Diffuse Interface Model of Electroporation

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Abstract

In this work, a model and simulation method to study the dynamics of pore formation and annihilation in a lipid membrane under an applied electric field has been developed. A continuum-level diffusive interface model (phase-field) method is applied to model the evolution of the pore in a lipid membrane patch. The numerical method and results are presented.

1 Introduction

Vesicles have biomedical applications as vectors for drug and gene delivery. Manufactured vesicles can be injected with drug molecules, or other particles such as DNA, which can in theory be delivered directly to a particular region. The dynamic behavior of lipid bilayer vesicles in an external flow is clearly part of the overall theory of potential drug delivery application. However, this only accounts for half of the story; an ability to release the interior of the drug in a controlled environment is crucial for any application. One possible appraoch is electroporation. A vesicle or lipid membrane under an electric field forms pores on the surface due to surface tension produced by the electric field. Controlled applications of electric pulses can induce the formation of a pore, which closes once the pulse is turned off. Many theories describing the electroporation process have surfaced in recent (and not so recent) years [18, 19, 4] however, the underlying physical process remains elusive.

The foundation for the pore dynamics simulation in this work is the phase-field model. This model stems from work done by [14, 3] and [1] beginning in the 1950s and has been applied to study a variety of physical phenomena. It has been applied to solidification dynamics, microstructure evolution and phase transition but it has also been applied to other situations such as viscous fingering [10, 11], fracture dynamics,[13] multi-phase flow [17, 2], vesicle dynamics [8, 9, 15], etc.

2 Theoretical Background

2.1 Transient Pores Model

The initial observation of pores on membranes did not involve the electrical behaviour. The possibility of spontaneous poration initially suggested by two groups and later on studied more carefully [16, 12]. The mechanism of pore formation/annihilation is described by two competitive deriving force: the energy per length along the pore edges γ, we call it line tension, and the membrane tension or the energy per area of the membrane of a flat pore-free membrane γ where it is simply called the surface tension. The energy of transient pore ΔW_p is then defined as follow:

$$\Delta W_p = \oint \gamma \, ds - \int \sigma_0 \, dA \tag{1}$$

Surface tension σ_0 is responsible for appearance of transient pores in vesicles and lipid membranes. The surface tension for the membrane in relaxed state is very small. However, due to many reasons such as thermal fluctuations or increased hydrodynamic pressure inside the vesicle the membrane eventually becomes tense and pore formation occurs. After the pore formation and releasing the surface tension, pores will eventually reseal, the deriving force here is the line tension γ. In Figure 1 the opening and closing deriving forces are shown.

2.2 Electroporation Model

Electroporation is a dynamic phenomenon that depends on the local transmembrane voltage U_m of the lipid membrane. The induced voltage over the lipid membrane creates an extra surface tension σ_e over the membrane in addition to the membrane tension σ_0 that already exists on the membrane. The overall surface tension then is $\sigma = \sigma_0 + \sigma_e$.

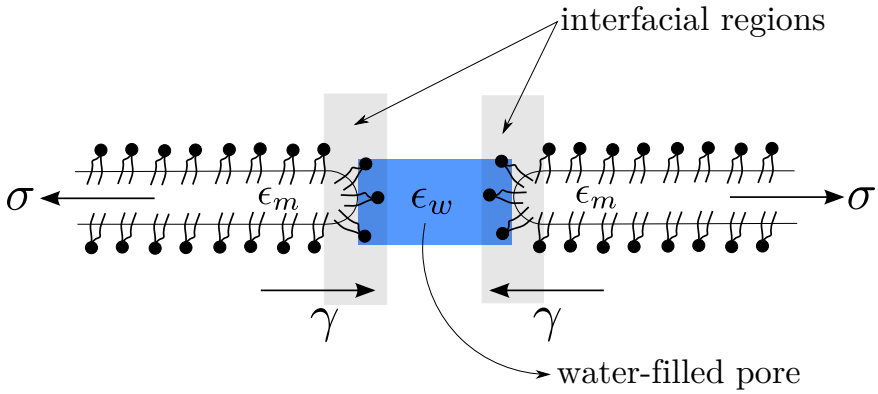

Figure 1: Schematic of one water-filled pore in a lipid membrane

Pore regions can be treated as having an energy associated with the change of its specific capacitance, C_{LW}, as lipid is replaced by water (a water-filled capacitor) shown in Figure (1). In the presence of a transmembrane electric field, the free energy of pore formation should be:

$$\Delta W_p = \oint_{\partial\Gamma} \gamma \, ds - \int_{\Gamma_p} \sigma_0 \, dA - \int_{\Gamma_p} \sigma_e \, dA \tag{2}$$

The last term is an additional surface tension due to electric potential induced over the membrane surface. Electric surface tension defined as [18]:

$$\sigma_e = \frac{1}{2} C_{LW} \bar{U}^2 \tag{3}$$

Here $\bar{U}$ is the spatially averaged transmembrane voltage,

$$\bar{U} = \frac{U_m A_m + U_p A_p}{A_m + A_p} \approx U_m \frac{A_m}{A} \tag{4}$$

where the membrane voltage U_m is the voltage across lipids and $U_p \approx 0$ is the voltage across conductive pores. The area consists of lipid molecules is A_m and the area filled with pores is A_p where the total area of the lipid membrane is $A = A_m + A_p$. The membrane voltage U_m can be obtained from:

$$U_m = U_0 \ (1 - \exp(-t/\tau_m)) \tag{5}$$

the time scale τ_m is defined as follow:

$$\tau_m = C_m L \frac{(\lambda^- + \lambda^+)}{(\lambda^+ \lambda^-)} \tag{6}$$

where $\lambda^{\pm}$ is the interior and exterior electrolyte (i.e. water) conductivity. This solution is the result of solving the electric field system of equation and the leaky dielectric assumption applied on the lipid membrane. Details are given in Appendix A.

The change of the pore's specific capacitance as water displaces lipid to form a pore is simply

$$C_{LW} = \left(\frac{\epsilon_w}{\epsilon_m} - 1 \right) C_m \tag{7}$$

Here $\epsilon_w = K_w \epsilon_0$ is the permittivity of water and $\epsilon_m = K_m \epsilon_0$ is the permittivity of lipid membrane, and C_m is the constant capacitance per area of a pore free membrane, i.e $C_m = \epsilon_m / h$ where h is the thickness of the membrane. Typically $K_w = 80$ and $K_m = 2$, so when the potential $\bar{U}$ increases ΔW decreases which means pore nucleation is more desirable.

3 Diffuse Interface Model

We are adopting the first order phase transition model. This model implies that broken membrane states (pore phase) have lower free energy than intact membrane states (lipid phase). This concept first introduced on the study of stability of soap films [6, 5]. This approach assumes at the presence of electric field the membrane breakdown occurs because it is energetically more desirable i.e. transitioning to more stable phase.

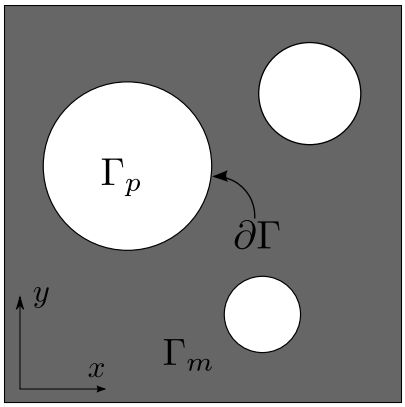

Figure 2: Schematic of the whole domain $\Gamma = \Gamma_m \cup \partial\Gamma \cup \Gamma_p$. Γ_m indicates lipid membrane phase, Γ_p is the pore phase, and $\partial\Gamma$ is the interface

The phase-field function ϕ is defined for two states $\phi = 1$ for lipid membrane (grey regions in Figure 2) and $\phi = 0$ for pores (voids in Figure 2), and the phase interfaces are replaced by thin layer across which ϕ changes its value between 0 to 1. The line tension energy in Equation 2 can be replaced with Ginzburg-Landau energy form [9, 7]. Therefore,

$$\Delta W_p\left[\phi\right] = \int_\Gamma \bar{\gamma}\,\left(\frac{\varepsilon}{2}|\nabla\phi|^2 + \frac{1}{\varepsilon}\,g\left(\phi\right)\right) - \int_\Gamma \sigma\left(1 - H(\phi)\right)c_0 \tag{8}$$

where $g(\phi) = \frac{1}{4}\phi^2(1-\phi)^2$ is a double-well potential function and ε a small length scale. The coefficient $\bar{\gamma}$ is related to the line tension coefficient γ by

$$\bar{\gamma} = \frac{3}{4}\,\gamma \tag{9}$$

The function $H(\phi)$ is the Heaviside or the step function. The smooth Heaviside function $H(\phi) \approx \frac{1}{2} + \frac{1}{2}\,\tanh\left(k\left(\phi - \frac{1}{2}\right)\right)$ were chosen in order to utilize the better separation behaviour of two phases where larger k corresponds to a sharper transition at $\phi = 1/2$. The coefficient c_0 is the area correction coefficient in order to keep the area constant

$$c_0 = \frac{\int_\Gamma (1-\phi)}{\int_\Gamma \left(1 - H(\phi)\right)} \tag{10}$$

The Allen-Cahn type dynamic formulation can be obtained from the energy functional in Equation 8:

$$\begin{aligned}\frac{\partial\phi}{\partial t} &= -M\,\frac{\delta\Delta W_p}{\delta\phi} + \eta(\mathbf{x},t)\\ &= -M\left(-\bar{\gamma}\,\varepsilon\,\nabla^2\phi + \frac{\bar{\gamma}}{\varepsilon}\,g'(\phi) + \sigma\,\delta(\phi)\,c_0\right) + \eta(\mathbf{x},t)\end{aligned} \tag{11}$$

where $g'(\phi) = \frac{1}{2}\left(\phi - 3\phi^2 + 2\phi^3\right)$ and also the Dirac's delta function $\delta(\phi) = dH(\phi)/d\phi$ is the derivative of Heaviside function. M is related to the time scale for atomic rearrangement from the disordered phase to ordered one called the mobility coefficient where can be related to the diffusion coefficient D and temperature T by the Einstein relation $D = M\,k_BT$, and the coefficient k_B is called is the Boltzman's constant, and $\eta(\mathbf{x},t)$ is the stochastic noise due to thermal fluctiuations and satisfies the relation $\langle\eta(\mathbf{x},t)\eta(\mathbf{x}',t)\rangle = 2M\,k_BT\,\delta(\mathbf{x}-\mathbf{x}')\,\delta(t-t')$.

4 Numerical Results

We are applying the finite-difference scheme. The non-dimensionalized Equation 11 can be obtained in the following:

$$\frac{\partial \phi}{\partial \tilde{t}} = \tilde{\gamma}\,\tilde{\varepsilon}\bar{\nabla}^2\phi - \frac{\tilde{\gamma}}{\tilde{\varepsilon}}\,g'(\phi) - \tilde{\sigma}\,\delta(\phi)\,c_0 + \tilde{\eta}(\tilde{\mathbf{x}},\tilde{t}) \tag{12}$$

A Solution to Electric Field

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