Modelling in conventional electroporation for model cell with organelles using COMSOL Multiphysics

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Abstract. Conventional electroporation is a formation of pores in the membrane cell due to the external electric field applied to the cell. The purpose of creating pores in the cell using conventional electroporation are to increase the effectiveness of chemotherapy (electrochemotherapy) and to kill cancer tissue using irreversible electroporation. Modeling of electroporation phenomenon on a model cell had been done by using software COMSOL Multiphysics 4.3b with the applied external electric field with intensity at 1.1 kV/cm to find transmembrane voltage and pore density. It can be concluded from the results of potential distribution and transmembrane voltage, it show that pores formation only occurs in the membrane cells and it could not penetrate into inside the model cell so there is not pores formation in its organells.

1. Introduction
Conventional electroporation is a formation process of temporary hydrophilic pores on the cell membrane surfaces. Electroporation phenomenon occurs when cells are exposed to external electric field and experiencing an increase of transmembrane voltages to a certain point because of electric field accumulation on cell membrane. The increased transmembrane voltages will trigger formation of pores at lipid double layer and allowing ions and big molecules to enter the cell. Conventional electroporation capabilities to form pores on cell membrane became a rapid-growth research topic, specifically at medicine, genes transportation, chemotherapy treatment, and tumor tissues ablation [1-4].

There are some researches in this area, but yet still a lot of unknown aspects from the electroporation phenomenon need to be investigated. In this research, cell model were constructed with generally electric parameter for electroporation method [2, 4, 5] and numerically interpreted by applying finite-element method supported by COMSOL Multiphysics 4.3b software. Thus, the increasing of transmembrane voltages and the density of pores which formed at cell membrane and organelles inside the cells on the conventional electroporation method can be observed.

2. Methodology
In this research, the cell models will be constructed on extracellular liquid (figure 1a), with organelles such as cell nucleus (figure 1b), endoplasmic reticulum (Fig. 1c), and mitochondria (figure 1d). Electric field is exposed from the left-hand side of the model and the electric-potential distribution at cell model determined by equation (1):
\[ \nabla \left( \sigma \nabla \Phi \right) - \frac{\partial}{\partial t} \left( \nabla \varepsilon \left( \nabla \Phi \right) \right) = 0 \]  \hspace{1cm} (1)

where \( \sigma \) and \( \varepsilon \) are respectively conductivity and permittivity at each region of the cell model. Derived from eq. (1), another equation which determined transmembrane voltage at cell membrane and organelle membrane can be obtained equation (2):

\[ \Psi_{\text{tm}} = \Phi(R + h) - \Phi(R) \]  \hspace{1cm} (2)

with \( R \) and \( h \) are respectively cell or organelle radius and membrane thickness.

Pore formation process at cell or organelle membrane approximated by asymptotic model equation, in equation. (3):

\[ \frac{dN(t)}{dt} = \alpha \exp \left( q \left( \frac{\Psi_{\text{tm}}(t)}{\phi_{\text{ep}}} \right)^2 \right) \left[ 1 - \frac{N(t)}{N_0} \exp \left( -q \left( \frac{\Psi_{\text{tm}}(t)}{\phi_{\text{ep}}} \right)^2 \right) \right] \]  \hspace{1cm} (3)

where \( \alpha \), \( q \), \( \Psi_{\text{tm}} \), \( \phi_{\text{ep}} \), and \( N_0 \) are respectively pore formation rate density, pore formation rate, transmembrane voltage determined by equation (2), membrane threshold voltage, and pore density at equilibrium. To solve equation (1) and (3) COMSOL Multiphysics 4.3b software will be applied. Combining two modules simultaneously – which are electric current to determine potential distribution and transmembrane voltage and weak form PDE to determine pore density. The shape of applied external electric field for conventional electroporation that used in this research can be seen at figure 2.

\[ \text{Figure 1.} \hspace{0.5cm} \text{(a) cell model used in this research, (b) cell nucleus, (c) endoplasmic reticulum, and (d) mitochondria.} \]
3. Results and discussions

Potential distribution in model cell when applied external electric field were given can be seen in figure 3. It could be observed at the beginning of the exposure, $t = 1$ microsecond (figure 3a) and at the near end of exposure, $t = 89$ microseconds (figure. 3b), the electric field were unable to penetrate the cell. Potential distribution values inside the model cell constantly at range 1.5 to 2 volt, even though the applied electric field at maximum intensity (1.1 kV/cm). Thus, on conventional electroporation the membrane of organelle inside the cell did not experienced an increasing of transmembrane voltage. Consequently, electroporation did not occur at nucleus cell membranes, endoplasmic reticulum, and mitochondria. Increasing transmembrane voltage only occurred at cytoplasm membrane (figure. 4a) causing formation of pores only occurred at these membranes (figure. 4b).

![Figure 3. Electric potential distribution for exposure of applied external electric field at, (a) $t = 1$ microsecond and (b) $t = 89$ microseconds.](image-url)
4. Conclusions

Using numerical intreperation supported by COMSOL Multiphysics 4.3b to solve the finite-element method for electroporation phenomenon is essential to understanding the electric potential distribution and pores formation in the model cell. The model cell used in this research includes representations of several organelles, such as mitochondria, endoplasmic reticulum, and nuclear cell, so it will be very usefull for study the electroporation phenomenon and for this research, it can be seen in figure 3 and figure 4, exposure of applied external electric field to the model cell for conventional electroporation could only trigger pores formation on cytoplasm membranes. The applied external electric field is not strong enough to penetrate into inside the model cell to create secondary electroporation in the membrane of organelles.

References

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