



*Research article*

## A comment to improve tumor-treating fields therapy

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**Abstract:** Recent investigations have shown that special frequencies and intensities of electromagnetic waves could control the differentiations of some types of cells. Using this fact, tumor-treating fields (TTFields) therapy has been proposed as a technique which uses alternating electric fields of intermediate frequency (~100–500 kHz) and low intensity (1–3 V/cm) to disrupt the cell divisions of tumors. However, this technique may have harmful effects on ionic liquids around normal cells. For example, electrodes could induce an extra electrical current within blood vessels. To observe these effects, we connected electrodes to a slide that includes water and some extra ions and put them under a 1000× microscope. We found that some ions, microbes and cells move toward negative electrons and some go away. These attractions of cells by electrodes could cause the destruction of the brain. We also found some electrical currents within the liquid emerge which absorb or repel water molecules and induce some bubbles. If these types of bubbles arise within the blood vessels, they can exert a force on the membranes of normal cells and destroy them. To avoid these problems, we suggest that electrodes should be replaced by some electromagnetic sender/receiver which emits some special frequencies. These frequencies could be absorbed only by blood vessels around the tumors because these vessels may be created only to provide the needed food for tumor cells and thus have a different potential and electrical current as compared to vessels around normal cells. Thus, these tumor vessels could act as the antenna for TTFields.

**Keywords:** tumor; TTFields; therapy, bubble; blood

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### 1. Introduction

One of best electromagnetic field therapy methods is tumor-treating fields (TTFields), which applies low-intensity, intermediate-frequency electrical fields to treat tumors [1–5]. The generating

device of this technique has been built by Novocure and was approved in the USA and Europe for the treatment of newly diagnosed and recurrent glioblastoma multiforme (GBM); it has been applied in clinical trials for several other cancer types [5,6].

To date, many investigations have been done on this therapy technique. For example, a paper has described the macroscopic spatial distribution of TTFields generated in the human head, and of the microscopic field distribution in tumor cells. In addition, preclinical and clinical findings related to TTFields and principles of its operation have been investigated [7]. In another study, the authors evaluated whether TTFields-mediated cell death can elicit antitumoral immunity and would thus be effectively combined with anti-PD-1 therapy [8].

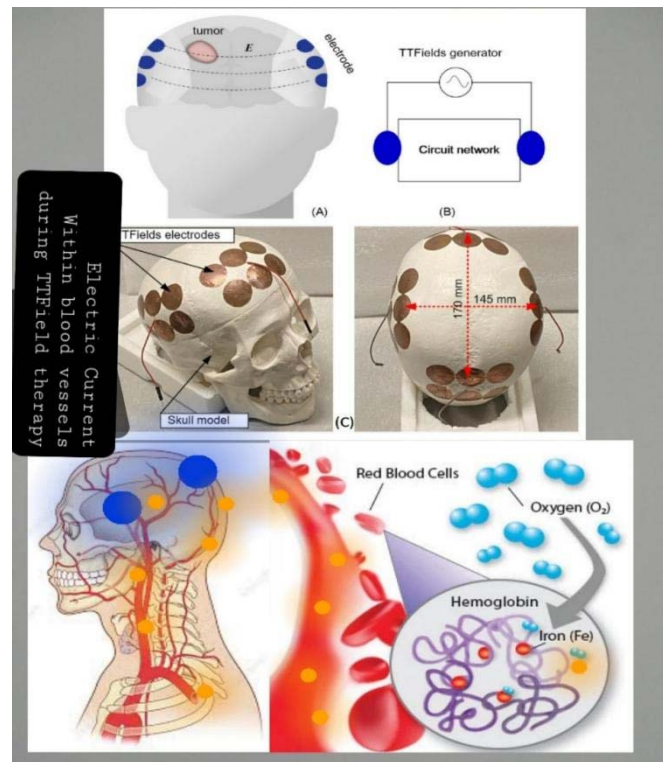
In another work, the authors have considered whether TTFields affect the regulation of autophagy in glioma cells. They found that autophagy is upregulated in glioma cells treated with TTFields, as demonstrated by an immunoblot analysis of the lipidated microtubule-associated protein light chain 3 [9]. Another group quantified Optune's duty cycle and predicted the steady-state temperature distribution in the head during GBM treatment [10]. Some other authors have provided an assessment of possible physical interactions between 100-kHz-range alternating electric fields and biological cells, as well as their nanoscale subcellular structures in particular [11].

In all of these investigations, electrodes have been located on the scalp. Thus, large currents may pass through healthy cells and destroy their membranes. We will show this by connecting electrodes to a slide including ionic liquid under a microscope. We will observe the induction of non-desired bubbles which could explode and destroy cells. To avoid this problem, we suggest long-distance radiation. This radiation should pass the normal cells and produce the needed voltage and frequency within the liquids or blood vessels around tumor cells.

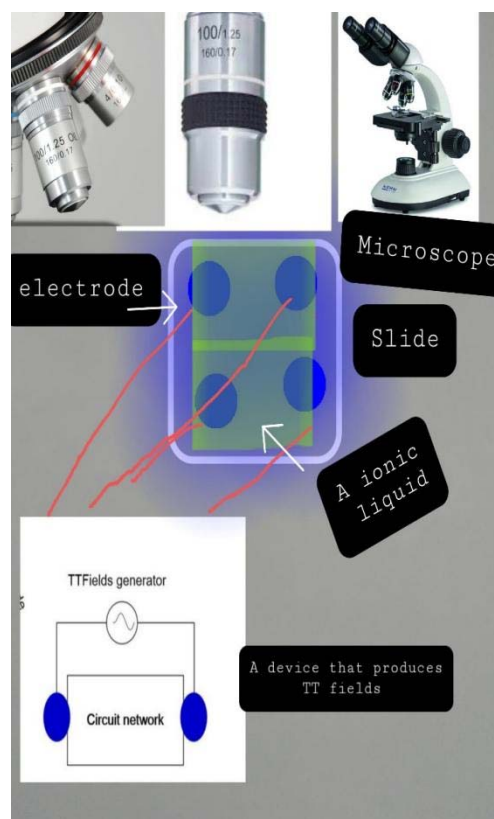
In Section II, we propose a method for considering the effects of electrodes on ionic liquids. In Section III, we show the results of our experiment. In Section IV, we discuss and propose a new TTFields therapy technique which has none of these harmful effects. The last section is devoted to the conclusion.

## 2. Materials and methods

In this section, we will show that electrodes on the scalp induce some electrical currents within the blood vessels of the brain. This is because that blood liquid includes ions and hemoglobin molecules. These molecules contain iron atoms which could act as the transmitter of waves and electrons or electrical currents. These currents could absorb or repel other molecules and produce some bubbles within the liquid. These bubbles could explode and destroy normal cells (see Figure 1). To observe these events, we need to connect a slide of ionic liquids to some electrodes and put it under a microscope (see Figure 2). Details of the materials and methods are given below.



**Figure 1.** Emergence of non-desired electrical current within blood vessels during TTFIELDS therapy.



**Figure 2.** Induction of bubbles within liquid by connecting electrodes to a slide of ionic liquid.

## 2.1. Materials

The materials of the experiment were as follows: microscope, electrodes, generator, water, oil, blood or other ionic liquid, wires, camera, milk and a sample of microbes.

## 2.2. Methods

First: We connected some electrodes to a generator which produces voltages and frequencies close to the applied voltage and frequency in the TTFields technique.

Second: We connected electrodes to a slide whose size is bigger than normal slides and could bear the electrical currents related to the electrodes. We put a 1–3-mm distance between the matter on the slide and electrodes.

Third: We mixed water with some ionic liquids. Blood is a very good choice; however, one can use a mixture of oil and water, or a mixture of milk and water.

Fourth: We built a sample of microbes within the liquids.

Fifth: We put the slide under a microscope and turned on the generator. We took some videos of the evolution within the liquids.

## 3. Results

In this section, we will discuss some observations of the induction of harmful bubbles by electrodes. In Figure 3, we observe that microbes and ionic molecules were attracted to an electrode. This is because most microbes and biological cells have charged particles on their membranes and could be attracted or repelled by electrodes. The same event may occur within the brain. Some cells could be more attracted and some less, and some distribution or destruction within the brain is likely to occur.

Regarding Figure 4, we added some ions and charged particles to the water and turned on the generator. It is clear that the electrical currents produced many bubbles, such as microbes, which could be seen less. Microbes may have disappeared through electrical currents and bubbles.

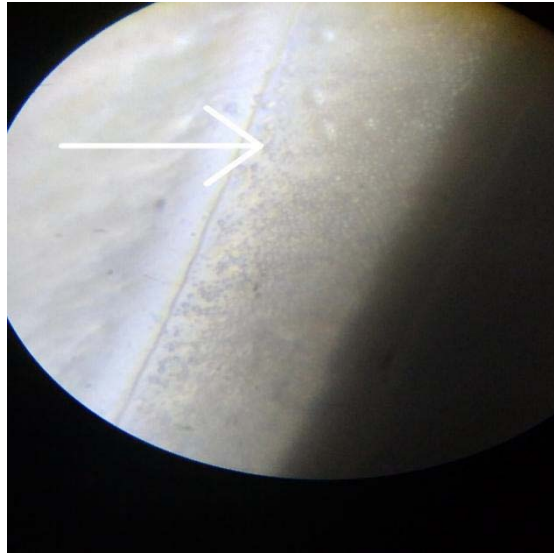
Regarding Figure 5, again, we repeated the experiment by using a sample of molecules and microbes which appeared within the milk. Before turning on the generator, the microbes and other molecules were in their natural size.

Regarding Figure 6, we turned on the generator. Some ionic molecules were excited and grew. They moved and caused the excitation and growth of other molecules and even microbes. The same event may occur within the brain, and, by using electrodes, some cells may have grown because membranes were formed from charged particles and could be affected by the electrodes.

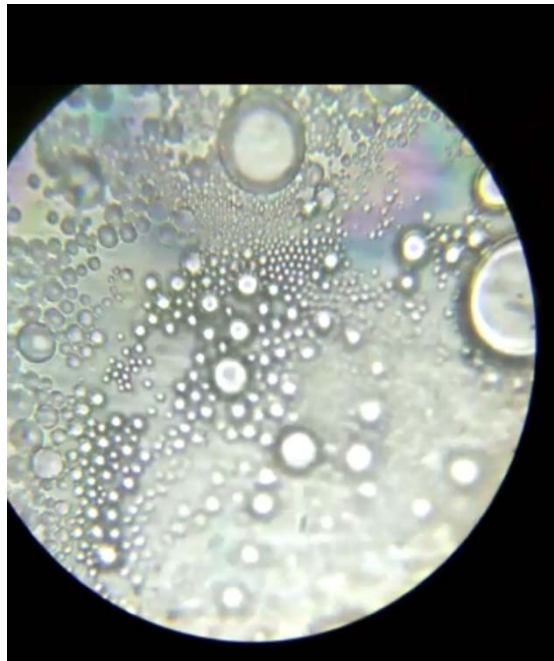
Regarding Figure 7, we put water under the microscope and turned on the generator. Later, some bubbles emerged, which were small at first.

Regarding Figure 8, we observed that small bubbles grew and became large. These large bubbles could destroy the structure of the cells. This event may be the main harmful effect of electrodes in the TTFields therapy method.

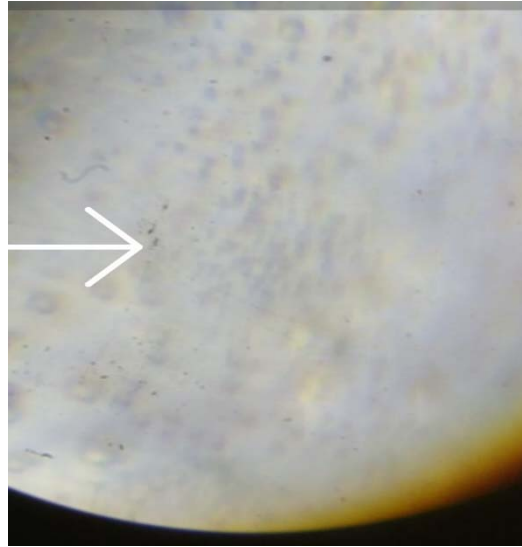
Regarding Figure 9, we observed that, with time, not only did the bubbles become very large, but the number of microbes grew because the microbes accepted new conditions; eventually, they used a new electrical cycle and obtained the required temperature and energy for growth.



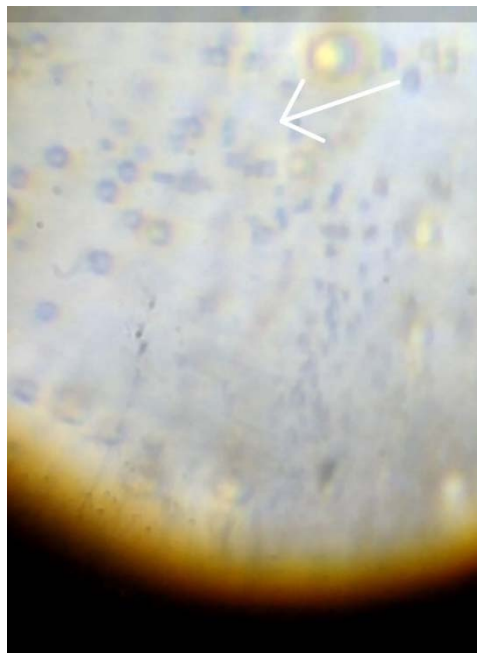
**Figure 3.** Attraction of microbes and ions by electrodes and electrical currents.



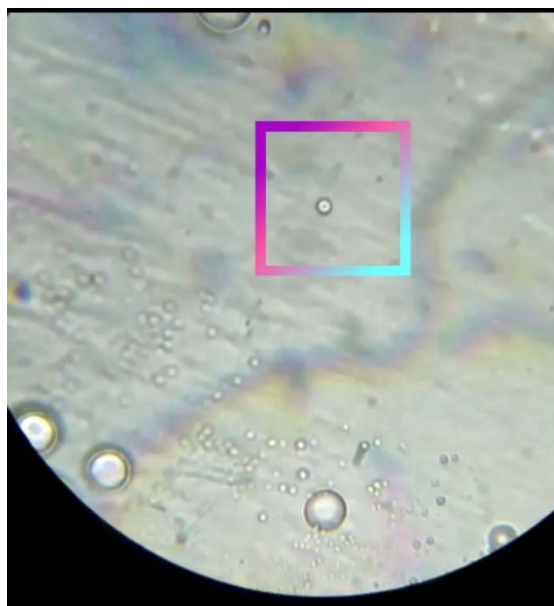
**Figure 4.** Emergence of many bubbles and disappearing microbes as a result of connecting a slide to the electrodes. The liquid was separated from the electrodes; however, its effects could be observed.



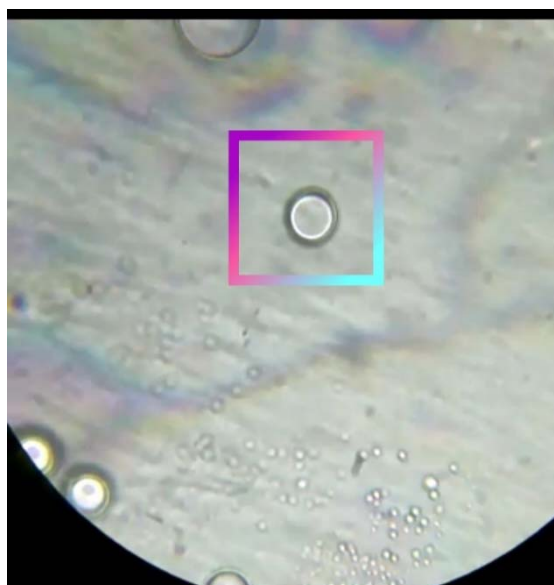
**Figure 5.** Sample of molecules and microbes within water and milk before turning on generator.



**Figure 6.** Effects of electrodes on the size of molecules and microbes after turning on generator.

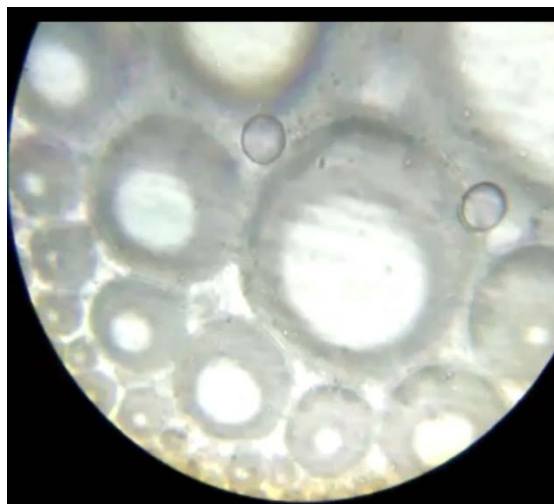


**Figure 7.** Emergence of small bubbles within the pure water connected to the electrodes. The electrodes had 1–3 mm of separation from the liquid.



**Figure 8.** Growth of bubbles within the pure water during electrode radiation.

Regarding Figure 9, we observed that, with time, not only did bubbles become very large, but the number of microbes grew because the microbes accepted new conditions; eventually, they used a new electrical cycle and obtained the required temperature and energy for growth.

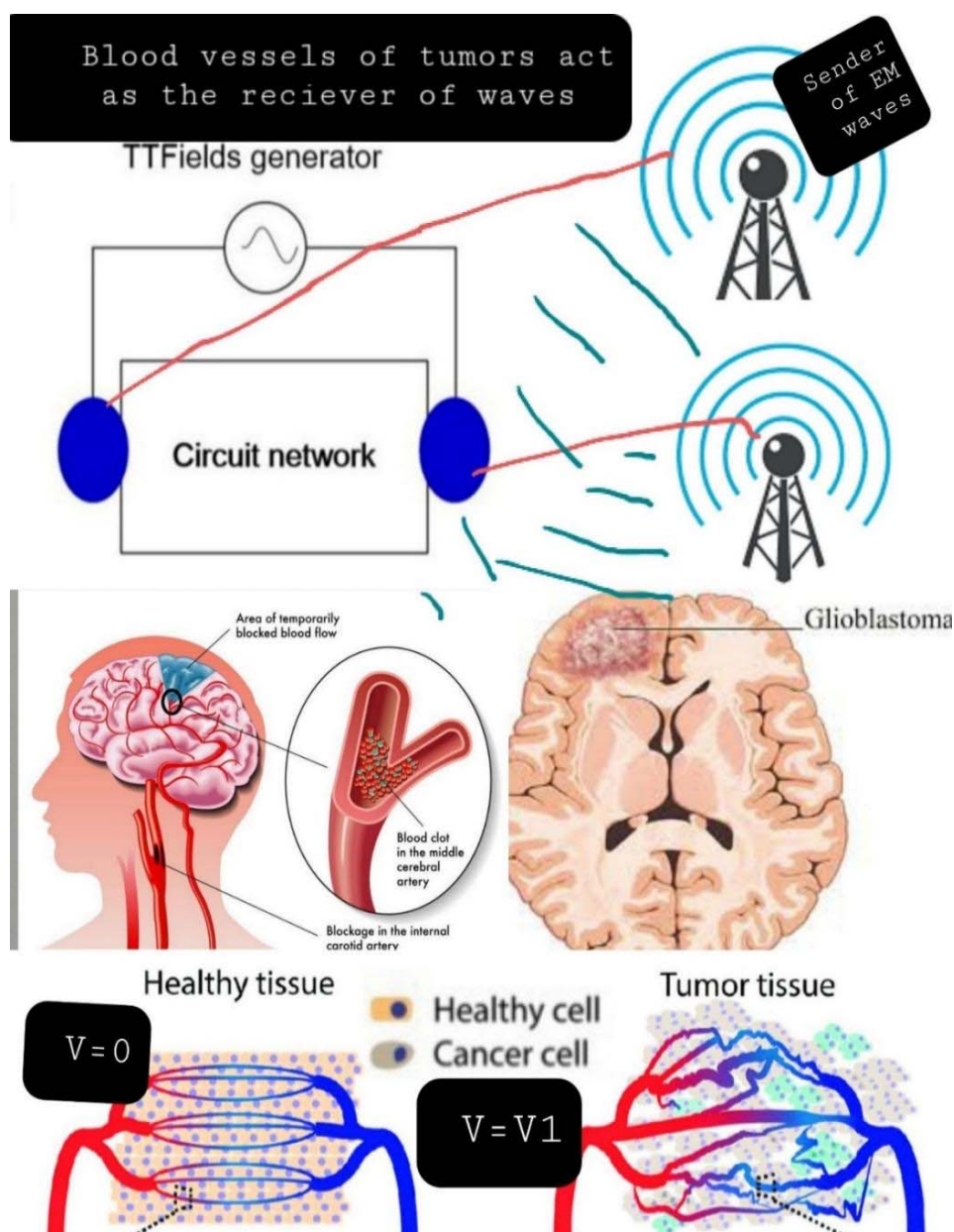


**Figure 9.** Growth of bubbles and increase in the number of microbes within a liquid as a result of electrode radiation.

#### **4. Discussion**

The above results show that electrode radiation could cause many harmful effects on blood and normal cells. To avoid these problems, we can use large, distant sources. It is known that tumor cells have different radiation sensitivities and structures than normal cells. Specially, some tumors form new blood vessels to supply their food. Each blood vessel contains many hemoglobin molecules and ions. Each hemoglobin molecule contains some iron atoms. These iron atoms could act like the antenna and receive electromagnetic waves. Based on these molecules and the differences between blood vessels around tumor and normal cells, we can design a sender which emits some special electromagnetic waves, and these waves could be received by molecules within the tumor blood vessels. These waves induce the needed frequency and voltage around tumor cells (see Figure 10).





**Figure 10.** Process of replacing electrodes through the use of distant electromagnetic sources and the induction of needed voltages around tumors by applying the differences between the blood vessels around tumor and normal cells.

## 5. Conclusions

To date, it is known that TTFields therapy is one of the best medical methods for curing tumors. However, in this paper, we have shown that electrodes on the scalp could induce some electrical currents within the blood vessels and other liquids around normal cells. These currents could cause the emergence of some big bubbles which apply force to cell structures and destroy them. We have suggested that electrodes are replaced by some electromagnetic senders/receivers. These senders emit some special waves which are received by blood vessels around tumors and produce the needed voltage and frequencies.

Maybe the question that arises is whether TTFields could be used to cure other diseases. To respond to this question, we should note that electromagnetic waves were able to prevent connections between microbes and cells. This is because electromagnetic waves can interact with charged particles within the microbial membranes and change their structures. Consequently, the microbes could not provide the needed potential for connections to cells, eventually causing their disease. The same event could occur for viruses also. Electromagnetic fields could interact with viral membranes and change their structures and potentials. Then, these viruses would not be able to enter into cells.

Another question that arises is how can we remove the noise that emerges from the motion of ions within the blood vessels in the TTFields technique. To solve this problem, we should know the separation distance between tumor cells and the main ionic currents. Then, we can apply a new potential which produces some ionic currents in the direction opposite to the initial currents and cancel their effects.

### Conflict of interest

The authors declare no conflict of interest.

### Author contributions

Contributions of all authors are the same.

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