Geometric PDEs and Cell Biology

Mathematical Models, Mathematical PDE Analysis, Numerical Analysis

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Tour of Mathematics

The aim of this talk is to introduce a number of interesting PDE problems involving complex domains with interfaces and free boundaries arising in some areas of cell biology.

- Describe some mathematical methodology which may be useful in the modelling and numerical simulation of protein interaction with biomembranes
- Describe Helfrich functional for two phase biomembranes
- Motivate study of PDEs on evolving complex domains
- Describe *Evolving surface finite element method*

Perspective

Although the content is predominantly mathematical / numerical analysis associated with PDEs our motivation is to provide mathematical methodology for use within in modelling processes in cell biology. In particular

- Analysis Based Modelling
- Analysis Based Computation

Analysis Based Modelling: What is involved?

- Mathematical modelling
  Here developments in large scale computing, analysis and numerical analysis allow more ambitious models!
- Formulation of PDEs In our context
  - Mechanics
  - Biochemistry
  - Geometry
- Analysis: each formulation may require its own version of the analysis
- ABC: Analysis Based Computation
  - Simulation + Parameter identification + Data assimilation + Learning + Prediction + Control
- Improve the model

This talk addresses Simulation.

Preserving the structure of variational problems

- Often PDE like problems: Given operator $\mathcal{A} : V \to V^*$ and $f \in V^*$ find $u \in V$ such that

$$\mathcal{A}u = f$$

are posed in a Hilbert space setting in which $\mathcal{V}$ and $\mathcal{H}$ are separable Hilbert spaces, $\mathcal{V}$ is dense in $\mathcal{H}$ and

$$\mathcal{V} \subset \mathcal{H} \subset \mathcal{V}^*$$

and we identify

$$(f, \cdot)_{\mathcal{H}} = \langle f, \cdot \rangle_{\mathcal{V}^*, \mathcal{V}}.$$

- A discretisation

$$\mathcal{A}_h u_h = f_h$$

might be to pose a variational problem in finite dimensional setting with a discrete space S_h and using discrete spaces $\mathcal{H}_h, \mathcal{V}_h$ as appropriate analogues of the continuous setting.

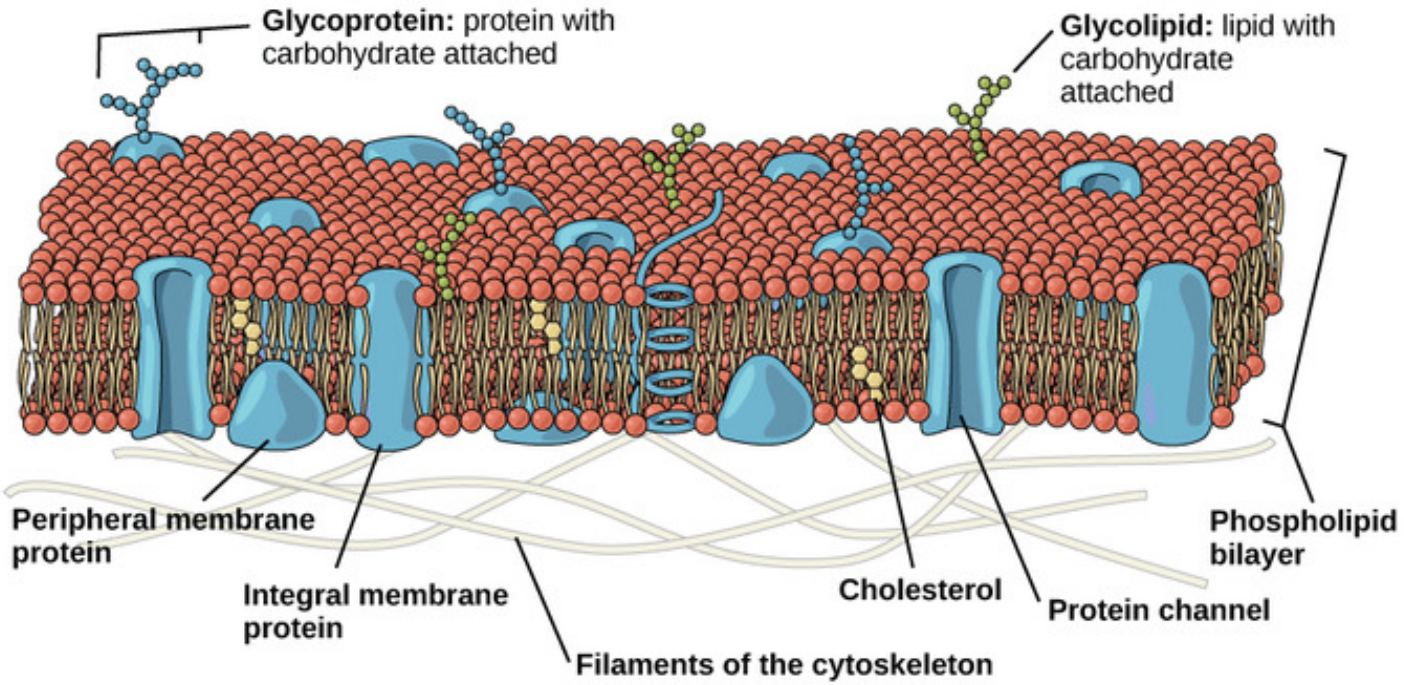
- The discrete space may not be a subset of $\mathcal{V}$ i.e. a *variational crime.* Can be dealt with by *prolongation* or in our setting *lifting*, $\mathcal{S}_h^\ell \subset \mathcal{V}$.

ABC Methodology

- Construct finite dimensional spaces as analogues of the continuous spaces
- Approximation theory
- Construct $\mathcal{A}_h$ - maybe from discrete analogues of bilinear forms in variational setting
- Well posedness of discrete problem Stability
- Perturbation bounds for bilinear forms Consistency
- Properties of discrete solution approximating properties of continuous solution
- Use discretization to extract well posedness for continuous problem Convergence
- Error analysis - maybe via well posedness of continuous problem and consistency

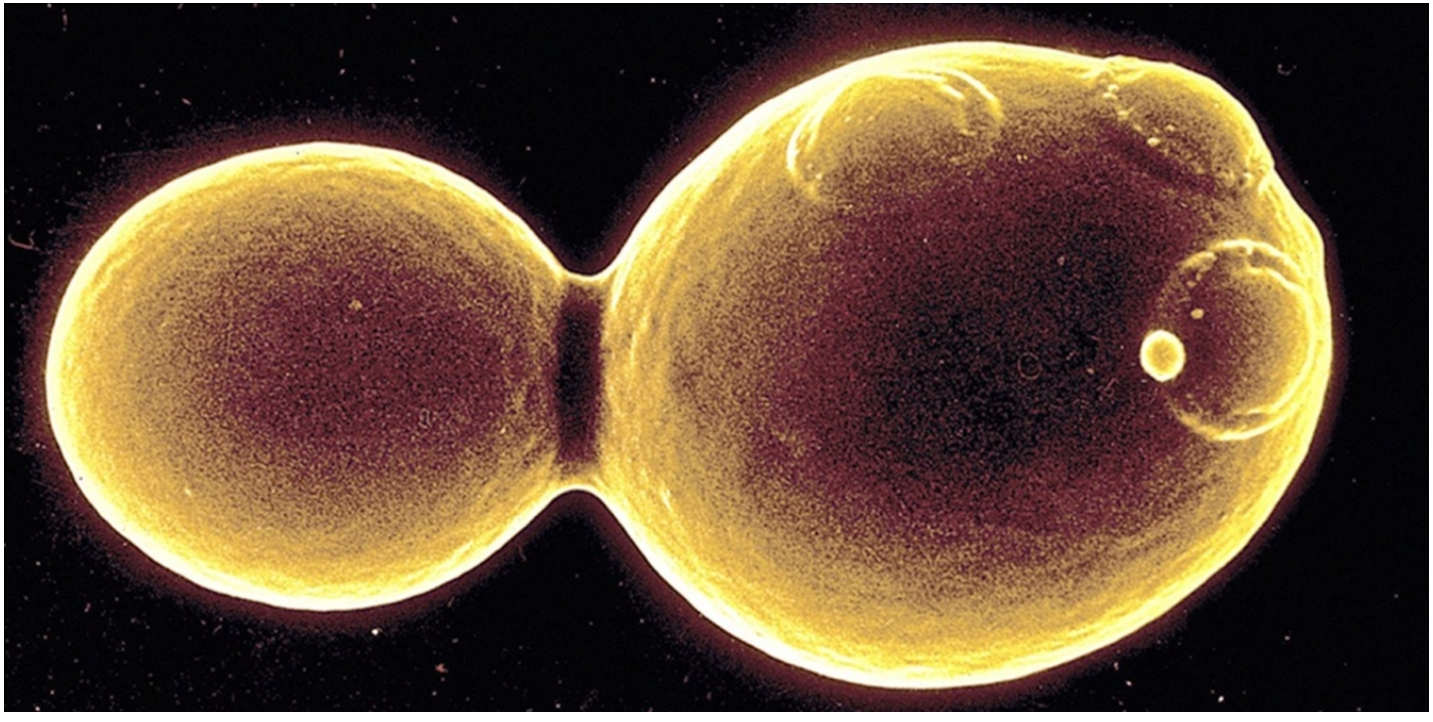
Some cartoons and experiments

Plasma Membrane



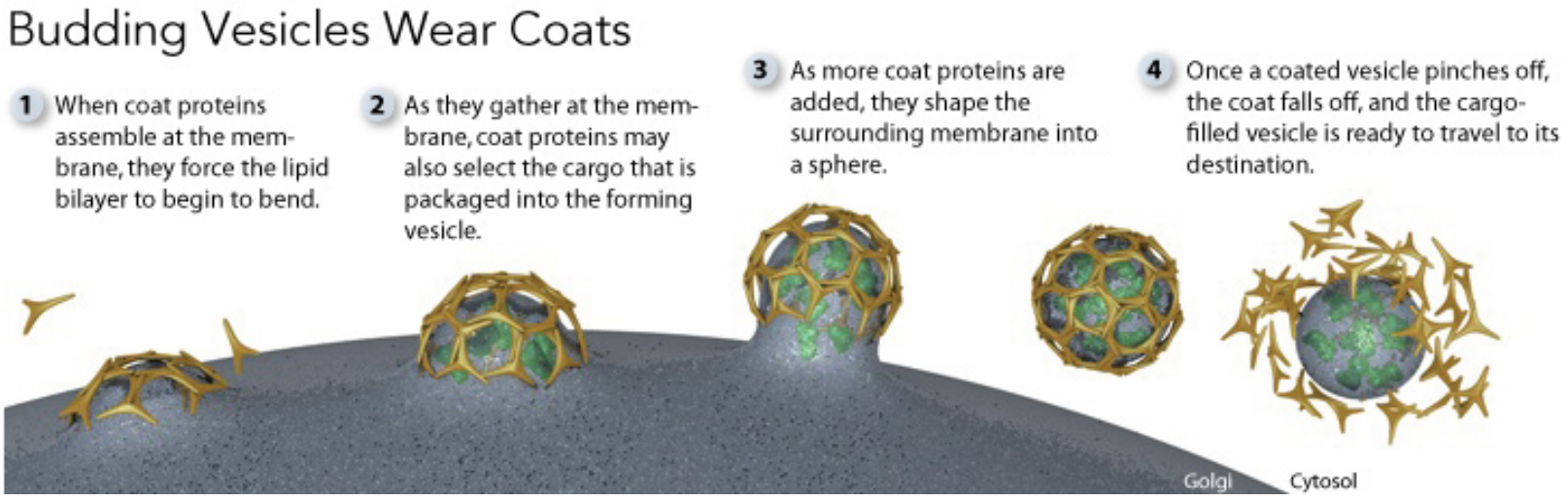
source:https://www.boundless.com/biology/textbooks/boundless-biology-textbook/cell-structure-4/eukaryotic-cells-60/the-plasma-membrane-and-the-cytoplasm-314-11447/

Membrane budding



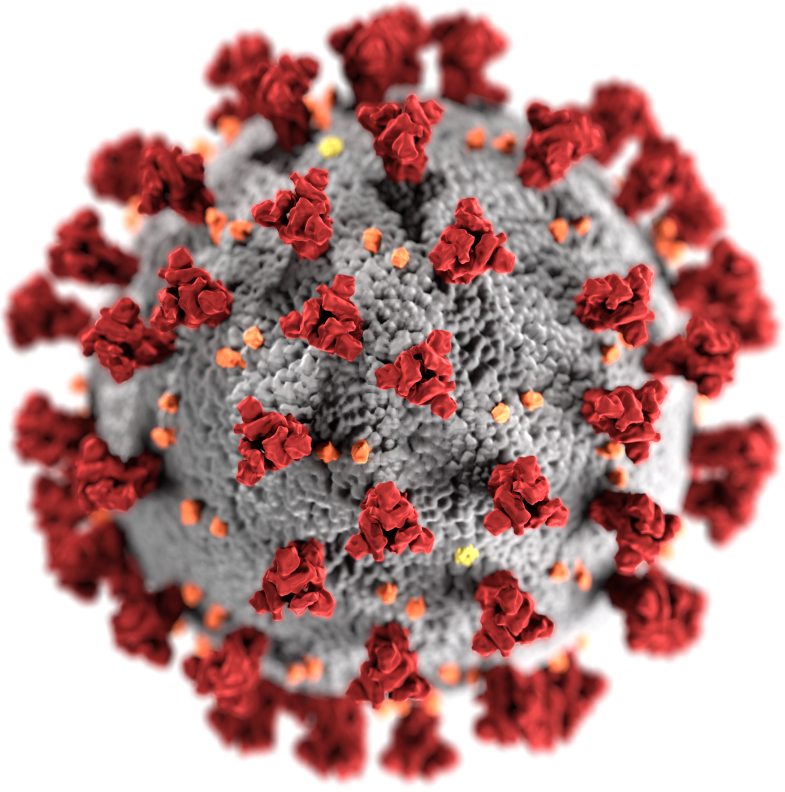
Source:
http://biology-pictures.blogspot.co.uk/2011/10/budding-yeast-picture.html

Vesicles transport cargo



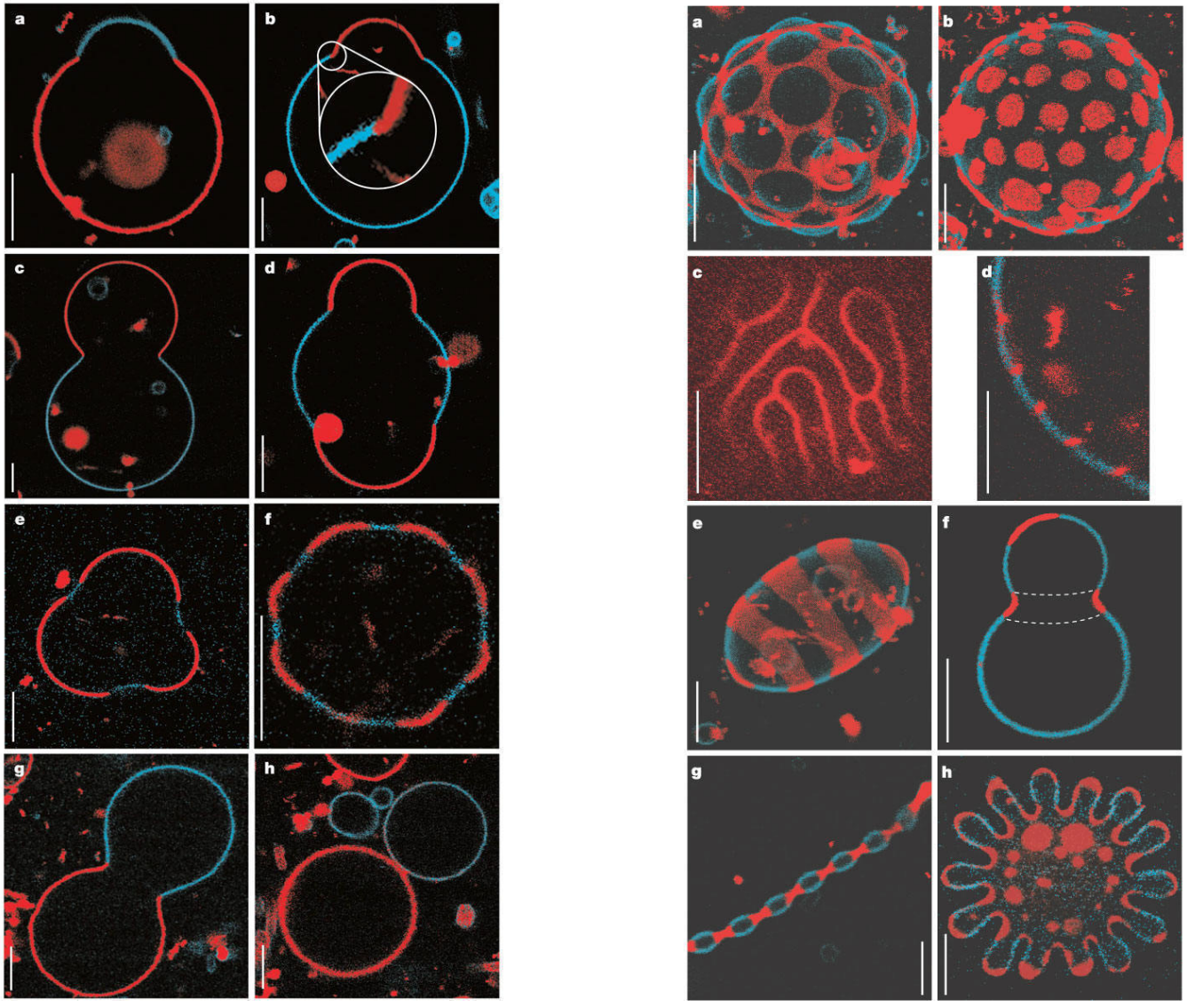
Source:
https://learn.genetics.utah.edu/content/cells/vesicles/

Corona Virus



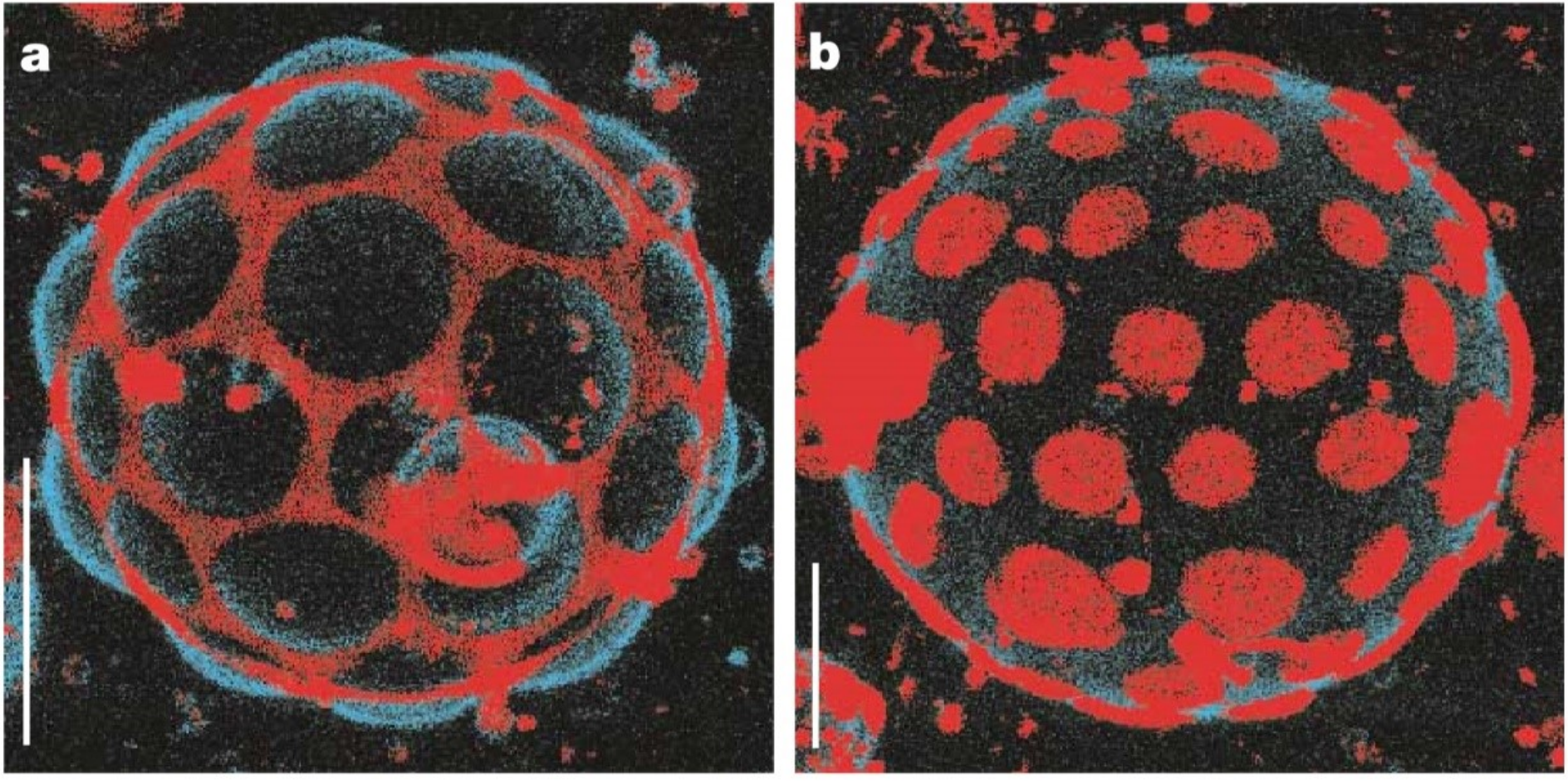
Source:
CDC/ Alissa Eckert, MS; Dan Higgins, MAM - This media comes from the Centers for Disease Control and Prevention's Public Health Image Library (PHIL)

Giant Unilamellar Vesicles (GUV):- Morphology and Phase Separation

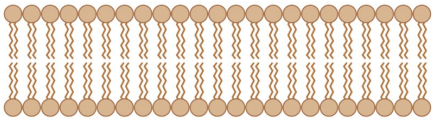


Giant unilamellar vesicles *Imaging coexisting fluid domains in biomembrane models coupling curvature and line tension* Baumgart, Hess, and Webb Nature. 425, pg 821 (2003)

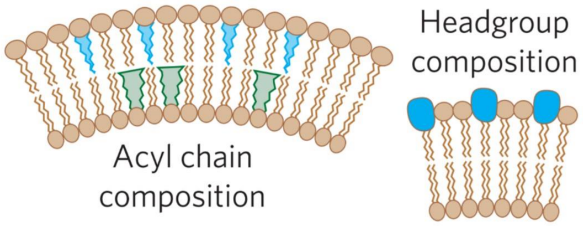
Lipid Rafts



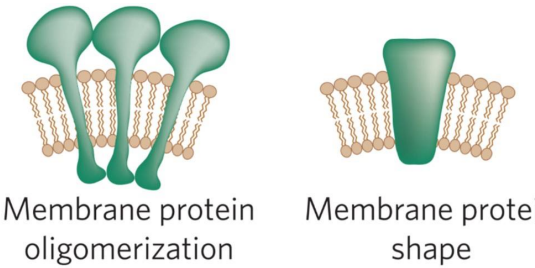
An example of large domain (rafts?) formation



(a) Undeformed phospholipid bilayer sheet



(b) Membrane deformation induced by lipid composition.



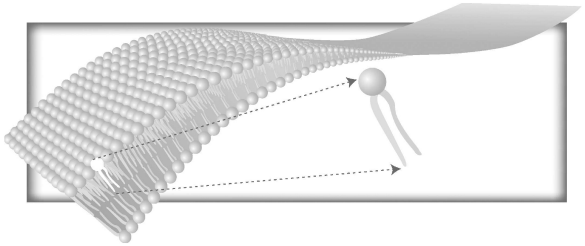
(c) Membrane deformation induced by proteins.

Examples of how membrane deformation can occur[1].

[1] **mcmahon2005membrane**.

Canham Helfrich Functional for Biomembranes

Cell membrane separates a cell from its environment.



- Bilayer consisting of lipid molecules (hydrophilic heads, lipophilic tails),
- resistance against deformations.

Diameter of a cell may be tens of mircons whilst bilayer width is measured in several nanometres. Bilayer is modelled as two-dimensional hypersurface $\Gamma \subset \mathbb{R}^3$.
Elastic energy:[Canham, Evans, Helfrich 1970s]

$$F_b = \int_\Gamma \frac{k_H}{2}(H - H_s)^2 + \int_\Gamma k_g g.$$

$H = H_1 + H_2$ mean curvature, $g = H_1 H_2$ Gaussian curvature,
k_H, k_g bending rigidities, H_s spontaneous curvature.
Gauss-Bonnet: k_G constant, $\partial\Gamma$ empty $\Rightarrow \int_\Gamma k_G H_G = k_G\, 2\pi\chi(\Gamma)$.

Two Phase Lipid Decomposition and Line Energy

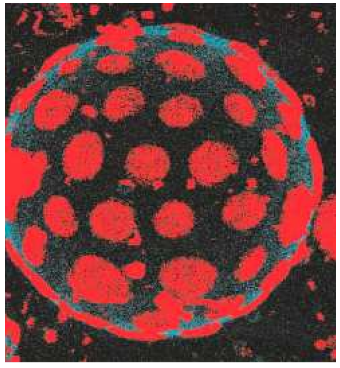
The lipid molecules may separate and form different phases.
Modelled by [Jülicher, Lipowsky 1993, 1996]:
The hypersurface $\Gamma := \partial\Omega$ is divided into two smooth domains

$$\Gamma_1 \text{ and } \Gamma_2$$

with a common boundary $\gamma = \partial\Gamma_1 = \partial\Gamma_2$.
Line energy:

$$F_l = \int_\gamma \bar{\sigma}$$

$\bar{\sigma}$ line energy coefficient (constant).



Aim: For $|\Gamma_1|$, $|\Gamma_2|$ and $|\Omega|$ given, compute (local) minima of

$$F = F_b + F_l = \sum_{i=1,2} \int_{\Gamma_i} \left(\frac{k_H^{(i)}}{2} (H - H_s^{(i)})^2 + k_g^{(i)} g \right) + \int_\gamma \bar{\sigma}.$$

Replace line energy by phase field functional

Cahn-Hilliard Functional

$$F_l^\varepsilon = \int_\Gamma \sigma\Big(\frac{\varepsilon}{2}|\nabla_\Gamma \phi|^2 + \frac{1}{\varepsilon}W(\phi)\Big).$$

$$W(\phi) = \tfrac{1}{2}(1-\phi^2)^2.$$

$$\Gamma_1 \sim \{\phi \approx 1\},\ \Gamma_2 \sim \{\phi \approx -1\}.$$

$$E_l^\varepsilon \overset{\varepsilon\to 0}{\longrightarrow} E_l = \int_\gamma \bar{\sigma}$$

in the sense of *Gamma convergence*.

Total energy:

$$E(\Gamma, \phi : \Gamma \to \mathbb{R}) = \int_\Gamma \underbrace{\frac{k_H(\phi)}{2}\big(H - H_s(\phi)\big)^2 + k_g(\phi)g}_{\text{bending energy}} + \underbrace{\sigma\Big(\frac{\varepsilon}{2}|\nabla_\Gamma\phi|^2 + \frac{1}{\varepsilon}W(\phi)\Big)}_{\text{line energy}}$$

[Elliott and Stinner 2010 J.Comp.Phys,, SIAM Applied Math.; 2013 Comm. Comp. Phys]

Equilibria obtained by applying gradient flow to an initial surface

Gradient flow dynamics: Find $\{(\Gamma(t), \phi(t))\}_t$ such that for all (w, η)

$$\big((v, \partial_t^\bullet \phi), (w, \eta)\big)_{L^2} := -\big\langle \delta F(\Gamma, \phi), (w, \eta)\big\rangle - \boldsymbol{\lambda} \cdot \big\langle \delta \boldsymbol{C}(\Gamma, \phi), (w, \eta)\big\rangle$$

Theorem: *The strong equations of the gradient flow are*

$$\begin{aligned}
v = &-\Delta_\Gamma\big(k_H(\phi)(H - H_s(\phi))\big) - |\nabla_\Gamma \boldsymbol{\nu}|^2 k_H(\phi)(H - H_s(\phi)) + \tfrac{1}{2} k_H(\phi)(H - H_s(\phi)) \\
&- \nabla_\Gamma \cdot \big(k_g'(\phi)(H\boldsymbol{I} - \nabla_\Gamma \boldsymbol{\nu})\nabla_\Gamma \phi\big) \\
&+ \sigma\varepsilon \nabla_\Gamma \phi \otimes \nabla_\Gamma \phi : \nabla_\Gamma \boldsymbol{\nu} + \sigma\big(\tfrac{\varepsilon}{2}|\nabla_\Gamma \phi|^2 - \tfrac{1}{\varepsilon} W(\phi)\big) H \\
&- \lambda_V + \big(\lambda_A - \lambda_\phi h(\phi)\big) H, \\
\omega(\varepsilon)\partial_t^\bullet \phi = &-\tfrac{1}{2}(H - H_s(\phi))^2 k_H'(\phi) + k_H(\phi)(H - H_s(\phi)) H_s'(\phi) - g k_g'(\phi) \\
&+ \varepsilon\sigma \Delta_\Gamma \phi - \tfrac{\sigma}{\varepsilon} W'(\phi) - \lambda_\phi h'(\phi),
\end{aligned}$$

plus constraints.

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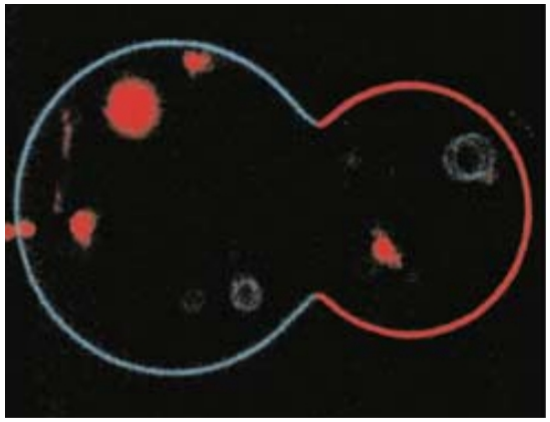
Relaxation Dynamics - Ideas and Methods

Aim: Numerical method based on surface finite elements.

Idea: Define appropriate relaxation dynamics.

- **Geometric evolution law**
  for the membrane surface
  of Willmore flow type
  (L^2 gradient flow of Willmore energy).
- **Partial differential equation on the evolving membrane surface**
  for the phase separation,
  using the phase field methodology.



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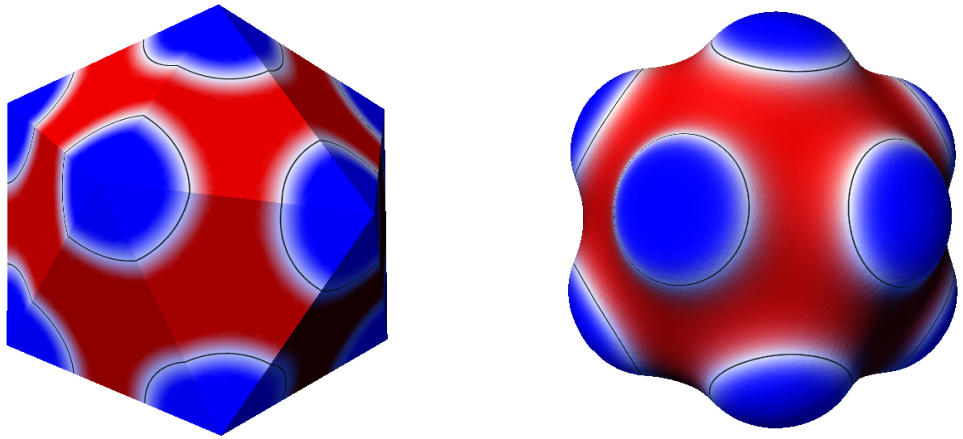
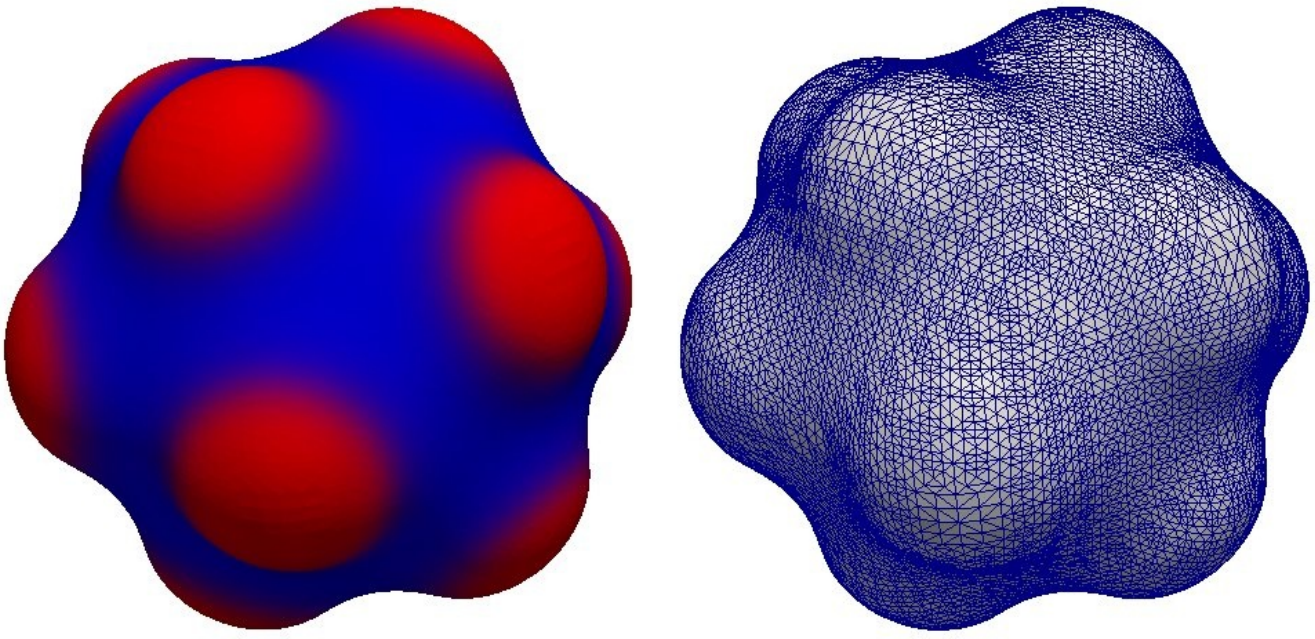
Multiple raft equilibria



Initial configuration and equilibrium shape for a vesicle with multiple rafts. Spontaneous curvature together with different bending rigidities can stabilize multiple domains of one phase embedded in another phase on vesicles close to spheres. Obtained by gradient flow relaxation of an initial shape shown on the left. Such multiple raft equilibria arise when the material parameters in the two phases are different.

Multiple raft equilibria



By considering the gradient flow with conserved Allen-Cahn dynamics we obtain the following system of PDEs

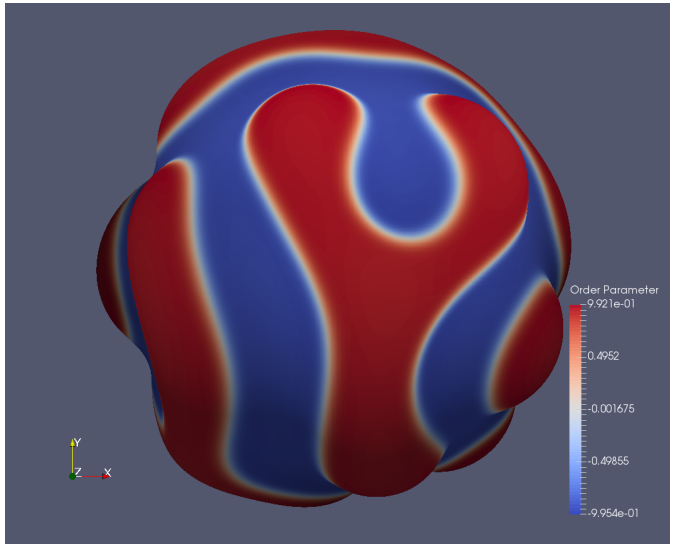
$$\begin{cases} \alpha_1 \phi_t + W'(\phi) - \epsilon^2 \Delta_\Gamma \phi + \Lambda \Delta_\Gamma h + \frac{2\Lambda h}{R^2} - \fint_\Gamma W'(\phi) = 0 & \Gamma \times (0,T) \\ \alpha_2 h_t - \left(\sigma - \frac{2\kappa}{R^2}\right) \Delta_\Gamma h + \kappa \Delta_\Gamma^2 h - \frac{2\sigma h}{R^2} + \Lambda \Delta_\Gamma \phi + \frac{2\Lambda \phi}{R^2} - \frac{\Lambda \alpha}{2\pi R^4} = 0 & \Gamma \times (0,T) \\ \phi(\cdot, 0) = \phi_0(\cdot) & \Gamma \times \{t = 0\} \\ h(\cdot, 0) = h_0(\cdot) & \Gamma \times \{t = 0\} \end{cases}$$

Solutions satisfy

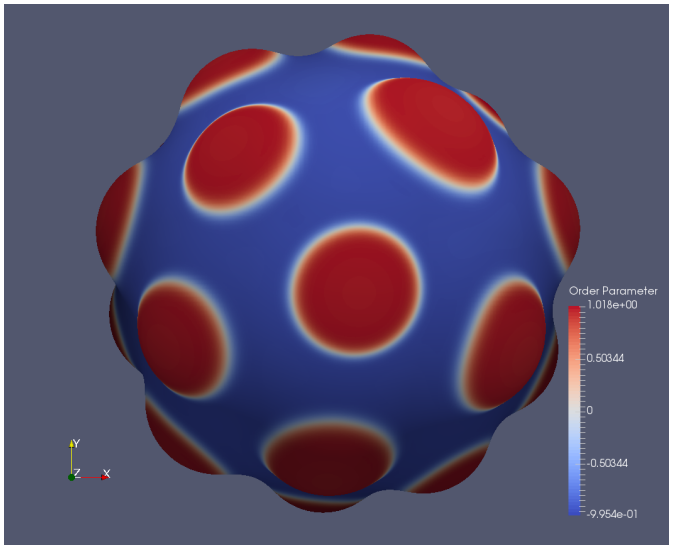
$$\frac{d}{dt} \mathcal{E}(\phi, h) \leq 0.$$

In contrast to the fully nonlinear system:
it can be shown that this system of PDEs satisfies suitable existence and uniqueness results.

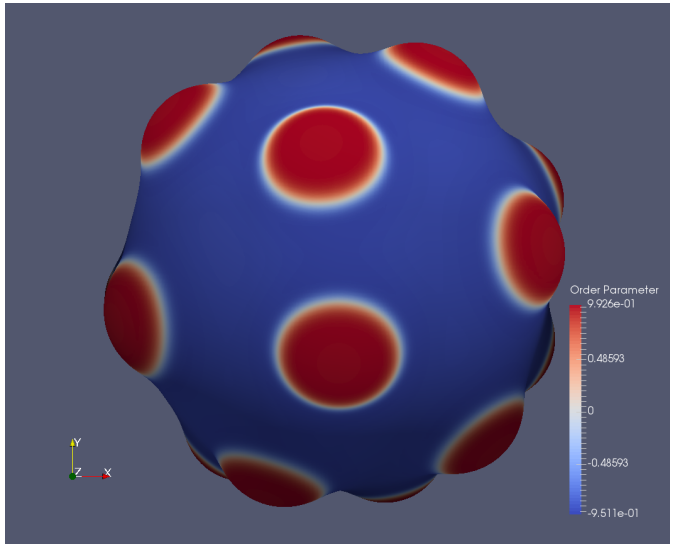
Varying the mean value of ϕ



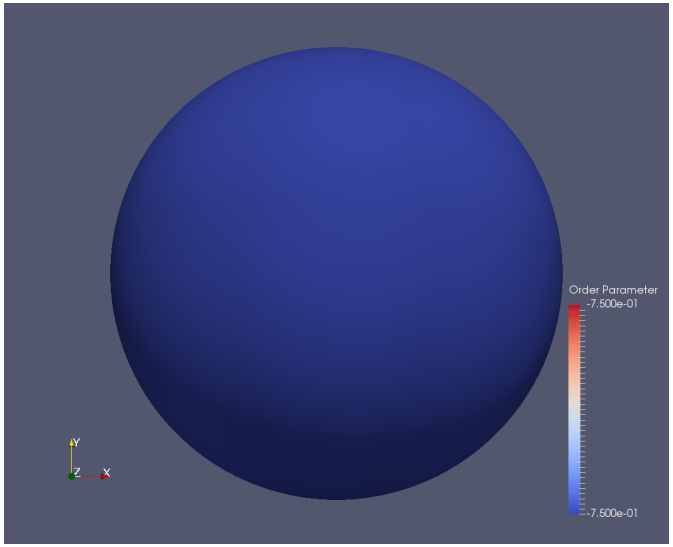
(a) $\phi_0 = \mathcal{R}$.



(b) $\phi_0 = -0.25 + \mathcal{R}$.



(c) $\phi_0 = -0.5 + \mathcal{R}$.



(d) $\phi_0 = -0.75 + \mathcal{R}$.

Almost stationary discrete solutions for varying values of ϕ

Particles on biomembranes: Outlook

Particle deformation

- Finite size particles treated as constraints on deformation and slope: general theory for flat domains
- Point particles treated as point Dirichlet constraints (hard and soft): general theory for flat and curved domains
- Point forces (maybe from filaments) treated as "Delta" measures

Particle interaction forces

- Finite size particles embedded in flat domains Graser and Kies (2017/18)
- Point particles on flat and curved surfaces thesis in progress Herbert
- Fluctuations and stochastic equations in progress

Receptor Ligand

- Coupled bulk surface semilinear equations
- Aysmptotic limits: Hele-Shaw/Stefan surface half Laplacian with Ranner and Venkataraman
- Existence on evolving domains with Alphonse and Terra
- Link to cell motility computational work with Stinner and Venkataraman

- Consider the following problem on the unit sphere, $\Gamma := \mathcal{S}^2(0,1)$, motivated by an application to biomembranes

$$\Delta_\Gamma^2 u + \Delta_\Gamma u - 2u = 8\pi\delta_N - 4x_3\log(1-x_3) - 4(1+3x_3), \ \Gamma \setminus \{X_i\}_{i=1}^{13}$$
$$u(X_i) = U(X_i) \quad \text{for } i = 1,...,13, \quad \int_\Gamma u = 0.$$

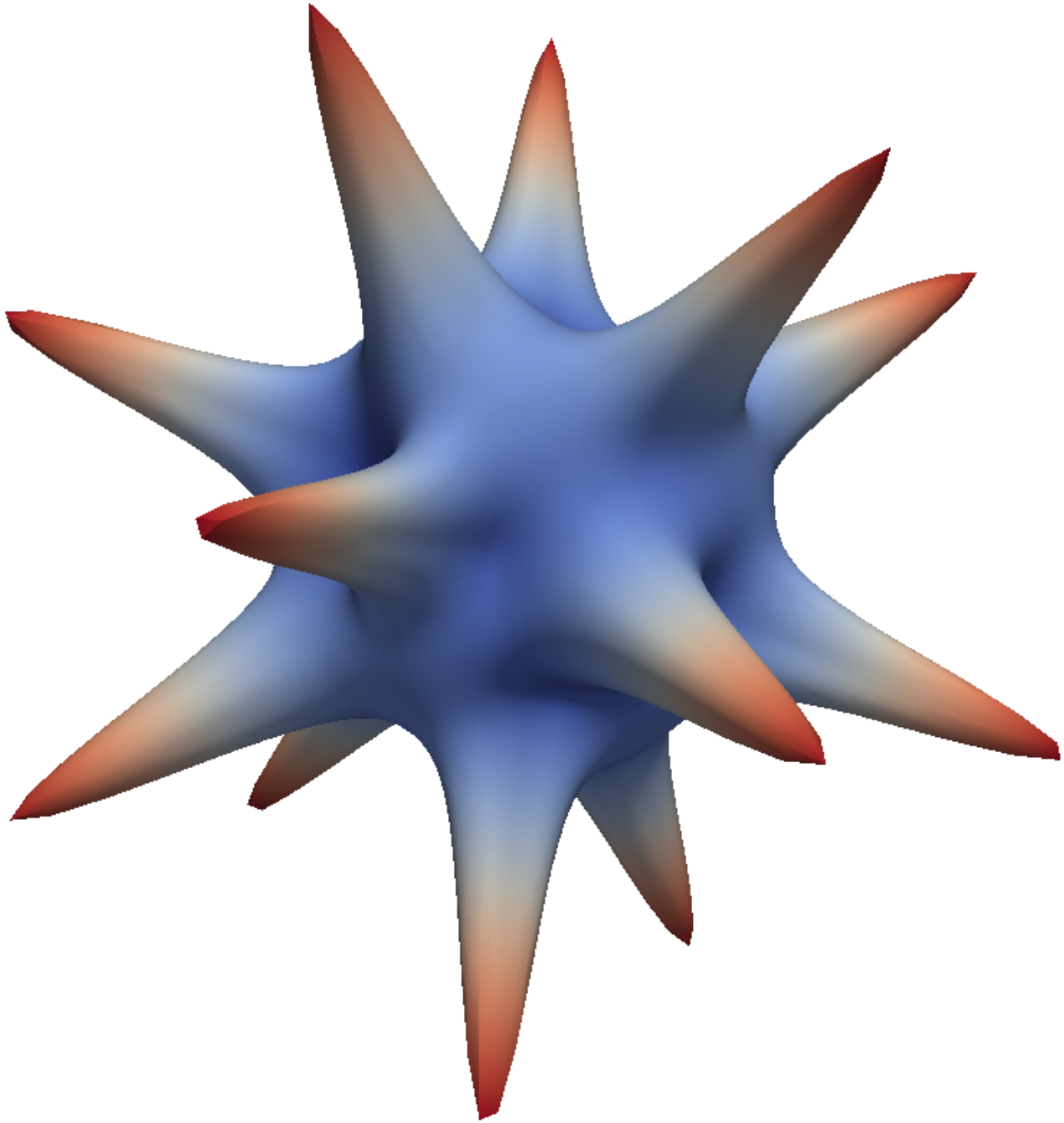
where

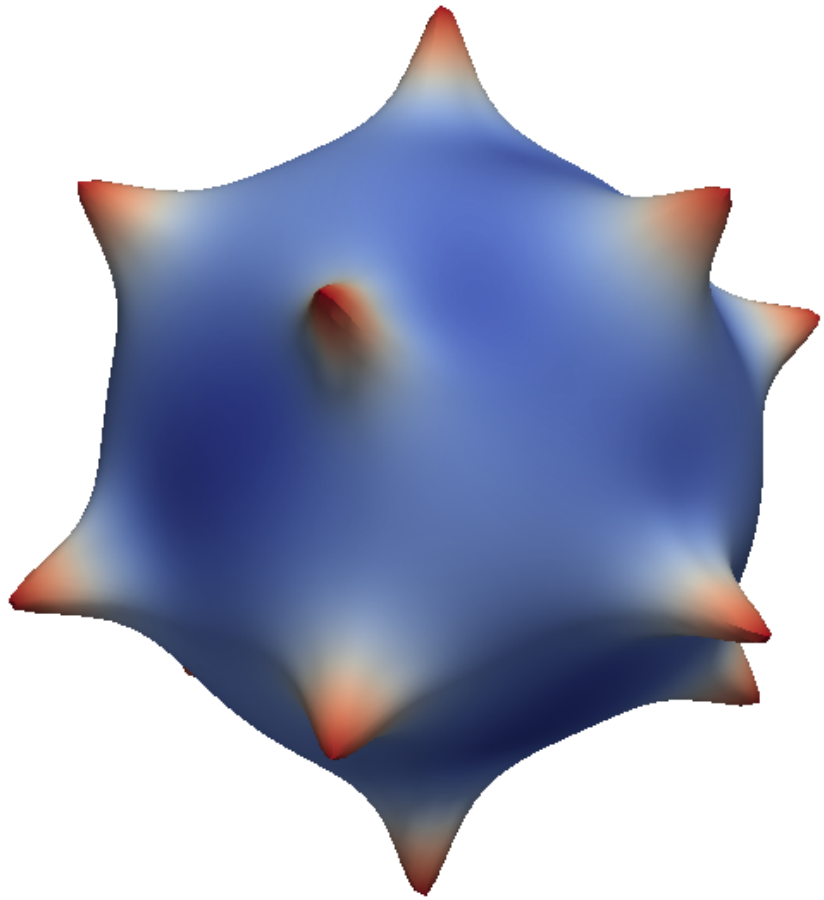
$$U(x) = (1-x_3)\log(1-x_3) - 2\pi(\log(4)-1).$$

We set $X_1 = (0,0,1)^T$ and X_i for $i = 2,...,13$ to be the remaining vertices of an icosahedron of unit radius.

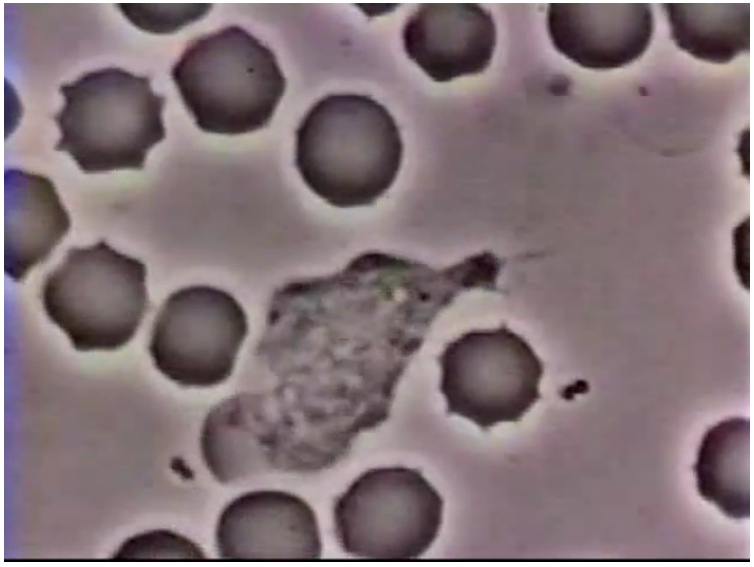
- An equivalent second order system is

$$-\Delta_\Gamma u + u - w = 0 \qquad \text{in } \Gamma,$$
$$u(X_i) = U(X_i) \text{ for } i = 1,...,13, \quad \int_\Gamma u = 0$$
$$3\Delta_\Gamma u - 2u - \Delta_\Gamma w + w = 8\pi\delta_N - 4x_3\log(1-x_3) - 4(1+3x_3) \qquad \text{in } \Gamma \setminus \{X_i\}_{i=1}^{13}.$$

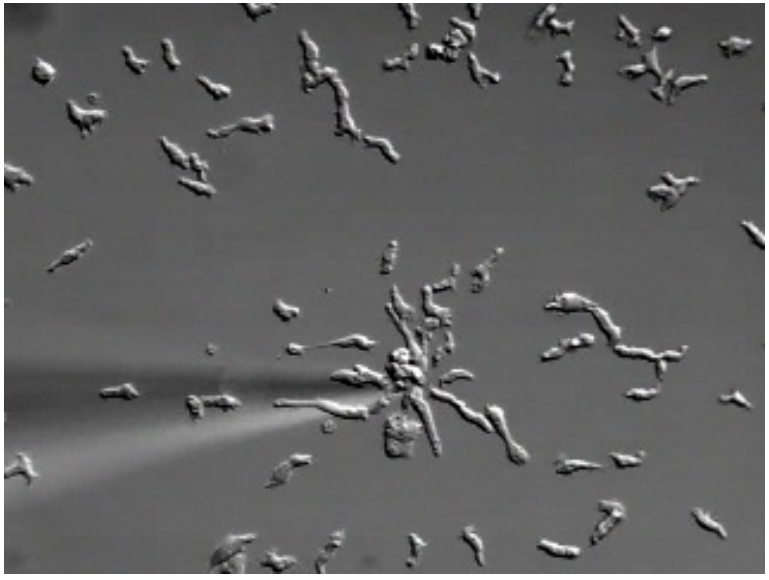




Chemotaxis

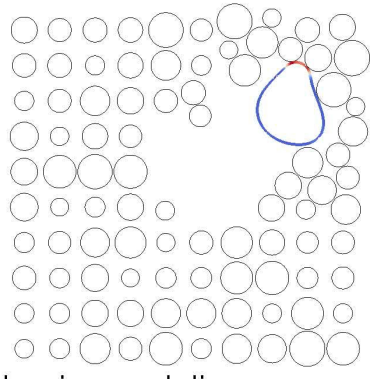


Neutrophil chasing a bacteria. Rogers Lab [1952]



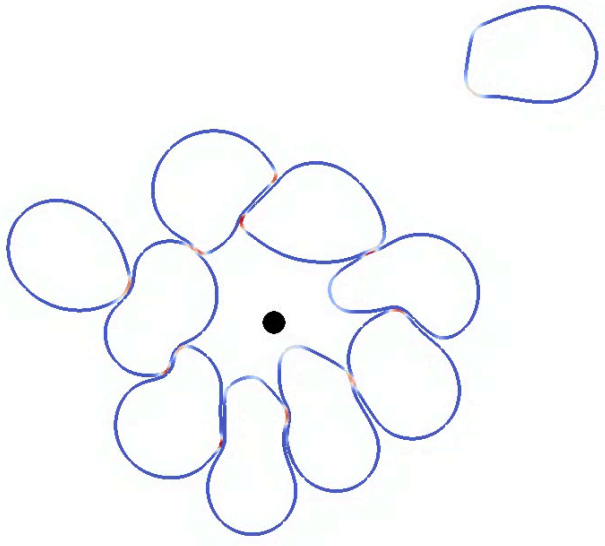
Multi cell chemotaxis. Firtel Lab.

Surface reaction diffusion and geometric evolution



Surface tension evolution

Simulation of chemotaxis in a field of obstacles : Roy. Soc. Interface [2012]Elliott, Stinner, Venkataraman



Simulation of multi-cell chemotaxis: Roy. Soc. Interface [2012] Elliott, Stinner, Venkataraman