Towards the computational design of smart nanocarriers

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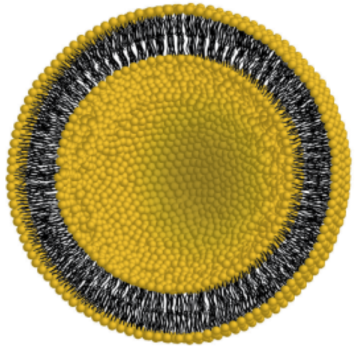
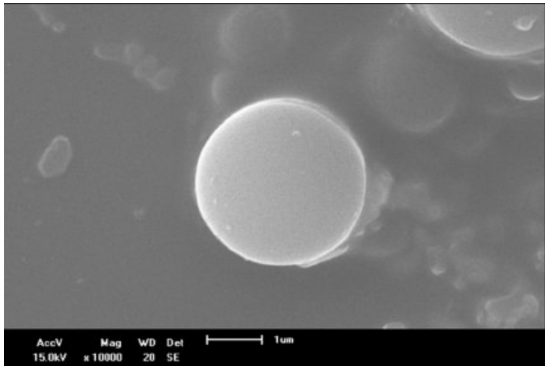
Liposomes

Liposomes (typical diameter <100 nm) are lipid vesicles with a bilayered membrane structure.



Liposomes are considered to be the most successful drug carriers.

Despite extensive research, only a few liposomal drugs have been approved by the U.S. Food and Drug Administration.

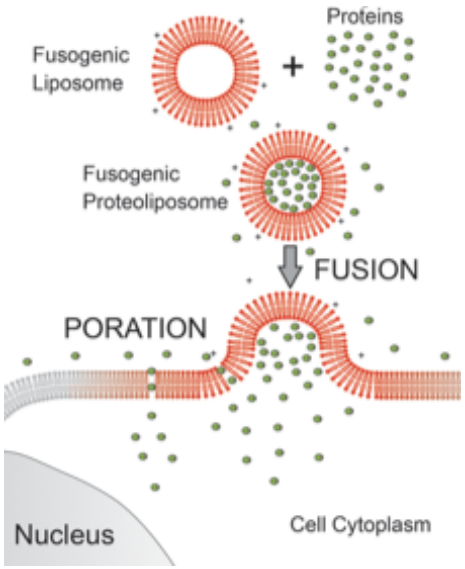


Key liposomal characteristics are

- high target selectivity
- enhanced target cell uptake
- limited toxicity

[Noble et al., *Trends Biotechnol.* 2014] [Jain-Jain, *Current Molecular Medicine* 2018]

A promising class of liposomes



Fusogenic liposomes are liposomes formulated to facilitate fusion.

Fusogenic liposomes successfully deliver biomolecules into cells. However, the fusion-inducing components needed for efficient delivery make these liposomes toxic in vivo.

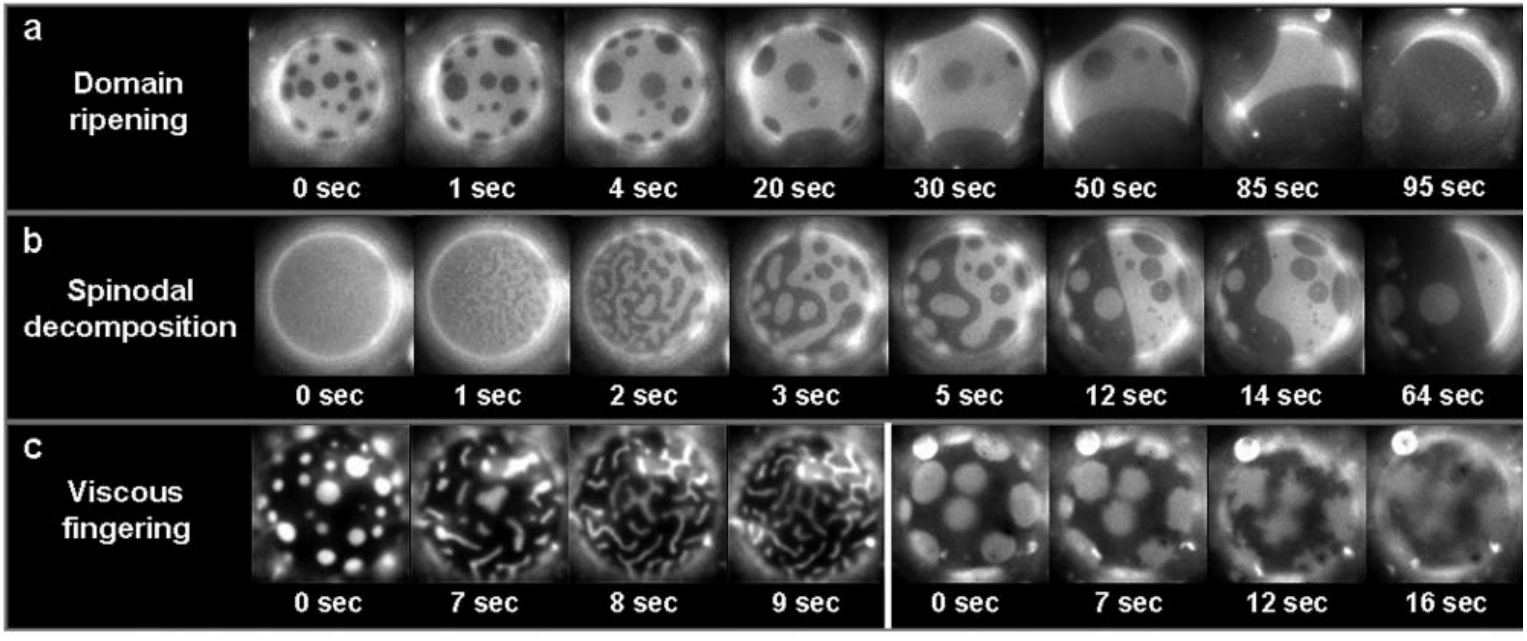
One needs to find a balance between fusogenicity and toxicity.

[Filion-Phillips, *Biochimica et Biophysica Acta* 1997] [Csiszar et al., *Bioconjug Chem.* 2010] [Dutta et al., *Bioconjug Chem.* 2010] [Kube et al., *Langmuir* 2017]

How can fusogenic liposomes be improved?

Possible solution: low concentrations of fusogenic lipids that can be presented in dense patches through phase separation.

[Veatch-Keller, *Biophysical journal* 2003]



Dark: liquid ordered phase. Bright: liquid disordered phase.

Our goal: to apply complementary mathematical, computational, and experimental tools to design and develop a new class of liposomal carriers, called patchy fusogenic liposomes.

Lateral phase separation with conservation

Conservation law for representative concentration c on $\Gamma \subset \mathbb{R}^3$:

$$\rho \frac{\partial c}{\partial t} + \operatorname{div}_\Gamma \mathbf{j} = 0$$

ρ: total density of the system

$\mathbf{j} = -M \nabla_\Gamma \mu$: diffusion flux (Fick's law, empirical)

$M = M(c)$: mobility coefficient

$\mu = \frac{\delta f}{\delta c}$: chemical potential

$f(c) = f_0(c) + \frac{1}{2}\epsilon^2 |\nabla_\Gamma c|^2$: total specific free energy

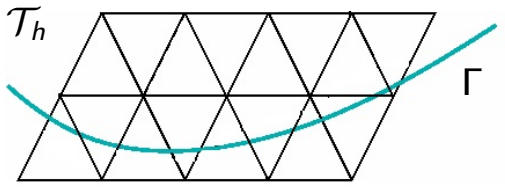
In order to have phase separation, f_0 must be a non-convex function of c.

Surface Cahn–Hilliard equation

$$\rho \frac{\partial c}{\partial t} - \operatorname{div}_\Gamma \left(M \nabla_\Gamma \left(f_0' - \epsilon^2 \Delta_\Gamma c \right) \right) = 0 \quad \text{on } \Gamma$$

TraceFEM: basic principles

We study for the first time a geometrically unfitted finite element method.



Idea

Use a trace space induced by FE functions for the bulk triangulation $\mathcal{T}_h$.

TraceFEM: basic principles

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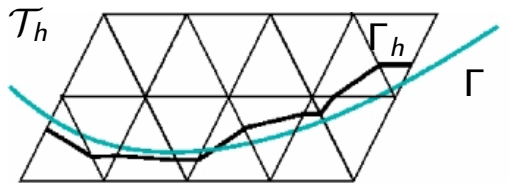

$\{\mathcal{T}_h\}_{h>0}$ is a triangulation of the domain

Γ_h is an approximation of Γ

For example:

$$\Gamma = \{\mathbf{x} \in \mathbb{R}^3 \mid \quad \phi(\mathbf{x}, t) = 0\}$$
$$\Gamma_h = \{\mathbf{x} \in \mathbb{R}^3 \mid \phi_h(\mathbf{x}, t) = 0\}$$

with $\phi_h = I_h(\phi)$, where I_h is a nodal interpolant.

[Olshanskii-Reusken-Grande, *SINUM* 2009]

TraceFEM: basic principles

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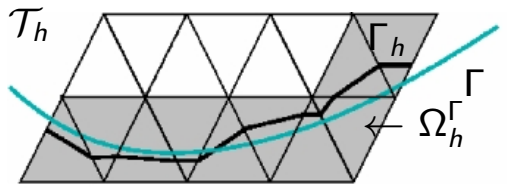


$\{\mathcal{T}_h\}_{h>0}$ is a triangulation of the domain

$\mathcal{T}_h^\Gamma$ is the subset of elements that have a nonzero intersection with Γ $\rightarrow \Omega_h^\Gamma$

Define

Define the outer space: $V_h = \{v \in C(\Omega_h^\Gamma) : v \in \mathbb{P}_1(T) \text{ for any } T \in \mathcal{T}_h^\Gamma\}$

And then define the trace space for V_h:

$$\text{interface FE space } V_h^\Gamma := \{\psi_h \in C(\Gamma_h) : \exists\, v_h \in V_h : \psi_h = v_h|_{\Gamma_h}\}.$$

[Olshanskii-Reusken-Grande, *SINUM* 2009]

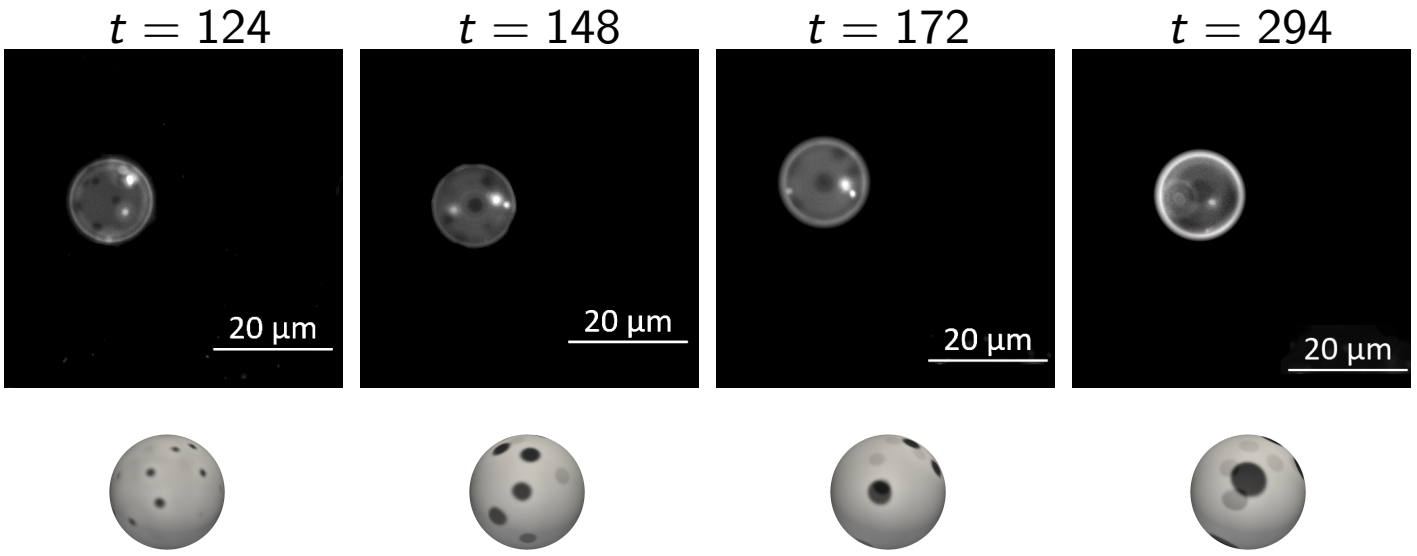
Advantages of TraceFEM

- Surface Γ is not meshed directly.
- Number of active degrees of freedom is optimal, it is comparable to methods in which Γ is meshed directly.
- Amenable to both space and time adaptivity.
- Effective condition numbers of matrices are comparable to common FEMs.
- If Γ evolves, Γ is not tracked by a mesh (Eulerian method).
- If Γ evolves, one recomputes matrices using the same data structures.

Qualitative comparison with Majd's experiments

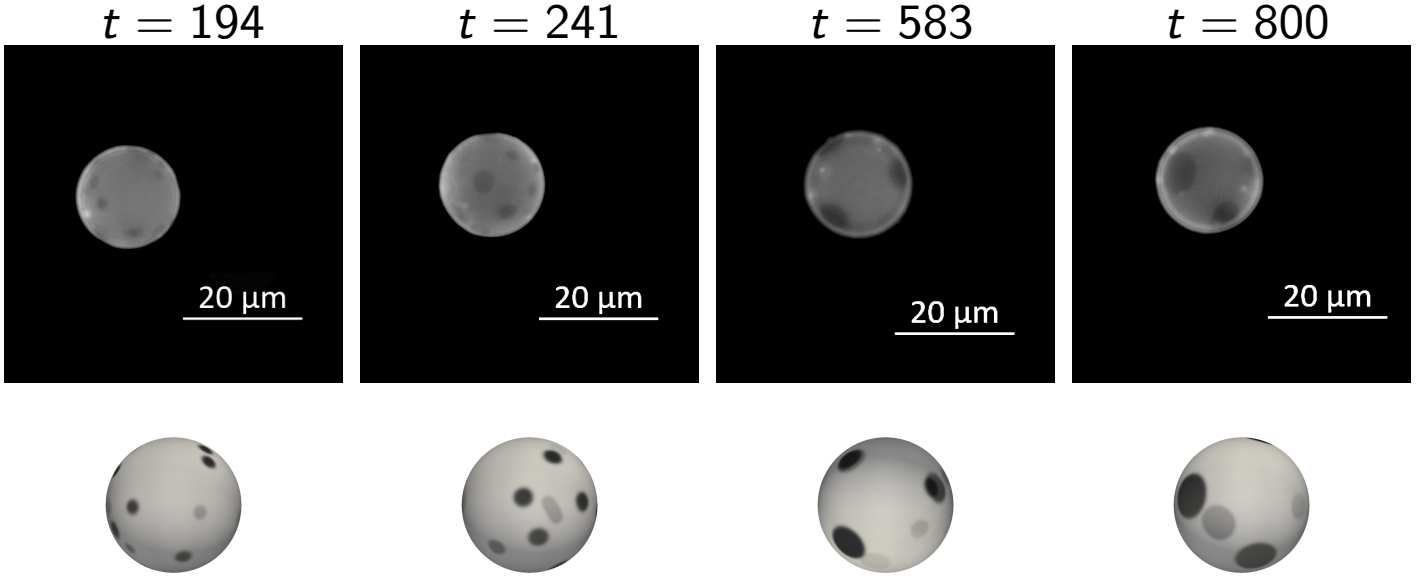
We compared our numerical results on steady surfaces with experiments conducted in Majd's lab for two membrane compositions:

- one yielding about 16% liquid ordered area fraction.



Qualitative comparison with Majd's experiments

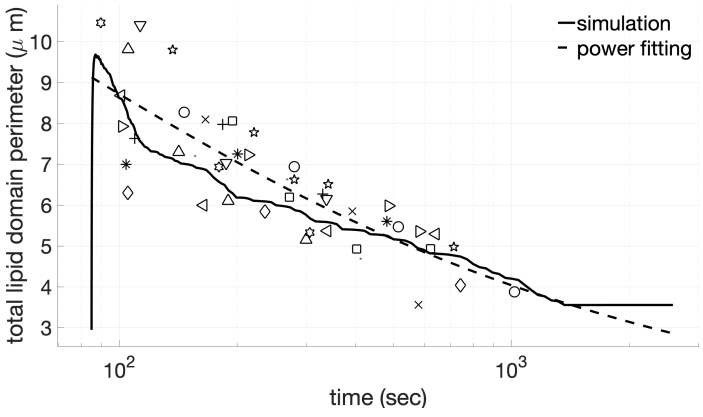
- Another yielding about 9% liquid ordered area fraction.

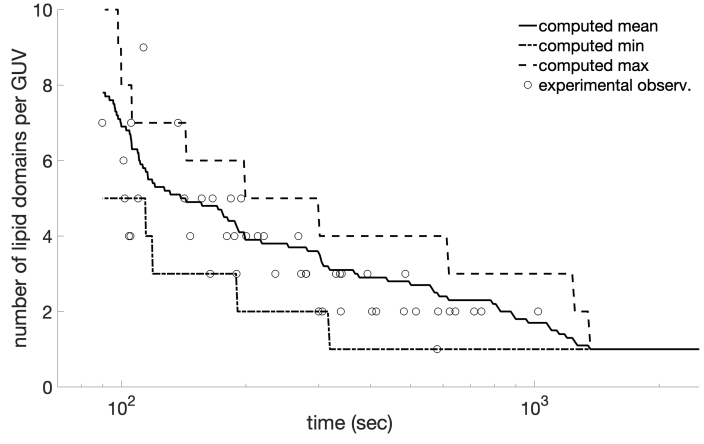


To set the initial state for numerical simulations, we relied on thermodynamic considerations.

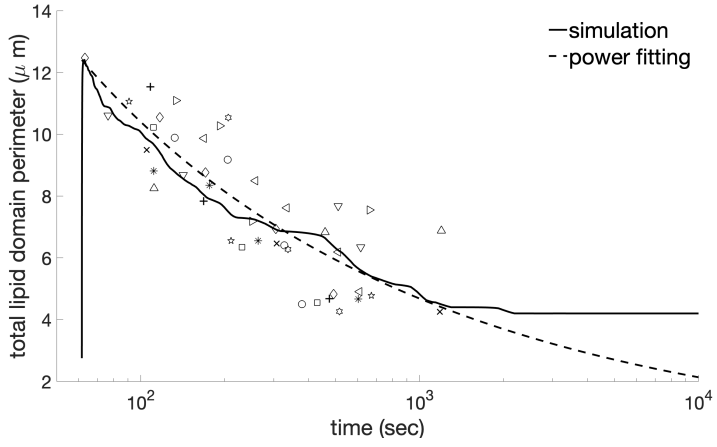
Quantitative comparison with Majd's experiments

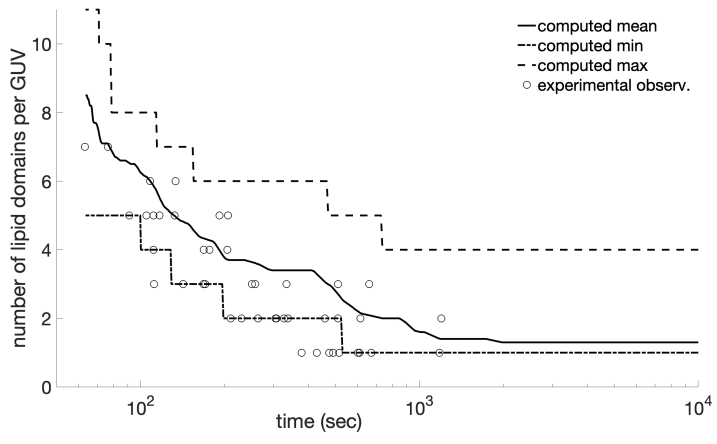
9% liquid ordered area fraction





16% liquid ordered area fraction





[Zhiliakov-Wang-Q-Olshanskii-Majd, *BAA* 2021]

Navier–Stokes–Cahn–Hilliard system

We proposed a more complex thermodynamically consistent phase-field model to capture the viscous and fluidic phenomena.

$$\underbrace{\rho(\partial_t \mathbf{u} + (\nabla_\Gamma \mathbf{u})\mathbf{u})}_{\text{inertia}} - \underbrace{\mathbf{div}_\Gamma(2\eta E_s(\mathbf{u})) + \nabla_\Gamma p}_{\text{lateral stresses}} = \underbrace{-\sigma_\gamma \epsilon^2 \mathrm{div}_\Gamma\left(\nabla_\Gamma c \otimes \nabla_\Gamma c\right)}_{\text{line tension}} + \underbrace{M\theta(\nabla_\Gamma(\theta\mathbf{u}))\nabla_\Gamma \mu}_{\text{chemical momentum flux}}$$

$$\underbrace{\mathrm{div}_\Gamma \mathbf{u} = 0}_{\text{membrane inextensibility}}$$

$$\underbrace{\partial_t c + \mathrm{div}_\Gamma(c\mathbf{u})}_{\text{transport of phases}} - \underbrace{\mathrm{div}_\Gamma\left(M\nabla_\Gamma \mu\right)}_{\substack{\text{phase masses exchange} \\ \text{Fick's law}}} = 0, \qquad \mu = \underbrace{f_0'(c) - \epsilon^2 \Delta_\Gamma c}_{\text{mixture free energy variation}}$$

Thanks to the term in red with $\theta^2 = \frac{d\rho}{dc}$, the model allows for a non-linear dependence of fluid density on the phase-field order parameter.

[Abels-Garcke-Grün, *M3AS* 2012]

Numerical method for the NSCH system

Two issues arise when dealing with surface and unfitted finite elements:

1. The numerical treatment of condition $\mathbf{u} \cdot \mathbf{n} = 0$
   $\longrightarrow$ add a penalty term to the weak formulation.
2. Possible small cuts of tetrahedra from $\mathcal{T}_h^\Gamma$ by the surface
   $\longrightarrow$ add certain volumetric terms to the finite element formulation

The decoupled linear finite element method we propose reads: At time step t^{n+1}, perform

- Step 1: Find (c^{n+1}, μ^{n+1}) such that

$$[c]_t^{n+1} + \operatorname{div}_\Gamma(c^{n+1}\mathbf{u}^n) - \operatorname{div}_\Gamma\left(M\nabla_\Gamma \mu^{n+1}\right) = 0,$$

$$\mu^{n+1} = \frac{\gamma_c \Delta t}{\epsilon}[c]_t^{n+1} + \frac{1}{\epsilon} f_0'(c^n) - \epsilon \Delta_\Gamma c^{n+1}.$$

The TraceFEM formulation will include terms for issue 2.

[Shen-Yang, *Discrete & Continuous Dynamical Systems* 2010]

Numerical method for the NSCH system

- Step 2: Find $(\mathbf{u}^{n+1}, p^{n+1})$ such that

$$\rho^n[\mathbf{u}]_t^{n+1} + \rho^{n+1}(\nabla_\Gamma \mathbf{u}^n)\mathbf{u}^{n+1} - \mathbf{P}\mathrm{div}_\Gamma(2\eta^{n+1}E_s(\mathbf{u}^{n+1})) + \nabla_\Gamma p^{n+1}$$
$$= -\sigma_\gamma c^{n+1}\nabla_\Gamma \mu^{n+1} + M\theta^{n+1}(\nabla_\Gamma(\theta^{n+1}\mathbf{u}^{n+1}))\nabla_\Gamma \mu^{n+1} + \mathbf{f}^{n+1},$$
$$\mathrm{div}_\Gamma \mathbf{u}^{n+1} = 0.$$

The TraceFEM formulation will include terms for issues 1 and 2.

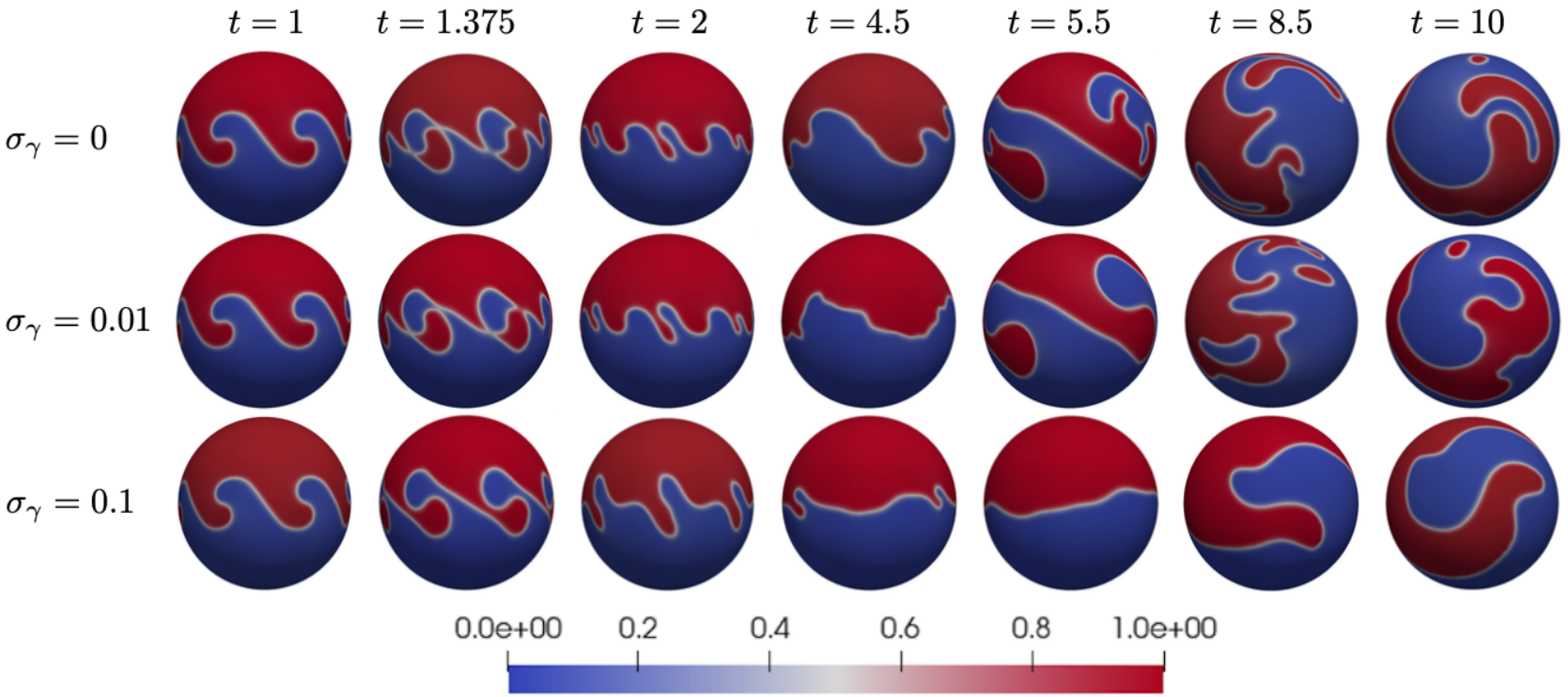
We have the following properties for our decoupled scheme:

- the resulting two algebraic systems are linear;
- the numerical solution satisfies the same stability bound as the solution of the original system under some restrictions on the discretization parameters.

[Palzhanov-Zhiliakov-Q-Olshanskii, *CMAME* 2021]

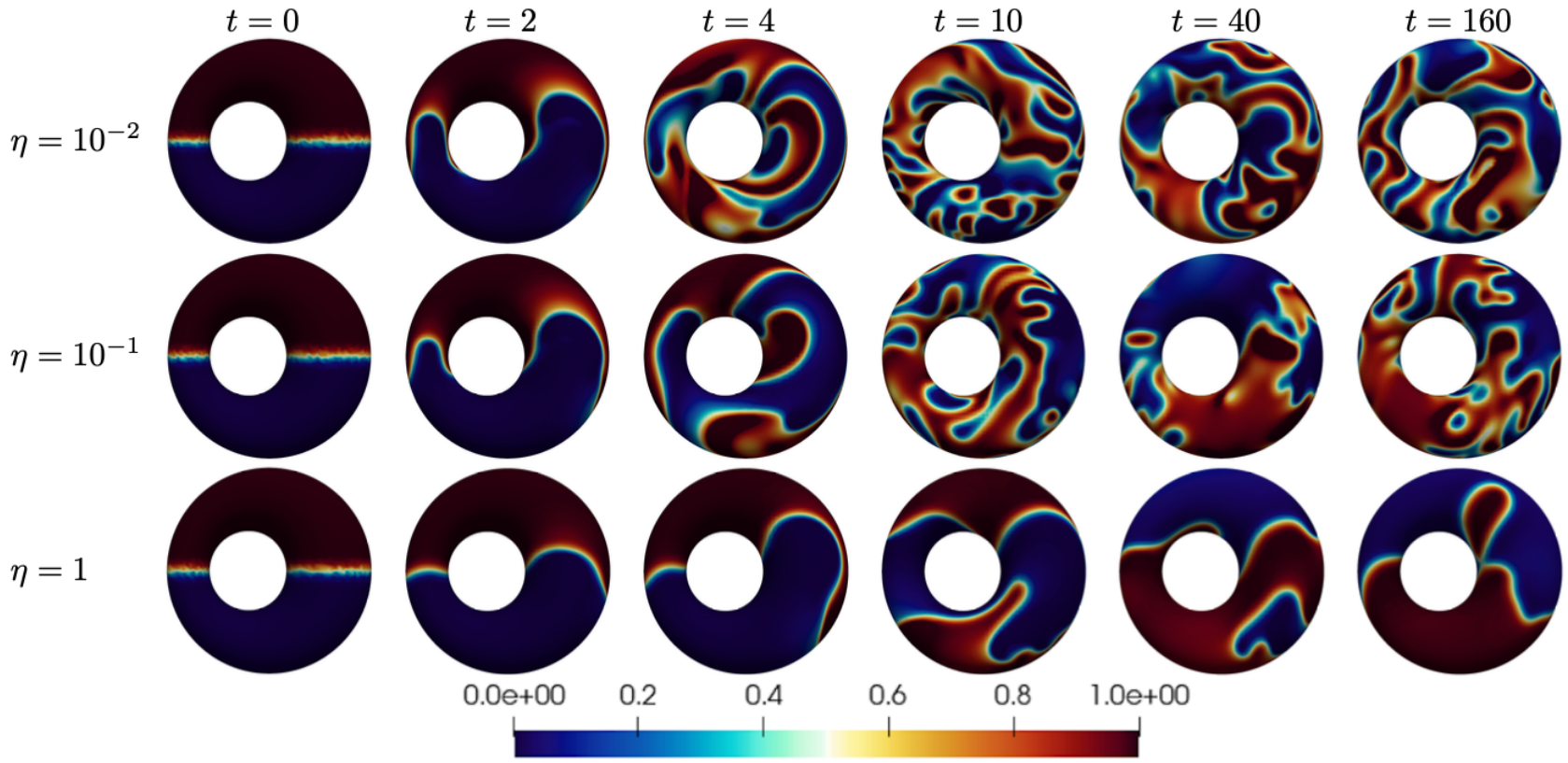
Kelvin–Helmholtz instability on a sphere

The KH instability arises when there is a difference in velocity at the interface between the two fluids and a perturbation is added to the interface. We consider fluids with matching densities ($\rho_1 = \rho_2 = 1$) and viscosities ($\eta_1 = \eta_2 = 10^{-5}$). [PLAY]



Rayleigh–Taylor instability on a torus

The Rayleigh–Taylor (RT) instability occurs when a gravity force is acting on a heavier fluid that lies above a lighter fluid. We take two fluids with densities $\rho_2 = 3$ and $\rho_1 = 1$ and matching viscosities $\eta_1 = \eta_2 = \eta$. We set $\sigma_\gamma = 0.025$. [PLAY]



Qualitative comparison with Majd's experiments

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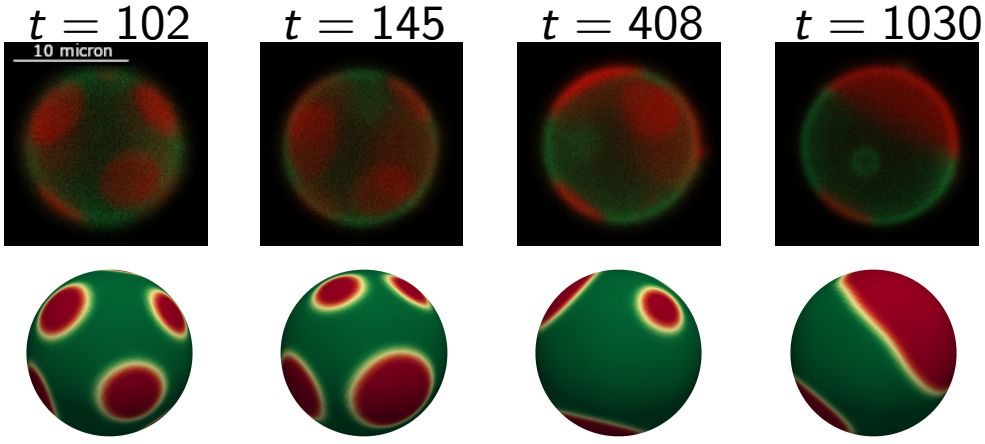
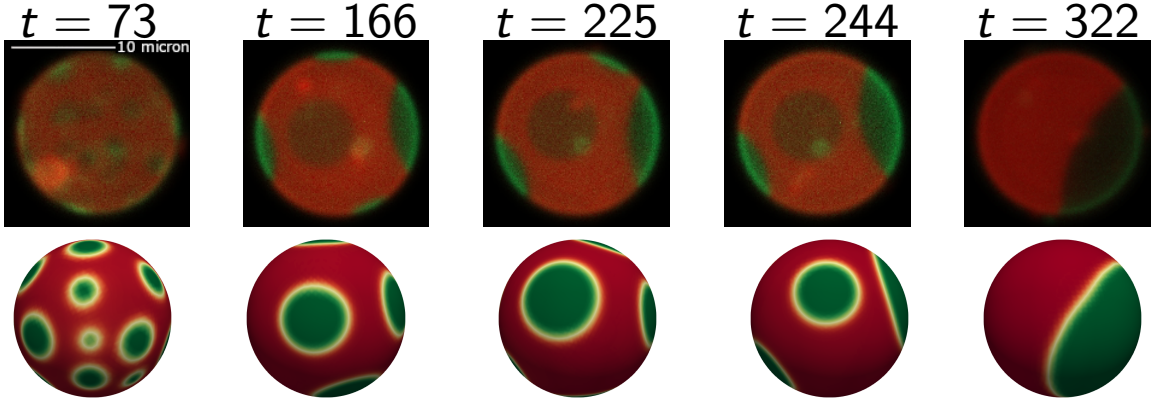
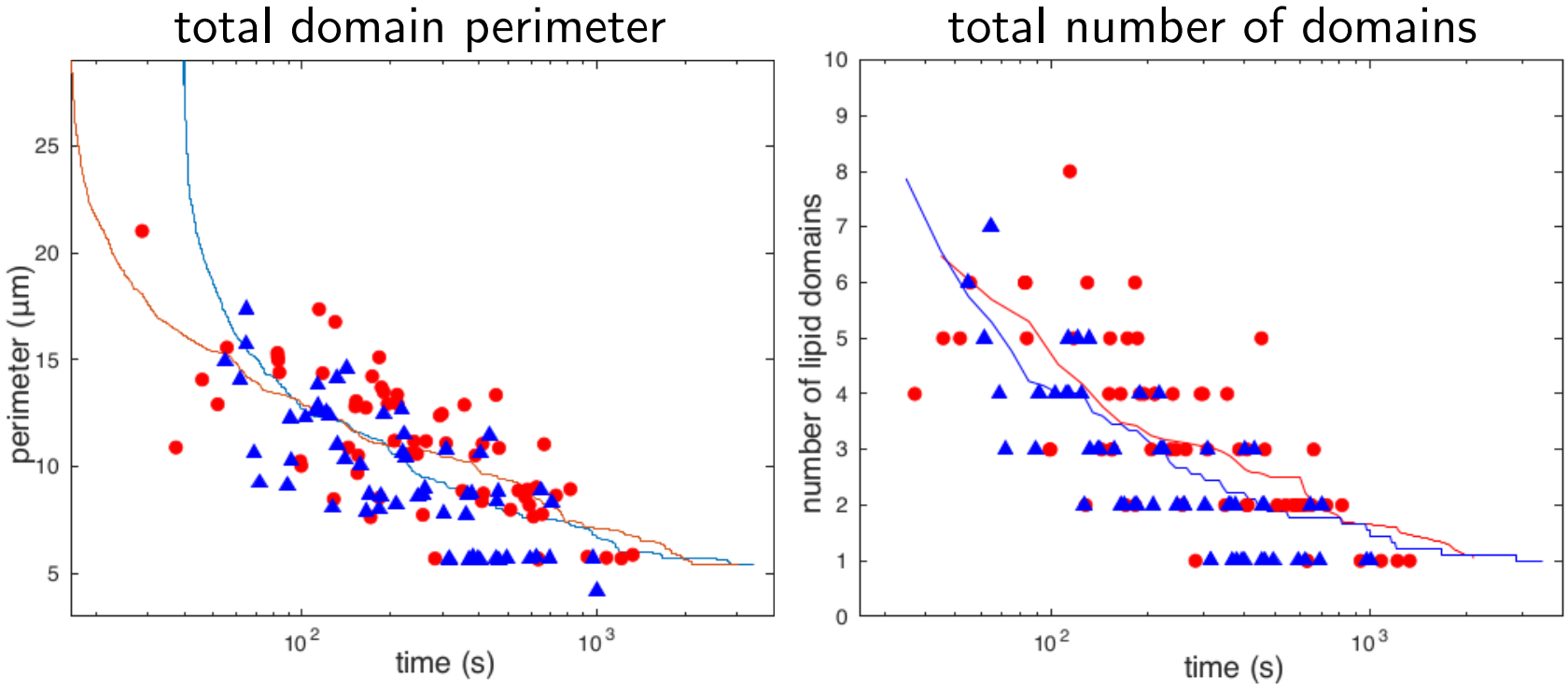


- another yielding about 30% liquid ordered area fraction.



Green: liquid ordered phase. Red: liquid disordered phase.

Quantitative comparison with Majd's experiments



Red dots: experimental data for 70% liquid ordered area fraction.
Red line: computed mean for 70% liquid ordered area fraction.
Blue triangles: experimental data for 30% liquid ordered area fraction.
Blue line: computed mean for 30% liquid ordered area fraction.

[Wang-Palzhanov-Q-Olshanskii-Majd, *BAA* 2022]

Lateral phase separation on an evolving surface

Using elementary tangential calculus, we derive a Cahn–Hilliard problem posed on an evolving material surface:

$$\dot{\rho} + \rho \mathrm{div}_\Gamma \mathbf{u} = 0 \quad \text{on } \Gamma(t)$$

$$\dot{c} - \rho^{-1} \mathrm{div}_\Gamma \left(M \nabla_\Gamma \left(\frac{1}{\epsilon} f_0' - \epsilon \Delta_\Gamma c \right) \right) = 0 \quad \text{on } \Gamma(t)$$

where $\dot{f}$ is the material derivative of f.

- Total conservation of mass
- Conservation of mass for one component

[Elliott-Ranner, *Numer. Math.* 2015]

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where $\dot{f}$ is the material derivative of f.

- The system is one-way coupled
- We are not aware of a minimization property for the Cahn–Hilliard problem in time-dependent domains $\rightarrow$ the system is no longer dissipative

[Elliott-Ranner, *Numer. Math.* 2015] [Yushutin-Q-Olshanskii, *JCP* 2019]

Oscillating ellipsoid

We consider time-dependent surface $\Gamma(t)$ to be an oscillating ellipsoid. As initial solution, we take:

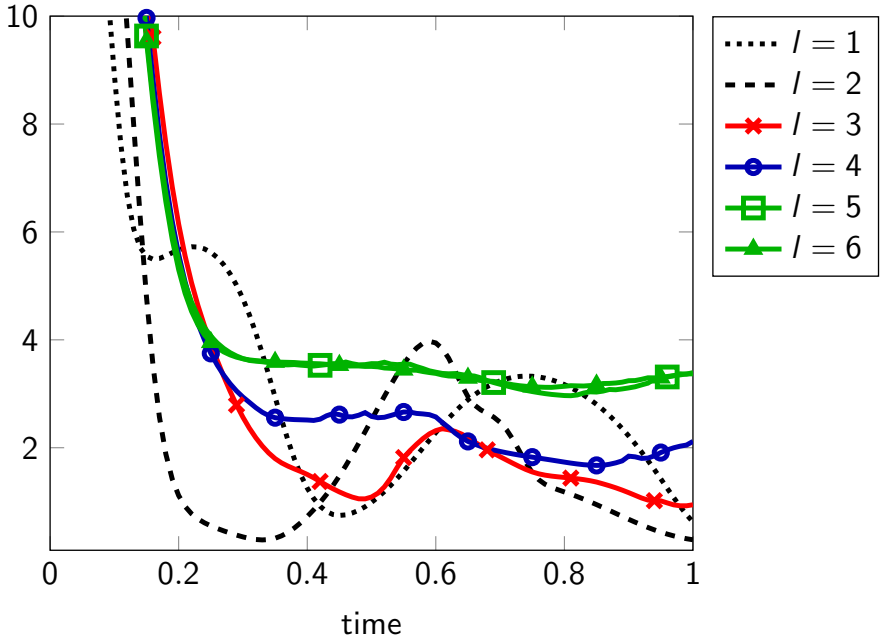
$$c_0 = 0.5 + 0.05\cos(2\pi x_1)\cos(2\pi x_2)\cos(2\pi x_3).$$

PLAY simulation for $\epsilon = 0.01$, $h_\ell = \frac{10/3}{2^{\ell+2}}$, $\Delta t = 0.01$.

Discrete Lyapunov energy:

$$E_h^L(c_h) = \int_{\Gamma_h} f(c_h) ds$$

[Elliott-Ranner, *Numer. Math.* 2015]



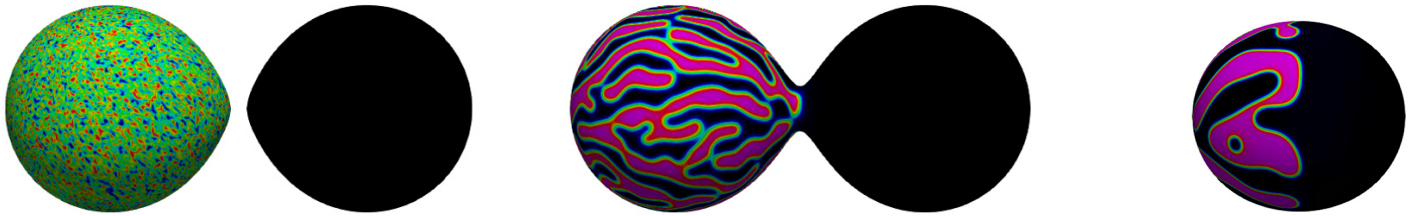
Pattern formation on colliding spheres

We consider two colliding spheres with the following initial condition:

- two-component mixture with random initial condition (1:1) for the sphere on the left;
- homogeneous phase for the sphere on the right.

We set $\epsilon = 0.01$.

$t = 0.23$ $t = 0.26$ $t = 1.23$



PLAY

[Yushutin-Q-Olshanskii, *JCP* 2019]

Conclusions

- We extended a well-known phase field model for two-phase incompressible flow.
- Because of our interest in biomembranes, the system is posed on an arbitrary-shaped closed smooth surface.
- We applied and analyzed an unfitted finite element method for its numerical approximation.
- We proposed a discrete scheme that decouples the fluid problem from the phase-field problem at each time step.

THANK YOU FOR YOUR ATTENTION!

[Olshanskii-Q.-Reusken-Yushutin, *SISC* 2018] [Yushutin-Q.-Majd-Olshanskii, *IJNMBE* 2019] [Yushitin-Q-Olshanskii, *JCP* 2019] [Zhiliakov-Wang-Q-Olshanskii-Majd, *BAA* 2021] [Palzhanov-Zhiliakov-Q-Olshanskii, *CMAME* 2021]
[Wang-Palzhanov-Q-Olshanskii-Majd, *BAA* 2022]

`http://www.igpm.rwth-aachen.de/DROPS/`