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Control of pore radius regulation for electroporation-based drug delivery

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ABSTRACT

Electroporation uses electric pulses to create transient, nonselective pores in a cell's membrane, allowing drugs to be delivered into the targeted cells. To ensure proper uptake of drug molecules, it is essential to control the radii of the pores and the time duration, for which the pores remain open. Electroporation is intrinsically a nonlinear dynamic process. A careful analysis of the electroporation dynamics reveals that, under variation of the magnitude of the input voltage, the equilibrium pore radius undergoes a pair of saddle-node bifurcations. As a result, there exists a range of pore radii that is physically unstable and thus cannot be maintained in conventional experiments. The bifurcations and the associated unstable regime impose restrictions on the operation of electroporation, limiting the sizes of deliverable drug particles. To overcome these problems, we design a novel control strategy to stabilize the originally unstable solutions. In contrast to the conventional control algorithms based on local stability analysis, the present control is globally stable. Numerical examples show that the control eliminates the original bifurcations and allows one to achieve a wide range of pore radii. The robustness and effectiveness of the control strategy would potentially enhance the application of electroporation.

1. Introduction

Electroporation is a technique to create transient pores in a cell's membrane by applying electric pulses. The technique has become a useful tool to deliver biologically active molecules into the cell [1–3]. As shown in Fig. 1, the procedure of electroporation utilizes electric pulses to temporarily disrupt the phospholipids bilayer of a cell to form pores, which are nonselective and allow any chemical species to penetrate the cell. Electroporation has many potential medical applications. For example, the technique can deliver chemotherapeutic drugs into tumor cells to treat cancers [4]. Recently, electroporation has been used in gene therapy to deliver DNA into a variety of tissues [5–9], which can consistently result in a 100- to 1000-fold enhancement of gene expression.

One key issue in electroporation is to create pores of an appropriate size to the intended application for a sufficient amount of time. For example, the pores should be at least 10 nm in diameter and last for more than 1 ms, in order to admit supercoiled DNA molecules [10]. On the other hand, electroporation may cause substantial tissue damage when the pores size is too large or the pores remain open for too long. Thus, the success of electroporation requires an appropriately designed protocol for pore creation. This is a difficult task because electroporation is a nonlinear dynamical process, whose input–output relation is not transparent. Thus, understanding nonlinear dynamics of electroporation becomes a critical factor to design and control electric pulses.

The purpose of this work is to investigate nonlinear phenomena during an electroporation process and to explore possible control mechanisms to improve the effectiveness of the process. Using bifurcation analysis, we investigate the relation

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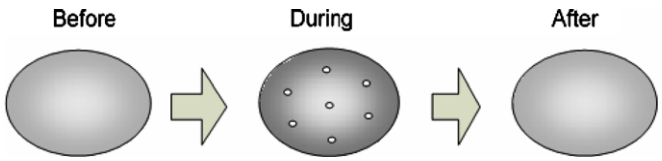

Fig. 1. Schematic illustration of an electroporation process: a strong electric pulse temporarily disrupts the membrane of a cell to form pores, which allow any chemical species to penetrate the cell.

between input voltage and the size of the created pores. The result demonstrates that a range of pore sizes is not achievable in experiments. Moreover, the bifurcation leads to a hysteresis phenomenon. These nonlinear phenomena bring a substantial challenge to design electric pulses, and thereby, limit the operation of electroporation.

Currently, the strength and duration of the electric field in electroporation are mainly determined by trial-and-error. Moreover, the common pulses used in experiments are open-loop controls, which suffer bifurcations and hysteresis. Recently, Ma and Zhang [11] proposed a feedback-linearization based nonlinear controller to regulate a target transmembrane potential. In this paper, we propose a new control algorithm to improve the two-phase protocol in regulating the pore size. A detailed analysis demonstrates the robustness and the efficacy of the algorithm. In addition, the control strategy is globally stable and allows one to achieve a wide range of pore radii.

This artcile is organized as follows: Section 2 introduces mathematical description of the physical processes of electroporation. A simplified mathematical model is presented based on a commonly adopted protocol. Then, Section 3 explores nonlinear dynamics of the model and demonstrates how bifurcations limite the operation of electroporation. A feedback control algorithm is introduced in Sectoin 4 to eliminate the bifurcations and to improve the efficiency of electroporation. Finally, Section 5 presents conclusions and discussions.

2. Problem description

Mathematical models have been developed to describe an electroporation process [12–14]. As discussed in detail in [14], the electroporation process can be represented as an electrical circuit model, see Fig. 2. Here, V_0 is the external voltage, R_s accounts for the resistance of the experimental setup, the cell's membrane is represented as the capacitor C, the resistance of the membrane is represented as the constant resistor R, I_p represents current through electropores. Then, the variation of the transmembrane potential V_m is governed by the following differential equation:

$$C\dot{V}_m + \left(\frac{1}{R_s} + \frac{1}{R}\right)V_m + I_p = \frac{V_0}{R_s}, \tag{1}$$

where the coefficients $C = C_m A_s$ and $R = R_m A_s$ stand for the total capacitance and resistance of the membrane, respectively. C_m and R_m are the surface capacitance and surface resistance of the membrane, and A_s represents the total area of pores. The current I_p can be formulated as follows:

$$I_p = K\frac{V_m}{R_p + R_i}, \tag{2}$$

where K is the number of pores, $R_p = h/(\pi g r^2)$ represents the pore resistance, and $R_i = 1/(2gr)$ represents the input resistance.

Hydrophobic pores are initially created when the transmembrane potential grows sufficiently large. Most such pores are quickly destroyed by lipid fluctuations; however, when a pore grows beyond a critical radius r_p, it will spontaneously convert to a long-lived hydrophilic pore [14]. Hydrophilic pores will immediately expand to the minimum-energy radius r_m [15]. The pore density N is governed by a first-order differential equation [15]

$$\dot{N} = \alpha e^{(V_m/V_{ep})^2}[1 - (N/N_0)e^{-(r_m V_m/r_p V_{ep})^2}], \tag{3}$$

where N_0 is the pore density when $V_m = 0mv$. α represents the creation rate coefficient, and V_{ep} stands for the characteristic voltage of electroporation.

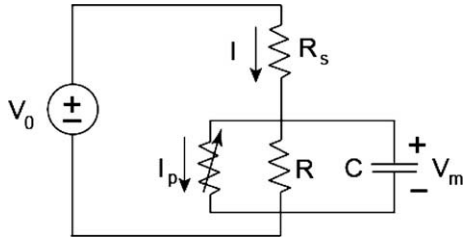

Fig. 2. Circuit representation of the electroporation process.