Membrane Deformation by Protein Inclusions

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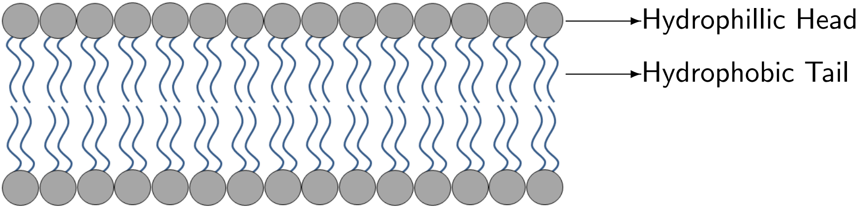
Contents

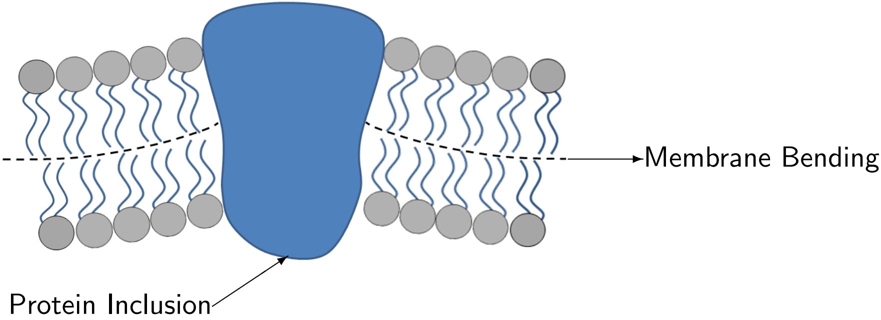
Biomembranes

Biomembranes are composed of phospholipid molcules, built from a hydrophilic phosphate 'head' and a hydrophobic lipid 'tail'. When immersed in water they form structures in which the heads point towards the water and the tails away. Biomembranes are composed of one such structure, the bilayer sheet.



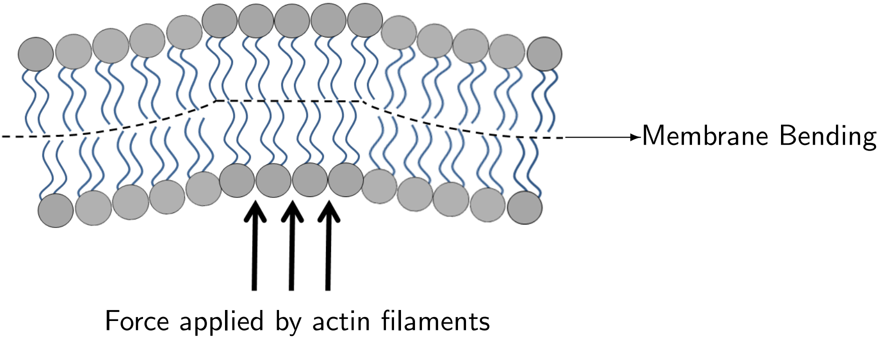
Biomembrane Deformation - Embedded Inclusions

Biomembranes can be deformed by the action of protein molecules. For example protein molecules can be embedded into the phospholipid bilayer and their shape can locally bend the membrane.



Biomembrane Deformation - Exterior Inclusions

Biomembrane deformation can also be caused by the action of exterior proteins. Actin filaments push against the membrane and cause it to bend.



Modelling Assumptions

- The membrane is a single elastic sheet and may be represented by the graph $\{(x, u(x)) \mid x \in \Omega\}$ where $\Omega \subset \mathbb{R}^2$ is some domain and $u(x)$ is the displacement of the membrane at x.
- Protein inclusions are modelled as single points.
- Inclusions may apply a point constraint to u (hard inclusions) or apply a point force to the membrane (soft inclusions).
- The energy due to the curvature of the membrane is given by the Helfrich energy functional.

Hard Inclusions - Fixed Heights Problem

We consider the (approximate) Helfrich energy functional given by

$$E(u) := \frac{1}{2}\int_{\Omega} \kappa|\Delta u|^2 + \sigma|\nabla u|^2.$$

Here $\kappa > 0$ is a constant called the bending modulus and $\sigma > 0$ is a constant accounting for the surface tension.
Let $N \in \mathbb{N}$ and take $X \in \Omega^N$ to be the inclusion locations. The inclusions apply the point constraints

$$u(X_i) = \alpha_i \; \forall 1 \leq i \leq N$$

for some $\alpha \in \mathbb{R}^N$. We look to minimise E over an appropriate subspace of $H^2(\Omega)$.

Hard Inclusions - Fixed Heights Problem

Suppose $\Omega \subset \mathbb{R}^2$ is bounded and Lipschitz. Let $V \subset H^2(\Omega)$ be chosen for appropriate boundary conditions, explicitly we may choose

$$V = \begin{cases} H^2(\Omega) \cap H^1_0(\Omega) & \text{for Navier boundary conditions,} \\ H^2_0(\Omega) & \text{for Dirichlet boundary conditions,} \\ H^2_{p,0}(\Omega) & \text{for Periodic b.c. with volume conservation.} \end{cases}$$

Define a convex subset of V:

$$K^X_\alpha := \{v \in V \mid v(X_i) = \alpha_i \ \forall 1 \leq i \leq N\}.$$

Define $L_\alpha \subset V$:

$$L_\alpha := \left\{v \in V \mid \forall 1 \leq i \leq N \ \exists Y_i \in \bar{\Omega} \text{ s.t. } v(Y_i) = \alpha_i \right\}$$

Hard Inclusions - Fixed Heights Problem

We consider the following minimisation problems.

1. Given α, X minimise $E(v)$ over $v \in K_\alpha^X$.
2. Given α minimise $E(v)$ over $v \in L_\alpha$.

That is we wish to find the minimal energy for a given configuration of inclusions imposing heights α and the minimal energy over all configurations which impose heights α.

We can solve these problems using very general methods and so first introduce a similar problem to which these methods can also be applied.

Hard Inclusions - Fixed Curvatures Problem

We consider the higher order approximation to the Helfrich energy functional given by

$$E(u) := \frac{1}{2}\int_{\Omega} \kappa_8|\Delta^2 u|^2 + \kappa_6|\nabla\Delta u|^2 + \kappa|\Delta u|^2 + \sigma|\nabla u|^2.$$

We require the higher regularity of u to apply pointwise constraints to the curvature.
Let $N \in \mathbb{N}$ and take $X \in \Omega^N$ to be the inclusion locations. The inclusions each apply three point constraints

$$(\partial^2_{xx}u(X_i), \partial^2_{xy}u(X_i), \partial^2_{yy}u(X_i)) = (\alpha_{3i-2}, \alpha_{3i-1}, \alpha_{3i})\ \forall 1 \leq i \leq N$$

for some $\alpha \in \mathbb{R}^{3N}$. We look to minimise E over an appropriate subspace of $H^4(\Omega)$.

Hard Inclusions - Fixed Curvatures Problem

Suppose $\Omega \subset \mathbb{R}^2$ is bounded and Lipschitz. Let $V \subset H^2(\Omega)$ be chosen for appropriate boundary conditions, for example we may choose

$$V = \begin{cases} H_0^4(\Omega) & \text{for Dirichlet boundary conditions,} \\ H_{p,0}^4(\Omega) & \text{for Periodic b.c. with volume conservation.} \end{cases}$$

Define a convex subset of V:

$$K_\alpha^X := \left\{ v \in V \mid \mathbf{D^2} v(X_i) = (\alpha_{3i-2}, \alpha_{3i-1}, \alpha_{3i}) \, \forall 1 \leq i \leq N \right\}.$$

Define $L_\alpha \subset V$:

$$L_\alpha := \left\{ v \in V \mid \forall 1 \leq i \leq N \, \exists Y_i \in \bar{\Omega} \text{ s.t. } \mathbf{D^2} v(X_i) = (\alpha_{3i-2}, \alpha_{3i-1}, \alpha_{3i}) \right\}$$

Abstract Quadratic Programming Problem

Definition (Quadratic programming problem (QPP))

Let V be a Hilbert Space, fix $N \in \mathbb{N}$, $\alpha \in \mathbb{R}^N$ and a set of linearly independent functionals $\{F_1, ..., F_N\} \subset V^*$. We thus define a convex subset $K_\alpha^F \subset V$ by:

$$K_\alpha^F := \{v \in V \mid F_j(v) = \alpha_j \, \forall \, 1 \leq j \leq N\} \, .$$

Let $a : V \times V \to \mathbb{R}$ be a bilinear, symmetric, bounded and coercive.
Let $l : V \to \mathbb{R}$ be a bounded linear functional.
Define $J : V \to \mathbb{R}$ by $J(v) := \frac{1}{2} a(v, v) - l(v)$.
We will say $u \in K_\alpha^F$ is a minimiser of J over K_α^F if

$$J(u) \leq J(v) \, \forall \, v \in K_\alpha^F \, .$$

Equivalent Problems

Lemma (Equivalent variational problems)

Using the notions in Definition 1, suppose $u \in K_\alpha^F$, then the following are equivalent:

1. $J(u) \leq J(v) \;\; \forall v \in K_\alpha^F$
2. $a(u, v-u) \geq l(v-u) \;\; \forall v \in K_\alpha^F$
3. $a(u, w) = l(w) \;\; \forall w \in K_0^F$

The final statement is useful to show the existence and uniqueness of such a minimiser.

Constructing the Minimiser

For each $1 \leq j \leq N$ we define $\phi_j \in V$ by the unique solution to:

$$a(\phi_j, v) = F_j(v) \, \forall \, v \in V.$$

Hence define the matrix $A = (a_{ij})_{i,j=1,\ldots,N}$ by $a_{ij} := a(\phi_i, \phi_j)$.
Finally, define $\phi_{N+1} \in K_0^F$ by the unique solution to:

$$a(\phi_{N+1}, v) = l(v) \, \forall \, v \in K_0^F.$$

Notice A is symmetric and invertible as it is defined by a symmetric, coercive bilinear functional applied to linear independent elements of V.

Constructing the Minimiser

Define $\lambda \in \mathbb{R}^N$ by $\lambda := A^{-1}\alpha$ and thus define $u^* \in V$ by:

$$u^* := \sum_{j=1}^{N} \lambda_j \phi_j + \phi_{N+1}.$$

Notice $u^* \in K_\alpha^F$, as for any $1 \leq i \leq N$ we have

$$F_i(u^*) = \sum_{j=1}^{N} \lambda_j F_i(\phi_j) + F(\phi_{N+1}) = (A\lambda)_i = \alpha_i$$

Now let $w \in K_0^F$, then

$$a(u^*, w) = \sum_{j=1}^{N} \lambda_j a(\phi_j, w) + a(\phi_{N+1}, w) = \sum_{j=1}^{N} \lambda_j F_j(w) + l(w) = l(w)$$

Thus $u^* \in K_\alpha^F$ satisfies the equivalent variational problem so it is a minimiser of J over K_α^F.

Global Minimisers

We now look to minimise J over all possible configurations which impose the constraints encoded by α, that is we minimise J over the set:

$$L_\alpha := \{v \in V \mid \exists G = (G_1, ..., G_N) \in \mathscr{G} \text{ s.t. } G_i(v) = \alpha_i \; \forall 1 \leq i \leq N\}\,.$$

Here we may choose $\mathscr{G} \subset (V^*)^N$ appropriately for each application. For example, for the fixed heights problem we set

$$\mathscr{G} = \left\{(\delta_{X_1}, ..., \delta_{X_N}) \mid X_1, ..., X_N \in \bar{\Omega}\right\}.$$

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Existence of Global Minimisers

Theorem (Existence of QPP global minimisers)

Suppose $\mathscr{G} \subset (V^*)^N$ is compact and that $L_\alpha \neq \emptyset$ then there exists a QPP global minimiser (a minimiser of J over L_α).

The proof follows by finding minimisers u_G of K_α^G for each $G \in \mathscr{G}$ and then finding the minimum of $J(u_G)$ over $\mathscr{G}$ using compactness. Having shown the existence of such global minimisers we now return to the fixed heights problem to better characterise them.

Global Minimisers - Fixed Heights Problem

For the fixed heights problem we have $V \subset C(\bar{\Omega})$. Take $\alpha = (\alpha_1, ..., \alpha_N) \in \mathbb{R}^N$ and wlog assume $\alpha_1 \leq \alpha_2 \leq ... \leq \alpha_N$.

- If $\alpha_1 \geq 0$ then $L_\alpha = L_{\alpha_N}$.
- If $\alpha_N \leq 0$ then $L_\alpha = L_{\alpha_1}$.
- If $\alpha_1 < 0 < \alpha_N$ then $L_\alpha = L_{(\alpha_1, \alpha_N)}$.

Hence all of these problems reduce to a problem with $N = 1$ or $N = 2$.

Fixed Heights Problem - $N = 1$ Case

Lemma ($N = 1$ case)

Suppose $N = 1$ and define $w \in V$ by the unique solution to $a(w, v) = l(v)\ \forall v \in V$, then the following holds.

- *$u \in L_\alpha$ is a minimiser over height α iff $u = w + \frac{\alpha - w(X)}{G(X,X)} G(X, \cdot)$ and $X \in \Omega$ is chosen minimising $\frac{1}{G(X,X)} |\alpha - w(X)|^2$ over Ω.*

In particular when $l = 0$ we have $w \equiv 0$ thus u depends linearly on α. The choice of X is to maximise $G(X, X)$, this is a maximal bending point and depends only upon Ω.

Maximal Bending Points

- The locations of maximal bending points are related to the distance from the boundary.
- Maximal bending points not necessarily unique.