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Metamaterial formalism approach for advancing the recognition of glioma areas in brain tissue biopsies

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Abstract: Early detection of a tumor makes it more probable that the patient will, finally, beat cancer and recover. The main goal of broadly defined cancer diagnostics is to determine whether a patient has a tumor, where it is located, and its histological type and severity. The major characteristic of the cancer affected tissue is the presence of the glioma cells in the sample. The current approach in diagnosis focuses mainly on microbiological, immunological, and pathological aspects rather than on the "metamaterial geometry" of the diseases. The determination of the effective properties of the biological tissue samples and treating them as disordered metamaterial media has become possible with the development of effective medium approximation techniques. Their advantage lies in their capability to treat the biological tissue samples as metamaterial structures, possessing the well-studied properties. Here, we present, for the first time to our knowledge, the studies on metamaterial properties of biological tissues to identify healthy and cancerous areas in the brain tissue. The results show that the metamaterial properties strongly differ depending on the tissue type, if it is healthy or unhealthy. The obtained effective permittivity values were dependent on various factors, like the amount of different cell types in the sample and their distribution. Based on these findings, the identification of the cancer affected areas based on their effective medium properties was performed. These results prove the metamaterial model capability in recognition of the cancer affected areas. The presented approach can have a significant impact on the development of methodological approaches toward precise identification of pathological tissues and would allow for more effective detection of cancer-related changes.

1. Introduction

Cancer is one of the leading causes of death worldwide, and its diagnosis is critical to initiate therapies [1]. The apoptosis of cancer cells plays a pivotal role in shaping of organs in tandem with cell proliferation, regulation, and the removal of defective as well as excessive cells in immune system [2–4]. Hence, it is imperative to develop sensitive detection technologies that allow to figure out if the biological tissue is cancerous.

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The rapid development of machine learning and particularly deep learning opens the wide avenues for the medical imaging community's interest in applying these techniques aiming to improve the accuracy of cancer screening [5]. Machine learning algorithms can analyse large amounts of data and solve complex tasks in a very short time [6,7]. The former can provide the fertile ground for helping physician to improve the accuracy and efficiency of making cancer diagnoses, selecting personalized therapies and predicting long-term outcomes. Artificial intelligence (AI) [8] describes a subset of machine learning that can identify patterns in data and take actions to reach pre-set goals without specific programming. Convolutional neural networks (CNNs) represent multiple inter-connected layers of AI algorithms that have learnable weights and can classify data with minimal pre-processing. Convolution is a mathematical operation that expresses the amount of overlap of one function as it is shifted over another function. The primary function of convolution in medical image processing is to extract features from input data. The CNN translates raw image pixels on the input end to scores at the output. When many CNN layers are stacked, they are called deep-CNNs. Deep CNNs exhibits several benefits in comparison with standard image reconstruction algorithms [9]. Despite all the advantages offered by the above described techniques, the main disadvantage of them is the tremendous computer resources required to fulfil the tasks. Doing so, the application of metamaterial based approaches will enable a more effective detection and identification of cancerous tissues with much less computer resources.

Recent studies of metamaterials [10–12] have created a large knowledgebase showing the importance of the metamaterial formalism in solving different types of biological problems [13–15]. Electromagnetic radiation in THz frequency range has provided a fertile ground for sensing, chemical and biomedical applications. THz metamaterials are made of periodically arranged sub-wavelength metal structures. It is worthwhile pointing out the similarity between the disordered metamaterials [16–18] and biological tissues and hence the applicability of the metamaterial formalism to treat the biological processes.

Calculation of effective permittivity of biological tissue has received tremendous attention during the past years. It is worthwhile noting that measurement of permittivity of biological tissue possessing nonlinear characteristics in frequency domain is quite a challenging task. [19,20]. From the contents of the above-mentioned literatures, there is no study applying metamaterial formalism for treating if the biological tissue is cancerous. This paper deals with the effective permittivity in biological system, especially brain, represented by the metamaterial formalism. Herein, we demonstrate a theoretical analysis on several typical models of effective permittivity in materials. We intend to explore the acceptability of the models in bio-tissues. The determination of the effective permittivity of the tissue samples allows for recognition of cancerous tissues.

2. Effective permittivity determination based on metamaterial formalism

Mouse brain tissue samples presented in Fig. 1 were used for investigations aiming to find out if the tissue is healthy. It is worthwhile noting, that 100 samples have been considered. Herein, we present only 4 of them. Histological sections were stained with standard haematoxylin and eosin dyes [21].

A popular method of measuring image features is to use algorithms that automatically partition an image into a set of regions of interest. This process is commonly called Segmentation [22]. To identify the location of different types of the cells composing the tissue sample, segmentation algorithms can be designed to locate the anticipated region boundaries and label all cells within a single continuous boundary as belonging to one region. Datasets of the cell types are created by taking into account geometrical shape, colour and size of the cells. From this segmentation a variety of measurements can be made using established methods [23]. A key benefit of this approach is in analysis time [24], which is much faster. Measurement by a predetermined software algorithm also allows results to be repeated without any inter-operator variation. We

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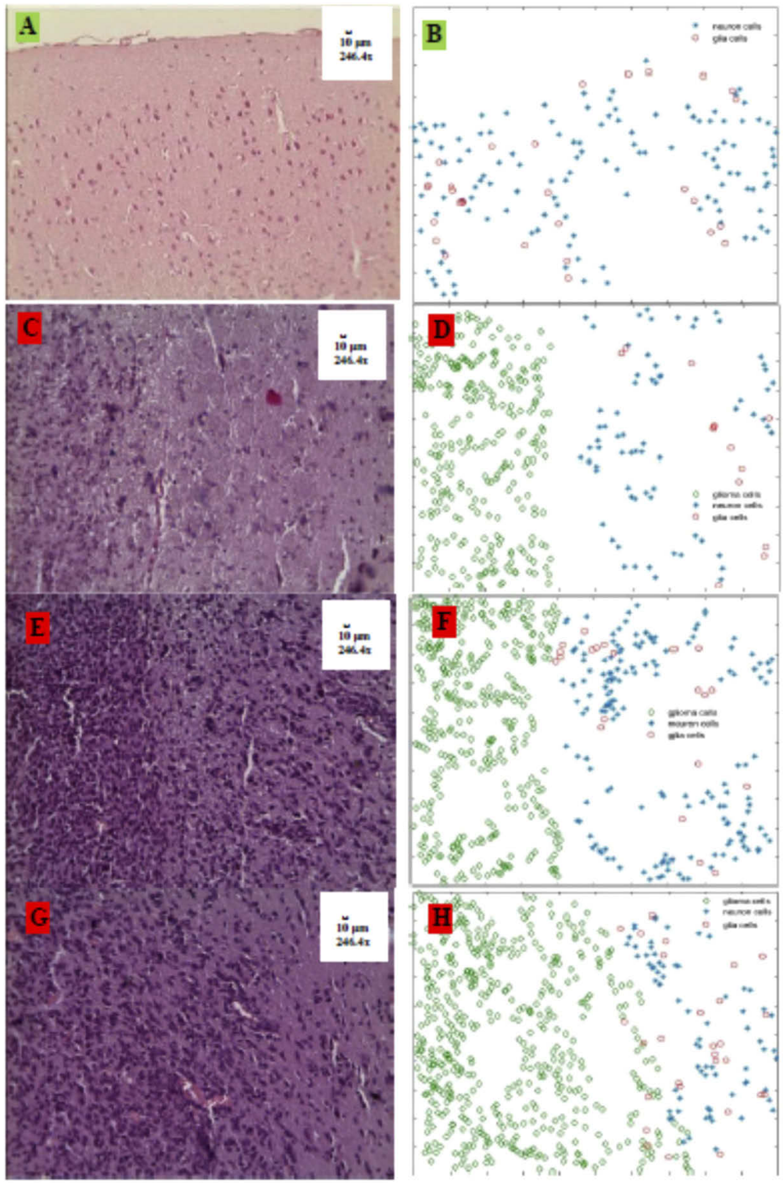

Fig. 1. Images of cancerous and non-cancerous mice brain biopsies (A, B – 39M, C, D – 138M, E, F – 153M, G, H – 154M). Glioma cells are marked with green hexagons, neuron cells – with blue asterisks, glia cells – with red circles. Tissue biopsies are presented in A, C, E, G Figures, digitized images made with "Digitizeit" software (www.digitizeit.de/)– in B, D, F, H.

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apply https://www.digitizeit.de/ software to distinguish all the cell types comprising the tissue under the consideration. The samples are saved by firstly providing examples of each cell type. Once the examples are provided, software is searching for the identical cells in the selected area of the tissue sample. It is worthwhile noting, that the geometrical size of the glioma cells is larger in comparison with other types. In other words, it is larger than 50 conventional units. On the contrary, glia cells are small and having a blue colour, the most prominent feature of the neuron cells at the images is the blurred colour. In other words, we implemented automated cell recognition and counting routine using *Digitizeit*, which is capable of distinguishing glioma cells from a background by training a software to recognize it. Contribution of the human beings at early stages of the cells database creation will be needed. The main advantage of the former approach is the faster operation time in comparison with OpenCV [25] for C# in Microsoft Visual Studio. The recognition algorithm based on Otsu thresholding, which is a threshold algorithm for picture segmentation that automatically selects the optimum value to separate two classes in a grey-level image [26], and colour detection form processed images for the cell size and position will require significant computer resources. It should be noted, that outputs are presented by the sets of x and y coordinates. In other words, finally we get the sets of the coordinates and each set corresponds to each cell group. The results were exported as .csv files. Matlab .m file is used to read the .csv file and to extract the information. The described technique allows us to plot datasets by using information about the coordinates. Moreover, the obtained data fully allows to apply metamaterial formalism. The chosen approach has a faster run time and requires less computer resources than cancer cell recognition techniques performed with OpenCV [25] for C# in Microsoft Visual Studio. Fluorescence microscopy and immunofluorescence techniques are employed as the typical methods for tumor cells identification and analysis, by imaging specific markers that depend on the phenotypes of the tumor cells [27]. However, application of such approaches stands for as quite challenging and complicated task. Namely, manual counting and analysis by trained technicians is needed. The former are prone to develop biased criteria and fatigue over time. This can lead to mistaken conclusions based on data. Aiming to achieve reliable reproducibility and deterministic interpretation one needs to implement a framework that can handle high data throughput in both, the hardware and software. Doing so, human intervention can be drastically minimized [28]. The metamaterial formalism stands for as a perfect tool seeking for the creation of the fully automated system without needs of the human intervention. Moreover, it allows to prevent the errors that might occur at the tissues digitizing stage. It is worthwhile mentioning, that the created techniques allow for calculating the critical limit of the glioma cells thus allowing to control the tumor development and even to prevent the cancer at the early stages. Although this limit has attracted particular research interest, the majority of past studies could only probe this limit by applying biological tissue digitization techniques. The iterative aspect of machine learning is important. Modes able to independently adapt to new data sources as they are exposed to new data. They capable of the learning from previous computations to produce reliable, repeatable results and based on them trustful conclusions in diagnostics minimizing the human subjectivism.

Figuring out whether the biological tissue is healthy, one needs to analyse it from the perspective of the effective medium approximation [29]. The application of the mentioned formalism is possible in case the geometry of the considered medium is clearly identified. Thus, we have applied image digitizer techniques aiming to identify the exact positions of all the cell types that the tissue consists of. Doing so, the coordinates of the glioma, glia and neuron cells were clearly depicted in samples presented in Fig. 1(A, C, E, G). It is of particular interest to examine the filling ratio of each type of the cells identified in the histograms. Moreover, the optical properties of each type of the cells should be described by applying Debye and Cole-Cole models [30]. Doing so, the complex dielectric spectrum for all cell types is provided in $\varepsilon(\omega)$ space.

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The cell shape and the shape of the intracellular structures are evaluated by means of the effective medium approximation. Establishment of tissue permittivity model for brain tissue biopsies would help us to simplify its complex structure. A typical theory is Debye model. It is very famous and explains many compositions well. Moreover, it was obtained on the basis of empirical formula [30]. It is a widely used model for studying the dielectric properties of biological tissues in frequency domain. Model of binary mixtures is usually used for investigating effective permittivity of mixture system because of its significance in understanding the intermolecular interactions. There are many well known permittivity models based on binary mixtures. However, they do not account for the frequency domain, for instance, the Bottcher-Bordewijk model [31], Maxwell-Garnett formula [32], Bruggeman formula [33] and Hanai formula [34]. Each theory can only be successfully applied to a certain type of composition. It is worthwhile noting, that the Bottcher-Bordewijk model suggests very well feasibility aiming to predict permittivity of a mixture [35], i. e. effective permittivity of the biological tissue sample. The model is represented as follows:

$$\frac{3\varepsilon_1}{2\varepsilon_{eff}+\varepsilon_1}f_1+\frac{3\varepsilon_2}{2\varepsilon_{eff}+\varepsilon_2}f_2=1 \tag{1}$$

Cell structure is of a random nature with some predictable average properties such as cell size and cell distribution density. It can be modelled by an aggregated of randomly distributed spherical shells. This model can be used to describe the two constituent materials. When the two-phase system is concerned, there is another famous model put forward by Skipetrov [36]. The former is obtained by solving Eq. (1) with respect to ε_{eff}, i. e.

$$\begin{aligned}\varepsilon_{eff} = {} & \frac{3\varepsilon_1 f_1}{4}-\frac{\varepsilon_2}{4}-\frac{\varepsilon_1}{4}+\frac{3\varepsilon_2 f_2}{4} \\ & -\frac{\sqrt{9\varepsilon_1^2 f_1^2-6\varepsilon_1^2 f_1+\varepsilon_1^2+18\varepsilon_1\varepsilon_2 f_1 f_2+6\varepsilon_1\varepsilon_2 f_1+6\varepsilon_1\varepsilon_2 f_2-2\varepsilon_1\varepsilon_2+9\varepsilon_2^2 f_2^2-6\varepsilon_2^2 f_2+\varepsilon_2^2}}{4},\end{aligned} \tag{2}$$

Here ε_1 denotes the permittivity of the neuron cells, ε_2 - of the glioma cells, f_1 and f_2 are the volume fractions of each cell type accordingly. Moreover, $\varepsilon_{\mathrm{eff}}$ is the effective permittivity describing effective properties of the medium. The dielectric properties $\varepsilon_k(\omega)$, $k=1$, 2, are calculated by using the Cole Cole spectral function [37].

$$\varepsilon_k=\varepsilon_k(\infty)+\frac{\varepsilon_k(0)-\varepsilon_k(\infty)}{1+(i\omega\tau_k)^{1-\alpha_k}}+\frac{\sigma_k}{i\varepsilon_0\omega} \tag{3}$$

with $\varepsilon_k(0)$ - static dielectric permittivity, $\varepsilon_k(\infty)$ - high frequency dielectric permittivity, τ_k – relaxation time, α_k – distribution parameter, σ_k – DC conductivity.

Doing so, the dependences of the effective permittivity upon frequency for different cases (differences in the volume fraction f, permittivities of the building blocks (cells)) have been obtained. The crucial result is the ability of the effective permittivity to behave in the extraordinary way characterized by the peak of effective permittivity curve in the certain case at the frequency range (0-10 THz) (Fig. 2) if the total amount of the glioma cells in the sample is greater than 5%. It is worthwhile noting, that one may experimentally determine the complex permittivity of material using Split Ring Resonator (SRR) metamaterial structure. A single SRR unit fabricated on a substrate arranged between transmitting and receiving probes acts as a test probe.

As shown from Fig. 2(a) effective permittivity values are negative. The tissue sample (with high likeness to the metamaterial) under consideration is not experiencing extraordinary behaviour. The former feature stands for as the description of the healthy tissue sample. It is worthwhile noting, that the biological tissue represented by the metamaterial (Fig. 2(b), 153 M) experiences extraordinary behaviour due to the certain amount of glioma cells in the sample being greater than the certain limit, i. e. 5%. We may conclude, that the tissue is unhealthy due to the extraordinary

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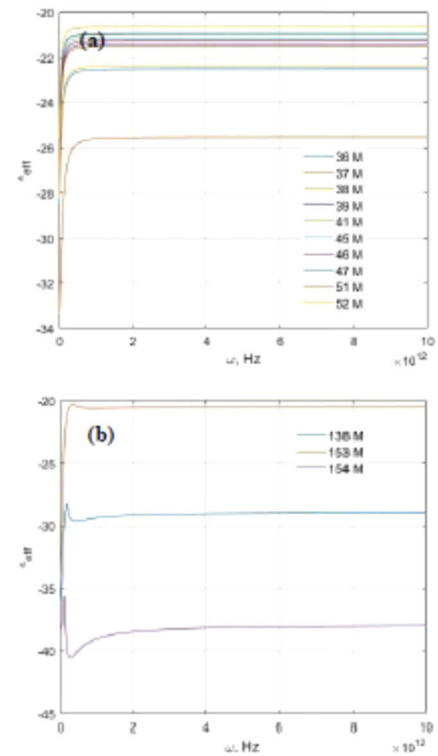

Fig. 2. Dependencies of the effective permittivities upon frequency for healthy (a) and unhealthy (b) samples.

behaviour of the effective permittivity curves, i. e. there is a certain peak at the frequency around 0.1 THz. Therefore, extraordinary behaviour appears, when presence of the unhealthy specimen(s) in the sample is greater than the certain limit. The high amplitude peak is observed in the case of 154 M sample. The former feature evidences the presence of the highly cancerous tissue zones. To conclude, one may figure out the stage of cancer by data depicted in Fig. 2(b). The higher amplitude of $\varepsilon_{\mathrm{eff}}$ corresponds to the late-stage cancer. Herein, stage refers to the extent of cancer and is based on factors such as how large the tumor is and if it has spread. Once the stage of cancer is known, it is possible to suggest the treatment and to make the prognosis.

Going further with what was described above as the extraordinary regime shift it becomes possible to evaluate pathological, healthy and intermediate "blocks" in the brain tissue biopsies (Fig. 3). Using this nomenclature 138M, 153M, 154M sample images were represented as the blocks of different colour (Fig. 3 B, D, F, H). Red blocks are assigned as a strongly affected with cancer, green – healthy, yellow – as intermediately populated with both types of the cells, non- and cancerous. It is worthwhile noting, that metamaterial experiences extraordinary behaviour for the intermediate case (yellow), for the highly affected zones (marked with red) effective permittivity ε_{eff} is strongly negative characterized by the jumps at the 0.1 THz frequencies.

Based on these results we suggest the highly effective recognition of the cancerous specimens in stained brain biopsies. Figure 3 clearly illustrates the role of the metamaterial formalism in detecting tumour regions. The schematic presenting the main steps of the applied techniques is shown in Fig. 4.

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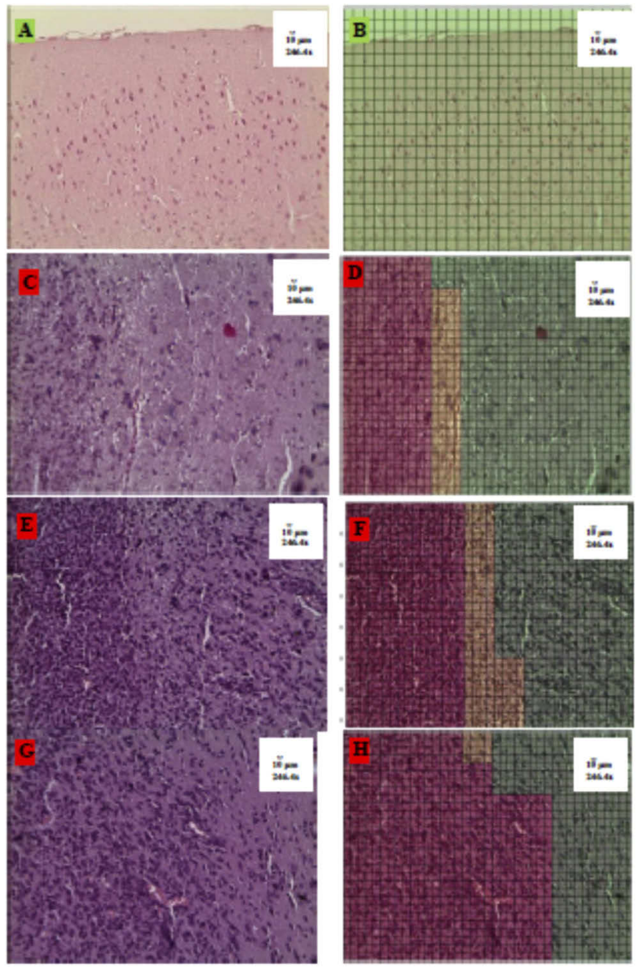

Fig. 3. Images of cancerous and non-cancerous mice brain tissue biopsies (A, B – 39M, C, D – 138M, E, F – 153M, G, H – 154M). Division of the tissue samples by the building blocks of different conditions is demonstrated, i. e. red – cancerous; green – healthy; yellow – intermediately populated. Tissue photos are presented in A, C, E, G Figures, Analysed images – in B, D, F, H.

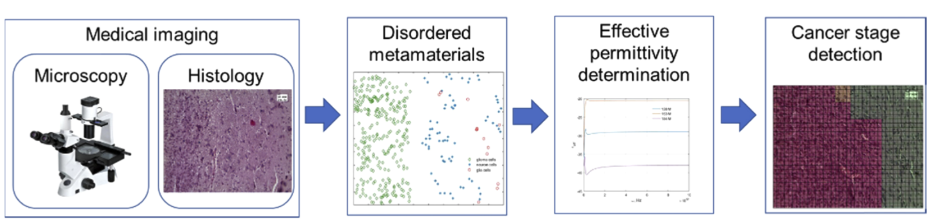

Fig. 4. Diagram of the methodology.

3. Conclusions

Aiming to approbate created algorithm the randomly chosen tissue samples (25 instances) have been considered. The described metamaterial approach allows for a precise recognition of the healthy and cancerous tissues. The obtained results have been approved by the histological analysis with 100% success rate. From the perspective of electromagnetism, organisms are composed of a large number of cells with different electromagnetic properties [38]. To conclude, we have demonstrated, that application of the metamaterial formalism to treat biological tissues under consideration works well, allowing to obtain effective permittivity plots that are strongly affected by the sample nature. Herein, we have investigated the effective permittivity parameter of brain from the theoretical point of view. Mechanism is analysed on effective permittivity in tissues based on its typical composition. Volume fraction of different cell types in brain is analysed based on the metamaterial approach. It is worthwhile noting, that metamaterial under consideration experiences extraordinary behaviour for intermediate cases. For the cancerous tissues effective permittivity is highly negative experiencing extraordinary jumps at the certain frequencies. Based on these considerations, it is possible to detect the damageability degree of the tissue building blocks. It is very meaningful to use the composite media model to explain the dielectric properties of the biological system aiming to recognize the cancerous tissues. Proposed technique allows to identify cancerous area automatically, without human involvement, and could help clinicians to treat the cancer.

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Disclosures

The authors declare no conflicts of interest.

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