Fluctuating Lipid Bilayer Membranes with Diffusing Protein Inclusions : Hybrid Continuum-Particle Model

J. K. Sigurdsson*, F. L. H. Brown‡, P. J. Atzberger*†

*Department of Mathematics, †Department of Mechanical Engineering,
‡Department of Chemistry and Biochemistry and Department of Physics, UC Santa Barbara

ABSTRACT

We use computational approaches, consistent with statistical mechanics and accounting for bi-directional membrane-protein coupling, to study the effective stiffness of a membrane with embedded proteins. As the number of proteins increases, protein inclusions increase the effective elastic stiffness of the bilayer membrane. We demonstrate how Phase Factor Averaging can be used to increase the numerical accuracy in a computationally efficient way.

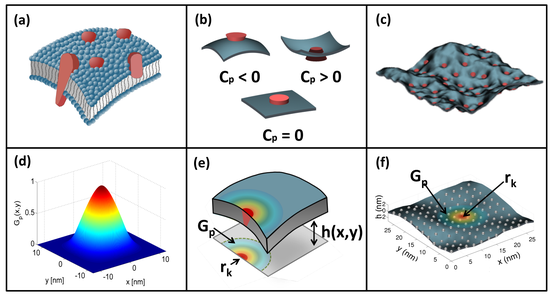


FIGURE 1. Describes how the proteins are locally coupled to the membrane

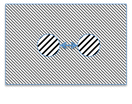
MODEL

- Hamiltonian
  - $\mathcal{H}[h,\mathbf{r}] = \mathcal{H}_0[h] + \sum_{k=1}^{N} \mathcal{H}_{\rm int}[h,\mathbf{r}_k] + \mathcal{H}_{\rm pp}[\mathbf{r}]$
- Helfrich Free Energy
  - $\mathcal{H}_0[h] = \frac{1}{2}\int_{\mathcal{A}_\perp} K_m\left(\mathcal{C}_m - 2\mathcal{C}_0\right)^2 + 2K'_m\mathcal{G}_m d\mathbf{x}$
  - $\mathcal{C}_m = \nabla^2 h = \partial_{xx}h + \partial_{yy}h$ is local mean curvature
  - $\mathcal{G}_m = \partial_{xx}h\partial_{yy}h - \partial_{xy}h\partial_{yx}h$ is Gaussian curvature

Homogenous

- Local Modification
  - $\mathcal{H}_{\rm int}[h,\mathbf{r}] = \frac{1}{2}\int_{\mathcal{A}_\perp} G_p(\mathbf{x}-\mathbf{r})\left(K_p(\mathcal{C}_m - 2\mathcal{C}_p)^2 - K_m(\mathcal{C}_m - 2\mathcal{C}_0)^2 + 2K'_p\mathcal{G} - 2K'_m\mathcal{G}_m\right)d\mathbf{x}$

- Steric Energy
  - $\mathcal{H}_{pp}[\mathbf{r}] \sim \sum \frac{1}{|\mathbf{r}_i - \mathbf{r}_j|^5}$



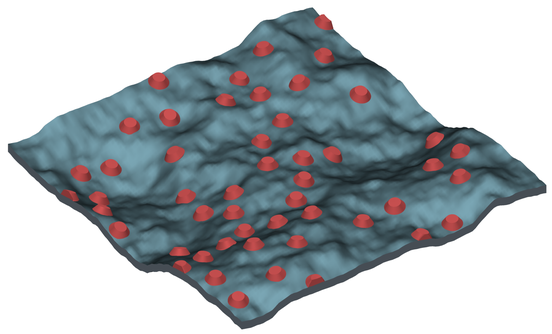


FIGURE 2. Proteins embedded in a lipid bilayer membrane.

DYNAMICS

- Membrane Dynamics
  - $\dot{h}(\mathbf{x},t) = \int \Lambda(\mathbf{y}-\mathbf{x})\mathbf{F}(\mathbf{y},t)d\mathbf{y} + \sqrt{2k_BT\Lambda}\xi(\mathbf{x},t)$
- Protein Dynamics
  - $\mathbf{r}_k(t) = \frac{D_0}{k_BT}\mathbf{f}_k + \sqrt{2D_0}\boldsymbol{\eta}_k(t)$
- Forces
  - $\mathbf{F} = -\delta\mathcal{H}/\delta h$ is the force acting on the membrane
  - $\mathbf{f}_k = -\nabla_{\mathbf{r}_k}\mathcal{H}$ is the force acting on protein k

EFFECTIVE STIFFNESS

For the homogenous membrane we have the following relationship between the fluctuations of the membrane in Fourier space and membrane bending modulus

$$\frac{1}{K_m} = \frac{\sigma_q^2 q^4}{k_BTL^2}, \qquad \sigma_q^2 =< |h_q|^2 > . \qquad (1)$$

We use this expression to fit the fluctuations of the heterogeneous membrane, which gives us an estimate for the effective bending stiffness of the membrane with flat protein inclusions. See Fig. 3.

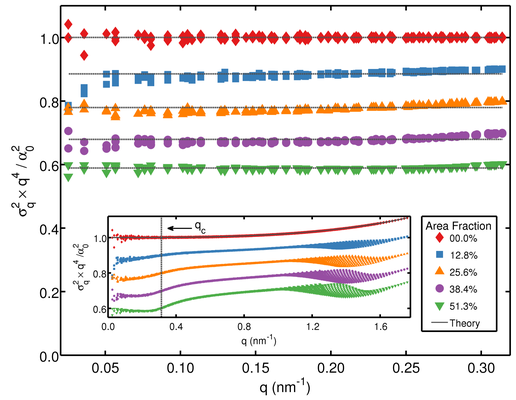


FIGURE 3. Membrane fluctuations for different area fraction of flat proteins in membrane including a fitting of Eq. (1). The inset shows the full spectrum of the fluctuations.

The following description is derived in [2]

$$\frac{1}{K_*} = \frac{1-\psi}{K_m} + \frac{\psi}{K_p} \qquad (2)$$

- ψ is the area fraction of proteins in membrane
- K_* is the effective stiffness of the membrane

We compare this result to our simulated results in Fig. 4.

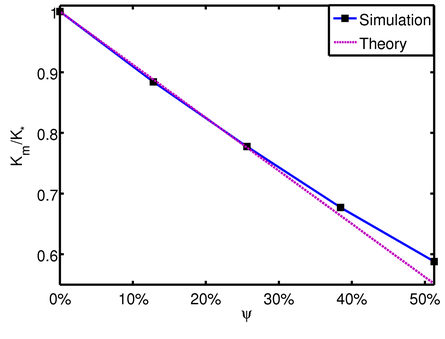


FIGURE 4. Effective bending stiffness of membrane, simulation results compared to the analytic description Eq. (2) derived in [2].

Parameter	Box dimension	Number of proteins	Protein area	Temperature	Bare protein diffusion coefficient	Bilayer bending modulus	Protein bending modulus	Saddle-splay moduli	Protein spontaneous curvature	Solvent viscosity
Symbol	L	N	A_p	T	D_0	K_m	K_p	$K'_{m(p)}$	C_p	η
Value	247.5 nm	0-100	100 nm^2	300 K	0.025 $\frac{nm^2}{ns}$	$5k_BT$	$40k_BT$	$-K_{m(p)}$	0 nm^{-1}	10^{-3}Pa · s

TABLE 1. Model Parameters

PHASE FACTOR AVERAGING

Special care is taken to reduce the numerical error that causes proteins to energetically favor lattice locations.

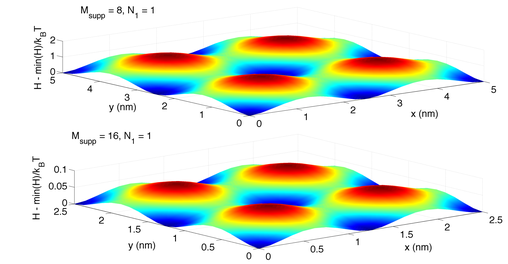


FIGURE 5. Energy landscape for minimum configuration as protein location is varied with respect to lattice locations, $C_p = 0.15nm^{-1}$.

Fig. 5 shows that this error is greatly reduced by making our spatial mesh finer. But making the spatial mesh finer by a factor of N_1 will result in N_1^3 reduction in the time step in addition to the N_1^2 additional computational cost of each step. The additional cost due to the time step reduction can be avoided by introducing a Phase Factor Averaging method. Namely,

$$[\widehat{\mathcal{F}}u]_{\mathbf{k}} = \frac{1}{N_s}\sum_{j=1}^{N_s} e^{i(\mathbf{q}\cdot\mathbf{s}_j)}[\widetilde{\mathcal{F}}(\mathcal{T}_{\mathbf{s}}u)]_{\mathbf{k}}, \qquad \mathcal{T}_{\mathbf{s}}u(\mathbf{x}) = u(\mathbf{x}-\mathbf{s}).$$

Fig. 6 shows the effect that this change in error has on the effective diffusivity of a curved protein in the membrane.

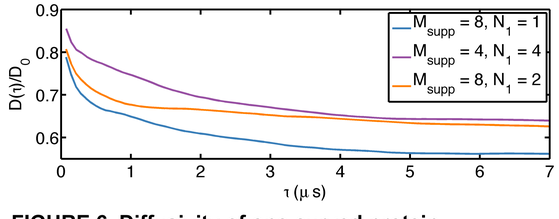


FIGURE 6. Diffusivity of one curved protein, $C_p = 0.15nm^{-1}$.

REFERENCES

[1] A. Naji, P.J. Atzberger, F.L.H. Brown, "Hybrid Elastic and Discrete-Particle Approach to Biomembrane Dynamics with Application to the Mobility of Curved Integral Membrane Proteins", *Phys. Rev. Lett.*, **102**: 138102, 2009.

[2] R.R. Nets, P. Pincus, "Inhomogeneous fluid membranes: Segregation, ordering, and effective rigidity", *Phys. Rev. E*, **52**:4114-4128 1995.