Numerical simulation of endocytosis

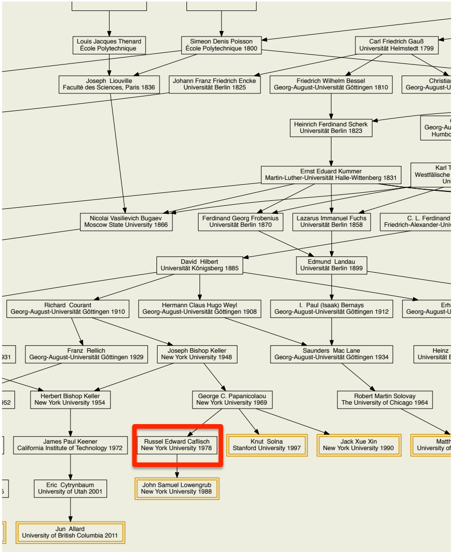
Diffuse interface models for membranes with curvature-inducing molecules

Sebastian Aland[1,2] Jun Allard[1] John Lowengrub (NYU PhD 1988) [2]

[1] Technische Universität Dresden, Germany
[2] University of California Irvine, USA

International Workshop on Multiscale Modeling and Simulation, UCLA, April 25, 2014
A 60^{th} birthday celebration for Russ Caflisch.

Mathematical genealogy



Mathematics Genealogy Project

Russel Edward Caflisch

MathSciNet

Ph.D. New York University 1978

Dissertation: *The Fluid Dynamic Limit and Shocks for a Model Boltzmann Equation*

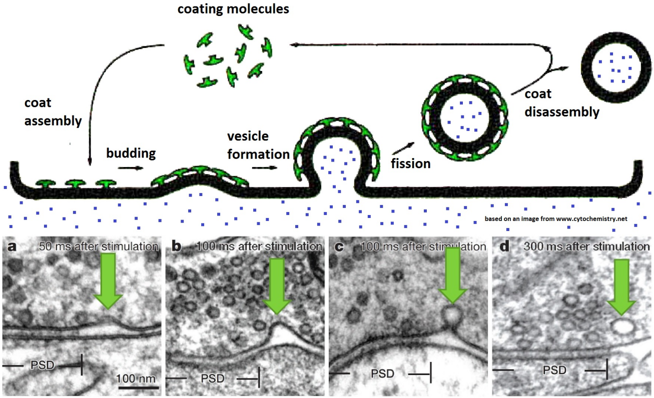
Advisor: George C. Papanicolaou

Students:

Name	School	Year	Descendants
Jonathan Luke	New York University	1986	1
Oscar Orellana	New York University	1987	
John Lowengrub	New York University	1988	14
Mahmoud Affouf	New York University	1989	
Michael Siegel	New York University	1989	2
Gabriella Puppo	New York University	1990	
Willliam Morokoff	New York University	1991	
Xiaofan Li	University of California, Los Angeles	1993	2
Bradley Moskowitz	University of California, Los Angeles	1993	
Hai Vu	University of California, Los Angeles	1993	
David Senouf	University of California, Los Angeles	1994	
Shin-Shin Kao	University of California, Los Angeles	1995	
Eliseo Chacon Vera	University of California, Los Angeles	1996	
Gregory Steele	University of California, Los Angeles	1996	
Frederic Gibou	University of California, Los Angeles	2001	
Suneal Chaudhary	University of California, Los Angeles	2004	
Youri Bae	University of California, Los Angeles	2005	
Pradeep Thivanaratnam	University of California, Los Angeles	2006	
Yang Wang	University of California, Los Angeles	2010	
Hem Wadhar	University of California, Los Angeles	2011	

According to our current on-line database, Russel Caflisch has 20 students and 42 descendants.

Curvature-mediated Endocytosis



Ultrafast endocytosis at mouse hippocampal synapses. From Watanabe et al. Nature 504, 242–247 (2014).

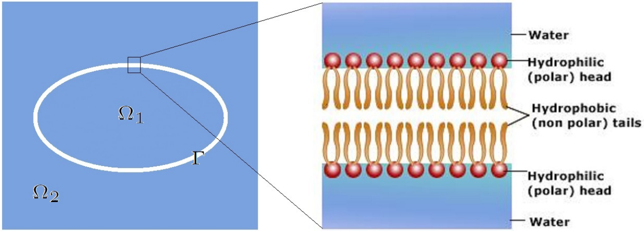
- central process for interaction of cells with their environment
- recent reports demonstrate that this process can happen ultrafast (ms)
- at these time scales hydrodynamics are important, they may limit the speed and influence distribution of membrane molecules and cargo

But how to model a membrane with curvature-inducing molecules in flow

?

1. Locally inextensible diffuse interface model
2. Including curvature-inducing membrane molecules
3. Numerical results
4. Summary

Biomembranes



Biomembranes in flow

- interface is a lipid bilayer
- lipids counteract bending $\Rightarrow$ bending stiffness force $\frac{\delta E}{\delta \Gamma}$

$$E[\Gamma] = \int_\Gamma \frac{b}{2}(H - H_0)^2 ds \qquad \text{(Helfrich energy)}$$

- lipids resist any compression/extension $\Rightarrow$ inextensibility:

$$\nabla_\Gamma \cdot \mathbf{v} = 0 \qquad \text{on } \Gamma$$

global area constraint

Define $\Omega = \Omega_1 \cup \Gamma \cup \Omega_2$.

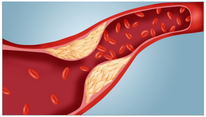
- inextensibility can be enforced globally instead of locally.
- the globally constrained model reads

$$\begin{aligned} \rho(\partial_t \mathbf{u} + \mathbf{u}\cdot\nabla\mathbf{u}) - \nu\Delta\mathbf{u} + \nabla p =& \frac{\delta E[\Gamma]}{\delta\Gamma}\delta_\Gamma + \lambda_{\text{global}} H\mathbf{n}\delta_\Gamma && \text{in } \Omega \\ \nabla\cdot\mathbf{u} =& 0 && \text{in } \Omega \\ \partial_t\Gamma =& \mathbf{u}_{|\Gamma} \end{aligned}$$

  where the global Lagrange multiplier λ_{global} is obtained by requiring

$$\frac{d}{dt}\int_\Gamma d\Gamma = \int_\Gamma H\mathbf{u}\cdot\mathbf{n}\, d\Gamma = 0$$

- leads to conserved membrane area, but can not prevent local membrane stretching/compression
- $\frac{\delta E}{\delta\Gamma} = -b\left(\Delta_\Gamma H + \frac{1}{2}H\left(H^2 - H_0^2\right)\right)\mathbf{n}$
- Inertia can be important in large/constricted blood vessels



local inextensibility constraint

- With local inextensibility constraints, the model reads:

$$\rho(\partial_t \mathbf{u} + \mathbf{u}\cdot\nabla\mathbf{u}) - \nu\Delta\mathbf{u} + \nabla p = \frac{\delta E[\Gamma]}{\delta\Gamma}\delta_\Gamma + \nabla\cdot(\delta_\Gamma \mathbf{P}\lambda) \quad \text{in } \Omega \qquad (1)$$

$$\nabla\cdot\mathbf{u} = 0 \quad \text{in } \Omega \qquad (2)$$

$$\partial_t\Gamma = \mathbf{u}_{|\Gamma}$$

- where the Lagrange multiplier force takes the form of a surface tension

$$\nabla\cdot(\delta_\Gamma\mathbf{P}\lambda) = \delta_\Gamma\nabla_\Gamma\lambda - \delta_\Gamma\mathbf{n}\lambda H$$

and is obtained by requiring

$$\mathbf{P}:\nabla\mathbf{u} = \nabla_\Gamma\cdot\mathbf{u} = 0 \qquad (3)$$

with the surface projection

$$\mathbf{P} = \mathbf{I} - \mathbf{n}\otimes\mathbf{n}; \qquad \mathbf{n} = \frac{\nabla\phi}{|\nabla\phi|}$$

But how to discretize the inextensible Navier-Stokes system (1),(2),(3) ?

local inextensibility constraint

- With local inextensibility constraints, the model reads:

$$\rho(\partial_t \mathbf{u} + \mathbf{u}\cdot\nabla\mathbf{u}) - \nu\Delta\mathbf{u} + \nabla p = \frac{\delta E[\Gamma]}{\delta\Gamma}\delta_\Gamma + \nabla\cdot(\delta_\Gamma \mathbf{P}\lambda) \qquad \text{in } \Omega \qquad (1)$$

$$\nabla\cdot\mathbf{u} = 0 \qquad \text{in } \Omega \qquad (2)$$

$$\partial_t\Gamma = \mathbf{u}_{|\Gamma}$$

- where the Lagrange multiplier force takes the form of a surface tension

$$\nabla\cdot(\delta_\Gamma\mathbf{P}\lambda) = \delta_\Gamma\nabla_\Gamma\lambda - \delta_\Gamma\mathbf{n}\lambda H$$

and is obtained by requiring

$$\mathbf{P}:\nabla\mathbf{u} = \nabla_\Gamma\cdot\mathbf{u} = 0 \qquad (3)$$

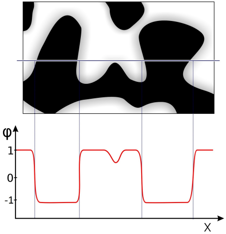
with the surface projection

$$\mathbf{P} = \mathbf{I} - \mathbf{n}\otimes\mathbf{n}; \qquad \mathbf{n} = \frac{\nabla\phi}{|\nabla\phi|}$$

But how to discretize the inextensible Navier-Stokes system (1),(2),(3) ?

Diffuse interface model

- Introduce a phase field ϕ to represent the fluid domains
- fixed interface thickness ϵ



Diffuse interface approximation of the bending energy [Du et al. Nonlin. 2005]:

$$E[\phi] \quad = \quad \int_{\Omega} \frac{\tilde{b}}{2\epsilon} \left(\epsilon \Delta \phi - \frac{1}{\epsilon} (\phi^2 - 1)(\phi + H_0) \right)^2 d\Omega.$$

Interface given by

$$\Gamma = \{x | \phi(x) = 0\}$$

Matched asymptotic expansion shows formal convergence

$$E[\phi] \to E[\Gamma] \qquad \text{for } \epsilon \to 0$$

.

Diffuse interface model

The diffuse interface Navier-Stokes equation with global constraints (model A) [Du& Wang, JCP, 2006]

$$\rho(\partial_t \mathbf{u} + \mathbf{u}\cdot\nabla\mathbf{u}) - \nu\Delta\mathbf{u} + \nabla p = \frac{\delta E[\phi]}{\delta\phi}\nabla\phi - \lambda_{\text{global}} f\nabla\phi - \lambda_{\text{volume}}\nabla\phi \qquad \text{in } \Omega$$

$$\nabla\cdot\mathbf{u} = 0 \qquad \text{in } \Omega$$

Advected diffuse Willmore-flow equation to advect the interface

$$\partial_t\phi + \mathbf{u}\cdot\nabla\phi = -\eta\left(\frac{\delta E}{\delta\phi} - \lambda_{\text{global}} f - \lambda_{\text{volume}}\right)$$

$$\frac{\delta E}{\delta\phi} = \left(\Delta(\tilde{b}f) - \frac{1}{\epsilon^2}(3\phi^2 + 2H_0\phi - 1)\tilde{b}f\right)$$

$$f = \epsilon\Delta\phi - \frac{1}{\epsilon}(\phi^2 - 1)(\phi + H_0)$$

where the global Lagrange multipliers $\lambda_{\text{global}}, \lambda_{\text{volume}}$ are obtained by requiring

$$\frac{d}{dt}\mathcal{V}(\phi) = \frac{d}{dt}\int_\Omega \frac{1}{2}(\phi+1)\, d\Omega = 0 \qquad \text{(volume constraint)}$$

$$\frac{d}{dt}\mathcal{A}(\phi) = \frac{d}{dt}\int_\Omega \frac{\epsilon}{2}|\nabla\phi|^2 + \frac{1}{4\epsilon}(\phi^2-1)^2\, d\Omega = 0. \qquad \text{(global area constraint)}$$

- membrane surface area is conserved, but local membrane stretching/compression still allowed

Diffuse interface model

The diffuse interface Navier-Stokes equation with global constraints (model A) [Du& Wang, JCP, 2006]

$$\rho(\partial_t \mathbf{u} + \mathbf{u}\cdot\nabla\mathbf{u}) - \nu\Delta\mathbf{u} + \nabla p = \frac{\delta E[\phi]}{\delta\phi}\nabla\phi - \lambda_{\text{global}} f \nabla\phi - \lambda_{\text{volume}}\nabla\phi \qquad \text{in } \Omega$$

$$\nabla\cdot\mathbf{u} = 0 \qquad \text{in } \Omega$$

Advected diffuse Willmore-flow equation to advect the interface

$$\partial_t\phi + \mathbf{u}\cdot\nabla\phi = -\eta\left(\frac{\delta E}{\delta\phi} - \lambda_{\text{global}} f - \lambda_{\text{volume}}\right)$$

$$\frac{\delta E}{\delta\phi} = \left(\Delta(\tilde{b}f) - \frac{1}{\epsilon^2}(3\phi^2 + 2H_0\phi - 1)\tilde{b}f\right)$$

$$f = \epsilon\Delta\phi - \frac{1}{\epsilon}(\phi^2 - 1)(\phi + H_0)$$

where the global Lagrange multipliers $\lambda_{\text{global}}, \lambda_{\text{volume}}$ are obtained by requiring

$$\frac{d}{dt}\mathcal{V}(\phi) = \frac{d}{dt}\int_\Omega \frac{1}{2}(\phi+1)\, d\Omega = 0 \qquad \text{(volume constraint)}$$

$$\frac{d}{dt}\mathcal{A}(\phi) = \frac{d}{dt}\int_\Omega \frac{\epsilon}{2}|\nabla\phi|^2 + \frac{1}{4\epsilon}(\phi^2-1)^2\, d\Omega = 0. \qquad \text{(global area constraint)}$$

- membrane surface area is conserved, but local membrane stretching/compression still allowed

1 Locally inextensible diffuse interface model

2 Including curvature-inducing membrane molecules

3 Numerical results

4 Summary

Diffuse interface model

Adding a local constraint, the diffuse interface model becomes (model B)
[Aland et al. (2014), J. Comput. Phys., in review. arXiv:1311.6558]

$$
\begin{aligned}
\rho(\partial_t \mathbf{u} + \mathbf{u}\cdot\nabla\mathbf{u}) - \nu\Delta\mathbf{u} + \nabla p =& \frac{\delta E[\phi]}{\delta\phi}\nabla\phi - \lambda_{\text{global}} f \nabla\phi - \lambda_{\text{volume}}\nabla\phi \\
& + \nabla\cdot(|\nabla\phi|\mathbf{P}\lambda) && \text{in } \Omega \\
\nabla\cdot\mathbf{u} =& 0 && \text{in } \Omega \\
\epsilon^2\nabla\cdot(\phi^2\nabla\lambda) + |\nabla\phi|\mathbf{P}:\nabla\mathbf{u} =& 0 && \text{in } \Omega \qquad (4)
\end{aligned}
$$

Advected diffuse Willmore-flow equation to advect the interface

$$
\begin{aligned}
\partial_t\phi + \mathbf{u}\cdot\nabla\phi &= -\eta\left(\frac{\delta E}{\delta\phi} - \lambda_{\text{global}} f - \lambda_{\text{volume}}\right) \\
\frac{\delta E}{\delta\phi} &= \left(\Delta(\tilde{b} f) - \frac{1}{\epsilon^2}(3\phi^2 + 2H_0\phi - 1)\tilde{b} f\right) \\
f &= \epsilon\Delta\phi - \frac{1}{\epsilon}(\phi^2 - 1)(\phi + H_0)
\end{aligned}
$$

- matched asymptotic analysis shows convergence of (4) to inextensibility constraint $\mathbf{P}:\nabla\mathbf{u} = 0$ on Γ and $\nabla\cdot(|\nabla\phi|\mathbf{P}\lambda) \to \nabla\cdot(\delta_\Gamma\mathbf{P}\lambda)$ for $\epsilon \to 0$

Diffuse interface model

Adding a local constraint, the diffuse interface model becomes (model B)
[Aland et al. (2014), J. Comput. Phys., in review. arXiv:1311.6558]

$$\begin{aligned}
\rho(\partial_t \mathbf{u} + \mathbf{u}\cdot\nabla\mathbf{u}) - \nu\Delta\mathbf{u} + \nabla p =& \frac{\delta E[\phi]}{\delta\phi}\nabla\phi - \lambda_{\text{global}} f\nabla\phi - \lambda_{\text{volume}}\nabla\phi \\
&+ \nabla\cdot(|\nabla\phi|\mathbf{P}\lambda) && \text{in } \Omega \\
\nabla\cdot\mathbf{u} =& 0 && \text{in } \Omega \\
\epsilon^2\nabla\cdot(\phi^2\nabla\lambda) + |\nabla\phi|\mathbf{P}:\nabla\mathbf{u} =& 0 && \text{in } \Omega
\end{aligned} \tag{4}$$

Advected diffuse Willmore-flow equation to advect the interface

$$\partial_t\phi + \mathbf{u}\cdot\nabla\phi = -\eta\left(\frac{\delta E}{\delta\phi} - \lambda_{\text{global}} f - \lambda_{\text{volume}}\right)$$

$$\frac{\delta E}{\delta\phi} = \left(\Delta(\tilde{b}f) - \frac{1}{\epsilon^2}(3\phi^2 + 2H_0\phi - 1)\tilde{b}f\right)$$

$$f = \epsilon\Delta\phi - \frac{1}{\epsilon}(\phi^2 - 1)(\phi + H_0)$$

- matched asymptotic analysis shows convergence of (4) to inextensibility constraint $\mathbf{P}:\nabla\mathbf{u} = 0$ on Γ and $\nabla\cdot(|\nabla\phi|\mathbf{P}\lambda) \to \nabla\cdot(\delta_\Gamma\mathbf{P}\lambda)$ for $\epsilon \to 0$

Correction of cumulated errors: Relaxation

Over time small errors in inextensibility may accumulate and lead to local membrane stretching
The following mechanism corrects accumulated errors and drives the system back to the relaxed state

- introduce a variable c to measure local stretching of the interface, initially $c(\mathbf{x},\mathbf{0}) = \mathbf{1}$, evolved by

$$\partial_t c + \mathbf{v} \cdot \nabla c + c \nabla_\Gamma \cdot \mathbf{v} = 0 \qquad \text{on } \Gamma, \tag{5}$$

- locations where c deviates from 1 represent regions of compression ($c > 1$) and stretching ($c < 1$)
- Hookes law gives strength of relaxation proportional to amount of local stretching:

$$P : \nabla \mathbf{u} = \zeta(c-1)/c \qquad \text{on } \Gamma$$

- or in diffuse domain form:

$$\epsilon^2 \nabla \cdot (\phi^2 \nabla \lambda) + |\nabla \phi| \mathbf{P} : \nabla \mathbf{u} = \zeta \frac{c-1}{c} |\nabla \phi| \qquad \text{in } \Omega \tag{6}$$

$\Rightarrow$ Model C

Correction of cumulated errors: Relaxation

To stabilize the interfacial advection equation

$$\partial_t c + \mathbf{v} \cdot \nabla c + c \nabla_\Gamma \cdot \mathbf{v} \;=\; 0 \qquad \text{on } \Gamma,$$

we add some small diffusion along the interface

$$\partial_t c + \mathbf{v} \cdot \nabla c + c \nabla_\Gamma \cdot \mathbf{v} - d_T \Delta_\Gamma c \;=\; 0 \qquad \text{on } \Gamma. \tag{7}$$

To discretize the equation it is extended off Γ using the diffuse domain approach [Rätz&Voigt, Comm.Math.Sci., (2006)]

$$\partial_t(|\nabla \phi| c) + \nabla \cdot (|\nabla \phi| \mathbf{v} c) - d_T \nabla(|\nabla \phi| \nabla c) \;=\; 0 \qquad \text{on } \Gamma.$$

Additionally diffusion in normal direction can be added to extend c constant in normal direction off Γ

$$\partial_t(|\nabla \phi| c) + \nabla \cdot (|\nabla \phi| \mathbf{v} c) - d_T \nabla(|\nabla \phi| \nabla c) - d_N \nabla(|\nabla \phi| \mathbf{n}\mathbf{n} \cdot \nabla c) \;=\; 0 \qquad \text{on } \Gamma.$$

- matched asymptotic expansion shows convergence to (7) for $\epsilon \to 0$
- conservation of c along the interface is ensured: $\int_\Omega |\nabla \phi| c = \text{const.}$, even on the discrete level

Governing Equations

Model A: standard model, only global inextensibility

Navier-Stokes equation to obtain the velocity

$$\begin{aligned}\rho(\partial_t \mathbf{u} + \mathbf{u}\cdot\nabla\mathbf{u}) - \nu\Delta\mathbf{u} + \nabla p =& \frac{\delta E[\phi]}{\delta\phi}\nabla\phi \\ & - \lambda_{\text{global}} f \nabla\phi - \lambda_{\text{volume}}\nabla\phi \\ \nabla\cdot\mathbf{u} =& 0\end{aligned}$$

Advected diffuse Willmore-flow equation to advect the interface

$$\partial_t\phi + \mathbf{u}\cdot\nabla\phi = -\eta\left(\frac{\delta E}{\delta\phi} - \lambda_{\text{global}} f - \lambda_{\text{volume}}\right)$$

$$\frac{\delta E}{\delta\phi} = \left(\Delta(\tilde{b}f) - \frac{1}{\epsilon^2}(3\phi^2 + 2H_0\phi - 1)\tilde{b}f\right)$$

$$f = \epsilon\Delta\phi - \frac{1}{\epsilon}(\phi^2 - 1)(\phi + H_0)$$

Governing Equations

Model B: with instantaneous local inextensibility

Navier-Stokes equation to obtain the velocity

$$\begin{aligned}\rho(\partial_t \mathbf{u} + \mathbf{u}\cdot\nabla\mathbf{u}) - \nu\Delta\mathbf{u} + \nabla p =& \frac{\delta E[\phi]}{\delta\phi}\nabla\phi \\ & - \lambda_{\text{global}} f \nabla\phi - \lambda_{\text{volume}}\nabla\phi + \nabla\cdot(|\nabla\phi|\mathbf{P}\lambda) \\ \nabla\cdot\mathbf{u} =& 0 \\ \epsilon^2\nabla\cdot(\phi^2\nabla\lambda) + |\nabla\phi|\mathbf{P}:\nabla\mathbf{u} =& 0\end{aligned}$$

Advected diffuse Willmore-flow equation to advect the interface

$$\partial_t\phi + \mathbf{u}\cdot\nabla\phi = -\eta\left(\frac{\delta E}{\delta\phi} - \lambda_{\text{global}} f - \lambda_{\text{volume}}\right)$$

$$\frac{\delta E}{\delta\phi} = \left(\Delta(\tilde{b}f) - \frac{1}{\epsilon^2}(3\phi^2 + 2H_0\phi - 1)\tilde{b}f\right)$$

$$f = \epsilon\Delta\phi - \frac{1}{\epsilon}(\phi^2 - 1)(\phi + H_0)$$

Governing Equations

Model C: with instantaneous local inextensibility and relaxation

Navier-Stokes equation to obtain the velocity

$$\begin{aligned}\rho(\partial_t \mathbf{u} + \mathbf{u}\cdot\nabla\mathbf{u}) - \nu\Delta\mathbf{u} + \nabla p =& \frac{dE[\phi]}{d\phi}\nabla\phi \\ & - \lambda_{\text{global}} f \nabla\phi - \lambda_{\text{volume}}\nabla\phi + \nabla\cdot(|\nabla\phi|\mathbf{P}\lambda) \\ \nabla\cdot\mathbf{u} =& 0 \\ \epsilon^2\nabla\cdot(\phi^2\nabla\lambda) + |\nabla\phi|\mathbf{P}:\nabla\mathbf{u} =& \zeta\frac{c-1}{c}|\nabla\phi|\end{aligned}$$

Advected diffuse Willmore-flow equation to advect the interface

$$\partial_t\phi + \mathbf{u}\cdot\nabla\phi = -\eta\left(\frac{\delta E}{\delta\phi} - \lambda_{\text{global}} f - \lambda_{\text{volume}}\right)$$

$$\frac{\delta E}{\delta\phi} = \left(\Delta(\tilde{b}f) - \frac{1}{\epsilon^2}(3\phi^2 + 2H_0\phi - 1)\tilde{b}f\right)$$

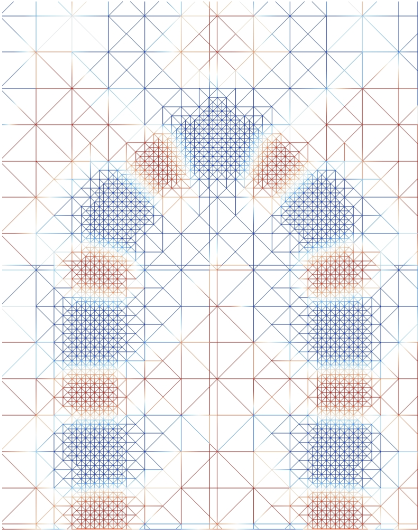
$$f = \epsilon\Delta\phi - \frac{1}{\epsilon}(\phi^2 - 1)(\phi + H_0)$$

An advection equation for the stretching measure c on the interface

$$\partial_t(|\nabla\phi|c) + \nabla\cdot(|\nabla\phi|\mathbf{u}c) - d_T\nabla\cdot(|\nabla\phi|\nabla c) - d_N\nabla\cdot(|\nabla\phi|\mathbf{n}\otimes\mathbf{n}\cdot\nabla c) = 0$$

Numerical treatment

- C++ FEM library AMDiS
- adaptive mesh
- 2D implementation
- P2 elements except for P1 for pressure
- direct solver: UMFPACK
- semi-implicit time discretization
- linearization by first order Taylor expansion
- remove stiffness due to bending forces using monolithic, implicit solvers (energy-stable-like)



Test scenario

We use a vesicle in shear flow to validate the model and investigate the influence of local inextensibility.

- Experimental results: Flow strength determines behavior: Tank treading (steady shape); Tumbling (non-steady rotating); Trembling (non-steady, non-rotating)

Test scenario

Numerical simulation of a vesicle in shear flow

- Re=1/200
- Be=20
- $H_0 = 0$
- viscosity ratio: 10

Convergence I

$$E_{\mathbf{v}} = \int_{\Omega} \epsilon^{-1}(1-\phi^2)^2 |\nabla_{\Gamma} \cdot \mathbf{v}| \approx \int_{\Gamma} |\nabla_{\Gamma} \cdot \mathbf{v}| \qquad \text{(instantaneous stretching)},$$

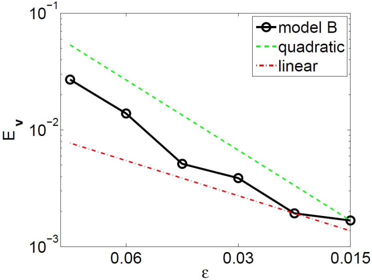
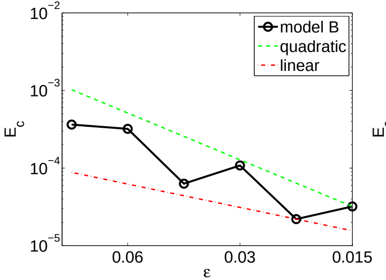


Figure: Convergence study showing super-linear decrease of the instantaneous stretching $E_{\mathbf{v}}$ as a function of the interface thickness ϵ for model B.

Convergence II

$$E_c = \int_\Omega \epsilon^{-1}(1-\phi^2)^2 |(c-1)/c| \approx \int_\Gamma |(c-1)/c| \qquad \text{(accumulated stretching).}$$



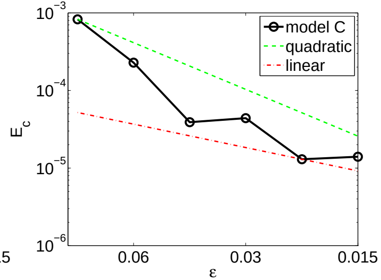


Figure: Convergence study showing super-linear decrease of E_c for decreasing ϵ, for models B (left) and C (right).

Model Comparison I

Model comparison of the time evolution of a vesicle in shear flow

model A model B model C

- different time evolutions, although the vesicle shapes look identical
- inextensibility in models B and C delays tumbling significantly

Model Comparison II

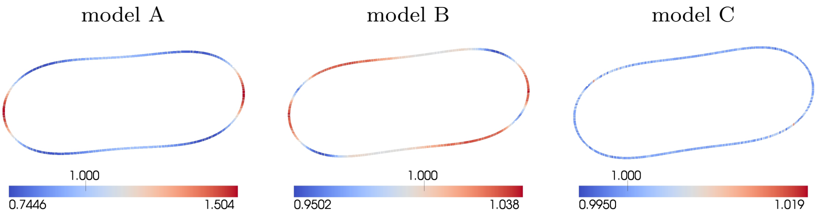


Figure: The value of c along the vesicle interfaces for the different models at time $t = 1$.

.

- model A shows strong compression at the tips, stretching at the sides
- model B suppresses local stretching/compression significantly
- model C shows no local stretching/compression

Model Comparison III

$$E_c = \int_\Omega \epsilon^{-1}(1-\phi^2)^2 |(c-1)/c| \approx \int_\Gamma |(c-1)/c| \qquad \text{(accumulated stretching).}$$

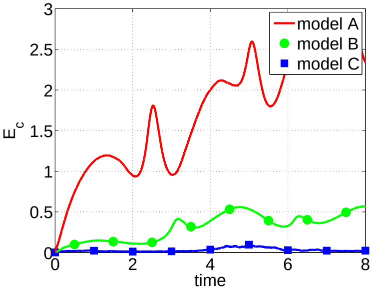


Figure: Comparison of accumulated stretching E_c for Models A (red), B (green) and C (blue)

Effect of inertia

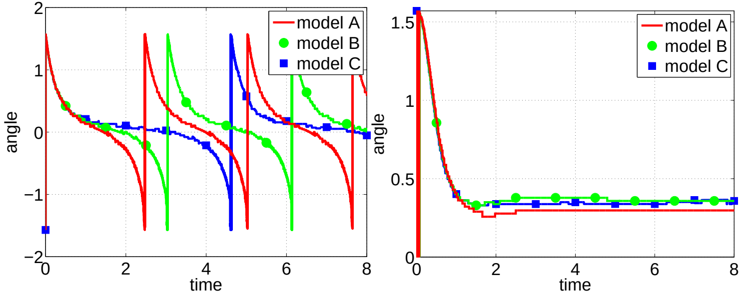


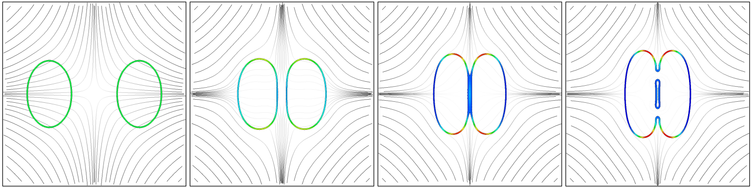
Figure: Model comparison of the inclination angle for $Re = 1/200$ (left). and $Re = 1$ (right).

- Inertia suppresses tumbling.
  (see also Salac & Miksis (2012); Laadhari et al. (2012); Kim & Lai (2012),..).

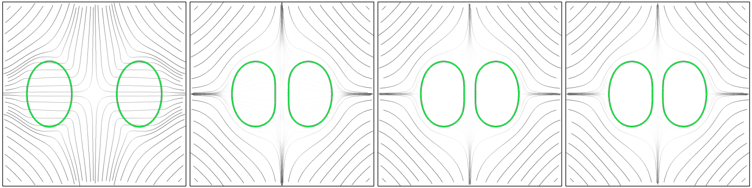
Interactions

Consider 2 vesicles in extensional flow

model A



model B / model C



1 Locally inextensible diffuse interface model

2 Including curvature-inducing membrane molecules

3 Numerical results

4 Summary

Bending energy including membrane molecules and flow

- Let $\Gamma_s \subset \Gamma$ be the molecule-covered part of the membrane.

  The total bending energy is

$$E = \underbrace{\int_{\Gamma_s} \frac{1}{2} b_s \left(H - H_0\right)^2 \ dA}_{\text{molecule bending}} + \underbrace{\int_{\Gamma} \frac{1}{2} b_m H^2 \ dA}_{\text{membrane bending}} + \underbrace{\int_{\Omega_1 \cup \Omega_2} \frac{\rho}{2} |\mathbf{u}|^2 dx}_{\text{kinetic energy}}, \qquad (8)$$

  where b_s and b_m are bending moduli of molecule and clean membrane, respectively.

- Introduce species concentration $s(x,t)$ to keep track of Γ_s, where $s = 1$ denotes complete coverage. Hence,

$$E = \int_{\Gamma} \frac{1}{2} b(s) \left(H - H_0(s)\right)^2 + \text{Polynomial}(s) \ dA \qquad (9)$$

- Inextensibility and pure advection of s allow to drop the last term
- Different choices for $b(s)$ and $H(s)$ possible

$$b(s) = (b_s - b_m) \cdot s + b_m \qquad H_0(s) = H_0 \cdot s$$

$$b(s) = \frac{(b_s + b_m) b_m}{(b_s + b_m) - s b_s} \qquad H_0(s) = H_0 \frac{b_s}{b_s + b_m} s$$

Energy variation

- Vary the energy by taking the time derivative

$$d_t E = \int_\Gamma b(s)\left(H - H_0(s)\right)\left(d_t H + \mathbf{n}\cdot\nabla H\ \mathbf{u}\cdot\mathbf{n}\right) + \frac{b(s)}{2}\left(H - H_0(s)\right)^2 H\mathbf{u}\cdot\mathbf{n}$$
$$+ \frac{\partial E}{\partial s} d_t s\ dA + \int_{\Omega_1\cup\Omega_2} \rho d_t\mathbf{u}\cdot\mathbf{u}\ dx$$

where

$$\frac{\partial E}{\partial s} = \frac{1}{2} b'(s)(H - H_0(s))^2 - b(s)(H - H_0(s))H_0'(s)$$

- Assume the following balance laws for momentum and mass conservation:

$$\begin{aligned}
\rho(\partial_t\mathbf{u} + \mathbf{u}\cdot\nabla\mathbf{u}) - \nabla\cdot(\nu\mathbf{D}) + \nabla p &= 0 \quad \text{in } \Omega_1\cup\Omega_2 && \text{(Navier-Stokes)}\\
\nabla\cdot\mathbf{u} &= 0 \quad \text{in } \Omega_1\cup\Omega_2 && \text{(incompressibility)}\\
\nabla_\Gamma\cdot\mathbf{u} &= 0 \quad \text{on } \Gamma && \text{(inextensibility)}\\
\partial_t s + \mathbf{u}\cdot\nabla s &= 0 \quad \text{on } \Gamma && \text{(species advection)}
\end{aligned}$$

where $\mathbf{D} = \nabla\mathbf{u} + \nabla\mathbf{u}^T$.

- Additionally assume the jump conditions for velocity and flow stress tensor

$$[-p\mathbf{I} + \nu\mathbf{D}]_1^2\cdot\mathbf{n} = \mathbf{F} + \nabla_\Gamma\lambda - H\mathbf{n}\lambda$$

- where $\mathbf{F}$ is yet unspecified interface force

Energy variation

- plugging in balance laws and jump conditions into the energy time derivative, eventually leads to

$$
\begin{aligned}
d_t E = \int_\Gamma & - \Delta_\Gamma \left(b(s)(H - H_0(s)) \right) \mathbf{u} \cdot \mathbf{n} - b(s)(H - H_0(s)) \|\nabla_\Gamma \mathbf{n}\|^2 \mathbf{u} \cdot \mathbf{n} \\
& + \frac{b(s)}{2} \left(H - H_0(s) \right)^2 H \mathbf{u} \cdot \mathbf{n} - \frac{\partial E}{\partial s} \nabla s \cdot \mathbf{u} + \mathbf{u} \cdot \mathbf{F} \, dA \\
& - \int_{\Omega_1 \cup \Omega_2} \frac{\nu}{2} |\mathbf{D}|^2 \, dx
\end{aligned}
$$

- 2^{nd} law of thermodynamics requires the surface intergral to vanish, hence the choice

$$
\begin{aligned}
\mathbf{F} = & \Delta_\Gamma \left(b(s)(H - H_0(s)) \right) \mathbf{n} + b(s)(H - H_0(s)) \|\nabla_\Gamma \mathbf{n}\|^2 \mathbf{n} \\
& - \frac{b(s)}{2} \left(H - H_0(s) \right)^2 H \mathbf{n} + \frac{\partial E}{\partial s} \nabla s
\end{aligned}
$$

gives decreasing energy

$$
- \int_{\Omega_1 \cup \Omega_2} \frac{\nu}{2} |\mathbf{D}|^2 \, dx
$$

sharp interface model

- We obtain the sharp interface model

$$
\begin{aligned}
\rho(\partial_t \mathbf{u} + \mathbf{u}\cdot\nabla\mathbf{u}) - \nabla\cdot(\nu\mathbf{D}) + \nabla p =& 0 \quad \text{in } \Omega_1 \cup \Omega_2 && \text{(Navier-Stokes)}\\
\nabla\cdot\mathbf{u} =& 0 \quad \text{in } \Omega_1 \cup \Omega_2 && \text{(incompressibility)}\\
\nabla_\Gamma\cdot\mathbf{u} =& 0 \quad \text{on } \Gamma && \text{(inextensibility)}\\
\partial_t s + \mathbf{u}\cdot\nabla s =& 0 \quad \text{on } \Gamma && \text{(species advection)}\\
\partial_t \Gamma =& \mathbf{n}\cdot\mathbf{u}_{|\Gamma} && \text{(interface advection)}
\end{aligned}
$$

$$
\begin{aligned}
[-p\mathbf{I} + \nu\mathbf{D}]\cdot\mathbf{n} = \nabla_\Gamma\lambda - H\mathbf{n}\lambda + \Delta_\Gamma\left(b(s)(H - H_0(s))\right)\mathbf{n} && \text{(jump condition)}\\
+ b(s)(H - H_0(s))\|\nabla_\Gamma\mathbf{n}\|^2\mathbf{n}\\
- \frac{b(s)}{2}\left(H - H_0(s)\right)^2 H\mathbf{n} + \frac{\partial E}{\partial s}\nabla s
\end{aligned}
$$

Diffuse energy variation

- start with the energy

$$E = \int_\Omega \frac{1}{2\epsilon}\tilde{b}(s)\left(\epsilon\Delta\phi - \frac{1}{\epsilon}(\phi^2-1)(\phi+\sqrt{2}\epsilon H_0(s))\right)^2 + \frac{1}{2}\rho|\mathbf{u}|^2 \, dx$$

- and assume similar balance laws

$$\rho(\partial_t\mathbf{u} + \mathbf{u}\cdot\nabla\mathbf{u}) - \nabla\cdot(\nu\mathbf{D}) + \nabla p = \nabla\cdot(|\nabla\phi|\mathbf{P}\lambda) + \mathbf{F} \quad (10)$$

$$\nabla\cdot\mathbf{u} = 0 \quad (11)$$

$$\xi\epsilon^2\nabla\cdot(\phi^2\nabla\lambda) + |\nabla\phi|\mathbf{P}:\nabla\mathbf{u} = 0 \quad (12)$$

$$\partial_t s + \mathbf{u}\cdot\nabla s = 0 \quad \text{in } \Omega \quad (13)$$

$$\partial_t\phi + \mathbf{u}\cdot\nabla\phi = -\gamma g \quad \text{in } \Omega \quad (14)$$

  where $\mathbf{F}$ is yet unspecified interface force, g is an unspecified source

- plug in balance laws into the energy time derivative to obtain $\mathbf{F}$ and g

Diffuse interface model for molecule-covered membrane

A locally inextensible Navier-Stokes equation to obtain the velocity

$$\rho(\partial_t \mathbf{u} + \mathbf{u}\cdot\nabla\mathbf{u}) - \nu\Delta\mathbf{u} + \nabla p = \frac{\delta E}{\delta\phi}\nabla\phi + \nabla\cdot(|\nabla\phi|\mathbf{P}\lambda) + \frac{\delta E}{\delta s}\nabla s$$

$$\nabla\cdot\mathbf{u} = 0$$

$$\epsilon^2\nabla\cdot(\phi^2\nabla\lambda) + |\nabla\phi|\mathbf{P}:\nabla\mathbf{u} = \zeta\frac{c-1}{c}|\nabla\phi|$$

A diffuse Willmore-flow equation to advect the interface

$$\partial_t\phi + \mathbf{u}\cdot\nabla\phi = -\eta\frac{\delta E}{\delta\phi}$$

$$\frac{\delta E}{\delta\phi} = \left(\Delta(bf) - \frac{1}{\epsilon^2}(3\phi^2 + 2H_0\phi - 1)bf\right)$$

$$f = \epsilon\Delta\phi - \frac{1}{\epsilon}(\phi^2 - 1)(\phi + H_0)$$

Instead of pure advection, we use an interfacial Cahn-Hilliard equation for the molecule concentration

$$\partial_t(|\nabla\phi|s) + \nabla\cdot(|\nabla\phi|\mathbf{u}s) - d_T\nabla\cdot(|\nabla\phi|\nabla\mu) - d_N\nabla\cdot(|\nabla\phi|\mathbf{n}\otimes\mathbf{n}\cdot\nabla\mu) = 0$$

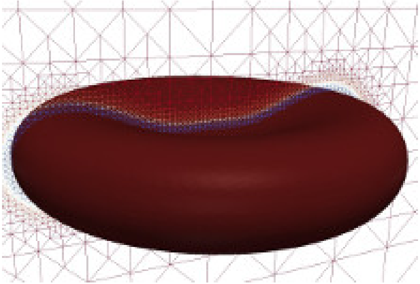
$$|\nabla\phi|\mu + \epsilon\nabla\cdot(|\nabla\phi|\nabla s) - \epsilon^{-1}|\nabla\phi|(4s^3 - 6s^2 + 2s) = 0$$

An interfacial advection equation for the stretching measure c

$$\partial_t(|\nabla\phi|c) + \nabla\cdot(|\nabla\phi|\mathbf{u}c) - d_T\nabla\cdot(|\nabla\phi|\nabla c) - d_N\nabla\cdot(|\nabla\phi|\mathbf{n}\otimes\mathbf{n}\cdot\nabla c) = 0$$

Numerical treatment

- C++ FEM library AMDiS
- adaptive mesh
- axisymmetric implementation
- P2 elements except for P1 for pressure
- direct solver: UMFPACK
- semi-implicit time discretization
- linearization by first order Taylor expansion
- non-stiff, implicit implementation



1 Locally inextensible diffuse interface model

2 Including curvature-inducing membrane molecules

3 Numerical results

4 Summary

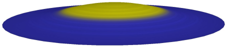
Clathrin-mediated endocytosis

Clathrin

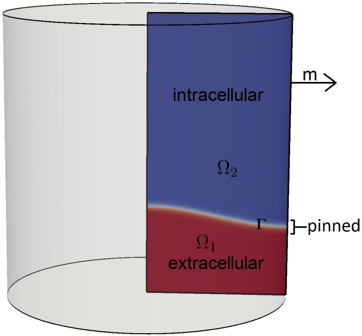
- prototype of a curvature-inducing molecule
- $b_c = 12 b_m$
- $H_0 = (14nm)^{-1}$

Test setup

- initially flat membrane with circular clathrin-covered region



- axisymmetric equations
- free stress BC for velocity
- membrane pinned at the outer boundary at 90° angle



Clathrin-mediated endocytosis: first results

radius of clathrin region: 20nm

- spontaneous curvature of clathrin induces budding
- no neck

Clathrin-mediated endocytosis: first results

radius of clathrin region: 20nm

- spontaneous curvature of clathrin induces budding
- no neck

Clathrin-mediated endocytosis: larger clathrin region

radius of clathrin region: 30nm

- spontaneous curvature of clathrin induces budding and forms a neck

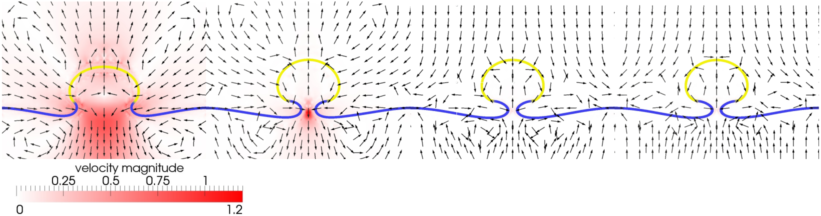
Clathrin-mediated endocytosis: larger clathrin region

radius of clathrin region: 30nm

- spontaneous curvature of clathrin induces budding and forms a neck

The effect of flow

With flow: small Willmore mobility such that the membrane is purely advected



- fluid must be squeezed out of the vesicle to build a neck
- tightening of the neck is inhibited by inextensibility

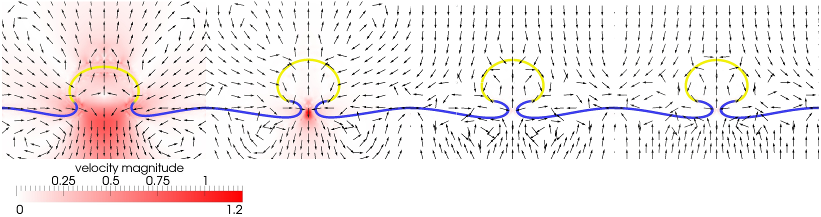
Without flow: large Willmore mobility is only driving force

- membrane moves as if no fluids are present
- neck tightens and vesicle finally pinches off flow results are in agreement with

biological observations, that an additional molecule (dynamin) is needed to trigger pinch-off

The effect of flow

With flow: small Willmore mobility such that the membrane is purely advected



- fluid must be squeezed out of the vesicle to build a neck
- tightening of the neck is inhibited by inextensibility

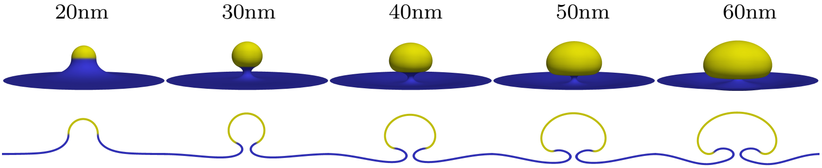
Without flow: large Willmore mobility is only driving force

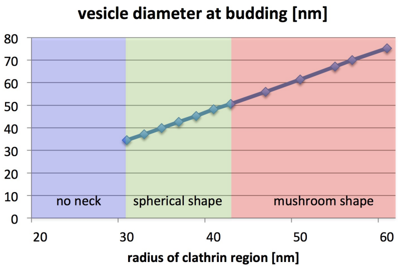
- membrane moves as if no fluids are present
- neck tightens and vesicle finally pinches off flow results are in agreement with

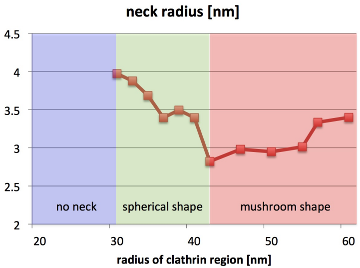
biological observations, that an additional molecule (dynamin) is needed to trigger pinch-off

Varying the clathrin region size: stationary state

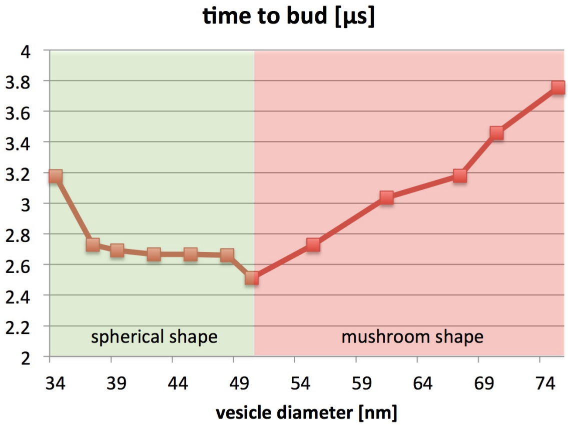
stationary shapes for various clathrin radii







Varying the clathrin region size: dynamics



- there is a critical (fastest) time for budding

1. Locally inextensible diffuse interface model
2. Including curvature-inducing membrane molecules
3. Numerical results
4. Summary

Inextensibility model

Theoretical results

- a local Lagrange multiplier was introduced to satisfy membrane inextensibility in diffuse interface methods (model B)
- convergence to sharp inextensibility condition was shown numerically for $\epsilon \to 0$
- asymptotic analysis shows convergence to $\nabla_\Gamma \cdot \mathbf{u} = 0$ for $\epsilon \to 0$
- a relaxation mechanism was proposed to drive the membrane back locally to an unstretched state (model C)

Numerical results

- the effectiveness of the approach was shown in shear flow scenario
- it was found that the treatment of the inextensibility constraint can crucially influence the vesicle dynamics
- local inextensibility inhibits multiple vesicles from close contact

Aland et al.; Diffuse interface models for locally inextensible vesicles; arXiv:1311.6558

Inextensibility model: outlook

Outlook

- include thermal fluctuations
- apply the model to other nm-scale cell contexts, e.g. receptor-ligand binding at cell-cell interfaces

Endocytosis model

Theoretical results

- a diffuse and sharp interface model were derived for concentration-dependent bending stiffness and spont. curvature
- derivation is in agreement with the 2^{nd} law of thermodynamics
- a modified diffuse interface equation is used to advect the molecule concentration on the membrane
- an axisymmetric implementation was used to show the effectiveness of the approach

Numerical results:

- hydrodynamics allow a very fast building of a neck (in a few μs)
- flow inhibits the tightening of the neck at a certain point
- there is a critical (smallest) neck radius and a critical (fastest) budding time

Outlook

- include attachment of bulk molecules to the membrane
- explore the dependency of the arrival rate of membrane molecules on flow
- explore intermediate dynamic shapes of the membrane and its influence on soluble molecules and cargo

Thank you!

Endocytosis model

Theoretical results

- a diffuse and sharp interface model were derived for concentration-dependent bending stiffness and spont. curvature
- derivation is in agreement with the 2^{nd} law of thermodynamics
- a modified diffuse interface equation is used to advect the molecule concentration on the membrane
- an axisymmetric implementation was used to show the effectiveness of the approach

Numerical results:

- hydrodynamics allow a very fast building of a neck (in a few μs)
- flow inhibits the tightening of the neck at a certain point
- there is a critical (smallest) neck radius and a critical (fastest) budding time

Outlook

- include attachment of bulk molecules to the membrane
- explore the dependency of the arrival rate of membrane molecules on flow
- explore intermediate dynamic shapes of the membrane and its influence on soluble molecules and cargo

Thank you!