Phase-Field Modeling of Lipid Membrane With Pores Under Applied Electrical Field

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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 and Helfrich free energy is used to study the bending energy contribution of pore dynamics. 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 [16, 17, 5] 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 [11, 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 [8, 9], fracture dynamics,[10] multi-phase flow [14, 2], vesicle dynamics [7, 12], etc.

2 Electroporation 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]. 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.

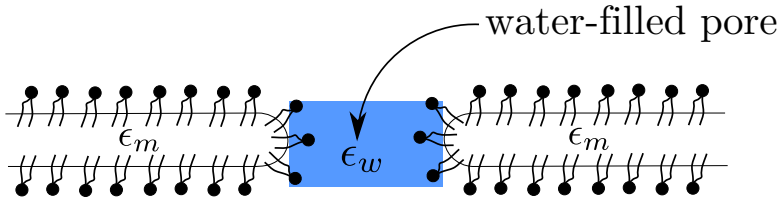

Figure 1: Schematic of one water-filled pore in a lipid membrane

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). It is been discussed that the voltage over a small pore is very close to the applied voltage $U_p \approx U = U_m$ due to the fact that the permittivity of pore is close to water (there is only %10 difference) and the resistivity of a pore is large compared to spreading resistance [16].

In the presence of a transmembrane electric field, the free energy of pore formation should be:

$$\Delta W_p = \oint \gamma \, ds - \int \sigma \, dA - \int \frac{1}{2} \, C_{LW} \, \bar{U}^2 \, dA \tag{1}$$

Where γ is the energy per length along the pore edges, we call it line tension. The surface tension σ is the energy per area of the membrane of a flat pore-free membrane. The last term is an additional surface tension due to electric potential induced over the membrane surface. Here $\bar{U}$ is the spatially averaged transmembrane voltage,

$$\bar{U} = \frac{U_m \, A_m + U_p \, A_p}{A_m + A_p} \approx U \tag{2}$$

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

$$C_{LW} = \left(\frac{\epsilon_w}{\epsilon_m} - 1 \right) C_m \tag{3}$$

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 $K_w = 2$ and $K_m = 80$, so when the potential U increases ΔW decreases which means pore nucleation is more desirable.

3 Theoretical Background

3.1 Sharp Interface Model

Here we start with the free energy functional of an open lipid membrane with free exposed edges: [15, 4]

$$E = \int_\Gamma \frac{1}{2}\,\kappa\,(H - C_0)^2 + \int_\Gamma \bar{\kappa}\,K + \int_\Gamma \sigma + \oint_{\partial\Gamma} \gamma \tag{4}$$

where H is the mean curvature, C_0 is called the spontaneous curvature, κ is the bending rigidity, $\bar{\kappa}$ is the Gaussian bending rigidity, σ is the surface tension and γ is the line tension.

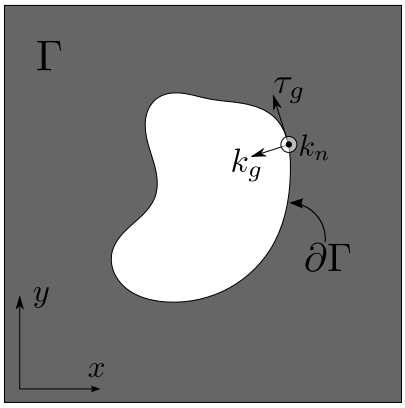

Figure 2: Schematic of flat open membrane with relevant curvatures

The first two integrals accounts for the curvature energy of the lipid membrane. The third integral accounts for the surface energy and the last one accounts for line energy due to exposed edges of the open lipid membrane. The shape equation then derived by taking the first variational derivative of Equation (4) [15],

$$\delta F = -2\,\sigma\,H + \kappa\,(2\,H + C_0)\,\Big(2\,h^2 - C_0\,H - 2\,K\Big) + \kappa\,\nabla_\Gamma^2\,(2\,H) = 0 \tag{5}$$

and on the boundaries ($\partial\Gamma$):

$$\bar{\kappa}\,(2\,H + C_0) + \bar{\kappa}\,k_n = 0, \tag{6}$$

$$-\,\kappa\,\mathbf{e_2}\cdot\nabla\,(2\,H) + \gamma\,k_n + \bar{\kappa}\,\frac{d\tau_g}{dS} = 0, \tag{7}$$

$$\frac{\kappa}{2}\,(2\,H + C_0)^2 + \bar{\kappa}\,K + \sigma + \gamma\,k_g = 0, \tag{8}$$

where k_n, k_g and τ_g are the normal curvature, geodesic curvature and torsion curvature, respectively. In the case of a flat lipid membrane such as the one shown in Figure (2) the curvature components in z direction are all zero. The normal curvature k_n and the mean curvature H and Gaussian curvature K vanish. Also the torsion curvature τ for planar surface vanishes too. The equations will decrease to:

$$\sigma + \gamma\,k_g = 0 \tag{9}$$

The hydrodynamic effect over the lipid membrane sheet is neglected here. [13] investigated the instability of lipid membrane in their one-dimensional model and the role of electro-hydrodynamic that modulates the lipid density and shape fluctuations were taken into account.Here the main assumption is that the flat lipid bilayer sheet remains flat and there is no change in the shape in normal direction. This means both mean curvature H and and normal curvature k_n vanish. And also the role of spontaneous curvature C_0 that determines the shape of lipid membrane is neglected.

3.2 Diffuse Interface Model

We start with the energy functional of the system. Introducing the phase-field function ϕ to distinguish two phases. The state $\phi = 1$ for lipid bilayer molecules and $\phi = 0$ for pore phase. The phase interfaces are replaced by thin layer across which ϕ changes its value. To achieve this we replace the energy functional in Equ. 4 with,

$$E[\phi] = \int_\Gamma \bar{\kappa}(\phi)\ K + \int_\Gamma \sigma(\phi) + \int_\Gamma \gamma \left(\frac{\epsilon}{2} |\nabla \phi|^2 + \frac{1}{\epsilon} g(\phi) \right) \tag{10}$$

The idea of replacing the line tension energy with Ginzburg-Landau energy form has been around for some time and has been used by [12].

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