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Theoretical Study for the Treatment of Pancreatic Cancer Using Electric Pulses

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Abstract—**Through the development of numerical models, this study describes how Non-Thermal Irreversible Electroporation (N-TIRE) of the pancreas presents certain challenges that can be alleviated through the use of non-puncturing plate electrodes and ultra-short electric pulses.**

I. Introduction

NON-THERMAL Irreversible Electroporation (N-TIRE) is a new, minimally invasive technique that has shown great promise for the ablation of tissue [1]. The procedure involves placing electrodes into or around a targeted tissue and delivering a series of low energy, intense but short microsecond electric pulses for approximately one minute. These pulses induce irreversible structural changes in the cell membranes of the targeted tissue that lead to necrotic cell death. Because N-TIRE affects only a single molecular component of the treated area, the cell membrane, it has the ability to create complete and predictable cell ablation with a sharp transition between normal and necrotic tissue. Further, because N-TIRE does not induce thermal damage in the ablated area, important components of the tissue such as extracellular matrix, major blood vessels, myelin sheaths, and nerves are preserved [2], and healthy tissue has the ability to re-grow into the treated area. The primary parameter for determining the extent of N-TIRE is the electric field to which the tissue is exposed [3]. Therefore, the size of the treated area is limited to the maximum voltage that can be applied through the electrodes prior to inducing thermal effects.

N-TIRE has been performed as an independent modality for tissue ablation in small animal models in the liver and on tumors, as well as in large animal models in the liver, prostate, and heart [2]. However, to date, the ablation of pancreatic tissue, including pancreatic adenocarcinomas, has not been performed with N-TIRE. The pancreatic duct cell is generally believed to be the progenitor of pancreatic adenocarcinoma. Pancreatic adenocarcinoma is the fourth leading cause of cancer death in the United States, and its diagnosis constitutes a median survival time of less than six months. Further, patients with the disease often elude diagnosis until its later stages are reached, as they show a lack of symptoms throughout the formative stages. Current treatments for pancreatic adenocarcinomas include surgical resection, chemotherapy, and radiotherapy, each of which has a minimal impact on the long term-survival rate of patients [4].

Treating pancreatic adenocarcinomas through the use of N-TIRE could help to improve the long term-survival rate, but the anatomical arrangement of the pancreas presents certain challenges to this technique. The pancreas is vulnerable to handling, and a single needle puncture can induce acinar cell necrosis [5], which greatly impairs organ function. Therefore, when performing N-TIRE, plate electrodes should be used around the outside of the pancreas, as opposed to needle electrodes inserted directly into the tumor site. However, the use of plate electrodes is hindered by the fact that the pancreas is covered by a thin connective tissue capsule that divides the organ into lobules [6]. This layer, due to its relatively high electrical permittivity, has the ability to trap a significant amount of charge, limiting the amount of inner pancreatic tissue that can be treated by N-TIRE. We believe that we can bypass (or electrically short) the connective tissue layer and treat a greater amount of internal pancreatic tissue at greater depths by reducing the duration of the applied electric pulse into the nanosecond time range.

II. Circuit Model Description

To investigate whether reducing the duration of the applied electrical pulse can reduce the voltage drop around the connective tissue layer (V_{ct}) and raise the voltage drop across the internal pancreatic tissue (V_p), we have developed an equivalent electrical circuit model of the pancreas that describes these tissue components (Fig. 1). The circuit is a "Debye-type" model, where each individual tissue component is represented by a parallel combination of a resistor and capacitor, and the individual components are connected in series to represent the entire organ.

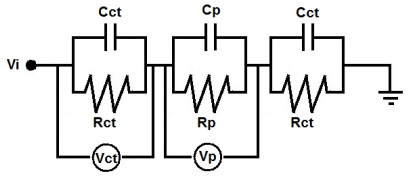

Fig. 1. Equivalent circuit model of the pancreas. A voltage (V_i) is applied at the energized plate electrode with the other set as ground, and the voltage drop across the connective tissue (V_{ct}) and pancreas (V_p) is determined.

In order to calculate the capacitances (C) and resistances (R) in the circuit model of the pancreas, data on the specific conductivity (σ) and relative permittivity (ε_r) of connective tissue and pancreatic tissue is needed. Biological tissue is neither a perfect dielectric nor a perfect conductor, and the values for σ and ε_r are dependent upon the frequency of the

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applied electric field [7]. In N-TIRE therapy, voltage is delivered to the electrodes in a square pulse waveform. The offset of the pulse causes the capacitor plates to discharge, leading to a change in direction of the capacitive current. Therefore, the duration of the pulse determines the frequency at which the current changes direction, and the pulse duration can be correlated to data defining the specific conductivity and relative permittivity at various frequencies. Data for connective tissue (estimated to be similar to wet skin) [8] and pancreatic tissue [9] was fit with a linear approximation for a frequency range of $1 \cdot 10^5$ Hz to $1 \cdot 10^8$ Hz. The appropriate values for specific conductivity and relative permittivity were selected from the plot (Fig. 2) at a frequency corresponding to the inverse of the pulse length in order to calculate the capacitance and resistance of the individual tissue components. Equation (1) can be used to calculate the tissue capacitance:

$$C = \frac{\varepsilon \cdot A}{d} \quad , \tag{1}$$

where $\varepsilon = \varepsilon_r \cdot \varepsilon_0$ and ε_0 is the permittivity of free space, d is the tissue depth, and A is the tissue area. Equation (2) can be used to calculate the tissue resistance:

$$R = \frac{d}{\sigma \cdot A} \quad , \tag{2}$$

where σ is the specific conductivity of the tissue. The area of the tissue was taken as the area of a single plate electrode on the BTX Tweezertrode (7mm diameter, BTX Harvard Apparatus), which is commonly used for electroporation in animal models. The tissue depth was taken to be 1mm (x 2) for the connective tissue layer, and 25mm for the internal pancreatic tissue, when the electrodes were placed around the head of the pancreas [10].

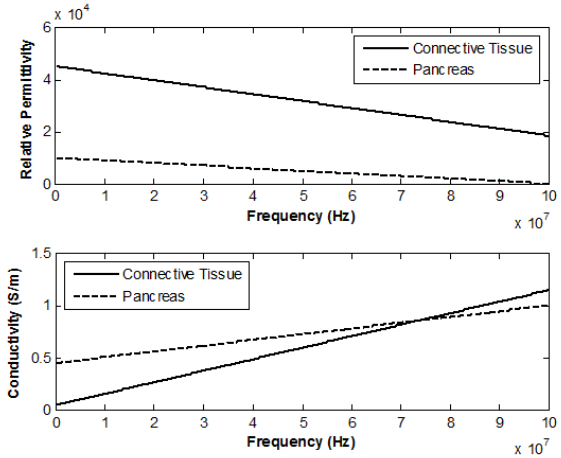

Fig. 2. Linear Approximation of the relative permittivity and specific conductivity of the connective tissue layer [8] and internal pancreatic tissue [9] from the referenced data points.

The circuit model was solved for the voltage drop across the connective tissue layer and internal pancreatic tissue in MATLAB using the Laplace transform method. Resistances and capacitances were reduced into single complex impedances for each individual tissue component in order to derive the transfer functions relating the input voltage to the voltage across the connective tissue layer and the voltage across the internal pancreatic tissue. An input voltage of 10,000 V was applied as a square pulse waveform for a specified duration. This voltage falls within the range of voltages commonly employed in N-TIRE and supra-poration procedures [11], which are described in the final section, and is used as a reference to gain insight into both procedures.

III. Finite Element Model Description

A finite element package (Comsol Multiphysics 3.5a) was used to determine the voltage and temperature distribution within the pancreas during N-TIRE treatment using the BTX Tweezertrode. A two-dimensional geometry was constructed to represent electrode placement around the connective tissue layer and internal pancreatic tissue. The dimensions of the electrodes and each tissue component were selected to match the description given in the circuit model, and the analyzed domain was large enough to avoid outer surface boundary effects. The primary mode of energy transfer in N-TIRE is through electrical conduction, and the treatment can be modeled as a coupled quasistatic electrical conduction and heat conduction problem [12].

The electric field distribution was determined by solving a simplified version of the complex Laplace equation with frequency independent conductivity parameters:

$$\nabla \cdot (\sigma \nabla \Phi) = 0 \quad , \tag{3}$$

where Φ is the electric potential and σ is the electrical conductivity of the tissue. This equation yields similar results to the complex equation when homogeneous tissue with constant conductivity and permittivity is modeled. The boundaries of the charged and grounded electrode surface were taken to be Φ = 10,000 V and Φ = 0 V, respectively. The boundaries between the connective tissue layer and pancreatic tissue were treated as continuous, while all other boundaries were treated as electrical insulation. The electrical conductivities of each tissue component were chosen to be the same as in the circuit model for a 10 ns and 10 µs pulse duration (Fig. 2).

Temperature was determined by solving a modified Pennes bioheat equation with the inclusion of a Joule heating term:

$$\nabla(k\nabla T) + w_b c_b (T_a - T) + q''' + \sigma|\nabla\Phi|^2 = \rho c_p \frac{\partial T}{\partial t} \quad , \tag{4}$$

where k is the thermal conductivity of the tissue, T is the temperature, c_b and c_p are the blood and tissue heat capacity, respectively, T_a is the arterial blood temperature, ρ is the tissue density, $\sigma|\nabla\Phi|^2$ is the joule heating term, q''' is the metabolic heat source term, and w_b is the blood perfusion coefficient. The metabolic heat source term and the blood perfusion coefficient are both taken to be zero due to the short duration of the electric pulses in N-TIRE procedures [13]. It was assumed that the tissue was initially at physiologic temperature (310.15 K). The boundaries between the connective tissue layer and pancreatic tissue were treated as continuous, while all other boundaries were treated as thermal insulation. All tissue components were taken to have identical thermal properties, where ρ = 1060 kg/m^3, c_p = 3600 J/(kg·K), and k = 0.502 W/(m·K) [12].

IV. Results

The results of the equivalent circuit model support the initial hypothesis that the connective tissue layer can be

electrically shorted. In Fig. 3a, a maximal reduction in voltage drop is observed across the connective tissue layer of 2000 V to 130 V after a 1000-fold decrease in pulse duration. However, this reduction is highly dependent upon the depth of the connective tissue layer. In the initial case, a single connective tissue layer was treated as a thin membrane (1 mm) around the pancreatic tissue (25 mm). However, in some cases, the connective tissue can extend into the pancreatic tissue in order to divide the organ into lobules, and it is possible that a pancreatic tumor may be situated below one of these regions. To simulate this case, we changed the parameters of the circuit model so that the depth of a single connective tissue layer (9 mm) was equal to the depth of the internal pancreatic tissue (9 mm), resulting in a total organ depth that was equivalent to the previous case. From (1) and (2) it is evident that increasing the tissue depth lowers the capacitance and raises the resistance.

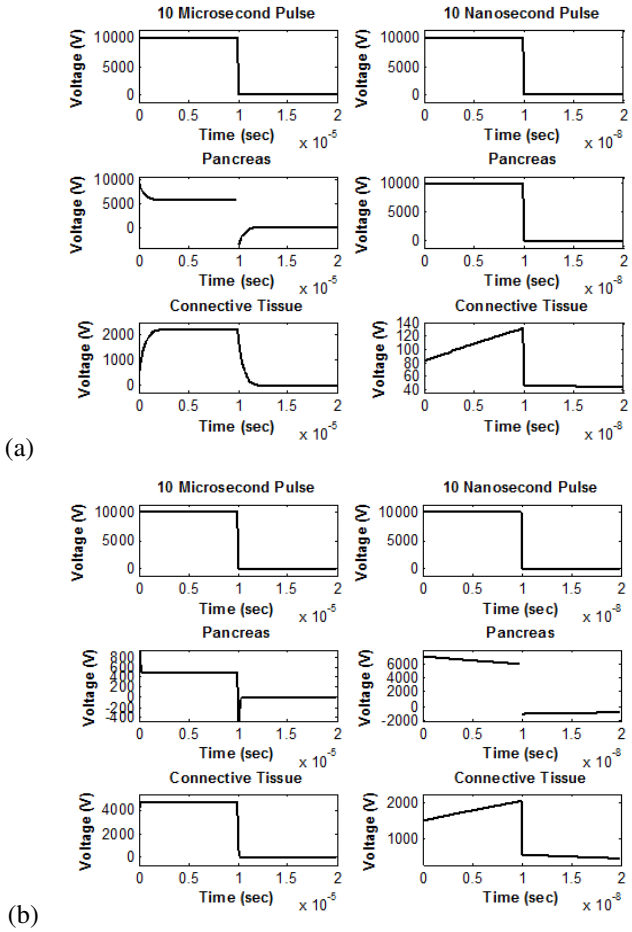

Fig. 3. Output of the circuit model showing the applied pulse (top), voltage across the internal pancreatic tissue (middle), and voltage across the connective tissue layer (bottom) for a 10 µs pulse (left) and 10 ns pulse (right). (a) The results indicate that shortening the pulse duration by a factor of 1000 is successful in reducing the voltage drop across the connective tissue and increasing the voltage drop across the pancreatic tissue. (b) The results indicate that increasing the proportion of connective tissue in the pancreas reduces the voltage drop across the pancreatic tissue. However, a shorter pulse length is still beneficial in minimizing this reduction.

The results shown in Fig. 3b indicate that a reduction in pulse length is still advantageous in reducing the voltage drop across the connective tissue layer, but the effect is less pronounced as in the previous case. Due to the increased resistance and decreased capacitance of the connective tissue layer, a further reduction in pulse length would be required to completely short the connective tissue layer in this case.

The results of the finite element model (FEM) show that for a 10 ns, 10,000 V square pulse, the temperature rise does not exceed 0.001 K (Fig. 4a), and for a 10 µs, 10,000 V square pulse, the temperature rise does not exceed 0.2 K (Fig. 4b). In the literature, 320 K is generally accepted as the point at which thermal damage begins to occur in tissues [12]. Therefore, the effects of hyperthermia in tissue damage are negligible in N-TIRE performed with the electrical parameters selected above, and the non-thermal benefits of the therapy are preserved. The voltage distribution seen in the FEM does not correlate well to the circuit model. The voltage drop across the internal pancreatic tissue predicted by the FEM (cross-section through center of domain) is 9400 V as compared to 9740 V predicted by the circuit model (steady-state capacitor charge), for the 10 ns pulse. For the 10 µs pulse, the voltage drop across the internal pancreatic tissue predicted by the FEM is 9110 V as compared to 5560 V predicted by the circuit model.

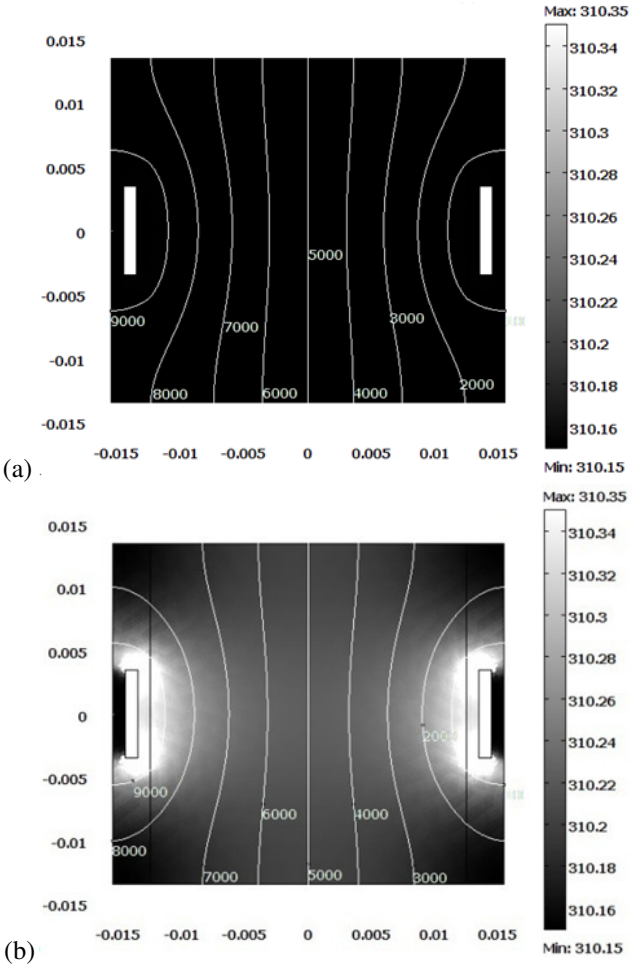

Fig. 4. Output of the finite element model (dimensions in meters) showing the surface temperature distribution (K) and the electric potential contours (V). (a) For a 10 ns, 10,000 V square pulse, the results indicate that the temperature rise in the tissue does not exceed 310.151 K. (b) For a 10 µs, 10,000 V square pulse, the results indicate that the temperature rise in the tissue does not exceed 310.35 K.

V. Discussion

From the developed models, it is evident that the voltage drop across the internal pancreatic tissue can be increased without the onset of thermal damage by reducing the pulse duration into the nanosecond time range. When nanosecond pulses are employed, irreversible structural changes in cell membranes that lead to necrosis no longer occur, as in N-TIRE. Rather, necrosis is delayed by limiting membrane permeabilization and allowing for most essential biochemicals to be retained, permitting time for apoptotic mechanisms to be triggered. This non-thermal technique, termed supra-poration, results in a similar transmembrane potential as in N-TIRE protocols (~1.3V), but the electrical current is directed through the cell (both plasma membrane and intracellular membranes) [11]. This can cause the permeabilization of calcium storage vesicles and subsequent release of calcium ions inside cells, responsible for the triggering of apoptosis [14].

Future models need to include both relative permittivity data and the ability to dynamically change the tissue properties, such as specific conductivity [15]. The electric field distribution in the tissue depends on geometry, specific conductivity, and relative permittivity. The specific conductivity of a tissue increases when a cell undergoes irreversible structural changes in its membrane due to the application of an external electric field. This, in turn, changes the electric field distribution within the tissue [11]. Neither the circuit model nor the FEM accounted for this change. Therefore, it is possible that after multiple pulses, pulse durations longer than predicted by the circuit model could bypass the connective tissue layer.

The FEM used a direct current analysis that didn't take into account the frequency dependent dielectric properties of the tissue, namely the relative permittivity, which accounts for charge confinement in the connective tissue layer of the circuit model. Therefore, the voltage distribution is independent of pulse duration and depends only on the specific conductivities of the non-homogeneous tissue components at the specified frequencies. This may account for differences seen in voltage drop across the pancreas between the FEM and circuit model. This may be corrected in future work by utilizing the complex Laplace equation in finite element models of non-homogeneous tissue.

The numerical models presented in this paper are only an approximation of real tissue systems. These preliminary results show that further investigations into the use of electric pulses for treating pancreatic cancer are warranted. Future work should include both *in vitro* and *in vivo* experimental studies that can validate the computational results and guide the development of treatment planning models.

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