c) Testing blood glucose level of the animal using tail puncture method.

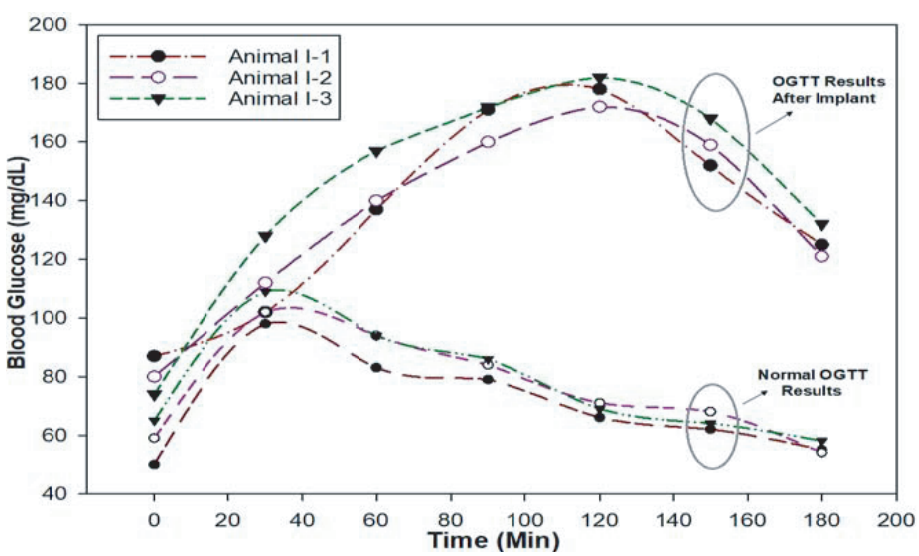


Figure 5. Glucose Infusion rate with normal OGTT and during in vivo sensor testing.

4. RESULTS ANALYSIS AND DISCUSSION

The antenna sensor is designed and simulated in the 3-layer phantom model using Ansoft HFSS.19 by considering dielectric properties of muscles ($\varepsilon r = 57.1$, $\sigma = 0.79\,\mathrm{S/m}$), fat ($\varepsilon r = 5.58$, $\sigma = 0.04\,\mathrm{S/m}$), and skin ($\varepsilon r = 46.7$, $\sigma = 0.69\,\mathrm{S/m}$) at 402 MHz [8]. The radiation pattern characteristics of the antenna in artificial tissue environment are presented in Fig. 6. The simulated and measured gains recorded are -13.33 and -21 dB, respectively. The specific absorption rate (SAR) is presented for the 3-layer phantom model. The maximum 1 g average SAR is observed at 1.1441 W/kg in the phantom, as shown in Fig. 7. These values meet the IEEE C-95, 1-1999 (1g-avg SAR < 1.6 W/kg) standards [20] and are below the standard level.

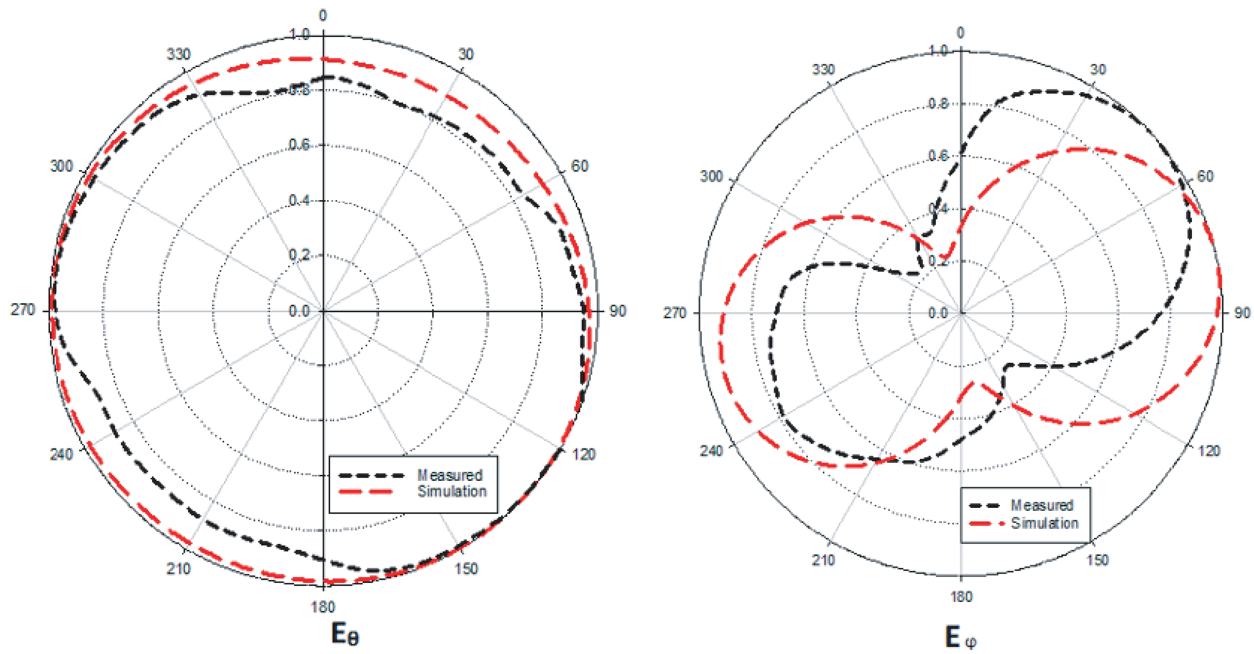


Figure 6. Simulated and measured normalized antenna radiation pattern (dBi) in artificial tissue environment at 405 MHz.

The antenna sensor was tested by observing the resonance frequency shift measured and correlated with three different animal models' real-time blood glucose levels. As shown in Fig. 8, though the antenna sensor operates in the required MICS frequency band, there is some variation in the measured and simulated values of the reflection coefficient due to fabrication errors.

The resonance frequency (f_r) of 406.3 MHz with S_{11} of -21.6 dB is observed in the simulation setup, whereas the resonance frequencies of 404.4, 403.9, and 402.7 MHz with -21.1, -18.6, and -16 dB of S_{11} are observed for animals I-1, I-2, and I-3, respectively. These results show that the antenna performance is affected by many factors implanted in the subject's body [7].

The measured frequency response concerning glucose level (Gl) is tabulated in Table 1 and plotted in Fig. 9. The resonance frequency shift for various glucose levels in all three animals is recorded in real-time. Some deviations are observed, and the response of the antenna sensor depends on various factors such as the blood glucose concentration, dielectric properties of animals, implant procedure, air gap, and body temperature. The frequency shifts (Δf) of 3.4, 5.1, and 6.3 kHz per mg/dL are observed for animals I-1, I-2, and I-3, respectively, with plotted versus blood glucose levels. The average of these three responses is found to be linear with a rate of 4.94 kHz per mg/dL. Based on these observations, a simple linear regression model ($f = y_0 + a * x$) is investigated and demonstrated in Fig. 10.

The details of predicted blood glucose levels based on the proposed model are given in Table 2. Observed % error is very low indicating the good correlation between expected values (Actual measured values by using commercial glucometer) and actual values (predicted by proposed linear regression

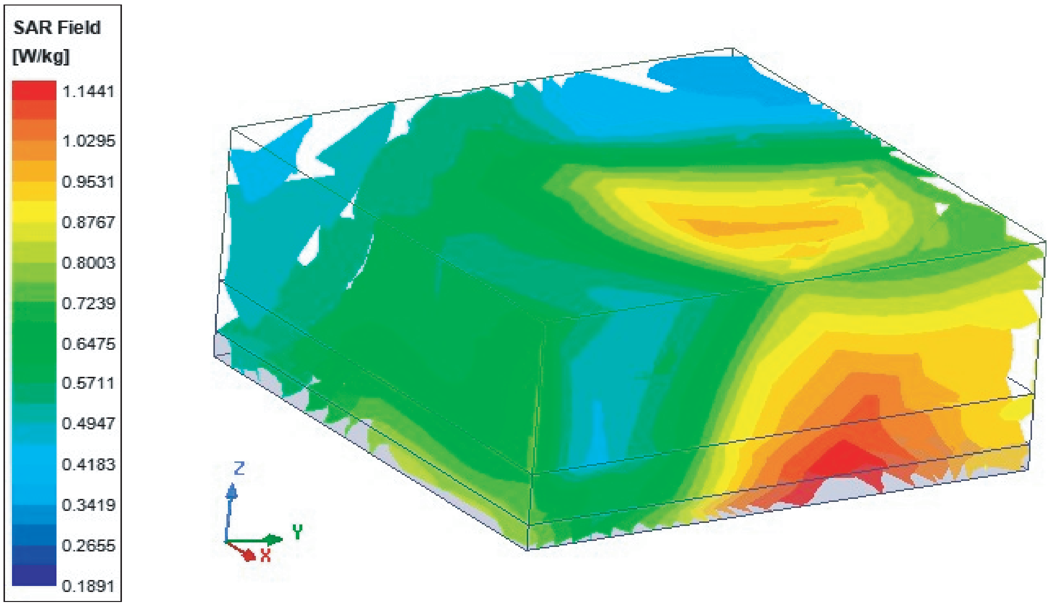


Figure 7. Simulated SAR value in 3-layer phantom.

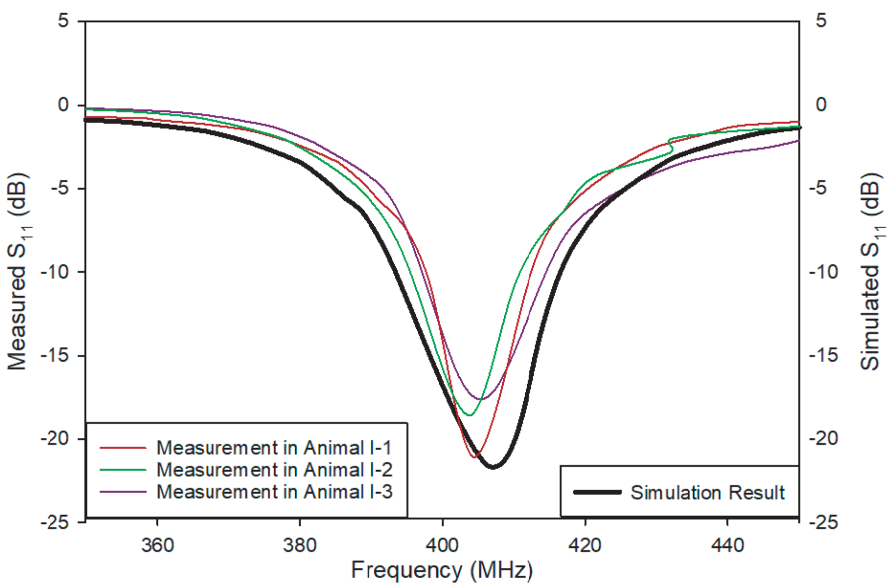


Figure 8. Simulated and measured reflection coefficient (S_{11}) frequency response.

model). Fig. 11 shows the linear correlation between expected and actual values.

All the points in the plots of Fig. 10 and Fig. 11 fall under the 95% prediction band (95% of the Y values to be found for certain X value will be within the interval range around the linear regression line), and the majority of points fall under 95% confidence band (There is 95% probability that the true best fit line for the data set lies within the confidence interval). The linear correlation coefficient R^2 is very close to 1, which indicates that the blood glucose data in the model are very closely related.

The performance of the proposed sensor is compared with various previously reported sensors as shown in Table 3.

The sensors reported in [4] and [5] are resonators. The blood glucose sensing capability of a microstrip patch antenna (MSA) is demonstrated in [6] and verified in this work. The testing method

Table 1. Measured change in frequency response with respect to variation in glucose level.

Animal I-1			Animal I-2			Animal I-3		
Gl (mg/dL)	f_r (MHz)	Δf (kHz)	Gl (mg/dl)	f_r (MHz)	Δf (kHz)	Gl (mg/dl)	f_r (MHz)	Δf (kHz)
102	404.4	-	112	403.87	-	125	402.725	-
130	404.335	65	121	403.825	45	132	402.69	35
137	404.2668	68.2	140	403.79	35	155	402.595	95
149	404.226	40.8	154	403.73	60	161	402.525	70
166	404.169	57	161	403.67	60	170	402.448	77
178	404.128	41	172	403.57	100	182	402.373	75

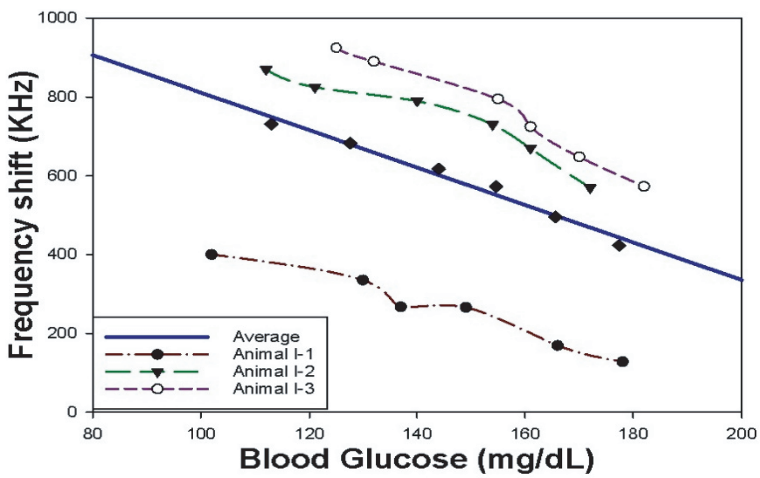


Figure 9. Measured relative frequency shift (Normalized) concerning blood glucose level in animals and frequency shift to blood glucose concentration.

Table 2. Measured blood glucose by using a commercial glucometer and predicted glucose values based on the proposed model for each animal.

Animal I-1			Animal I-2			Animal I-3		
Expected value	Actual Value	% Error	Expected value	Actual Value	% Error	Expected value	Actual Value	% Error
102	104.38	2.33	112	115	2.68	125	127.11	1.69
130	121.71	6.37	121	125	3.31	132	132.85	0.65
137	140.47	2.53	140	132.81	5.13	155	148.44	4.23
149	151.25	1.51	154	145.94	5.24	161	159.65	0.84
166	166.72	0.43	161	160	0.62	170	172.23	1.31
178	177.5	0.28	172	180	4.65	182	184.26	1.24

used in [6] records only instantaneous blood glucose levels, but the actual time measurement of varying blood glucose levels was not considered. The operating frequency for this design is 10 GHz, which is much greater than the MICS and the wireless medical telemetry service (WMTS) band. High resonance frequency reduces the size of the antenna, but at such high frequency, the human tissue will absorb more

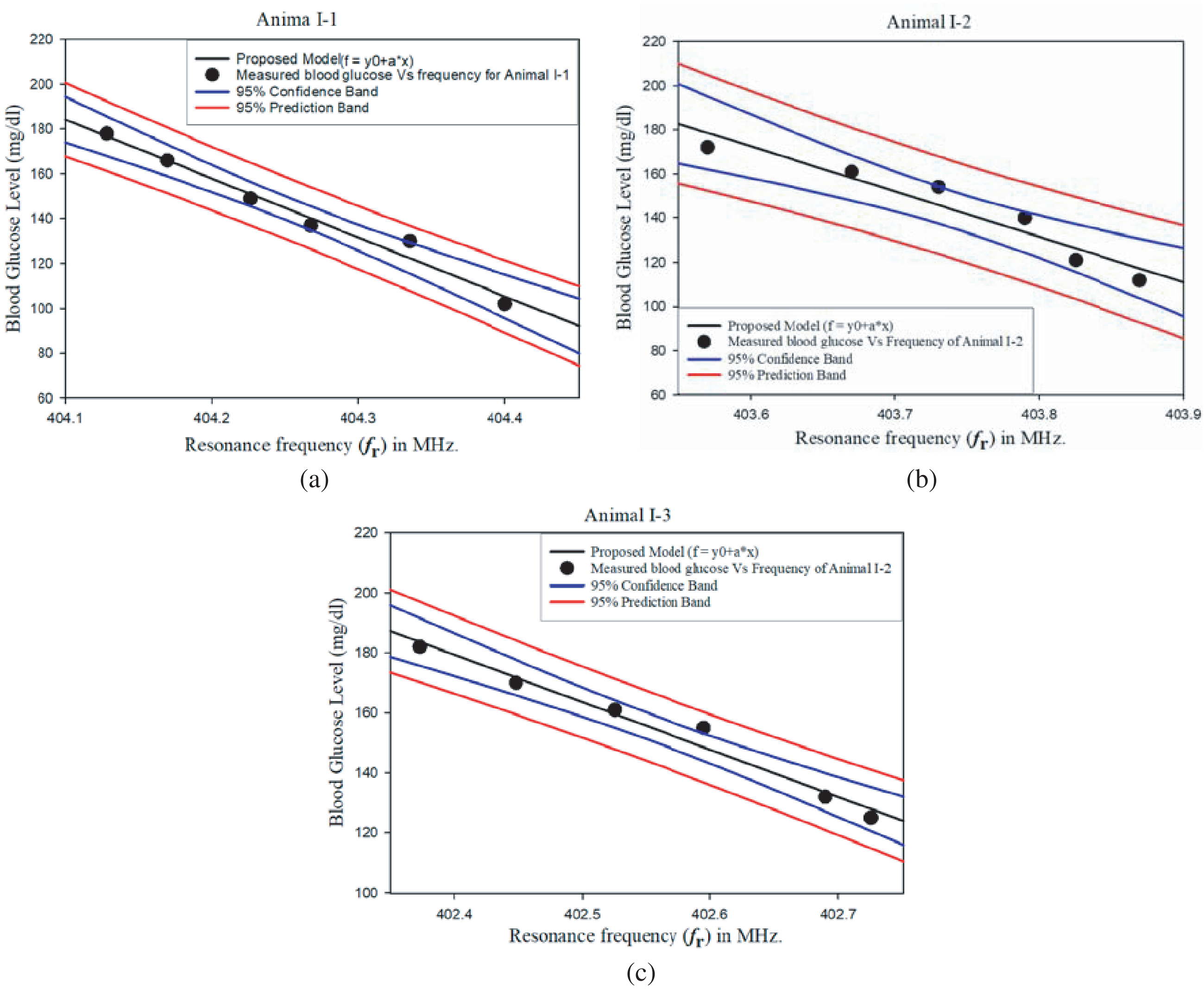


Figure 10. Linear regression curve fitting for the readings of animal. (a) I-1. (b) I-2. (c) I-3.

Table 3. Performance comparison for various glucose sensors.

Ref. No.	Sensor Type	Volume (mm^3)	Resonance Frequency	Sensor Testing	Sensitivity Per mg/dl
[4]	*L-C* tank Resonator	16	0.5 GHz	*In vitro*	105 kHz
[5]	Split Ring Resonator	14.4	2 GHz	*In vitro*	1.07 kHz
[6]	Micro-strip Patch	36.1675	10 GHz	(a) *In vitro* (SBF)	97 kHz
				(b) *In vitro* (Pig Blood)	67 kHz
This Work	**Micro-strip Patch**	**330.9**	**405 MHz**	***In vivo* *(Rat)***	**4.94 kHz**

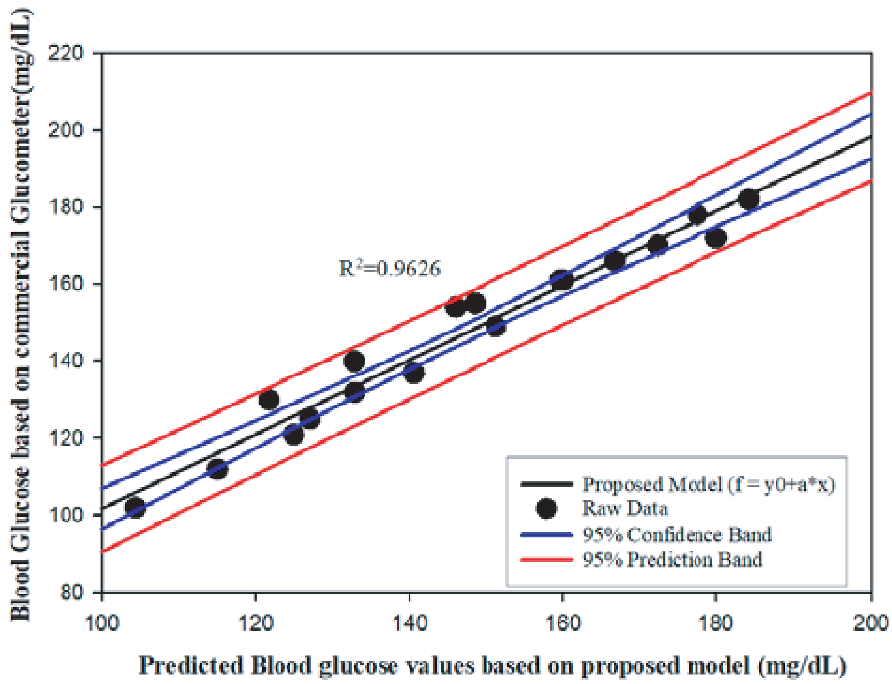


Figure 11. Relationship between measured blood glucose by using a commercial glucometer and predicted glucose values based on the proposed model.

energy resulting in a poor transfer of high-quality signals. It is also observed that greater sensitivity in the antenna sensor is achieved due to the high resonance frequency. Hence, the proposed MSA is the best candidate for an implantable antenna glucose sensor within the desired frequency band as it overcomes the drawbacks of antenna sensors reported in the literature.

Table 4 provides the qualitative comparative analysis of surgical implant procedures in the rat. All the procedures reported are focused on the investigation of antenna performance in the model animal.

Table 4. Comparison of surgical implant procedure in rats.

Ref. No.	Antenna Volume (mm^3)	Operating Band	Animal Model	Application
[7]	1322.5	ISM, MICS	Rat	Communication between base station and implantable device
[8]	204 and 399	MICS	Rat	
[9]	362 and 127	ISM	Rat	
Proposed work	**330.9**	**MICS**	**Rat**	**Communication** between base station and implantable device **And Glucose sensing**

The proposed protocol and sensor reported in this manuscript is better than other similar methodologies in terms of the antenna performance and blood glucose sensing capability. The proposed method allows the practitioners/researchers to record many blood glucose variations in less time.

5. CONCLUSIONS

In this article, a multilayered implantable biosensor for continuous glucose monitoring is designed. The protocol for testing an implantable antenna biosensor for continuous glucose monitoring using OGTT has been developed and implemented. A 330.9 mm^3 antenna biosensor is intended for the MICS band with a maximum measured gain of −21.1 dB and 1-g average SAR of 1.1441 W/kg. The sensor is implanted, and the results are tested on three rats as animal models. The real-time-frequency shifts regarding the corresponding glucose levels in the three subject animals' bodies are measured. Though the frequency responses of the antenna sensor in all three animal models are slightly different, the relation between frequency shift and blood glucose level is quite similar. Furthermore, the linear response of the average frequency shift and blood glucose level is observed with a sensitivity of 4.94 kHz per mg/dL. A simple linear regression model is investigated to validate the working of the sensor. It is observed that the linear correlation coefficient R^2 is very close to 1, which indicates that blood glucose data in the model are very closely related. The result shows that the proposed implantable antenna can be used for continuous glucose monitoring. The proposed work can be extended to miniaturization of antenna, the study of safety measures, long-term implant, and use of bio-compatible materials for encapsulation.

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