Warwick, June 1-5, 2009

Multiscale modeling of lipid and surfactant systems

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Acknowledgements

Papers, parameters & movies: www. softsimu.org

Younger

Teemu Murtola

PhD student

Andrea Catte. PDF

HDL cholesterol, nanodisks with proteins

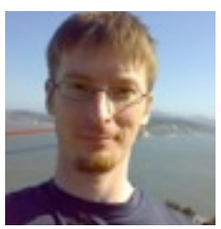
Maria Sammalkorpi (Princeton)

postdoc

Slightly older

Tomasz Róg (Tampere/Helsinki)

postdoc, Academy of Finland Fellow



Ilpo Vattulainen (Tampere/Helsinki)

Mikko Haataja (Princeton)

Samuli Ollila (PhD student)
Emma Falck (at Boston Consulting)
Perttu Niemelä (at VTT)
Michael Patra (at Zeiss)

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CIHR IRSC

NSERC CRSNG

SHARCNET™

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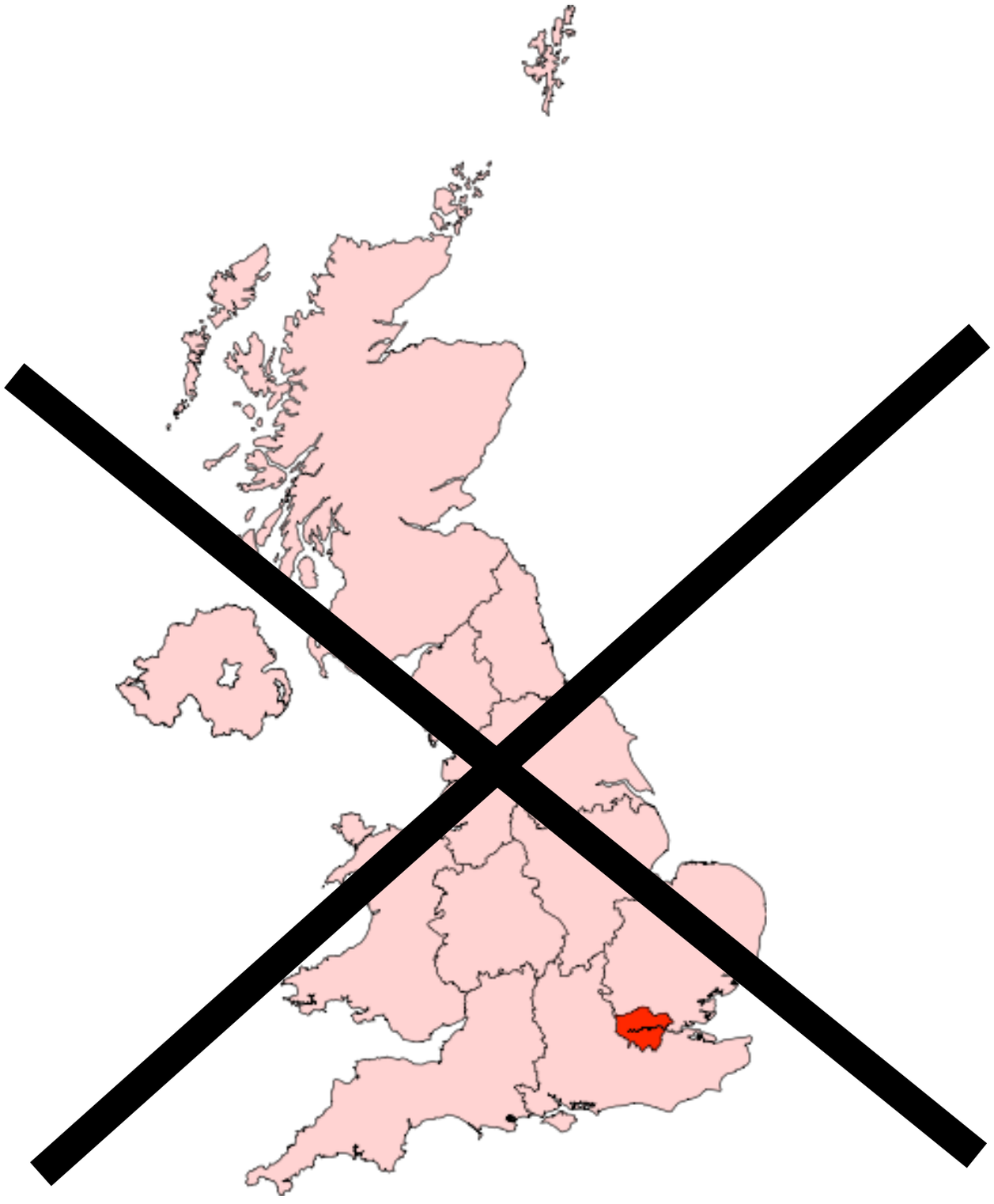
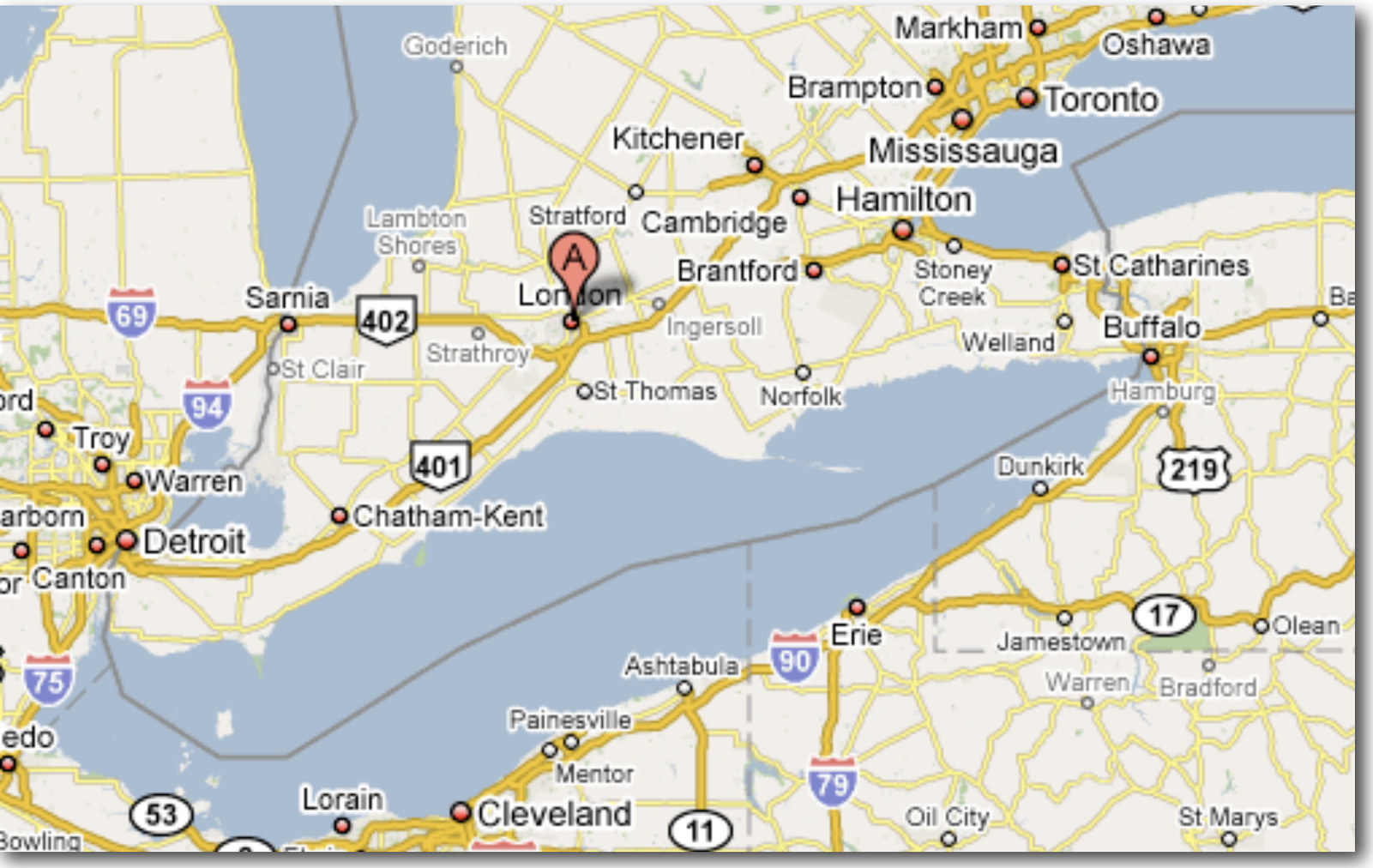
Western

...but where is London, Ontario...





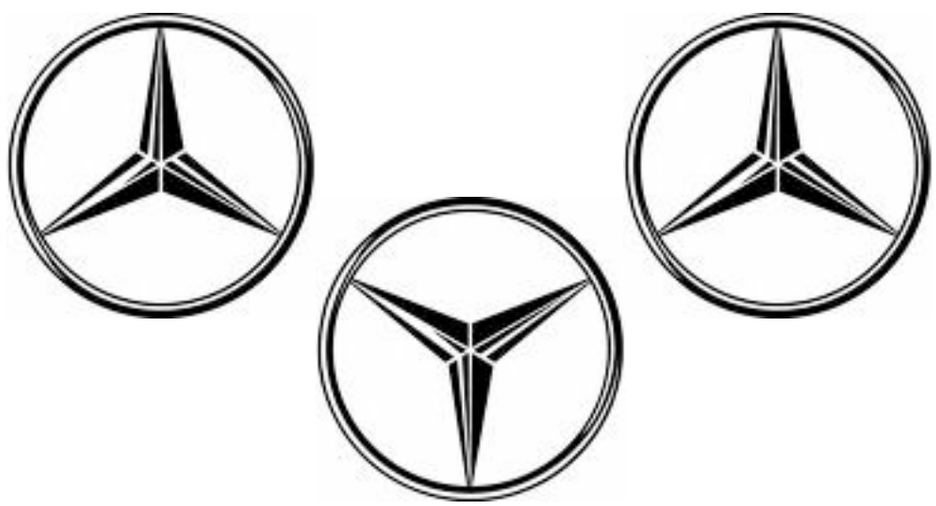
Dates back to 1793 - the city was founded 1826
Population: 352,395 (greater area: 457,720)

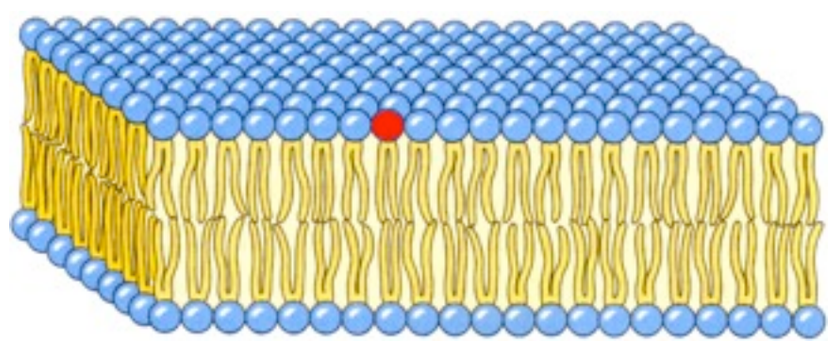
Downtown London.

What's on the plate?

Movies: www.softsimu.org

- **Membrane dynamics: diffusion in single-component lipid membranes.** Structure has been studied a lot but dynamics has received surprisingly little attention. A new mechanism is suggested.
- **Surfactants**. Micellation & micelle fission
- **Coarse graining using structural data from MD.** First using a simple system of NaCl & water and keeping solvent, then moving to a solvent free membrane.





Many time & length scales

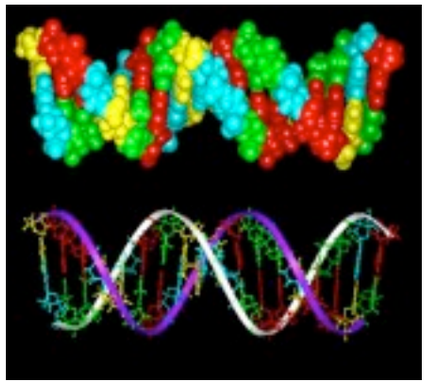
How to bridge the scales - no single method is applicable in all cases.

Macroscale:

- times > 1 sec
- lengths > 1μ
- phase field models, FEM,…

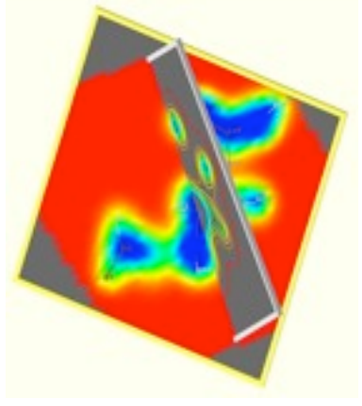
Mesoscale:

- times ~ 10^{-8} – 10^{-2} sec
- lengths ~ 10-1000 Å
- DPD, coarse-graining



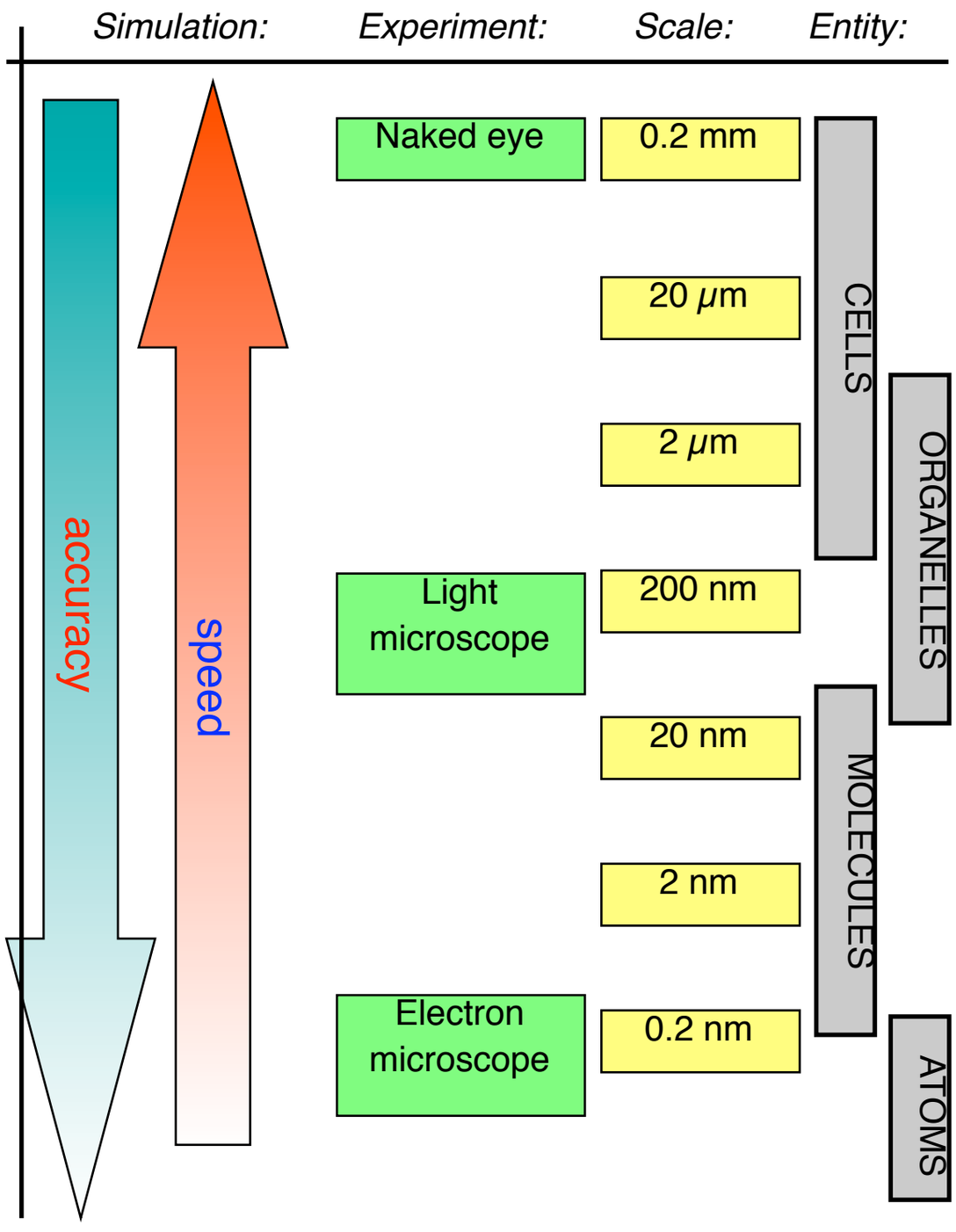
Atomistic scale:

- times ~ 10^{-15} – 10^{-9} sec
- lengths ~ 1-10 Å
- Molecular Dynamics, Monte Carlo

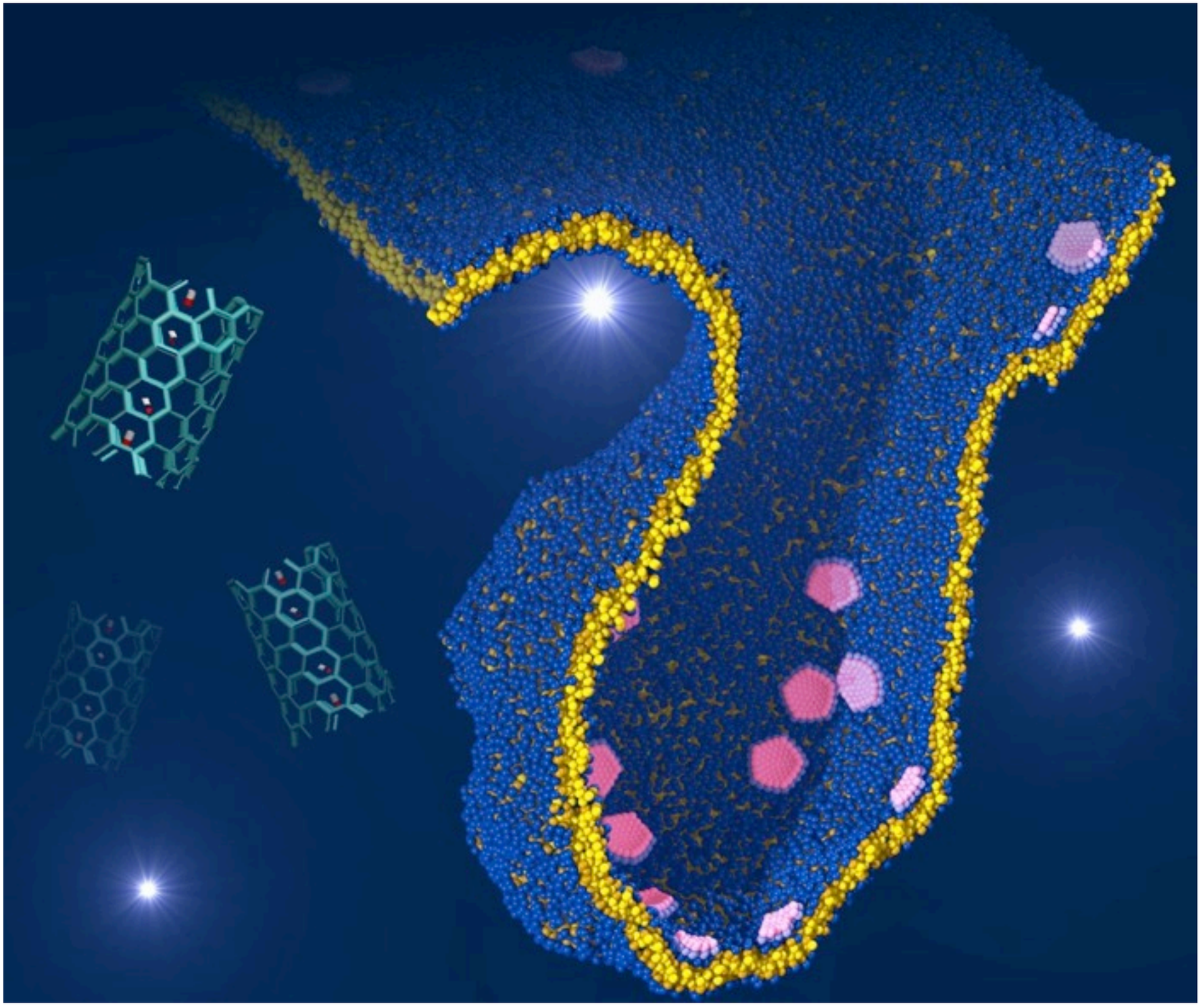


Subatomistic scale:

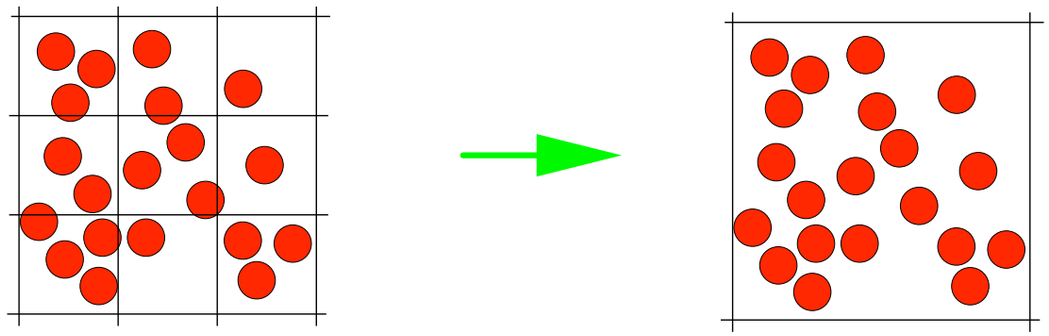
- electronic structure
- ab initio, Green functions



Aim: multiple scales in time and space



Multiscale modeling of emergent materials: biological and soft matter.
Murtola, Bunker, Vattulainen, Deserno, Karttunen, Phys. Chem. Chem. Phys., 2009, 11, 1869



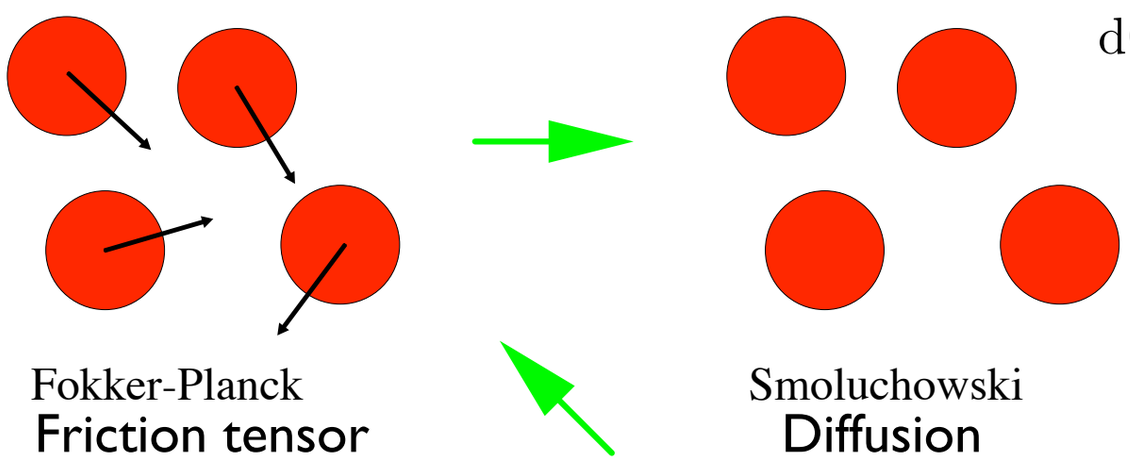
Fick
Continuity equation

Thermodynamics
No equation of motion

$$\partial_t c = -\nabla \mathbf{J} \quad \& \quad \mathbf{J} = -\frac{c}{\zeta}\nabla\mu + \tilde{\mathbf{J}}$$

$$\frac{\partial}{\partial t}P(x,t) = -\sum_i \left[\mathbf{V}_i \cdot \frac{\partial}{\partial \mathbf{Q}_i} + \mathbf{F}_i^{\mathrm{CC}} \cdot \frac{\partial}{\partial \mathbf{P}_i}\right] P(x,t)$$

$$+ k_{\mathrm{B}}T \sum_{ij} \frac{\partial}{\partial \mathbf{P}_i} \cdot \boldsymbol{\zeta}_{ij}(Q) \cdot \left[\frac{\partial}{\partial \mathbf{P}_j} + \frac{\mathbf{P}_i}{M_i k_{\mathrm{B}} T}\right] P(x,t)$$



Fokker-Planck
Friction tensor

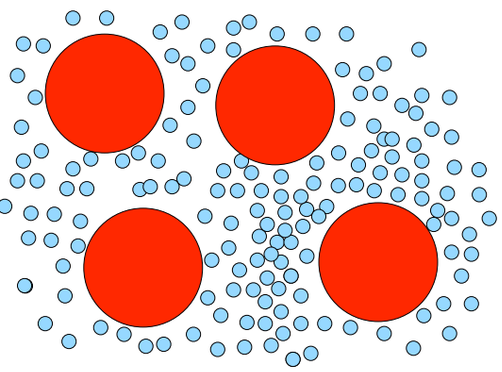
Smoluchowski
Diffusion

$$\mathrm{d}\mathbf{Q}_i = \mathbf{V}_i \mathrm{d}t \qquad \text{and} \qquad \mathrm{d}\mathbf{P}_i = \mathbf{F}_i^{\mathrm{CC}}\mathrm{d}t - \sum_j \boldsymbol{\zeta}_{ij}(Q)\cdot\mathbf{V}_j \mathrm{d}t + \mathrm{d}\tilde{\mathbf{F}}_i$$

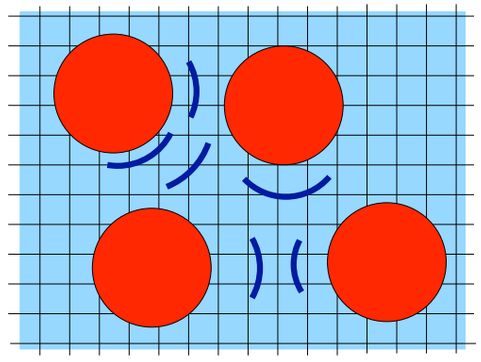
$$\rho_{\mathbf{r}}(z) = \sum_i m\bar{\delta}(\mathbf{r} - \mathbf{q}_i)$$

$$\mathbf{g}_{\mathbf{r}}(z) = \sum_i \mathbf{p}_i\bar{\delta}(\mathbf{r} - \mathbf{q}_i)$$

$$e_{\mathbf{r}}(z) = \sum_i e_i\bar{\delta}(\mathbf{r} - \mathbf{q}_i)$$



Classical Mechanics
Collisions in ps



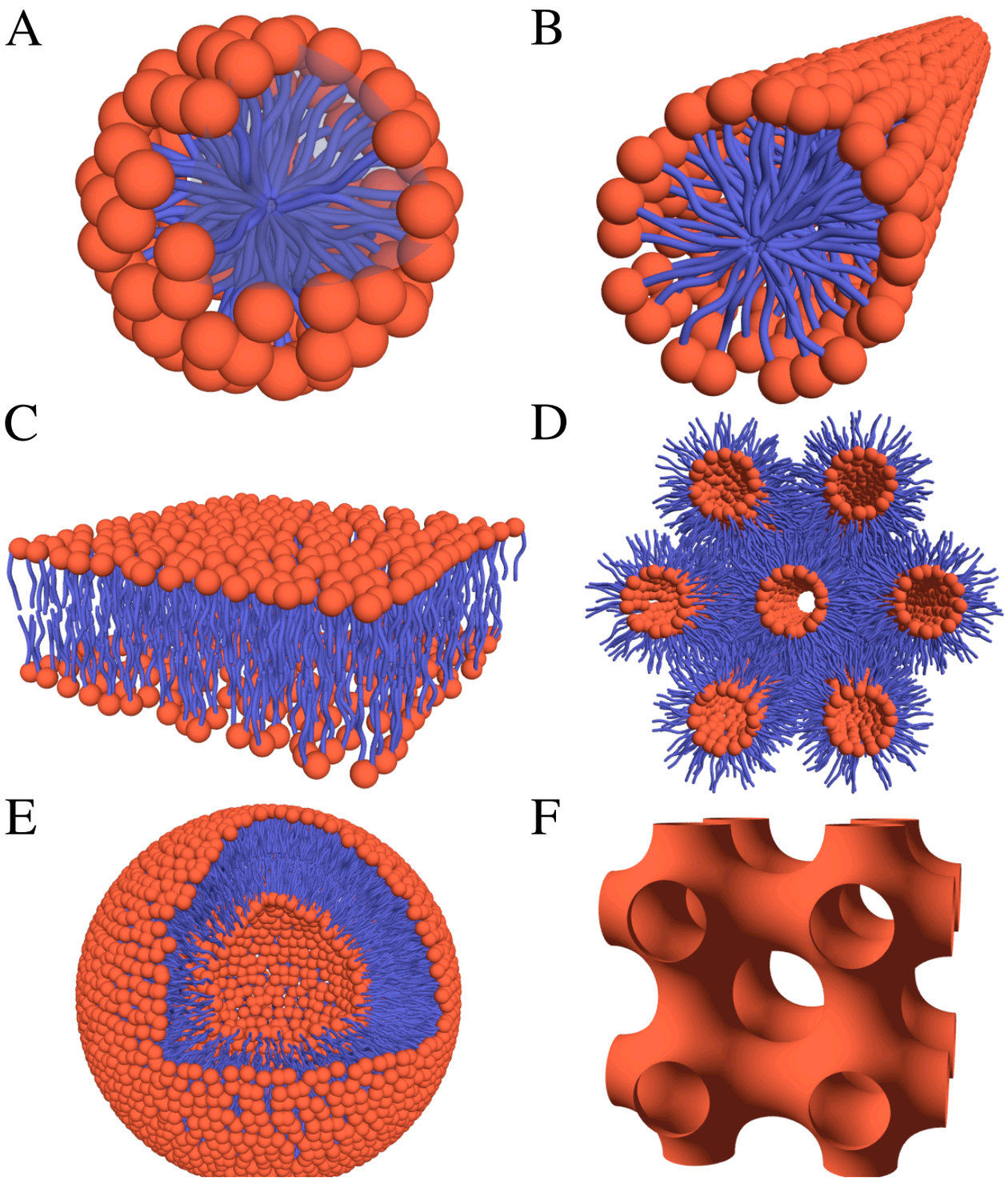
Hydrodynamics
Collective motions

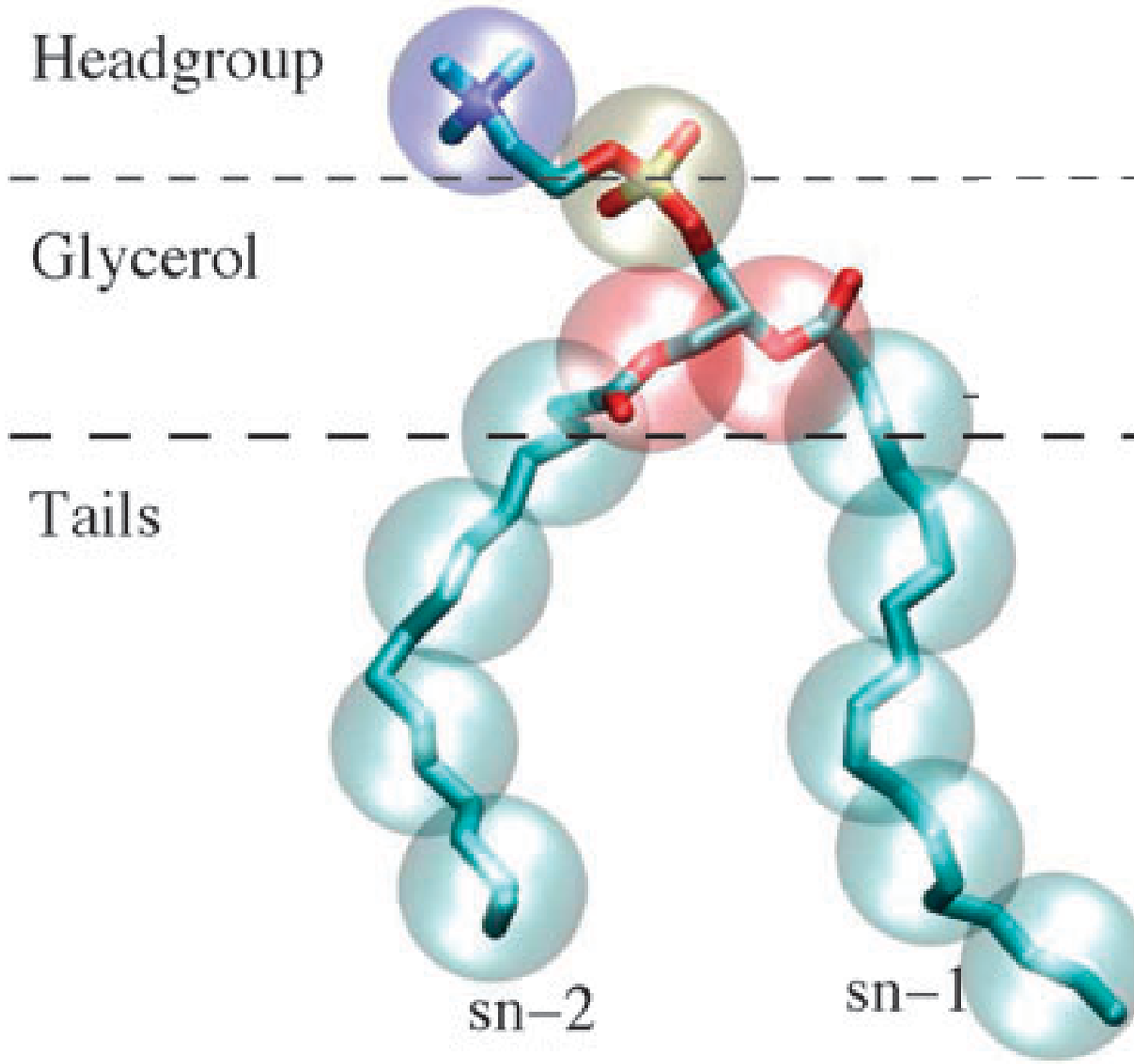
$$\dot{\mathbf{q}}_i = \frac{\partial H(z)}{\partial \mathbf{p}_i}, \qquad \dot{\mathbf{Q}}_i = \frac{\partial H(z)}{\partial \mathbf{P}_i}$$

$$\dot{\mathbf{p}}_i = -\frac{\partial H(z)}{\partial \mathbf{q}_i}, \qquad \dot{\mathbf{P}}_i = -\frac{\partial H(z)}{\partial \mathbf{Q}_i}$$

- P. Español 'Statistical Mechanics of Coarse-Graining' in Novel Methods in Soft Matter Simulations, Karttunen, Vattulainen and Lukkarinen (Eds.), Springer Verlag (2004).

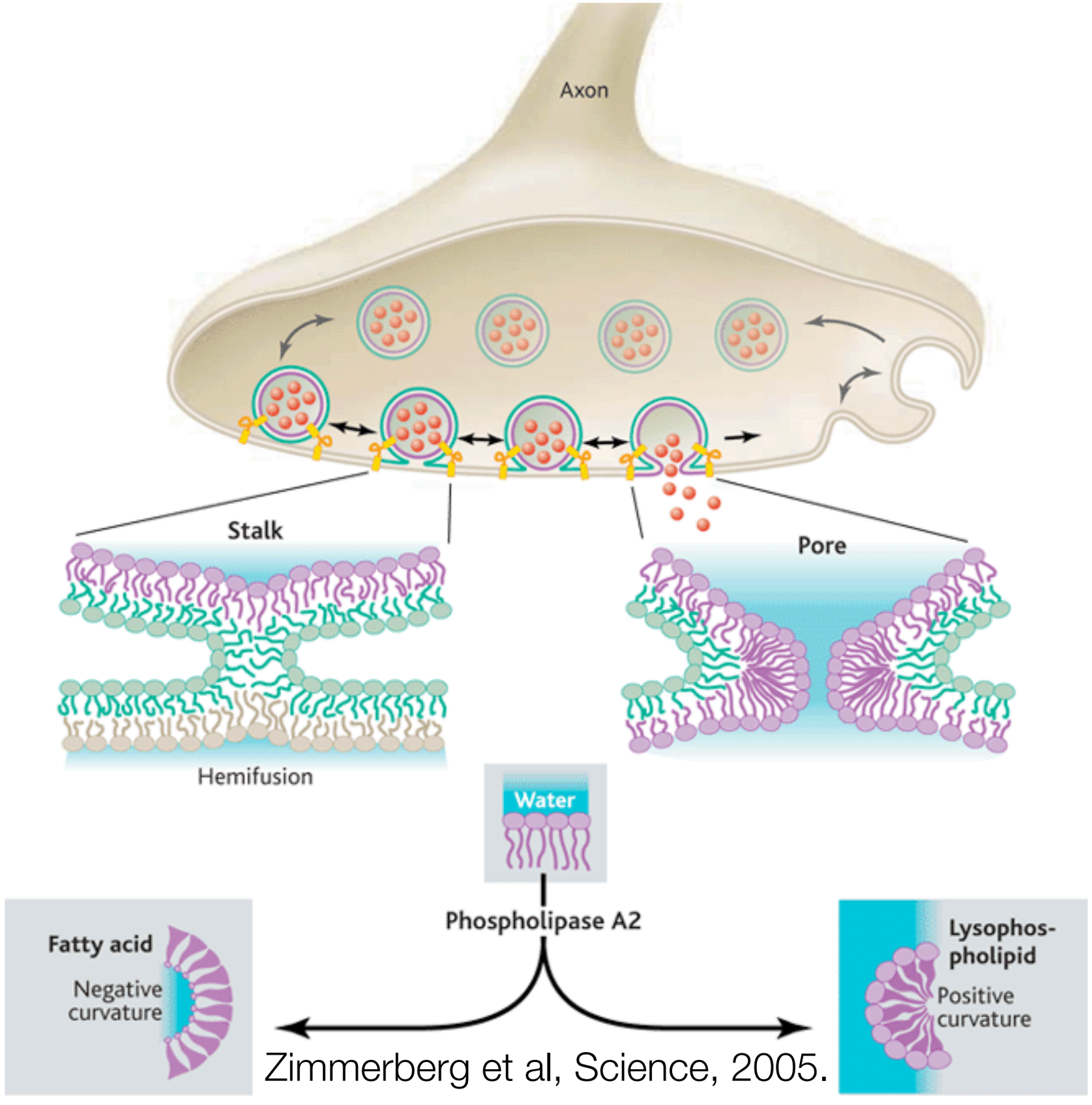
Lipids & surfactants





Figs. T. Murtola, PhD thesis

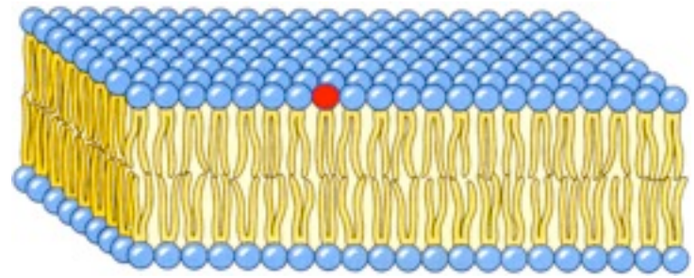
Membrane dynamics is vital!



Zimmerberg et al, Science, 2005.

Membrane dynamics

Falck et al., JACS 130, 44 -08; PRL 97, 238102 -06
Falck et al., BJ 87, 1076 -04; BJ 89, 745 -05



A challenge for simulations at many different scales.

Why?

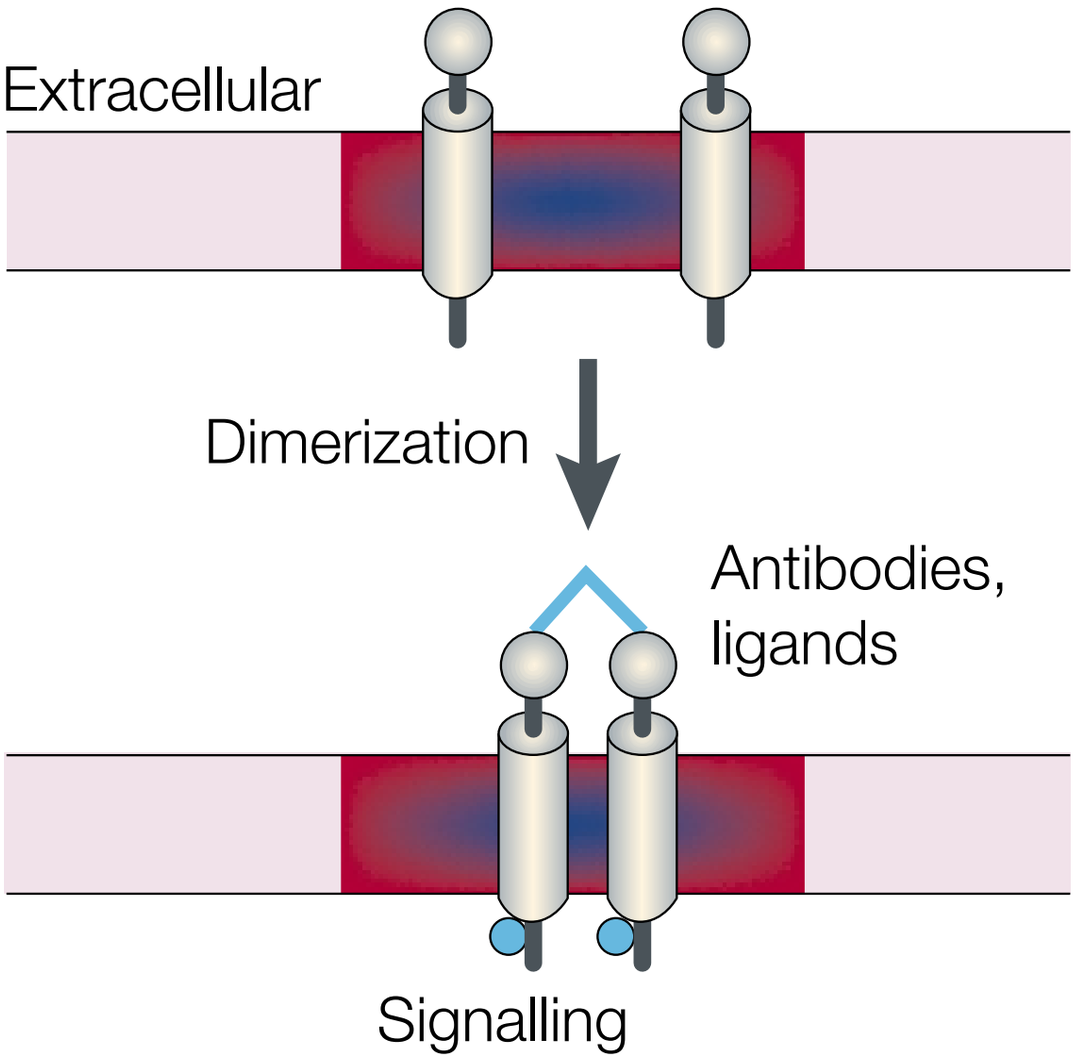
- The role of fluctuations in membranes has been not been studied yet even the main transitions depends on them: continuous or weakly first order?
- ***Mechanisms behind lipid diffusion are still not well understood***
- Living systems are not static (& they are typically out of equilibrium)
- The Singer-Nicholson fluid mosic model is not enough to describe dynamics
- **Biology:** rafts, **signalling**, lateral pressure, interactions with proteins, pore formation, etc.

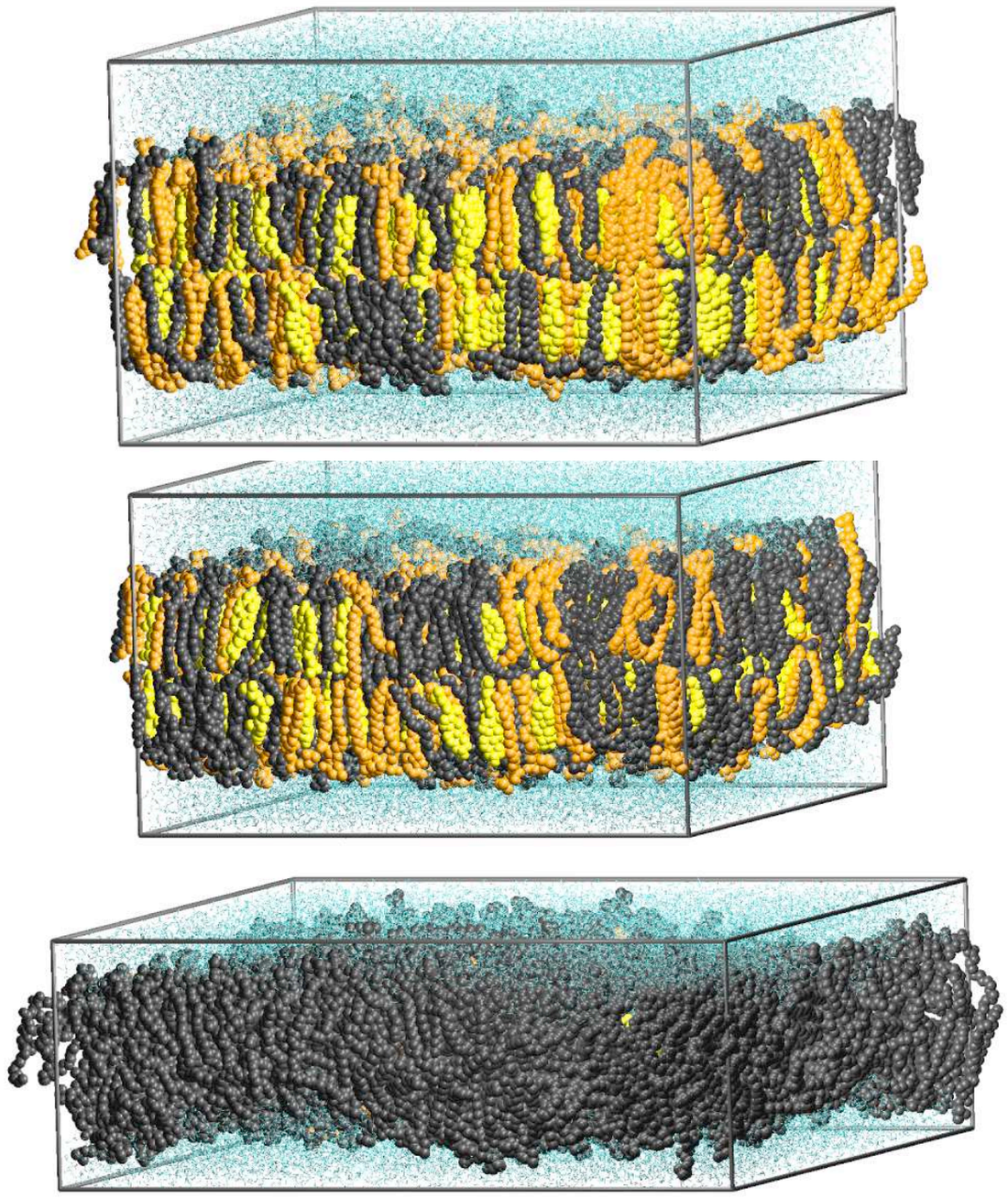
In addition: lipid composition matters and in all eukaryotic membranes cholesterol has a special role.

We start by looking at diffusion.

Membranes: role of rafts

Niemelä et al., PLoS Comput. Biol. 3, e34 (2007)
Vaino et al., J. Biol. Chem. 281, 348 (2006)





Simons, Toomre, Nature Reviews Molec. Cell Biol. 2000;
Munro, Cell 2000

Classic view: membranes are quite static. **WRONG:** Bilayers/membranes are dynamic! Biological systems are inherently complex at all levels; structure-function, signalling, etc.

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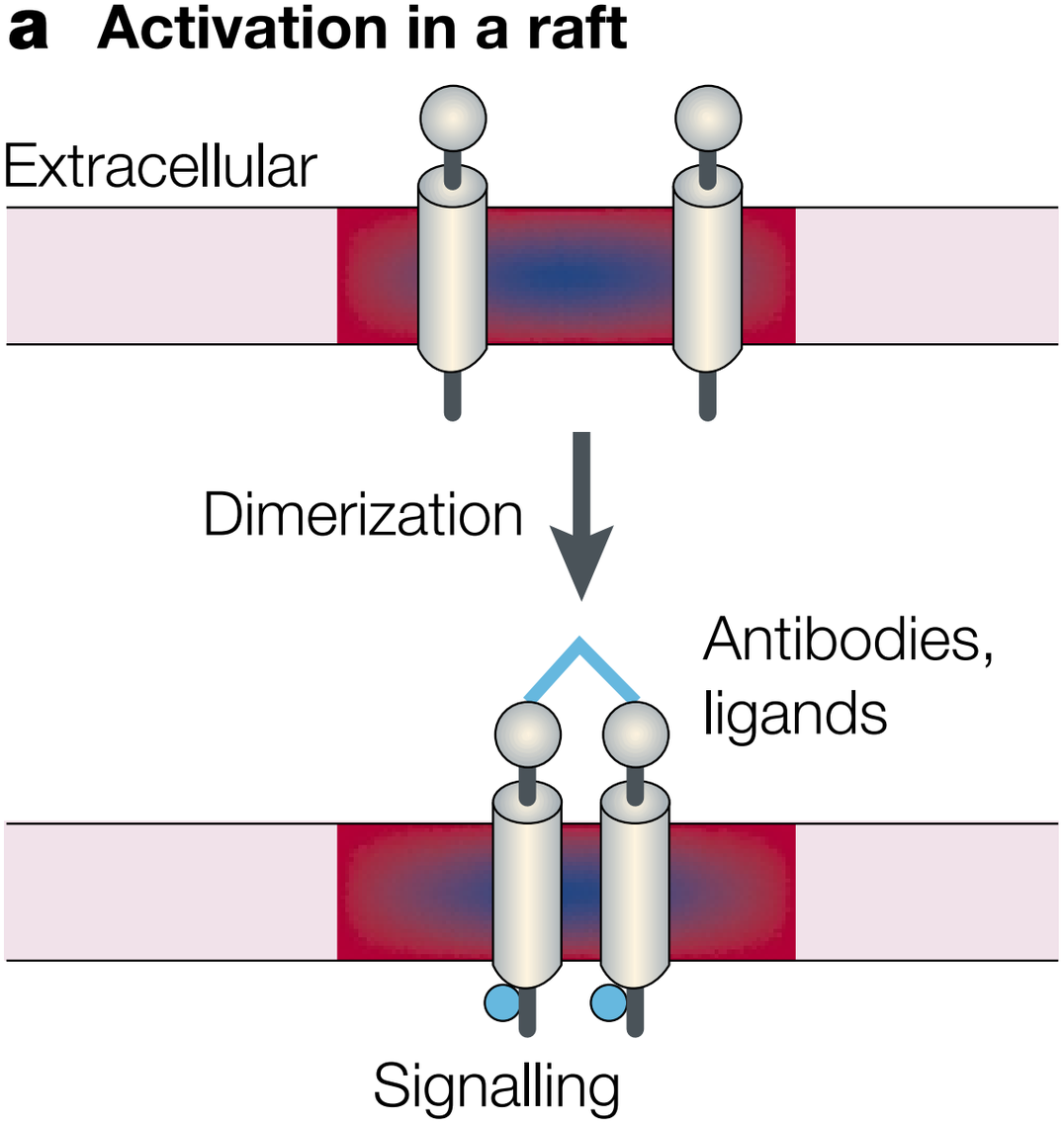

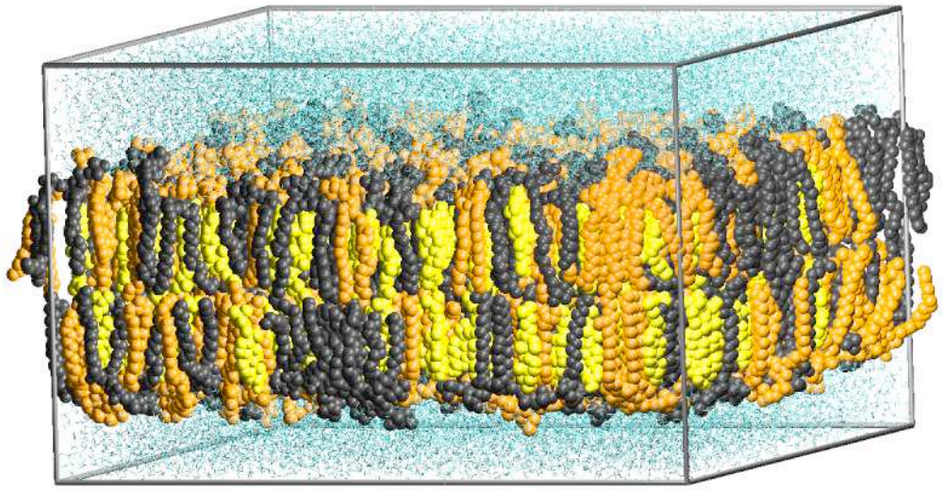

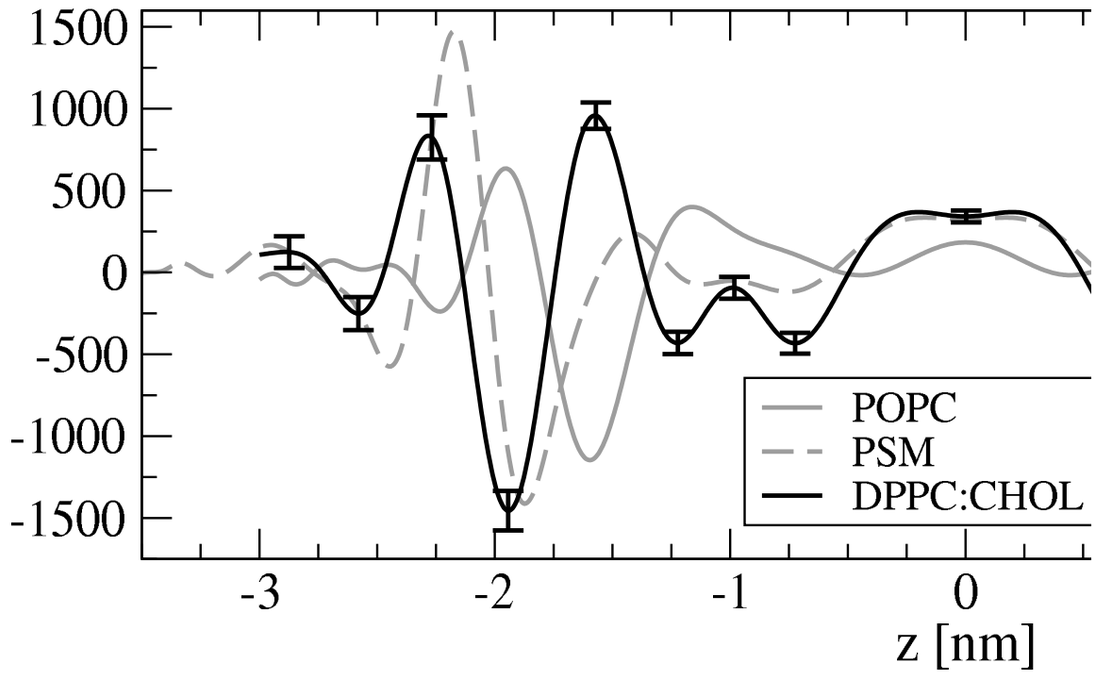

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Classic view: membranes are quite static. **WRONG:** Bilayers/membranes are dynamic! Biological systems are inherently complex at all levels; structure-function, signalling, etc.

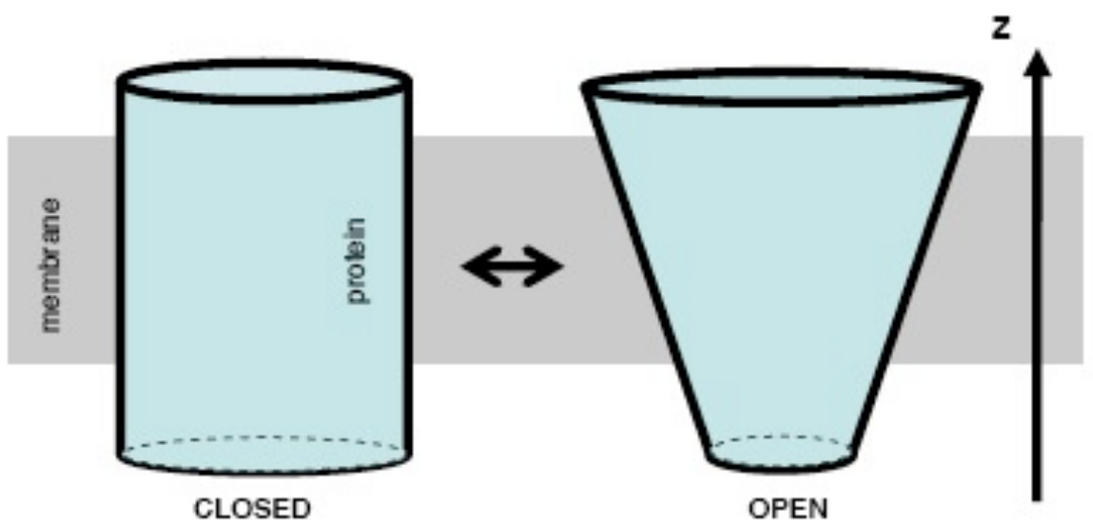
Effect on proteins

The work against lateral pressure (p(z)) profile to change the shape of a cavity occupied by a protein as it changes conformation from closed to open:

$$\Delta W = \int p(z)\Delta A(z)\mathrm{d}z$$

In the case of **MscL, the difference between the non-raft and raft cases is 3-9 k_BT**. This strongly supports the idea that the lipid environment regulates the activity. This has also strong influence on binding affinities and partitioning (cytochrome).

These findings also provide support to the idea that changes in lateral pressure may be very important in general anesthesia (R. Cantor -98).



More: Niemelä, Ollila, Róg, Vattulainen, Karttunen, J. Struct. Biol, (2007).

To jump or not to jump?

Falck et al., JACS 130, 44 -08; PRL 97, 238102 -06
Over 300 ns, systems from 128 to 4608 lipids. T=323 K

Existing paradigm: Lipid diffusion is rattle-in-a-cage, punctuated by jumps.

- Experimental results differ by 2 orders of magnitude. Interpretation:
  - *QENS:* fast motion (König et al, J. Phys. II -92; Tocanne et al, Prog. Lipid. R. -94)
  - *FRAP:* slow, random walk motion (Vaz & Almeida, BJ -91)
- rattle-in-a-cage has been demonstrated (Wohlert & Edholm, JCP, 2006)
- random walk has been demonstrated (Sonnleitner et al. BJ 1999)
- ***jumps have never been shown to exist - a hypothesis to interpret QENS exps.***

Our goal: Study the physical mechanism(s) behind lipid diffusion.

- **For jumps to dominate**: in a 30 ns trajectory one should observe about 4 discontinuous jumps per lipid. One can make a simple estimate using

$$\ell^2 \sim 4Dt \quad \text{with} \quad D \approx 1.5 \times 10^{-7}\mathrm{cm}^2/\mathrm{s} \quad \text{and} \quad \ell = 0.7\mathrm{nm}$$

- In large systems, one should see 1000's of jumps.

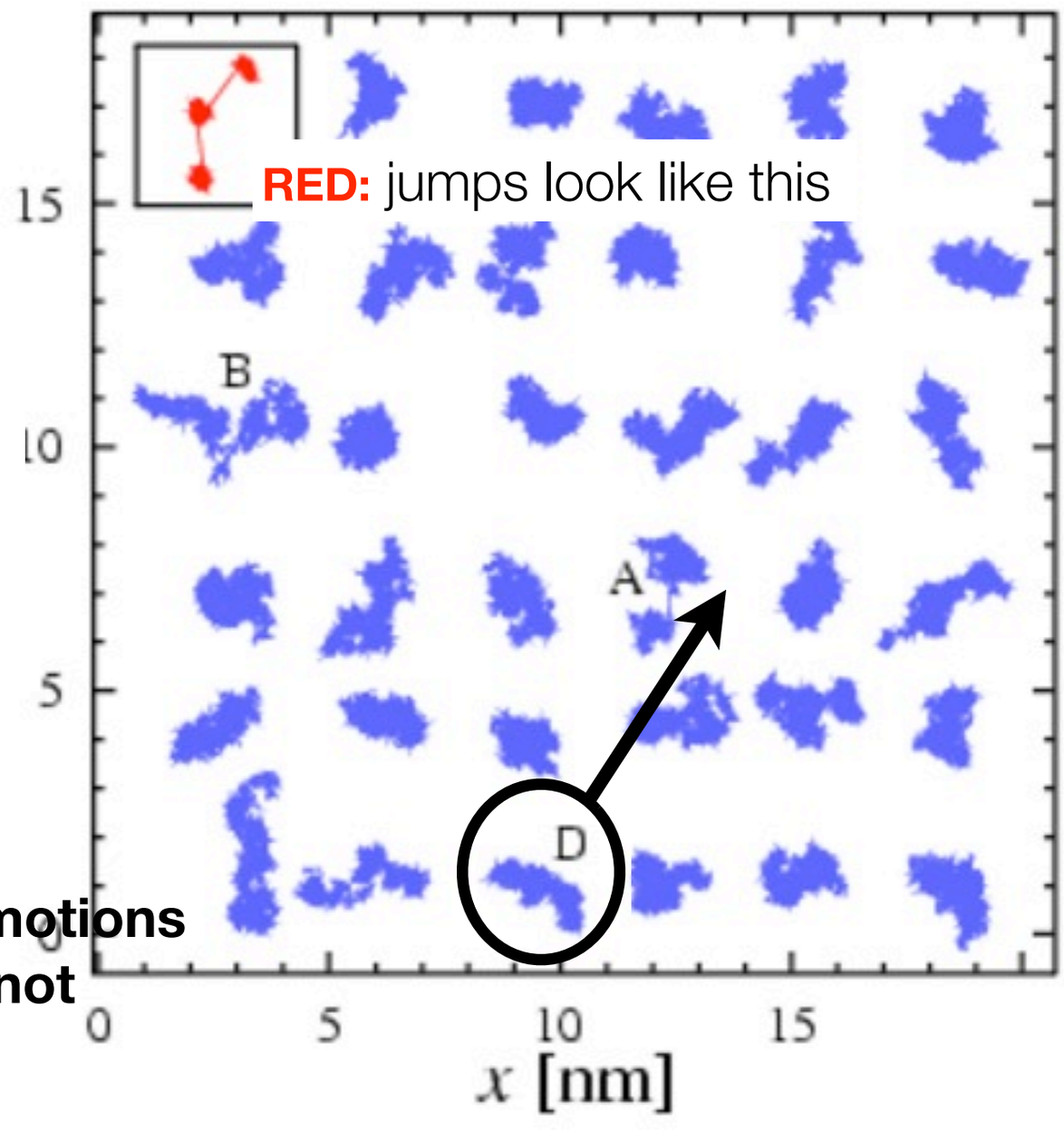
Short times: correlations

Falck et al., JACS 130, 44 (2008).
Over 300 ns, systems from 128 to 4608 lipids. T=323 K

Observation: in over 300 ns, less than 10 such jumps were seen (100 ps time scale)

- Lipid diffusion cannot be dominated by jumps
- Then, what is the mechanism?
- How do the lipids move in relation to their neighbors?
- Are the motions correlated?
- If so, what is the range and time scale?

Diffusion of individual lipids over 30 ns



Conclusion: in short time scales, motions are strongly correlated, jumps do not dominate.

Question: How about longer time scales?

Short times: correlations

Falck et al., JACS 130, 44 (2008).
Over 300 ns, systems from 128 to 4608 lipids. T=323 K

Observation: in over 300 ns, less than 10 such jumps were seen (100 ps time scale)

- Lipid diffusion cannot be dominated by jumps
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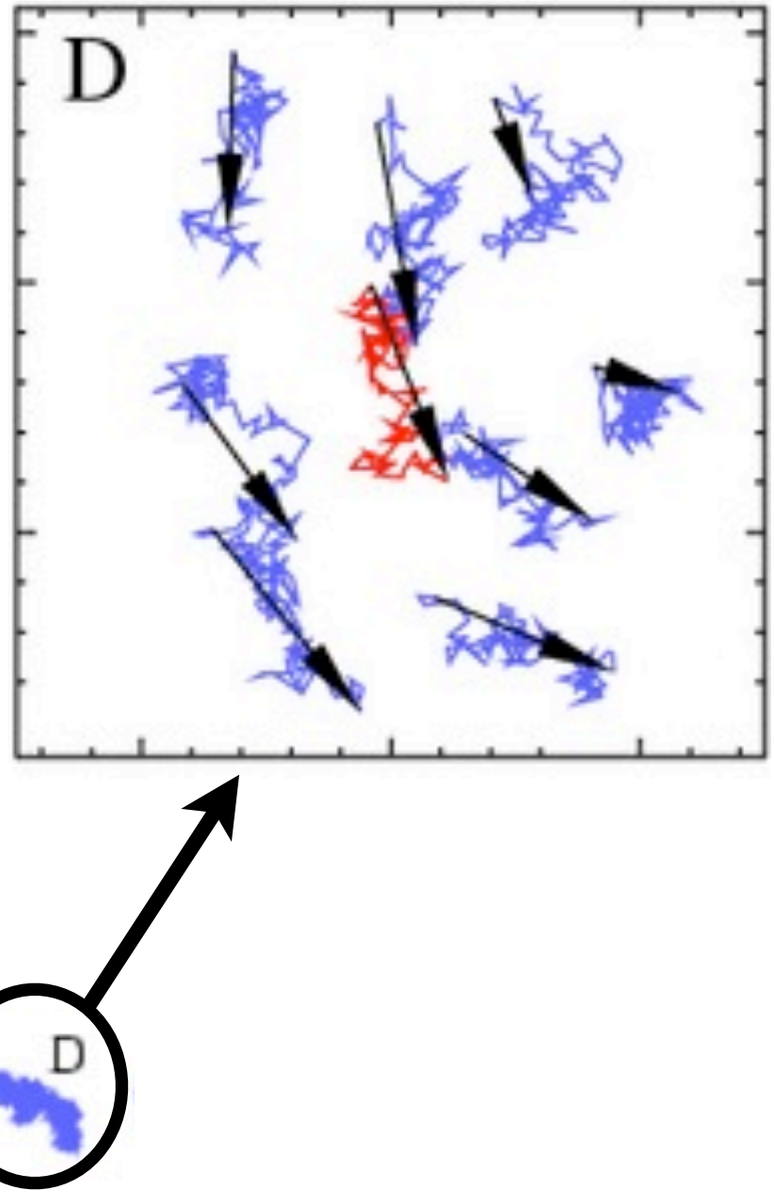
- How do the lipids move in relation to their neighbors?
- Are the motions correlated?
- If so, what is the range and time scale?

Motions of nearest neighbors over 1 ns.



Neighbor motions are correlated, no jumping out of cages.

Conclusion: in short time scales, motions are strongly correlated, jumps do not dominate.

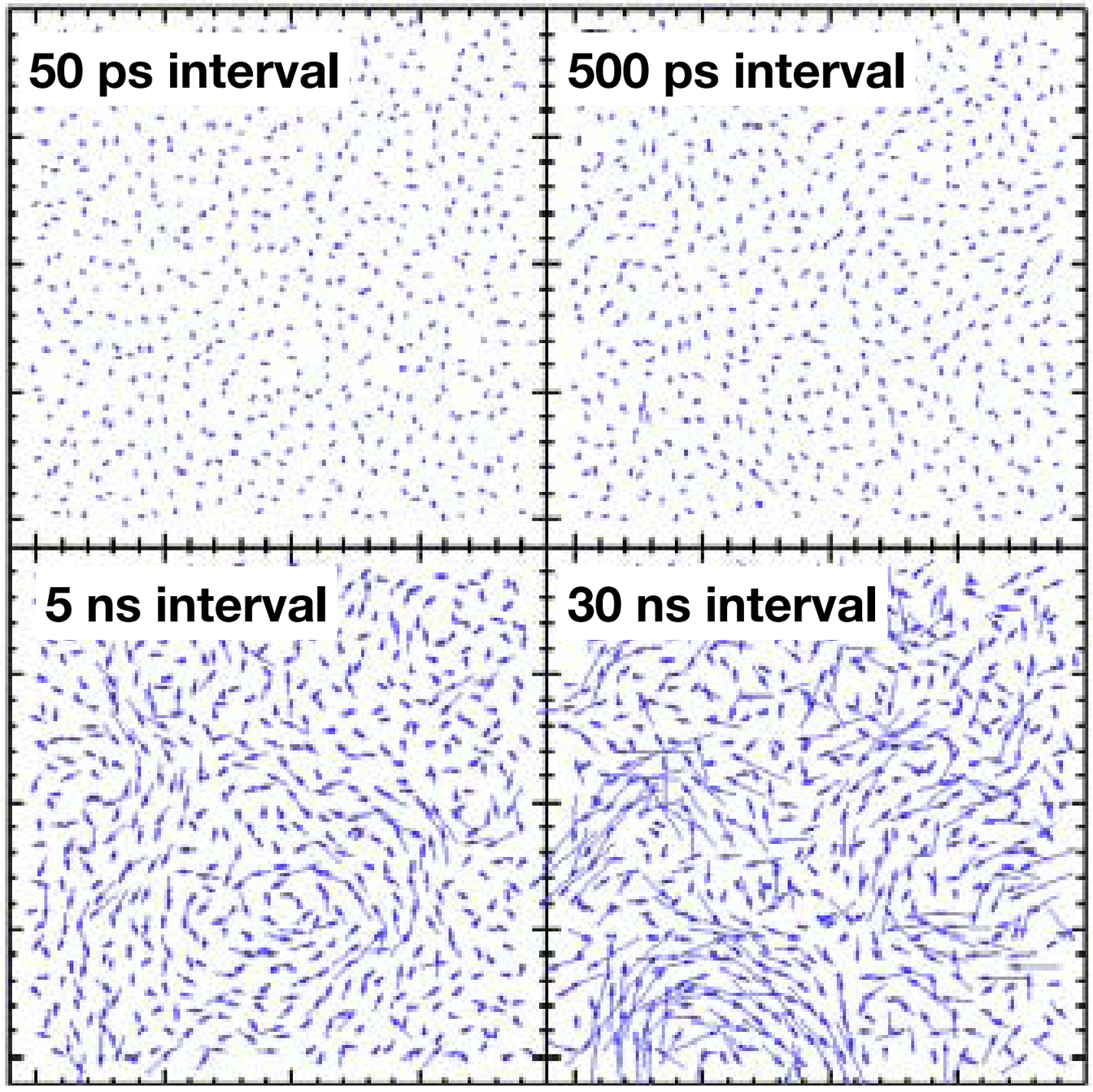
Question: How about longer time scales?

Long times: collective motion

Falck et al., JACS 130, 44 -08; PRL 97, 238102 -06

Movies: www. softsimu.org

Let's vary the time window (1152 lipids, about 20 x 20 nm):



Long times: collective motion

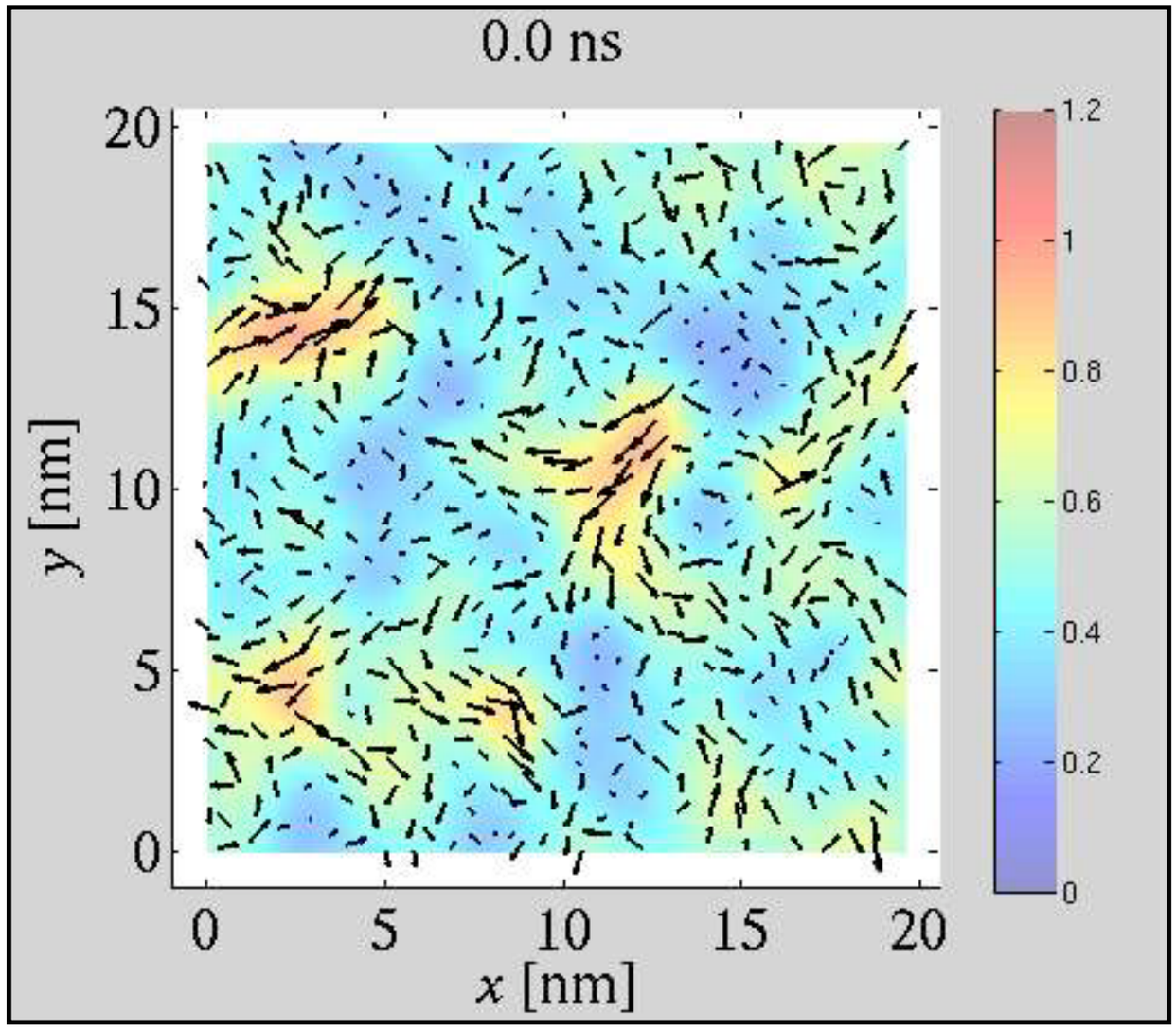
Falck et al., JACS 130, 44 -08; PRL 97, 238102 -06

Movies: www. softsimu.org

Flow patterns are not coupled to fluctuations of any particular structural quantity.

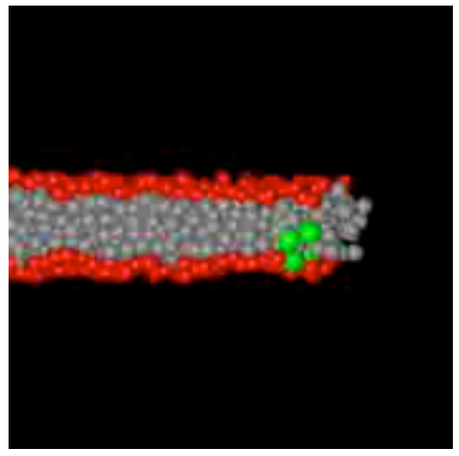
The **concerted motions** probably arise from a **complex interplay** between density fluctuations, undulations and thickness fluctuations, lipid interactions, interactions between lipids and solvent molecules.

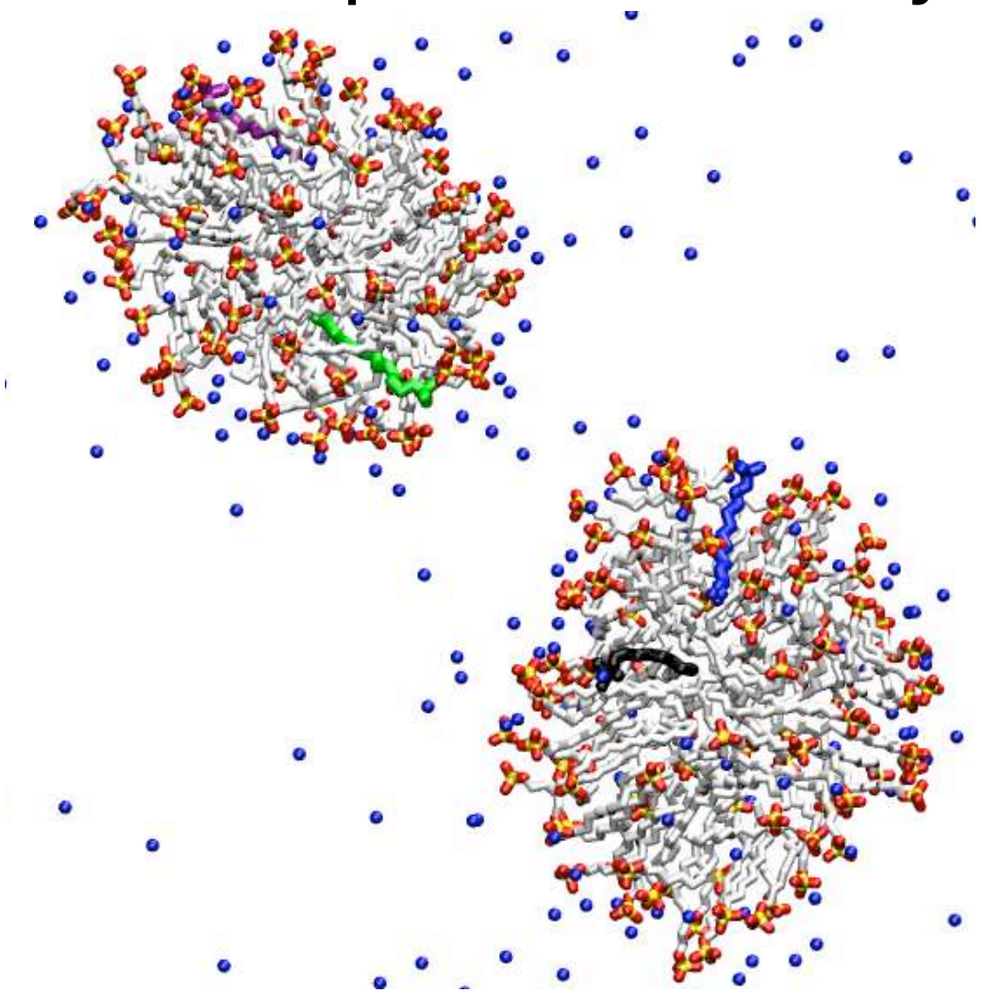
These flow patterns may have an **effect on biological functions**, including signalling and pore formation.

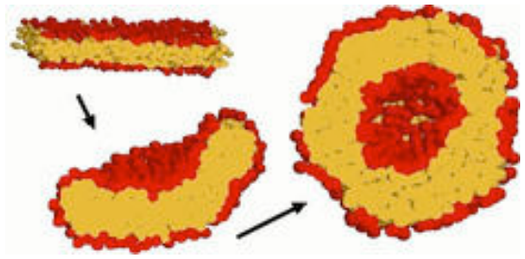


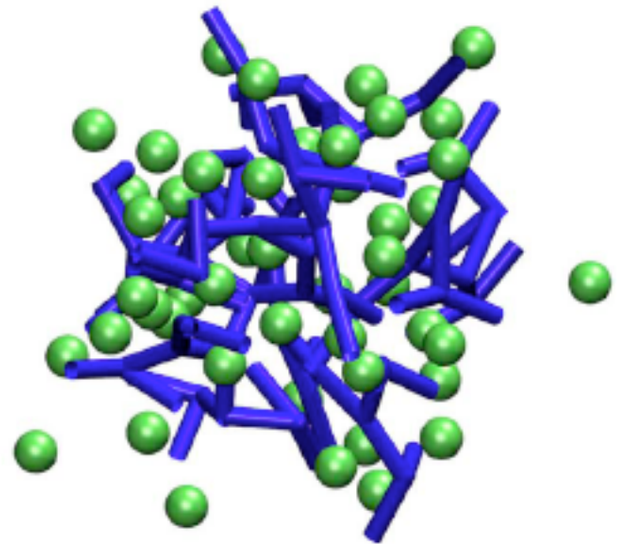
New paradigm: Lipid diffusion may be dominated by correlations and collective motions.

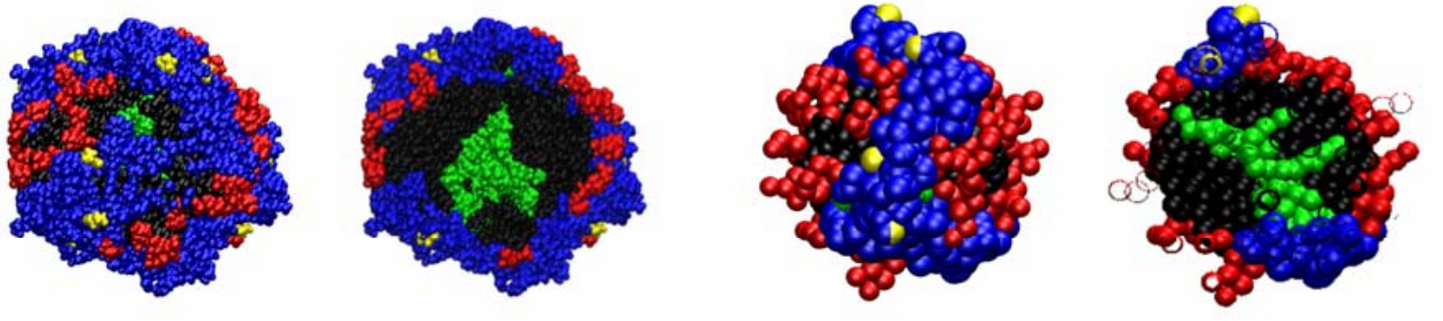
Let’s move from the flatlands to spherical objects.





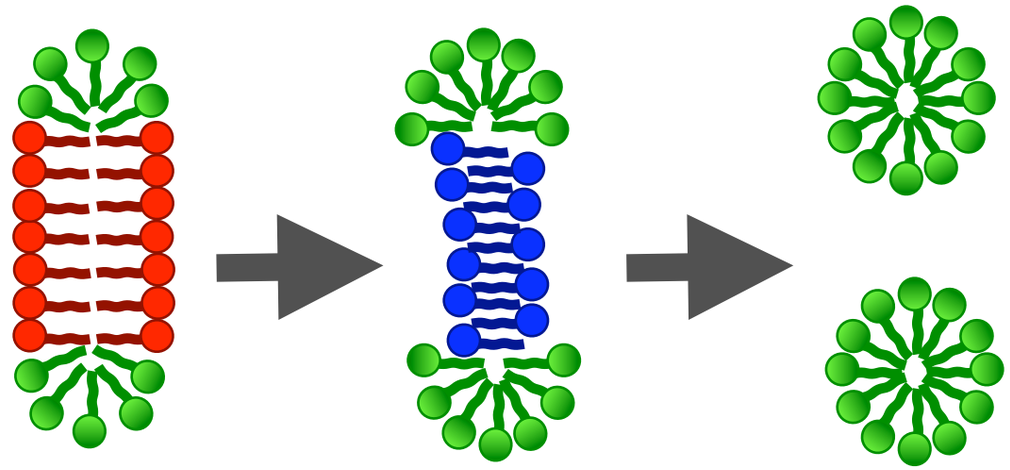






Fission/fusion pathway

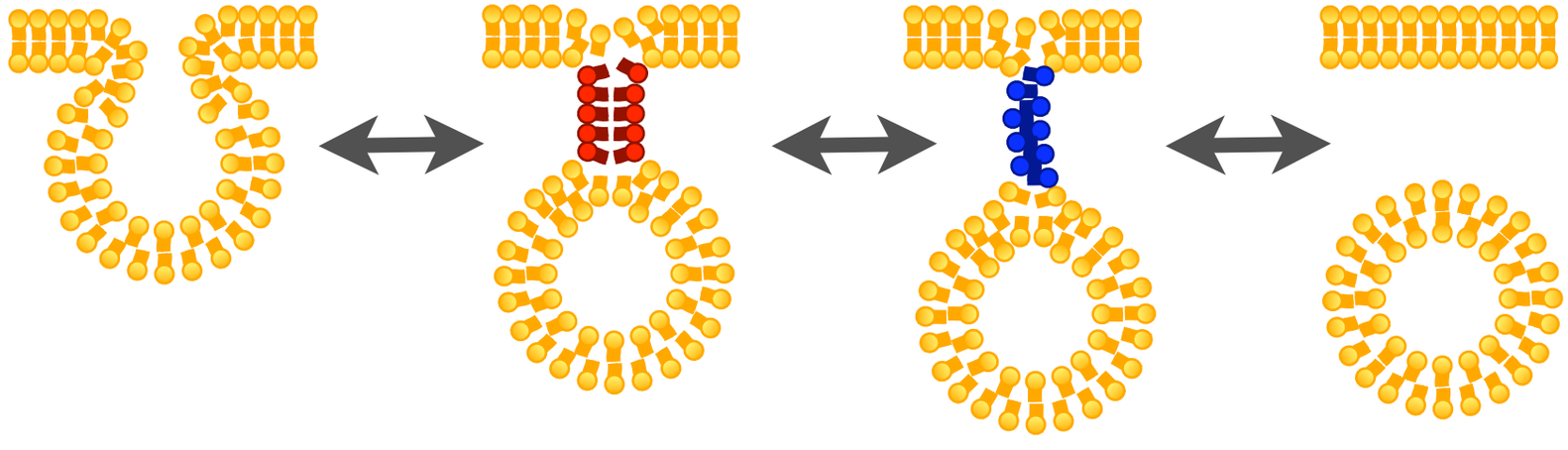
Observed micelle
fission pathway



Elongated micelle

Interdigitating stalk

Proposed bilayer
budding / fusion pathway



Interdigitating stalk

Sammalkorpi, Karttunen, Haataja:

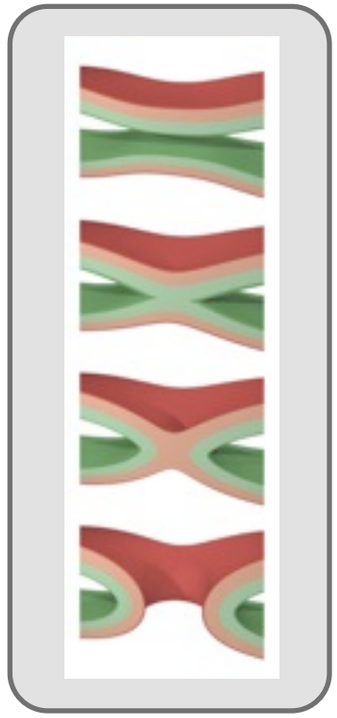
Model: J. Phys. Chem. B 111:11722 (2007)
Fission: JACS 130:17977 (2008)
Salt: J. Phys. Chem B. 113:5863 (2009)

Micelles: fusion and fission

Why?

- Membrane fusion and fission are fundamental to cellular function and survival. Examples: endo- and excytosis, recycling, viral entry & drug delivery

- All of the above are inherently dynamic processes involving complex kinetics



Fusion - lot of research has been done (Jahn & Grubmüller):

- X-rays: evidence of a short stalk (Yang & Huang)

- Simulations: pore mediated pathway (Marrink & Mark)

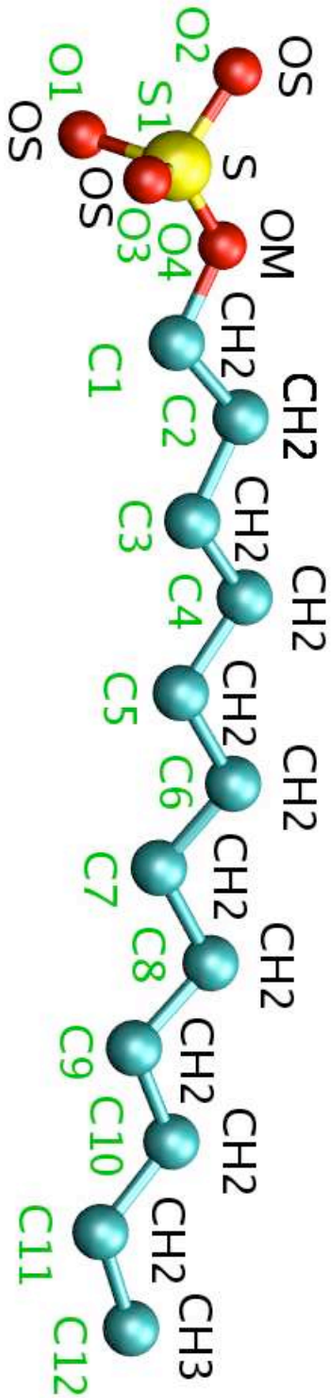
Fission:

- **Difficult to access experimentally**: pioneering work by Rharbi & Winnick who showed the importance of electrostatics on fragmentation

- **Computationally:** Pool and Bolhuis were the first to simulate fission with solvent and to study transition paths. Markvoort et al.: existence of a short stalk using CG-MD.

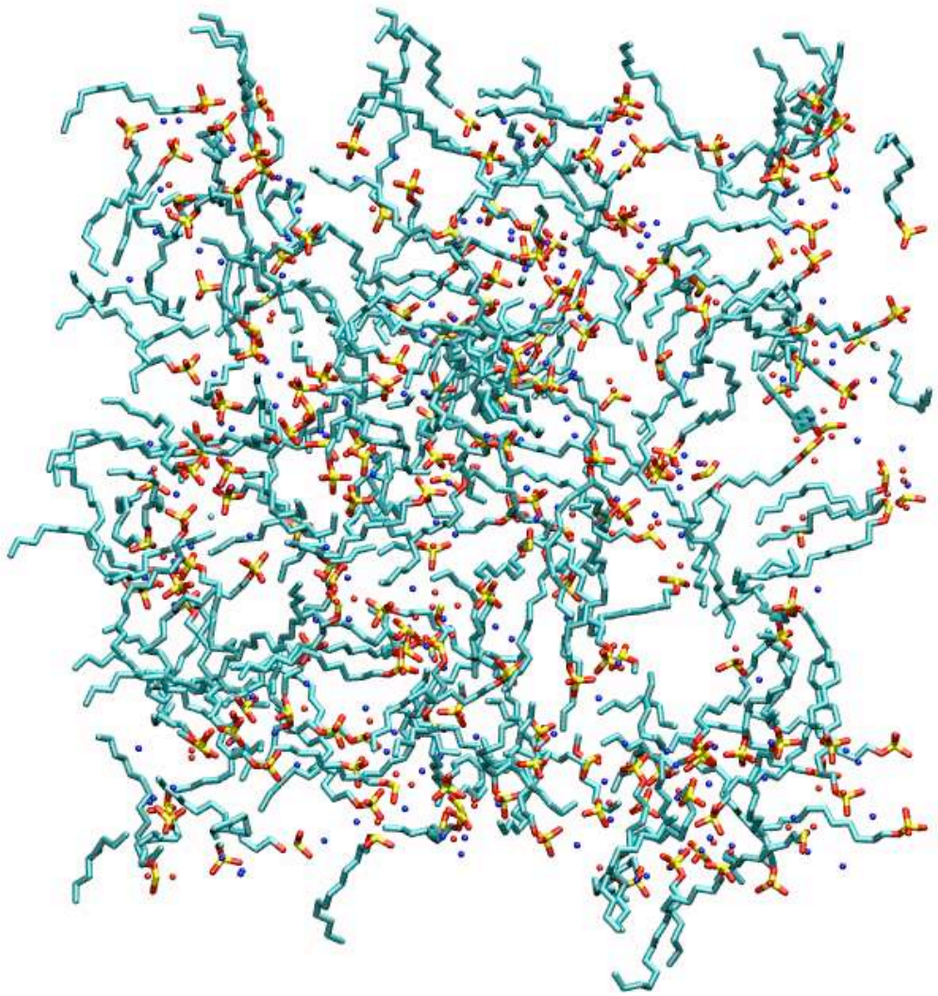
SDS & Initial configuration

200-400 ns microscopic simulations: total over 2μs
Parameters available at www.softsimu.org



red: negative

Random initial configuration

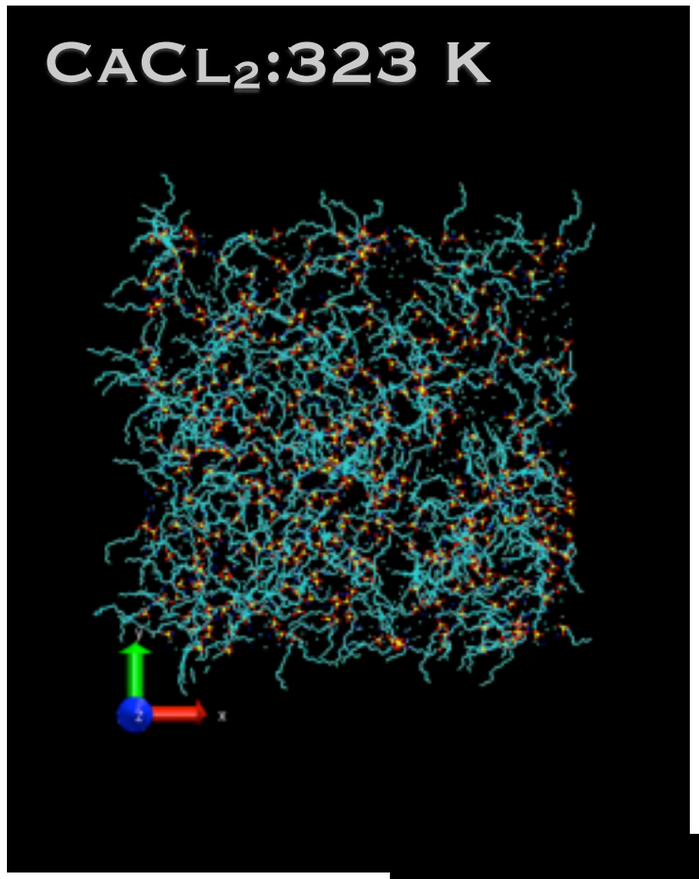


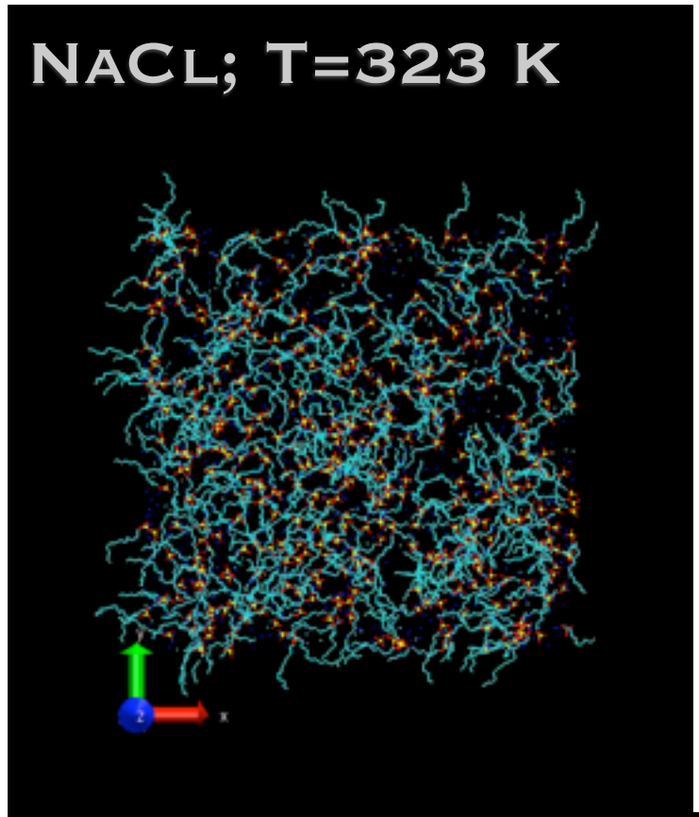
- **Simulation engine:** Gromacs
- **Explicit water:** SPC
- **NpT ensemble**
- **Force-field:** Gromacs/Gromos
- **Explicit counterions & salt**
- **SDS model:** verification of charge distribution with Gaussian
- **Constraints:** LINCS (SDS), SETTLE (water)
- **Electrostatics:** PME

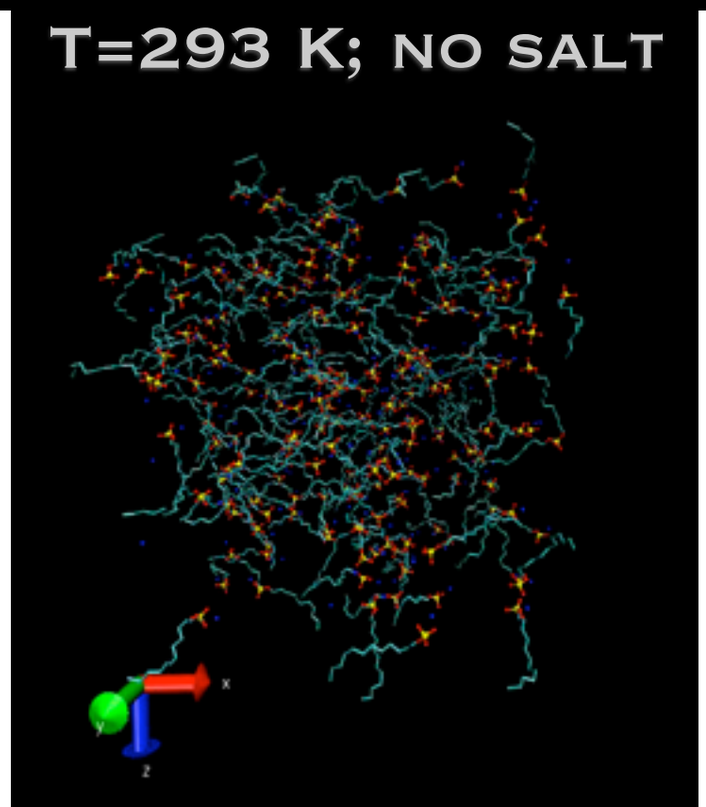
A wide range of temperatures, and surfactant and salt concentrations were studied.

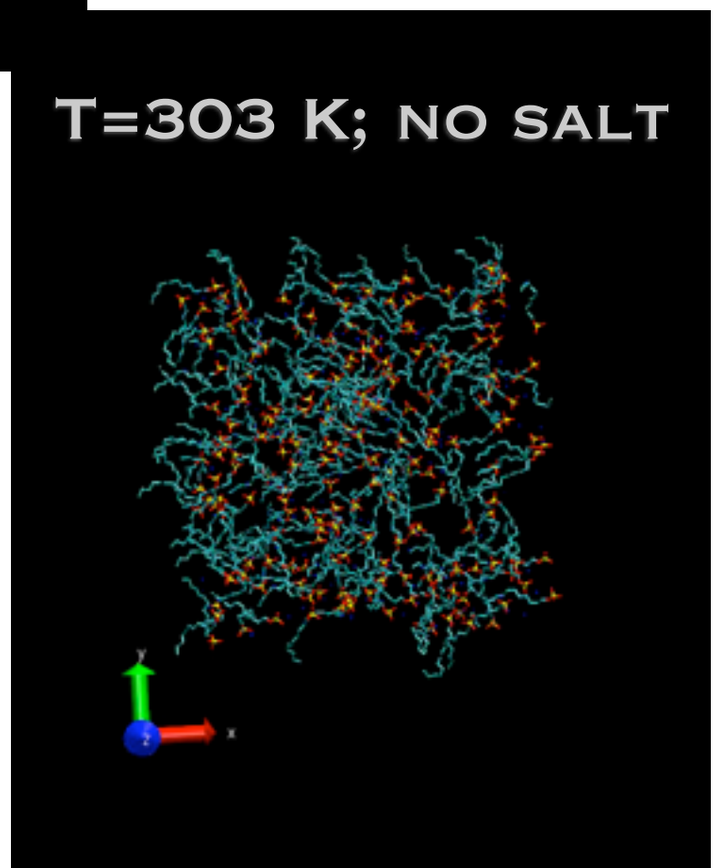
Micellation: salt & temperature

Fully 3D. Periodic boundary conditions







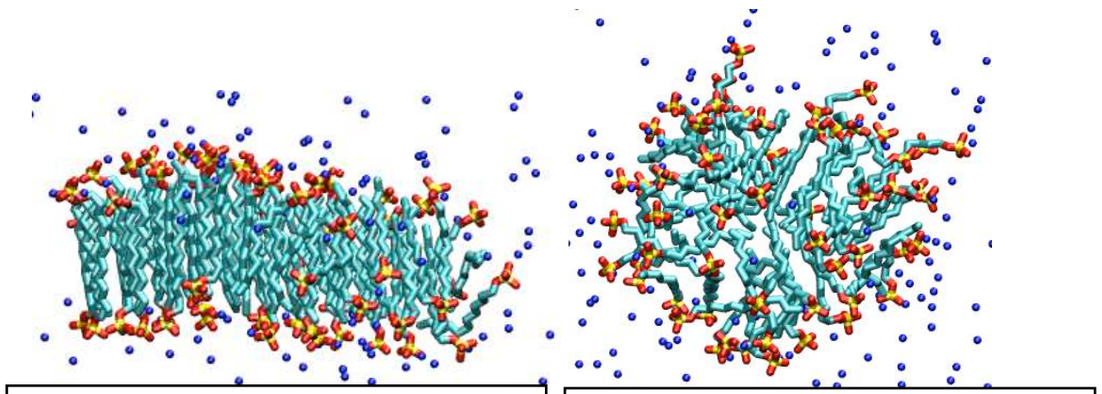


Size distribution & evolution

Transition: 288 - 297 K

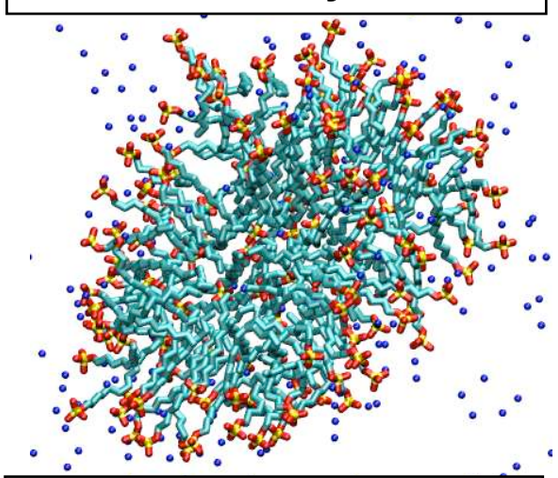
test systems: 400 SDS & 200mMol with 50,000 waters

- Band: micelle
- fusion events: strips combine
- fuzziness: classification was problematic

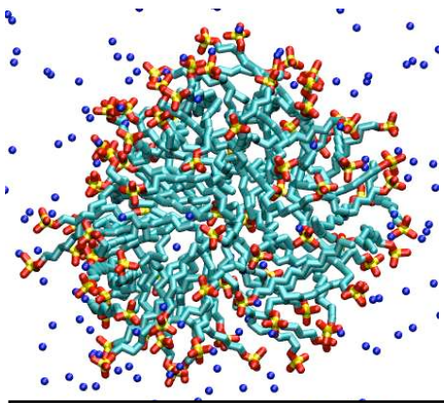


T=273 K; crystalline

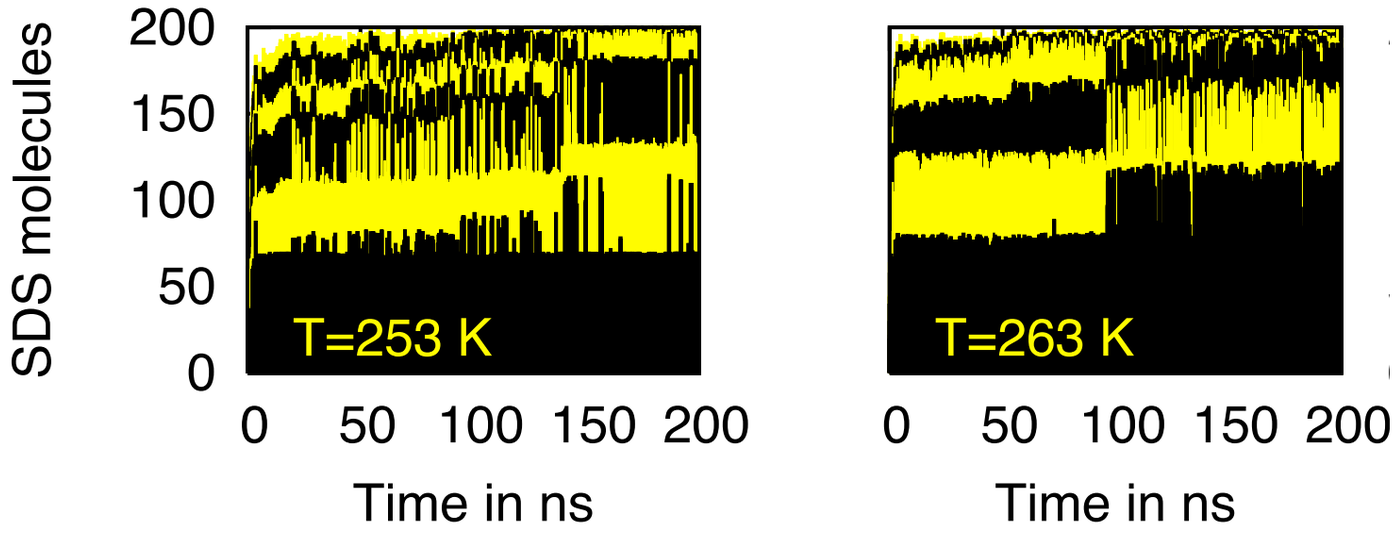
T=293 K; spherical

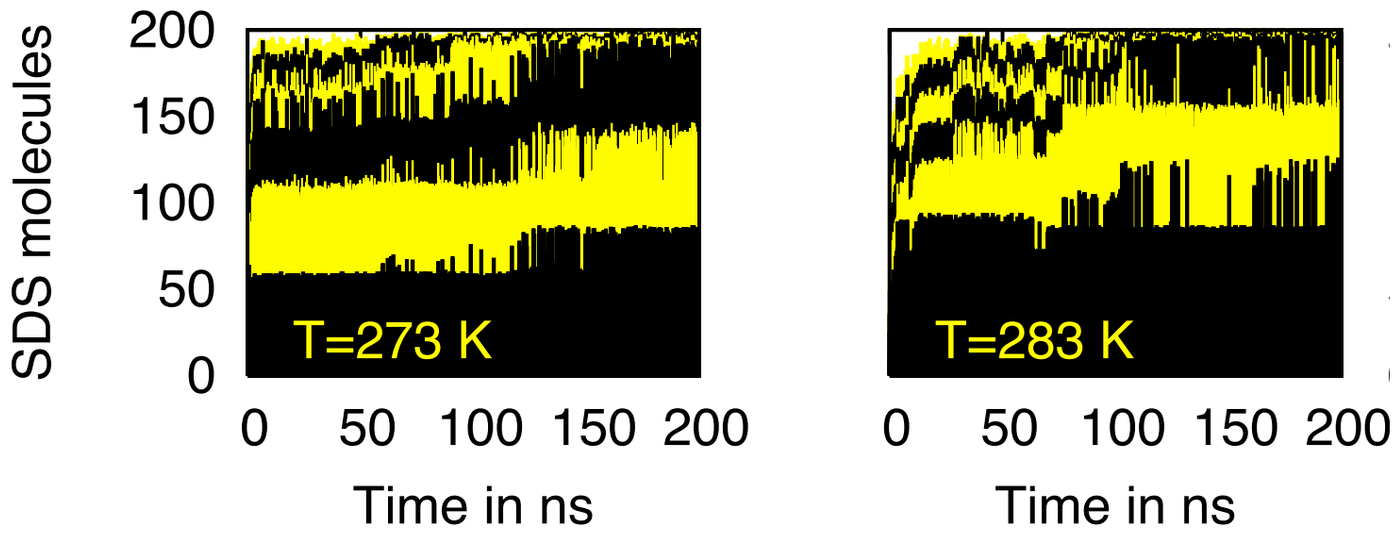


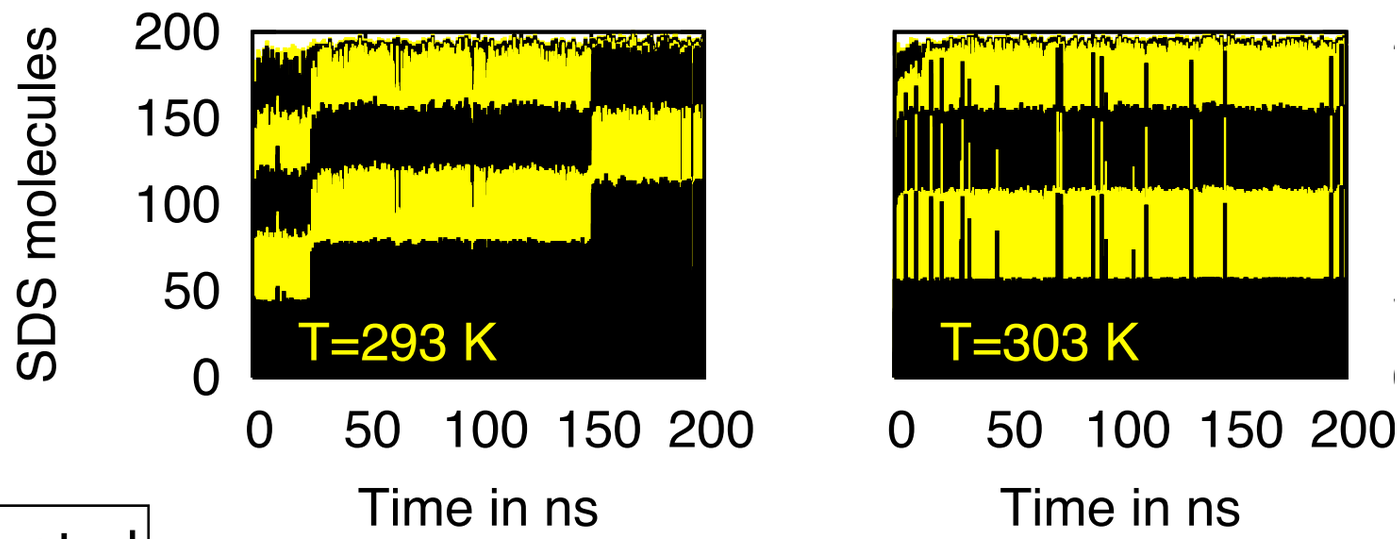
T=313 K; elongated



T=323 K; slightly elongated





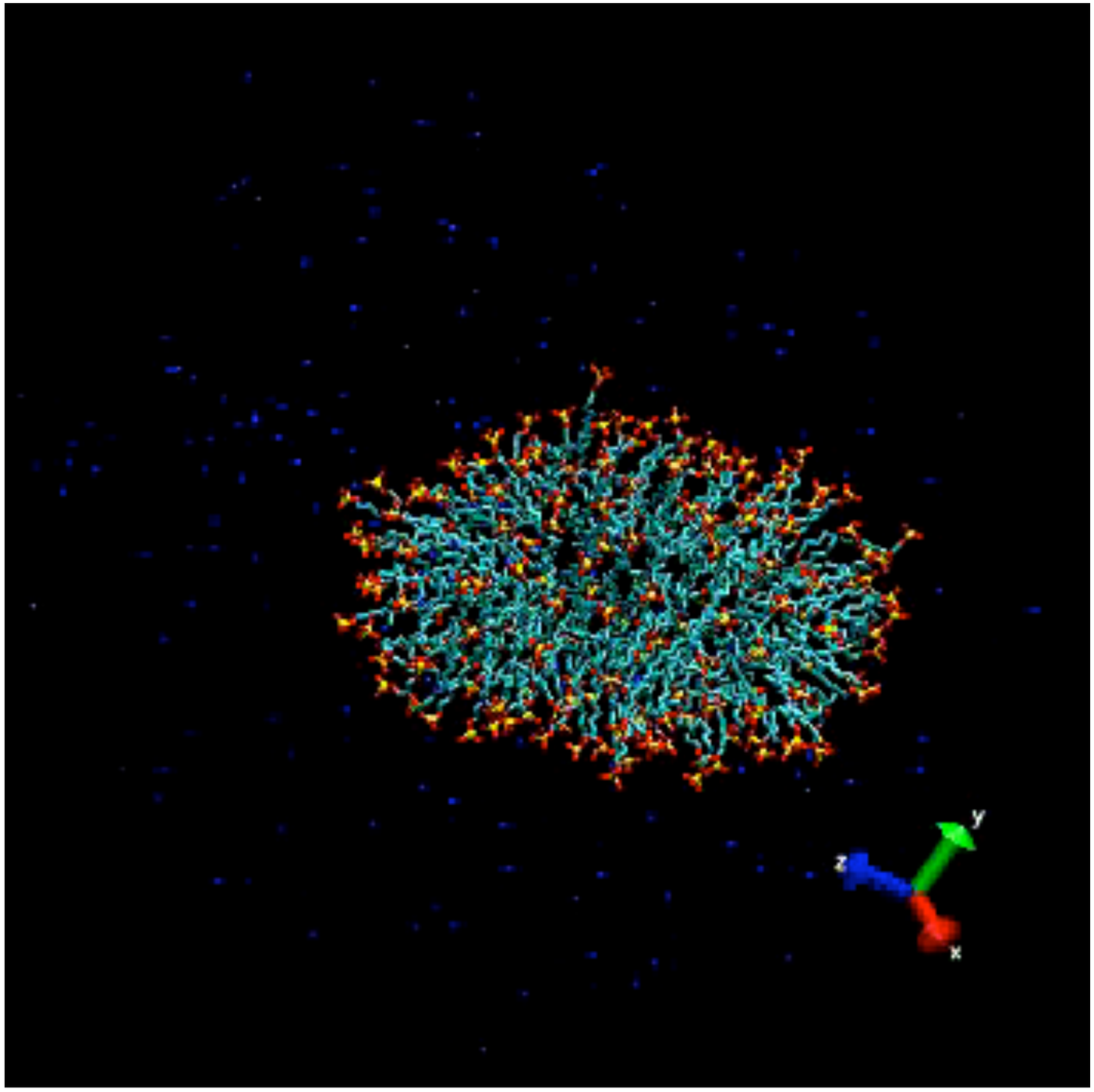


Animation of fission

Sammalkorpi, MK, Haataja, JACS 2008

T=323 K, N(SDS)=186.

- **Starting point**: large micelle from simulations with $CaCl_2$
- **Procedure:** Remove $CaCl_2$
- **Provides access to micelle fission kinetics:**
  - size changes
  - surfactant motion
  - deformations
  - leakage
  - complexation with large molecules
  - free energy changes

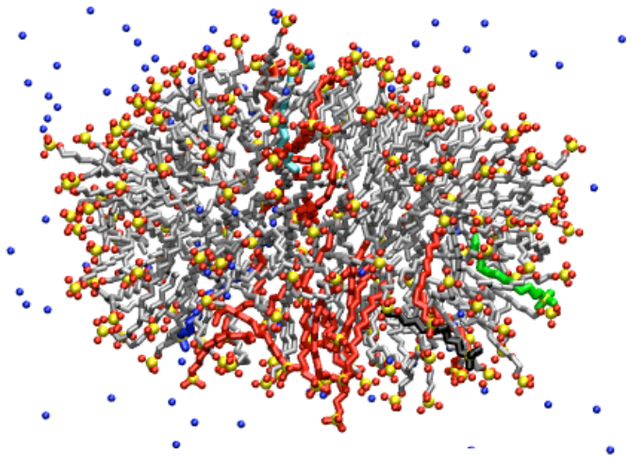


Snapshots

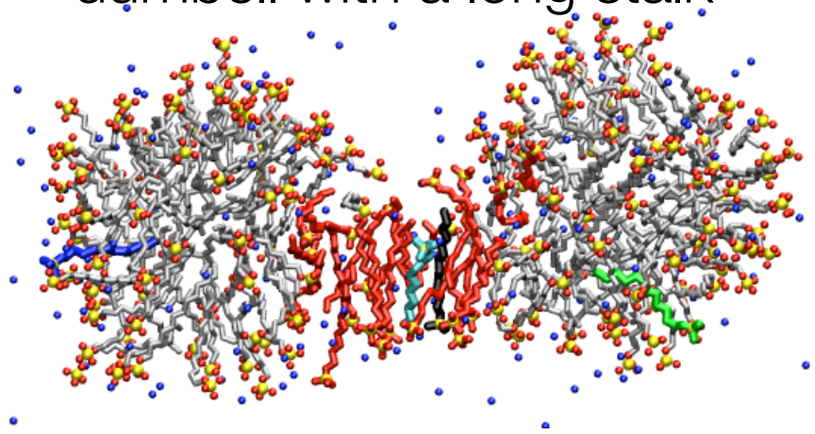
Sammalkorpi, MK, Haataja, submitted

T=323 K, N(SDS) = 186; pre-equilibrated for 200 ns

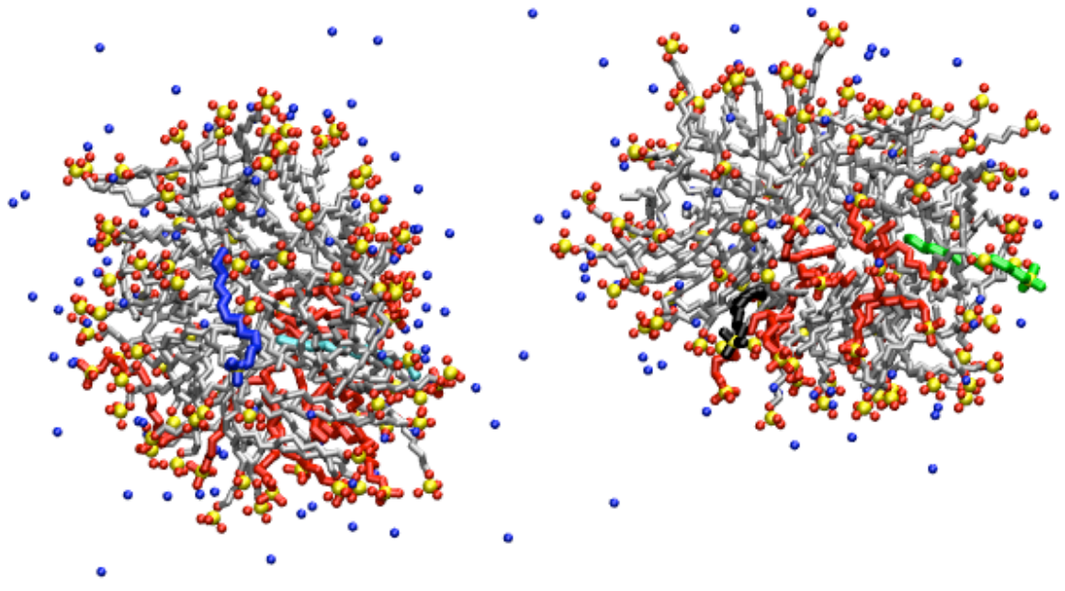
Decrease in salt concentration:



After 4 ns: formation of a dumbell with a long stalk



After 6 ns: two micelles of (about) equal size



- **Interdigitation**: almost complete
- **Diameter of the neck:** only slightly larger than the length of an SDS molecule
- **High degree of ordering:** the molecules almost almost gel-like
- **Areas** of negative curvature and splay-like conformations
- **High degree of ordering:** neighbors are highly correlated
- **Agreement with experiments:** increased salt -> decrease fission rate (Rharbi & Winnick)

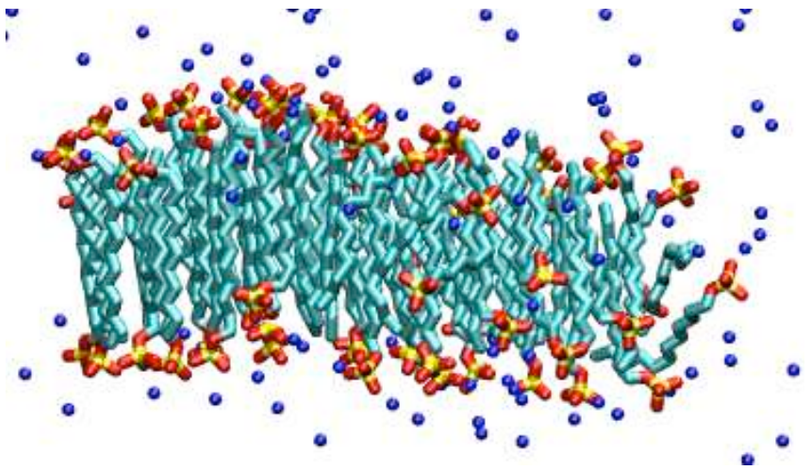
Animation of fission: halt

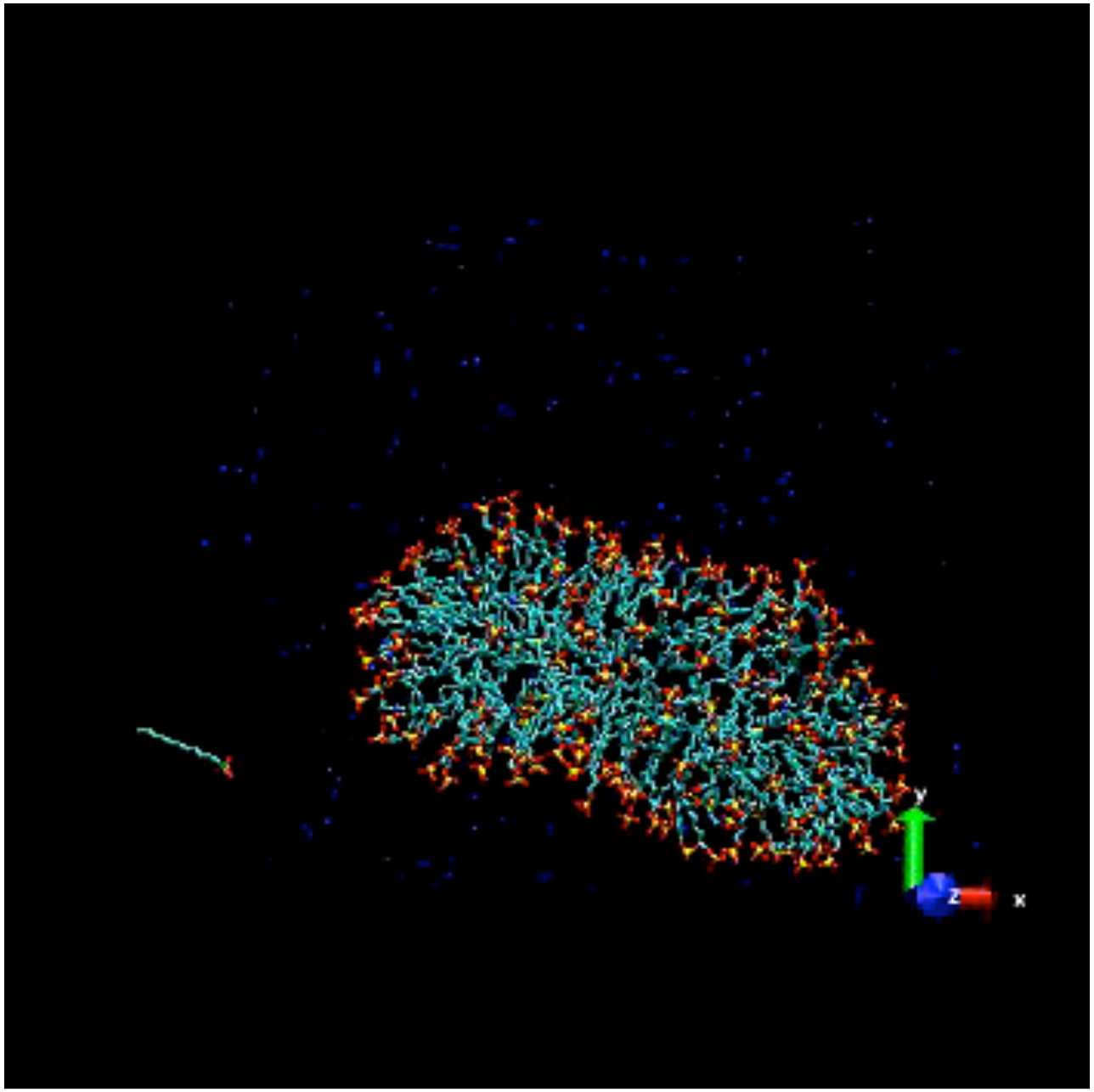
NOTE: Periodic boundary conditions
T=323 K, N(SDS)=186.

It is possible to control and
even to halt fission by varying the
salt concentration and/or temperature.

- **Intermediate maintained**: for 30 ns
  (previous: fission after 6 ns)

Stalk (transient) looks crystalline:



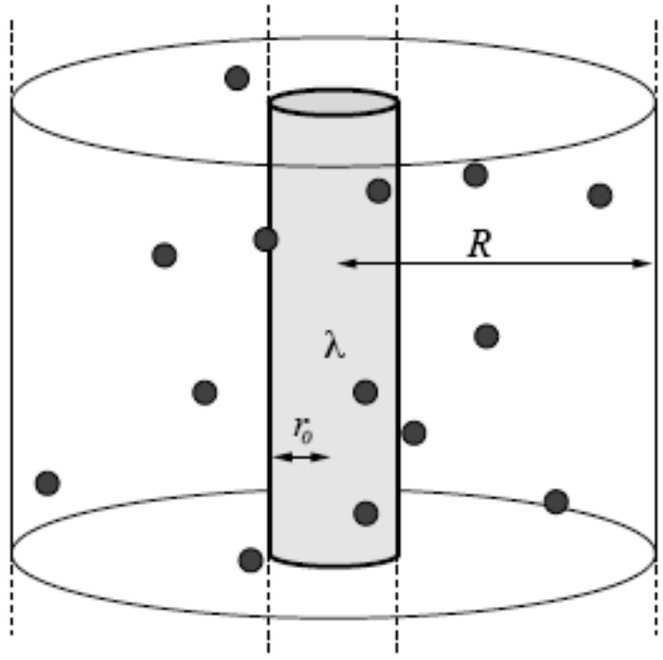


- **Ordering:** neighbors are highly correlated
- **Interdigitation**: almost complete
- **Diameter of the neck:** length of an SDS

Physical mechanisms 1

Importance of electrostatic interactions:

Upon changing the ionic strength, the Coulombic screening length changes which leads to strong fluctuations.



Consequences:

- **Fluctuations** lead to the formation of the dumbell which shape fluctuates very strongly.
- **Formation of a highly intedigitated neck:**, stretchable and stable; low mobility, no contact with water.
- **Counterions have a dual role:** In a dilute system, counterions are not bound to the micelle but escape to the solution -> *instability.* But the same counterions help to stabilize the stalk which is cylindrical (condensation)

Physical mechanisms 2

Lord Rayleigh, Phil. Mag. 14, 184 (1882).
Deserno, Eur. Phys. J. E 6, 163 (2001).

Rayleigh instability:

Surface tension wants to minimize the area but the electrostatic repulsion leads to deformations. When the size of the droplet increases, capillary instabilities will break the droplet.

- **Difficulty:** Charge neutrality (*Deserno 2001*); the micelle is charged and surrounded by salt and counterions. Seen as pearl-necklace conformations in polyelectrolytes (*Micka, Holm, Kremer, 1999*).

- **Ion condensation:** Ions can condense on the surface or they can even penetrate the micelle. The two lead to different scenarios

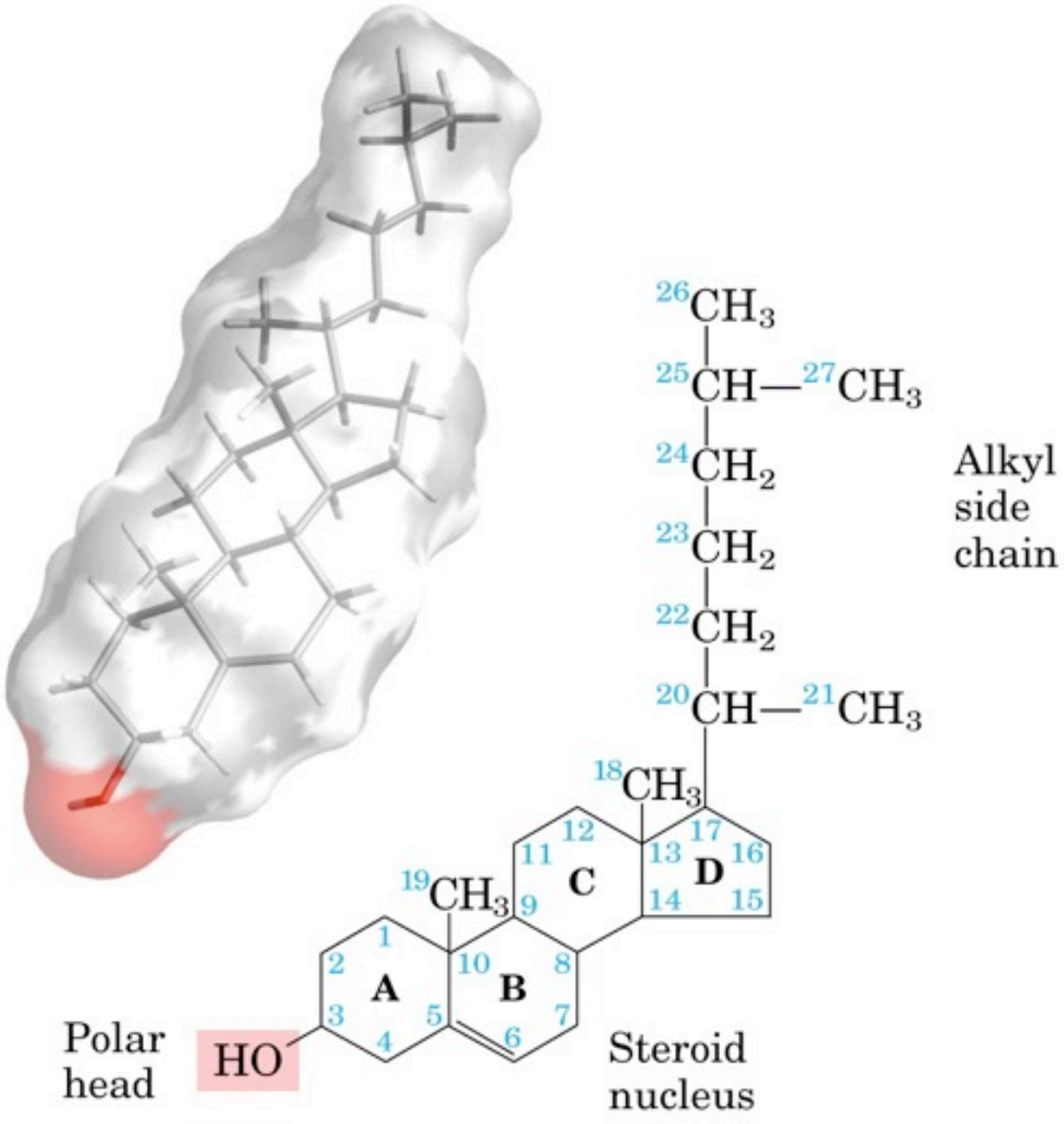
  - **No penetration**: condensation on the surface leads to screening of the electric field - the droplet size is increases

  - **Penetration:** The Bjerrum length plays a crucial role and the equilibrium droplet become very large

Cholesterol

- In membranes (eukaryotic cells)
- Four fused rings
- Precursors for steroid hormones and bile acids
  - Sex hormones
  - Regulation of Na^+
  - Anti-inflammatory properties
  - Vitamin A: vision and pigmentation
  - Vitamin D: formation of bones
  - Vitamin E: antioxidant

  - **RAFTS!** Cholesterol seems to be unique in its ability to enhance raft formation!



Nelson & Cox: Lehninger Principles of Biochemistry, 3rd ed.

Cholesterol

- In membranes (eukaryotic cells)
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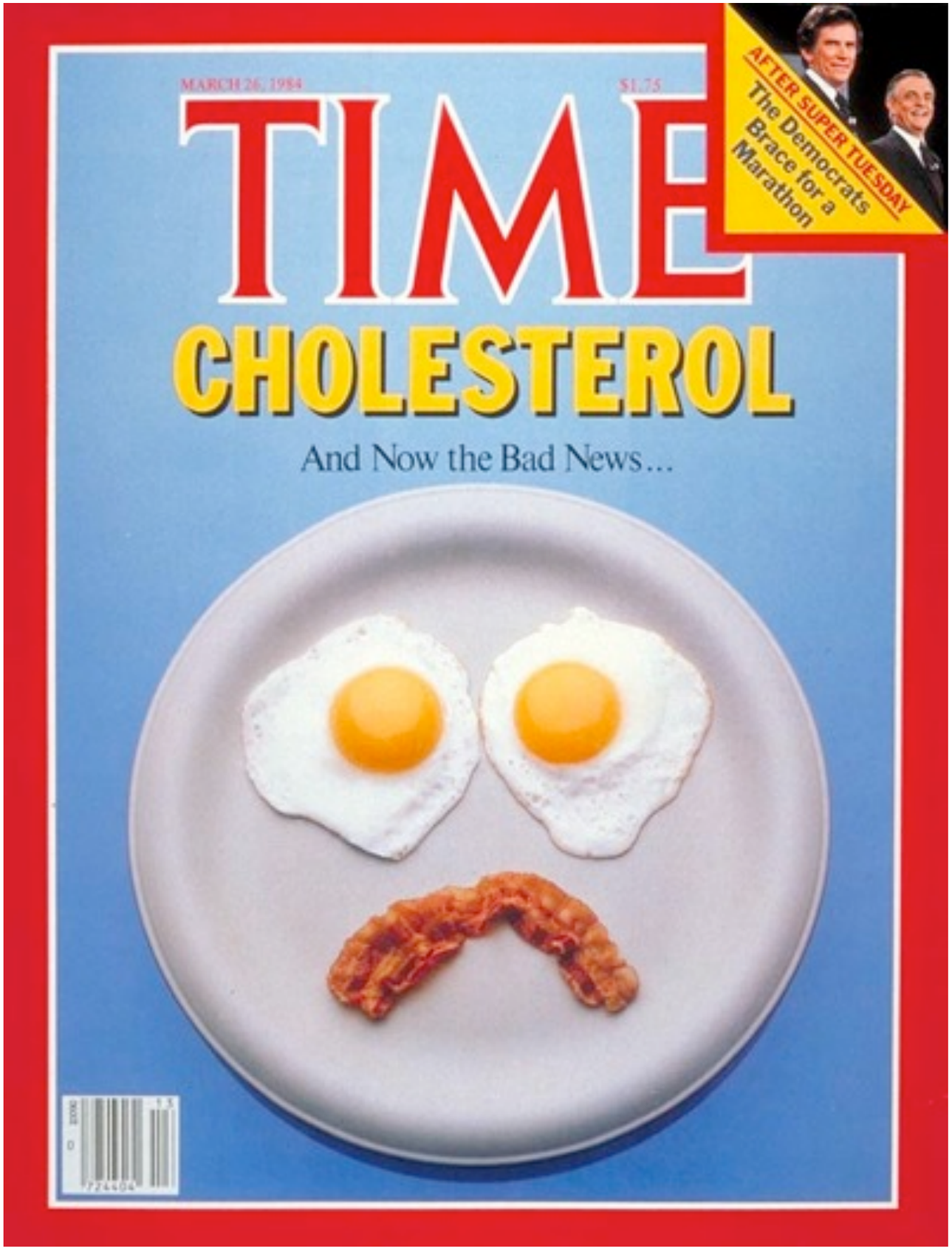
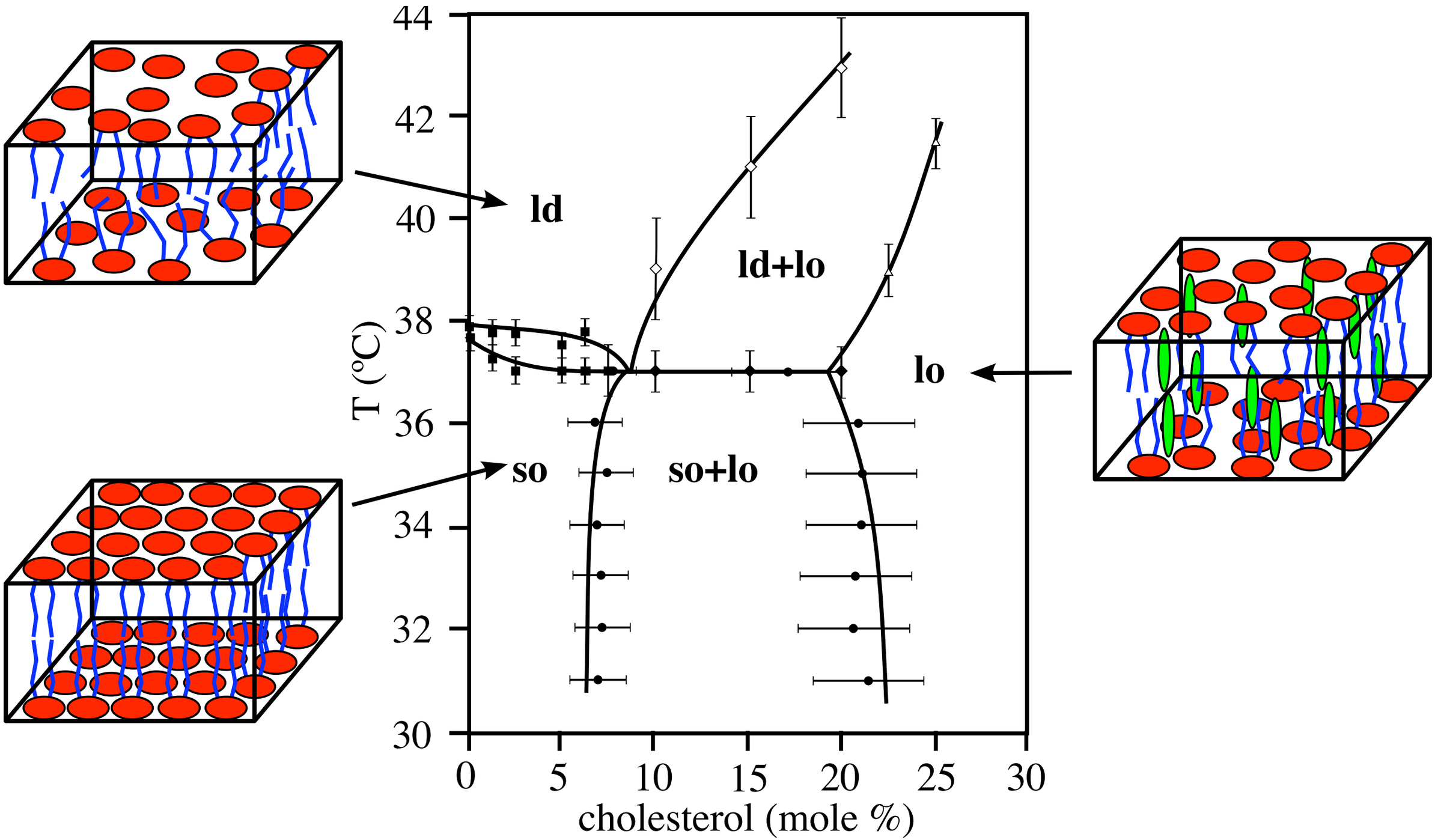
  - **RAFTS!** Cholesterol seems to be unique in its ability to enhance raft formation!



Phase diagram: DPPC + cholesterol

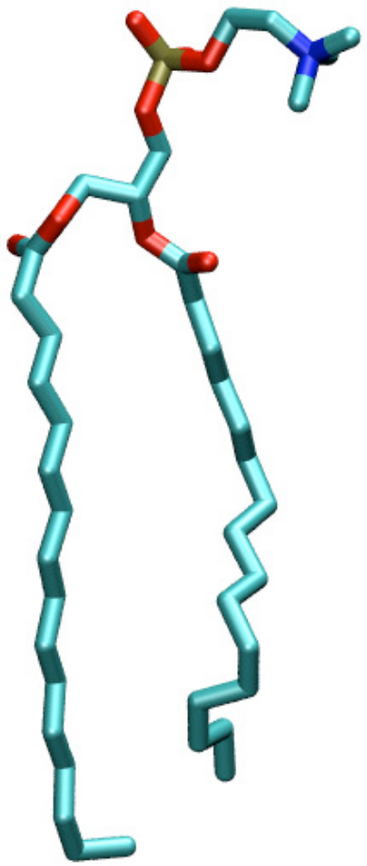


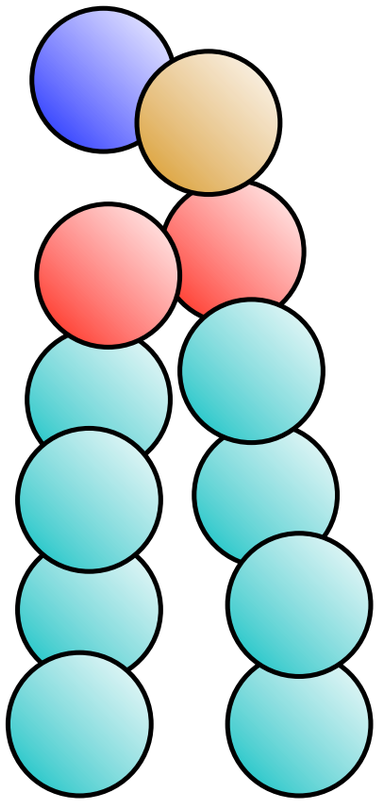
M. R. Vist and J. H. Davis, Biochemistry 29, 451 (1990)

Lipids at different resolutions

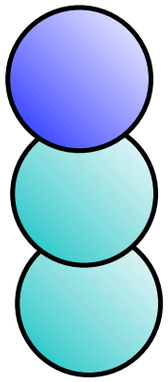
Figs: T. Murtola PhD thesis

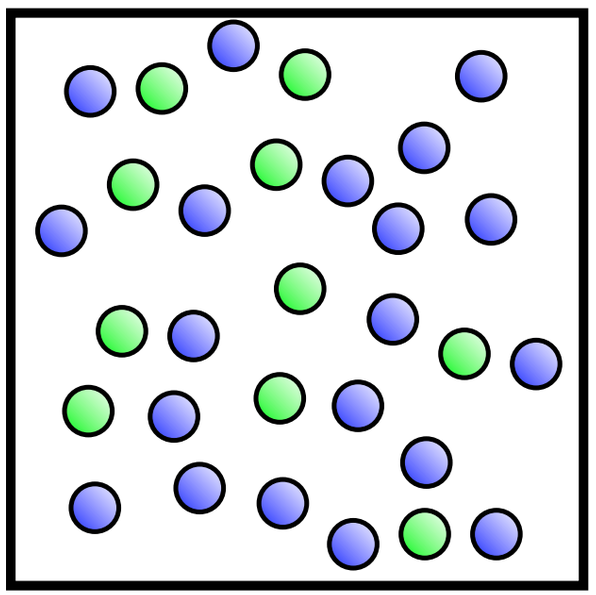
United-atom model: aliphatic hydrogens are not represented explicitly

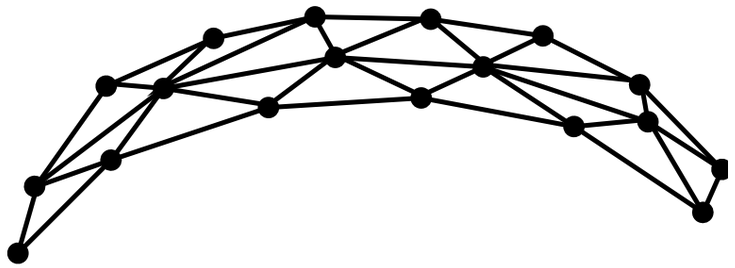




Coarser particle models: chemical identity is lost. Focus on generic behavior.



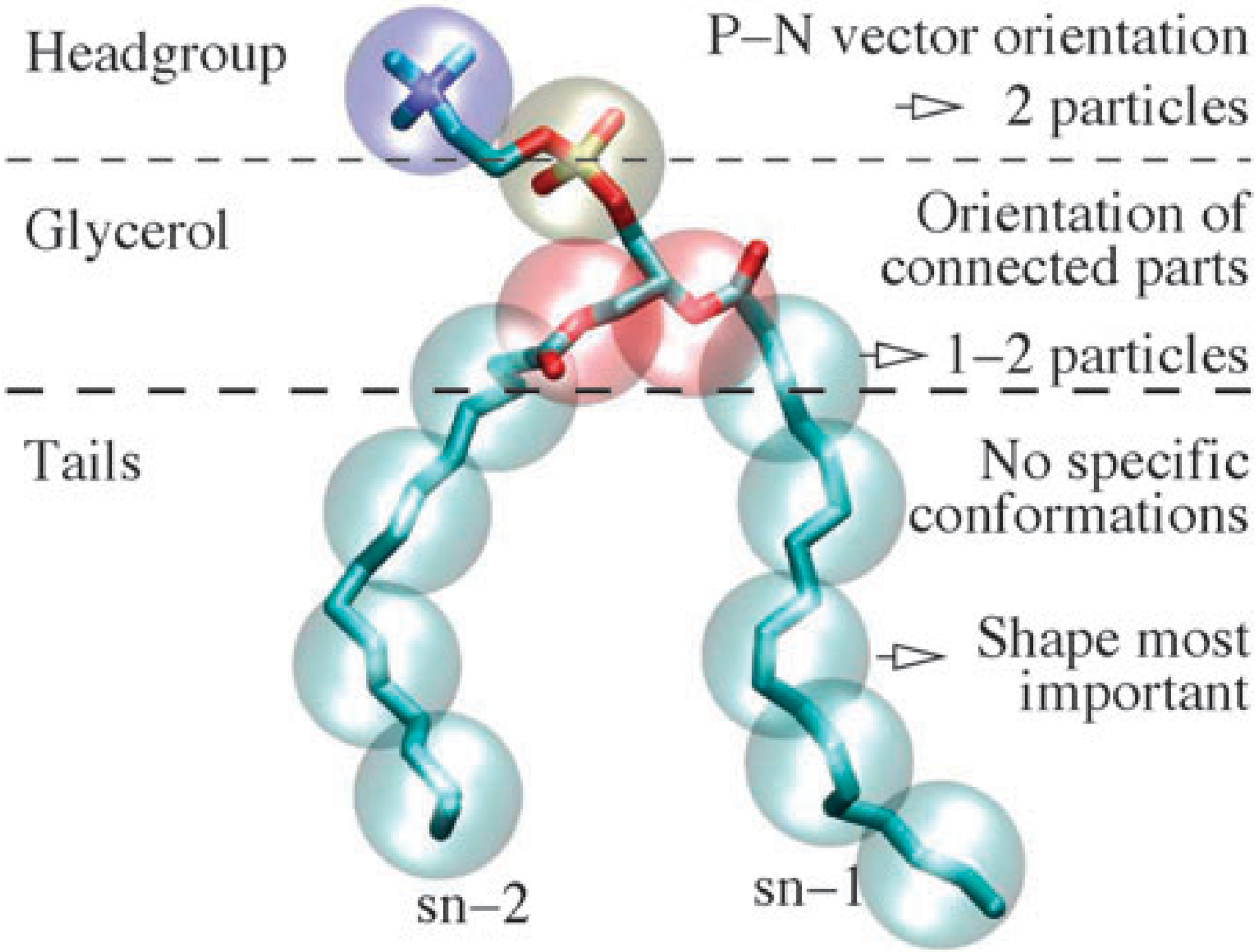




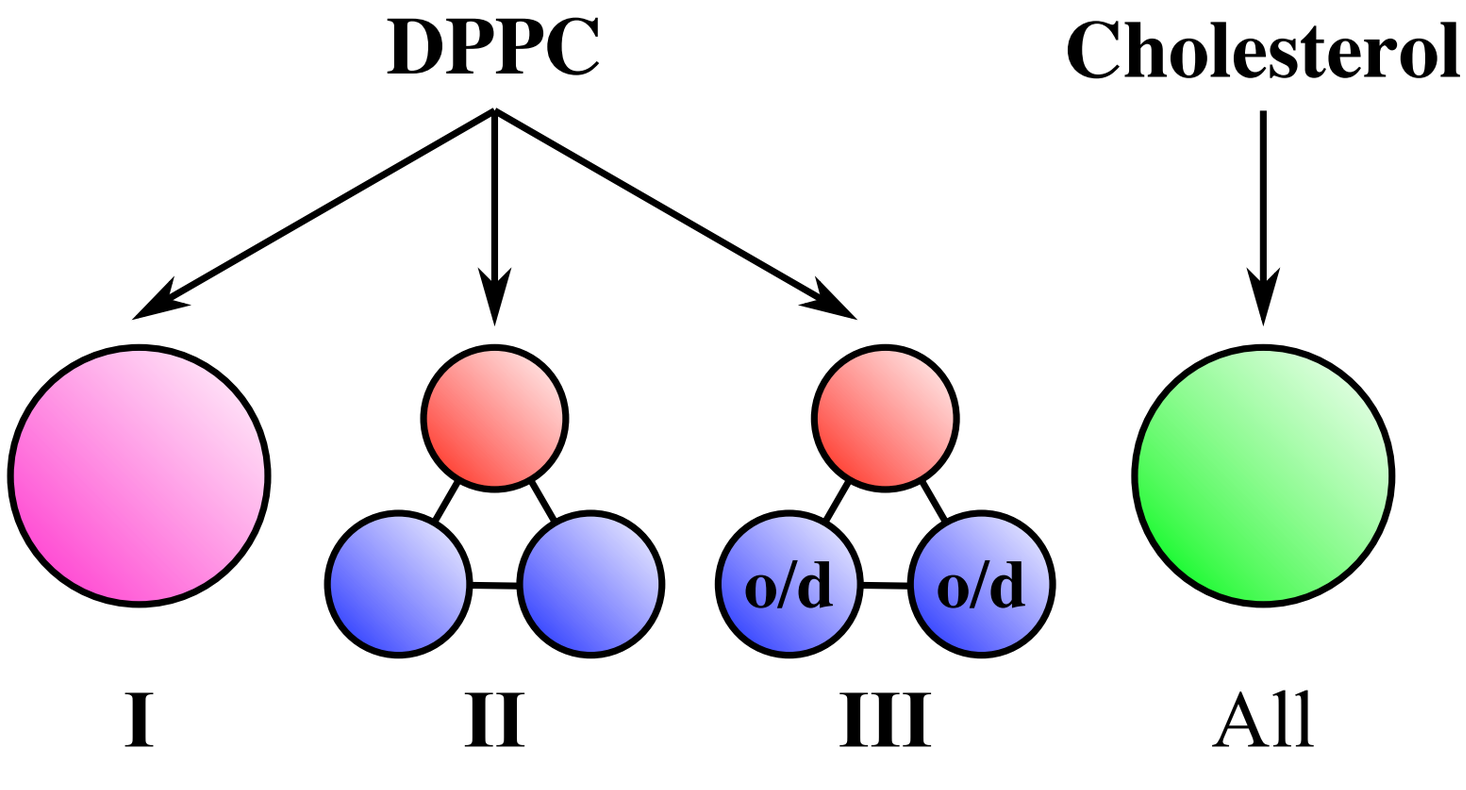
Semi-atomistic/superatom model where each bead describes a few heavy atoms.

Continuum models: describe a bilayer as an elastic manifold (upper) and/or to describe local structure (lower)

Groups


Headgroup
P–N vector orientation
2 particles
Glycerol
Orientation of connected parts
1–2 particles
Tails
No specific conformations
Shape most important
sn–2
sn–1

DPPC-chol CG models



[I] T. Murtola, E. Falck, M. Patra, M. Karttunen, and I. Vattulainen. 2004. Coarse-grained model for phospholipid / cholesterol bilayer. J. Chem. Phys., 121:9156– 9165.

[II] T. Murtola, E. Falck, M. Karttunen, and I. Vattulainen. 2007. Coarse-grained model for phospholipid/ cholesterol bilayer employing inverse Monte Carlo with thermodynamic constraints. JCP 126:075101.

[III] T. Murtola, M. Karttunen, and I. Vattulainen. 2009. Systematic coarse-graining from structure using internal states: Application to phospholipid/cholesterol bilayer. JCP, accepted.

Henderson's theorem

Volume 49A, number 3 PHYSICS LETTERS 9 September 1974

A UNIQUENESS THEOREM FOR FLUID PAIR CORRELATION FUNCTIONS

R.L. HENDERSON
Department of Physics, University of Guelph, Guelph N1G 2W1 Ontario, Canada

Received 5 August 1974

It is shown that, for quantum and classical fluids with only pairwise interactions, and under given conditions of temperature and density, the pair potential $v(r)$ which gives rise to a given radial distribution function $g(r)$ is unique up to a constant.

The Henderson theorem is analogous to the Hohenberg-Kohn theorem (Phys. Rev. 136, B864 (1964)):

The electron density, together with the (known) electron number N, completely defines the Hamiltonian of the system (within an additive constant).

Henderson's theorem

Classical or a quantum system is described by the Hamiltonian

$$H = \sum_i \frac{p_i^2}{2m} + \frac{1}{2}\sum_{i \neq j} u(|\boldsymbol{r}_i - \boldsymbol{r}_j|)$$

It gives a unique pair correlation function g(r). Henderson's theorem says that the g(r) gives a unique Hamiltonian up to a constant. That can be proven using the Gibbs-Bogoliubov inequality

$$F_2 \leq F_1 + \langle H_2 - H_1 \rangle_1$$

canonical average proper for H_1

two systems with Hamiltonians H_1 and H_2

The above holds if and only if H_2-H_1 is independent of all degrees of freedom. Then $g_1(r)$ and $g_2(r)$ can differ only by a constant.

Don't believe the above? Try the following: assume that there are 2 systems that are identical except that the pair potentials are different.

Then, if $g_1(r)$ and $g_2(r)$ are identical, the above says that
$u_2(r)$-$u_1(r)$=constant. Write down the free energies for both systems and you'll end up with 0<0.

Inverse Monte Carlo

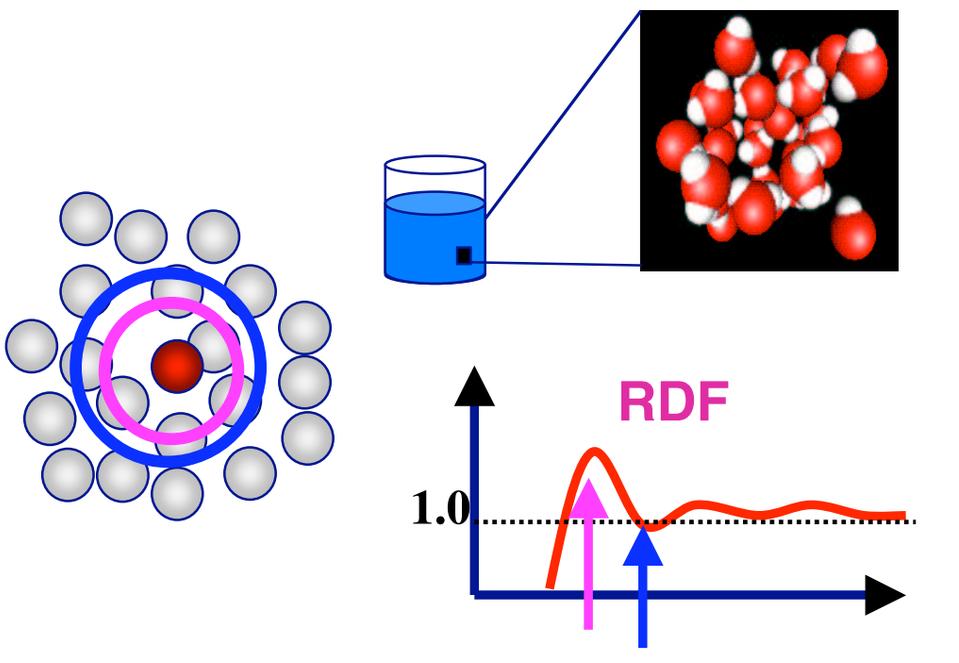
MODEL
Interaction potential

DIRECT ⇄ INVERSE

PROPERTIES
Radial distribution functions

Inverse Monte Carlo:

- **Reconstruct potentials from experimental RDFs**
- **Construct potentials from detailed simulations**



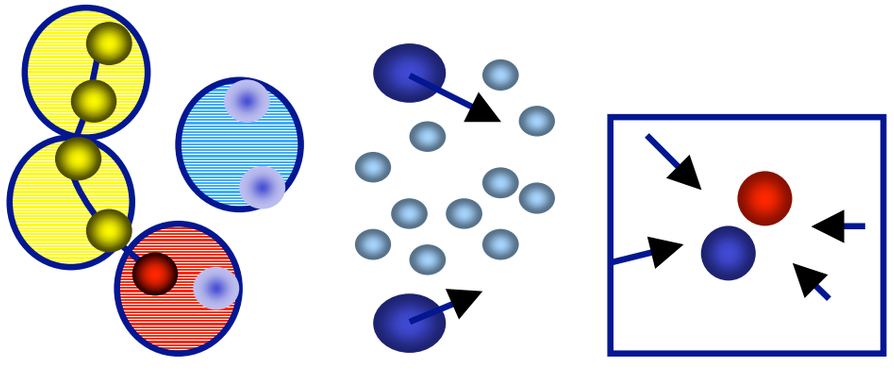
$$V_{PMF}(r) \equiv -k_B T \ln g(r)$$

Dissipative Particle Dynamics:

- **Coarse-grained description**
- **Energy transfer to microscopic degrees of freedom via collisions**
- **Produces the canonical ensemble**

$$\vec{F}_i = \sum_{j \neq i} \vec{F}_{ij}^{\,C} + \vec{F}_{ij}^{\,D} + \vec{F}_{ij}^{\,R}$$

conservative — dissipative — random



Lyubartsev, Karttunen, Vattulainen, Laaksonen, Soft Materials -04
Murtola, Falck, Karttunen, Vattulainen, JCP -05, -07

IMC

Central idea of Inverse Monte Carlo: Adjust effective interactions to match the target RDF in an iterative fashion.

Potentials: represented by a piecewise constant grid approximation

V_α potential in bin α

S_α number of particle pairs in that bin

Relation to RDF: $\langle S_\alpha \rangle = g_\alpha N_p A_\alpha / V$

N_p number of particle pairs in the system

V total volume of the system

During each iteration, the derivatives of $\langle S_\alpha \rangle$ with respect to V_β can be calculated for all pairs We can then express the changes in $\langle S_\alpha \rangle$ to the first order in terms of changes in V_β as

$$\Delta \langle \boldsymbol{S} \rangle = A \Delta \boldsymbol{V} \qquad A_{\alpha\beta} = \frac{\partial S_\alpha}{\partial V_\beta} = -\frac{\langle S_\alpha S_\beta \rangle - \langle S_\alpha \rangle \langle S_\beta \rangle}{k_\mathrm{B} T}$$

How to improve?

To minimize finite-size effects:

the simulations during the IMC procedure should be carried out with a system that is identical in size to the system from which the target RDFs were determined. In some cases, the effective potentials produced in this way do not generalize to larger systems.

For example: effective interactions may become **too attractive** to maintain uniform density.

However: larger systems form dense clusters separated by **empty space**, which is typically unphysical.

One possible solution: use surface tension

$$\gamma = \frac{1}{V}\left(\langle E_{kin}\rangle + \frac{1}{2}\left\langle \sum_{i<j} f_{ij} r_{ij} \right\rangle\right)$$

Murtola, Falck, Karttunen, Vattulainen, JCP (2007).

Surface tension

Condensation effects can be characterized by surface tension.

We define the surface tension γ of the coarse-grained model as

$$\gamma = \frac{1}{V}\left(\langle E_{kin}\rangle + \frac{1}{2}\left\langle \sum_{i<j} f_{ij} r_{ij} \right\rangle\right)$$

virial

If this is close to zero or negative in simulations of small systems, larger systems may not be stable. This is the case for the highest cholesterol concentrations.

Situations where thermodynamic properties, particularly the pressure, of the coarse-grained model do not match the underlying atomistic model have also been encountered in other coarse-graining approaches. Proposed solutions include:

1. iterative adjustment of the pressure followed by re-optimization of the interactions
2. imposing additional constraints on the instantaneous virial due to effective interactions

S. Izvekov and G. A. Voth, J. Chem. Phys. 123, 134105 (2005).
D. Reith, M. Putz, and F. Müller-Plathe, J. Comp. Chem. 24, 1624 (2003).

Notice

One should note that the surface tension cannot be directly related to the surface tension in the atomistic simulations.

This is because the effective potentials are in general volume dependent.

Hence, the correct value of γ is not necessarily the same as the surface tension in the atomistic simulations, which has been proposed to be zero in equilibrium.

Because of these considerations, the value of γ has to be fixed using other quantities. Here, we used area compressibility

Models: note cholesterol alwats a single particle

Model I

Constrained in 2D
Speedup: 8 orders
of magnitude.
System size:
100 nm x 100 nm

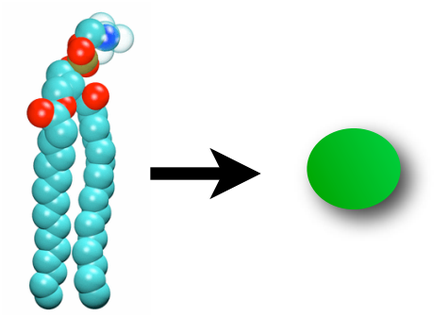
Model II

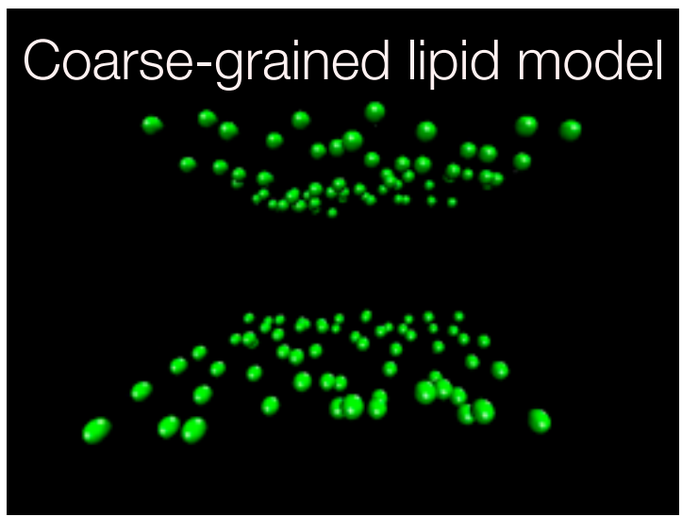
- sn-1 & sn-2 are different
- bonded interactions
- centre of mass used
- 7 non-bonded
- 10 bonded interactions

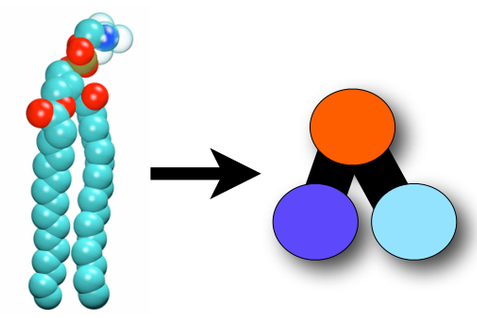
Model III

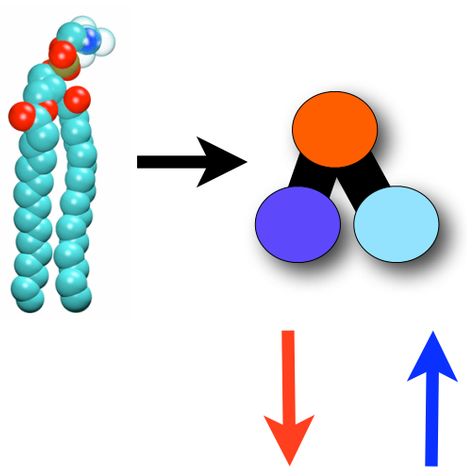
- sn-1 & sn-2 are different
- bonded interactions
- centre of mass used
- internal state:
  1. orderd
  2. disordered
- Needs extra internal energy terms

- Nielsen et al., PRE 59:5790 -99



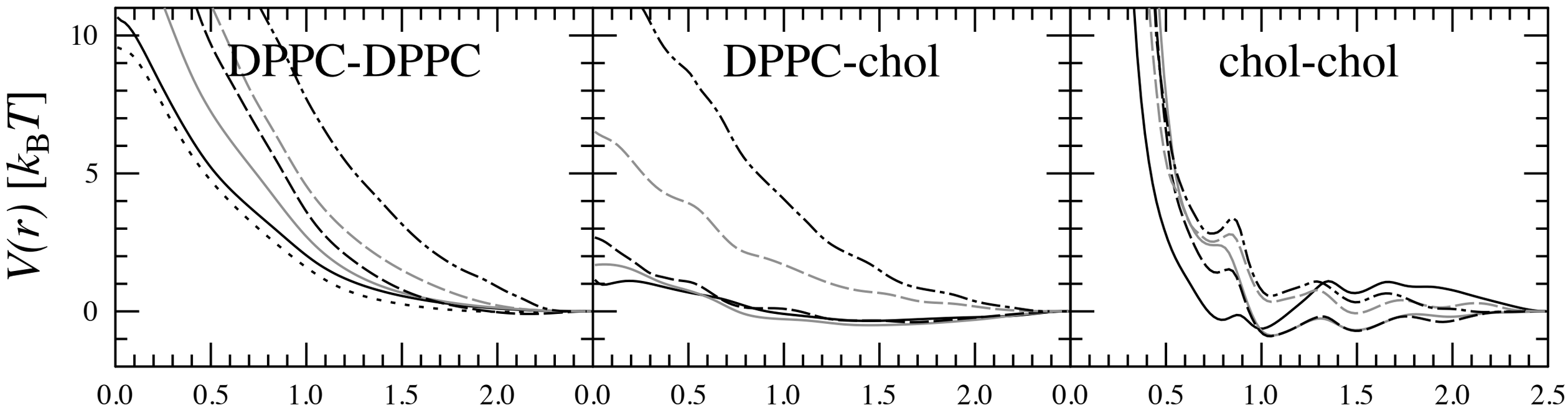




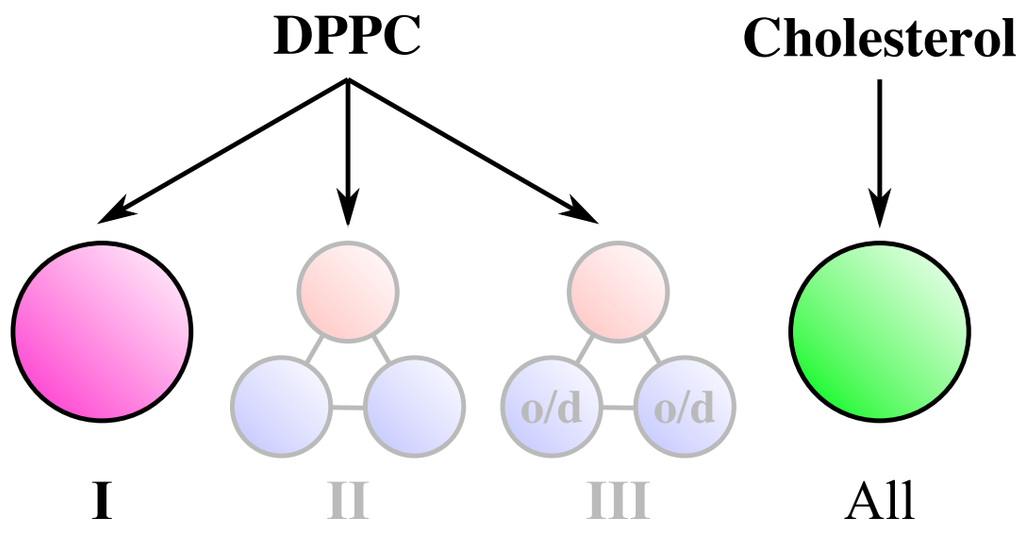


$$H = \sum_{\alpha} S_{\alpha} V_{\alpha} + \Delta E n_d + E_{\text{fluct}} \delta {n_d}^2$$

Model I



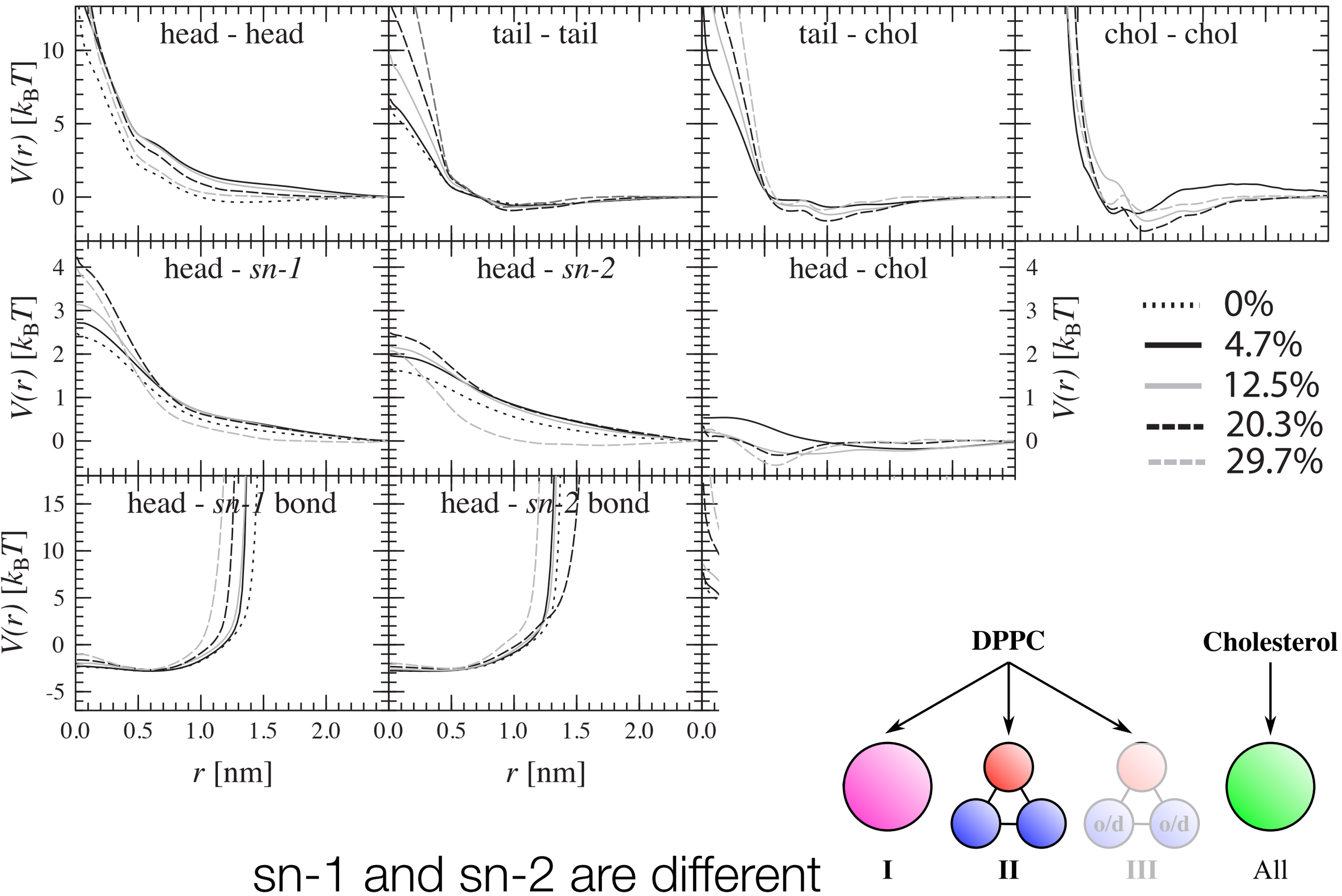
0 %
4.7 %
12.5 %
20.3 %
29.7 %
50.0 %



Model II

Text

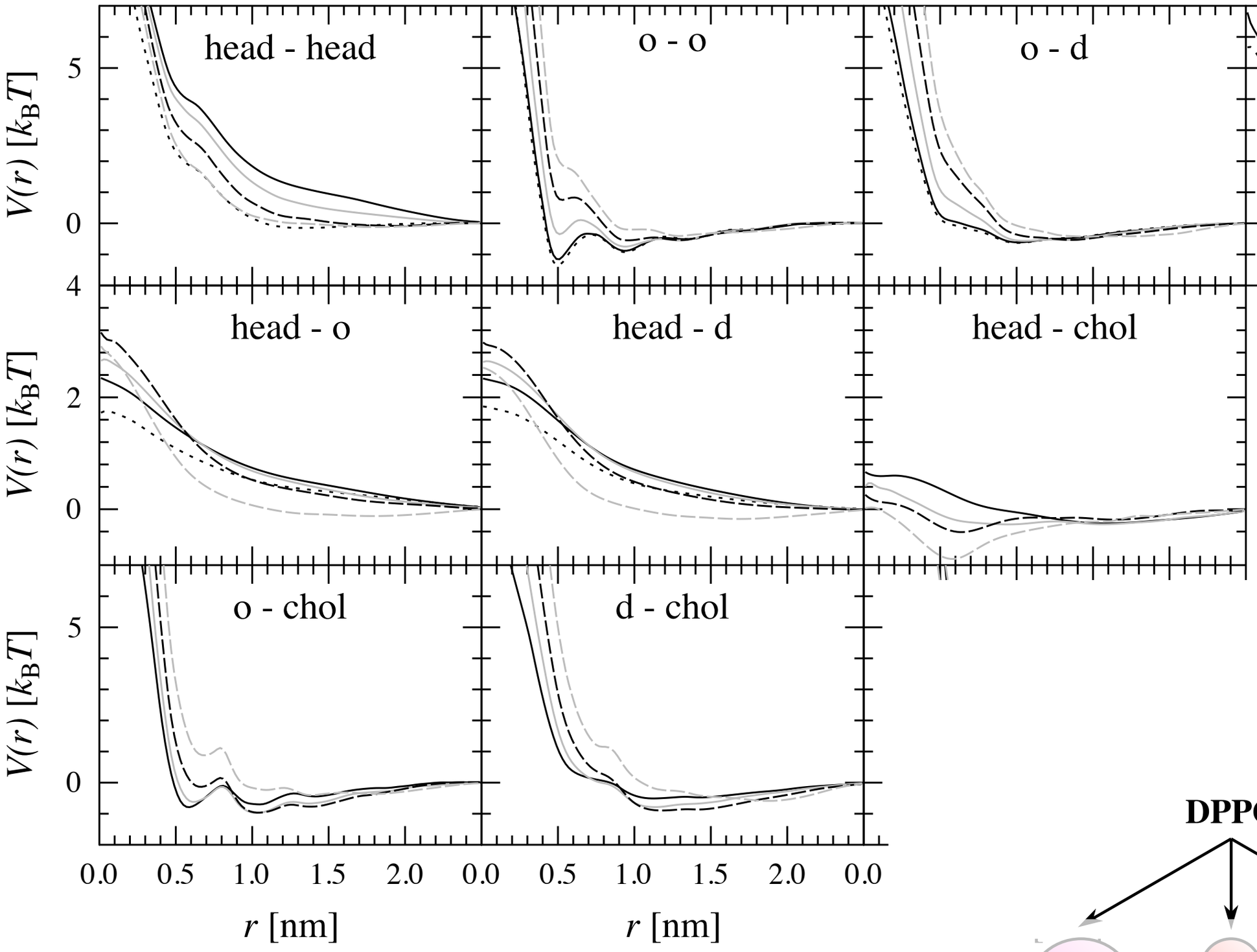
Text

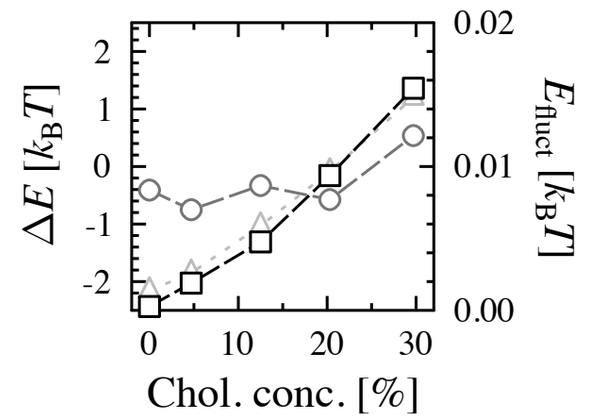


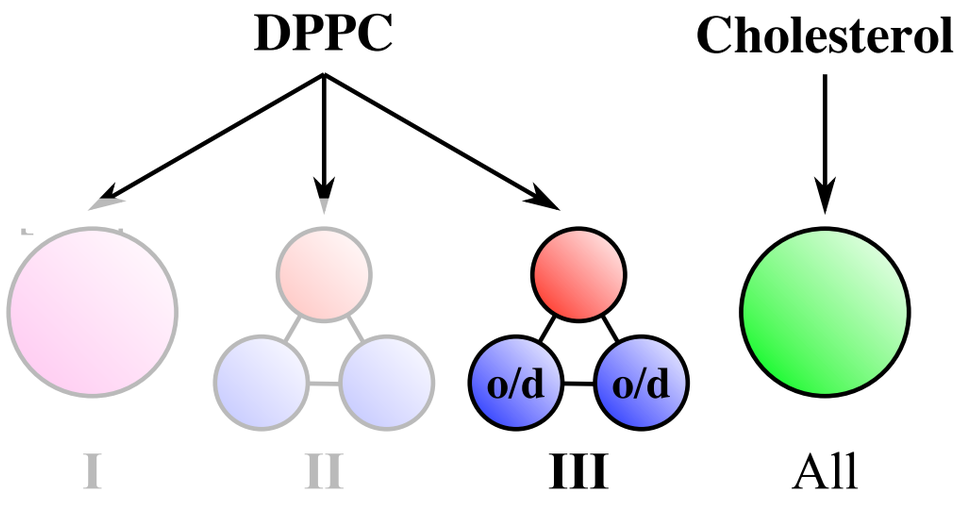
sn-1 and sn-2 are different

Model III

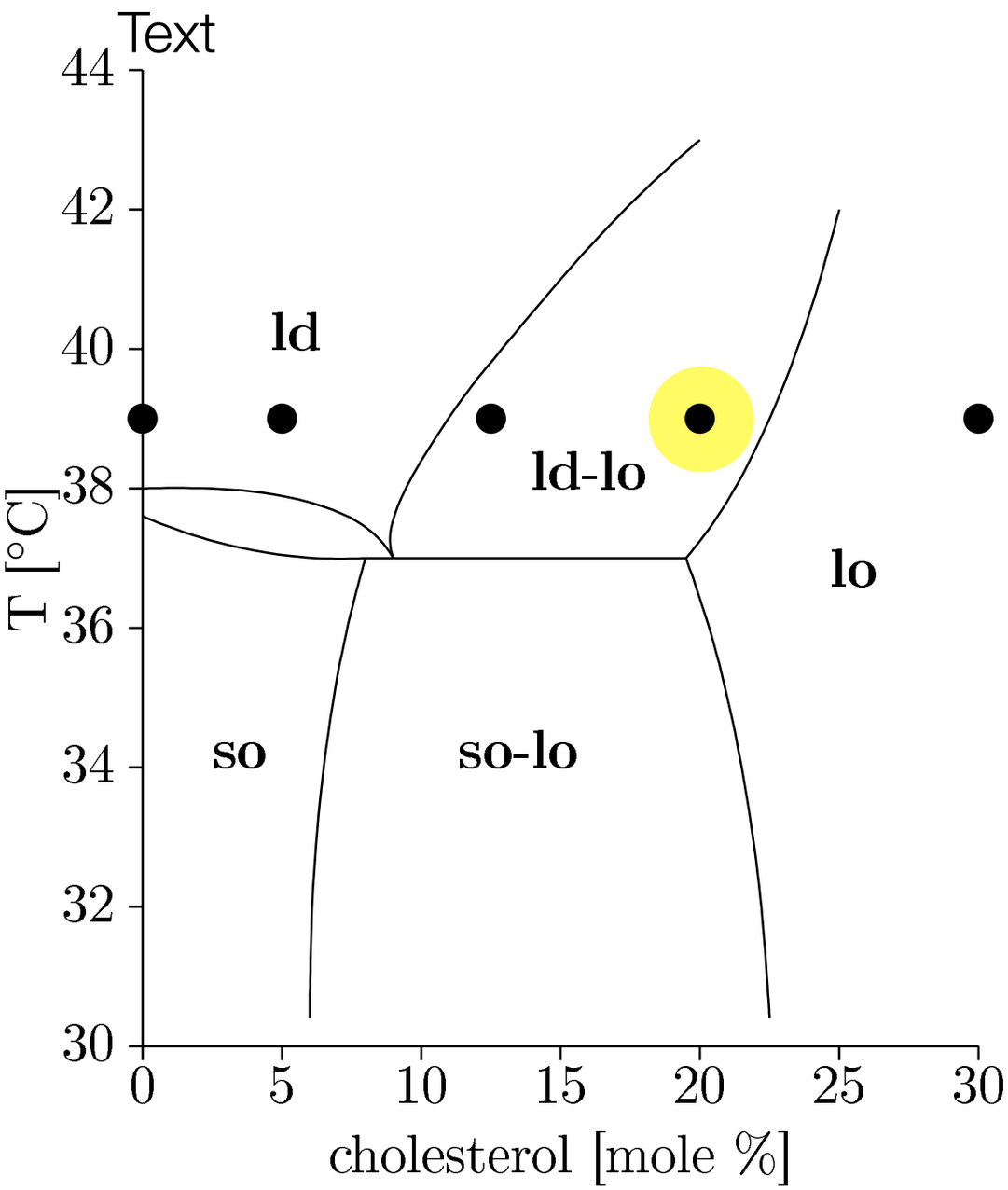
Murtola, Karttunen, Vattulainen, accepted for publication in JCP

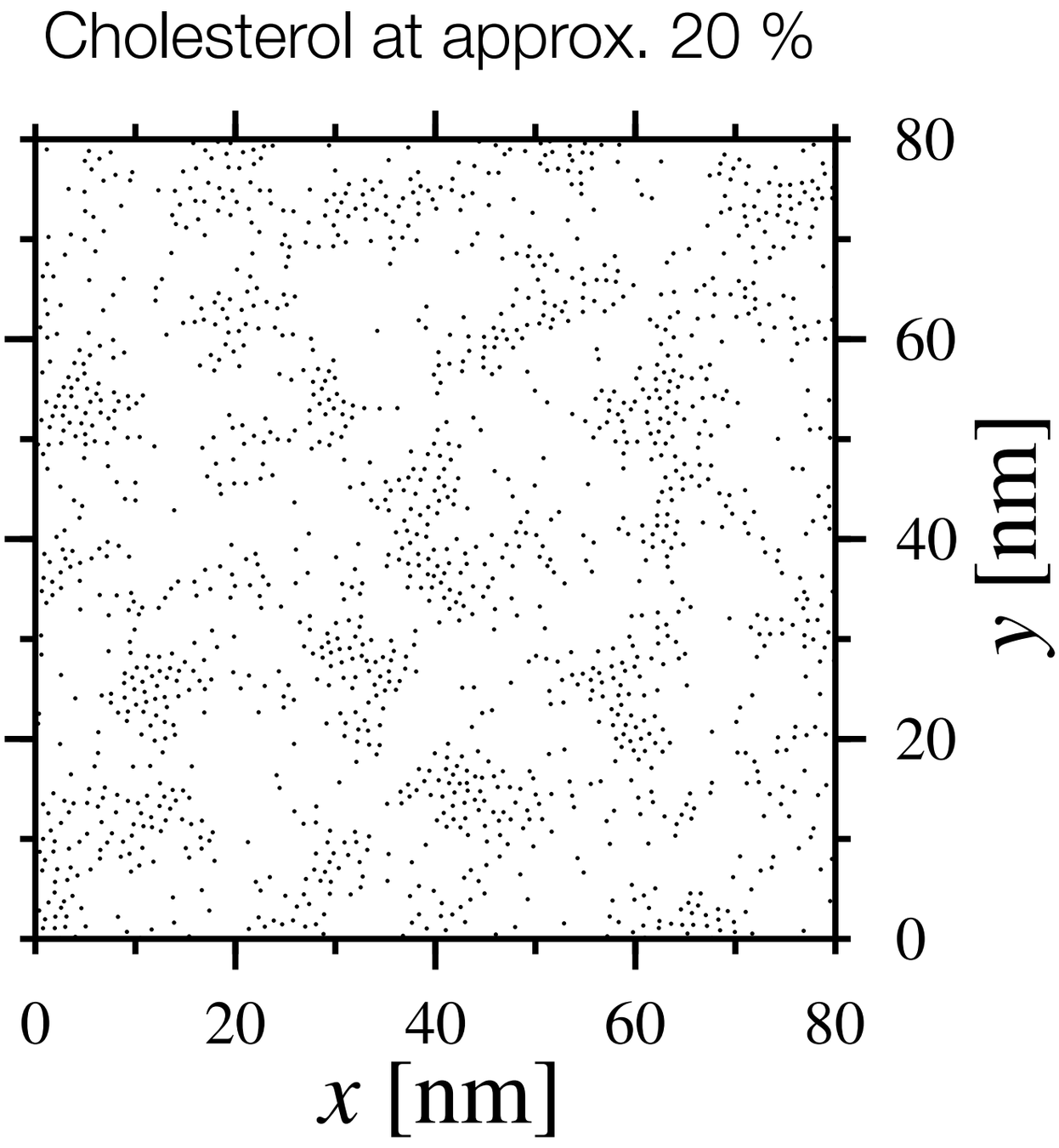






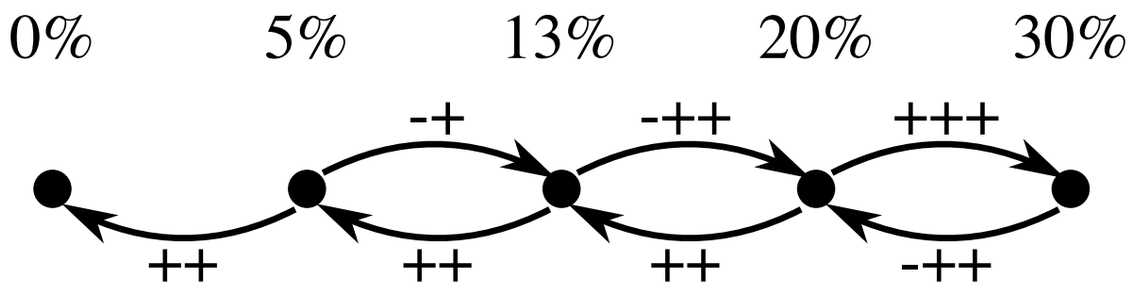
Cholesterol & clustering at 20%





Murtola, Falck, Karttunen, Vattulainen, JCP (2007).

Transferability between concentrations



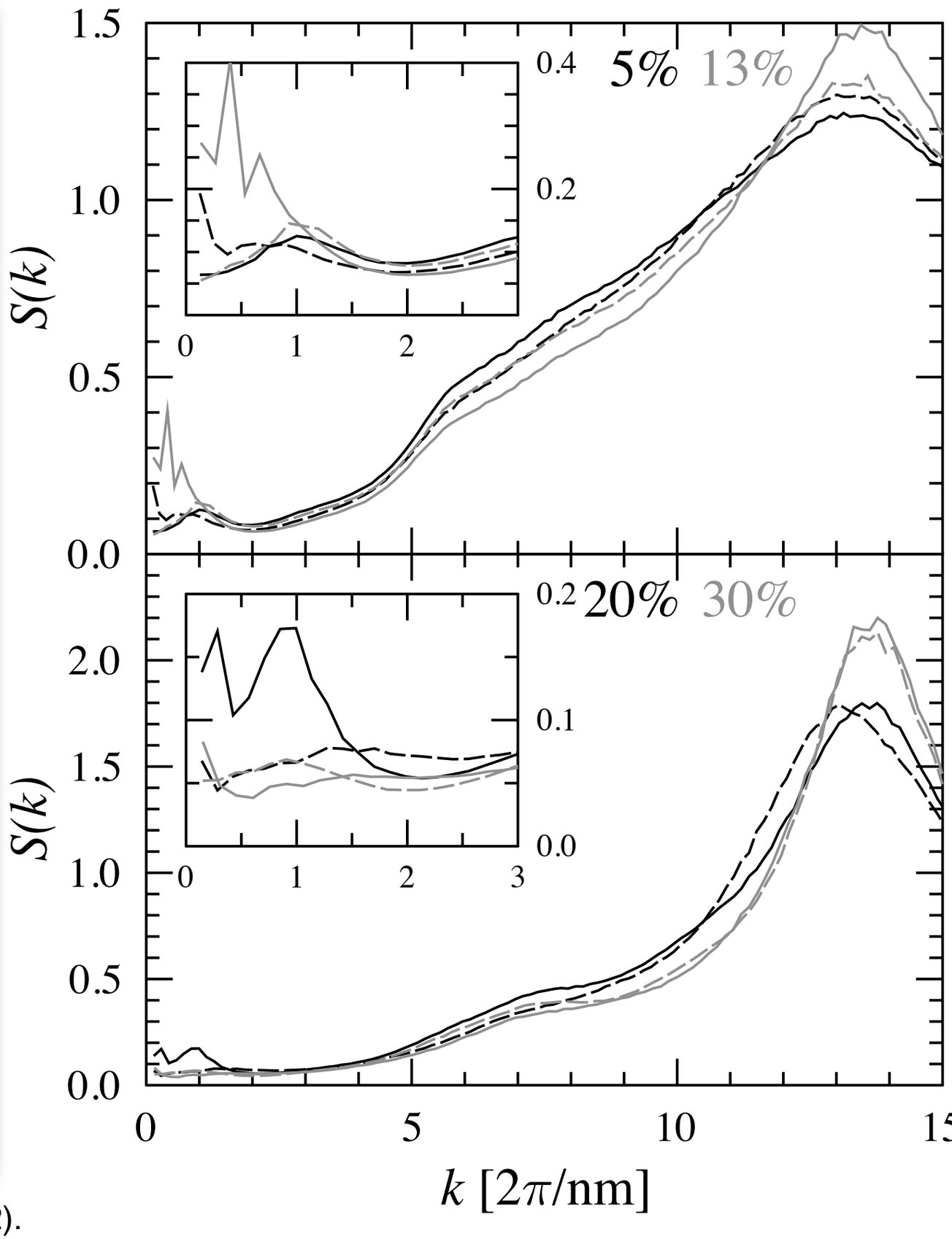
The first +/- stands for (qualitative) reproduction of small behavior of S (k)

The second + for qualitative reproduction of the nearest-neighbor peak in S (k)

Third + for quantitatively nearly correct S (k) away from the small k region

solid line: the correct S(k)

dashed line: by the transferred interactions



In practise: very different potentials lead to the same RDF

P. G. Bolhuis and A. A. Louis, Macromolecules 35, 1860 (2002).

Conclusions

- Fluctuations play an important role in defining membrane properties.
- ***A new paradigm for lipid diffusion is suggested.*** Neighbor-neighbor correlations and concerted motion may dominate.
- Biological importance: rafts, signalling, lateral pressure
- ***Coarse graining using structural data.*** IMC is possible approach. It does not come without problems but can be used to reach systems sizes over 100nm x 100nm
- ***Micelles***: new fission mechanism for charged micells.