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DIELECTRIC SPECTROSCOPY OF GLUCOSE TURNOVER IN CANCEROUS TISSUE MODEL

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Abstract: *The article focuses on dielectric spectroscopy, measurement and calculation of dielectric properties of normal and carcinoma tissue phantoms. Special attention is paid to the investigation of dielectric properties of carcinoma tissue model with different water and glucose content. The paper devotes itself to investigation of dielectric qualities of pure glucose, glucose in solutions as well as in phantoms of biological tissues directing the attention at its manifestation at tumours cells investigation by means of microwaves. Experimental results from these areas are given and their evaluation is presented.*

Key words: *carcinoma tissue, dielectric properties, Warburg effect, microwave frequencies, dielectric spectroscopy, glucose*

INTRODUCTION

The pathological differences between normal and cancerous cells affect their composition and morphology and shape their dielectric spectrum.

Microwave techniques for biomedical applications aimed at cancer treatment or diagnosis, either by imaging or spectroscopy, are promising. Their use relies on knowledge of the dielectric properties of tissues, especially on a detectable difference between malignant and normal tissues.

The microwave dielectric method has been one of the most reliable techniques for investigation of the dynamic structure of macromolecules and dielectric relaxation measurements have been applied to various biological tissues [1-2]. This and other similar information inspired us to pay attention to observation of some materials behavior in biological tissues, particularly in carcinoma tissues. Because the cancerous cells function anaerobic, their glucose turnover is very high and tumors have higher water content than the corresponding normal tissue. Many cancer cells consume glucose avidly and produce lactic acid rather than catabolizing glucose via the TCA cycle (citric acid cycle), which is key for generating ATP (adenosine triphosphate) in nonhypoxic normal cells [3]. Cancer cells display high levels of glucose uptake and lactate production. The shift toward amount of glucose increasing and lactate production in cancer cells, even in the presence of adequate oxygen, is termed the Warburg effect or aerobic glycolysis. Since hypoglycaemia has been shown to be tumouricidal for cancers that display the Warburg effect, various schemes to block glucose utilization have been investigated. But in vivo it is difficult to selectively target glucose utilization in malignant cells without harming normal cells.

In terms of dielectric properties, one would expect cancerous tissue to have higher relative permittivity and conductivity at microwave frequencies compared to normal tissue. Morphological in cancerous tissue changes affect the dielectric properties in the frequency range of γ dispersion.

To use of the electrical characteristics of tissue to understand, image, or treat cancerous tissue relies on the availability of good representative data across the dielectric spectrum of normal and cancerous tissue.

Any changes in tissue physiology produce changes in the tissue electrical properties [2]. This principle has been used to identify or monitor the presence of various illnesses, such as cancer, or conditions such as body fluid shift, blood flow, cardiac output, and muscular dystrophy.

1 THEORY AND DISPERSION MODEL

Large differences exist in dielectric properties of biological materials. These differences are determined, to a large extent, by the fluid content of material. For example, blood and brain conduct electric current relatively well. Lungs, skin, fat and bone are relatively poor conductors. Liver, spleen, and muscle are intermediate in their conductivities.

The dielectric properties of biological tissues are highly dispersive due to the cellular and molecular relaxation, generated by different parts of the tissues at different frequencies. In the microwave region the dominant relaxation is the dipolar relaxation of free water molecules. Therefore, the dielectric properties of the

tissues in microwave region are highly correlated to the water content. At the frequencies in microwave region (~10^9 Hz) the rotations of the polar molecules in the water begin to lag behind the electric field oscillations.

For biological tissues and polymers, the dielectric dispersion can consist of several components associated with small side chain movements and the whole macromolecular movement.

Therefore biological materials like markedly heterogeneous material do not exhibit single time constant relaxation behaviour which corresponds with single relaxation Debye-type response [1]

$$\dot{\varepsilon} = \varepsilon_\infty + \frac{\varepsilon_\mathrm{s} - \varepsilon_\infty}{1 + \mathrm{j}\omega\tau}, \qquad (1)$$

where the time constant (relaxation time) $\tau = \frac{1}{RC}$ corresponds to a relaxation frequency $f_\mathrm{r} = \frac{1}{2\pi\tau}$, which is the half way between its low and high frequency values, the limiting values of permittivity, ε_∞ and ε_s, are known as static and optical relative permittivity, respectively and ω is angular frequency.

In concentrated systems, as well as biological tissues the electrical interaction between the relaxing species will usually lead to a distribution of relaxation time, $p(\tau)$ and with the help of this distribution, the following relation is used

$$\dot{\varepsilon} = \varepsilon_\infty + (\varepsilon_\mathrm{s} - \varepsilon_\infty)\int_0^\infty \frac{p(\tau)}{1 + \mathrm{j}\omega\tau}\mathrm{d}\tau - \mathrm{j}\frac{\sigma_\mathrm{i}}{\omega\varepsilon_0}, \qquad (2)$$

where σ_i is the static ionic conductivity of the medium by a constant field influencing very low frequencies.

To enable a more wide-band model of the heterogeneous tissue properties the time constant can be divided in several regions to match different type of relaxation. Due to the complexity and composition of biological tissues is such that each dispersion region may be broadened by multiple contributions to it. The broadening of dispersion could be empirically accounted for by introducing a distribution parameter, thus giving an alternative to the Debye equation, (2). Gaussian, Cole-Cole, Fuoss-Kirkwood, and Davidson-Cole are some of the distribution function introduced in [2]. The most useful distribution was first introduced by Cole and Cole [2], which leads to

$$\dot{\varepsilon} = \varepsilon_\infty + \frac{\varepsilon_\mathrm{s} - \varepsilon_\infty}{1 + (\mathrm{j}\omega\tau)^{1-\alpha}} \qquad (3)$$

where α represents the distribution parameter which is a measure of broadening of dispersion and ionic conductivity is for microwave frequencies in (3) ignored.

Frequently experimental results yield a circular arc, rather than a semicircle, with its centre below the abscissa in graphical interpretation of imaginary part of complex permittivity ε'' against real part of complex permittivity ε'. There is a variety of other shapes obtained in practice, such as the skewed arc in which the high frequency end of the arc approximates to a straight line. Anything other than a perfect semi-circle is now taken as evidence of co-operative effects within the dielectric like biological tissues.

Both Debye (1) and Cole-Cole (3) models are examples of physically realizable system. The complex permittivity of a physically realizable system follows the Kramers – Krönig relations [4].

Due to the complexity and composition of normal and cancerous tissues, [4] extended Cole-Cole model is commonly used as physic-based compact representations of wideband frequency dependent dielectric properties

$$\dot{\varepsilon} = \varepsilon_\infty + \sum_n \frac{\Delta\varepsilon_n}{1 + (\mathrm{j}\omega\tau_n)^{1-\alpha_n}} \qquad (4)$$

where $\Delta\varepsilon_n = \varepsilon_\mathrm{s} - \varepsilon_n$, and ε_n is relative permittivity appertaining to one relaxation process, In this model ε_∞, $\Delta\varepsilon$, τ are variable parameters chosen to fit the experimental data. We set the α, which is an empirical parameter that accounts for the observed broad distribution of relaxation time constants in tissue, to 0.6 [1-2].

Equation (4) is used in wide frequency band between 10 Hz – 100 GHz by individually choosing the parameters for different tissues.

2 EXPERIMENTAL RESULTS

We have investigated the very glucose and on the other hand its behaviour in the tissue. Although pure glucose is not present in living organism we considered for useful to have separate value of its relative permittivity for its successive concentration in solution and tissues as well as influence on microwave signal.

Microwave technique provides a great range of measuring methods [4] for the complex permittivity determination from gases via liquids, up to solid materials according to the dielectric in question.

The measurement usually exploits an approximate knowledge of complex permittivity or some methods assuring its unambiguous determination is chosen (e.g. some of waveguide methods). In spite of that a considerable unhomogenity of investigated dielectric materials, in our case biological tissues phantoms and also owing to a polysemy of results obtained from measurement (e.g. periodicity of functions used in computations) causes some uncertainty in determination of the complex permittivity of the final product.

For complex permittivity of normal and cancerous tissue phantom with various glucose content measurements we have chosen the waveguide Hippel's method. This method has proved successful for the measured phantoms and it behaves to the most accurate methods for dielectric properties of biological materials measurement.

The measurements were carried out in frequency of two microwave bands –from 4.5 GHz to 16 GHz [5]. The experimental set-up for both bands is in Fig. 1.

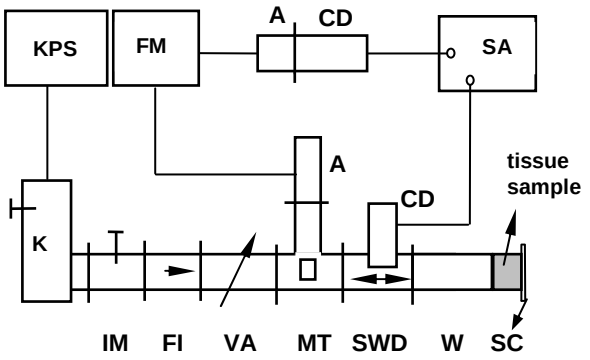

Fig.1: Experimental set-up for complex dielectric constant measurement. K – klystron, KPS – klystron power supply, FM – frequency meter, SA – selective amplifier, IM – impedance match, FI – ferrite isolator, VA – variable attenuator, MT – magic T, SWD – slotted section, W – waveguide, SC – short circuit, A – adapter, CD – crystal detector

A new approach to this problem [6] with the theoretical reason and its verification on the material with a known permittivity and also measurement results on the material used in technical practice.

The whole procedure lies in the fact that through this method is unambiguously determined real part of complex permittivity ε, (in some cases loss factor $\mathrm{tg}\delta$, too) and on the basis of known ε it is possible to proceed to the choice to some of known methods enabling to obtain $\mathrm{tg}\delta$.

Our method uses a rectangular waveguide filled with the measured sample and our approach provides a technique how to obtain the wavelength in the investigated sample λ_{gd}. After taking all circumstances relating to electromagnetic waves in waveguides propagation we can obtain for the wavelength λ_{gd} in the waveguide filled with the dielectric sample [7]

$$\lambda_{\mathrm{gd}} = \frac{\lambda_0}{\sqrt{\varepsilon - \left(\frac{\lambda_0}{\lambda_{\mathrm{c}}}\right)^2}}, \qquad (5)$$

where λ_0 is the wavelength in free space and λ_{c} is critical wavelength in waveguide. As λ_0 and λ_{c} are known and our approach gives the way how to obtain λ_{gd}, ε can be unambiguously calculated from the formula [7]

$$\varepsilon = \left(\frac{\lambda_0}{\lambda_{\mathrm{gd}}}\right)^2 + \left(\frac{\lambda_0}{\lambda_{\mathrm{c}}}\right)^2, \qquad (6)$$

which follows from (5). First we have verified this method on the material with the known relative permittivity (Plexiglas – $\varepsilon = 2.2 \div 3.4$ for microwave frequencies region) and the obtained values of minima positions in dielectric sample in waveguide are plotted in Fig. 2.

From graph, Fig. 2 it is easy to get λ_{gd} and from (6) to calculate ε. For the measured Plexiglas sample the relative permittivity ε = 2.6.

In the same way we have measured the pure glucose and glucose in solution dielectric properties.

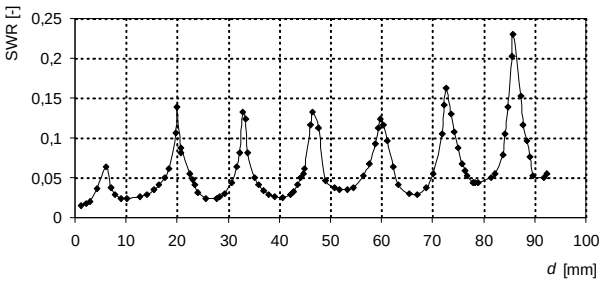

Fig.2: Dependence of standing wave ratio (SWR) on the sample depth for Plexiglas

The samples of pure glucose and of healthy and cancerous tissue phantoms (physiological solution of glucose) were putted in a rectangular waveguide for X-band. The samples of glucose were made from solid dried pure glucose and the measuring frequency was 8200 MHz at all measurements. The waveguide was filled up with close fitting pure glucose sample. By successive shortening the sample and permanent measuring the absolute value of minima $\dot{E}_{\mathrm{min}}$ and maxima $\dot{E}_{\mathrm{max}}$. The standing wave ratio (SWR) by using relation [5]

$$\mathrm{SWR} = \frac{\left|\dot{E}_{\mathrm{min}}\right|}{\left|\dot{E}_{\mathrm{max}}\right|} \qquad (7)$$

of pure glucose was measured under condition of the new method mentioned above which allows determining of investigated sample dielectric constant unambiguous value, Fig. 3.

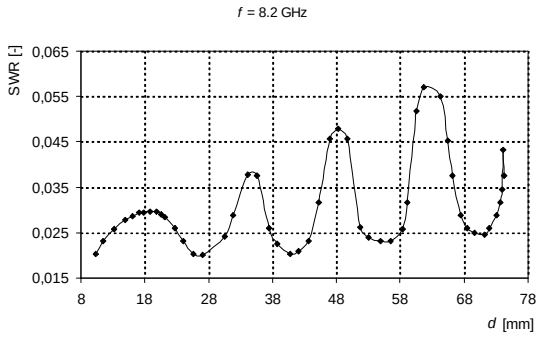

Fig.3: Dependence of SWR on the length of pure glucose sample

As it is possible to establish the wavelength in the waveguide filled with the sample from the graph, the dielectric constant could be calculated. Knowing λ_0, λ_{c} and having read $\lambda_{\mathrm{gd}} = 28$ mm from the graph the

dielectric constant of glucose was from (6) calculated $(\varepsilon = 2.37)$.

After having obtained reliable values of dielectric constant of glucose we could proceed to the next step of our intention that is to find out the dielectric constant of water solution with glucose.

For this purpose we have used the same previous waveguide method as for the dependence SWR on the sample length of glucose.

The dependence of SWR on solution level for individual glucose solutions in water are plotted in Fig. 4. As in the Fig. 4 individual curves show minima and maxima from which λ_{gd} could be obtained and dielectric constants from (6) calculated. In consequence of higher attenuation in water solutions only $\lambda_{gd}/2$ and $\lambda_{gd}/4$ could be measured.

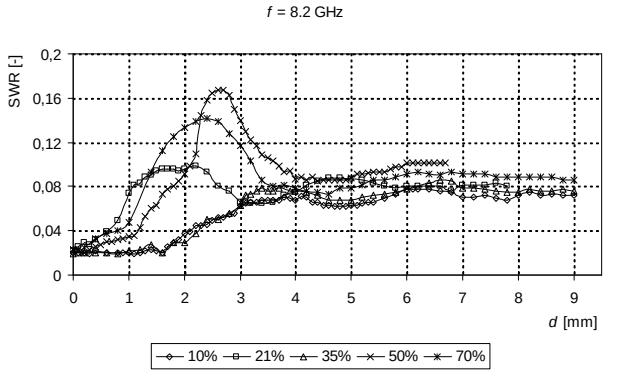

Fig.4: Dependence of standing wave ratio (SWR) on the solution water – glucose level

In the same way as for pure glucose there were from (6) calculated dielectric constants for individual water solutions of glucose and the results are plotted in Fig. 5.

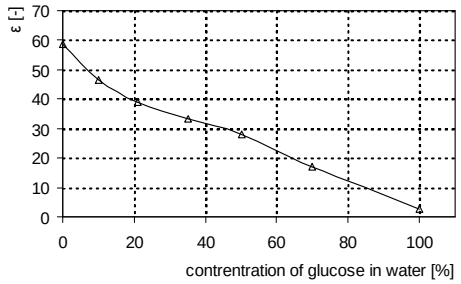

Fig.5: Dependence of solutions dielectric constant on concentration of glucose in water

3 CONCLUSION

The knowledge of dielectric properties on the one hand of the very glucose and on the other hand its influence on the dielectric constant of solutions gives a good jumping-off point for investigation $\dot{\varepsilon}$ in solution compound from more phases as it is in blood too. This knowledge can help to make action of microwaves on tumour cells more effective.

The knowledge of biological tissues dielectric properties has been one of the keys to increasing our understanding of their structure and function in normal and pathological state. The obtained results for pure glucose and water solution of glucose relative permittivity value give a reliable way out for the investigation of glucose turnover in healthy and cancerous tissue.

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