Nonlinear Supra-Electroporation in Realistic Stem Cell Morphologies

Somen Baidya
Department of Computer Science and Electrical Engineering
University of Missouri–Kansas City
Kansas City, MO, 64110, USA
sbg58@mail.umkc.edu

Ahmed M. Hassan
Department of Computer Science and Electrical Engineering
University of Missouri–Kansas City
Kansas City, MO, 64110, USA
hassanam@umkc.edu

***Abstract*—Exposing cells to ultrashort electric field pulses can lead to the permeabilization of the membranes of the internal cell organelles, such as the nucleus, which is termed as supra-electroporation. In this paper, we study the supra-electroporation of stem cells with realistic morphologies under nanosecond electrical pulse stimulation. For such short pulses, the cell and the nucleus membranes exhibit non-linearity in their conductance. Therefore, we used a non-linear model for the cells' membranes, coupled with a quasi-static electromagnetic solver, and obtained the solution using a commercial Finite Element Method (FEM) solver. The results show that the outer shape of the cell has a strong effect on the magnitude and the spatiotemporal patterns of the electric field inside the cell, which affects the rate of the supra-electroporation of the nucleus. These variations in the rate of the supra-electroporation of the nucleus can guide the selective targeting of desired cells with specific shapes.**

***Keywords*—Nonlinear, Stem Cells, Supra-Electroporation.**

I. Introduction

Cell membrane presents an insulating barrier to several molecules and foreign objects and it regulates the ion exchange between the extracellular and intracellular mediums. The semipermeable nature of the cell membrane can be changed by using external electrical excitation of different pulse width and amplitude, allowing the intake of chemotherapeutic drugs, proteins, gene transfection, extraction of molecules from cell, or even cell death for certain excitations [1]. When the excitation pulse width is in the nanosecond range, which is smaller than the membrane charging time, the induced electric field can manipulate the membrane permeability of intracellular components as well (i.e., the nucleus or the endoplasmic reticulum) [1]. This phenomena of regulating the intracellular organelles by engineering the excitation field parameter is known as Supra-Electroporation.

The goal of this study is to quantify the effect of cell morphology on the rate of supra-electroporation. Realistic cell shapes were obtained from the stem cell database developed by the National Institute of Standards and Technology (NIST) [2]. The database is divided into ten families and exhibits a wide range of variations in cell morphology, nucleus morphology, and the relative location of the nucleus inside the cell. In the following section, we will describe the nonlinear model used to simulate the supra-electroporation of these stem cells with realistic morphologies.

II. Methodology

In this study, we have used one cell map from each of the ten families and used a symmetrical 2D cross-section of the cells and embedded nuclei to incorporate in our model. Each cell cross-section from all the ten families are identified according to their microenvironment name as depicted in Fig. 1. Using the known material properties (i.e., conductivity, permittivity) of the extracellular medium, the intracellular medium, and the cell membrane, we can solve Laplace Equation (1) to derive the electric field distribution and voltage inside and outside of the object. At any point on the cell membrane, a different value of the intracellular and extracellular voltage can exist based on the cell's shape. The difference of these voltages, at a point (i, j) is referred to as the transmembrane voltage of the cell membrane (V_m^{ij}). Under the effect of a sufficiently large electrical excitation, the transmembrane voltage induced on the membrane reaches its threshold for permeabilization (V_{ep}). The physical representation of this phenomenon is depicted by the density of pores formed on the cell and nucleus membrane (N_{ij}), which follows a nonlinear relationship with the transmembrane voltage (2). Initially, the cell and nucleus membranes have an equilibrium pore density (N_0). As the transmembrane voltage reaches its threshold, the pore density also saturates, resulting in a significant increase in the membrane conductivity(σ_m^{ij}), hence increasing the membrane's permeability (3):

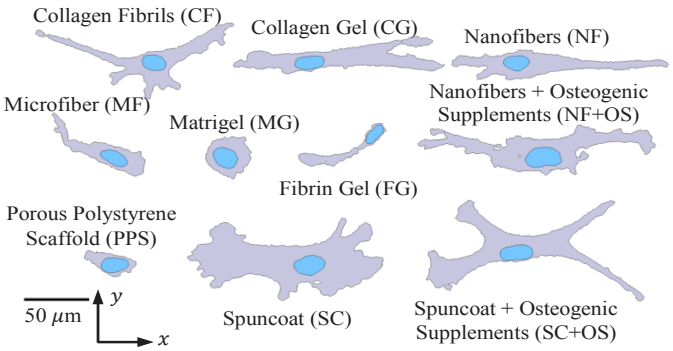

Fig. 1. 2D cross-sections of the ten different cell shapes and embedded nucleus used in this study.

$$\nabla^2 V = 0, \tag{1}$$

$$\frac{dN_{ij}(t)}{dt} = \alpha e^{\left(\frac{V_m^{ij}}{V_{ep}}\right)^2}\left(1 - \frac{N_{ij}(t)}{N_0 e^{q\left(V_m^{ij}/V_{ep}\right)^2}}\right), \tag{2}$$

$$\sigma_m^{ij}(t) = \sigma_{m0} + N_{ij}(t)\sigma_p * \pi r_p^2 * K. \tag{3}$$

In (3), r_p and σ_p are the pore radius and pore conductivity, respectively. The nonlinearity of the physics arises from the correlation between the pore density and the membrane conductivity (3), which eventually effects the field distribution around the membrane (1). For our study, we have designed and implemented the aforementioned physics on both cell and nucleus membrane using COMSOL Multiphysics, a commercial finite element method solver. We have incorporated the Electric Current (Time Domain) solver to solve (1) and a weak form PDE solver to solve (2) in the Multiphysics domain. The external excitation field used in

This work is supported in part by the NIST Grant 70NANB15H28 and by the University of Missouri-Kansas City, SGS Research Award.

Submitted On: September 11, 2020
Accepted On: September 11, 2020

https://doi.org/10.47037/2020.ACES.J.351132

this study was a 16 kV/cm pulse with 71 ns pulse duration accompanied by 6 ns rise time and 10 ns fall time. Since we are interested in electroporation of the internal organelles in this study, we modelled our excitation field in the supra-electroporation region of the pulse strength-duration map reported in [3]. The excitation field strength in this observation was in the range of "*cell survival*" as reported in [3]. To the best of our knowledge, the exact electrical properties of the stem cells reported in the NIST database were not characterized and therefore we used the electrical parameters of a general cell model [4]. In the subsequent results, we highlight only the characteristics of the nucleus membrane, although the nonlinear membrane was implemented on both the cell and nucleus membrane.

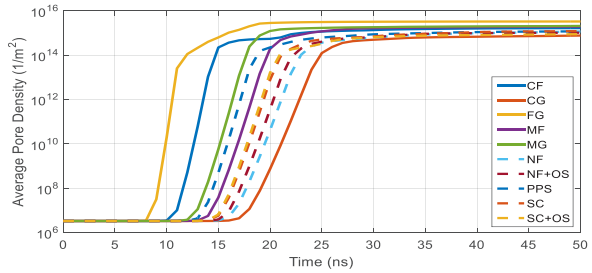

Fig. 2. Average pore density on the nucleus membrane of all ten cell sections in Fig. 1 versus time.

III. Result and Discussion

The induced transmembrane voltage is largely impacted by the orientation and location of cell with respect to direction of electric excitation. To maintain consistency in this regard, we diagonalized the cell with embedded nucleus along their largest gyration tensor, using their respective polarizability matrix information [5], then we translated the cell and the nucleus such that center of mass of the nucleus coincides with the origin before taking the 2D cross-section at the center of the cell (Fig. 1).

A. Average Pore Density on Stem Cell Sections

The pore density profile of all the ten nuclei from the cell sections considered in this study is depicted in Fig. 2. The average pore density is calculated by taking a line integral of the pore density along the perimeter of the nucleus ($\int N_{ij(t)}.dl \,/\, \int dl$). As can be observed, CG nucleus demonstrates the slowest response, since the cell shape distribution is larger along the electric excitation direction. The slanted alignment of the FG cell and embedded nucleus results in faster pore density saturation under identical electrical excitation. There is also a significant difference in the saturated pore density, depicting the variation in cell shape is a major contributor to supra-electroporation characteristics.

B. Variable Nucleus Location

To illustrate the effect of relative position of the nucleus inside the cell, we performed a parametric study by varying the nucleus location inside SC cell section, as depicted in Fig. 3 and Fig. 4. For simplicity, we have combined simulation from three different nucleus position and only demonstrated the field distribution at time $t = 25\ ns$ after the excitation starts as shown in Fig. 3. The internal electric field strength due to external excitation remains unperturbed by the position of the nucleus. As shown in Fig. 3, the presence of protrusions in the membrane creates a non-uniform electric field distribution inside the cell. As a result, the nucleus at position (a) experiences the fastest rate of electroporation, as shown by the blue curve in Fig. 4, because it experiences the largest electric field as shown in Fig. 3 (refer to nucleus at position (a)). The nucleus at position (b) experiences the slowest rate of electroporation since it is at the location where the internal electric field is minimum. Therefore, by controlling the electroporation time, the results in Fig. 2-Fig. 3 can be used for the selective supra-electroporation of cells with specific morphologies and nucleus positions. Moreover, the rate of supra-electroporation was found to vary with the direction of the field excitation which can also be leveraged for the selective targeting of specific cell shapes and orientations.

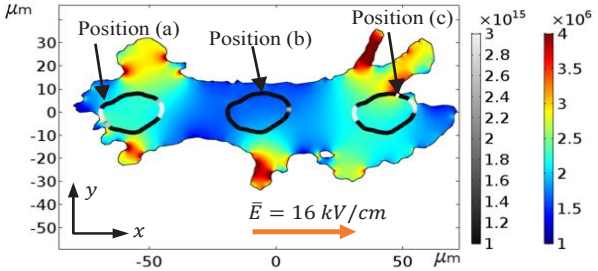

Fig. 3: Electric field distribution of SC cell section at $t = 25\ ns$ as the nucleus location is varied; *rainbow* color bar represents the electric field distribution (V/m) and *grayscale* color bar represents the pore density ($1/m^2$) at the nucleus membrane at the same instant for various nucleus location.

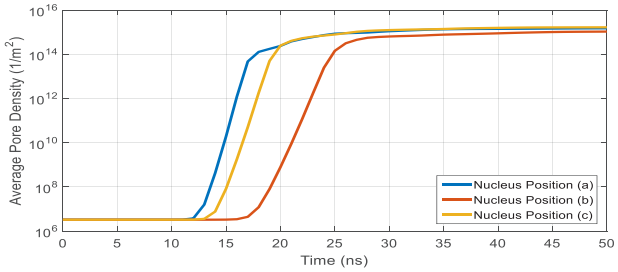

Fig. 4. Average pore density on the nucleus membrane at the three positions depicted in Fig. 3.

IV. Conclusion

In this paper, the supra-electroporation behavior of realistic cell morphologies was studied using a nonlinear computational model. The findings of this study draw the conclusion that, the morphology and the relative location of the cell's nucleus, play a significant role on the rate of electroporation of the nucleus membrane and can be used to guide the targeting of specific cells.

References

[1] L. Rems and D. Miklavčič, "Tutorial: Electroporation of cells in complex materials and tissue," Journal of Applied Physics, vol. 119, no. 20, p. 201101, May 2016.

[2] https://isg.nist.gov/deepzoomweb/fileBrowsing/3D/

[3] J. C. Weaver, K. C. Smith, A. T. Esser, R. S. Son, and T. R. Gowrishankar, "A brief overview of electroporation pulse strength–duration space: A region where additional intracellular effects are expected," Bioelectrochemistry, vol. 87, pp. 236-243, Oct. 2012.

[4] K. C. Smith and J. C. Weaver, "Active mechanisms are needed to describe cell responses to submicrosecond, megavolt-per-meter pulses: cell models for ultrashort pulses," Biophys. J., vol. 95, no. 4, pp. 1547-1563, Aug. 2008.

[5] S. Baidya, A. M. Hassan, W. Al-Shaikhli, B. A. P. Betancourt, J. F. Douglas, and E. J. Garboczi, "Analysis of Different Computational Techniques for Calculating the Polarizability Tensors of Stem Cells With Realistic Three-Dimensional Morphologies," IEEE Transactions on Biomedical Engineering, vol. 66, no. 7, pp. 1816-1831.