

Membrane deformation and induced interactions between pointwise inclusions

Graham Hobbs

Joint work with - C.Elliott (Warwick),
R.Kornhuber, C.Gräser and M.-W.Wolf (FU Berlin)

Applied PDEs Seminar, 4th November 2014



THE UNIVERSITY OF
WARWICK

EPSRC
Pioneering research
and skills

Contents

Introduction

Point Constraints

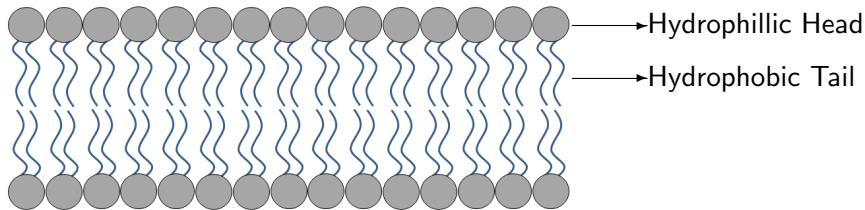
Point Curvature Constraints

Point Forces



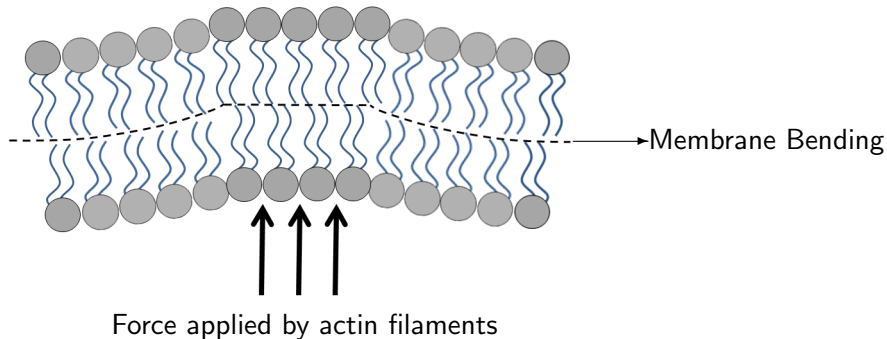
Biomembranes

Biomembranes are composed of phospholipid molecules, 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.



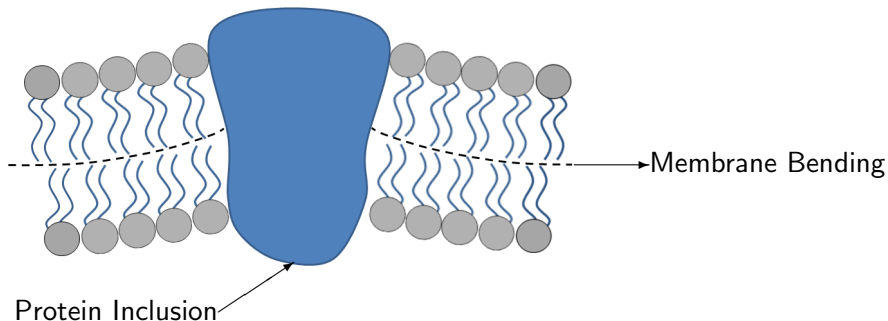
Biomembrane Deformation - Exterior Inclusions

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



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.



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 or apply a point force to the membrane.
- ▶ The energy due to the curvature of the membrane is given by the Helfrich energy functional.

Energy Functional

We consider the (approximate) Helfrich energy functional given by

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

- ▶ $\kappa > 0$ is the bending modulus.
- ▶ $\sigma > 0$ accounts for the surface tension.

The natural space to define J on is $H^2(\Omega)$.

We augment this energy functional in a variety of ways to produce our various models for membrane deformation.

Fixed Heights Problem

We first consider inclusions applying a point constraint to the displacement u .

This corresponds to the action of actin filaments anchored to the cytoskeleton.

Let $N \in \mathbb{N}$ and take $X \in \Omega^N$ to be the inclusion locations. The inclusions apply the point constraints

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

for some $\alpha \in \mathbb{R}^N$.

We look to minimise J over an appropriate subspace of $H^2(\Omega)$ subject to these constraints.

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

$$V = \begin{cases} H^2(\Omega) \cap H_0^1(\Omega) & \text{for Navier boundary conditions,} \\ H_0^2(\Omega) & \text{for Dirichlet boundary conditions,} \\ H_{p,0}^2(\Omega) & \text{for Periodic b.c. with volume conservation.} \end{cases}$$

Define a convex subset of V :

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

Define $L_\alpha \subset V$:

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

Fixed Heights Problem and Global Minimisation

We consider the following minimisation problems.

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

That is, given constraints α , we wish to:

1. Minimise the energy for a given configuration of inclusions.
2. Minimise the energy over all possible configurations.

We have existence and uniqueness for (1) and existence for (2) but no general uniqueness.

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 $\{F_1, \dots, F_N\} \subset V^*$. 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 $a : V \times V \rightarrow \mathbb{R}$ be bilinear, symmetric, bounded and coercive.

Let $l : V \rightarrow \mathbb{R}$ be a bounded linear functional.

Define $J : V \rightarrow \mathbb{R}$ 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. $J(u) \leq J(v) \quad \forall v \in K_\alpha^F$
2. $a(u, v - u) \geq l(v - u) \quad \forall v \in K_\alpha^F$
3. $a(u, w) = l(w) \quad \forall w \in K_0^F$

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:

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

Hence define the matrix $A = (a_{ij})_{i,j=1,\dots,N}$ by $a_{ij} := a(\phi_i, \phi_j)$.

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

Finally, define $\phi_{N+1} \in V$ by the unique solution to:

$$a(\phi_{N+1}, v) = I(v) \quad \forall v \in V.$$

Constructing the Minimiser

Define $\lambda \in \mathbb{R}^N$ by $\lambda := A^{-1} [\alpha - F(\phi_{N+1})]$ 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

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

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:

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

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

$$\mathcal{G} = \{(\delta_{X_1}, \dots, \delta_{X_N}) \mid X_1, \dots, X_N \in \bar{\Omega}\}.$$

Existence of Global Minimisers

Theorem (Existence of QPP global minimisers)

Suppose $\mathcal{G} \subset (V^)^N$ 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 $G \in \mathcal{G}$ and then finding the minimum of $J(u_G)$ over \mathcal{G} using compactness.

Global Minimisers - Fixed Heights Problem

We can reduce the global minimisation problem (2) to one of two cases.

Take $\alpha = (\alpha_1, \dots, \alpha_N) \in \mathbb{R}^N$ and wlog assume $\alpha_1 \leq \alpha_2 \leq \dots \leq \alpha_N$.

- ▶ 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 $N = 1$ then the following holds.

- ▶ $u \in V$ is a minimiser over height α iff $u = \frac{\alpha}{G(X, X)} G(X, \cdot)$ and $X \in \Omega$ is chosen maximising $G(X, X)$ over Ω .

Here $G(\cdot, \cdot)$ denotes the Green's function of $\kappa\Delta^2 - \sigma\Delta$ in Ω with the boundary conditions imposed by V .

We call X maximising $G(X, X)$ a maximal bending point.

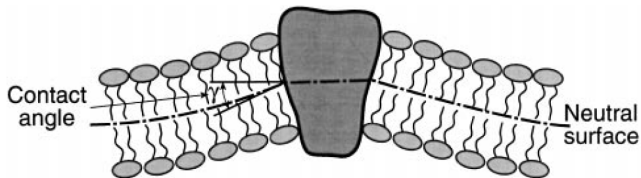
There is a similar condition for the $N = 2$ case.

Maximal Bending Points

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

Curvature Constraints

We will now consider embedded inclusions.



These inclusions enforce a constraint upon the gradient of u around their boundary.

We model them as point inclusions by enforcing curvature constraints at a point.

Fixed Curvatures Problem

We now wish to apply point curvature constraints to u , ie point constraints to u_{xx} , u_{xy} and u_{yy} .

We cannot use our previous approach as $H^2(\Omega) \not\subset C^2(\Omega)$.

We consider the augmented Helfrich energy functional given by

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

Now we consider $\tilde{J}(\cdot)$ as a functional on $H^4(\Omega) \subset C^2(\bar{\Omega})$.

Fixed Curvatures Problem

Let $N \in \mathbb{N}$ and take $X \in \Omega^N$ to be the inclusion locations. The inclusions each apply three point constraints

$$(u_{xx}(X_i), u_{xy}(X_i), u_{yy}(X_i)) = (\alpha_{3i-2}, \alpha_{3i-1}, \alpha_{3i}) \quad \forall 1 \leq i \leq N$$

for some $\alpha \in \mathbb{R}^{3N}$.

We look to minimise $\tilde{J}(\cdot)$ over an appropriate subspace of $H^4(\Omega)$ subject to these constraints.

Hard Inclusions - Fixed Curvatures Problem

Suppose $\Omega \subset \mathbb{R}^2$ is bounded and Lipschitz. Let $V \subset H^4(\Omega)$ 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 :

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

Define $L_\alpha \subset V$:

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

Fixed Curvatures Problem and Global Minimisation

We consider the following minimisation problems.

1. Given α, X minimise $\tilde{J}(v)$ over $v \in K_\alpha^X$.
2. Given α minimise $\tilde{J}(v)$ over $v \in L_\alpha$.

That is, given constraints α , we wish to:

1. Minimise the energy for a given configuration of inclusions.
2. Minimise the energy over all possible configurations.

We have existence and uniqueness for (1) and existence for (2) but no general uniqueness.

Penalty Method - Soft inclusions

Consider the energy functional $J_\varepsilon : V \rightarrow \mathbb{R}$ given by

$$J_\varepsilon(u) := \tilde{J}(u) + \frac{1}{2\varepsilon} \sum_{i=1}^{3N} (D_i(X_i) - \alpha_i)^2.$$

We may find unique u_ε minimising J_ε over V .

We may view the fixed curvatures problem as the limit problem of the above. That is $u_\varepsilon \rightarrow u$ as $\varepsilon \rightarrow 0$ with u minimising J over K_α^X .

This problem also has some physical meaning, the penalty parameter ε can be used to account for the inclusions' rigidity.

Membrane Mediated Interactions

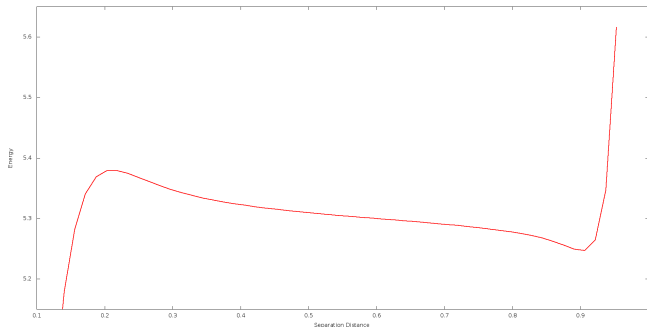
Given two inclusions we can vary their positions and solve the first minimisation problem for each configuration.

We then plot the resulting minimal energy values as a function of the inclusions' separation to produce an interaction potential.

A membrane mediated interaction is precisely the force obtained by taking the gradient of the interaction potential.

Interaction Between Identical Conical Inclusions

We model conical inclusions by applying point constraints to Δu . Identical conical inclusions repel each other, this behaviour is captured by our model.



This plot shows the interaction energy between two identical conical inclusions, which is repulsive over the relevant separation distances, 0.2-0.8.

Point Forces

Now we consider the energy functional:

$$E(u, X^+, X^-) := \frac{1}{2} \int_{\Omega} \kappa |\Delta u|^2 + \sigma |\nabla u|^2 dx - \alpha \sum_{i=1}^{N^+} u(X_i^+) + \beta \sum_{i=1}^{N^-} u(X_i^-)$$

defined on some $V \subset H^2(\Omega)$.

This accounts for inclusions applying a point force rather than a constraint.

We treat the problem similarly however, looking for minimisers for a fixed configuration of inclusions and then over all configurations.

Point Forces - Global Minimisers

We can show:

- ▶ Existence and uniqueness for minimising $E(u, X^+, X^-)$ over V with fixed X^+, X^- .
- ▶ Existence for minimising $E(u, X^+, X^-)$ over $V \times \bar{\Omega}^{N^+ + N^-}$.

The inclusions display a clustering behaviour at the global minimisers.

Clustering - One Class of Inclusion

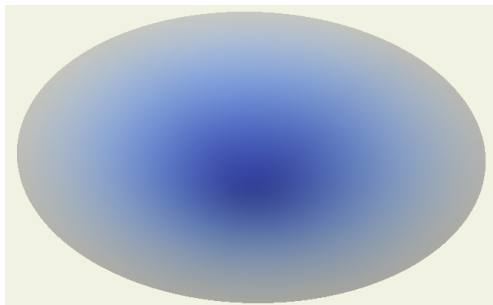
When we have inclusions of only one class we have the following theorem.

Theorem (Clustering for one class minimisers)

Suppose $N^+ > 0$ and $N^- = 0$ (or $N^- > 0$ and $N^+ = 0$). Then $(u, X) \in V \times \bar{\Omega}^{N^+}$ (resp. $\bar{\Omega}^{N^-}$) is a global minimiser iff $X_j = Y \in \Omega$ for each j and $u = \alpha N^+ u_Y$ (resp. $u = -\beta N^- u_Y$) where (u_Y, Y) is a global minimiser for the one particle problem with $N^+ = 1, N^- = 0$ and $\alpha = 1$.

Interaction Effects

We can examine the effect of the interactions by solving the fixed inclusions problem numerically and then moving the inclusions proportional to ∇u .



We see the clustering effect for one class minimisers.

Clustering - Two Classes of Inclusions

For $N^+ = N^- > 0$ the behaviour is precisely determined by the $N^+ = N^- = 1$ problem.

There are two possibilities for the locations X^+, X^- at a global minimum for the $N^+ = N^- = 1$ problem.

1. Both $X^+, X^- \in \Omega$.
2. $X^+ \in \Omega$ and $X^- \in \partial\Omega$ (or vice versa).

Which possibility holds is dependent upon the ratio $\sqrt{\kappa/\sigma}$ which is a relevant length scale for inclusion interactions.

Interaction Length Scale

The smaller the ratio κ/σ , the quicker the membrane-mediated interaction between inclusions decays.

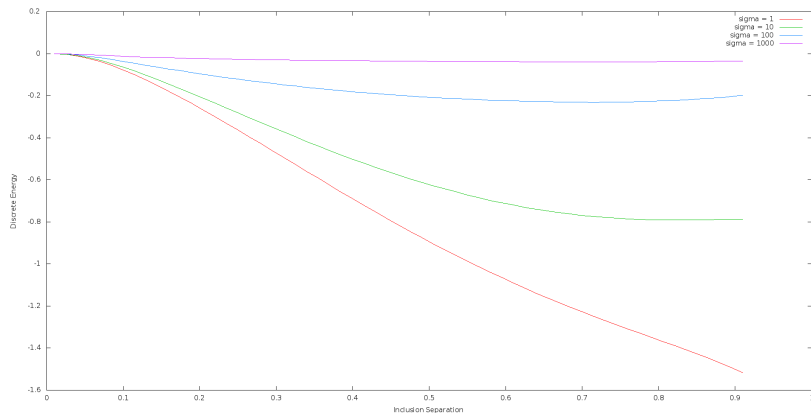
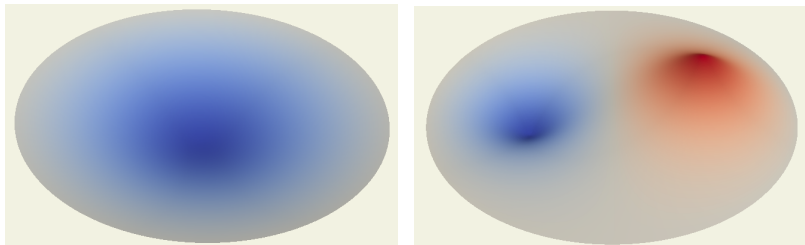


Figure: Interaction potential for opposite inclusions, varying σ .

Possible Global Minimisers

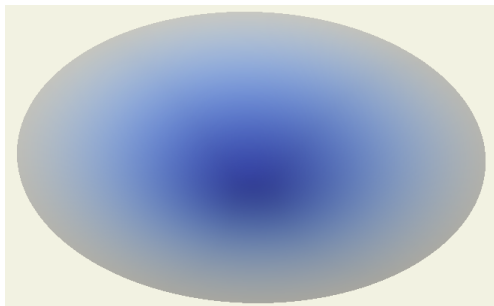


When we have $\kappa = \sigma = 1$ the interaction has sufficient length so that an inclusion at the centre can repel the other onto the boundary.

For $\kappa = 1, \sigma = 100$ the interaction length is shorter and the resulting minimiser has both inclusions inside the domain.

Interaction Effects

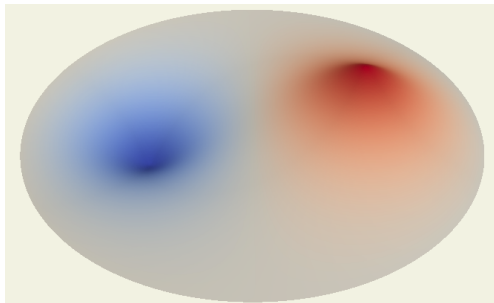
We can use the numerical gradient flow type approach to see the formation of each form of global minimiser.



In the first case, $\kappa = \sigma = 1$, we see the clustering of one class in the centre and the other class being repelled to the boundary.

Interaction Effects

We can use the numerical gradient flow type approach to see the formation of each form of global minimiser.



In the second case, $\kappa = 1$, $\sigma = 100$, we see the clustering of each class within the domain.