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NUMERICAL ANALYSIS OF ELECTRIC FORCE DISTRIBUTION ON TUMOR MASS IN DC ELECTRIC FIELD EXPOSURE

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ABSTRACT

Researchers have used electric fields as a new therapeutic strategy to treat cancer for the past 15 years. Tumor Treating Fields (TTFields) is an alternating electric field-based cancer therapy approved by the US FDA to treat glioblastoma multiforme (GBM). ECCT (Electro-Capacitive Cancer therapy), a DC charged-discharged electric field (EF) cancer therapy, also shows a performance inhibiting cell proliferation. ECCT affects the cancer lesions to cause simultaneous death of the cancer cell and detached off of the surrounding tissue. The author hypothesizes that the EF produces an electric force that is not homogeneous throughout the tumor mass and generates a strong dielectrophoresis force. The force affects microtubules polymerization during mitosis and causes mitotic arrest. To examine this hypothesis, we performed a numerical simulation of the EF distribution and calculated the force acting on the tumor mass generated by the EF. We analyzed DC electric field exposure on a cancer lesion using a single lesion 2D circular model, calculated the EF intensity on the lesion using the Finite Element Method, and the dielectrophoresis force distribution to quantify the treatment efficacy. The results showed that the distribution of EF intensity was not homogeneous at the lesion-medium boundary and homogeneous within the lesion. The EF intensity is highly dependent on the dielectric constant of the medium and the applied voltage difference that may affect the effectiveness of the treatment. Variations in lesion diameter had no significant effect on the EF intensity distribution and,

hence the effectiveness of the therapy. It is considered that EF exposure by ECCT generated strong force on the lesion-medium boundary that could cause detachment of the tumor mass from the surrounding tissue.

Keywords: cancer cell, lesion, electric field, dielectrophoresis force, dielectric constant, TTFields, ECCT

INTRODUCTION

The biological effects of electric field exposure were studied widely using an alternating electric field (TTFields) of low intensity and medium frequency. In the past 15 years, researchers have confirmed that an electric field of 1 V/cm can disrupt cancer cell growth [1], mainly during the mitotic phase of cell division, with the highest electric field intensity occurring on the cleavage furrow [2,3]. The FDA approved TTFields as an electric field treatment for clinical use patients with GBM in 2015 [4,5].

TTFields therapy has been shown to disrupt microtubule polymerization, resulting in cell death or slowed growth of cancer cells [1]. Several studies showed that the orientation of the external electric field toward dividing cells affects the efficacy of electric field treatment against cancer cells [1-3]. ECCT (Electro-Capacitive Cancer therapy), a direct current (DC) charged-discharged based electric fields cancer therapy, has also shown inhibition of cell proliferation [6-8].

In the publication of studies in mice using ECCT, it was shown that cancer masses did not undergo a shrinkage process as occurs in conventional cancer therapy but died simultaneously and detached off of the surrounding tissue [7]. However, this phenomenon has not well-explained how the tumor lesion is separated from the surrounding tissue. In this paper, we hypothesized that the electric field produces an electric force that is not homogeneous throughout the tumor mass and exerts a strong electric force concentrated on the lesion's surface and causes the lesion to detach from the surrounding tissue.

The electric field therapy generates dielectrophoresis force which emerges when the electric field intensity distribution is not uniform [9,10]. The dielectrophoretic force is a significant factor that affects cell death during mitotic cell division. It was interfering with the polymerization process of the microtubules and preventing cell division into two identical daughters. The force generated by dielectrophoresis is sufficient to promote antimitosis in cancer cells [11,12]. To test the above hypothesis, we developed a tumor lesion model, performed a numerical simulation of the electric field distribution, and calculated the force acting on the tumor mass generated by the electric field.

METHOD

Some biology cells have been observed by adopting forms other than spheres. However, to simplify the simulations, we conducted a circular 2D form of tumor lesion and evaluated the electric field distribution around the lesion.

Simulation of the Distribution of Electric Field Intensity on Tumor Lesion

Simulations of the electric field distribution and numerical analysis of the lesion inside the medium were conducted using the Finite Element Method (FEM) to understand the impact of the electric field on the lesion. The simulations were set out using electrical parameter values as shown in Table 1, in which physiology saline is used as the lesion's extracellular media. The simulation is conducted at 100 kHz (β-dispersion) with a minor frequency change to compensate for dispersion and consider permittivity frequency-independent [13].

The lesion's potential distribution as a function of the external electric field is consistent with the Laplace equation:

$$\nabla^2\phi = 0 \tag{1}$$

with the requirements that the mediums' boundaries meet:

$$\phi_1 = \phi_2 \tag{2}$$

where ϕ is the electric potential, and subscripts 1 and 2 are the two-part of the boundary.

Equations 1 and 2 can be solved using the Legendre function such that the potential distribution can be obtained. The electric field intensity distribution is given as:

$$E = -\nabla\phi \tag{1}$$

The dielectrophoretic force, or $F_{DEP,}$ is defined as [14]:

$$F_{DEP} = 2\pi\varepsilon_m K_{CM} r^3_{MT} \nabla E^2 \tag{4}$$

where ε_m, ε_c is dielectric constant for medium and cancer cells respectively, r_{MT} is tubulin dimer radius, and K_{CM} knows as Clausius-Mossotti function is given by:

$$K_{CM} = \frac{\varepsilon_c - \varepsilon_m}{\varepsilon_c + 2\varepsilon_m} \tag{5}$$

Thus, the magnitude of F_{DEP} for lesions located in the same medium is proportional with:

$$F_{DEP} \propto \nabla E^2 \tag{6}$$

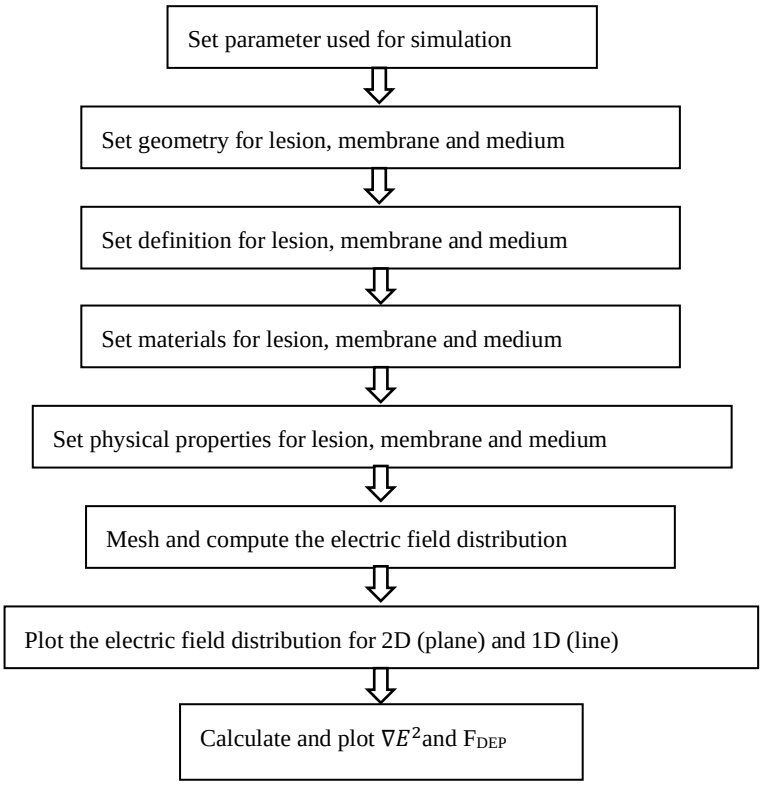
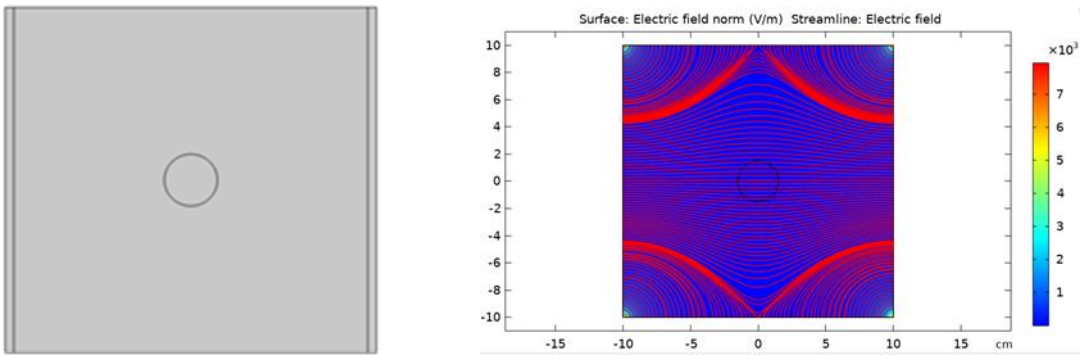


FIGURE 1. The flowchart of research methods.

TABLE 1. Electrical parameters of the lesion

Parameter	Value	References
The permittivity of the membrane	5	[15]
The permittivity of the lesion	73	[15]
The permittivity of the air	1	[16]
The permittivity of the saline	73	[16]
The permittivity of the water	80	[17]
The permittivity of the white matter	2110	[17]
The thickness of the membrane	5.10^{-6} m	

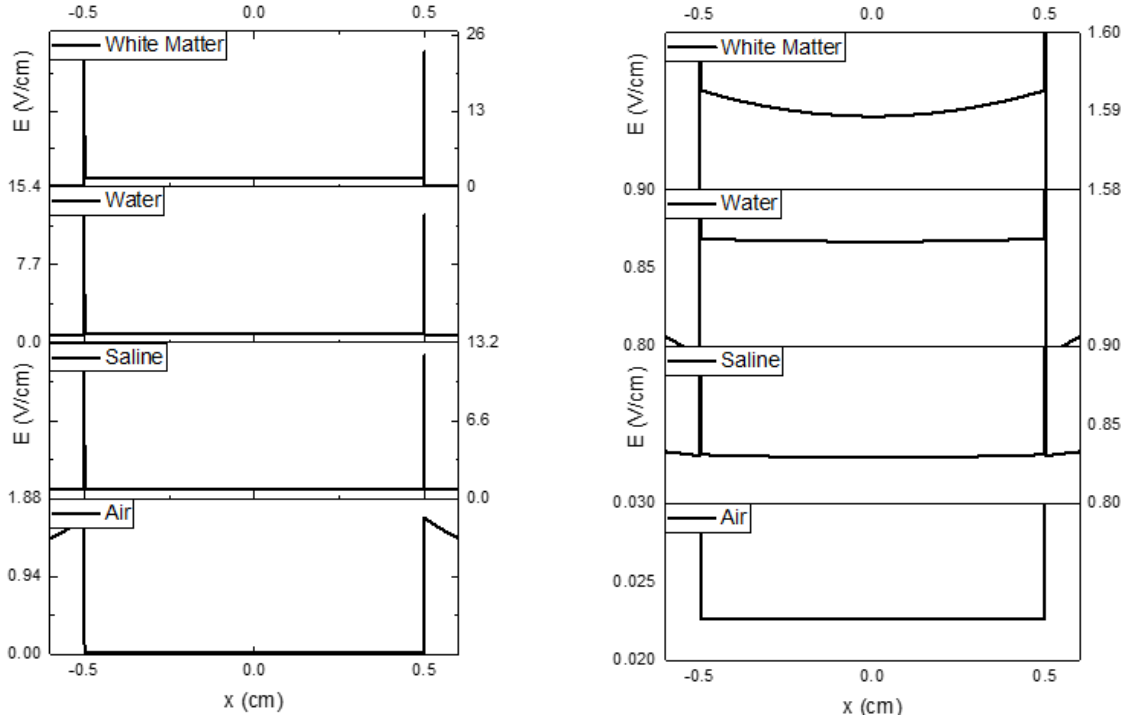


(a) (b)

FIGURE 2. (a) Schematic diagram of the circular shape model of the lesion with 3 cm in radius inside the saline medium placed between applied voltages of + 15 V and -15 V (total voltage difference 30 Vpp) with medium dimension 20 cm x 20 cm; (b) Distribution of electric field intensity.

RESULT AND DISCUSSION

The distribution of electric field intensity and the dielectrophoretic force is calculated and presented in this section. The membrane is omitted from analysis as the electric field intensity distribution is essential in the lesion boundary and inside the lesion.



(a) (b)

FIGURE 3. The EF intensity distribution on the lesion in various mediums with the radius of 1 cm and applied voltage difference between electrodes is 20 Vpp on a) lesion-medium boundary and b) inside the lesion.

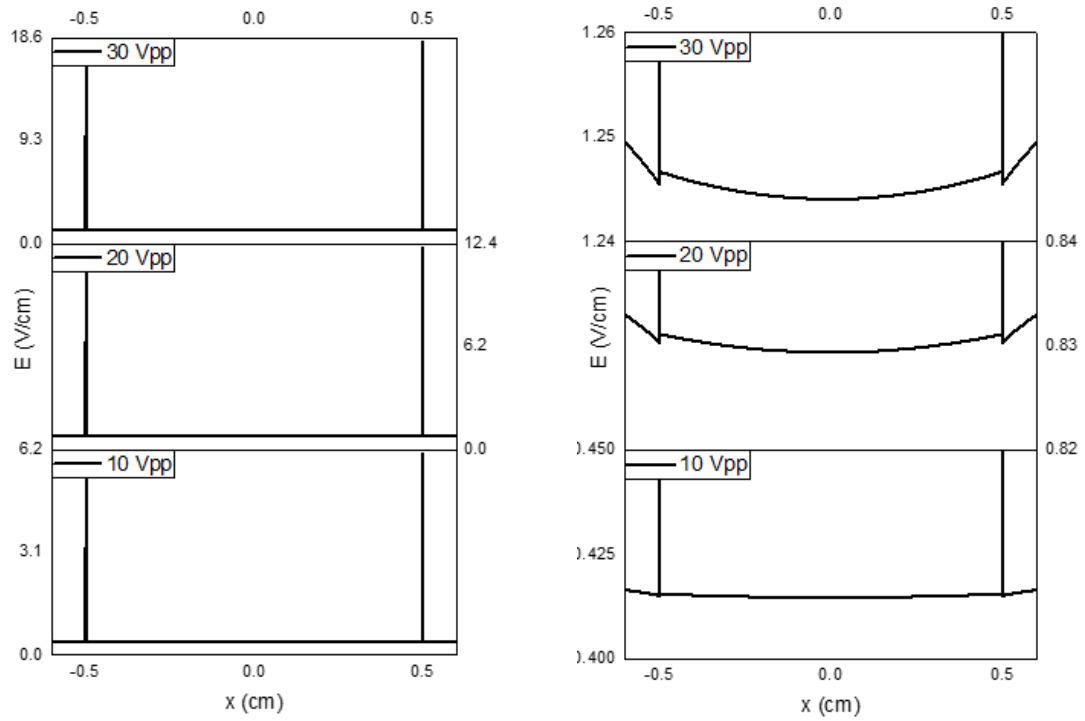
FIGURE 3 showed that the electric field intensity rises sharply at the boundary between the medium and lesion (FIGURE 3.a), while the electric field is relatively flat (FIGURE 3.b). The increasing electric field intensity is due to the significant dielectric constant difference between the medium and the lesion.

The highest electric field intensity occurred when a white matter medium surrounded the lesion ($\varepsilon_r = 2110$), i.e., the highest dielectric constant medium. In contrast, the lowest electric field intensity differs when the lesion is in the air medium ($\varepsilon_r = 1$), i.e., the lowest dielectric constant medium. When the lesion was in saline medium ($\varepsilon_r = 73$) and water ($\varepsilon_r = 80$), the electric field intensity difference was relatively the same, both at the medium-lesion boundary and within the lesion. However, the electric field intensity inside the lesion in the water medium is relatively higher because the dielectric constant of water is higher than saline. The EF intensity inside the lesion surrounded by the saline medium conforms with that reported by Xian, in which EF intensity is the strongest in the two ends of lesions and the range 0.89 – 0.94 V/cm [12].

Electric field intensity (EF) inside the lesion is relatively low and homogenous (FIGURE 3.b). The value is due to the homogeneity of the dielectric constant in the lesion. The intensity of the electric field in the lesion depends on the dielectric constant of the medium. The higher the dielectric constant of the medium, the higher the electric field intensity within the lesion.

Eilon reported that an electric field of 1 - 3 V/cm exposed to cancer cells could cause antimitotic effects[1]. Exposure to 1 V/cm showed that EF inhibits proliferation, while EF more than 2.5 V/cm caused complete proliferation arrest. Figure 3.a confirms that the applied voltage of 20 Vpp exposed to the lesion in the air medium can produce an electric field intensity at the lesion-medium boundary exceeding 1 V/cm, so that a cancer cell located at the boundary may experience proliferation disruption. Meanwhile, the EF intensity in the white matter media exceeds 3 V/cm, which may cause cell death to cancer surrounded by the media.

The intensity of the electric field in the lesion is very low, i.e., below 1 V/cm, except for the lesion surrounded by the white matter medium, which is up to 1.59 V/cm. Consequently, only cancer cells in lesions surrounded by white matter may experience impaired proliferation.



(a) (b)

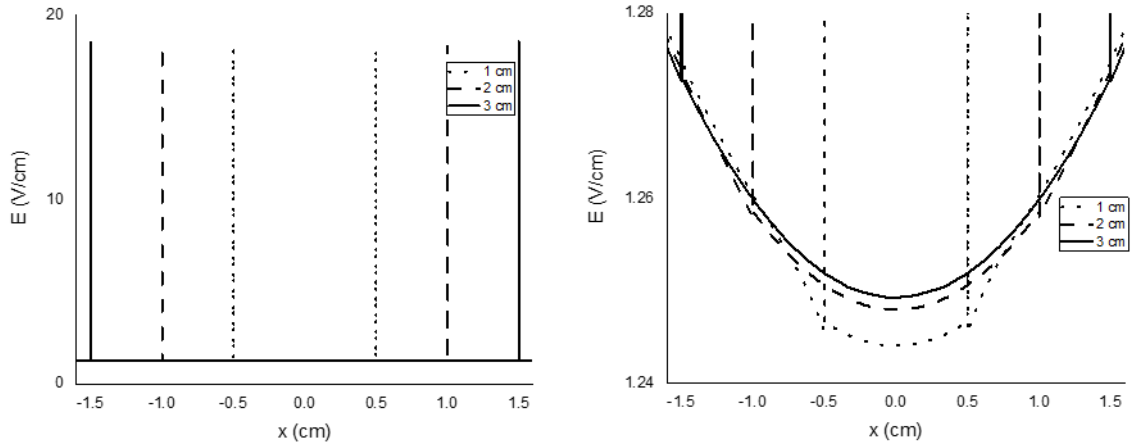
FIGURE 4. The distribution of the EF intensity with lesion radius of 1 cm surrounded by saline medium with various applied voltages difference (Vpp): a) lesion edges and b) lesion interiors

FIGURE 4.a indicates that the strongest electric field occurs at the interface between the medium and lesion. The increasing intensity of the electric field is caused by the high electric potential difference between the medium and the and lesion. Since an electric field is a gradient of electric potential, this significant difference increases the strength of the electric field. The applied voltage difference of 10 Vpp at the two electrodes in the saline medium can generate

an electric field intensity at the lesion-medium boundary up to 6.2 V/cm. Consequently, the cancer cells located at the boundary may experience complete proliferation arrest.

FIGURE 4.b indicates that the intensity of the electric field inside the lesion is less than 1 V/cm, except for that with an applied voltage difference of 30 Vpp between the two electrodes. The applied voltage difference of 30 Vpp causes cancer cells in the lesion to experience an electric field of 1.24 V/cm, leading to possible impaired proliferation.

FIGURE 5 shows that the lesion diameter does not significantly affect the electric field intensity distribution at the lesion edge (FIGURE 5.a) and inside the lesion (FIGURE 5.b). This result may be due to the electric fields exposed to the lesion are relatively unchanged despite the size of the lesions.



(a) (b)

FIGURE 5: The distribution of the electric field intensity on lesion placed in a saline medium in various radius and applied voltage difference on both electrodes of 30 Vpp on: a) lesion edges and b) lesion interiors.

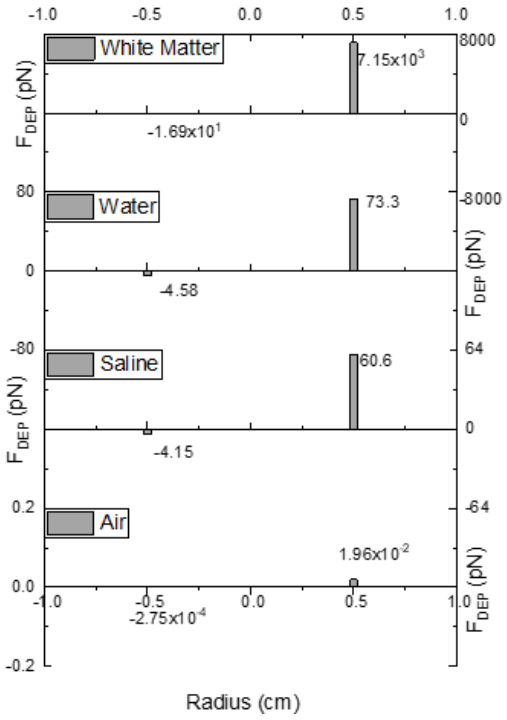
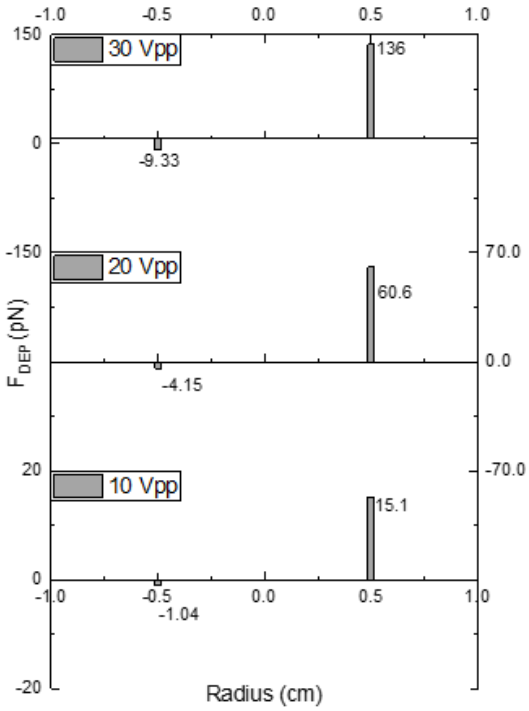


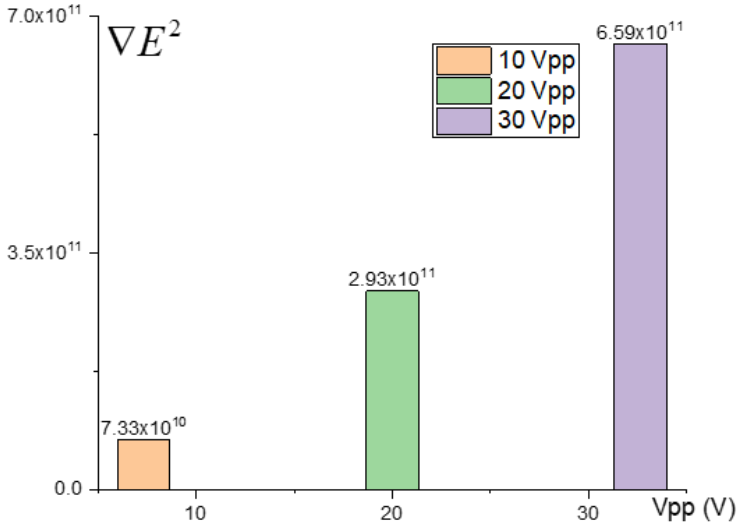
FIGURE 6. Dielectrophoretic force at lesion with the radius of 1 cm in various mediums placed between electrodes with an applied voltage difference of 20 Vpp

FIGURE 6 showed that cancer cells in the boundary surrounded by white matter would experience the most potent force, while those in the air medium would experience the lowest force. Cancer cells in the boundary surrounded by saline or water medium will experience relatively similar dielectrophoresis force, as the difference in the dielectric constant between media is similar. The higher the constant dielectric mediums would enhance more efficacy treatment for cancer cells. In contrast, the homogeneity of the dielectric constant of cancer cells inside the lesion is relatively low and homogeneous and significantly impacts the treatment effectiveness. Xian study showed that during mitosis, the most EF intensity is concentrated in cleavage furrow with ∇E^2 in the range 10^{13} V^2/m^3 and generated F_{DEP} in the range of 10^{-12} pN [18]. These values are comparable with our simulation results in air medium, while in saline medium, F_{DEP} is in the range of 100 pN, generating a much larger force than air.

FIGURE 7.a showed that the EF intensity generated by the applied voltage difference between the two electrodes reaches a maximum value at the lesion-medium boundary and a minimum value in the area in the middle of the lesion. Hence, the treatment's effectiveness may be considered to reach its optimum condition in the areas with a maximum electric field intensity gradient, i.e., at the lesion-medium boundary. However, the effectiveness of treatment may become less optimum when it is located in the area with homogeneous electric fields intensity, i.e., inside the lesion. In line with FIGURE 7, the effectiveness of the treatment may be improved by increasing the applied voltage difference between the electrodes. FIGURE 7.b shows that the increased applied voltage difference (Vpp) strongly correlated with the increasing gradient of square EF.

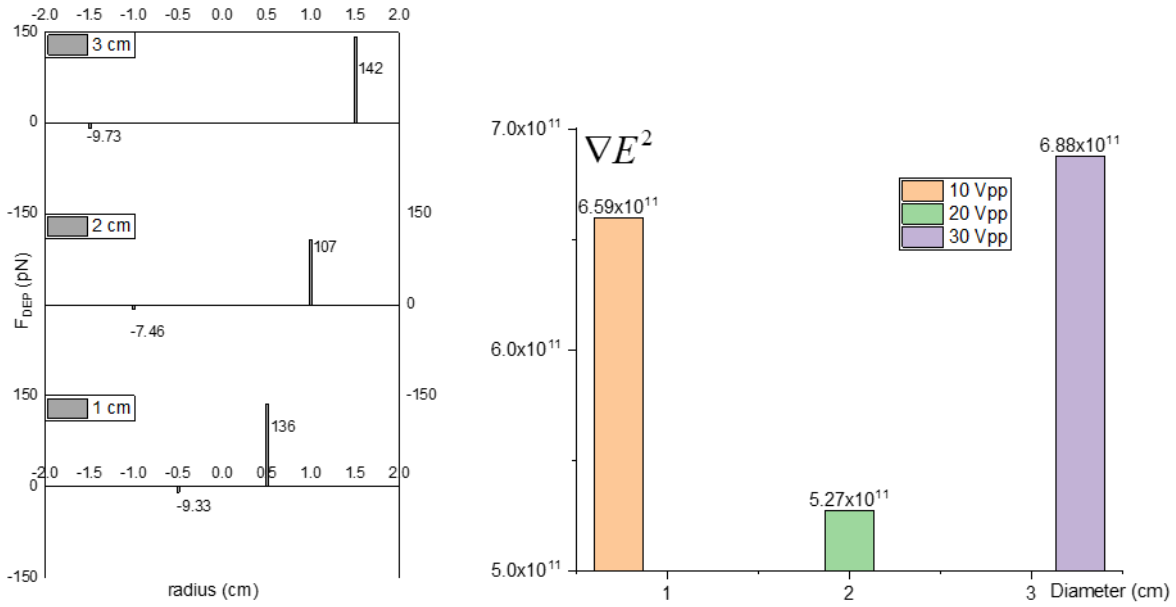


(a)



(b)

FIGURE 7. a) Dielectrophoretic forces at lesion with the radius of 1 cm on the saline medium with various applied voltage differences; and b) their gradient of the square electric field.



(a) (b)

FIGURE 8. Dielectrophoretic forces at the lesion on the saline medium with an applied voltage difference between the electrodes 20 Vpp with various lesion diameter a) and their gradient of square electric field b).

FIGURE 8 shows that the difference in lesion size does not significantly affect the gradient of square EF nor the dielectrophoretic force generated near the lesion-medium boundary. This effect is because the dielectrophoresis force is strongly related to tubulin dimer size, not the lesion size. FIGURE 8.b shows that the increased lesion diameter does not correlate with the gradient of square EF.

Our results showed that the DC electric fields generated strong EF intensity at the lesion-medium boundary that could cause antimitotic effects on the cancer cells. The therapeutic effectiveness of DC electric fields may be increased by increasing the applied voltage difference.

The strong FDEP on the lesion-medium boundary may be considered as a strong factor that directly affects the detachment of the lesion from the surrounding tissue. These findings give insight that the application of direct current charged-discharged electric fields is quite promising and requires further exploration.

CONCLUSION

This study was conducted to evaluate the hypothesis that ECCT produces inhomogeneous EF exposure in the tumor mass to inhibit the proliferation of cancer cells. The 2D circular-single lesion model was used for numerical analysis.

The results showed that the distribution of EF intensity in the lesion was not homogeneous at the lesion-medium boundary and homogeneous within the lesion. The EF intensity at the lesion-medium boundary and within the lesion is highly dependent on the dielectric constant of the medium. The higher the dielectric constant, the higher the EF at the lesion-medium boundary and within the lesion. This high intensity of EF may strongly correlate with the

effectiveness of therapy. The intensity of EF increased with increasing Vpp. This increase might boost the effectiveness of therapy. Changes in lesion diameter had no significant impact on the intensity of the generated EF and the effectiveness of its therapy.

Significant differences in the electrical properties of the tumor mass and surrounding tissue resulted in a significant difference in the distribution of EF intensity and the force generated at the boundary. Therefore, it is considered that EF exposure generated by ECCT could possibly cause detachment of the tumor mass from the surrounding tissue. For future studies, the effect of Van der Waals forces on microtubules polymerization needs to be further studied, and relevant experiments need to be performed.

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