Multi Physical Field Simulation of Irreversible Electroporation

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Abstract. Irreversible electroporation (IRE) uses non thermoelectric pulse to ablate tumours, which is an effective cancer treatment method. The pulse is transmitted through a minimally invasive needle electrode inserted into the target tissue and causes cell death by creating nanoscale membrane defects.Irreversible electroporation has been shown to be safe and effective in the treatment of tumours of the brain, liver, kidney, pancreas and prostate located near key blood vessels and nerves. Determining the parameters accurately of the applied pulsed electric field to kill all tumour cells and minimize damage to healthy tissue is the key to the success of IRE for the treatment of malignant tumours. In this paper, according to the researches of irreversible electroporation in the treatment of tumour in recent years, the distribution of electric field and temperature in tissue during IRE is calculated by numerical method, which provides a methodological basis for the treatment of tumour ablation with IRE.

1. Introduction
Irreversible electroporation (IRE) based on the biological effect theory of pulsed electric field is a new tumour treatment method, which uses non thermal pulse to ablate tumour [1]. This technology destroys the stability of tumour cell membrane surface by applying high-voltage pulsed electric field with microsecond pulse width around tumour cells, forming multiple hydrophilic micro-pores on the surface, thus destroying cell homeostasis and eventually leading to cell death [2]. Since the mechanism of cell death does not depend on extreme temperature, irreversible electroporation can be safely performed near major blood vessels and nerves. Therefore, as a feasible treatment, it is a feasible choice for unresectable tumours and functional limited resection. Irreversible electroporation has been used to treat liver, kidney, pancreas, prostate and other tumours [3-5]. The key technology of irreversible electroporation in the treatment of malignant tumour lies in the accurate design of treatment scheme according to the type. The location and size of tumour, i.e. the parameters of external pulsed electric field, including electric field intensity, pulse width, pulse frequency, pulse number, number of electrodes, arrangement of electrodes in tissues, etc., can completely kill tumour cells [6-9].

Numerical simulation is a conventional method to evaluate irreversible electroporation. It evaluates irreversible electroporation by predicting current, temperature rise and electric field in tissues under the action of electric pulse [10-11]. The main advantage of using numerical simulation (in-silico experiment) is that tissue samples (ex-vivo experiment) or volunteers (in-vivo experiment) are not required. It can also predict and plan treatment outcomes in heterogeneous and complex tissue environments [12-17]. Therefore, the purpose of our study is to establish a time-dependent numerical model, which can accurately display the electric field distribution and temperature rise of the treated tissue during the whole duration of the electrical pulse by considering the tissue capacitance, cell membrane and other
factors. We hope that the experimental results of the combination of space and time of electroporation will eventually lead to the improvement of treatment planning tools.

2. Material and Method

2.1. Numerical Method for Electrical Field Distribution

Electric field distribution in the models of tissue exposed to electroporation pulses can be determined by solving the equation (Eq. 1) for scalar electric potential. Namely, if we neglect the capacitive transient and time course of conductivity increase during the pulse, we may assume that the current density in tissue is divergence free and electric potential satisfies:

\[ \nabla \cdot (\varepsilon \nabla \phi) = -\rho \]

where, \( \phi \) is electric potential, \( \rho \) is charge density, \( \varepsilon \) is permittivity.

Applied voltage (model input) was modeled as Dirichlet’s boundary condition on the contact surface between electrode and tissue geometry. For the model input values we used the amplitudes of the electroporation pulses applied in vivo [18]. In order to mathematically separate the conductive segment from its surroundings we applied Neuman’s boundary condition (\( nJ = 0 \)), where \( nJ \) is the normal electric current density [Am]).

2.2. Numerical Method for Temperature Distribution

For any linear relationship between applied power and temperature change, if the temperature increase response to a brief period of heating can be characterized (with either calculation or experiment), then a convolution of that response with the timecourse of the heating will give an accurate prediction of the temperature through the entire timecourse. Linearity has been used to combine spatial precomputed temperature responses of multi-transmit array fields for safety evaluations for a fixed heating exposure. In this work the superposition of thermal responses through time is used to compute temperature through the entire duration of an MRI exam with a time-varying spatial distribution of the fields.

As an example of what can be considered a linear relationship, consider the Pennes’ bioheat equation:

\[ \rho c \frac{\partial T}{\partial t} = \nabla \cdot (k \nabla T) - W \rho_w c_w (T - T_w) + Q + \rho SAR \]

where \( c \) is heat capacity, \( \rho \) is tissue mass density, \( k \) is thermal conductivity, \( W \) is a parameter related to blood perfusion rate [19-20], \( Q \) is the heat generated by metabolism, \( SAR \) is Specific energy Absorption Rate and the subscript \( w \) indicates values for blood flowing in to the local region. which in three spatial dimensions can be written as:

\[ \rho c \frac{\partial T}{\partial t} = k \left( \frac{\partial^2 T}{\partial x^2} + \frac{\partial^2 T}{\partial y^2} + \frac{\partial^2 T}{\partial z^2} \right) - W \rho_w c_w (T - T_w) + Q + \rho SAR \]

where, \( x \), \( y \) and \( z \) [m] are the spatial coordinates. The three-dimensional heat equation can be discretized as:

\[ \rho c \frac{T^{new} - T}{\Delta t} = k \left( \frac{T_{x+} - 2T + T_{x-}}{2\Delta x^2} + \frac{T_{y+} - 2T + T_{y-}}{2\Delta y^2} + \frac{T_{z+} - 2T + T_{z-}}{2\Delta z^2} \right) - W \rho_w c_w (T - T_w) + Q + \rho SAR \]

where \( T \) and \( T^{new} \) [°C] are the current and new temperatures respectively; \( \Delta t \) [s] is the temporal resolution; \( \Delta x \), \( \Delta y \) and \( \Delta z \) [m] are the spatial resolutions; and the subscripts \(-x\), \(-y\), \(-z\), \(+x\), \(+y\), \(+z\) refer to one positive or negative step in each spatial direction with respect to the location of \( T \) and \( T^{new} \).
In this form, the three-dimensional heat equation has a total of seven unknown new temperature values for every location of (two in each spatial direction plus the central point). The equation could potentially be solved in this form using the Crank-Nicolson (CN) method (Crank and Nicolson, 1947), which combines explicit and implicit form of the right-hand side and is unconditionally stable. CN method works well with one-dimensional heat equations which can be solved in the tridiagonal matrix form. However, in three dimensions, this would result in a sparse matrix with seven diagonal matrix bands, which is computationally heavy to solve. This problem can be overcome by using so-called alternating direction implicit (ADI) method (Ames, 1977) which applies the CN method one direction at a time using two intermediate temperature fields \( T^* \) and \( T^{**} \) before obtaining the new temperature field \( T^{\text{new}} \).

By applying the ADI method first in \( x \)-direction the equation (1) becomes:

\[
T^{*} - \frac{k \Delta t}{\rho c \Delta x^2} \left[ \left( T_{sx} - 2T + T_{sx+1} \right) + \left( T_{sx} - 2T^* + T_{sx+1}^* \right) \right] + \frac{k \Delta t}{\rho c \Delta y} \left( T_{zy} - 2T + T_{zy+1} \right) + \frac{k \Delta t}{\rho c \Delta z} \left( T_{sz} - 2T + T_{sz+1} \right) + \frac{-W \rho \alpha c_{lw}(T - T_{lw}) + Q + \rho S A R}{\rho c} \tag{5}
\]

By sorting the new and current temperatures on the left and right sides, respectively, the equation can then be written as:

\[
\left( 1 + r_1 \right) T^* - \frac{k \Delta t}{\rho c \Delta x^2} + \frac{k \Delta t}{\rho c \Delta y} \left( T_{zy} - 2T + T_{zy+1} \right) + \frac{k \Delta t}{\rho c \Delta z} \left( T_{sz} - 2T + T_{sz+1} \right) = \frac{W \rho \alpha c_{lw}(T - T_{lw}) + Q + \rho S A R}{\rho c} \tag{6}
\]

where, \( r_1 = \frac{k \Delta t}{\rho c \Delta x^2} \), \( r_2 = \frac{k \Delta t}{\rho c \Delta y} \), \( r_3 = \frac{k \Delta t}{\rho c \Delta z} \).

Now, on the left-hand side, there are three unknown temperature values \( T^*, T^{**} \) and \( T_{sx}^{**} \) while the right-hand side is known. A tridiagonal matrix is obtained by solving the equation over the whole spatial domain. This can be efficiently done by using a tridiagonal matrix algorithm, such as the Thomas algorithm (Ames, 1977), to obtain the unknown intermediate temperature values \( T^*, T^{**} \) and \( T_{sx}^{**} \) for every \( x, y \) and \( z \). Next, by applying ADI method in \( y \)-direction, the equation (A.3) becomes:

\[
T^{*} - \frac{k \Delta t}{\rho c \Delta y^2} \left[ \left( T_{sy} - 2T + T_{sy+1} \right) + \left( T_{sy} - 2T^* + T_{sy+1}^* \right) \right] + \frac{k \Delta t}{\rho c \Delta x} \left( T_{sx} - 2T + T_{sx+1} \right) + \frac{k \Delta t}{\rho c \Delta z} \left( T_{sz} - 2T + T_{sz+1} \right) + \frac{-W \rho \alpha c_{lw}(T - T_{lw}) + Q + \rho S A R}{\rho c} \tag{7}
\]

which again can be sorted by placing the unknown temperature values on the left and the known values on the right:

\[
\left( 1 + r_1 \right) T^* - \frac{k \Delta t}{\rho c \Delta y^2} + \frac{k \Delta t}{\rho c \Delta x} \left( T_{sx} - 2T + T_{sx+1} \right) + \frac{k \Delta t}{\rho c \Delta z} \left( T_{sz} - 2T + T_{sz+1} \right) = \frac{W \rho \alpha c_{lw}(T - T_{lw}) + Q + \rho S A R}{\rho c} \tag{8}
\]

This can again be solved using the tridiagonal matrix algorithm to obtain \( T_{sy}^{**}, T^{**} \) and \( T_{sx}^{**} \) for every \( x, y \) and \( z \). Finally, the \( z \)-direction values can be solved to obtain the new temperature field as:
\[ T_{\text{new}} = \frac{1}{2} \left[ \left( \frac{T_{x_x} - 2T + T_{x_{sx}}}{2} \right)^2 + \left( \frac{T_{y_y} - 2T + T_{y_{sy}}}{2} \right)^2 + \left( \frac{T_{z_z} - 2T + T_{z_{sz}}}{2} \right)^2 \right] + r_1 \left[ \left( \frac{T_{x_x} - 2T + T_{x_{sx}}}{2} \right)^2 + \left( \frac{T_{y_y} - 2T + T_{y_{sy}}}{2} \right)^2 + \left( \frac{T_{z_z} - 2T + T_{z_{sz}}}{2} \right)^2 \right] \]

which can be expressed as:

\[
\begin{align*}
-\frac{r_3}{2} T_{x_x}^\text{new} + (1 + r_1) T_{x_x}^\text{new} - \frac{r_1}{2} T_{x_x}^\text{new} = & \frac{r_1}{2} T_{x_x}^x + \frac{r_1}{2} T_{x_x}^y + \frac{r_1}{2} T_{x_x}^z + \frac{r_1}{2} T_{x_x}^w \\
+ \frac{r_2}{2} T_{y_y}^x + \frac{r_2}{2} T_{y_y}^y + \frac{r_2}{2} T_{y_y}^w + \frac{r_2}{2} T_{y_y}^z + \frac{r_2}{2} T_{y_y}^z \\
+ (1 - \frac{r_1}{2} - r_2 - r_1) T_{x_x}^x T_{y_y}^y T_{z_z}^z + \left( -\frac{W \rho c_{\text{ct}}}{\rho c} (T - T_{\text{st}}) + Q + \rho \text{SAR} \right)
\end{align*}
\]

Solving this equation for every \( x, y \), and \( z \) gives the new temperature values \( T_{x_x}^\text{new}, T_{y_y}^\text{new} \) and \( T_{z_z}^\text{new} \) over the whole spatial domain. All three iterations for \( x, y \) and \( z \) directions above have to done for each time step. However, because the solution is unconditionally stable, the time step can be much larger than it would be in the explicit case. The errors of ADI solution are in the order of \( O(\Delta t)^3 \) and \( O\left( \max[\Delta x, \Delta y, \Delta z]\right)^3 \), which gives it an advantage over the explicit methods, whose errors are typically \( O(\Delta t) \) and \( O\left( \max[\Delta x, \Delta y, \Delta z]\right)^3 \).

2.3. Model reconstruction

Here, we reconstruct the ablation volume using contrast-enhanced magnetic resonance imaging (MRI) data from human clinical trials, and calculate the induced electric field intensity and temperature rise by using 2.1 and 2.2 methods.

Figure 1 The front view, side view, top view and 3D simulation diagram of irreversible electroporation were performed on the focus area of human liver

Specifically, a numerical model of the electrode in the ablation volume was established and the dynamic conductivity function was changed until the calculated current matched the current measured
during the clinical trial. The front view, side view, top view and 3D structure of the model are shown in Figure 1.

3. Results and Discussions

Figure 2 shows the distribution of electric field and temperature in liver during the application of electric pulse. By observing the experimental results of electric field and temperature distribution between two electrodes in the electroporation pulse sequence, it is obvious that the electric field intensity near the two needle electrodes increases, and the electric field intensity decreases with the increase of the distance from the electrode. Moreover, in the whole liver region, the temperature almost did not rise, only the temperature rise near the needle electrode was less than 0.5 °C. It is worth noting that in the dynamic model, due to the effect of electroporation, the electric field diffuses from the electrode, so a higher electric field value is observed.

Fig. 2 Electric field distribution and temperature distribution of irreversible electroporation in liver: electric field distribution on the left; temperature distribution on the right

4. Conclusion

Irreversible electroporation (IEP) has become a hot topic in recent years due to its outstanding advantages. Its core advantages include short treatment time, no heat sink effect, complete ablation and suitable for the parts that are difficult to reach by surgery or can not be reached by cold or thermal ablation. The irreversible electroporation rise of the electric field and the temperature distribution of the body are not revealed by numerical calculation. A series of research results show that numerical simulation is a powerful tool to optimize the parameters of irreversible electroporation of malignant tumor, and is also the basis of treatment scheme design. The multi physical field simulation algorithm model developed by us is faster and more efficient, improves the clinical timeliness, and provides the possibility for real-time evaluation of intraoperative schemes.

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