

*minimal models for lipid membranes:
local modifications around fusion objects*

Giovanni Marelli

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PhD defense



GEORG-AUGUST-UNIVERSITÄT
GÖTTINGEN

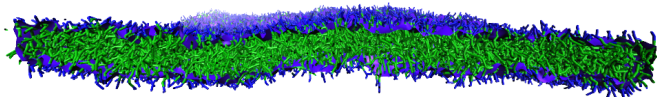


SFB 803



structures and morphologies

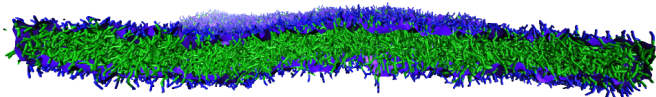
lipid



bilayer

structures and morphologies

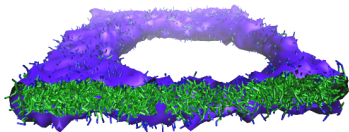
lipid



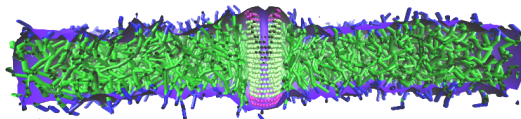
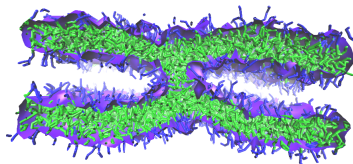
bilayer

fusion objects

pore



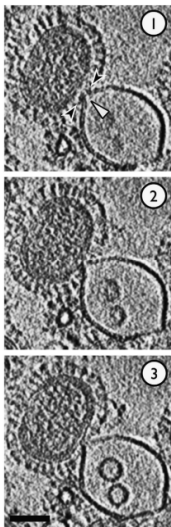
stalk



transmembrane protein

how does membrane fusion work?

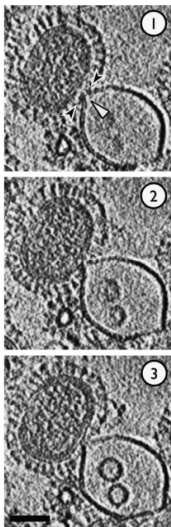
viral fusion



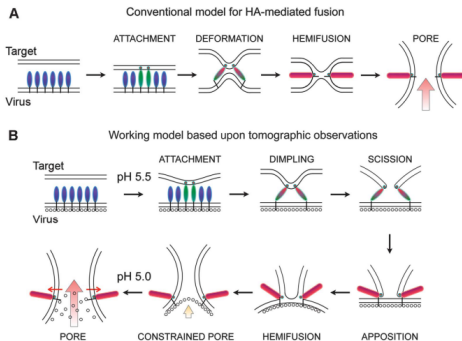
K. K. Lee *EMBO J.* 29, 1299 (2010)

how does membrane fusion work?

viral fusion



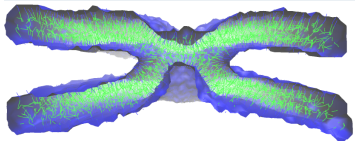
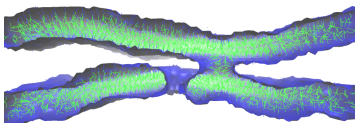
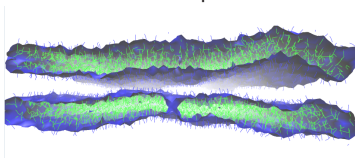
possible (heuristic) explanations?



K. K. Lee *EMBO J.* 29, 1299 (2010)

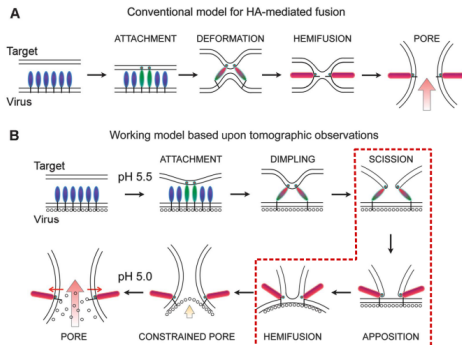
how does membrane fusion work?

artificial pore



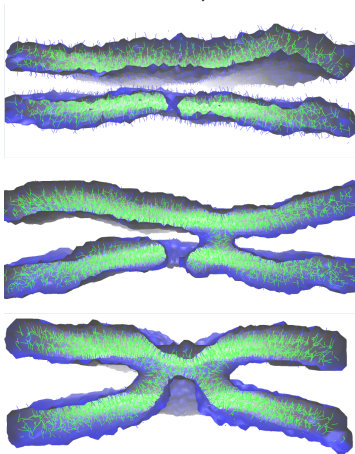
- capture morphology change and dynamics
- isolate metastable states

possible (heuristic) explanations?



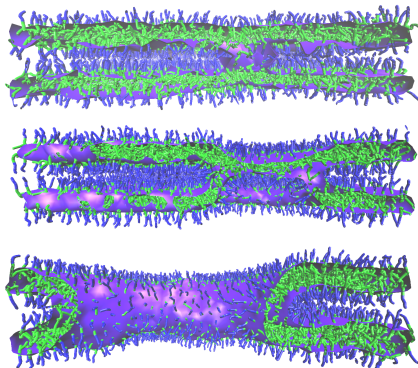
how does membrane fusion work?

artificial pore



- capture morphology change and dynamics
- isolate metastable states

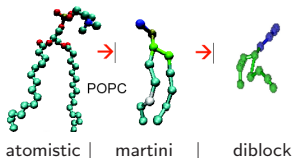
under lateral tension, low hydration



- identify the fusion pathways
- estimate energies and times
- role of the peptides

minimal models for collective phenomena in lipid membranes

lipids as diblocks

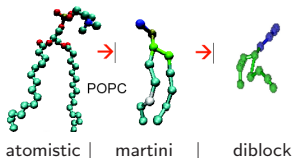


coarse-grained solvent-free soft

- large time scales, many lipids
- computational efficiency
- sampling from thermal fluctuations

minimal models for collective phenomena in lipid membranes

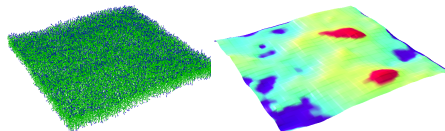
lipids as diblocks



coarse-grained solvent-free soft

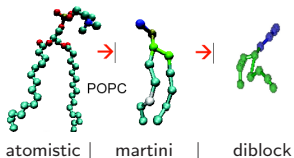
- large time scales, many lipids
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membranes as continuum sheets



minimal models for collective phenomena in lipid membranes

lipids as diblocks



mechanical properties of unperturbed membranes:

- time and length scales
- energetic contributions

local modifications by fusion objects

- thickness and density profiles in simulations and numerical calculations
- superposition of effects

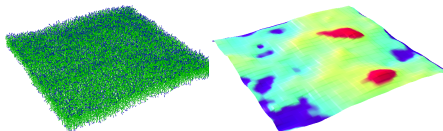
lipid mediated interactions

- the peptides stabilize the pore
- the peptide lowers the line tension of the pore

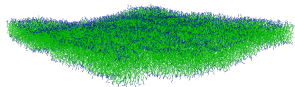
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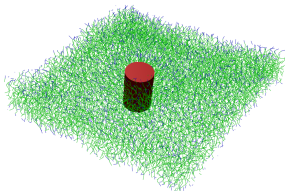


planar membranes



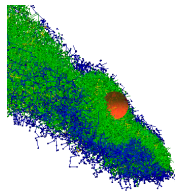
- reference values

protein/lipid interactions



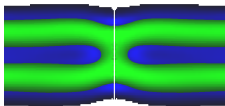
- superposition of effects

hydrophobic stability



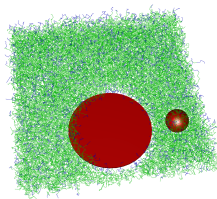
- conditions for stability

stalk morphologies



- universality of structures in models and experiments

pore/protein interactions

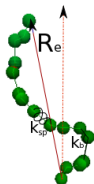


- superposition of thickness profiles

bonded (harmonic spring, bending):

$$\frac{U_{sp}}{k_B T} = \sum_{i=1}^{N_b-1} \frac{k_{sp}}{2} (\mathbf{r}_i - \mathbf{r}_{i+1})^2$$

$$\frac{U_b}{k_B T} = \sum_{i=2}^{N_b-1} k_b (1 - \cos \theta_{i\pm 1})$$



solvent-free, coarse-grained model

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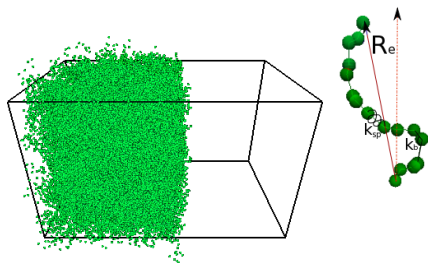
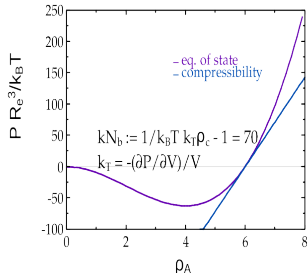
$$\frac{U_b}{k_B T} = \sum_{i=2}^{N_b-1} k_b (1 - \cos \theta_{i\pm 1})$$

non bonded (density functional):

$$\frac{H_{nb}[\rho]}{k_B T} = \int \frac{d^3 r}{R_e^3} \left(\frac{v_{AA}^2}{2} \rho_A^2 + \frac{v_{AAA}^3}{3} \rho_A^3 \right)$$

corresponding eq of state:

$$\frac{P R_e^3}{k_B T} = \rho + \frac{v_{AA}}{2} \rho_A^2 + \frac{2}{3} v_{AAA} \rho_A^3$$



(fluid/vapor phase coexistence)

the virial coefficients are set by ρ_{coex} and the $k N_b$:

$$v_{AA} = -2 \frac{k N_b + 3}{\rho_{coex}} \quad v_{AAA} = \frac{3}{2} \frac{k N_b + 2}{\rho_{coex}^2}$$

M. Hömberg and M. Müller, *J. Chem. Phys.* **132**, 155104 (2010)

solvent-free, coarse-grained model

bonded (harmonic spring, bending):

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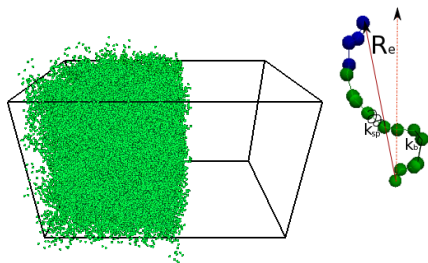
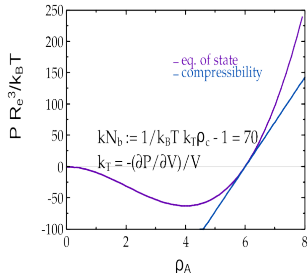
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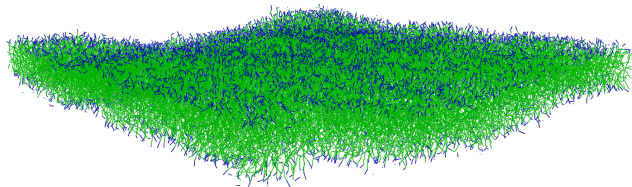
$$v_{AA} = -2 \frac{k N_b + 3}{\rho_{coex}} \quad v_{AAA} = \frac{3}{2} \frac{k N_b + 2}{\rho_{coex}^2}$$

mixed virial coefficient

$$\chi N \stackrel{MF}{=} \rho_{coex} \left(v_{AB} - \frac{1}{2} (v_{AA} + v_{BB}) \right)$$

M. Hömberg and M. Müller, *J. Chem. Phys.* **132**, 155104 (2010)

planar lamellar membrane



- time scale
- length scale
- coupling moduli
- fluctuation spectrum

diffusivity

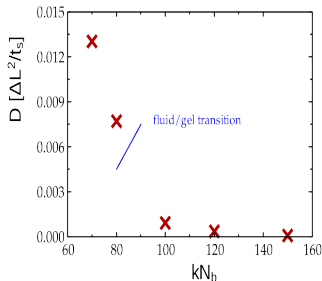
$$D = \lim_{t \rightarrow \infty} \frac{\langle (\mathbf{x}(t) - \mathbf{x}(0))^2 \rangle}{4t}$$

timestep: $1[\Delta t_s] \simeq 8[ps]$

(martini $0.04[ps]$, atomistic $4[fs]$)

K. Weiß and J. Enderlein, *ChemPhysChem* **13**, 990 (2012)

- varying kN_b



diffusivity

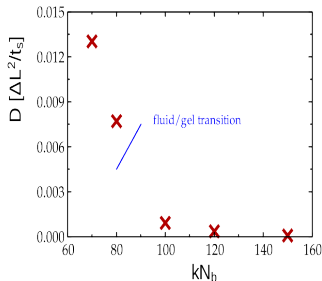
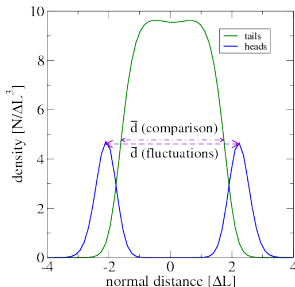
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- varying kN_b



thickness

$$\bar{d} = 3.25$$

$$1[\Delta L] \simeq 1.08[nm]$$

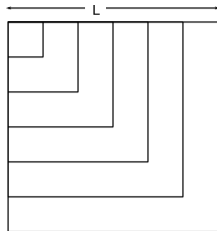
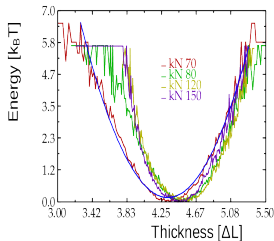
N. Kučerka et al. *Biophysica Acta* **1808**, 2761 (2011)

we sample from *thermal fluctuations*

$$\Delta F_s = \int dx dy \frac{k_s}{2} \frac{(s(x, y) - \bar{s})^2}{\bar{s}^2}$$

s fluctuating quantity, k_s coupling constant, L patch area.

harmonic approximation



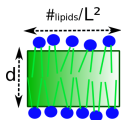
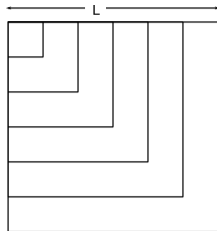
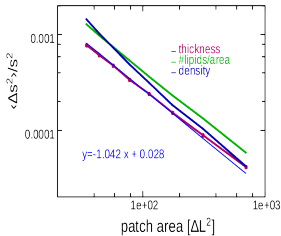
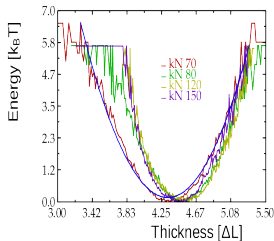
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$$\Delta F_s = \int dx dy \frac{k_s}{2} \frac{(s(x, y) - \bar{s})^2}{\bar{s}^2}$$

$$\frac{1}{k_s} = \lim_{L \rightarrow \infty} \frac{L^2 \langle (s - \bar{s})^2 \rangle_L}{\bar{s}^2}$$

harmonic approximation

standard deviation



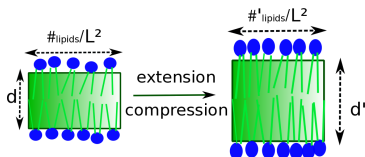
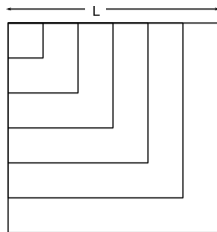
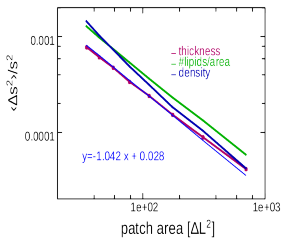
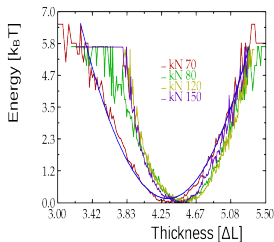
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harmonic approximation

standard deviation



$$\sigma = \rho d$$

thickness $(d - \bar{d})^2$
 lipids/area $(\sigma - \bar{\sigma})^2$
 density $(\rho - \bar{\rho})^2$

$$k_{el} = 22.7 [k_B T / \Delta L^2]$$

$$k_{com} = 38.7 [k_B T / \Delta L^2]$$

$$k_{melt} = 34.6 [k_B T / \Delta L^2]$$

$$\frac{\langle \Delta \sigma^2 \rangle}{\bar{\sigma}^2} = \frac{\langle \Delta \rho^2 \rangle}{\bar{\rho}^2} + \frac{\langle \Delta d^2 \rangle}{\bar{d}^2}$$

$$\frac{1}{k_{com}} = \frac{1}{k_{melt}} + \frac{1}{k_{el}}$$

we sample from *thermal fluctuations*

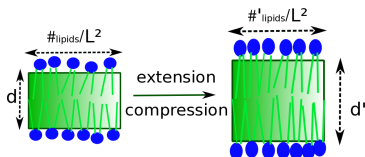
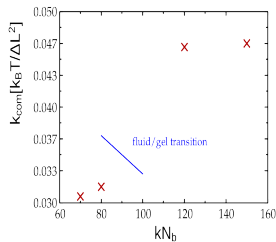
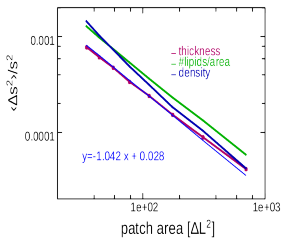
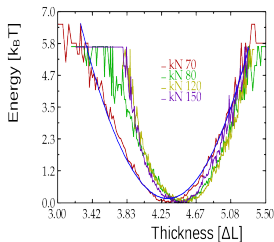
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harmonic approximation

standard deviation

compressibility



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 lipids/area $(\sigma - \bar{\sigma})^2$
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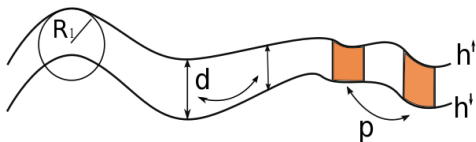
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$$\frac{\langle \Delta \sigma^2 \rangle}{\bar{\sigma}^2} = \frac{\langle \Delta \rho^2 \rangle}{\bar{\rho}^2} + \frac{\langle \Delta d^2 \rangle}{\bar{d}^2}$$

$$\frac{1}{k_{com}} = \frac{1}{k_{melt}} + \frac{1}{k_{el}}$$

bending (height), peristaltic (thickness), protrusion (lipid separation)

$$F = \frac{1}{2} \int dx dy \left(k_{ben} \left(\frac{1}{R_1} + \frac{1}{R_2} \right) + k_{el} \frac{(d-\bar{d})^2}{d^2} + k_{melt} \frac{(\rho-\bar{\rho})^2}{\bar{\rho}^2} \right) \text{ Helfrich model}$$



bending:

 k_{ben} bending rigidity

peristaltic:

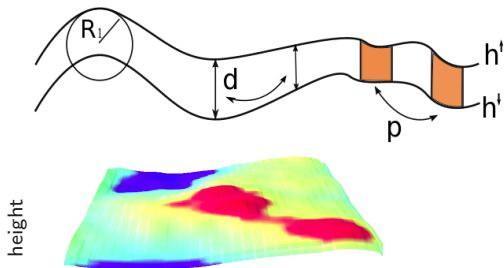
 k_{el} elastic coupling c_0 spontaneous curvature a area/lipids $\zeta := c_0 - a \partial_a c_0$

protrusion:

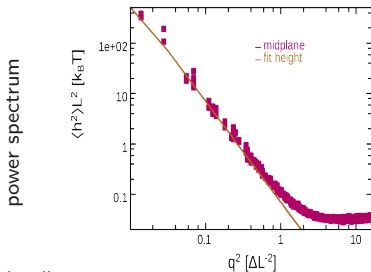
 k_λ protrusion rigidity γ_λ microscopic surface tension

bending (height), peristaltic (thickness), protrusion (lipid separation)

$$F_{ben} = \frac{1}{2} \int dx dy k_{ben} (\nabla^2 h(x, y))^2 \quad \text{Monge representation}$$



$$\langle h^2(\mathbf{q}) \rangle L^2 = \frac{1}{k_{ben} q^4}$$



bending:

 k_{ben} bending rigidity $14.3 [k_B T]$

peristaltic:

 k_{el} elastic coupling c_0 spontaneous curvature a area/lipids $\zeta := c_0 - a \partial_a c_0$

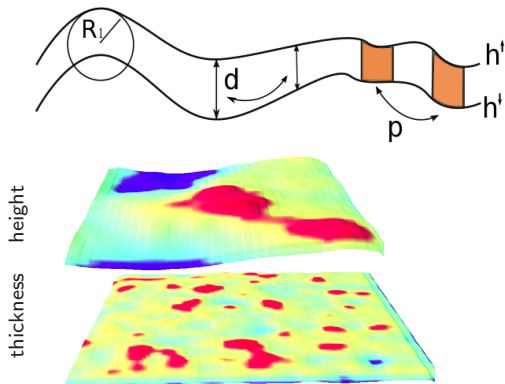
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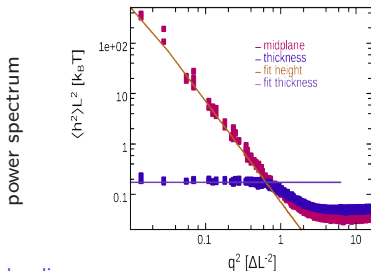
$$F_{ben} = \frac{1}{2} \int dx dy k_{ben} (\nabla^2 h(x, y))^2$$

$$F_{per} = \frac{1}{2} \int dx dy k_{el} \frac{d^2(x, y)}{\bar{d}^2}$$



$$\langle h^2(\mathbf{q}) \rangle L^2 = \frac{1}{k_{ben} q^4}$$

$$\langle d^2(\mathbf{q}) \rangle L^2 = \frac{1}{k_{el} / \bar{d}^2}$$



bending:

 k_{ben} bending rigidity $14.3 [k_B T]$

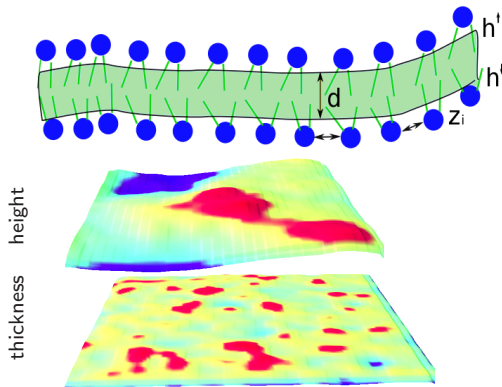
peristaltic:

 k_{el} elastic coupling $1.74 / \bar{d}^2 [k_B T / \Delta L^4]$ c_0 spontaneous curvature a area/lipids $\zeta := c_0 - a \partial_a c_0$

protrusion:

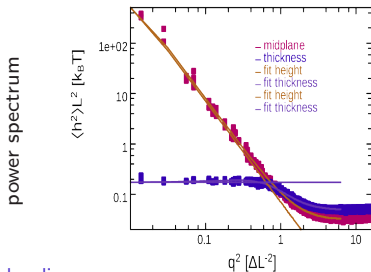
 k_λ protrusion rigidity γ_λ microscopic surface tension

bending (height), peristaltic (thickness), protrusion (lipid separation)



$$\langle h^2(\mathbf{q}) \rangle L^2 = \frac{1}{k_{ben} q^4} + \frac{1}{2(k_\lambda + \gamma_\lambda q^2)}$$

$$\langle d^2(\mathbf{q}) \rangle L^2 = \frac{1}{k_{ben} q^4 - 4\zeta k_{ben} q^2 + k_{el}/d^2} + \frac{1}{2(k_\lambda + \gamma_\lambda q^2)}$$

Brannigan and Brown, *Biophys. J.* 92, 864 (2007)

bending:

 k_{ben} bending rigidity $12.5 [k_B T]$

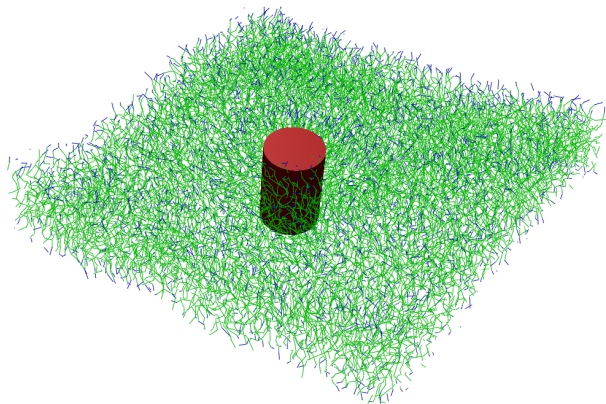
peristaltic:

 k_{el} elastic coupling $1.96/\bar{d}^2 [k_B T/\Delta L^4]$ c_0 spontaneous curvature a area/lipids $\zeta := c_0 - a\partial_a c_0 = 0.14/\bar{d} [\Delta L^2]$

protrusion:

 k_λ protrusion rigidity γ_λ microscopic surface tensionwe extract: k_{ben} , ζ , k_{el}

hydrophobic inclusion



- radial thickness profile
- weakening of the membrane
- continuum model
- superposition of effects
- pore stabilisation

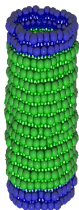
cylindrical transmembrane protein

cluster of connected monomers

radius $1[\Delta L]$

hydrophobic mismatch 1.3

$N_b/A = 38[\Delta L^{-2}]$



contact angle and thinning

cylindrical transmembrane protein

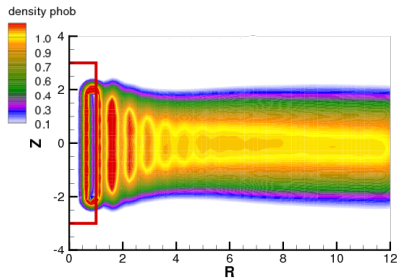
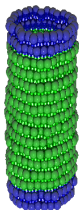
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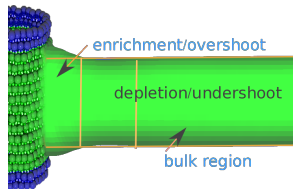
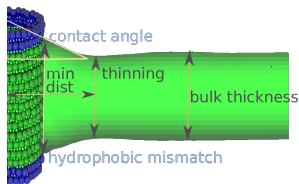
hydrophobic mismatch 1.3

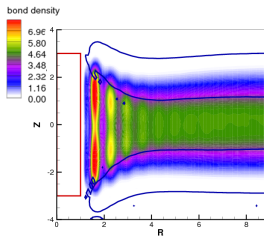
$N_b/A = 38[\Delta L^{-2}]$

$\theta_c = 31^\circ$

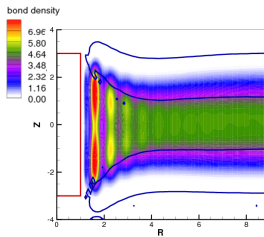


radial thickness profiles





- bond length



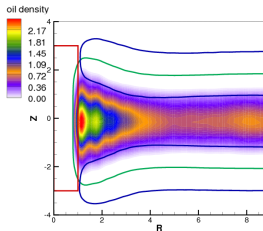
- bond length



oil molecule:

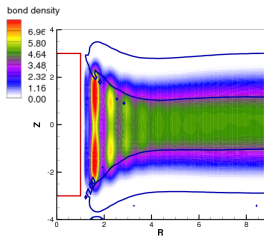
- dodecane
- hydrocarbon tail

oil partitions close to the peptide



- density of the oil

- the oil loses its translational entropy
- acts as a sensor to partition where most of the stress is



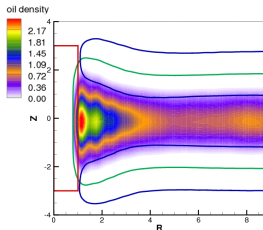
- bond length



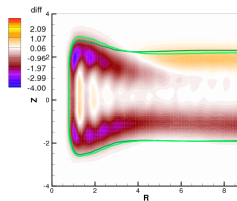
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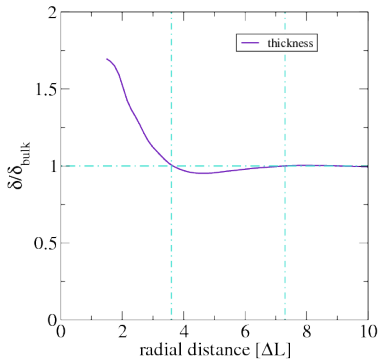


- point to point hydrophobic density difference with and without oil

- the oil loses its translational entropy
- acts as a sensor to partition where most of the stress is

mean separation

rescaled to the bulk value
thickness from the polar/apolar density
intersection

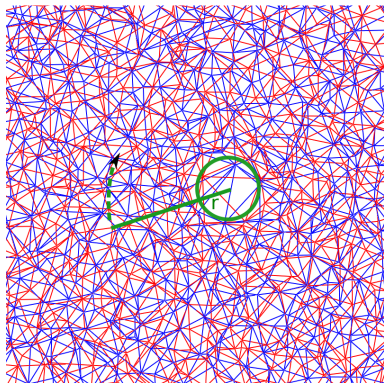


- thickness
- mean area

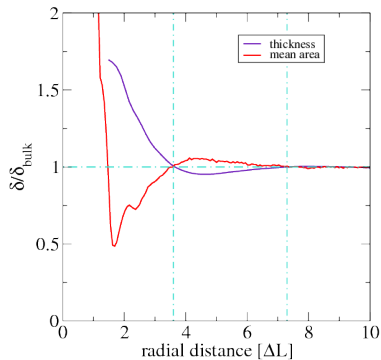
mean separation

rescaled to the bulk value
thickness from the polar/apolar density
intersection
bead number normalization

upper and lower monolayers

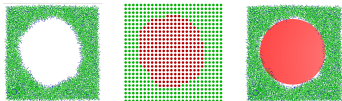


Delaunay triangulation



- thickness
- mean area

lowering the line tension of the pore

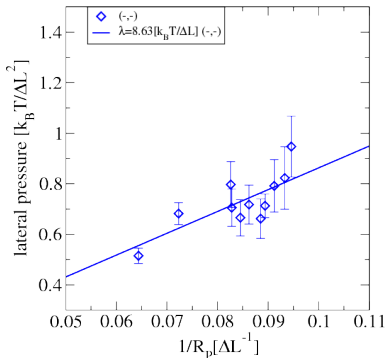


classical nucleation theory

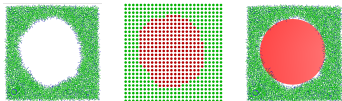
$$G = G_0 + 2\pi R_p \lambda - \pi R_p^2 P_l$$

line tension of the pore in NVT
ensemble

$$P_l = \frac{\lambda}{R_p}$$



lowering the line tension of the pore



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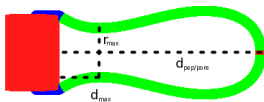
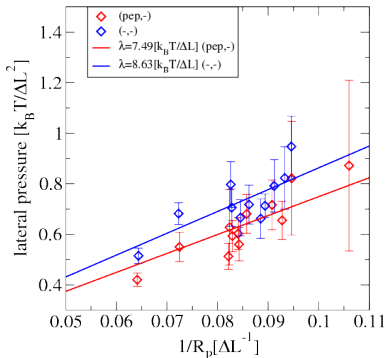
line tension of the pore in NVT ensemble

$$P_l = \frac{\lambda}{R_p}$$

- the peptide lowers the line tension of the pore

"pore's radius correction"

$$P_l = \frac{\lambda}{R_p} \left(1 - \alpha_{pep} \frac{N_{pep}}{R_p} \right)$$



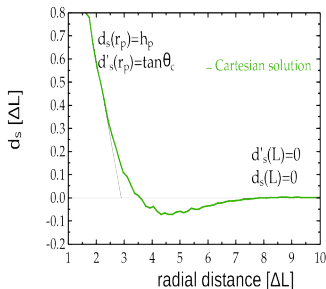
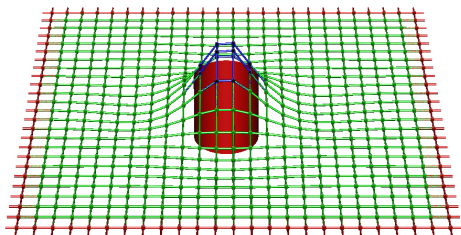
elastic model

$$F = \int dx dy \quad \frac{k_{ben}}{2} (\nabla^2 d_s)^2 + 4k_{ben} c_0 \nabla^2 d_s + 2 \frac{k_{ben} \zeta}{d} d_s \nabla^2 d_s + \frac{k_{el}}{2d^2} d_s^2$$

$$d_s(x, y) := d(x, y) - \bar{d} \quad \text{Euler Lagrange equations:} \quad \frac{\delta F}{\delta d_s} = 0$$

$$\left(k_{ben} \nabla_c^4 + \frac{4k_{ben} \zeta}{d} \nabla_c^2 + \frac{k_{el}}{d^2} \right) d_s(x, y) = 0 \quad \nabla_c^2 := \begin{pmatrix} \partial_x^2 & 0 \\ 0 & \partial_y^2 \end{pmatrix}$$

sketch



B. West, F. L. H. Brown and F. Schmid, *Biophys. J.* **96**, 101 (2009)

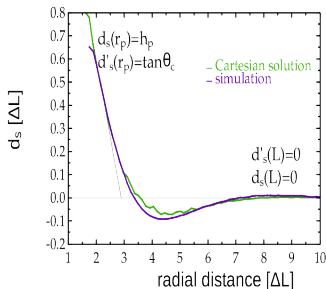
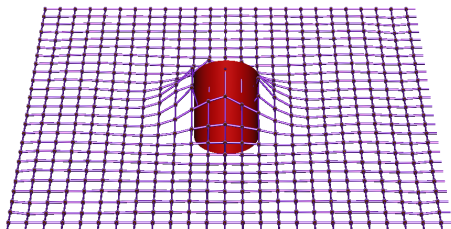
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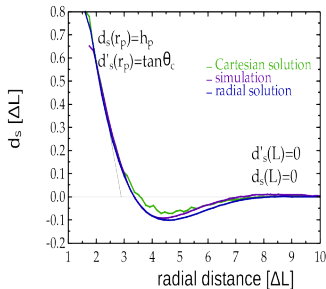
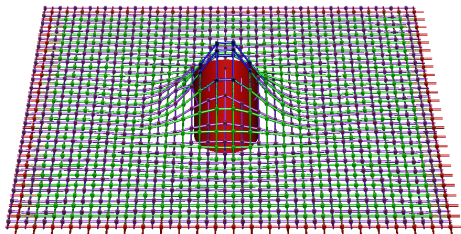
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sketch



B. West, F. L. H. Brown and F. Schmid, *Biophys. J.* **96**, 101 (2009)

elastic model

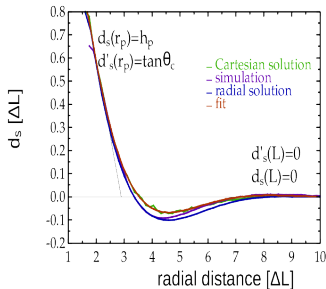
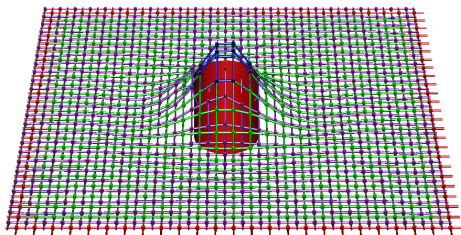
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fitting equation: $A e^{-r/\xi} \frac{\sin(kr)}{r} \quad \xi = 2.2[\Delta L] \quad k = 0.88[\Delta L^{-1}]$

sketch

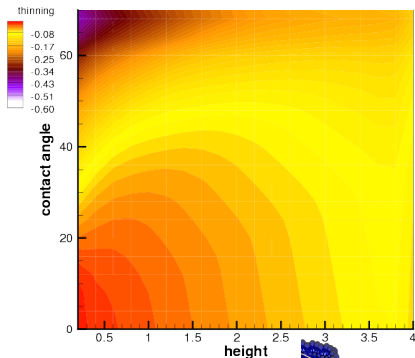


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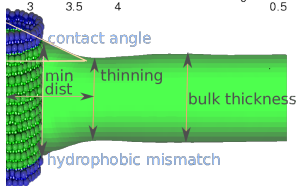
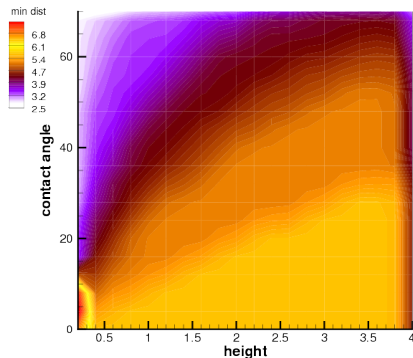
thickness characteristics

the solution of the continuum model is 10 000 times faster than simulations

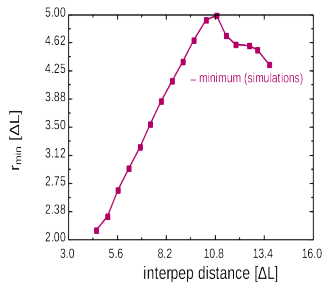
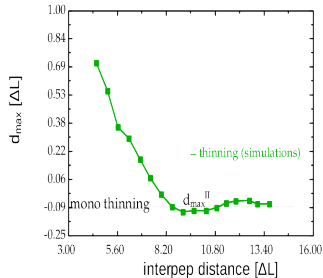
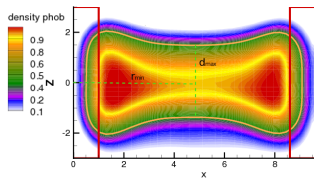
maximum thinning d_{max}



minimum distance r_{min}



two inclusions

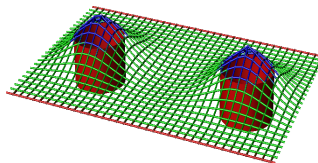
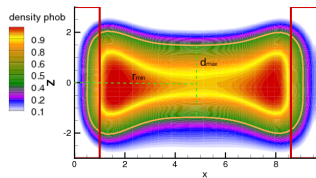


- r_{min}^{II} : minimum splits in two
- d_{max}^{II} : superposition effect is stronger

clusterisation of gramicidins:
(hydrophobic matching)

T. Harroun et al *Biophys. J.* 76, 937 (1999)

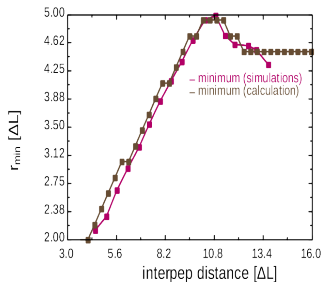
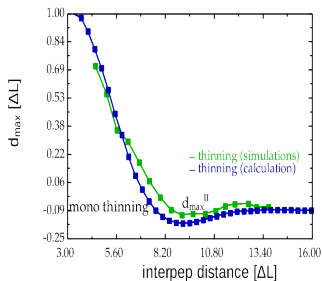
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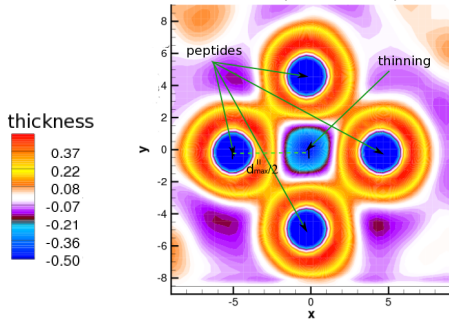
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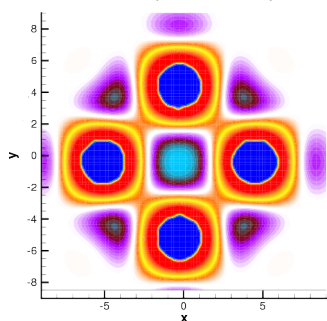
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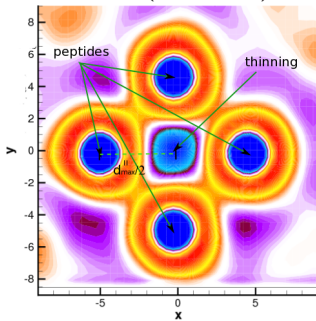
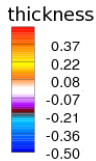
thickness (simulations)



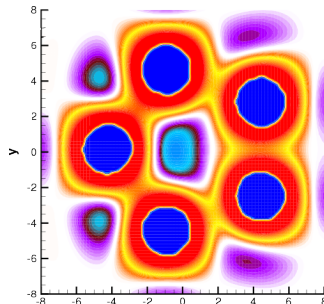
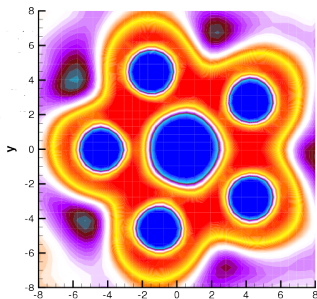
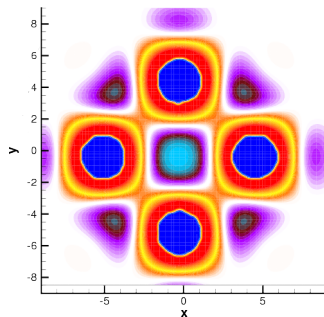
thickness (calculations)



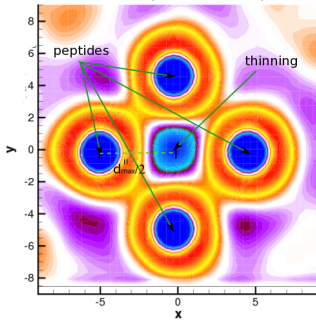
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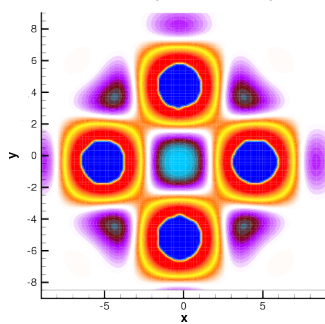
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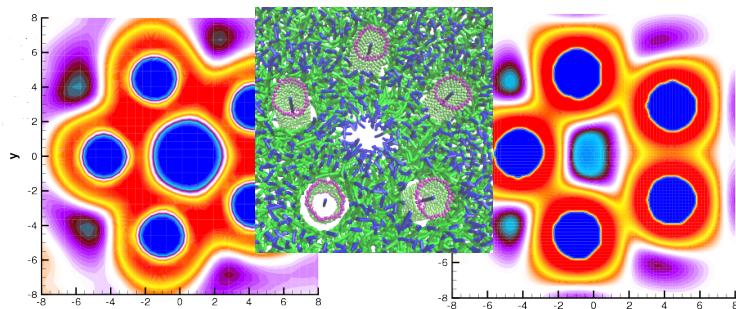
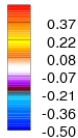
thickness (simulations)



thickness (calculations)



thickness



unperturbed membranes

- **sampling from thermal fluctuations**
 - *time and length scale*
 - *energetic contributions*
- **power spectrum**
 - *material properties*
 - *parametrisation of the continuum model*

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 - *undershoot below the bulk value*
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 - *at the interface with the peptide (pore's rim and stalk's ends)*
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minimal models

- *fast and fine exploration of phenomena*
- *tuned by more detailed models*
- *confirm the multiscale approach (universality of stalk's morphologies) (bilayer repulsion)*

lipid/peptide

- **dynamics**

- *study the peptide diffusion by changing the peptide description*
- *study the lipid diffusivity depending on the radial distance from the peptide*

lipid/peptide

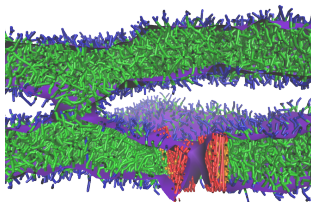
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stalk/pore/peptides

- **competing line tensions**

- interactions between a boundle of peptide and a stalk



thank you for your attention

acknowledgments

- Marcus Müller
- Yuliya Smirnova
- Jelger Risselada
- Martin Hömberg
- Kostas Daoulas
- Ulrich Welling

foundings: SFB project



simulation technique: MD + MDPD thermostat

characteristic:

- the total force is the sum of the conservative, random and dissipative forces

$$\mathbf{F}^{tot} = \mathbf{F}^c + \mathbf{F}^r + \mathbf{F}^d$$

- the forces are pairwise

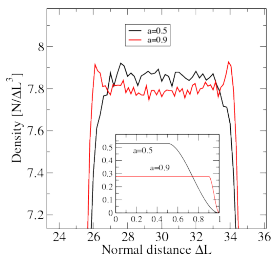
$$\mathbf{F}_i^{tot} = \sum_j \mathbf{F}_{ij}^c + \mathbf{F}_{ij}^r + \mathbf{F}_{ij}^d$$

- the forces are softened via a weighting function

$$\mathbf{F}_{ij} = \mathbf{F}_{ij} w(r_{ij})$$

- local density dependence
- “pragmatic extension of the classical DPD that allows one to prescribe the thermodynamic behavior of a system”*

- NPT*
- NVT*
- NP_tT* tensionless membrane.



P. Español and P. B. Warren *Europhys. Lett.* **30** 191 (1995)

S. Y. Trominov et al. *J. Chem. Phys.* **117** 9383 (2002)

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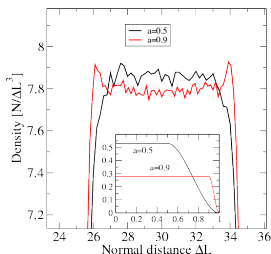
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features of the multibody DPD:

- local density dependence
- “pragmatic extension of the classical DPD that allows one to prescribe the thermodynamic behavior of a system”

ensembles

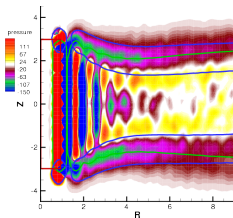
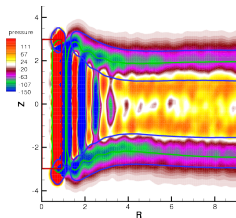
- NPT
- NVT
- NP_tT tensionless membrane.

$$P_{\alpha\beta}(r, z) = k_B T \rho(r, z) + k_B T \rho(r, z) + \frac{1}{V} \sum_{ij}^{(r, z)} \frac{dU_{ij}}{dr} \frac{x_{ij}^\alpha x_{ij}^\beta}{|x|}$$

normal component $P_z^l(r, z) = P_{zz}(r, z) - \frac{P_{\theta\theta}(r, z) + P_{rr}(r, z)}{2}$

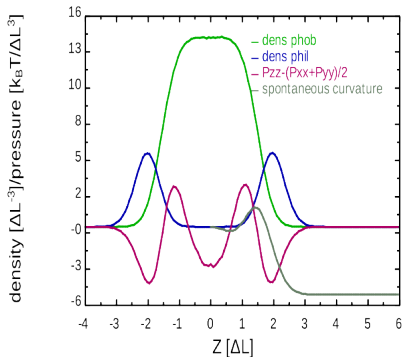
no oil

with oil



- identification of the interface
- position of the relaxation by the oil

calculation of the spontaneous curvature



lateral pressure

$$P_{zz}^l(r, z) = P_{zz}(r, z) - \left(\frac{P_{xx}(r, z) + P_{yy}(r, z)}{2} \right)$$

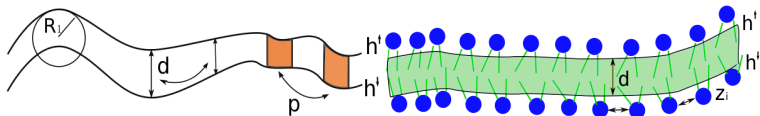
spontaneous curvature

$$k_{ben} c_0 = \int_0^L dz z P_{zz}^l(z)$$

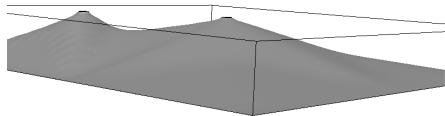
$$c_0 = -0.36[\Delta L^{-1}]$$

normal lateral pressure profile

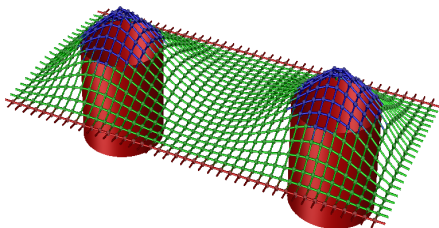
$$\begin{aligned}
 F &= \int dx dy \left(k_{ben} 2(\nabla^2 h)^2 + k_\lambda (z^{+2} + z^{-2}) \right. \\
 &+ \gamma_\lambda \left((\nabla z^+)^2 + (\nabla z^-)^2 + \nabla h \nabla z^+ / 2 + \nabla d \nabla z^- \right) \\
 &+ \frac{k_{com}}{2} d^2 + k_{ben} c_0 \nabla^2 d + \frac{k_{ben} \zeta d}{\bar{d}} \nabla^2 d + \frac{k_{ben}}{2} (\nabla^2 d)^2 \left. \right)
 \end{aligned}$$



comparison with the solution of the differential equation in 2d

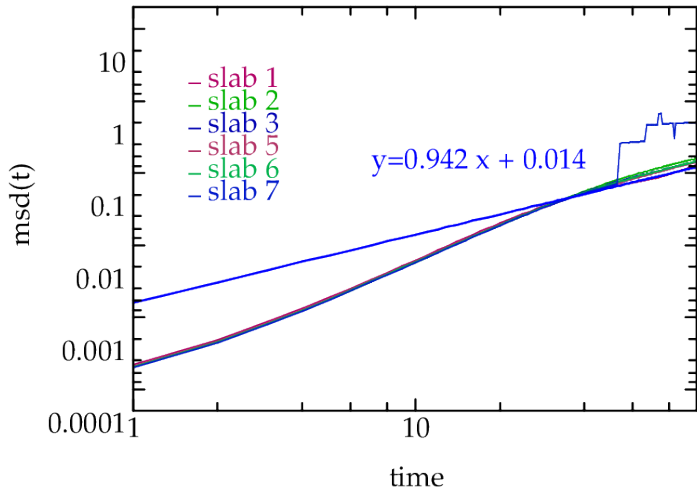


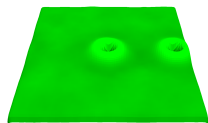
finite elements calculation (surface evolver)



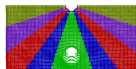
finite differences calculation

mean square displacement in radial slabs

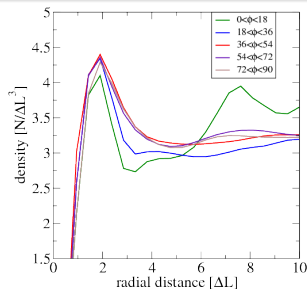




density plot around the inclusions

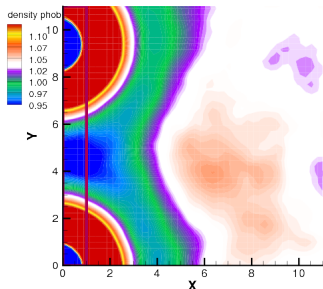


division in sectors by angles



minimum distance and depth

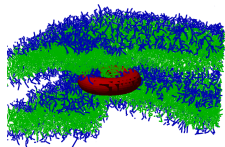
- the membrane is thinner between the two inclusions



- the position of the minimum shifts

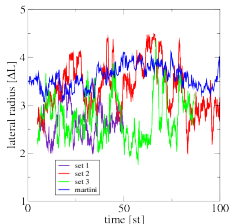
stiffness of a circular stalk

we search iteratively a torus surrounding the stalk with:

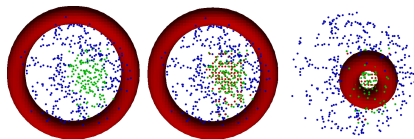


- the smallest lateral radius
- the largest normal radius
- the most contact with heads
- the less contact with tails

radial evolution

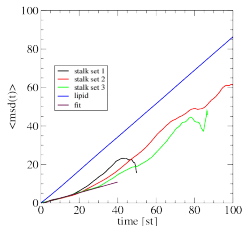


we count the beads inside the torus



- the **center of mass** of the beads is the torus position
- the **radius** of the torus is $r_t = \sqrt{A}/2\pi$, A the area occupied by the beads

diffusivity



$$D_{stalk} = D_{lipid}/3$$

exp data

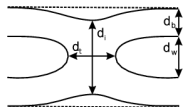
PhD thesis of S. Aeffner

radial density profiles - model/scale dependence

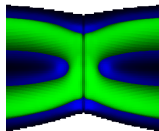
dft, implicit solvent

Martini force field,
explicit solvent

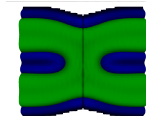
flexible chains, explicit
solvent



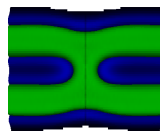
$$\begin{aligned} d_t/d_s &= 1.6 - 1.8 \\ d_t/d_b &= 2 \\ d_s/d_b &= 1.13 - 1.33 \end{aligned}$$



$$\begin{aligned} d_t^*/d_s^* &= 2 \\ d_t^*/d_b^* &= 2.5 \\ d_s^*/d_b^* &= 1.2 \end{aligned}$$

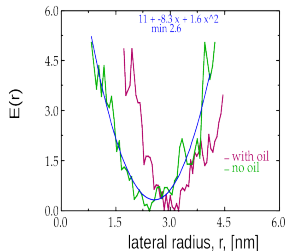


$$\begin{aligned} d_t^*/d_s^* &= 2.1 \\ d_t^*/d_b^* &= 2.1 \\ d_s^*/d_b^* &= 1.0 \end{aligned}$$



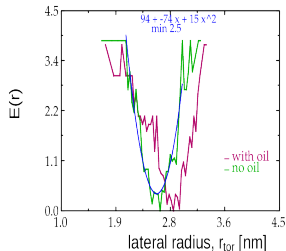
$$\begin{aligned} d_t^*/d_s^* &= 2.9 \\ d_t^*/d_b^* &= 2.2 \\ d_s^*/d_b^* &= 0.77 \end{aligned}$$

dft



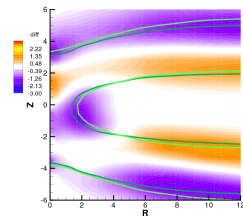
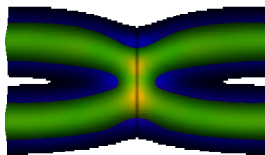
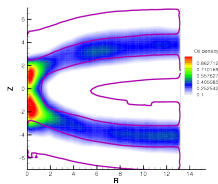
stiffness

Martini



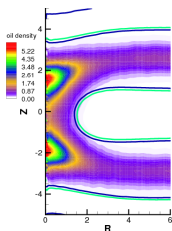
addition of small oil chains in the bilayers

dft 10%

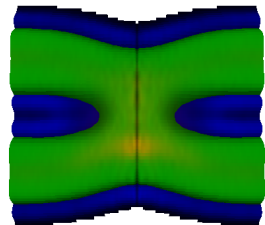


oil partitioning

Martini 15%



density profile



tails density difference

