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Mikrovlnné neinvazivní monitorování koncentrace glukózy v krvi

Microwave Non-Invasive Blood Glucose Concentration Monitoring

Summary

This lecture is dedicated to the non-invasive method of monitoring blood glucose concentration in diabetic patients based on detection of changes in the dielectric properties of biological tissues. The lecture is divided into two parts. In the first part a comparison of two possible phantoms of blood-glucose solutions is performed. The second part is dedicated to the design and evaluation of sensor based on artificial transmission line. It was found that the achieved sensor sensitivity to the concentration of glucose in blood, is very good. Based on the available analysis we can also assume that, if necessary, further increase the sensitivity of the sensor is possible. At the end of the lecture the main results are concluded and the outlook for future research is presented.

Souhrn

Tato přednáška je věnována metodě neinvazivního monitorování koncentrace glukózy v krvi u pacientů s diabetem založené na detekci změn dielektrických vlastností biologických tkání. Přednáška je rozdělena na dvě části. V první části je provedeno srovnání dvou možných fantómů roztoků krev-glukóza. Druhá část se věnuje návrhu a ohodnocení senzoru založeného na umělém přenosovém vedení. Bylo zjištěno, že dosažená citlivost senzoru na koncentraci glukózy v krvi, je velmi dobrá. Na základě dostupné analýzi lze také předpokládat, že v případě potřeby je další zvýšení citlivosti senzoru možné. Na závěr přednášky jsou shrnuty hlavní výsledky a představen výhled pro budoucí výzkumnou činnost.

Klíčová slova

mikrovlnná technika, neinvazivní měření, koncentrace glukózy v krvi, senzory, metamateriály, lékařeská diagnostika

Key Words

microwave technology, non-invasive measurement, blood glucose concentration, sensors, metamaterials, medical diagnostics

Contents

1 Introduction

The methods currently considered for non-invasive monitoring of blood glucose concentration include e.g. bioimpedance spectroscopy, fluorescence techniques, infrared spectroscopy, optical polarimetry, Raman spectroscopy, reverse iontophoresis and ultrasound, but none of them have found practical use yet.

There are currently four companies developing non-invasive BGC monitoring systems.

Cnoga Medical Ltd. [1] and Integrity Applications [2] launched their non-invasive BGC measurement systems in some markets in 2012 and in 2014, respectively. TensorTip CoG from Cnoga Medical uses near-infrared spectroscopy [1], while GlucoTrack from Integrity Applications [2] combines ultrasound, electromagnetic (EM) field and temperature measurements. Both of these sensors are calibrated by means of invasive measurements. The former is recommended for patients with type 2 diabetes mellitus only, and the latter passed clinical trials with only 96.5% of the measured data in A and B region of Clarke Error Grid. Another system, patented by Otis at al. [3], utilizes an electrochemical sensor integrated into the contact lens to measure glucose concentration in tears and the idea was further developed by Google Inc. [4]. And finally, MediWiSe [5] is developing a microwave (MW) system with working frequency range around 65 GHz, utilizing metamaterial (MTM) surfaces to reduce reflections on the tissue-sensor interface. MediWiSe announced they would open pre-orders for their MW device in late 2016.

Several research groups employ for noninvasive BGC measurement the dependence of dielectric properties of blood on glucose concentration in the MW frequency range. Sensors based on MW resonators or transmission (TL) line sections detect the shift of resonance frequency and the change of electrical length, respectively, caused by the change of glucose concentration [6, 7]. Some of the developed MW sensors were not validated experimentally [8]. The sensors were tested by means of numerical simulations, detecting glucose concentrations in water-glucose solutions. The sensors were based on ring, spiral and double spiral microstrip (MS) resonators. Performance of the spiral resonator was shown to be the most promising. In [9], MS monopole antenna was tested numerically on a layered model of biological tissues. In [10], six different MS resonators were compared numerically in terms of sensitivity, with the highest observed sensitivity being that of the spiral MS resonator.

In vitro studies have been conducted, using various types of sensors with various solutions (phantoms of human blood-glucose solutions): a sensor based on a rectangular MS patch antenna with both physiological saline-glucose as well as pig blood-glucose solutions in [11], an MS TL section with aqueous- and blood-glucose solutions in [12], waveguide with a goat blood-glucose solution in [13], a spiral MS resonator with blood phantom in [14] and with pig blood in [15].

In vivo studies tested a spiral MS resonator against a thumb [16] and on the wrist [17]. A split ring resonator was tested in [18]. All three studies have shown that it is possible to predict blood glucose concentrations in real time. In [18], encouraging agreement with

the readings of an invasive glucometer was shown.

It has been reported that MW sensors based on MTM TLs can achieve significantly higher sensitivity levels than sensors based on conventional TL (more than 10 times higher) [6, 19–21]. In these studies, the interaction is very dependent on the chosen unit cell and especially on how the unit cell is implemented.

Due to the higher reported sensitivity, MTM sensors were proposed and successfully used for detecting small changes in EM properties of the material under test (MUT). Consequently, MTM sensors were proposed even for detecting biomedical quantities, e.g. immobilized antibodies, single strained DNA [22] as well as DNA hybridization [20] and others. Even though the increased sensitivity of MTM sensors was demonstrated experimentally, it has been concluded that, in theory, this sensitivity can be significantly improved even further.

For the development of an EM non-invasive glucose monitoring system, knowing the dielectric properties of blood-glucose solutions is very important. Some authors mention that the dielectric properties of some solutions reportedly mimic the dielectric properties of blood-glucose solutions, e.g. physiological saline-glucose [23] and blood plasma-glucose solutions [24, 25]. In [26, 27], it was shown that glucose influences the dielectric properties of blood significantly, but a mathematical model was not published. Mathematical models of dielectric properties of blood-glucose solutions were published in [28, 29] and for readers convenience dielectric properties of blood glucose solutions determined by the models are plotted in Fig. 2.1. In [12], the authors measured the dielectric properties of blood-glucose solutions but their mathematical model was not published.

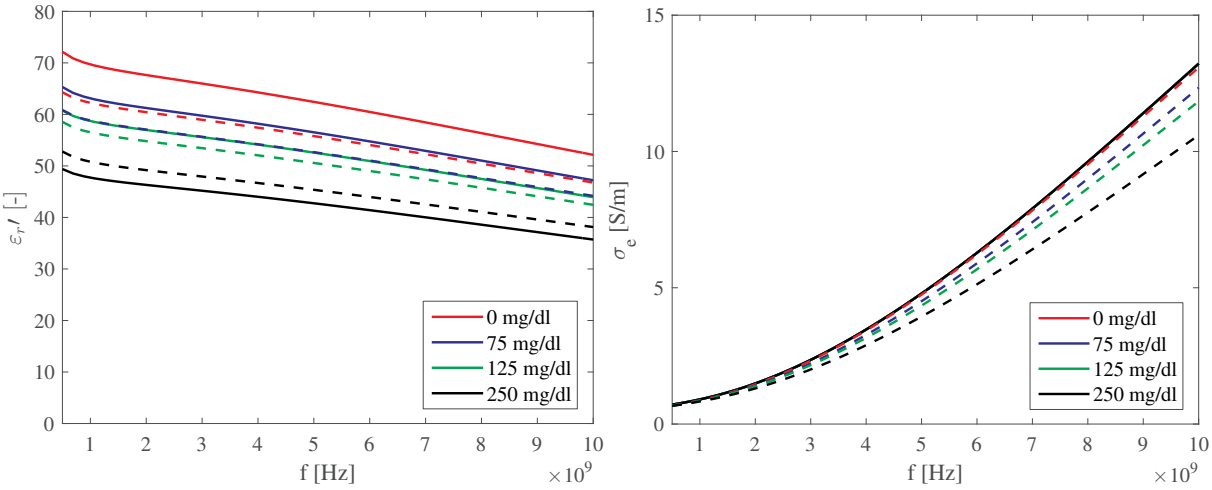
This lecture is based on our journal papers [11,30] and contributes to the state-of-the-art in non-invasive blood glucose concentration (BGC) monitoring in following two areas.

In Chapter 3, a suitability of two different liquid phantoms of blood glucose solutions as phantoms for development of microwave sensors for noninvasive blood glucose monitoring is compared. The two phantoms are physiological saline-glucose and pig blood-glucose solutions. For this purpose a simple microwave sensor is developed for in vitro monitoring of blood glucose levels. The sensor consists of a microstrip antenna and of a small rectangular container on the top of the antenna. The container is filled with one of the liquid phantoms. Both phantoms with different glucose concentrations ranging from 0 to 500 mg/dl are considered. Dependence of sensor's resonant frequency on glucose concentration of LUTs is both estimated by aid of numerical simulations as well as measured. The results are discussed and compared with some results reported in literature.

As mentioned above, artificial TL sensors have already been proposed for some biomedical applications. In Chapter 4, to the authors' best knowledge, it is the first time these sensors are proposed for non-invasive blood glucose concentration measurement. Furthermore, in Chapter 4, a corresponding numerical model of the sensor implemented in microstrip technology is created in the commercial full-wave numerical simulation tool COMSOL Multiphysics and virtually tested by means of numerical simulations. Blood-glucose solution models with various blood glucose concentrations are used as a model of a biological tissue under test. Furthermore, a possible methodology for performing non-invasive tests is proposed. Sensitivity of the sensor developed here is compared to a sensor based on a section of a conventional microstrip transmission line of the same length and width. The main goal of the Chapter 4 is to show the potential and the issues of such sensors and to propose some ways to overcome these identified issues.

2 Dielectric Properties of Blood-Glucose Solutions

As mentioned already in the Introduction, to the author's best knowledge, mathematical models of blood-glucose solutions were created in [28, 29], only. Both models are created by the same research group and therefore the later model should be more accurate. The later model shows lower changes in relative permittivity than the first one for the same glucose concentrations (Fig. 2.1 (a)). In the former model, equivalent conductivity is not a function of glucose concentration (all solid lines are ploted on each other in the Fig. 2.1 (b)). An important prerequisite for microwave measurement of glucose concentration in the blood is significant variability in glucose concentration together with minimal differences in concentration of other blood components. While the blood glucose concentration in a patient with diabetes compared to physiological values differ significantly, the changes of concentration of other blood components (namely Na, K, Cl, Ca) were studied in [24] and were evaluated as insignificant. In [18], investigation of the effects of increasing glucose concentration on the sensor response as well as the effects of endogenous common interferents, i.e., common sugars, vitamins (ascorbic acid), and metabolites (uric acid) were performed. It was found out that maltose, fructose, and galactose produce only small changes, at least three times less than the effects of glucose, and that other endogenous interferents have no significant direct effect.



(a) (b)

Figure 2.1: Dielectric properties of blood-glucose solutions (relative permittivity (a) and equivalent conductivity (b)) according to mathematical models published in [28] (solid lines) and in [29] (dashed lined).

3 Liquid Phantoms of Blood Glucose Solutions

As mentioned above, the two phantoms under consideration are physiological saline-glucose and pig blood-glucose solutions. And as it will be described in more details in this chapter the simple microwave sensor is developed for in vitro monitoring of blood glucose levels. This sensor consists of a microstrip antenna and of a small rectangular container on the top of the antenna. The container is filled with one of the liquid phantoms.

3.1 Methods

LUTs, Models of Their Dielectric Properties and Preparation

The glucose-concentrations in LUTs were chosen both physiological as well as non- physiological concentrations. The non-physiological concentrations considered here are still realistic as they can be reached by diabetes patients.

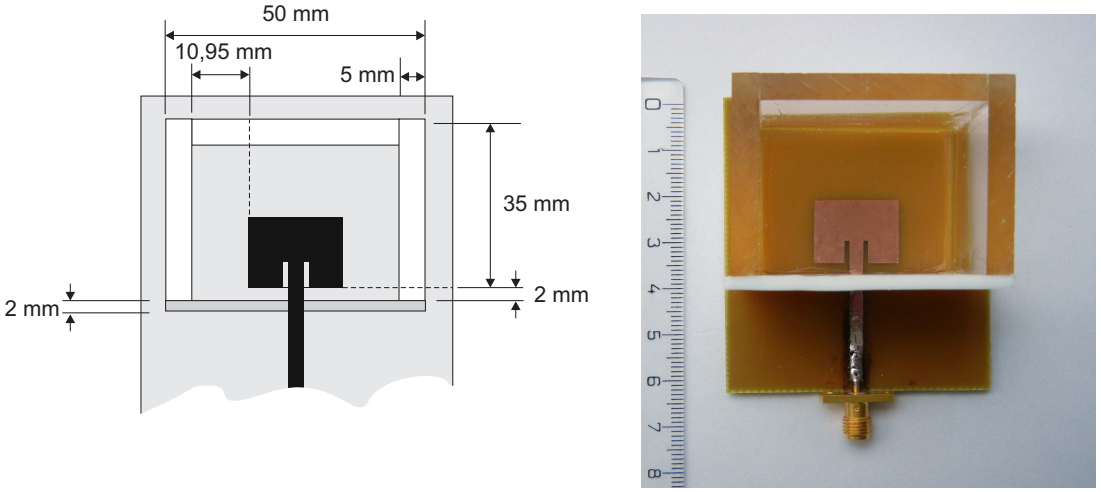
For numerical design and evaluation of the sensor, mathematical models of dielectric properties of physiological saline-glucose and blood-glucose solutions were adopted from [31] and [28], respectively. It has to be noted that the model from [28] is based on measurements using the commercial system Dielectric Probe Kit with the Slim Probe, both from company Keysight Technologies (formerly Agilent) [32]. Since it is difficult to use this equipment for the liquids with inhomogeneous surface (blood samples have such surface), the measured data are correspondingly negatively influenced. Nevertheless, to the authors' best knowledge, there is no other mathematical model for blood-glucose solutions dielectric properties.

Both models were implemented in MATLAB [33] and imported into COMSOL Multiphysics numerical model of the sensor. The numerical model of the sensor was subsequently used for sensor optimization as well as for further numerical investigations performed here.

Physiological saline-glucose solutions were prepared with 250, 500 and 1000 mg/ml glocose concentrations. The pig blood samples were taken in a slaughterhouse by slaughterhouse employees into 9 ml test tubes with K3 EDTA (anti-clotting agent). Pig blood-glucose solutions were prepared by adding an amount of D-glucose into 25 ml of pig blood. Obtained four samples had following glucose concentrations reference value, reference value + 125 mg/dl, reference value + 250 mg/dl and reference value + 500 gm/dl.

Sensor Based of Rectangular Patch Antenna Geometry

Microwave sensor is based on the MS patch antenna. The preliminary dimensions were calculated using well-known design rules [34] in such a way it resonates (with the empty



(*a*) (*b*)

Figure 3.1: (*a*) Simplified technical drawing of the container (top view). Lucite (*upper and side walls*) and PTFE (*lower wall*). Container height is 3 cm,(*b*) photograph of the realized microwave sensor (top view).

container) at 5 GHz. The antenna layout is shown in Fig. 3.1 and the dimensions are as follows. The substrate is FR4 with substrate height equal to 1.5 mm. The width of feeding MS transmission line is equal to 2.8 mm. SMA panel connector was used. Patch width and length are equal to 18.1 mm and 13.6 mm, respectively. The container dimensions from the top view are shown in Fig. 3.1 and its height is equal to 30 mm. Side walls of the container are made from PTFE and Lucite according to Fig. 3.1 (*a*). Filling the container with LUT shifts resonant frequency of the sensor to about 2 GHz (depends on used LUT and its glucose concentration). The sensor was first numerically modeled and subsequently fine-tuned (in terms of low reflection coefficient at the resonant frequency) in COMSOL Multiphysics.

The manufactured sensor with the empty container is shown in Fig. 3.1 (*b*). Measurement of reflection coefficient has been performed using VNA Rohde&Schwarz FSH8.28. The VNA was calibrated using full one port calibration. Calibration was done with calibration kit ZV-Z170 50.

For physiological saline-glucose solutions in total 27 independent (after each measurement the LUT was removed from the container and the container was cleaned) measurements were performed. In total 6 measurements were performed for each sample except of 250 mg/dl, where five measurements were performed only.

For reference sample (without added glucose) of pig blood five independent measurements were performed. Three pig blood samples with different glucose amount added were measured as well. In total 8 independent measurements were performed for pig blood samples.

3.2 Results and Discussion of Chapter 3

By a simple comparison of dielectric properties of both LUTs it is clear, that the same change in glucose concentration produces bigger changes of the dielectric properties of blood-glucose solution than of physiological saline-glucose solution.

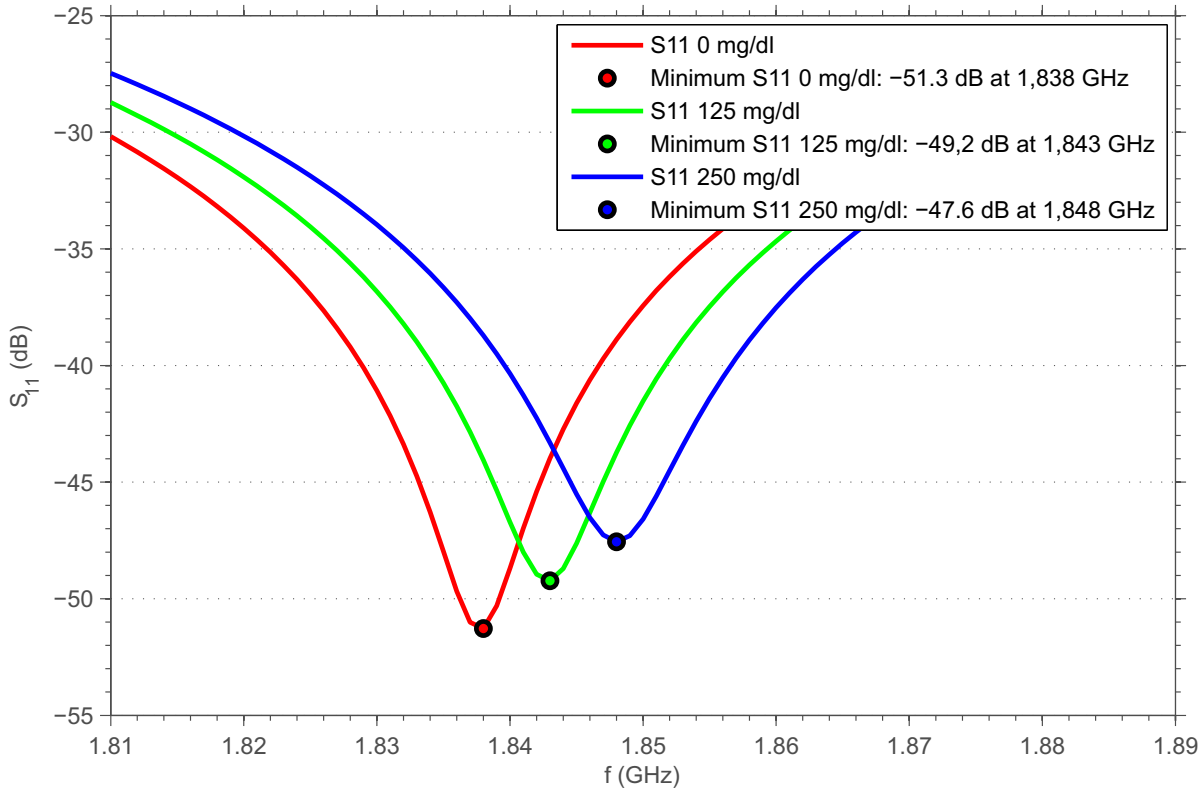
The magnitudes of reflection coefficients of the sensor depending on frequency, LUT and different glucose concentrations were simulated and are plotted in Fig. 3.2. The numerical results confirm the above mentioned statement. The glucose concentrations chosen for the numerical simulations were 0, 125 and 250 mg/dl. By the physiological saline-glucose solutions the resonant frequenecy shifts about 5 MHz if glucose concentration changes from 0 to 125 or from 125 to 250 mg/dl. By the blood-glucose solutions there are much bigger resonant frequenecy shifts. If glucose concentration changes from 0 to 125 mg/dl and from 125 to 250 mg/dl the frequency shifts 200 and 300 MHz, respectively.

The measurements were performed at the room temperature (23 °C). The goal was just to investigate whether the shifts of the sensor's resonant frequency depending on glucose concentration is comparable with those numerically simulated and whether they are sufficient for estimation of the glucose concentration in LUT.

Fig. 3.3 shows measured sensor resonant frequencies dependent of LUT and glucose concentration. For the physiological saline-glucose solutions (Fig. 3.3 (a)) there is no statistically evident relation between the glucose concentration and resonant frequency. This is consistent with the fact that already for 0 mg/dl glucose concentration and 6 independent measurements the measured resonant frequencies lies in an interval between 1.666 and 1.682 GHz. This shift is even bigger than the predicted shift for glucose concentration change from 0 to 250 mg/dl. Probably minimal temperature and/or volume change of LUT produced bigger change of resonant frequency than the change in glucose concentration itself. On the other hand, the trend shown in Fig. 3.3 (b) for pig blood-glucose solutions is clear. The shifts of sensor resonant frequencies corresponding to change in glucose concentration between ref. value and ref. value + 125, ref. value + 125 and ref. value + 250 and between ref. value + 250 and ref. value + 500 mg/dl are 43, 43, 86 MHz, respectively.

There is also a significant difference, by a factor of 4.7 to 7, between measured and simulated changes of resonance frequency.

In [28], measurement of frequency shift of another sensor was performed and reported resonant frequency shift there was about 125 MHz for glucose concentration change from 91 and 330 mg/dl. If a linear dependence is considered this would lead to a slope of 65 MHz for 125 mg/dl concentration change. The difference between the resonant frequency shift reported in [28] and here is only by a factor of $65/43 = 1.5$. It has to be noted, that our measurements were performed at the room temperature while the measurements reported in [28] were performed at 37 °C. Another explanation could be that the considered sensors have different sensitivity.



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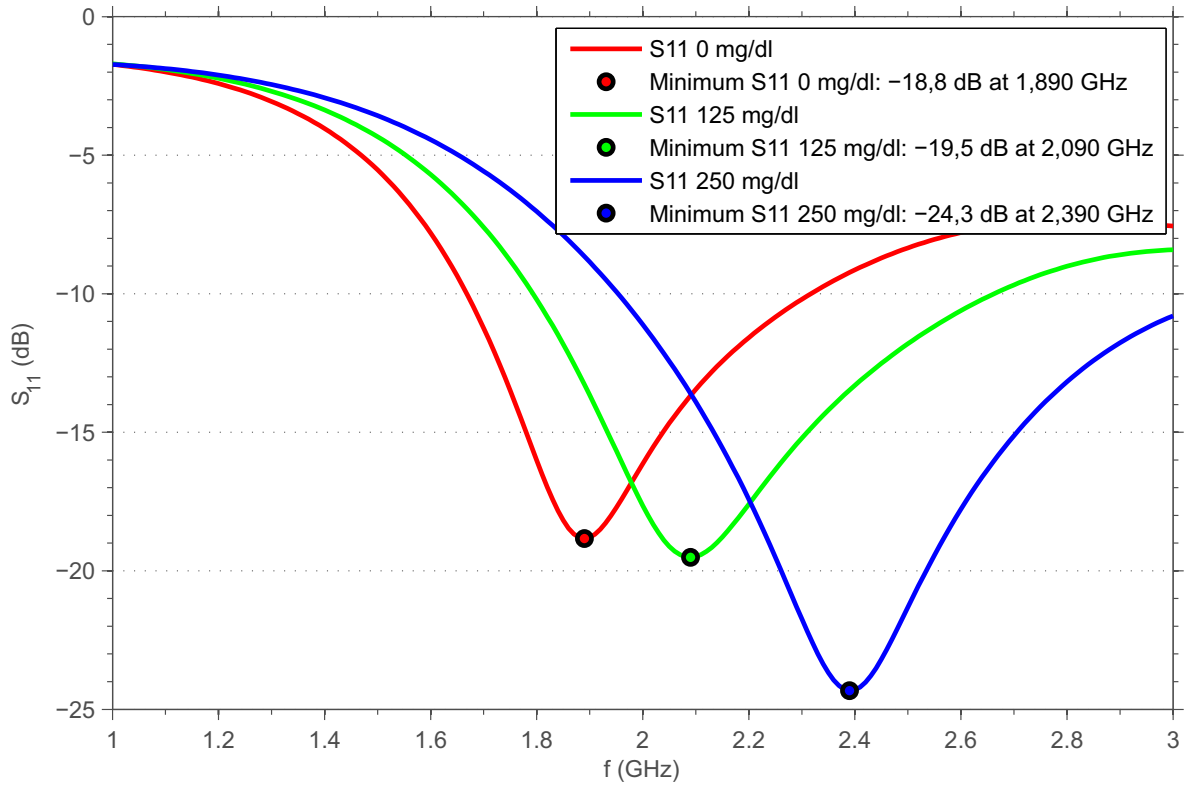
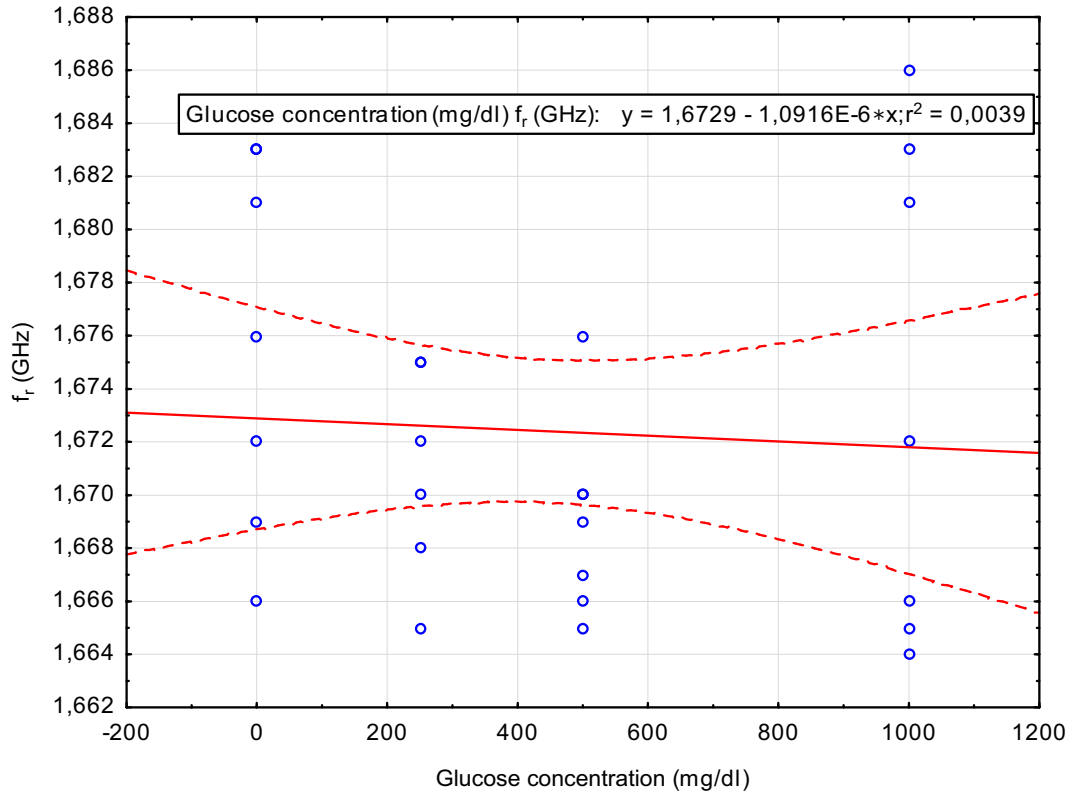


(*b*)

Figure 3.2: Computed S_{11} of the sensor with container virtually filled with (*a*) physiological saline-glucose solutions [31] and (*b*) blood-glucose solutions [28].

Even though a difference of factor 1.5 is not satisfactory, it is much better than a factor 4.7 - 7. This is an indication that mathematical model of dielectric properties of blood-glucose solutions reported in [28] should be improved by repeating the measurements presented there. Also we can conclude that physiological saline-glucose solutions are not a suitable model of blood for the purpose of development of non-invasive blood glucose monitoring system.



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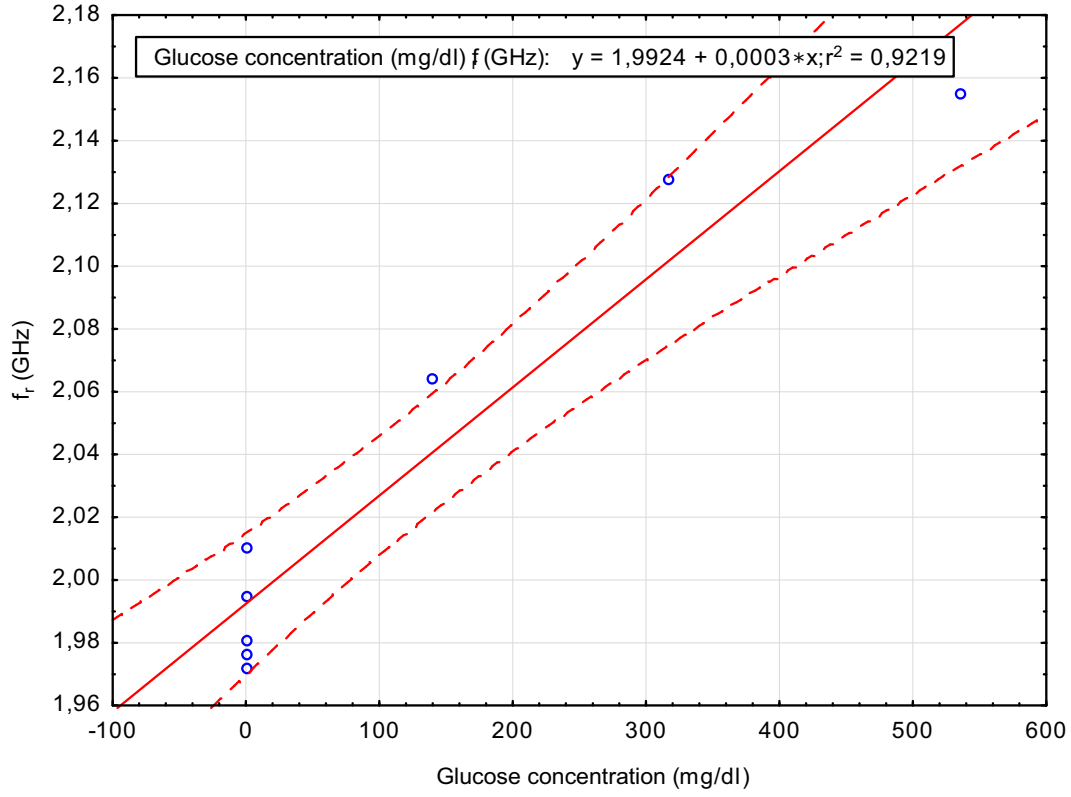

(*b*)

Figure 3.3: Dependence of sensor resonant frequencies (*a*) on glucose concentration of physiological saline-glucose solutions and (*b*) on glucose concentration of pig blood-glucose solutions, dashed red lines denotes 95 % confidence interval.

4 Sensor Based on Artificial Transmission Line Section

In this section, as mentioned above, a microwave sensor based on an artificial transmission line is proposed and designed for non-invasive blood glucose monitoring. The design starts with creation of a numerical model of the sensor in the commercial full-wave numerical simulation tool COMSOL Multiphysics. The numerical model includes blood-glucose solution models with various blood glucose concentrations. The sensitivity of the sensor is virtually estimated by means of numerical simulations and compared to a sensor based on a section of a conventional microstrip transmission line of the same length and width. Some issues of the sensor are discussed and ways to overcome the issues are proposed.

4.1 Methods

Sensor Geometry and Numerical Model

The sensor proposed here is a passive two-port sensor based on an artificial TL section implemented in the MS technology. Artificial TLs, as considered here, are inspired by conventional TLs, additionally equipped with serial capacitors and shunt inductors so that their electrical properties mimic the electrical properties of a 1D metamaterial (MTM). The sensor consists of N_c unit cells and each unit cell is comprised of a serial interdigital capacitor and a shunt MS inductor grounded on one end using a cylindrical via hole. Each of these distributed circuit elements possesses an intrinsic shunt capacity and serial inductance, collectively forming a composite right left handed (CRLH) structure. A layout and a whole sensor are, for $N_c = 4$, depicted in Figs. 4.1 and 4.3, respectively. A single unit cell is depicted in Fig. 4.2. On the top of the sensor (covering the metallic layout of the TL) a thin coating layer is proposed. The coating layer constitutes the side of the sensor that is virtually in a direct contact with the biological tissue under test. On the ground plane side, two SMA connectors are placed. The numerical ports assigned to the SMA connectors are used for the evaluation of S-parameters. In a future prototype, the coating layer should prevent electrostatic discharge to ports of a vector network analyzer as well as reduce the loss at the sensor resulting from the dielectric and conductive loss in the biological tissue under test. In the present study, the biological tissue under test is modeled using blood-glucose solutions. Some sensor dimensions, if not dependent on other parameters or not included in the parametric study, are listed in Tab. 4.1. Dielectric properties of different domains in the numerical model are listed in Tab. 4.2. Dielectric properties of the substrate and coating layer are adopted from the GML1000 substrate from GIL Technologies. The height of the substrate, the coating layer and the blood-glucose solution is 1.5 mm, 0.1/0.2 mm, 60 mm, respectively.

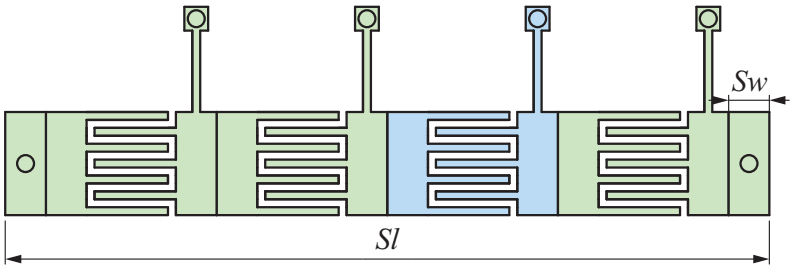

Figure 4.1: Layout of the proposed artificial TL sensor with four unit cells. A single cell is marked blue. The figure does not show proper proportions. Sensor dimensions are listed in Tab. 4.1 or in Sec. 4.1.

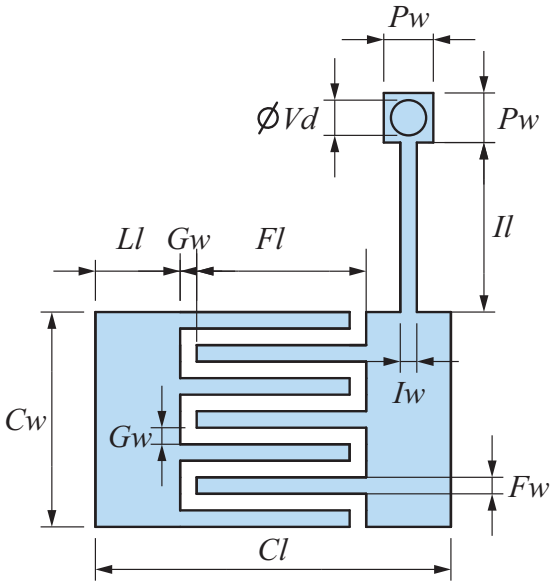

Figure 4.2: Layout of the unit cell of the proposed artificial TL sensor. Figure does not show proper proportions and dimensions of the sensor are listed in Tab. 4.1.

Table 4.1: Dimensions of the sensor

Parameter Name	Parameter Value	Parameter Description
Gw (mm)	0.1	Gap Between Fingers
Iw (mm)	0.1	Inductor width
Vd (mm)	0.5	Via Diameter
Vw (mm)	1	Via Pad Width
Sw (mm)	1.6	Side Pad Width
Ll (mm)	0.2	TL Section Length
Sl (mm)	20	Sensor Length
Nf (-)	7, 9, 11	Number of Fingers
Nc (-)	5, 7, 9	Number of unit cells

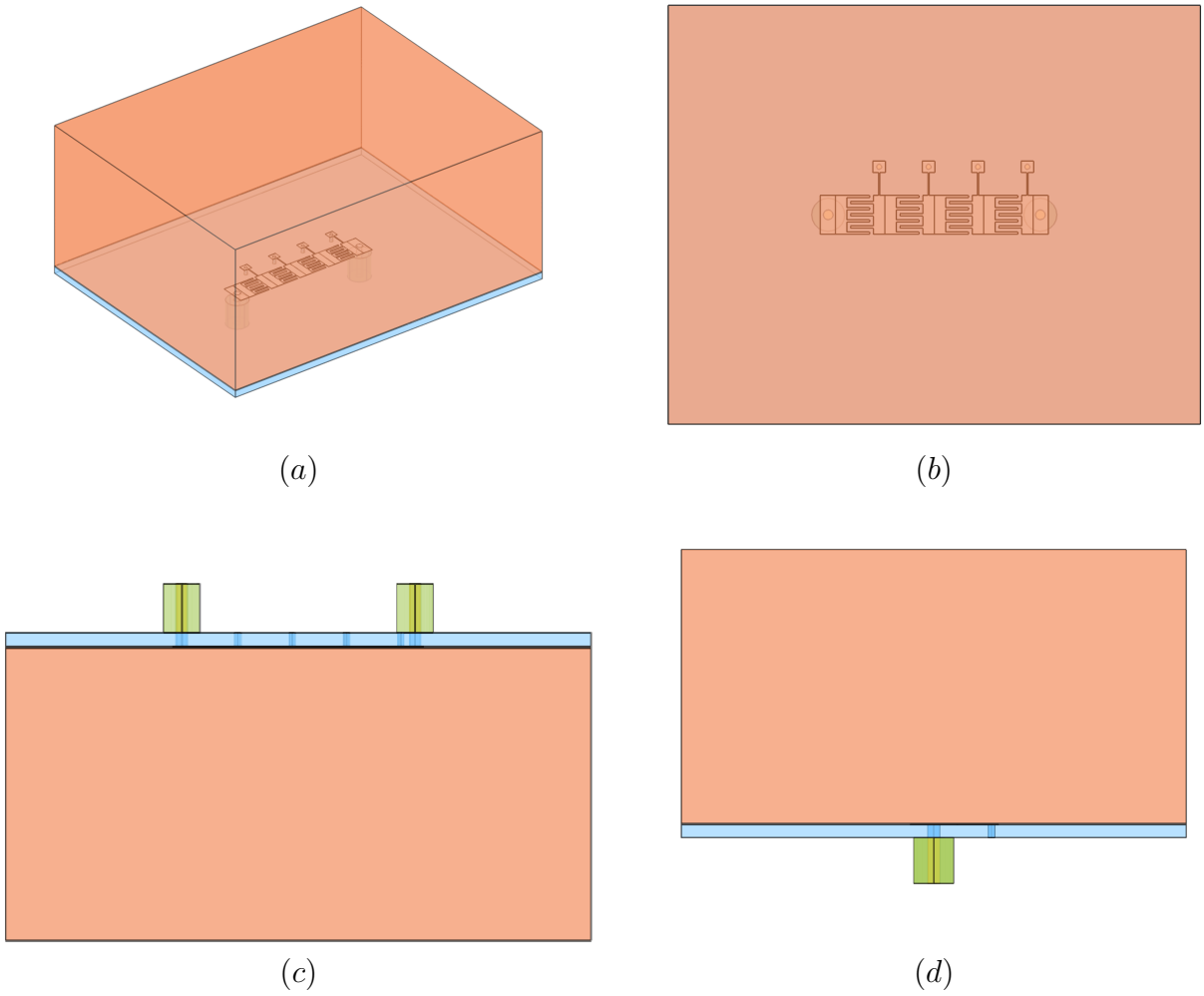

Figure 4.3: Sensor and model of biological tissue (a) perspective view, (b) xy view, (c) zx view, (d) yz view.

Table 4.2: Dielectric properties of different domains of numerical model

Domain	Relative Permittivity ε_r (-)	Equivalent Conductivty σ_e (S/m)
Substrate @ 2 GHz	3.24	0.0014
Coat. layer @ 2 GHz	3.24	0.0014
Blood Gluc. Solution	Defined in [28]	Defined in [28]

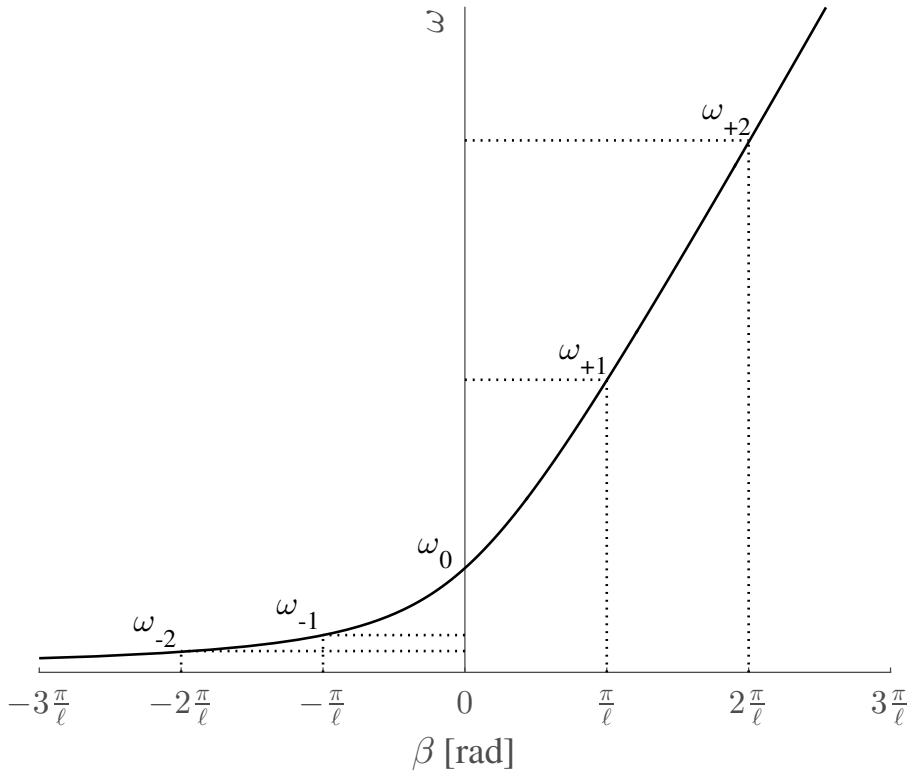

Figure 4.4: Dispersion diagram of a lossless balanced CRLH TL (adapted from [35])

Working Principle

The phase constant β of a TL is dependent, among others, on its effective permittivity. Since the dielectric properties of blood glucose solutions are dependent on the glucose concentration, the phase constant β of the considered sensor is dependent on its effective dielectric properties. The phase of the transmission coefficient S_{21} of the sensor is influenced as well. The electrical quantity that is measured using a VNA is the phase shift difference of the transmission coefficient S_{21}: $\Delta\varphi = \varphi_2 - \varphi_1 = \ell\beta_2 - \ell\beta_1 = \ell\Delta\beta$ on a single working frequency f. While the β of a conventional transmission line would be linear (for the frequency-independent effective permittivity), it is well-known (e.g. [35]) that MTM CRLH transmission lines show a non-linear dispersion diagram $\beta(\omega)$, as depicted for illustrative purposes in Fig. 4.4. For frequencies in the vicinity of the lower cut-off frequency, they show a region where, due to the negative hyperbolic dispersion diagram $\beta(\omega)$, the phase of S_{21} changes rapidly.

Model of Dielectric Properties of Blood-Glucose Solution

In the current work, a mathematical model of dielectric properties of blood-glucose solution was adopted from [28], implemented as a MATLAB [33] function and imported into a COMSOL Multiphysics [36] numerical model of the sensor. Within the model, the real part of the complex permittivity of BG solution is dependent on frequency as well as glucose concentration, while the imaginary part is frequency-dependent only. Relative permittivity and equivalent conductivity of blood for different BGC are listed in Tab.

Table 4.3: Dielectric properties of blood glucose solutions at 2 GHz for different BGC [28].

BGC (mg/dl)	Relative Permittivity ε_r (-)	Equivalent Conductivty σ_e (S/m)
0	69.4325	1.4895
25	67.2436	1.4895
50	65.0547	1.4895
75	62.8658	1.4895
100	60.6768	1.4895
125	58.4879	1.4895
150	56.2990	1.4895
175	54.1101	1.4895
200	51.9211	1.4895
225	49.7322	1.4895
250	47.5433	1.4895

Table 4.4: Different conditions regarding blood glucose concentrations [37].

Different Conditions	BGC	
	(mmol/l)	(mg/dl)
Hypoglycemia	< 4	< 60
Normal Glycemia	4 - 6	72 - 108
Hyperglycemia for fasting adult	> 11.1	> 200
Hyperglycemia 2 hours after meal	> 7	> 126

4.3. Ranges of BGC corresponding to hypoglycemia, normal glycemia, hyperglycemia are listed for readers' convenience in Tab. 4.4. In this thesis, BGC in range from 0 to 250 mg/dl will be considered, covering physiological as well as non-physiological concentrations. Even though physiological BGC ranges from 72 to 108 mg/dl, non-physiological concentrations as high as 250 mg/dl can be observed in diabetes patients.

Parametric study and methodology of BGC evaluation

In the performed parametric study, the length of the sensor was set to 2 cm in order to ensure a compact size, reduce the number of parameters as well as to make performance comparisons of different sensors easier. Just for the purpose of comparison, the split ring resonator sensor, published in [18], has an outer diameter of the split ring of 2.9 cm and the overall sensor (including shielding) diameter of approximately 3.5 cm. Furthermore, we considered two different numbers of fingers $N_f = 7$ and 10 and width of gap between the fingers $G_w = 0.1$ mm. The parametric study considered three different numbers of unit cells $N_c = 4$, 5, 6, 7 and 9 with different numbers of fingers of interdigital capacitors $N_f = 7$,7, 7, 9 and 11, respectively. Furthermore, different width of unit cell C_w according to other parameters were considered. For each set of parameters, the length of inductors I_l was adjusted to keep the lowest resonance frequency for BGC = 125 mg/ml

Table 4.5: Parameters of considered ATL sensors

ATL sensor	N_c	N_f	f_{res} (GHz)	t_{coating} (mm)	Cw (mm)	Fl (mm)	Il (mm)
A	5	7	2.02	0.2	1.3	2.86	2.1
B	5	7	1.963	0.2	2.0	2.86	1.3
C	7	9	1.982	0.2	1.7	1.85	2.85
D	7	9	1.989	0.1	1.7	1.89	2.55
E	9	11	2.011	0.1	2.1	1.36	2.85

at approximately 2 GHz.

Evaluation of each sensor sensitivity starts with a simulation for BGC = 125 mg/dl. The working frequency of the sensor should be approximately 2 GHz and equal to the lowest resonance frequency − a peak of simulated $|S_{21}|$. For each set of parameters the BGC was increased from 0 to 250 mg/ml in increments of 25 mg/ml. The amplitude and phase of S_{21} was recorded. Furthermore, the difference between the phase of S_{21} for the corresponding BGC and the phase of S_{21} for BGC = 125 mg/dl was evaluated. Some numerical results and the corresponding parameter sets of the parametric study are listed in Fig. 4.5 and Tab. 4.5, respectively. The phase differences for some parameter combinations and considered BGCs are plotted in Fig. 4.5.

4.2 Results and Discussion of Chapter 4

In similar way, as each sensor sensitivity was evaluated in 4.1, the sensor could be used in *in vivo* measurements. The working frequency could be set to the value of the measured lowest resonance frequency, and the phase of S_{21} at the same frequency can be used as reference for later phase measurements. Since the calibration curve (Fig. 4.5) of the sensor E is nearly linear, a two point patient-specific calibration could be sufficient. The two necessary BGC points could be obtained via an invasive technique.

The performance of sensors developed here was compared to performance of sensors based on sections of conventional MS TLs virtually placed in vicinity of the blood glucose solution. For the purpose of the comparison a 2D numerical model of the MS TL cross-section was set, keeping the same cross-section as of the sensor (the same substrate, strip and coating layer thicknesses; the same permittivity and conductivity of the substrate, coating layer and of the blood glucose solution; MS TL width equals to C_w). By means of the 2D numerical simulations, it was possible to estimate a complex propagation constant of such MS TL sensor depending on the BGC of the blood glucose solution. Considering the length of the MS TL and two extreme values of BGC, 0 and 250 mg/dl, it was possible to estimate maximal phase shifts of the conventional MS TL sections. 2 cm-long MS TLs with strip width of 1.3 and 2.1 mm shifts the phase of transmission coefficient at 2 GHz, about 6.03° and 4.64°, respectively. Artifical TL sensors with C_w of 1.3 and 2.1 shown maximal phase shifts of 23° and 73°, respectively. The here developed artificial TL sensors have sensitivity of a factor from 4 to 16 times higher (for the same strip thickness) than the conventional MS TL sensors.

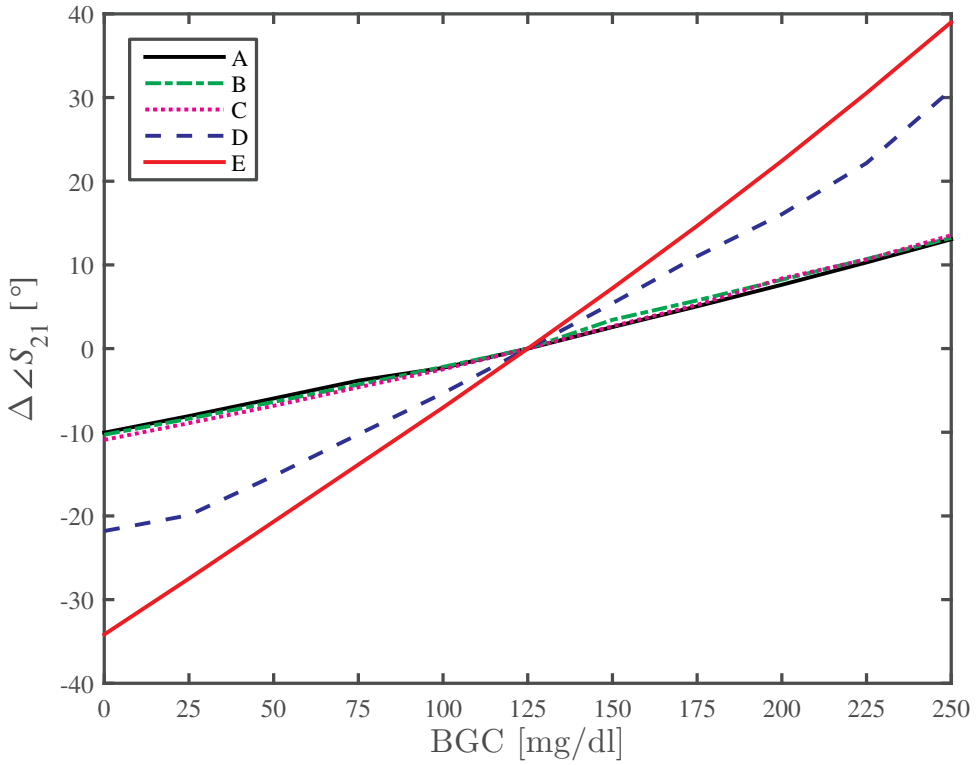

Figure 4.5: Phase shift of S_{21} as a function of BGC. A−E correspond to five different artifical TL sensors listed in Tab. 4.5.

During the development of the sensor, it has been observed, that the thickness of the coating layer influences two important sensor properties. Without the coating layer, the amplitude of S_{21} is very low and it could be a problem to accurately measure the phase of the transmission coefficient. On the other hand, too thick coating layer decreases the coupling between the biological tissue and EM waves propagating along the sensor and degrades the sensitivity. Please note the effect of coating layer thickness on sensitivity as well as on magnitude of trasmission coefficient is evident from results listed in Fig. 4.5.

In Fig. 4.5, results for sensors A and B which differes mainly in their thickness show no significant sensitivity difference.

In our numerical model the parameter Ll was set to a fixed value. Therefore any change of number of unit cells, while the total length of the sensor S_l was kept the same led to a decrease of a serial capacity per unit cell. Therefore we had to, for increased number of N_c, increase also number of fingers N_f in order to maintain resonance frequency at approximately same value.

5 Conclusions and Outlook

In this Chapter, a microwave sensor for in vitro blood glucose level monitoring was designed, manufactured and tested using two LUTs with different glucose concentrations, namely physiological saline-glucose and pig blood-glucose solutions. Resonant frequency shifts of the sensor depending on LUT and its glucose concentration were simulated as well as measured. No trend of shifts of resonant frequencies for physiological saline-glucose solutions were detected by measurements. The shifts are probably masked by shifts caused by small changes of dielectric properties of LUT due to small changes of room temperature. The shifts of resonant frequencies for pig blood-glucose solutions showed clear linear trend with a slope which could be used for estimation of glucose level. Based on the results obtained in this chapter it can be concluded that the physiological saline-glucose solutions are, at least in the considered frequency range, not suitable models of blood-glucose solutions for experimental design/evaluation of blood glucose level monitoring systems.

The sensor presented in the Chapter 3 has not been optimized in terms of sensitivity. Furthermore, it is not small enough for a non-invasive in vivo measurements. Such sensor should fit on an earlobe or could be placed above one of arteries e.g. on wrist, temple, behind the knee, etc.

Furthermore, a planar compact microwave sensor based on an artificial transmission line was proposed for non-invasive blood glucose monitoring. Corresponding numerical model was built and a parametric study was performed with the goal to find dimensions of the sensor leading to sensitivity suitable for accurate monitoring of glucose in blood. The achieved sensitivity was compared to a sensitivity of a sensors based on a section of conventional MS transmission line of the same length and width. The sensitivity of the sensor proposed here is up to 16 times higher compared to the conventional MS TL sensor. Due to relatively high number of different parameters and flexibility of the artificial transmission lines, proven already in previous works [38,39], it is probable, that the sensitivity can be further increased.

Currently, our sensors based on ATL are manufactured. First they will be tested on blood-glucose solutions and later in healthy volunteers. Depending on the test results sensors will be adapted and tested again. In case sensors show reliable results in healthy volunteers they will be tested clinically in collaborations with colleagues at 3rd Medical Department, 1st Faculty of Medicine, Charles University and General Faculty Hospital in Prague.

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H-index (with self citations)	3
No. of citations WoS	42

Selected Journal Publications in Last 5 Years

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