LAMBDA :

The in-plane viscosity of lipid membrane is at least one hundred times that of water. Dissipation of energy, at length scales comparable to the bilayer, is thus critically dependent on membrane position and velocity. An effective and practical way to model spatially varying friction is to define a dissipation function accounting for the various components of the strain tensor [ref]. For the bilayer in water, we will use the dissipation function

$$\Delta = \int_D \sum_{i,j=1}^{2} \mu_{ij}(x)(R(x)D[u]R^T(x))_{ij}^2 \, dx.$$

Here $R(x)$ is the rotation matrix for the coordinate frame parallel to the neutral surface, $D[\mathbf{u}] = \frac{1}{2}(\nabla \mathbf{u} + \nabla \mathbf{u}^T)$ is the strain tensor, and $\mu_{ij}(x)$ is the component dependent viscosity. To illustrate, the values $\mu_{11} = \mu_{21}$ account for in-plane shearing, while μ_{12} accounts for inter-monolayer shearing. In practice, the rotation matrix is established along the neutral surface and the value is extended to the proximal velocity grid points. In the aqueous region, the viscosity and rotation matrix are set to the viscosity of water and the identity matrix resp. Moreover, to march forward in time, the membrane position and velocity are fixed points of the functional iteration–the dissipation coefficients are known prior to determining the velocity as a low Reynolds number solution to the Navier-Stokes equations.

We may derive a system of evolution PDE from the dissipation function Δ using the maximum dissipation principle (MDP). The principle states that the sum of the conservative forces (fluid acceleration $\rho(\mathbf{u}_t + \mathbf{u} \cdot \nabla \mathbf{u})$, pressure gradients ∇p, and membrane forces $\mathbf{f}$) are balanced by the dissipative force $\frac{1}{2}\frac{\delta \Delta}{\delta \mathbf{u}}$, the Euler-Lagrange derivative of the dissipation function with respect to velocity. This form of the momentum balance equation, which reduces to the Navier-Stokes equations isotropic, is then coupled to the incompressibility condition and the condition that bilayer lipids move with velocity $\mathbf{u}$. To see that that the assumptions on our dissipation agree with continuum mechanical principles, we note that the frictional stress derived from the MDP is symmetric and depends linearly on the strain.

A determination of pore expansion will lead to outcomes that are important in and of themselves. For the first time, realistic energetic values of a fusion pore will be known. Second, we will obtain characteristic asymptotic bilayer shapes which biophysicists may then incorporate into their own calculations of pore growth. This will be a significant advance over pore geometries assumed in the past and still used today [Jackson]. But the primary outcomes of this study will be to determine the controls of fusion pore growth, determine the energy dissipation, and provide a way to predict the time course of pore expansion, over the range that the identified parameter controls expansion.

The subject of Aim 4 is not merely of physical relevance but has interesting, purely theoretical applications. The mathematical analysis of the bilayer model gives rise several new problems in the calculus of variations. For example, one must establish the existence and regularity of a surface and director field which minimize the sum of the splay and tilt energies. The problem can be extended from one to two monolayers coupled by the incompressibility condition. Next, one may ask whether the addition of tilt decreases energy when bending is generalized to splay and how does this effect depend on the respective moduli. The study

of these nonlinear and domain dependent problems will require the development of new mathematical tools, beyond combing our knowledge of liquid crystals and harmonic maps [ref] with that of the bending and Willmore energy minimizers [ref].

COMPARING MODELS

Final Remark. There are possibly many ways to address the problem of fusion pore growth. Aside from being able to directly evaluate the consequences of the anisotropic dissipation and constitutive relationships of bilayers on its motion, we have presented in this proposal two additional membrane representations (ODI and TFE) and one would like to know whether these representations model the phenomena accurately. Other than the assumption of axial symmetry, the representations in Aim 4 and Aim 3 are identical. Therefore, to show the correspondence between the representations, we will reproduce the results of Aim 4 using the ODI model. To include fluid motion (which is believed to be less important in Aims 1 and 2 than in Aim 4), we will include a biphasic viscosity using the lipid labeling function and apply the appropriate kinematic transport conditions for the phase and director fields [ref].

EQUATION FROM CMS PAPER TO GO INTO BROADER IMPACTS SECTION

...given as $E = K_B B + \gamma L + K_S \frac{(A-A_\mathrm{r})^2}{2A_\mathrm{r}} + \sigma A$ where

$$A = \frac{3}{2\sqrt{2}} \int_D \alpha(\bar{\phi}) \left[\frac{\epsilon}{2} |\nabla \phi|^2 + \frac{1}{\epsilon} F(\phi) \right] \, dx, \quad B = \frac{3}{4\sqrt{2}} \int_D \alpha(\bar{\phi}) \epsilon \left[\Delta \phi - \frac{1}{\epsilon^2} F'(\phi) \right]^2 \, dx,$$
$$L = \frac{9}{8} \int_D \left(\frac{\epsilon}{2} |\nabla \phi|^2 + \frac{1}{\epsilon} F(\phi) \right) \left(\frac{\epsilon}{2} |\nabla \bar{\phi}|^2 + \frac{1}{\epsilon} F(\bar{\phi}) \right) \, dx$$

approximate the membrane area, bending energy, and pore circumference respectively and where $\alpha(p) = \frac{1}{2}(\tanh(\xi p) + 1), \bar{\alpha}(p) = \mathrm{sech}^2(\xi p), \xi > 0$ are cut-off functions labeling the position of the pore.