3D pressure distributions in lipid bilayer systems

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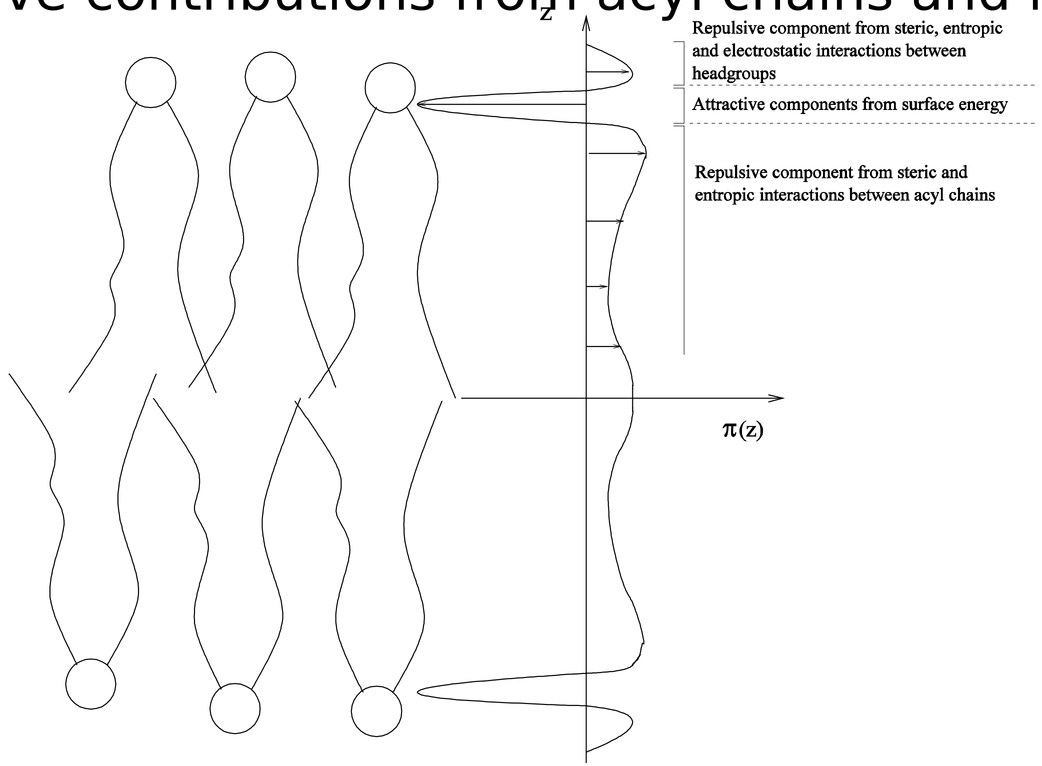
Origin of nonconstant lateral pressure profile in bilayer

- Acyl chains mixed with water -> decrease of entropy
- Two phases (acyl chains and water) -> surface energy(tension)
- Surface tension tends to minimize the surface area
- Repulsive contributions from acyl chains and headgroups



Lateral pressure profile is related to elastic properties of bilayer

- S. Safran, **Statistical Thermodynamics of Surfaces, Interfaces, and Membranes**

$\pi(z)$ = lateral pressure profile
γ = surface tension
K_A = Area compressibility modulus
k = bending modulus
$\bar{k}$ = Gaussian curvature modulus
z = normal coordinate of bilayer
A = area of membrane
c_0 = spontaneous curvature

$$\gamma = \int \pi(z)dz$$

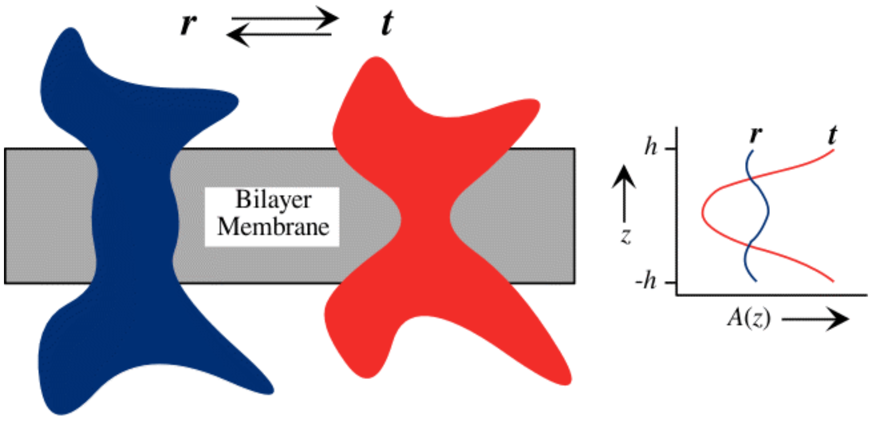
$$kc_0 = \frac{1}{2}\int \pi(z)zdz$$

$$\bar{k} = -\int \pi(z)z^2dz$$

- Integrals are over bilayer

Lateral pressure profile and proteins

- R. S. Cantor, J. Phys. Chem. B 101, 1723 (1997): Protein has to do work against the pressure profile when changing the shape
- Pressure profile depends on lipid composition and amount of anesthetics -> work depends as well (R. S. Cantor, Biochemistry 36, 2339 (1997))

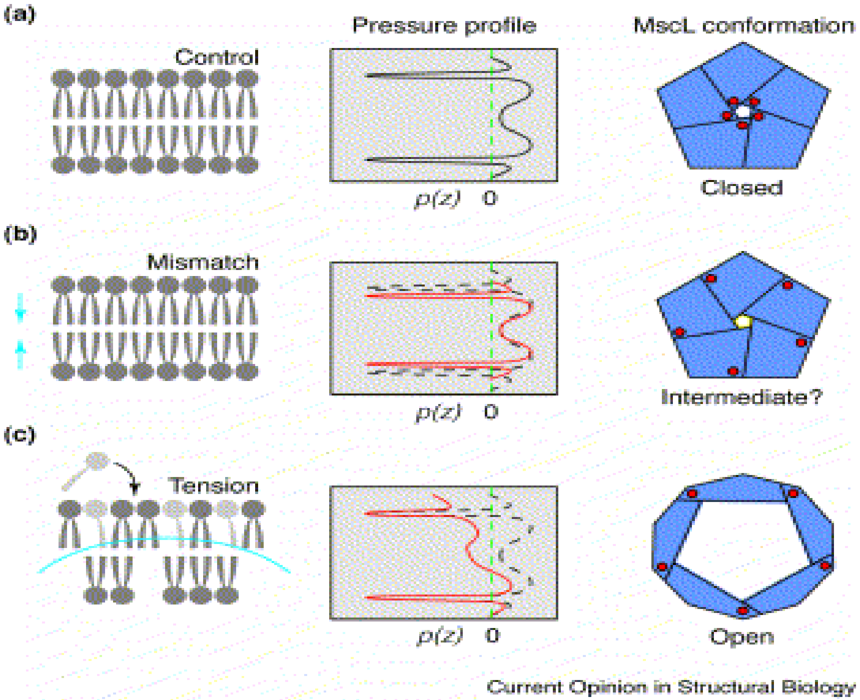


Lateral pressure profile and proteins: Experiments

- Perozo et al. (Curr. Opin. Struc. Biol. 13, 432 (2003)):

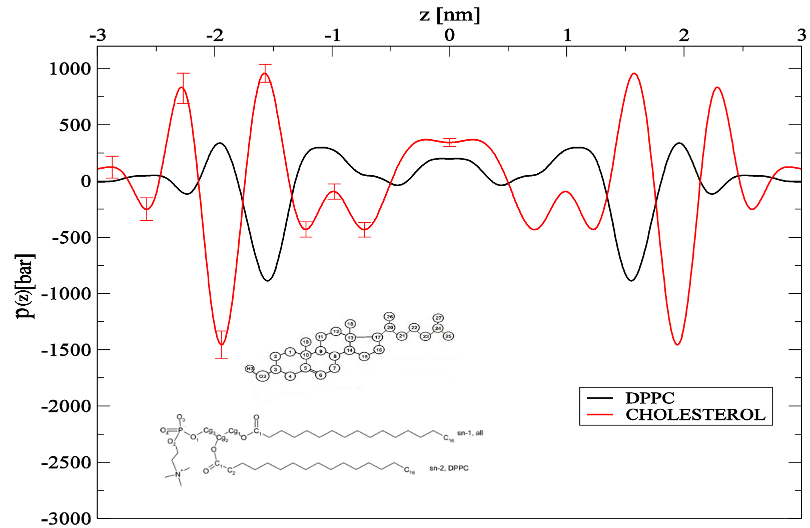
  - **Results:** Incorporation of lysophospatidylcholine into the external leaflet increases channel activity

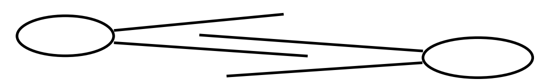
  - **Suggested explanation:** Asymmetric pressure profile favors the open state of MscL

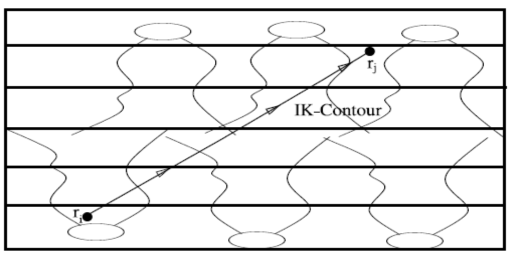


Previous work

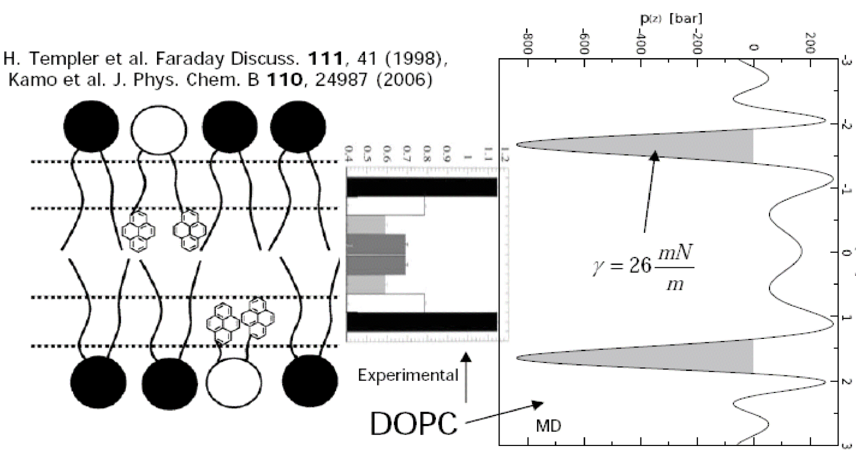
- **Measuring pressure profile experimentally is extremely difficult**
- **Several theoretical studies about pressure profiles in planar bilayers.**
- **Pressure profiles depend on lipid composition**
- **- Sterols:** O. H. S. Ollila et al. J. Struct. Biol. **159**, 311 (2007)
  - Raft-like: P. Niemelä et al. PLoS Comput. Biol. **3**, 304 (2007)
  - Polyunsaturated: O. H. S. Ollila et al. J. Phys. Chem. B **111**, 3139 (2007)
  - Ethanol: E. Terämä et al. submitted to J. Phys. Chem. B (2007)







R. H. Templer et al. Faraday Discuss. **111**, 41 (1998),
T. Kamo et al. J. Phys. Chem. B **110**, 24987 (2006)



Experimental approximations:

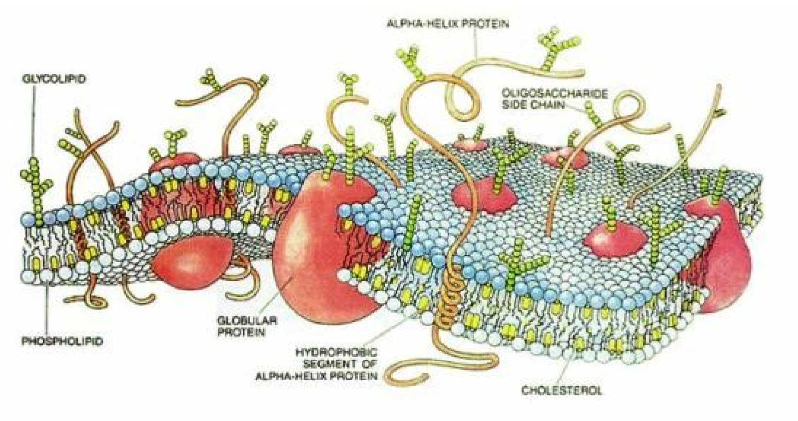
$$\gamma \approx (30-35)\,\frac{mN}{m}$$

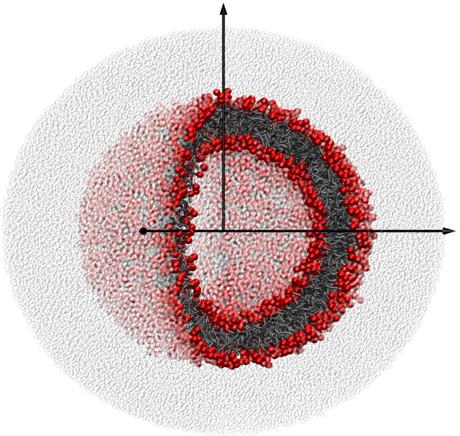
D. Marsh Biochim. Biophys Acta **1286**, 183 (1996)

O. H. S. Ollila et al. J. Phys. Chem. B **111**, 3139 (2007)
O. H. S. Ollila et al. J. Struct. Biol. **159**, 311 (2007),
P. Niemelä et al. PLoS Comput. Biol. **3**, 304 (2007)

3D pressure distribution

- Pressure distribution in membrane protein system?
- Pressure distribution in vesicles and other curved systems (droplets,HDL,LDL,etc.)
- Systems with phase coexistence





We use coarce grained MD simulations

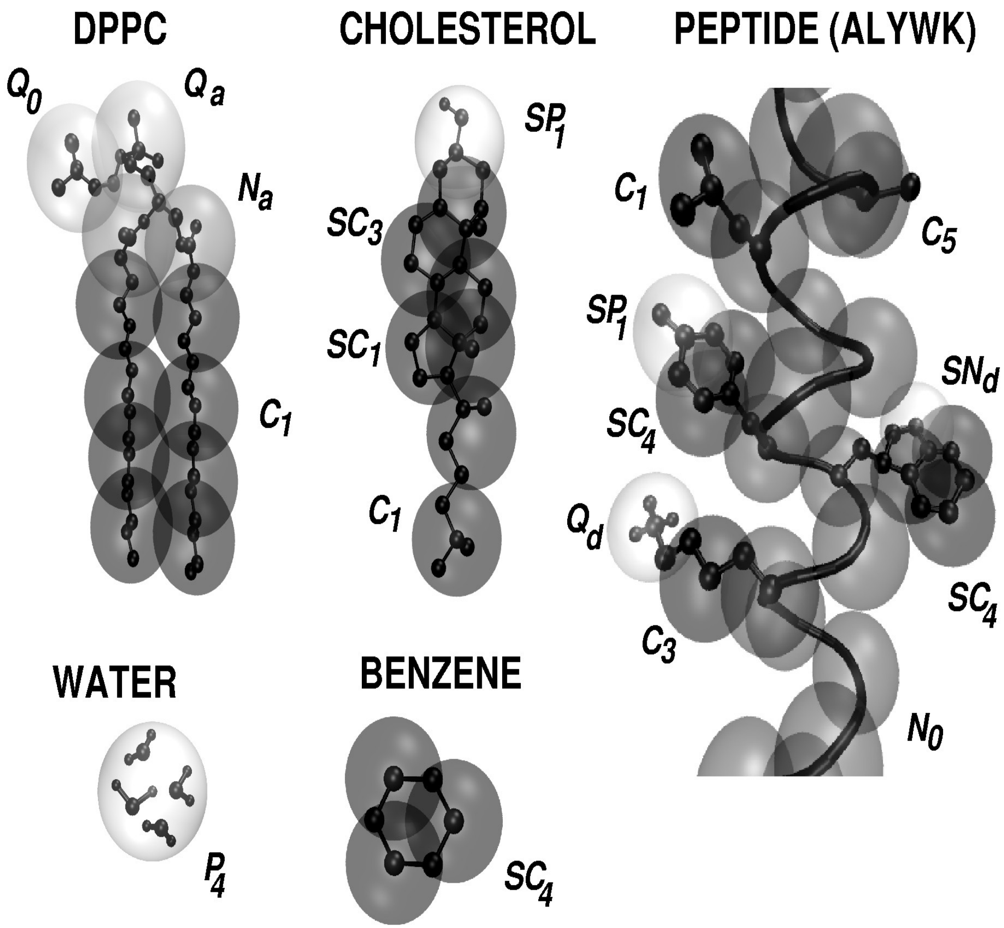
- Martini force field (S.J Marrink et al. JPC-B 111:7812-7824)

- Newton's equation of motion

$$m_i \frac{d^2 \mathbf{x}_i}{dt^2} = \mathbf{F}_i \equiv -\nabla_{\mathbf{r}_i} V(\mathbf{r}_1,\ldots,\mathbf{r}_N)$$

$$V = \sum_{bonds} \frac{k_{ij}^{a_0}}{2}(r_{ij}-a_{ij})^2 + \sum_{angles}\frac{k_{ijk}^{\theta_0}}{2}(\theta_{ijk}-\theta_{0_{ijk}})^2 +$$

$$\sum_{dihedrals} k^{\phi}(1+\cos(n(\phi-\phi^0))) + \sum_{i,j}[\frac{A_{ij}}{r_{ij}^{12}} - \frac{B_{ij}}{r_{ij}^{6}}] + \sum_{i,j}\frac{q_i q_j}{4\pi\varepsilon_0 r_{ij}}$$



How to calculate the 3D pressure field?

- Divide system into 3D grid
- Calculate local pressure tensor for each grid point

$$P^{\alpha\beta}(\mathbf{R}) = \left\langle \sum_i m_i v_i^\alpha v_i^\beta \delta(\mathbf{R} - \mathbf{r}_i) + \sum_i \sum_{j<i} F_{ij}^\alpha \int_{C_{ij}} \delta(\mathbf{R} - \mathbf{l})\, \mathrm{d}l^\beta \right\rangle_t$$

V = Volume
$\mathbf{v_i}$ =velocity of particle i
$\mathcal{C}_{ij}$ =contour from particle i to j
m_i = mass of particle i
$\mathbf{F_{ij}}$ =force between particles i and j

- The pressure for a volume is the average over field

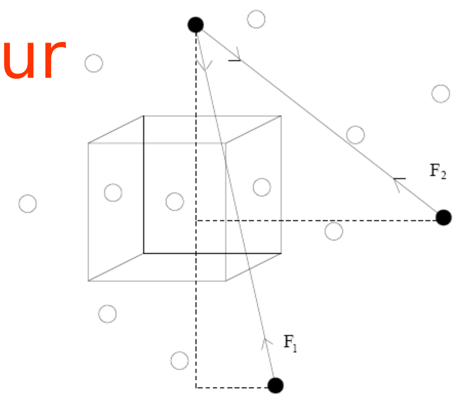
$$\mathbf{P}_V(t) = \frac{\int_V \mathbf{P}(\mathbf{R},t)\mathrm{d}\mathbf{R}}{\int_V \mathrm{d}\mathbf{R}} = \frac{\int_V \mathbf{P}(\mathbf{R},t)\mathrm{d}\mathbf{R}}{V}$$

- Contour is ambigous, we use I-K contour

$$p_V^{\alpha\beta} = \frac{1}{V}\sum_{i\in V} m_i v_i^\alpha v_i^\beta + \sum_n \frac{1}{nV}\sum_{\langle j\rangle}\sum_{\langle k,l\rangle}$$

$$(\nabla^\alpha_{j_k} U^n - \nabla^\alpha_{j_l} U^n) \times \frac{r^\beta_{j_l j_k}}{N}\sum_{\lambda=0}^{N} f_V\left(\mathbf{r}_{j_l} + \frac{\lambda}{N}\mathbf{r}_{j_l j_k}\right),$$

$$f_V(\mathbf{r}) = \begin{cases} 1 & \text{if } \mathbf{r} \in V \\ 0 & \text{if } \mathbf{r} \notin V \end{cases}$$



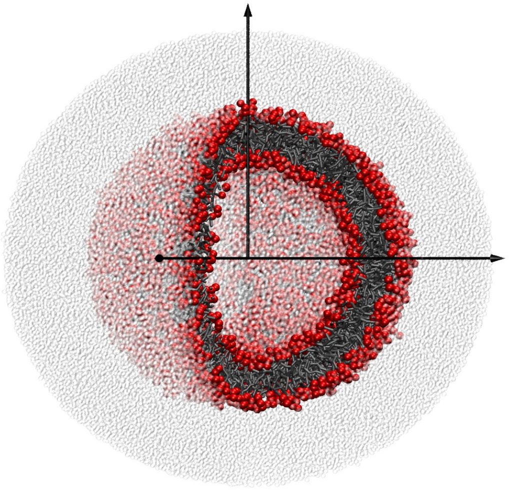
How to calculate 3D pressure field?

- Divide system into 3D grid
- Calculate pressure tensor for each cube
- Transform the tensor to useful coordinate system, e.g. spherical

$$\mathbf{P}' = \mathbf{T}\mathbf{P}\mathbf{T}^T$$

- Take average respect to symmetry of the system (spherical, cylindrical,...) e.g. spherical

$$P'(R) = \langle P'(R, \theta, \phi) \rangle_{\theta,\phi}$$



$\mathbf{P}(\mathbf{x}, \mathbf{y}, \mathbf{z})$ = pressure tensor in cartesian coordinates

$\mathbf{P}'(\mathbf{r}, \theta, \phi)$ = pressure tensor in spherical coordinates

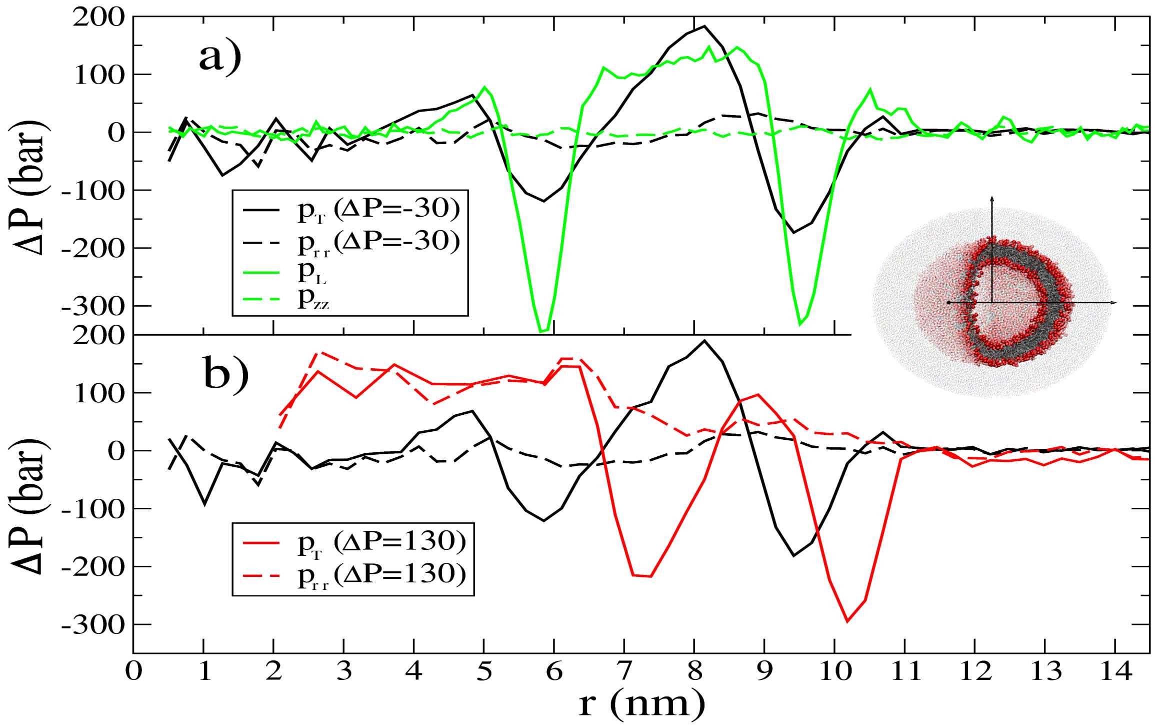
$\mathbf{T}$ = transformation matrix spherical coordinates

Pressure distribution in a vesicle

- DOPC vesicle vs. DOPC bilayer: asymmetry and broader peaks
- Vesicles with pressure difference Δp =-30 and Δp =130 between inside and outside (Hyperosmotic shock)
- Pressure difference induces tension into the bilayer
- Only for large vesicles:

$$\Delta p = \frac{2\sigma(R)}{R} .$$

- Δp=-30bar → -(1-6) mN/m
- Δp=130bar → (45-91) mN/m
- e.g. MscL gating tension (10-20) mN/m

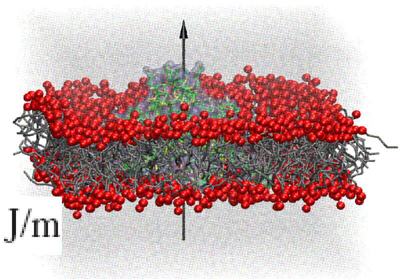


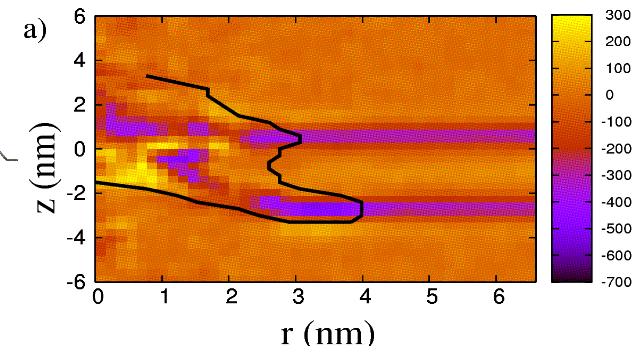
Pressure distribution in bilayer including MsCL

- Mechanosensitive channel protein MscL simulated in DOPC bilayer
- Total lateral tension -38 mN/m to keep the protein in open state
- We assume cylindrical MsCL
- Pressure and tension as a function of radius in cylindrical coordinates

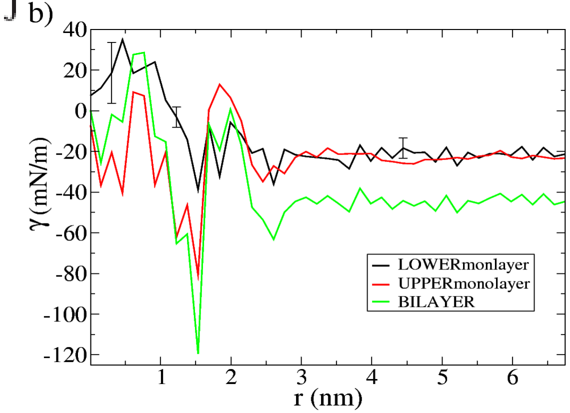
- Tensions:
- lower leaflet -14mN/m
  upper -23 mN/m

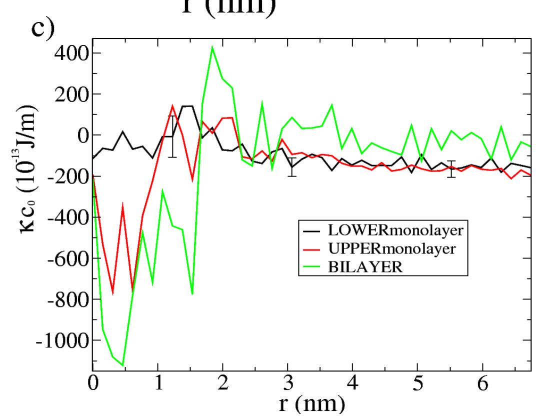
- $kc_0 = \frac{1}{2}\int \pi(z) z d = (-151 \pm 6) \times 10^{-13}$ J/m





- Experimentally $\kappa = (0.1 - 6) \times 10^{-19}$ J
- We get $c_0 = 0.025 - 1.5\,(\text{nm})^{-1}$
- Corresponds R<40 nm
- Open MscL tends to curve membrane





Conclusions

- 3D pressure distribution calculations are useful for e.g. vesicles, membrane protein systems, lipoprotein particles (HDL, LDL) , systems with phase separation, ...
- Pressure difference and membrane tension also for small vesicles
- Open MscL induces curvature

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THANKS FOR YOUR ATTENTION !