
CURVATURE-DRIVEN FEEDBACK ON AGGREGATION-DIFFUSION OF PROTEINS IN LIPID BILAYERS

A PREPRINT

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August 19, 2021

Electronic Supplementary Information

A Model development

A.1 Stress tensor on a surface

The stress tensor Σ represents the state of stress at any location of the membrane and includes both the in-plane normal and shear stresses as well as out-of-plane shear stress due to bending. Each column of the stress tensor Σ constitutes the traction vector on the curve drawn on the membrane, known as the stress vector, and is represented as

$$\Sigma^\alpha = N^{\alpha\beta} \mathbf{a}_\beta + S^\alpha \mathbf{n}, \quad (\text{S1})$$

where N is the surface stress tensor, S represents the shearing force due to bending, and \mathbf{a}_β (for $\beta = 1, 2$) represents the surface tangent vector normal to the curve. The local equilibrium of forces, in the tangential and normal directions, is given by [1]

$$\nabla \cdot \mathbf{N} - \mathbf{S} \cdot \mathbf{b} = 0, \quad (\text{S2})$$

$$\nabla \cdot \mathbf{S} + \mathbf{N} : \mathbf{b} + p = 0, \quad (\text{S3})$$

with

$$\mathbf{N} = \zeta + \boldsymbol{\pi} + \mathbf{b} \cdot \mathbf{M} \quad \text{and} \quad \mathbf{S} = -\nabla \cdot \mathbf{M}. \quad (\text{S4})$$

Here, ζ and \mathbf{M} are the elastic stress and moment tensors, \mathbf{b} is the curvature tensor, and $\boldsymbol{\pi}$ is the viscous stress tensor. The elastic stress and moment tensors can be obtained from the energy density for an incompressible membrane as [1, 2]

$$\begin{aligned} \zeta &= -2\kappa(H - \ell\sigma)\mathbf{b} - 2\bar{\kappa}K\mathbf{a} - \xi\mathbf{a}, \\ \mathbf{M} &= \kappa(H - \ell\sigma)\mathbf{a} + \bar{\kappa}(2H\mathbf{a} - \mathbf{b}), \end{aligned} \quad (\text{S5})$$

where ξ is the Lagrange multiplier that imposes the incompressibility constraint and \mathbf{a} is the metric tensor of the surface. The surface tension λ is related to ξ with the following expression [1]

$$\lambda = -(\xi + W). \quad (\text{S6})$$

The viscous stresses obey the constitutive relation [3]

$$\boldsymbol{\pi} = 2\nu[\mathbf{d} - w\mathbf{b}]. \quad (\text{S7})$$

Here,

$$\mathbf{d} = (\nabla\mathbf{v} + \nabla\mathbf{v}^T)/2, \quad (\text{S8})$$

is the rate-of-strain tensor expressed in terms of the velocity field \mathbf{v} (see [2–4] for details). w is the normal velocity of the surface, given by

$$w = \mathbf{n} \cdot \mathbf{r}_t, \quad (\text{S9})$$

where \mathbf{r} is the position vector of a material point on the surface.

A.2 Dimensionless governing equations

Here we summarize the governing equations for the coupled dynamics of the system in the dimensionless form. The tangential force balance equation becomes

$$\begin{aligned} \nabla \tilde{\lambda} - 4\tilde{w}\nabla \tilde{H} + 2(\nabla \cdot \tilde{\mathbf{d}} - \nabla \tilde{w} \cdot \tilde{\mathbf{b}}) \\ = -\nabla \phi \left[\frac{2\hat{B}\hat{S}}{\hat{T}} \log \frac{\phi}{1-\phi} - \frac{4\hat{L}\hat{S}}{\hat{T}} (\tilde{H} - \hat{L}\hat{S}\phi) - \frac{\hat{A}\hat{B}\hat{S}}{\hat{T}} (2\phi - 1) - \frac{\hat{A}\hat{B}}{\hat{T}} \Delta \phi \right], \end{aligned} \quad (\text{S10})$$

along with the surface incompressibility relation,

$$\nabla \cdot \tilde{\mathbf{v}} = 2\tilde{w}\tilde{H}. \quad (\text{S11})$$

The normal force balance relation takes the following form

$$\begin{aligned} \Delta(\tilde{H} - \hat{L}\hat{S}\phi) + 2(\tilde{H} - \ell L\sigma_s\phi)(2\tilde{H}^2 - \tilde{K}) - 2\hat{B}\hat{S}\tilde{H} \left[\phi \log \phi + (1-\phi) \log(1-\phi) \right] + \frac{\hat{A}}{2}\phi(1-\phi) \\ + \frac{\hat{A}}{4\hat{S}}|\nabla \phi|^2 \Big] - 2\tilde{H} \left[(\tilde{H} - \ell\sigma_s L\phi)^2 + \frac{\tilde{\kappa}}{\kappa}\tilde{K} \right] - \hat{T}[\tilde{\mathbf{b}} : \tilde{\mathbf{d}} - w(4\tilde{H}^2 - 2\tilde{K})] = \tilde{p} + \hat{T}\tilde{\lambda}\tilde{H}. \end{aligned} \quad (\text{S12})$$

The mass conservation of proteins is given by

$$\begin{aligned} \phi_t + Pe \nabla \cdot (\tilde{\mathbf{v}}\phi) = \Delta \phi \left[\frac{1}{1-\phi} + \frac{2\hat{L}^2\hat{S}}{\hat{B}}\phi - \hat{A}\phi \right] - \phi \left[\frac{2\hat{L}}{\hat{B}}\Delta H + \frac{\hat{A}}{2\hat{S}}\Delta^2\phi \right] \\ + \nabla \phi \cdot \left[\nabla \phi \left(\frac{1}{(1-\phi)^2} + \frac{2\hat{L}^2\hat{S}}{\hat{B}} - \hat{A} \right) - \frac{2\hat{L}}{\hat{B}}\nabla \tilde{H} - \frac{\hat{A}}{2\hat{S}}\nabla(\Delta\phi) \right]. \end{aligned} \quad (\text{S13})$$

A.3 Governing equations in the linear Monge regime

The continuity condition and tangential force balance simplify as

$$\nabla \cdot \mathbf{v} = 2wH, \quad (\text{S14})$$

and,

$$\begin{aligned} \nabla \lambda + \nabla^2 \mathbf{v} + \nabla(\nabla \cdot \mathbf{v}) - 4w\nabla H - 2\nabla w : \nabla \nabla z = \\ -\nabla \phi \left[\frac{2\hat{B}\hat{S}}{\hat{T}} \log \frac{\phi}{1-\phi} - \frac{4\hat{L}\hat{S}}{\hat{T}} (H - \hat{L}\hat{S}\phi) - \frac{\hat{A}\hat{B}\hat{S}}{\hat{T}} (2\phi - 1) - \frac{\hat{A}\hat{B}}{\hat{T}} \nabla^2 \phi \right]. \end{aligned} \quad (\text{S15})$$

The normal force balance Equation (S12) reduces to

$$\begin{aligned} \nabla^4 z - 2\hat{L}\hat{S}\nabla^2 \phi - 2\hat{B}\hat{S}\nabla^2 z \left[\phi \log \phi + (1-\phi) \log(1-\phi) \right] + \frac{\hat{A}}{2}\phi(1-\phi) + \frac{\hat{A}}{4\hat{S}}|\nabla \phi|^2 + \frac{\hat{L}^2\hat{S}}{\hat{B}}\phi^2 \Big] \\ - \hat{T}(\nabla \mathbf{v} + \nabla \mathbf{v}^T) : \nabla \nabla z = p + \hat{T}\lambda\nabla^2 z. \end{aligned} \quad (\text{S16})$$

Finally, the transport equation for the protein density field Equation (S13) takes on the following form:

$$\begin{aligned} \phi_t + Pe \nabla \cdot (\mathbf{v}\phi) = \nabla^2 \phi \left[\frac{1}{1-\phi} + \frac{2\hat{L}^2\hat{S}}{\hat{B}}\phi - \hat{A}\phi \right] - \phi \left[\frac{2\hat{L}}{\hat{B}}\nabla^2 H + \frac{\hat{A}}{2\hat{S}}\nabla^4 \phi \right] \\ + \nabla \phi \cdot \left[\nabla \phi \left(\frac{1}{(1-\phi)^2} + \frac{2\hat{L}^2\hat{S}}{\hat{B}} - \hat{A} \right) - \frac{2\hat{L}}{\hat{B}}\nabla H - \frac{\hat{A}}{2\hat{S}}\nabla(\nabla^2 \phi) \right]. \end{aligned} \quad (\text{S17})$$

A.4 Linear stability analysis in the linear Monge regime

We substitute the following normal modes into Equation (27) and Equation (28),

$$\phi' = \Phi e^{\alpha t} e^{i2\pi \mathbf{k} \cdot \mathbf{x}} \quad \text{and} \quad z' = Z e^{\alpha t} e^{i2\pi \mathbf{k} \cdot \mathbf{x}}, \quad (\text{S18})$$

yielding the relations

$$\begin{aligned} Z \left[16\pi^4 k^4 + 8\pi^2 k^2 \hat{B} \hat{S} \left(\phi_0 \log \phi_0 + (1 - \phi_0) \log(1 - \phi_0) \right) \right. \\ \left. + \frac{\hat{A}}{2} \phi_0 (1 - \phi_0) + \frac{\hat{L}^2 \hat{S}}{\hat{B}} \phi_0^2 \right] + 4\pi^2 k^2 \hat{T} = -8\pi^2 k^2 \hat{L} \hat{S} \Phi, \end{aligned} \quad (\text{S19})$$

and

$$\alpha \Phi = -4\pi^2 k^2 \Phi \left[\frac{1}{1 - \phi_0} + \frac{2\hat{L}^2 \hat{S}}{\hat{B}} \phi_0 - \hat{A} \phi_0 \right] - 16\pi^4 k^4 \phi_0 \left[\frac{\hat{L}}{\hat{B}} Z + \frac{\hat{A}}{2\hat{S}} \Phi \right]. \quad (\text{S20})$$

Eliminating variables Z and Φ , we obtain the dispersion relation given in Equation (29).

A.5 Numerical methods

We solved the dimensionless governing equations in the linear Monge regime (Equation (S14) to Equation (S17)) numerically inside a square domain with periodic boundary conditions. Numerical simulations were performed on a spatial uniform grid of size 64×64 for the lower value of \hat{S} (200). However, we considered a finer uniform grid of size 128×128 for the higher values of \hat{S} (500, 1000, and 2000), where we observed smaller sizes of protein aggregates. We used a finite difference scheme to solve the transport equation for the protein density (Equation (S17)), whereas the velocity (Equation (S14) and Equation (S15)) and the shape (Equation (S16)) were solved using a Fourier spectral method [5, 6]. A semi-implicit scheme was used for the time marching for the protein density ϕ with a time step $\Delta t = 3 \times 10^{-4}$, where the nonlinear terms involving velocity and curvature were treated explicitly. In contrast, the nonlinear aggregation-diffusion terms were treated with linear implicit terms. The resulting transport equation is shown below

$$\begin{aligned} \frac{\phi^{n+1} - \phi^n}{\Delta t} + Pe \nabla \cdot (\mathbf{v}^{\overline{n+1}} \phi^{n+1}) = \nabla^2 \phi^{n+1} \left[\frac{1}{1 - \phi} + \frac{2\hat{L}^2 \hat{S}}{\hat{B}} \phi - \hat{A} \phi \right]^{\overline{n+1}} - \phi^{n+1} \left[\frac{2\hat{L}}{\hat{B}} \nabla^2 H^{\overline{n+1}} \right] \\ + \phi^{\overline{n+1}} \left[\frac{\hat{A}}{2\hat{S}} \nabla^4 \phi^{n+1} \right] + \nabla \phi^{n+1} \cdot \left[\nabla \phi \left(\frac{1}{(1 - \phi)^2} + \frac{2\hat{L}^2 \hat{S}}{\hat{B}} - \hat{A} \right) - \frac{2\hat{L}}{\hat{B}} \nabla H - \frac{\hat{A}}{2\hat{S}} \nabla (\nabla^2 \phi) \right]^{\overline{n+1}}, \end{aligned} \quad (\text{S21})$$

where the superscript $\overline{n+1}$ indicates the explicit terms for time step $n+1$, for which the currently available values were considered. The explicit terms were further updated using an iterative scheme, and within each iteration, velocity and shape were recalculated for the updated values of protein density. The iterations were performed within a time step until convergence was achieved. For the convergence within a time step, we used a tolerance of 5×10^{-7} . When the differences between values of variables from successive iterations fell below the tolerance, we considered the values of the variables to be converged in that time step. The Fortran code for the numerical simulation is available on https://github.com/armahapa/protein_aggregation_in_membranes.

B Supplementary figures

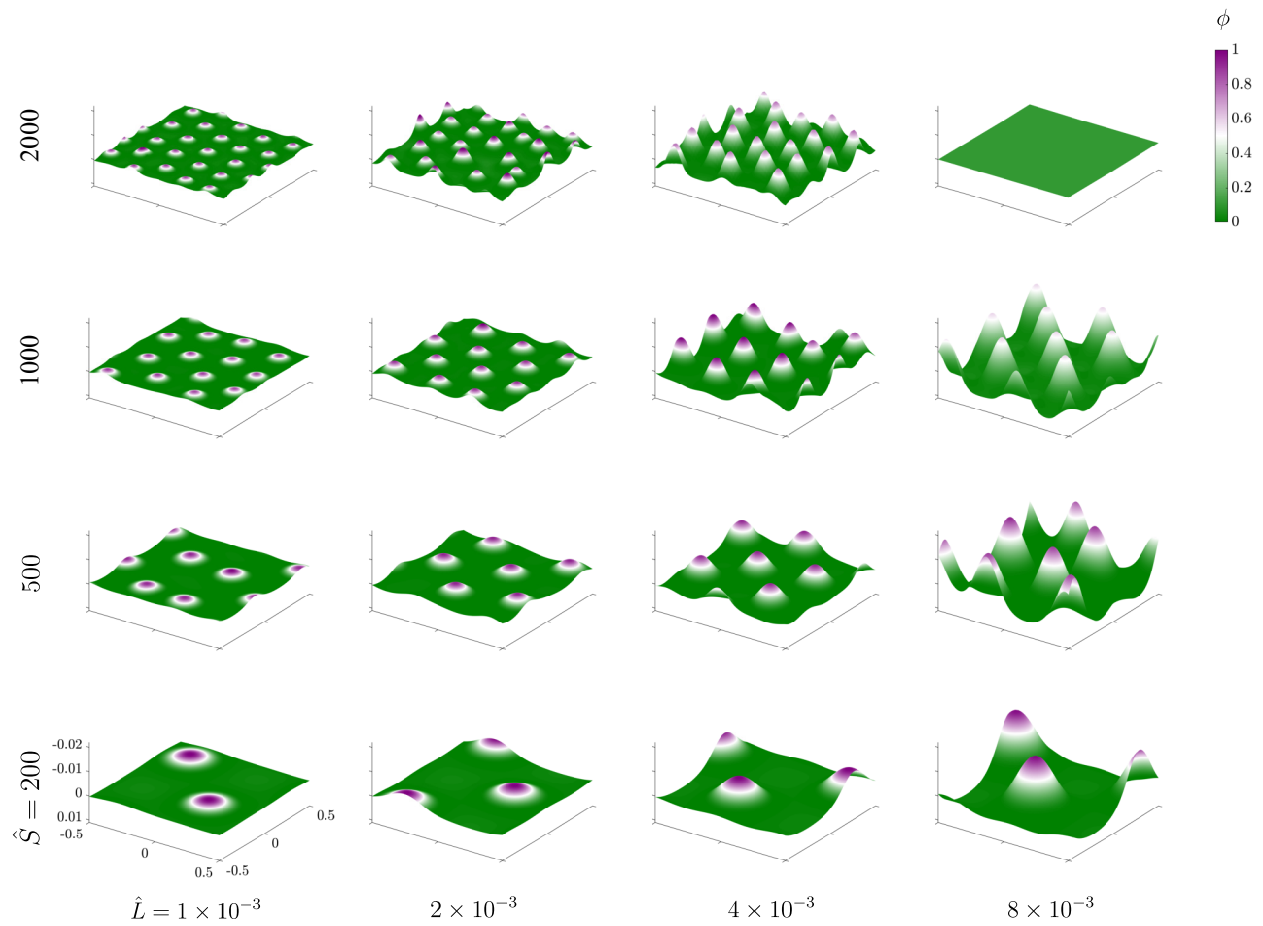


Figure B.1: Protein distribution on the deformed membrane at a long time mimicking the steady state in the plane of \hat{L} and \hat{S} , with $\hat{A} = 25$.

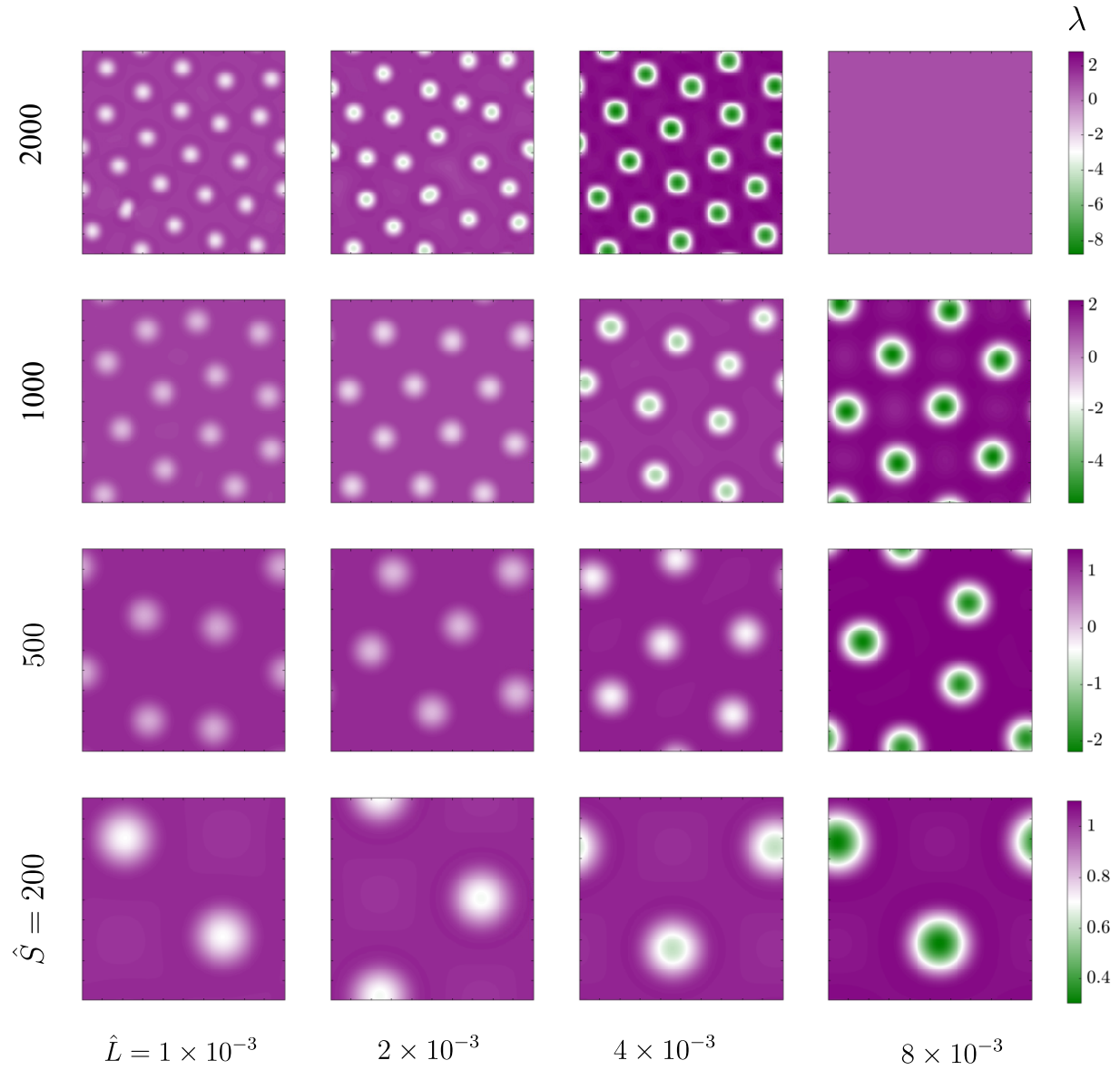


Figure B.2: Membrane tension on the projected membrane surface at a long time mimicking the steady state in the plane of \hat{L} and \hat{S} , with $\hat{A} = 25$.

C Supplementary movies

Movie M1: Time evolution of the protein density on a flat square membrane of area $1 \mu\text{m}$ for $\hat{A} = 25$ and $\hat{S} = 200$ in the Cahn-Hilliard case.

Movie M2: Time evolution of the protein density on a flat square membrane of area $1 \mu\text{m}$ for $\hat{A} = 25$ and $\hat{S} = 500$ in the Cahn-Hilliard case.

Movie M3 Time evolution of the protein density on a flat square membrane of area $1 \mu\text{m}$ for $\hat{A} = 25$ and $\hat{S} = 1000$ in the Cahn-Hilliard case.

Movie M4: Time evolution of the membrane deformation and protein density in a square membrane of size $1 \mu\text{m}^2$ for $\hat{A} = 25$, $\hat{S} = 200$ and $\hat{L} = 8 \times 10^{-4}$ for the fully coupled system.

Movie M5: Time evolution of the membrane deformation and protein density in a square membrane of size $1 \mu\text{m}^2$ for $\hat{A} = 25$, $\hat{S} = 1000$ and $\hat{L} = 8 \times 10^{-4}$ for the fully coupled system.

Movie M6: Time evolution of the membrane deformation and protein density in a square membrane of size $1 \mu\text{m}^2$ for $\hat{A} = 25$, $\hat{S} = 2000$ and $\hat{L} = 8 \times 10^{-4}$ for the fully coupled system.

References

- [1] D. J. Steigmann. “Fluid Films with Curvature Elasticity”. *Arch. Ration. Mech. Anal.* 150.2 (1999), pp. 127–152.
- [2] A. Mahapatra, D. Saintillan, and P. Rangamani. “Transport phenomena in fluid films with curvature elasticity”. *J. Fluid Mech.* 905.A8 (2020), pp. 1–31.
- [3] P. Rangamani et al. “Interaction between surface shape and intra-surface viscous flow on lipid membranes”. *Biomech. Model. Mechan.* 12.4 (2013), pp. 833–845.
- [4] P. Rangamani, K. K Mandadap, and G. Oster. “Protein-induced membrane curvature alters local membrane tension”. *Biophys. J.* 107.3 (2014), pp. 751–762.
- [5] H. Hasimoto. “On the periodic fundamental solutions of the Stokes equations and their application to viscous flow past a cubic array of spheres”. *J Fluid Mech.* 5.2 (1959), pp. 317–328.
- [6] S. Safran. *Statistical thermodynamics of surfaces, interfaces, and membranes*. CRC Press, 2018.