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Calculation and Simulation a multiple electrode pair configuration for antitumor treatment

Abstract

Electrochemical therapy (EchT) for the treatment of cancer is becoming increasingly popular. The objective of this work is to calculate and simulate the spatial distributions of electric potential, electric field, temperature, tissue damage and pH fronts generated by a configuration of multiple pairs of electrodes that maximizes the greatest destruction of tumor volume. It is concluded that multiple equivalent electrode pair configurations are effective in tumors solid, large, deep and elongated (diameters > 8 cm), depending on the distance (d) between and/or between pairs of electrodes; which represents one more option when conventional therapies fail. The combination of EChT with existing therapies increases the synergy of the antitumor effect, does not generate metastasis and potentiates the use of this therapy for the treatment of tumors.

Keywords: Electrochemical therapy, Electrodes, Tumors solid, pH fronts

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Introduction

In recent years, cancer is a disease that affects all levels of society and has become the second leading cause of morbidity and mortality. The OMS reports that 14 million people have been affected and 8.2 million have died from this pathology, and it is expected to increase from 14 to 22 million cases in the coming decades.[1] In Cuba, more than 22 655 people died from malignant tumors in the period (2012-2020).[2] This number has been increasing in the last years; being, the first cause that causes more useful damages to the life expectancy of Cubans;[3] which constitutes a health, social and environmental problem; so it immediately arises the need for the application of new effective therapeutics Electrochemical therapy consists of the application of a very low intensity direct electric current (CED) to the tumor by means of the insertion of two or more electrodes in its interior and/or vicinity connected to a suitable current source. The Cuban Bioelectricity Group of the National Center of Electromagnetism (CNEA) of the University of Oriente in the province of Santiago de Cuba. Cuba; focuses its efforts in proposing different two-dimensional (2D) and three-dimensional (3D) physical-mathematical models.[4-7] to optimize the spatial distributions of the electrical potential (Φ), the intensity of the electric field (E), electric current density (J), the temperature (T), pH fronts and tissue damage percentage (PDT) generated by different geometries of multiple pairs of electrodes (or individual electrodes) that are inserted colonially and/or non-colonially into the tumor.[4-7] Physico-mathematical models are a fast and efficient method for understanding these three aspects and their results do not require long times or large material resources, such as the experiment,[8-10] in vitro[11,12] and in vivo.[13] However, complete remission of this histological variety of tumor is not observed in any mouse and the overall antitumor effectiveness of EChT induced by the electrode pairs is comparable to that of other single electrode arrays used.[8] The distance between electrodes ($0.5 \leq d \leq 1$) cm has been used in the experiment to reveal the different findings around the anode, cathode and in regions between them and away from these electrodes.[14] Gonzalez and Suarez et al.[15,16] report that the spatial pattern of tissue damage (results not shown), pH fronts, spatial profiles in terms of electric potential, electric field/electric current density and temperature, follow the geometry of the electrode arrays according to simulations performed with models 2D[5,13] and 3D;[11,12,17] as shown in Figure 1.

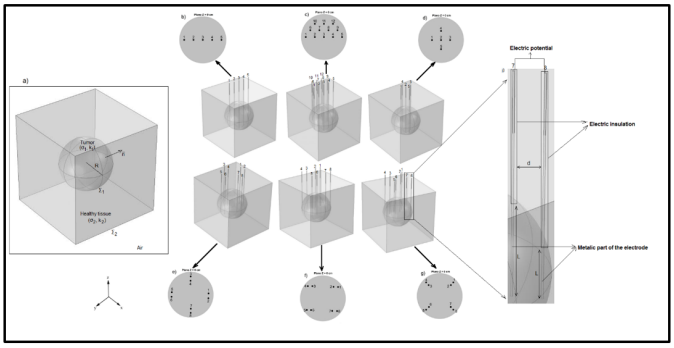

Figure 1 Different geometries of multiple single electrodes and pairs of electrodes inserted into the tumor. a) Schematic representation of the spherical tumor surrounded by its surrounding healthy tissue. b) Schematic representation of a spherical tumor surrounded by its surrounding healthy tissue. $\Sigma_1 y \Sigma_2$ represent tumor-surrounding healthy tissue and surrounding healthy tissue-air interfaces, respectively. b) Geometry of multiple single electrodes inserted along the tumor diameter. c) Geometry of several layers of single electrodes. d) Geometry of multiple single electrodes inserted non-collinearly into the tumor. e) Geometry of multiple single electrodes inserted non-collinearly into the tumor. f) Geometry of multiple pairs of electrodes inserted into the tumor at 0; 90; 180 and 360°. g) Geometry of multiple pairs of electrodes inserted into the tumor at 45; 135; 225 and 315°, with the electrode pairs directed towards the center of this electrode array. Electrodes 2; 4; 6 and 8 are the anodes (positive electrodes). Electrodes 1; 3; 5 and 7 are the cathodes (negative electrodes). Source: This figure appears in the scientific article.[10] (Courtesy of the author of the correspondence, Dr. C. Luis Enrique Bergues Cabrales).

The EChT is simple, safe, effective, low cost, induces minimal adverse effects in the body; it is usually applied only once, up to three times at most, and constitutes a therapeutic option when conventional therapies fail or cannot be applied. Furthermore, the antitumor effect

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of EChT is enhanced when combined with chemotherapy, tumor necrosis factor alpha, interleukin-2, interferon gamma, radiotherapy, hyperthermia, phototherapy and saline solutions, reducing the doses of the latter by up to 10%;[5,10] that compared to radiotherapy and chemotherapy, stimulates the immune system after its application.[4] This makes it possible to combine EChT with therapeutic vaccines, as is done with ECT and the existing ones improves the quality of life of oncology patients; however this type of therapy (alone and/or in combination) has not been recognized as an established and standardized because the optimal dose and electrode arrangements have not been established and the effects of distant metastasis and the activation of the different cellular and humoral elements of the immune system after application in oncology patients have not been evaluated due to the lack of understanding of the mechanism of action; therefore, the objective of this investigation is to calculate and simulate an optimal configuration of multiple pairs of electrodes (or single electrodes) in order to maximize the percentage of tumor destruction, with minimal damage to surrounding healthy tissue, which induces the highest values of folding time, percentage of regression and anti-tumor growth retardation, based on an updated scientific search on the use and application of EchT, in the experimental, clinical and preclinical part, in the treatment of tumors.[18]

Material and methods

Model considerations

The assumptions of the model were assumed according to.[5-7]

4.2. Calculation of spatial distributions of electric potential, electric field and temperature.

In both tissues, the electric field and temperature were calculated from $\vec{E}_i = \nabla \phi_i$ and the stationary Pennes equation (1).

$$\nabla \bullet (k_i \nabla T_i) - w_{b_i} c_{b_i} \rho_{b_i} (T_i - T_a) + q_i''' + \sigma_i \left|\nabla \Phi_i\right|^2 = 0 \quad (1)$$

where i = 1 represents the tumor and i = 2 the surrounding healthy tissue. T_a is the arterial temperature and T_i, the temperature induced in each medium. T_1 and T_2 satisfy the boundary conditions of the following equation (interface) (2).[19]

$$\Sigma: T_1\big|_\Sigma = T_2\big|_\Sigma \text{ y } \kappa_1 \partial T_1 / \partial \hat{n}\big|_\Sigma = \kappa_2 \partial T_2 / \partial \hat{n}\big|_\Sigma \quad (2)$$

The parameters κ_i, cb_i, ρb_i, wb_i and q''' are the tissue thermal conductivity, specific heat capacity, blood mass density, blood perfusion ratio and metabolic heat generation of each tissue, respectively.

The electrical potential in the tumor (ϕ_1)and (ϕ_2)the electrical potential in the surrounding healthy tissuethat satisfy the border conditions, according to the following expression.[20]

$$\phi_1\big|_\Sigma = \phi_2\big|_\Sigma \text{ y } \acute{o}_1 \partial \phi_1 / \partial \hat{n}\big|_\Sigma = \acute{o}_2 \partial \phi_2 / \partial \hat{n}\big|_\Sigma \quad (3)$$

4.3. Calculation of pH fronts

The calculation of the space-time distribution of the 2D pH fronts was described through in silico modeling in a multi-electrode geometry by the Nernst-Planck equations for the concentration of H^+, OH^-, Cl^- and Na^+ ions in an electrolyte, as expressed in.[5]

In this work, an experimental study two groups of at least 10 female BALB/c/Cenp mice were formed. In all biomodels, 2 X 10^5 F3II mammary carcinoma cells will be implanted subcutaneously in the right flank. The conformation of the experimental groups will be performed at the time of starting electrotherapy treatment, when the tumors reach a volume between 0.5 and 1 cm3 (approximately 30 to 35 days postinoculation of the cells) (POT 05.01.03.002), with registration code AETM 0318 and date 09/22/2017. The configuration of multiple pairs of equivalent electrodes was inserted to the tumor directly and the other end of the electrode was coupled to the ONCOCED by means of electrical conduction cables. This equipment has its technical file and its verification, by means of Certificates, by the Territorial Office of Standardization of Santiago de Cuba and the LABET of Havana. Cuba. The electrodes are platinum needles 50 mm long and 0.7 mm in diameteraccording to. For the calculation, simulation and meshing of the tumor geometry, a computer program was used that has implemented the values of the chemical, physical, mechanical and thermal parameters of the tumor and the surrounding healthy tissue, the electrode material (platinum) and the equations shown above.

Results

In the Table 1 shows the maximum and minimum values of the electric field strength and temperature generated by the equivalent configuration of multiple pairs of electrodes on the tumor and surrounding healthy tissue in the planes (z = 0, 1,25, 2,1 cm).

Electrode arrangements (C_i)	**Tissue-induced parameters**			
	Tumor		**healthy**	
Planes (cm)	$EE_{1máx(EE1mín)}$ (V/cm)	$TT_{1máx}(TT_{1mín})$ (°C)	$EE_{2máx}$ (V/cm)	$TT_{2máx}$ (°C)
Z = 0	94,01(0,00)	110.07(38,15)	47,59	37,14
Z = 1,25	94,01(0,00)	99,31(38,15)	47,25	38,15
Z = 2,1	94,15(0,00)	65,12(39,14)	47,15	38,24

where $EE_{1máx}$ ($EE_{1mín}$) is the maximum and minimum electric field value in the tumor, $TT_{1máx}$($TT_{1mín}$) of maximum and minimum temperature in the tumor, $EE_{2máx}$maximum electric field in healthy tissue and $TT_{2máx}$ of maximum temperature in healthy tissue.

In the Figure 2 decribes the spatial distributions of Φ(a), E (b) and T (c) that generate the equivalent electrode configurations (C_1) in the radius tumor (R = 2,5 cm) and the surrounding healthy tissue in the z = (0, 1,25 2.1)cm planes, according.[6]

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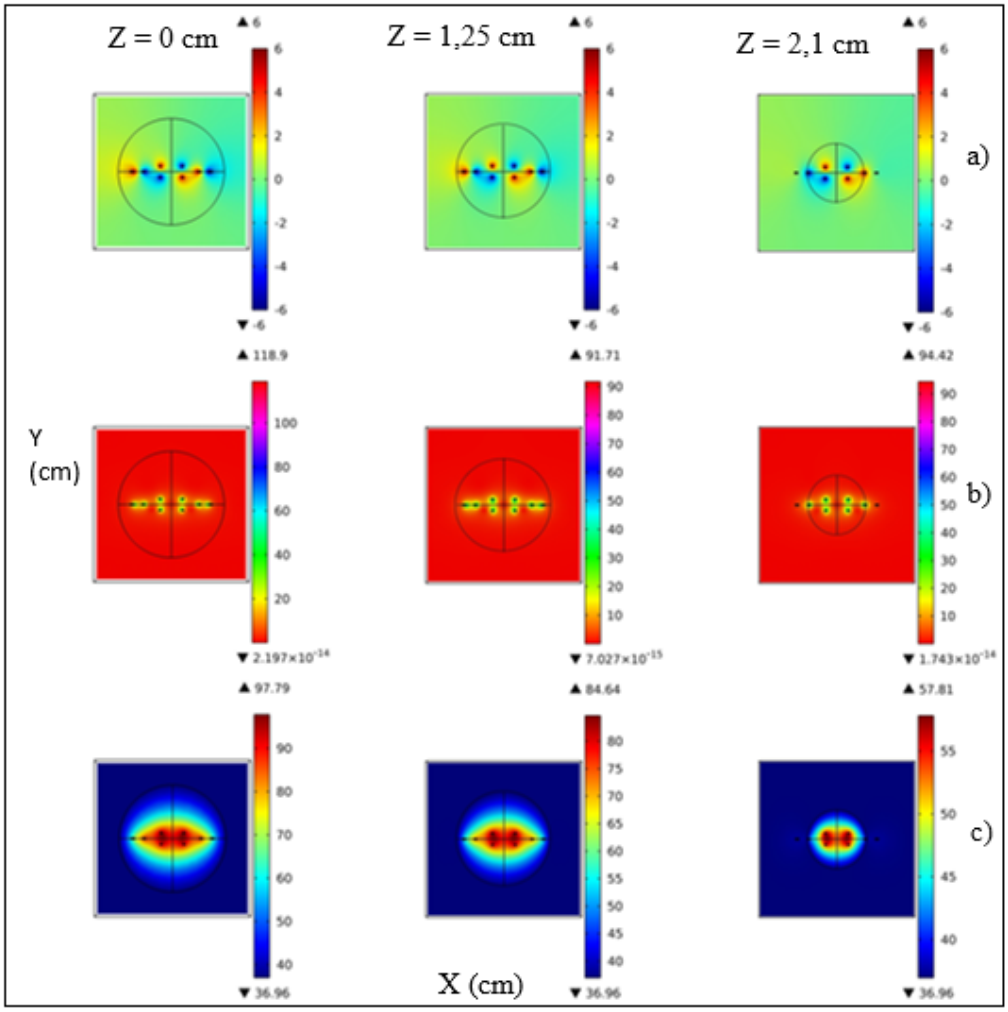

Figure 2 Spatial distributions of electric potential intensity (a), electric field (b) and temperature (c) for the equivalent configuration of electrodes inserted in the radius tumor (R = 2,5 cm).

In the figure 3 reveals the space-time patterns of the pH fronts generated by the geometry of multiple pairs of equivalent electrodes inserted into the tumor) and the healthy tissue surrounding the tumor for t = 300 s (Figure 4a), 600 s (Figure 4b), 900 s (Figure 4c), 1200 s (Figure 4d) and 1500 s (Figure 4e) during the application of EChT.

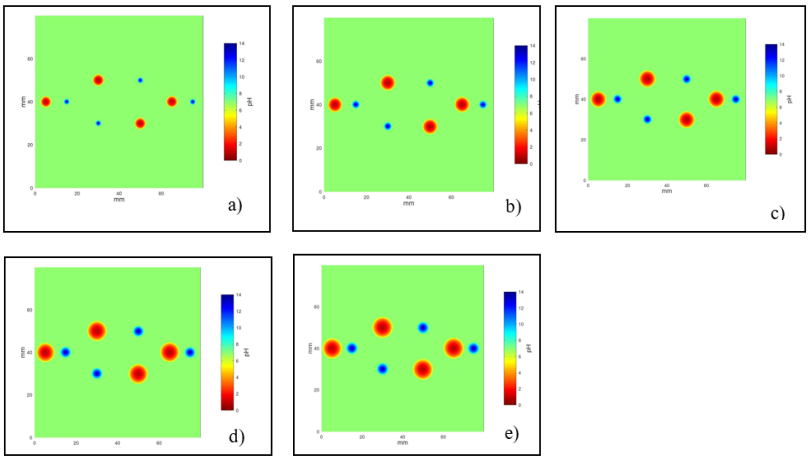

Figure 3 Map of space-time distributions of the pH fronts generated by the geometry of the multiple electrode pair configuration (C_l) in the z = 0 mm plane for different time instants (s) during the application of electrochemical therapy, with respect to the x-axis.[5,21]

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Discussion of results

Table 1 revealed that the highest configuration-generated (C_1) values in tumor of $EE_{1max(EE1min)}$ between 88.19(0,00) and 88,40(0,00) V/cm were observed (for z = 0 and 2,1 cm) and decreased (for z = 1,25 cm) and $TT_{1max(TT1min)}$ values between 74,52(37,54) and 60.18(37,48) °C (for z = 0 and z = 1,25 cm) and decreased (for z = 2.,1 cm) and in healthy tissue the highest E_{E2max} values of 50,18 (V/cm) were shown (for z =0); It was also observed that the temperature T = (37≤ T ≥ 42)°C is uniformly distributed over most of the tumor volume; therefore, significant tissue damage is perceived as the spatial distributions of Φ and E adopt the geometry of the electrode array in each Z-plane as expressed by.[11] In the f 4 shows that for t = 0 s, the electrodes inserted in the electrolyte, but without the application of the EChT, do not change the pH value = 7 in the whole study region; therefore, there are no pH fronts and the PDT = 0%. However, in the experiment necrosis is observed only in the insertion zone of each anode and cathode in tumor[5,8,14,17,18,22] and potato[7,16] This necrosis is explained by the mechanical damage caused by the insertion of the electrode into the biological tissue. For t > 0 s (when EChT is applied), the pH values ≤ 5 (around the anode) and pH ≤ 10 (around the cathode) obtained from the in silico simulation agree with those reported in other in vitro,[22] in silico,[7] preclinical,[4,18] clinical,[15] ex vivo[23] and potato experimental studies. In addition, these pH values are reported in other previous theoretical studies, when other types of electrode arrays are used.[24] The configuration (C_1) is effective for the treatment of large, deep and elongated solid tumors, since it has a higher percentage of tumor destruction in correspondence with the distance (d) between/inter of the electrode arrays; which allows to perform a protocol to patients with different types of tumors and to potentiate this type of therapy combined with the existing ones and allows to convert inoperable tumors into operable ones; which allows to improve the quality of life of the patients and the surrounding environment; and can be used for the treatment of large and deep tumors. However, in other configurations multiple electrode pairs are recommended in order to intensify the inhomogeneous distribution of T in the entire tumor volume, consistent with those of acidic and basic pH fronts, such as the proposed Soba y cols.[4,25-27]

Conclusion

Electrochemical therapy is a simple, easy, effective and low-cost therapy for the treatment of patients with cancer-specific diseases; it increases the synergy of the antitumor effect, does not generate metastasis, converting inoperable tumors into operable ones, since it raises the psycho-social and environmental standard of living of the patients by about 50%, and its use is enhanced when combined with existing therapies, which allows their rehabilitation and reincorporation into daily life, and thus represents another alternative when conventional therapies fails.

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