A Dynamic Model of Fusion Pores in Lipid Bilayers

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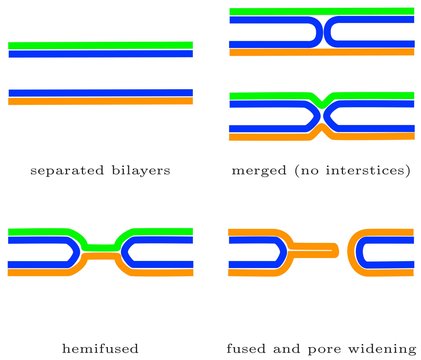
Overview

Long Term Goal To simulate viral fusion. Viral fusion involves physical forces. If the force interactions can be discovered, then mechanistic function can be altered. The stages leading to fusion: merging, hemifusion, pore formation, and pore widening are simulated by a field theory.



Modeling Challenges

⋆ Unlike atomistic or MD simulation, time courses for variational methods are seconds long and deformations are comparable to fusion geometry.

⋆ Presents changes in topology, e.g. from in the stage from hemifusion to fusion, and complex arrangements of bilayer.

⋆ Has 3D geometry and multiscale interactions, e.g. edge tension and fluid momentum.

⋆ Pore formation, a process fundamental to fusion, involves a local dislocation in the bilayer structure.

References

[1] Brochard-Wyart, de Gennes, and Sandre, Transient pores in stretched vesicles: role of leakout. *Physica* A 278 (2000).

[2] Cohen and Melikyan, *The Energetics of Membrane Fusion from Binding, through Hemifusion, Pore Formation, and Pore Enlargement.* J. Membrane Biology. 199, 1, (2004).

[3] Kozlovsky and Kozlov, *Stalk Model of Membrane Fusion: Solution of Energy Crisis.* Biophysical Journal, 82 (2002).

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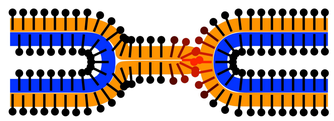
Variational Hamiltonian

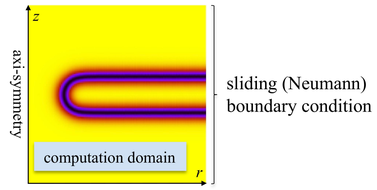
The Hamiltonian encodes

Helfrich (bending) + Water-bilayer interface & Lipid alignment (dislocations, e.g tilt and pores)

$$E[\phi,\mathbf{d},\rho] = \int \underbrace{\left[B|\text{div }\mathbf{d}|^2 + \frac{(|\mathbf{d}|^2-1)^2}{4\epsilon_1}\right]\left[\frac{(\phi^2-1)^2}{4\epsilon}+\epsilon_0\right]}_{\text{bending}}$$
$$+ \underbrace{W\left(\frac{\epsilon|\nabla\phi|^2}{2}+\frac{(\phi^2-1)^2}{4\epsilon}\right)}_{\text{phase field}} + \underbrace{\frac{k|\nabla\rho|^2}{2}+\frac{K_t\epsilon\rho^2}{2}\left|\nabla\phi-|\nabla\phi|\mathbf{d}\right|^2}_{\text{lipid alignment}}\,dx$$

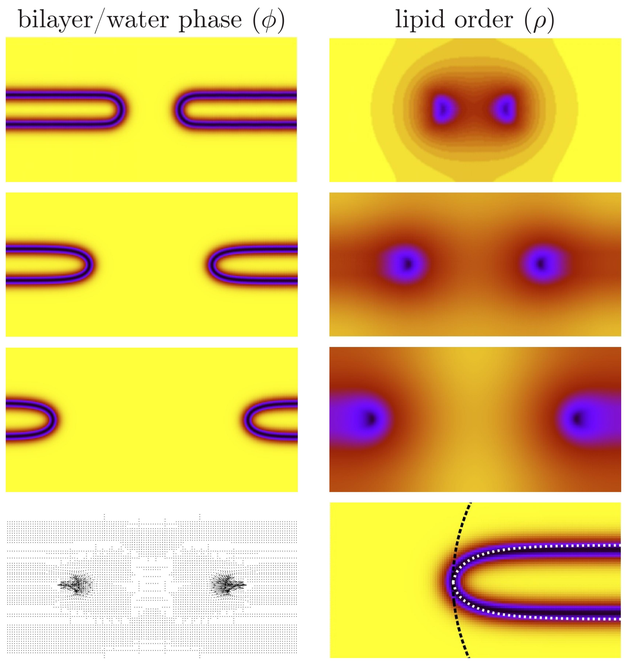


Example: In the transition from hemi-fusion to fusion, the lipid alignment deviates (red) from the normal of the lipid phase. This apparent dislocation is mediated by the field parameter ρ.



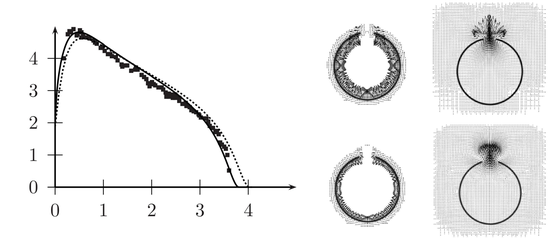
Field variables are defined on a uniform rectangular grid. A toroidal geometry is initially assumed–the shape of the bilayer, defined by the macroscopic phase field ϕ, changes according to energy minimization and fluid transport.

Simulation for Pore Enlargement



Left: Force is concentrated near pore rim. Right: A traveling self similar solution to mean curvature motion (white) plotted over pore rim. The catenoid (black), with this aspect ratio, is typically much smaller in radius.

Comparisons of Field Theory



Radius of a lipidic pore as a function of time as calculated by classical continuum mechanical and variational methods.

Classical Mechanics	Field Theory
⋆ geometry and shape are assumed at length scales where energy dependence is highly sensitive	⋆ bilayer is a macroscopic phase vs. a planar surface
	⋆ no shape assumptions
⋆ neglects some (possibly dominant) friction	⋆ model based on physical principles of energy dissipation
⋆ accurate and quick evaluation of physical quantities	⋆ large problem size and lengthy calculation

Yet both classical and field theories yield results which are quantitatively the same.

Energetic Variational Approach

Motion is defined by first expressing kinematic relationship for field variables and then establishing the force from variational derivatives.

$$\begin{array}{ccc} E[\phi,\mathbf{d},\rho] & \xrightarrow{\text{discretization}} & E_h[\phi_h,\mathbf{d}_h,\rho_h] \\ \delta\downarrow & & \downarrow\nabla \\ \mathbf{F} & \xrightarrow{\text{discretization}} & \mathbf{F}_h \end{array}$$

Modeling Advantages of Variational Method

⋆ Avoids high order meshing schemes to calculate force and bilayer position

⋆ Automatically satisfies energy dissipation principle

⋆ Force calculated on the fly; avoids complicated algebra and calculates interactions correctly

⋆ Large time steps may be assumed