Numerical calculation for effectively simulating the electric field in electroporated tissue

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Abstract At present, cell membrane perforation technology has been widely used in biology and clinical medicine. Therefore, it is important to master the change pattern of perforated cell membrane potential to further improve the research and application of cell perforation technology. Among them, numerical simulation is an important tool to noninvasively study the effects of tissue properties, electrode arrangement and pulse transmission scheme during electroporation. In this paper, an improved Newton's method is used to predict pulse voltages and to verify the fit of the method used in this paper for different tissue parameters in a numerical computational model developed specifically for electroporation. The purpose is to improve the reference for researchers to provide faster and more accurate iterative algorithms when studying the electroporation mechanism. The comparative analysis of simulation results between this paper and COMSOL software shows that the method can improve the accuracy of predicting the electric field distribution, reduce the number of iterations, and the effect is well fitted under different tissue parameters. We believe that this knowledge will contribute to a better understanding of in vivo electroporation kinetics and improve electroporation treatment planning techniques.

1. Introduction
Under the action of a high-intensity pulse field, the cell's transmembrane voltage changes. When the cell transmembrane voltage exceeds its critical value (approximately 500 to 1,000 mV), repairable pores are formed in the cell membrane. If the cell transmembrane voltage is further increased, irreparable pores will be generated in the membrane, causing cell death[1][2]. The small holes in the cell membrane allow ions, DNA, drug molecules, etc. that cannot enter the cell membrane under normal physiological conditions to easily enter the membrane. At present, cell membrane perforation technology has been widely used in biology and clinical medicine, such as the realization of gene transfection, electrochemotherapy, and the treatment of tumor cells. Therefore, grasping the change law of perforated cell membrane potential helps us understand and control the degree of perforation and cell death of suspension cells under the action of an external pulse field, which is of great significance to further improve the research and application level of cell perforation technology. Despite the interest in this technology, its practical application has been hampered by the lack of a full understanding of the processes that occur during electroporation.

Numerical simulation is a routine method to evaluate tissue electroporation by predicting the current, temperature increase and electric field of electrical pulses in the treated tissue[3][4]. The advantage of using numerical simulations is that they do not require in vitro or in vivo experiments and can also predict treatment outcomes in heterogeneous and complex tissue environments[5]. On the other hand,
its drawback lies in the complexity of the different tissue types and anatomical structures in numerical simulations, as well as the highly nonlinear and time-dependent response of the tissue to the applied voltage, which cannot be simulated even by the most advanced numerical computational methods available[6].

The currently accepted model of electroporation can be summarized in the following equation [7]:

\[ -\nabla \cdot (\sigma \nabla \varphi) = 0 \]  
\[ \sigma = f(E) \]  

Equation (1) is a charge conservation equation in Laplace form that can describe the state of electroporated tissue at the end of a long pulse or pulse sequence under tissue steady-state conditions. However, this limits the ability to study the time course of conductivity changes and electric field distribution during pulse transport. Therefore, these models can only be verified by voltage and current measurements at the end of the pulse transport. Langus et al. developed a numerical model to accurately predict the electrical pulse current over a wide range of applied pulse voltages, durations, and repetition frequencies [8][9]. In the numerical model calculation, a stable electric field distribution must be obtained. Usually, Newton's method is used to solve the nonlinear equations to iteratively generate the electric field. However, the Newton's method is quite complex to calculate. In addition to calculating the gradient, it is necessary to calculate the second-order partial derivative matrix and its inverse matrix, which is very large in terms of both computation and storage, and both increase with the number of dimensions N. This problem becomes more prominent when N is very large. However, more accurate and fast iterative methods are needed in the study and validation of numerical models of electroporation.

In this paper, an improved Newton iterative method (INM) is used with two differences from the Newton method. First, INM uses the rank-one technique to correct the Jacobian in each iteration. Second, INM utilizes the function value of the previous iteration point [10]. A comparative analysis of the COMSOL simulation results shows that the method can improve the accuracy of the electric field distribution, reduce the number of iterations, and take an important step in the field of electroporation computer simulation experiments.

2. Methods

2.1. Iterative method for E-field distribution

We consider the system of nonlinear equations:

\[ F(x) = 0 \]  

where \( F: \mathbb{R}^n \to \mathbb{R}^n \) is a continuously differentiable function. Newton’s method is the most widely used method in applications. The linearization of equation (3) at an iteration point \( x_k \) is

\[ F(x_k) + J(x_k)s = 0 \]  

where \( s = x - x_k \) and \( J(x_k) \) is the Jacobian matrix of \( F(x_k) \) at \( x_k \). For notation purposes, let \( F_k = F(x_k) \) and \( J_k = J(x_k) \).[10] give the improved Newton’s method for system of nonlinear equations:

let \( x_0 \) be given an initial approximation to the solution of (4) such that \( J_0 \) is non-singular and choose \( \varepsilon_0 \).

The step for obtaining \( x_{k+1}, k=1,2,\ldots \) are:

Step 1. Let \( b_0 = 0, \varepsilon = \varepsilon_0 \) and set \( k = 0 \).

Step 2. If \( \| F_k \| \leq \varepsilon \), stop.

Step 3. Compute \( F_{k+1}b_{k+1}^T \) and \( x_{k+1} \) by

\[ F_{k+1}b_{k+1}^T = y_{k+1}^T(\frac{y_{k+1} - J_k s_{k+1}}{y_{k+1}^T y_{k+1}}) \frac{F_k s_{k+1}^T}{s_{k+1}^T s_{k+1}} \]
\[ x_{k+1} = x_k - (J_k + F_k b_k^T)^T F_k \]

Step 4. Set \( k = k + 1 \). Go to Step 2.

End

2.2. Numerical model

In order to be able to distinguish different pulse widths, number of pulses and pulse repetition frequency in the numerical simulation of electroporation, Langus et al. developed a digital model as follows[8]:

\[
\vec{j} = \vec{j}_\sigma + \vec{j}_C
\]

\[
\vec{j}_\sigma = \sigma(\rho_{por}, \vartheta_\sigma, \vartheta_T) \vec{E}
\]

\[
\sigma(\rho_{por}, \vartheta_\sigma, \vartheta_T) = (\sigma_{MIN} + (\sigma_{MAX} - \sigma_{MIN})\rho_{por} (1 - \alpha_\sigma \exp(-\frac{\vartheta_\sigma}{\tau_\sigma}))(1 + \alpha_T \log(1 + \vartheta_T))
\]

\[
\rho_{por}(E, \Delta t, \rho_{por}^{-1,\Delta t}) = \max\left(\frac{E - E_{MIN}}{E_{MAX} - E_{MIN}}, \rho_{por}^{-1,\Delta t} \exp\left(-\frac{\Delta t}{\tau_{por}}\right)\right)
\]

\[
\vartheta_\sigma(E, \Delta t, \vartheta_\sigma^{-1,\Delta t}) = \alpha_\sigma \vartheta_\sigma \Delta t + \vartheta_\sigma^{-1,\Delta t} \exp\left(-\frac{\Delta t}{\tau_{por}}\right)
\]

\[
\vartheta_T(E, \Delta t, \vartheta_T^{-1,\Delta t}) = \alpha_T \vartheta_T \Delta t + \vartheta_T^{-1,\Delta t} \exp\left(-\frac{\Delta t}{\tau_T}\right)
\]

\[
\vec{j}_C(E, \Delta t, \vec{E}^{-1,\Delta t}) = \frac{\alpha_C}{R_C} (E - \vec{E}^{-1,\Delta t}) \exp\left(-\frac{\Delta t}{R_C C}\right)
\]

Table 1 includes 14 model parameters of the numerical model. The current density \( \vec{j} \) flowing through the tissue is the sum of the conductive current density \( \vec{j}_\sigma \) and the capacitive current density \( \vec{j}_C \). The conductivity \( \sigma \) is a function of three auxiliary variables: the degree of porosity \( \vartheta_\sigma \), the pore damage indicator \( \vartheta_\sigma \), and the thermal damage indicator \( \vartheta_T \). These three variables are functions of the local electric field magnitude \( E \), time step \( \Delta t \) and their own value from the previous time step. The first part of is a linear model for the variance of tissue conductivity \( \sigma_{MIN} + (\sigma_{MAX} - \sigma_{MIN})\rho_{por} \) which equation(7) is supplemented with an additional term \( (1 - \alpha \exp(-\frac{\vartheta_\sigma}{\tau_\sigma})) \) constructed by analysing the shape of the measured current during application of the first pulse. The second term \( (1 + \alpha_T \log(1 + \vartheta_T)) \) models the rising envelope of measured current with increasing number of applied pulses. The subsidiary variable level of poration \( \rho_{por} \) (equation(8)) has a value in the range of [0, 1] and sets an upper limit on local tissue conductivity based on the local electric field magnitude \( E \). The subsidiary variables poration damage indicator \( \vartheta_\sigma \) (equation(9)) and thermal damage indicator \( \vartheta_T \) (equation(10)) increase proportionally to the local electric field magnitude during application of the electric pulse and decrease exponentially between the pulses.

Table 1 Values of model parameters after fitting responses of in silico simulation to ex vivo measurements.

| Symbol   | Description            | Value (range where applicable) |
|----------|------------------------|---------------------------------|
| \( \sigma_{MIN} \) | Initial tissue conductivity | 0.065 S/m                        |
The currently accepted charge conservation equation of the electroporation model (equation (1)) cannot be used as the intrinsic equation of our proposed model because of the storage or release of charge in the lipid bilayer membrane within the tissue volume. The model uses the charge conservation equation with a charge source/sink term:

$$\nabla \cdot (\sigma \cdot \vec{E}) = \frac{\partial q}{\partial t}$$  \hspace{1cm} (12)

Combining equation (11) and equation (12), we write down the proposed intrinsic constitutive equation:

$$\nabla \cdot (\sigma \cdot \vec{E}) = \frac{\alpha_c}{R_c} \left( \vec{E} - \frac{E(\tau_\sigma)}{R_c} \right) \exp\left( -\frac{\Delta t}{R_c C} \right)$$  \hspace{1cm} (13)

For each time step of the electric field, this paper uses the Newton iteration method and the improved Newton iteration method to compare equation (13), and sets the convergence criterion of the two iteration methods to $1e^{-8}$. The tissue conductivity $\sigma$ was adjusted in each iteration step according to equations (7)-(10), and since these equations explicitly depend on the electric field $\vec{E}$ no convergence check for subsidiary variables $\rho_{por}$, $\vartheta_{\sigma}$ and $\vartheta_{T}$ was performed. Model implemented in python and 12 processor under CentOS 8.0 and reaching the steady state $\vec{E}$.

3. Test Results and Discussions

3.1 Validation of numerical method

Table 2 shows the quantified parameters (maximum value of electric field (Max-E), 99th percentile (E-99th), 95th percentile (E-95th), mean (E-mean)) of the electric field generated by Newton's method (NM) and the Improved Newton's method (INM) compared with the electric field intensity inside the tissue simulated by FEA software COMSOL. Table 3 shows the comparison of the errors and the number of iterations for the NM and INM parameters. From the results, it can be seen that INM outperforms NM in terms of the accuracy of the generated electric field and the number of iterations. The advantages of
the INM iterative algorithm are also validated in this paper to provide a reference for the optimal selection of future iterations of the numerical computational model for biological tissues.

Table 2 Comparison of the electric field generated by NM and INM with the original electric field quantitive parameters

| Methods | Max-E(V/cm) | E-99th | E-95th | E-mean |
|---------|-------------|--------|--------|--------|
| NM      | 94.41       | 10.22  | 4.06   | 0.54   |
| INM     | 96.57       | 10.30  | 4.13   | 0.56   |
| COMSOL  | 98.34       | 11.19  | 4.16   | 0.58   |

Table 3 The error comparison and the number of iterations of the parameters of NM and INM

| Methods | Relative Error | Iterations |
|---------|----------------|------------|
|         | Max-E         | E-99th     | E-95th | E-mean |           |
| NM      | 4.01%         | 0.87%      | 2.20%  | 0.66%  | 10 times  |
| INM     | 1.82%         | 0.79%      | 0.07%  | 0.18%  | 4 times   |

In this paper, we simulate the pulse sequence and test the distribution of the electric field intensity on the time scale. Since the simulation process uses the same tissue type, in order to verify whether the results produce a good fit because of the use of the same material parameters. In this paper, in the first batch of simulations (Test 1), the parameter $\sigma_{MAX}$ was optimized for each sequence, while the values of the other parameters were the same in all cases. In the second batch of simulations (Test 2), the average value of the parameter $\sigma_{MAX}$ from the first batch of simulations was used. The results of the 2 simulations are shown in Fig.1. It can be seen from the figure that good fits can be obtained for both 2 methods.

4. Conclusion

Currently, cell membrane perforation technology has been widely used in the fields of biology and clinical medicine. Therefore, mastering the change rule of perforated cell membrane potential is of great significance for further improving the research and application level of cell perforation technology. Among them, numerical simulation is an important tool to non invasively study the effects of tissue characteristics, electrode arrangement and pulse transmission scheme during electroporation. In this paper, an improved Newton's method is used to predict the pulse voltage in a numerical calculation model specially developed for electroporation and verify the fitting effect of the method used in this paper under different tissue parameters. The purpose is to improve researchers to provide a faster and
more accurate iterative algorithm reference when studying electroporation mechanism. Through the comparative analysis of the simulation results of this article and the COMSOL software, it can be seen that this method can improve the accuracy of predicting electric field distribution, reduce the number of iterations, and the effect is also well fitted under different tissue parameters. We believe that this knowledge will help to better understand electroporation kinetics in vivo and improve electroporation treatment planning techniques.

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References
[1] Potter H. Electroporation in biology: methods, applications, and instrumentation[J]. Analytical biochemistry, 1988, 174(2): 361-373. (in United states)
[2] Dev S B, Rabussay D P, Widera G, et al. Medical applications of electroporation[J]. IEEE Transactions on Plasma Science, 2000, 28(1): 206-223. (in United states).
[3] Sel D, Cukjati D, Batiuskaite D, et al. Sequential finite element model of tissue electropermeabilization[J]. IEEE Transactions on Biomedical Engineering, 2005, 52(5): 816-827. (in United states).
[4] Garcia P A, Pancotto T, Rossmeisl Jr J H, et al. Non-thermal irreversible electroporation (N-TIRE) and adjuvant fractionated radiotherapeutic multimodal therapy for intracranial malignant glioma in a canine patient[J]. Technology in cancer research & treatment, 2011, 10(1): 73-83. (in United states).
[5] Denzi A, Strigari L, Di Filippo F, et al. Modeling the positioning of single needle electrodes for the treatment of breast cancer in a clinical case[J]. Biomedical engineering online, 2015, 14(S3): S1. (in United Kingdom).
[6] Kos B, Zupanic A, Kotnik T, et al. Robustness of treatment planning for electrochemotherapy of deep-seated tumors[J]. The Journal of membrane biology, 2010, 236(1): 147-153. (in United states).
[7] Corovic S, Lackovic I, Sustaric P, et al. Modeling of electric field distribution in tissues during electroporation[J]. Biomedical engineering online, 2013, 12(1): 16. (in United Kingdom).
[8] Langus J, Kranjc M, Kos B, et al. Dynamic finite-element model for efficient modelling of electric currents in electroporated tissue[J]. Scientific reports, 2016, 6(1): 1-11. (in United Kingdom).
[9] Ivorra A, Mir L M, Rubinsky B. Electric field redistribution due to conductivity changes during tissue electroporation: experiments with a simple vegetal model[C]/World Congress on Medical Physics and Biomedical Engineering, September 7-12, 2009, Munich, Germany. Springer, Berlin, Heidelberg, 2009: 59-62.(in Germany).
[10] Saheya B, Chen G, Sui Y, et al. A new Newton-like method for solving nonlinear equations[J]. SpringerPlus, 2016, 5(1): 1269. (in Germany).