A Highly Sensitive Interdigital Biosensor for Cancer Cells Dielectric Characterization Using Microwave Frequencies

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Abstract— **This paper describes the design and assessment of a highly sensitive micro biosensor functioning at microwave frequencies. The proposed technique allows single step dielectric characterization and measurement of human cells. In this work, two resonators are etched on the center of the planar device. Their microscopic sensing area is an Inter-Digital Capacitor (IDC) used to guarantee an intense electric field, especially between 15 and 35 GHz. Hence, the inter resonators detection capabilities are demonstrated on normal (HaCaT) and cancerous (Glial) biological cells, which are shaped as solid octagonal with the electrical proprieties found in the literature. Experimental results on human cells are presented showing the biosensor's ability to differentiate at least two particular cell types by means of frequency.**

Keywords - biosensors; inter-digital; capacitor; planar resonator; biological cell.

I. INTRODUCTION

In electrical approaches, the term dielectric spectroscopy, which describes the interaction of an electromagnetic field with biological elements, has become a topic of increasing research interest in many fields, including biological and medical fields [1][2].

Dielectric spectroscopy is therefore highly important in non-invasive characterization of living biological cells [3]. Moreover, microwave frequencies can be used in different biological researches for investigating the properties of living matter by means of electromagnetic waves. Thus, at high frequency, the electric field penetrates biological elements unimpeded so that significant induced that wavelengths are roughly equal to the dimensions of living matter [4]. Also, dielectric proprieties which are related to biological parameters of tested cells are ideally done in a label-free manner and with electromagnetic readout.

Moreover, water is the single most abundant chemical fund in cells, accounting for 70 % or more of the total cell mass [5]. It shows relaxation (γ) dispersion that is suitable for microwaves, with a corresponding frequency located around 20 GHz [6], by means of its molecular reorientation dynamic. It is now possible in this range to better understand cancer mechanisms that constitute strong challenges to the biologists and physicians communities.

Several kinds of bio-detection methods have been adapted for the development of tools dedicated to both manipulation and analysis, even with a low number of cells. In particular, we mention the high sensitivity mechanical method [7][8], optical (using fluorescence properties) [9][10] or even electrical method. Nevertheless, specific markers are used in order to have an efficient way to discriminate cells, which can strongly modify cell properties and damage them. Contrarily, electronic detection methods [11][12] become interesting as they can be label-free.

Based on similar sensor topology, this paper presents a CoPlanar Waveguide (CPW) resonator based on IDC structure. The CPW-fed IDC biosensor has been designed using standard microelectronics technologies which permits to attain cell scale. In order to integrate the IDC sensor on lab-on-chip, its planar configuration makes it a good candidate for this system approach which is used also for microfluidic method [13].

We propose an original biosensor design based on microwave frequency impedance measurement for biological cells. The biosensor is designed and simulated using a full-wave electromagnetic simulation tool. Thanks to its structure, this bio detection technique presents the advantage of working with a very limited number of cells. The presented biosensor successfully discriminates between different cell types by means of frequency shifts.

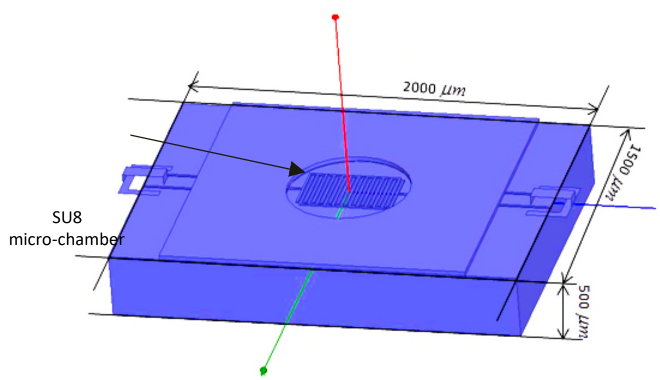

Figure 1. 3D view of proposed biosensor

After a review of the analysis, the modeling and the characterization of this microwave resonator (Section 2), the simulation results on the two types of human cells, normal (HaCaT) and cancerous (Glial) cells are shown in Section 3 and the dielectric parameters are extracted. Finally, conclusions are given in Section 4.

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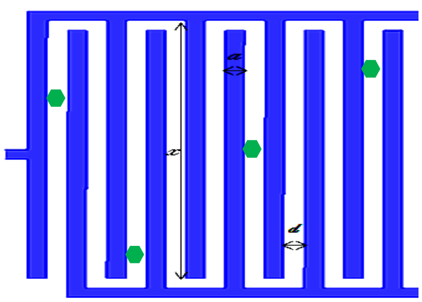
II. Biosensor Design

A. RF design

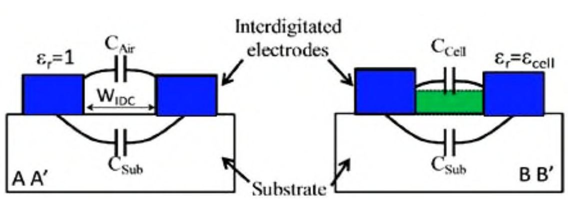
Using the electromagnetic simulation software High Frequency Structure Simulator (HFSS), the biosensor was designed to have several structural resonances between 15 and 35 GHz when a biological cell was present.

Hence, the proposed cell biosensor design is based on a coplanar resonator structure made with an inter-digital capacitor. The sensor is designed on a 500 um thick fused silica substrate for its low loss properties in the RF frequency domain and its transparency that allows easy observation of cells through it. Indeed, molecular properties of pure glass substrate provide a suitable and comfortable surface for cell growth and colonization. Moreover, metal lines are made of gold for its biocompatibility and its fast conductivity, with thickness up to 7µm. As shown in Figure 1, a 20 um thick SU8 resist layer is deposited on the sensor surface to delimitate the micro-culture chambers in order to allow locating cells only in the areas where the EM field is strongly concentrated (between comb capacitor fingers).

The dimensions of the proposed coplanar resonator biosensor, as shown in Figure 2 and Table I, are optimized to resonate at microwave band frequency.



(a)



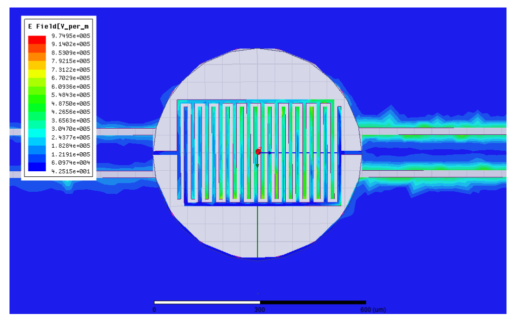
(b)

Figure 2. (a) Top view and (b) cross view of IDC structure

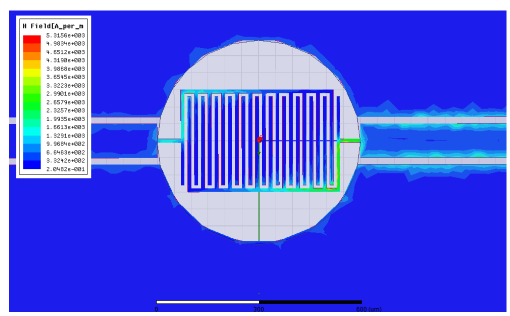
TABLE I. Dimension details of proposed structure

x	Length of finger	270
a	Width of finger	10
d	Spacing between fingers	10
n	No of finger	24
h	Height of substrate	500
ε_{sub}	Dielectric constant of a substrate	3.78
ε'_r	Dielectric constant of a test cell	--

As illustrated in Figure 3(a), at resonance frequency the IDC lines concentrate on most of the electric field. The electric field between fingers is 9.749×10^5 V/m and near inductor is 6.097×10^4 V/m. On the contrary, the magnetic field, as shown in Figure 3(b), is minimum at the IDC area at 5.315×10^3 A/m and near the inductor is 2.048 A/m.



(a)



(b)

Figure 3. (a) Electric and (b) magnetic field distribution in the coupling comb capacitor.

Accordingly, these areas will be highly sensitive to any dielectric perturbation and have to be carefully designed to efficiently interact with cells. So, spaces between these metal lines are set to 10 um that represent dimensions in the same range than cell size offering a better interaction with the microwave signal.

B. *IDC Structure*

IDC is the main constituent of the proposed design, and each element is discussed as follows. The dimensions of the IDC structure are shown in Figure 2. The coplanar geometry can be transformed into a parallel plate geometry using a conformal transformation technique [14]. The capacitance of the IDC (C_{IDC}) can now be calculated as:

$$C_m = nx(C_{air} + C_{sub})\,pF\,, \tag{1}$$

where x is the length of the IDC finger, n the total number of fingers, and C_{air} and C_{sub} are the line capacitance of coplanar strip with air and dielectric substrate, respectively. C_{air} and C_{sub} are given as [15]:

$$C_{air} = 4\varepsilon_0 \varepsilon'_r \frac{K(k'_1)}{K(k_1)}\, pF/cm, \tag{2}$$

$$C_{sub} = 2\varepsilon_0 (\varepsilon_{sub} - 1) \frac{K(k'_2)}{K(k_2)}\, pF/cm, \tag{3}$$

$$k_1 = \left(1 + \frac{2a}{2d+a}\right)\left(\sqrt{\frac{1}{1+\frac{2a}{d}}}\right), \tag{3}$$

$$k'_1 = \sqrt{1 - k_1^2}, \tag{4}$$

$$k'_2 = \frac{\sinh\left(\frac{\pi a}{4h}\right)}{\sinh\left(\frac{\pi}{2h}\left(\frac{a}{2}+d\right)\right)} \times \sqrt{\frac{\sinh^2\left(\frac{\pi}{2h}\left(\frac{3a}{2}+d\right)\right) - \sinh^2\left(\frac{\pi}{2h}\left(\frac{a}{2}+d\right)\right)}{\sinh^2\left(\frac{\pi}{2h}\left(\frac{3a}{2}+d\right)\right) - \sinh^2\left(\frac{\pi a}{4h}\right)}}, \tag{5}$$

$$k_2 = \sqrt{1 - k_2'^2}, \tag{6}$$

$$\frac{K(k)}{K(k')} = \frac{2}{\pi}\ln\left(2\sqrt{\frac{1+k}{1-k}}\right) \tag{7}$$

III. SIMULATION RESULTS

In this section, we present the frequency response of the designed sensor before and after addition of a sample with different permittivities and losses at different positions on the sensor.

A. *Exprement作 verification and Discussion*

After modeling the sensor, the resonance frequency of the biosensor in this work is chosen to be between 15 and 35 GHz and two peaks in the microwave frequency band are observed, as frequencies above 10 GHz allow penetrating the intrinsic content of biological cells. It is the case that biological cells of interest are too small with an average diameter about ~10 µm. As the sensor sensitivity is concerned, the region of the resonator is, therefore, optimized to increase interaction between the EM fields and cells. In the present sensor design, 10 µm gaps have been used.

The investigations focued on two cell types: HaCaT cell, which represents normal cells with measured relative effective permittivity of 42 ± 3 and conductivity of 1.8 ± 0.3 S/m at 18 GHz and Glial cell, which represent tumor cells with measured relative effective permittivity of 36 ± 3 and conductivity of 0.1 ± 0.02 S/m at 18 GHz [15].

For all simulation results, we suppose that the cells are in dry condition. This supposition is deemed fundamental because signal absorption losses at high frequencies present by aqueous saline solutions, which degrade RF performances of the device.

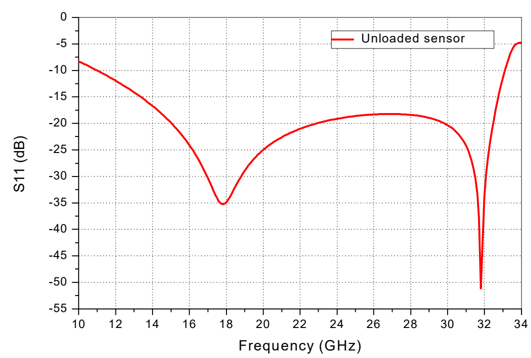


Figure 4. The simulated magnitude of the transmission coefficient (S11) of the resonator biosensor is unloaded.

Cancer cells are modeled as solid octagonal (Figure 2), with a radius of 10 µm and the implemented medium is equivalent to ≈ 8 cells. As shown in Figure 4, the simulated reflection spectrum (S11) presents two peak frequencies at 17.8 GHz and 31.8 GHz, respectively, when the detection area is empty (unloaded). Figure 5 illustrates the simulated magnitude of the reflection coefficient (S11) of the coplanar resonator biosensor when the interdigital capacitor lines are loaded with a single normal (HaCaT) cells. Figure 6 depicts the simulated reflection spectrum (S11) of the biosensor, when the gaps between sensitive lines are loaded with cancerous (Glial) cells. The interaction (field/cells) in this region creates an electromagnetic perturbation frequency shift in S11 response, whose amount varies from a cell type to another.

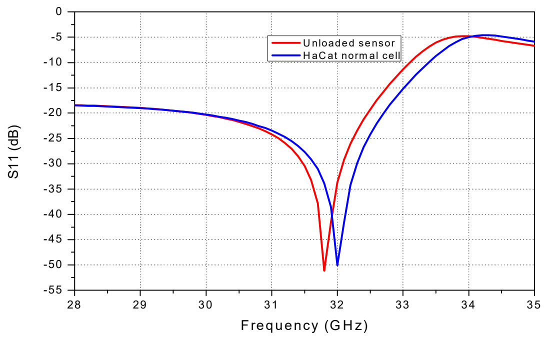


Figure 5. The simulated magnitude of the transmission coefficient (S11) of the biosensor when is loaded with a normal (HaCaT) cell

Hence, the effect of eight living HaCaT cells on the biosensor have been observed resulting in a frequency shift of about 200 MHz and an increase of the S11 parameter of about 0.7 dB while Glial cells show a frequency downshift of 200 MHz and a slight decrease of 11.7dB in the S11 parameter.

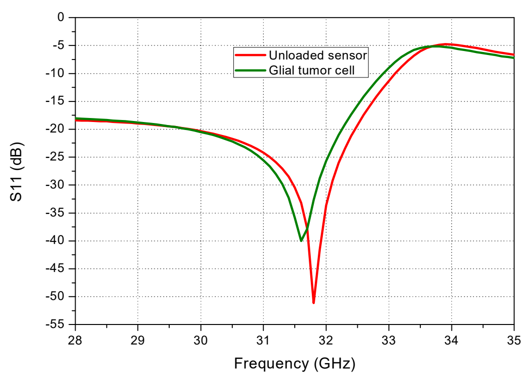


Figure 6. The simulated magnitude of the transmission coefficient (S11) of the biosensor when is loaded with a cancerous (Glial) cell

Nevertheless, according to these simulation results, the biosensor can discern between the two cell types. In practice, the cell's global permittivity can be extracted with a good accuracy probably on a large frequency band around the sensor resonance frequency.

IV. CONCLUSION

The developed sensor model has the advantage of differentiating permittivity based on the resonant frequencies and is well adapted for low concentration conditions. The results confirm the hypothesis that the electrical characteristics of normal and cancerous cells are different. These preliminary simulation results can be used for other cell types discrimination. It was also highlighted that these simulations can become a relevant alternative to conventional labeling techniques and could be more suitable for complex and sensitive biological samples studies. The practical realization of these sensors always remains a challenge for us, especially as it requires a very high level technology. Another interesting direction will be to develop analytical modeling of the sensor resonant frequency versus the biological media permittivity, based on graphene substrate.

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