TECHNISCHE UNIVERSITÄT DRESDEN

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Cell motility - a continuum approach

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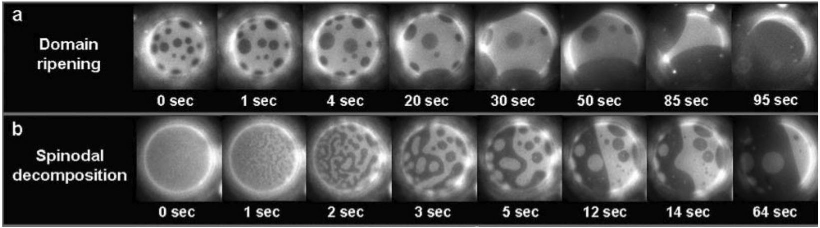
Outline

- phase separation and coarsening in cell membranes
  large-scale phase separation vs. dynamically stable microdomains
- crawling cells
  mechanical interactions and complex reactions within cytoplasm and on cellular membrane
- mathematical tools
  diffuse domain description

GUV's

- two-phase system - lipid-ordered and lipid-disordered phase
- phase separation



Veatch, Keller; Biophys. J. **85** (2003) 3074

Mathematical model

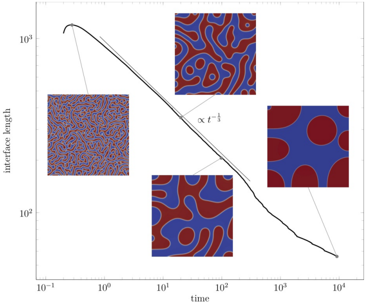
- two-phase system - driving force is line tension
- surface Cahn-Hilliard equation

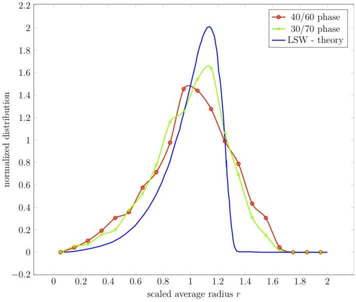
$$\partial_t \phi = \Delta_\Gamma \frac{\delta \mathcal{E}_1[\phi]}{\delta \phi}, \qquad \mathcal{E}_1[\phi] = \int_\Gamma \frac{\epsilon}{2}\gamma |\nabla_\Gamma \phi|^2 + \frac{1}{\epsilon}\frac{\phi^2(1-\phi)^2}{4}\, d\Gamma$$

Rätz, AV; Comm. Math. Sci. **4** (2006) 575

Scaling and self-similarity

- scaling law for size of islands
- self-similar island size distribution





Backofen, Witkowski, AV; preprint (2012)

consistent with Ising model

Discrepancy between in vitro and in vivo results

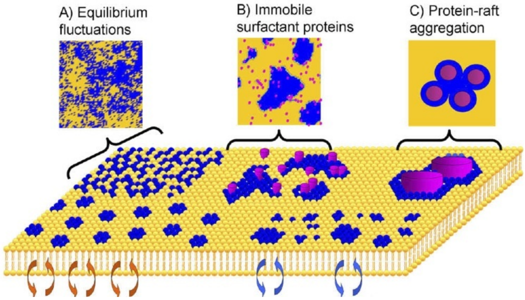
- model membranes - phase separation and coarsening
- cell membranes - heterogeneity on a submicrometer scale persits

Simons, Ikonen; Nature **387** (1997) 569

lipid rafts - today understood as heterogeneity as a result of interactions of lipids with proteins, the cytoskeleton and fluid interactions, as well as effects due to curvature

Theoretical concepts

- two-phase system - lipid raft phase, enriched in cholesterol, proteins and saturated lipids and a matrix phase



Fan, Sammalkorpi, Haataja; FEBS Lett. **584** (2010) 1678

Modeling approaches

- transient compositional fluctuations driven by thermal noise

  Veatch, Soubias, Keller, Gawrisch; PNAS **104** (2007) 17650

- hybrid lipids as line active components to reduce line tension

  Brewster, Safran; Biophys. J. **98** (2010) L21

- membrane viscosity and bulk fluid interactions

  Fan, Han, Haataja; J. Chem. Phys. **133** (2010) 045019

- pinning effects due to membrane proteins and cytoskeleton

  Yethiraj, Weisshaar; Biophys. J. **93** (2007) 3113

- ...

Membrane viscosity and bulk fluid interactions

- two-phase flow of Newtonian bulk fluids
- advected interface with Boussinesq-Scriven law

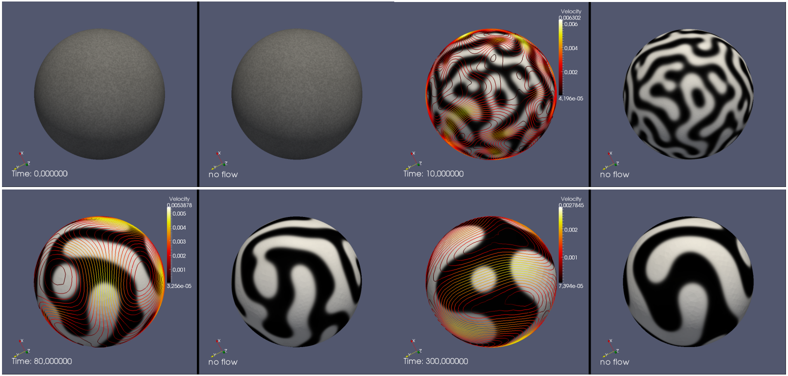
large Safmann-Delbrueck number $l_H = \mu_\Gamma / \mu$
decouples bulk from surface fluid

- surface Navier-Stokes-Cahn-Hilliard equation
(stream function formulation)

$$\begin{aligned} \partial_t \phi + J(\psi, \phi) &= \Delta_\Gamma \frac{\delta \mathcal{E}_1[\phi]}{\delta \phi} \\ \partial_t \Delta_\Gamma \psi + J(\psi, \Delta_\Gamma \psi) &= \mu_\Gamma (\Delta_\Gamma^2 \psi + 2 \nabla_\Gamma \cdot (K \Delta_\Gamma \psi)) + f \end{aligned}$$

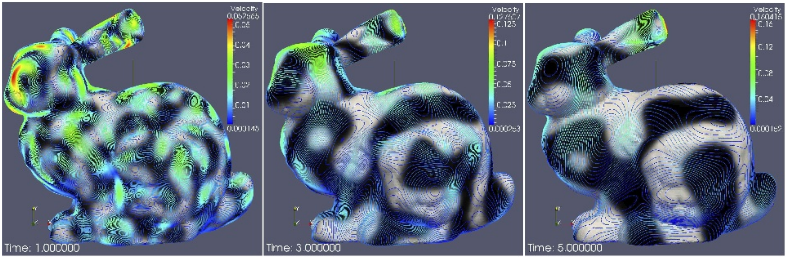
Nitschke, AV, Wensch, preprint (2012)

Flow shows the opposite effect



Nitschke, AV, Wensch, preprint (2012)

Can be done on arbitrary surfaces



- strong coupling between curvature and flow field

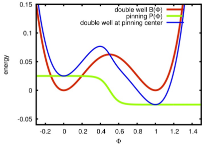
Pinning effects

- membrane proteins - favorable energetic interaction with one phase
- interaction with membrane skeleton - pinned to filaments

modified surface Cahn-Hilliard equation

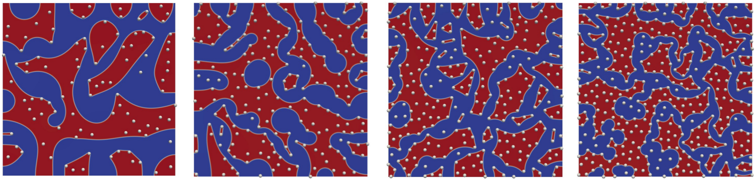
$$\partial_t \phi = \Delta_\Gamma \frac{\delta \mathcal{E}_1[\phi]}{\delta \phi}, \qquad \mathcal{E}_1[\phi] = \int_\Gamma \frac{\epsilon}{2}\gamma |\nabla_\Gamma \phi|^2 + \frac{1}{\epsilon}\frac{\phi^2(1-\phi)^2}{4} + V(x)P(\phi)\, d\Gamma$$

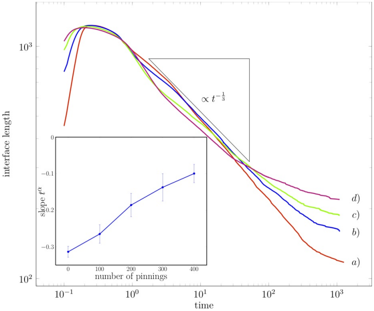
$$V(x) = \sum_i^N \exp(-\frac{(x-x_i)^2}{\sigma^2}); \qquad P(\phi) = \tanh(a(\frac{1}{2}-\phi))$$

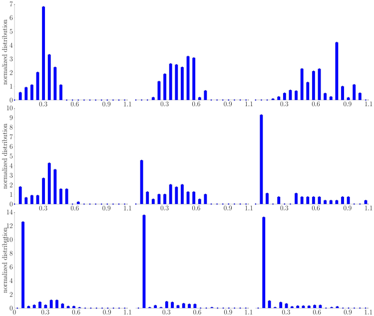


Backofen, Witkowski, AV; preprint (2012)

Local pinning potential







Local pinning potential

- slowing down of coarsening
- broadening of size distribution
- no self-similarity

consistent with random-field Ising model

Ehrig, Petrov, Schwille, Biophys. J. **100 (2011) 80, Fischer, Vink; J. Chem. Phys. 34 (2011) 055106**

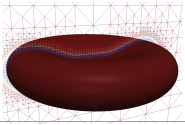
Elastic properties of membrane

Helfrich energy

$$\mathcal{E}_2[\Gamma] = \frac{1}{2}\int_\Gamma b_N(H - H_0)^2 + \sigma \, d\Gamma$$

- inertia forces of membrane are neglected
- bulk fluid is highly viscose
- with constraint to ensure volume conservation

$$k\mathbf{u}_\Gamma = -\frac{\delta \mathcal{E}_2}{\delta \Gamma}$$



Elastic properties of membrane

Helfrich-type energy

$$\mathcal{E}[\Gamma, \phi] = \frac{1}{2} \int_{\Gamma} b_N(\phi)(H - H_0(\phi))^2 + \sigma(\phi) \, d\Gamma$$

themodynamically consistent evolution equations

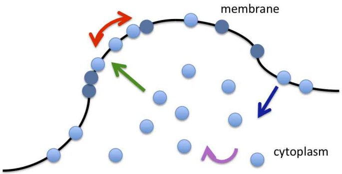
$$\begin{aligned} \frac{D}{Dt}\phi + \phi \nabla_\Gamma \cdot \mathbf{u}_\Gamma &= \Delta_\Gamma \frac{\delta \mathcal{E}}{\delta \phi} \\ k\mathbf{u}_\Gamma &= -\frac{\delta \mathcal{E}}{\delta \Gamma} + \phi H \frac{\delta \mathcal{E}}{\delta \phi}\mathbf{n} - u \nabla_\Gamma \frac{\delta \mathcal{E}}{\delta \phi} \end{aligned}$$

Lowengrub, Rätz, AV; Phys. Rev. E **79 (2009) 031926, Sohn, Tseng, Li, AV, Lowengrub; J. Comput. Phys. 229 (2010) 119; Li, Lowengrub, AV; Comm. Math. Sci. 10 (2012) 645**

- allows to model coarsening, budding and fission

Cell motility

- crawling cells move by protruding a cell front and retracting the cell rear
- driven by reorganization of actin cytoskeleton
- push by actin polymerization and contract by reaction with myosin
- described through protein interactions
- signaling network of small GTPases



Marth, AV; preprint (2012)

Reaction-diffusion model

$$
\begin{aligned}
\frac{D}{Dt} u_i + u_i \nabla_\Gamma \mathbf{u}_\Gamma &= d_i \Delta_\Gamma u_i + f_i(u_0, u_1, \ldots, u_n) + q_i(u_0, u_1, \ldots, u_n, U_i) \\
\frac{D}{Dt} U_i &= D_i \Delta U_i + F_i(U_0, U_1, \ldots, U_n) \quad \text{in } \Omega \\
D_i \nabla U_i \cdot \mathbf{n} + u_i \mathbf{u}_\Gamma \cdot \mathbf{n} &= q_i(u_0, u_1, \ldots, u_n, U_i) \quad \text{on } \Gamma
\end{aligned}
$$

- u_i concentration of membrane bound protein, e.g. *membrane bound active and inactive states of GTPase*
- U_i *concentration of protein in cytoplasma, e.g. complexes of cytoplasmic GTPase*

allows for Turing instability for different d_i, D_i and attachment / detachment coefficients $q_i = \alpha U_i (1 - \sum_i u_i) - \beta u_i$

Rätz, Röger; preprint (2012); Marth, AV; preprint (2012)

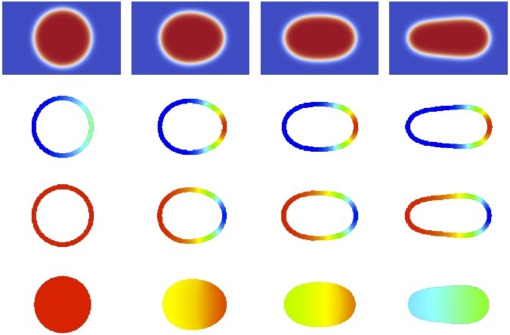
Combine with Helfrich model

$$k\mathbf{u}_\Gamma = -\frac{\delta\mathcal{E}_2}{\delta\Gamma} + \sum_{i=1}^{n}\alpha_i u_i \mathbf{n} + \sum_{i=1}^{n}\beta_i U_i \mathbf{n}$$

Shao, Rappel, Levine; Phys. Rev. Lett. **105 (2010) 108104; Marth, AV; preprint (2012)**

Sheet like protrutions - lamellipodia

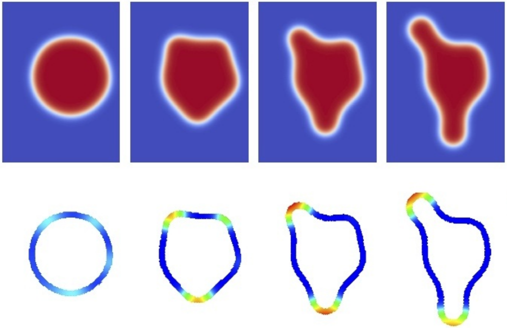
Turing instability resulting from different d_i and D_i



Marth, AV; preprint (2012)

Rod like protrutions - filopodia

Turing instability resulting from different d_i

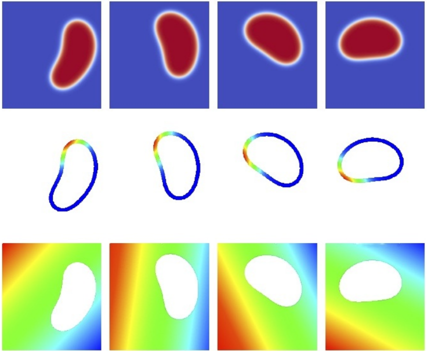


Marth, AV; preprint (2012)

Controling polarization by spatial signals

amplification of spatial signal by gradient of chemoattractants

$$\frac{D}{Dt}u_1 + u_1 \nabla_\Gamma \mathbf{u}_\Gamma = d_1 \Delta_\Gamma u_1 + f_1(u_1, u_2) + q_1(u_1, u_2, U_1) - \nabla_\Gamma \cdot (u_1 \nabla_\Gamma c)$$



Solving equation in evolving domains

- equations on surfaces

$$\frac{D}{Dt}u_i + u_i \nabla_\Gamma \mathbf{u}_\Gamma = d_i \Delta_\Gamma u_i + q_i(u_1, \dots, u_n, U_i)$$

$\Rightarrow$

$$\frac{D}{Dt}(|\nabla\phi| u_i) + u_i |\nabla\phi| \nabla_\Gamma \mathbf{u}_\Gamma = d_i \nabla_\Gamma \cdot (|\nabla\phi| \nabla_\Gamma u_i) + |\nabla\phi| q_i(u_1, \dots, u_n, U_i)$$

- equation in bulk

$$\frac{D}{Dt}U_i = D_i \Delta U_i, \quad D_i \nabla U_i \cdot \mathbf{n} + u_i \mathbf{u}_\Gamma \cdot \mathbf{n} = q_i(u_1, \dots, u_n, U_i)$$

$\Rightarrow$

$$\frac{D}{Dt}(\phi U_i) = D_i \nabla \cdot (\phi U_i) + |\nabla\phi| q_i(u_1, \dots, u_n, U_i)$$

Rätz, AV; Comm. Math. Sci. **4 (2006) 575; Li, Lowengrub, Rätz, AV; Comm. Math. Sci. 7 (2009) 81; Teigen, Li, Lowengrub, Wang, AV; Comm. Math. Sci. 7 (2009) 1009**

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