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 [15, 16, 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 [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 [7, 8], fracture dynamics,[10] multi-phase flow [14, 2], vesicle dynamics [6**?**], 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 [13, 9]. 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:

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

Surface tension σ 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_{elec} over the membrane in addition to the membrane tension σ that already exists on the membrane.

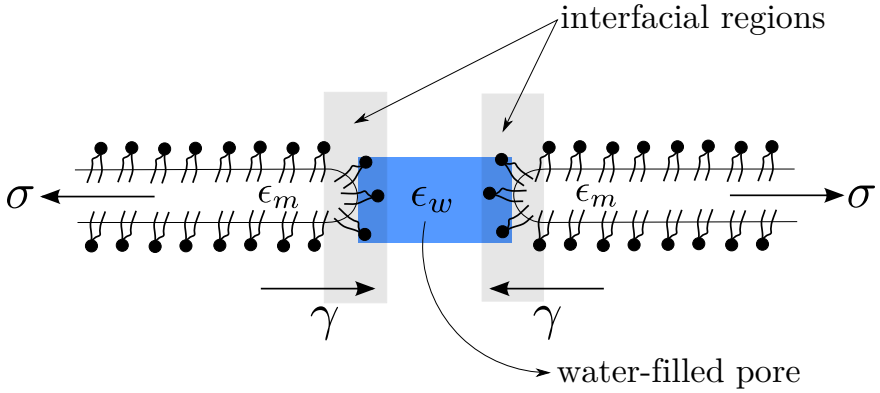

Figure 1: Schematic of one water-filled pore in a lipid membrane

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 [15].

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

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

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,

$$\bar{U} = \frac{U_m \, A_m + U_p \, A_p}{A_m + A_p} \approx U \tag{3}$$

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

$$C_{LW} = \left(\frac{\epsilon_w}{\epsilon_m} - 1 \right) C_m \tag{4}$$

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 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 [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.

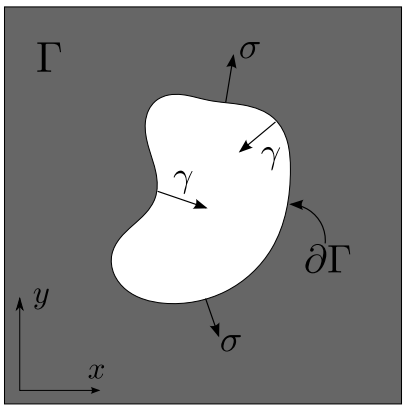

Figure 2: Schematic of flat open membrane with relevant curvatures

The phase-field function ϕ is defined for two states $\phi = 1$ for lipid membrane (lipid molecules) and $\phi = 0$ for pore (void in Figure 2 phase, and the phase interfaces are replaced by thin layer across which ϕ changes its value. To achieve this we replace the energy functional in Equation **??** with,

$$E\left[\phi\right] = \int_\Gamma \sigma\left(\phi\right) + \int_\Gamma \gamma \, \left(\frac{\epsilon}{2} |\nabla \phi|^2 + \frac{1}{\epsilon} \, g\left(\phi\right) \right) \tag{5}$$

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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