Computers Crunching Lipids – From Cell Membranes to Lipoproteins

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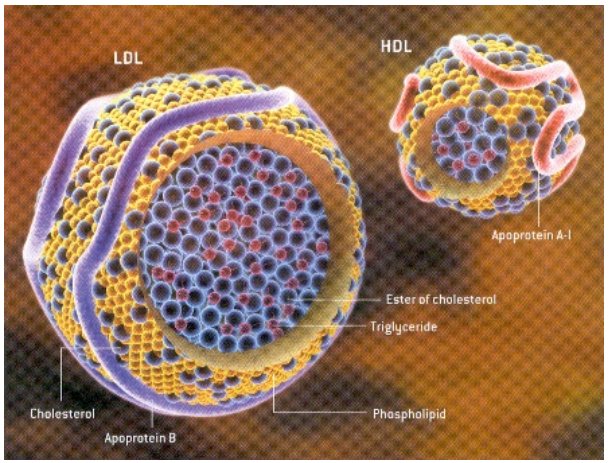
FINLAND



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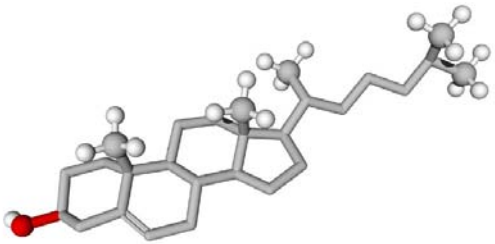
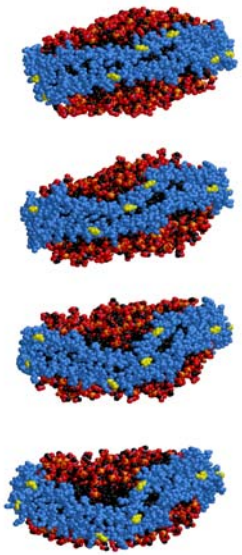
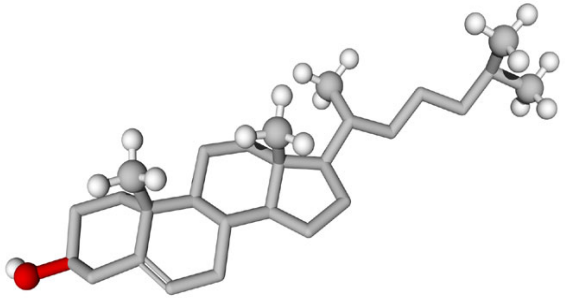
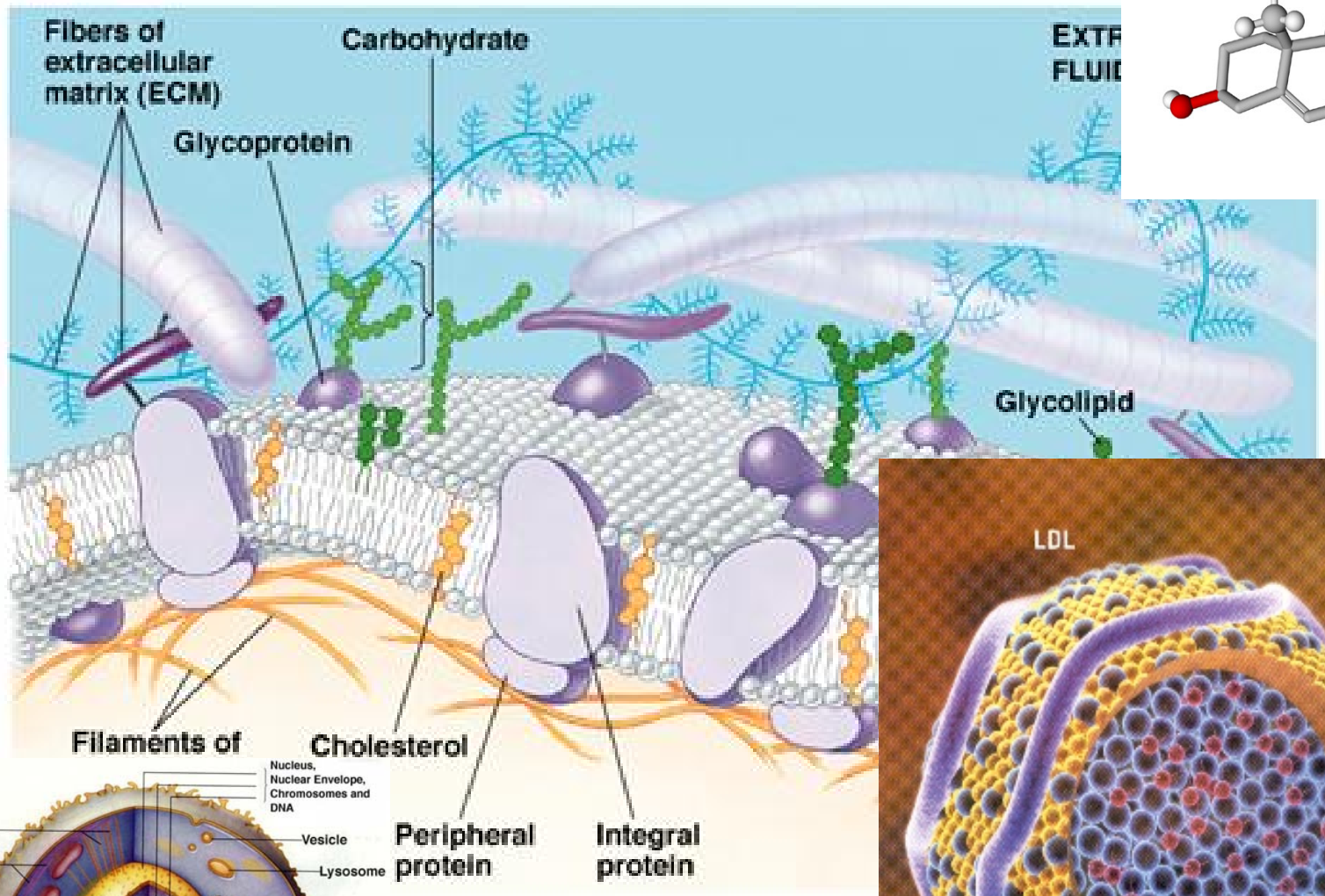


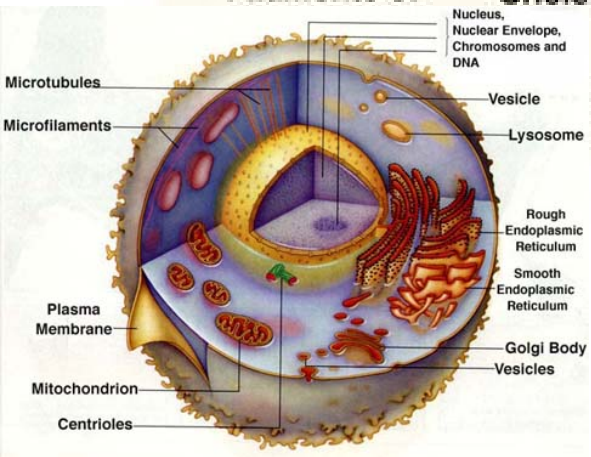


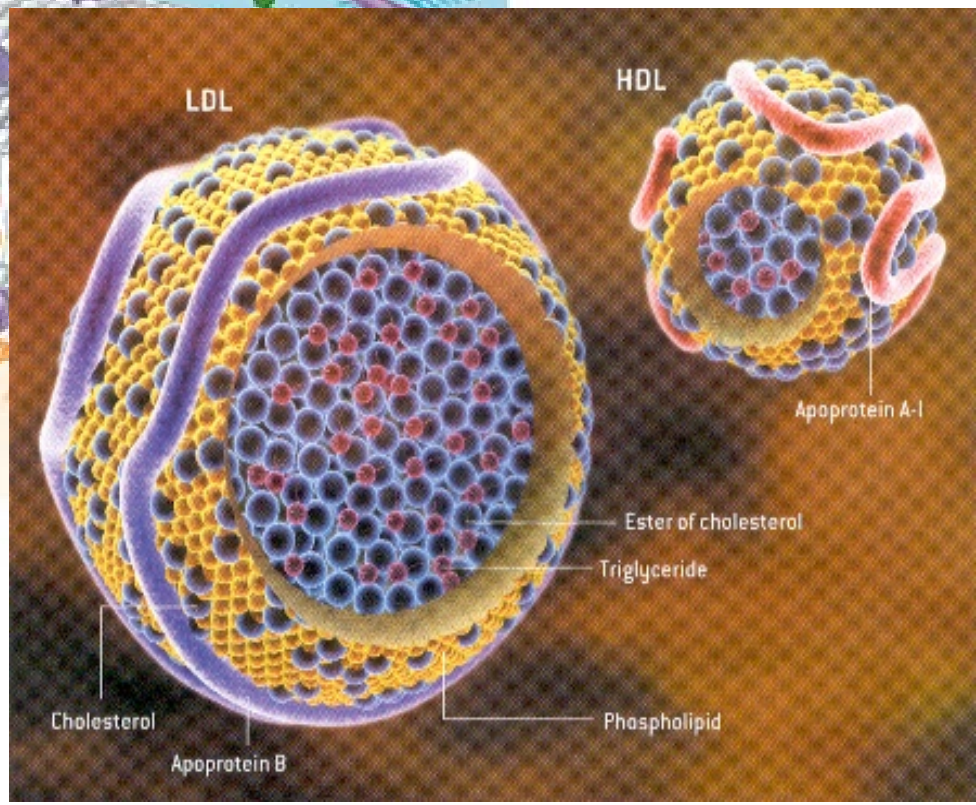
Cholesterol Everywhere



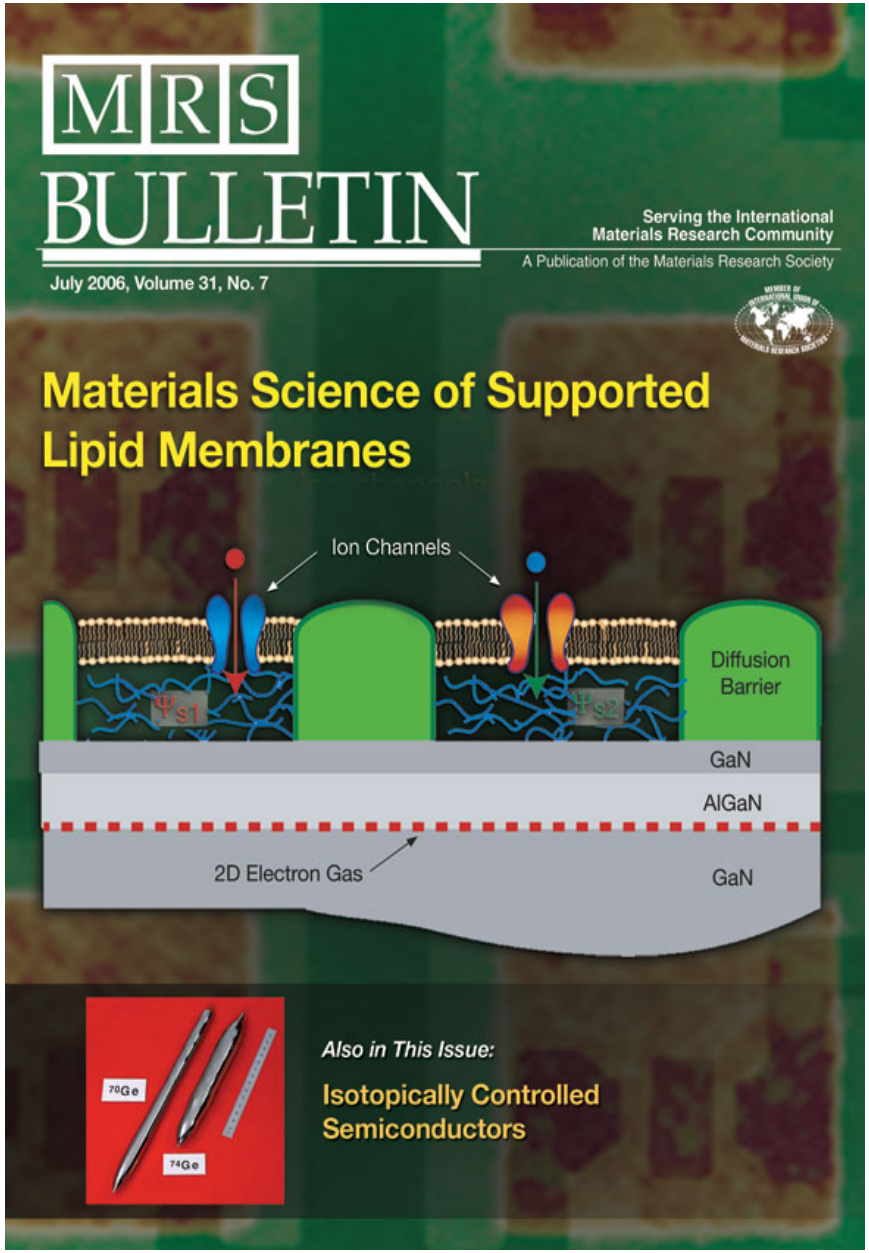


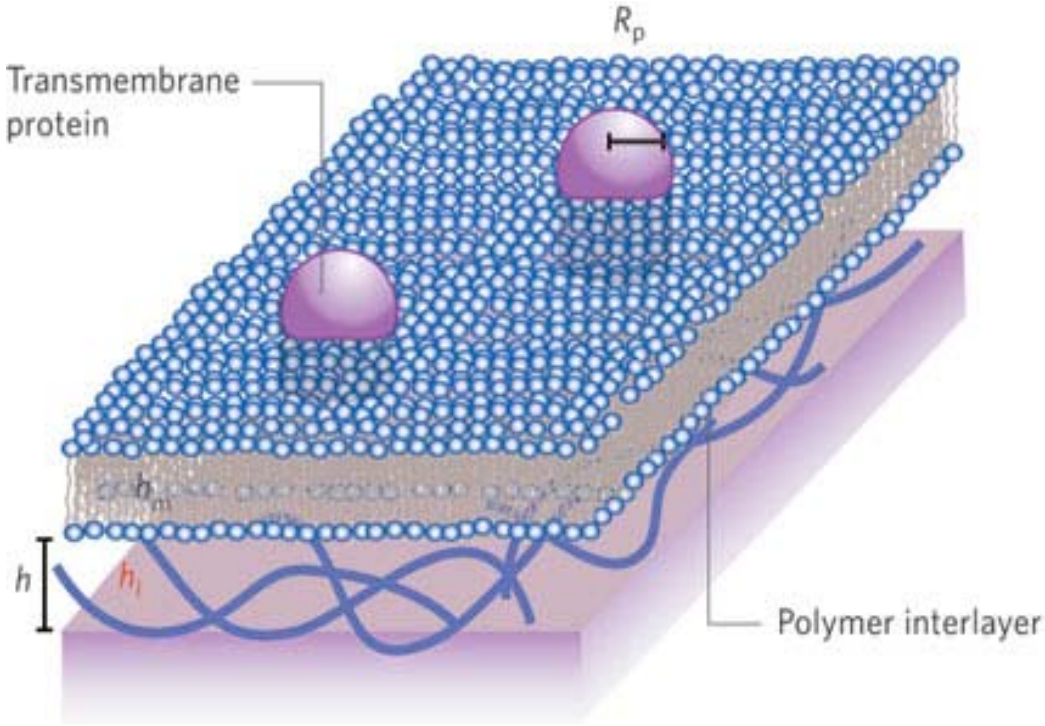
complexity & scales !!!

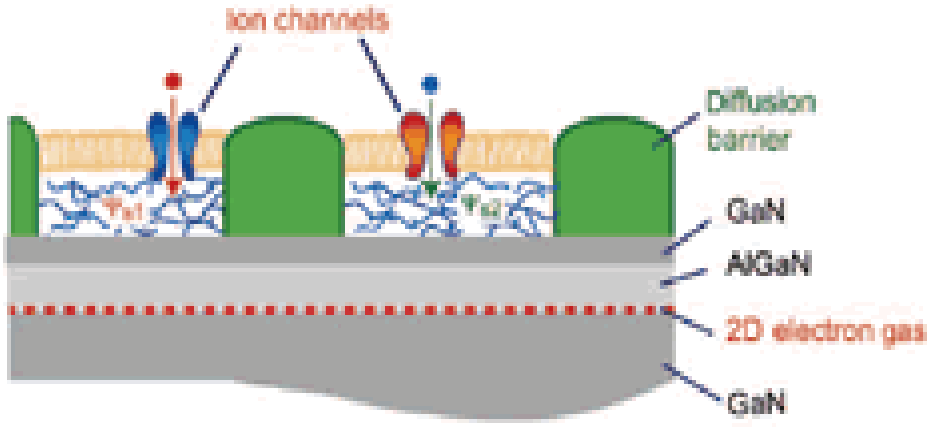




Membrane Proteins as Biosensors



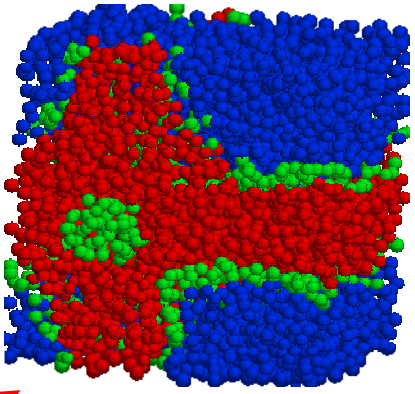




Multi-scale modeling

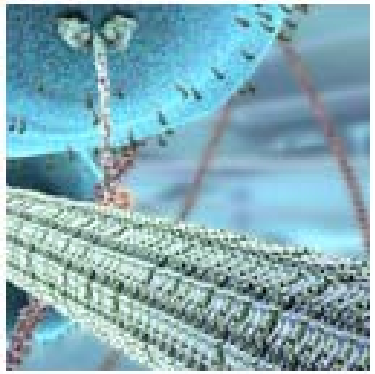
Mesoscale:

- effective interactions
- collective phenomena
- long-range effects

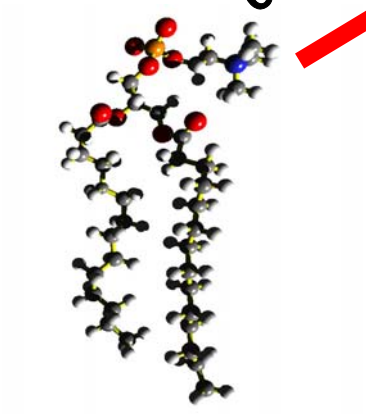


Macroscale:

- times ~1 s
- scales ~ 1μ
- large scales



Coarse graining

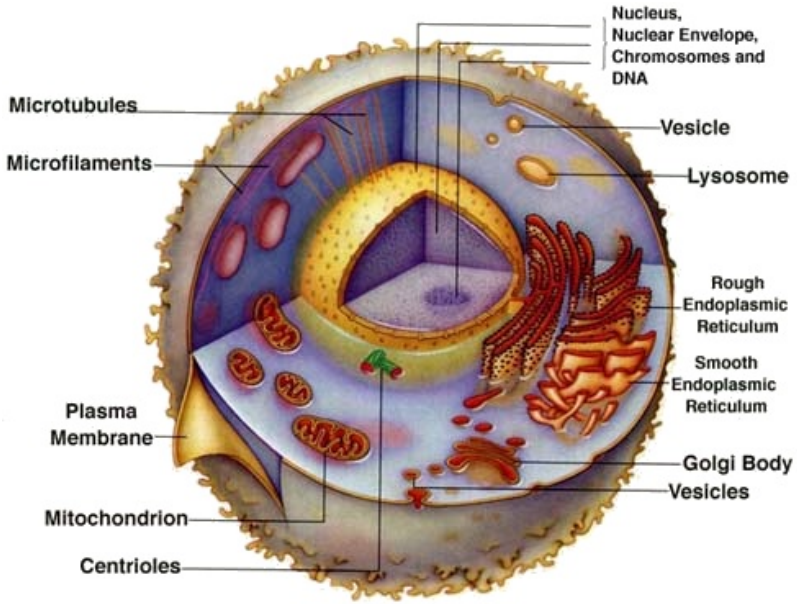


Multi-scale modeling

1. Development of coarse-graining techniques for molecules and their interactions
2. Bridging atomistic and CG models in applications to actual problems

Atomistic picture:

- microscopic accuracy
- interatomic forces
- intermolecular interactions

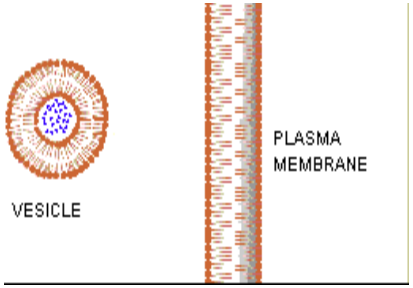


Modeler's toolbox

Various scales, various methods

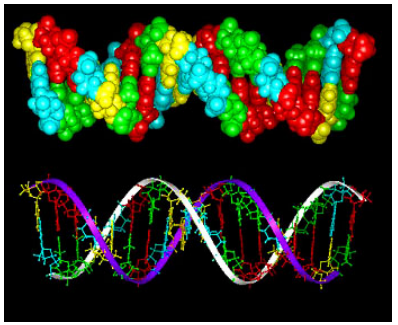
Macroscale:

- times > 1 *sec*
- scales > 1μ
- phase field models, FEM



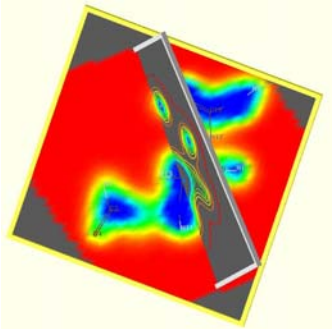
Mesoscale:

- times ~ 10^{-8} – 10^{-2} *sec*
- scales ~ 100 - 10000 Å
- DPD, coarse graining



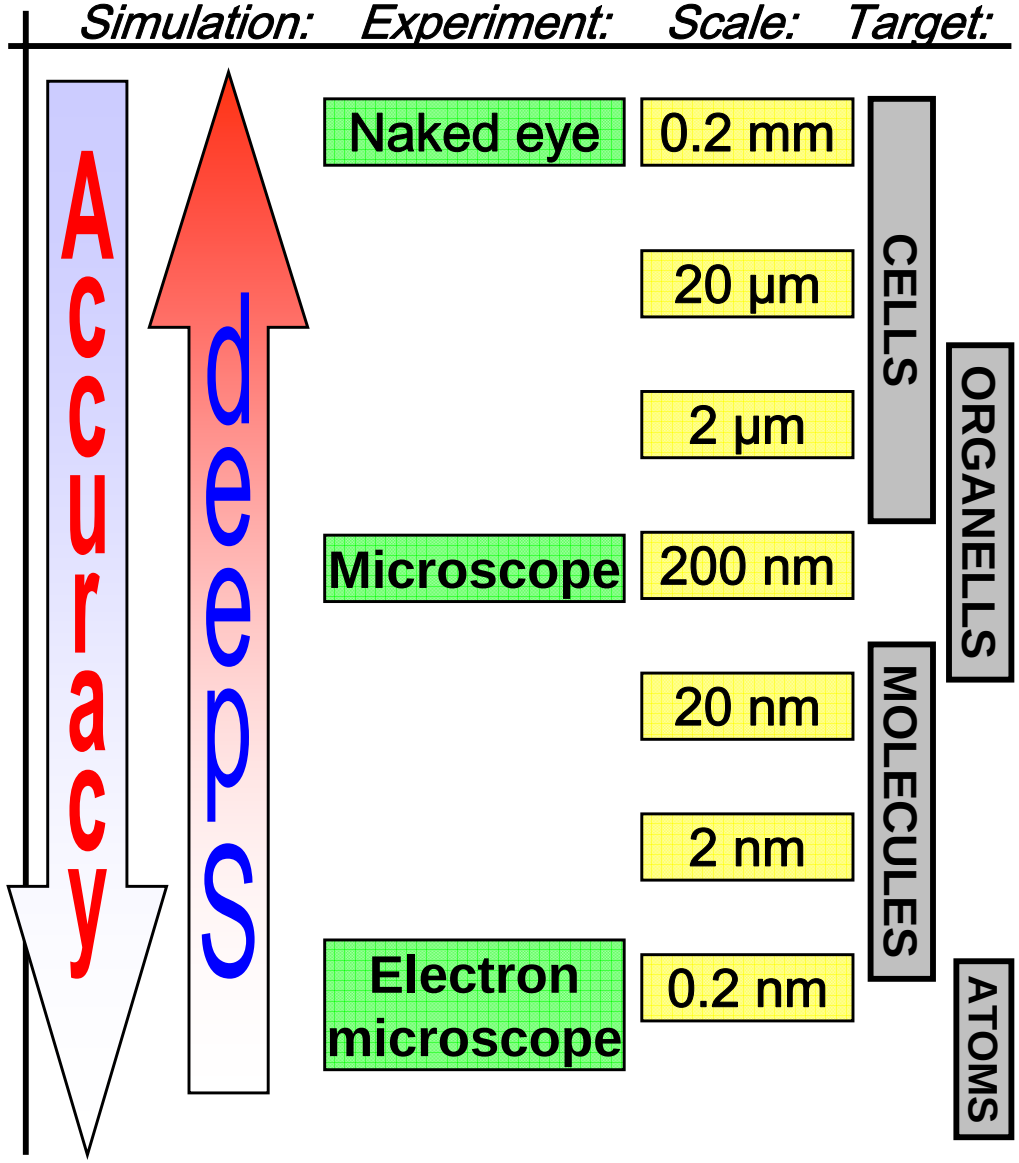
Atomistic scale:

- times ~ 10^{-15} – 10^{-9} *sec*
- scales ~ 1 - 100 Å
- Classical MD, MC



Subatomistic scale:

- electronic structure
- ab initio
- Green's functions

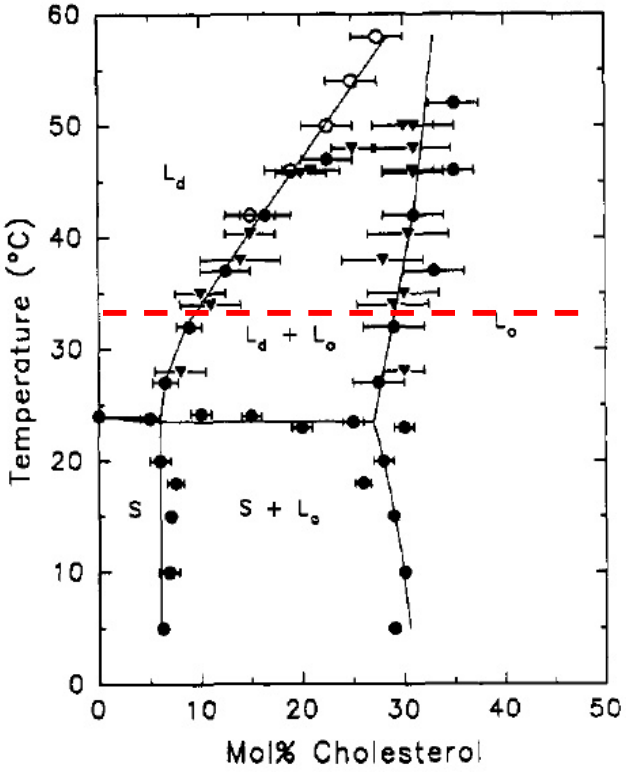


Limits of Atomistic Simulations

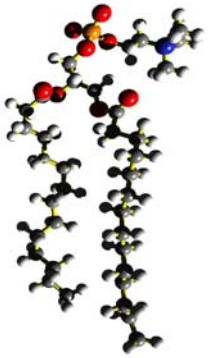
Example for a DPPC/Cholesterol lipid membrane: pros and cons of atomistic simulations for systems of this kind

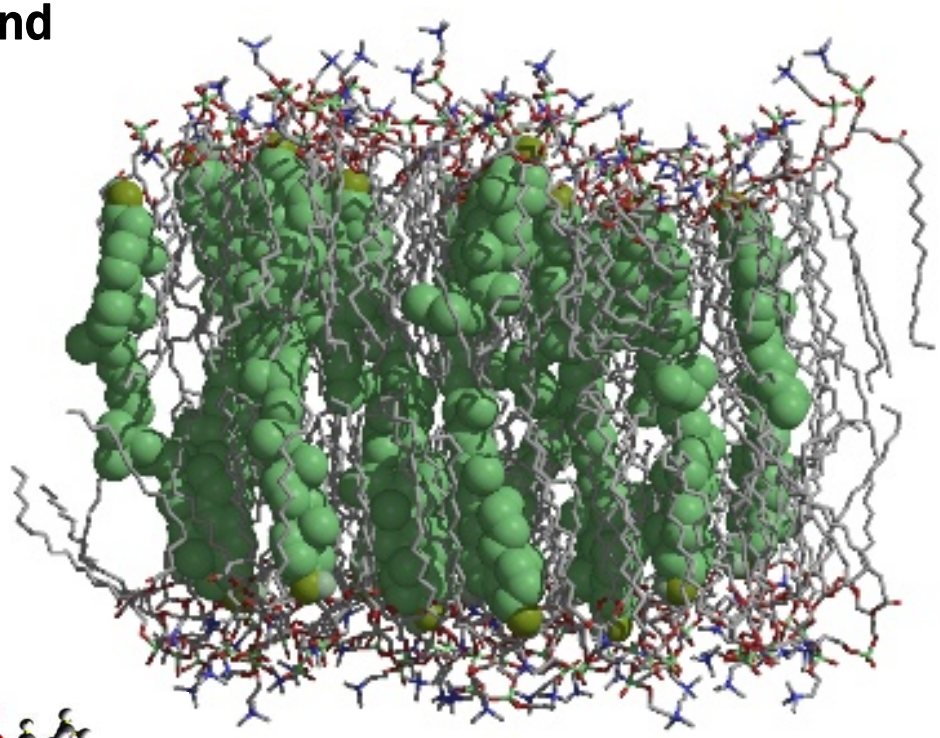
Classical MD (Gromacs):

- 128 DPPC + Chol molecules + water
- 6 cholesterol concentrations
- Simulated time: 100 ns each



Phase diagram based on experiments: Almeida et al. (1992)



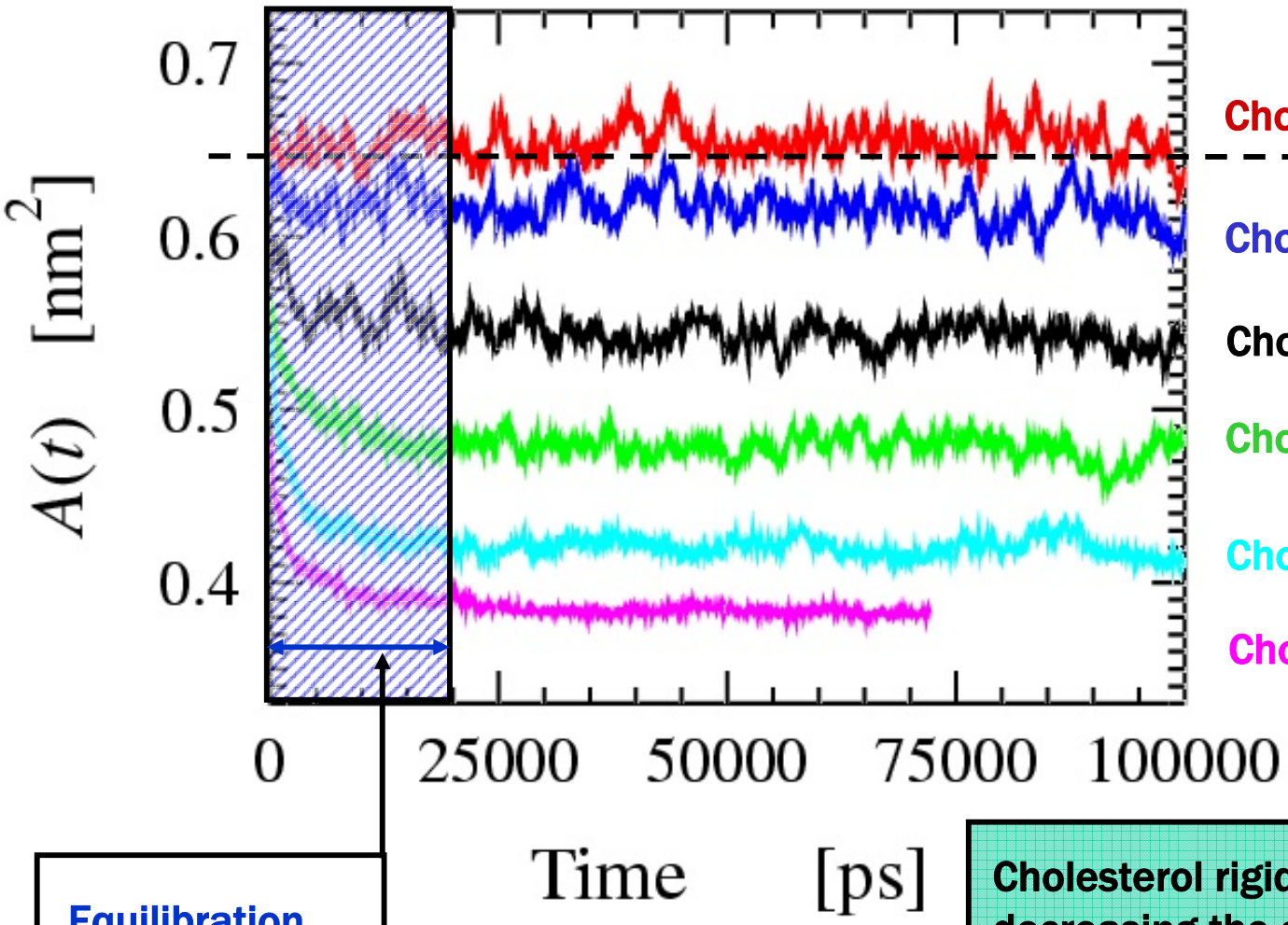


Insight given by atomic-scale modeling in complex biosystems?

[Falck et al., Biophys J 87, 1076 (2004)]

Area per Lipid in Bilayer Plane

DPPC + Cholesterol binary mixture



Experiment:

Pure DPPC

0.64 nm²

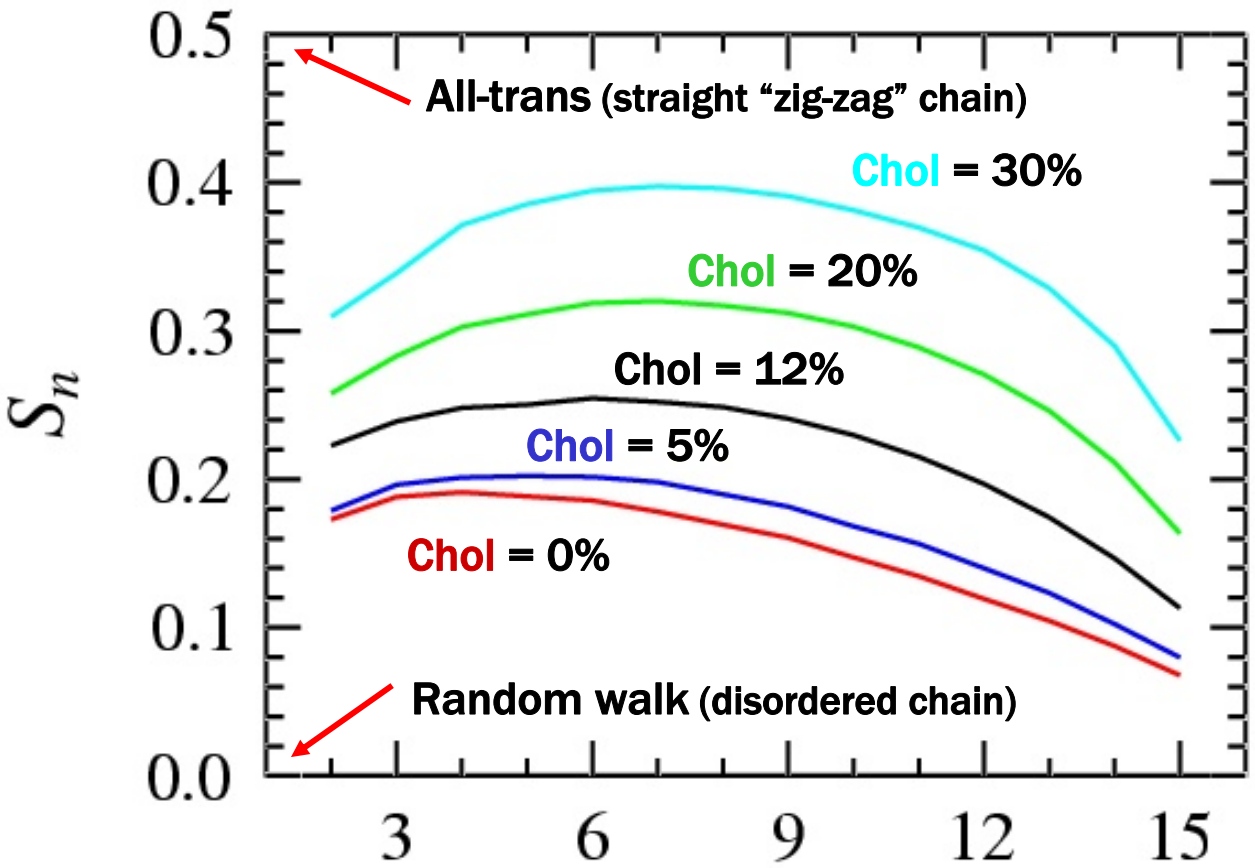
Equilibration for 20 ns

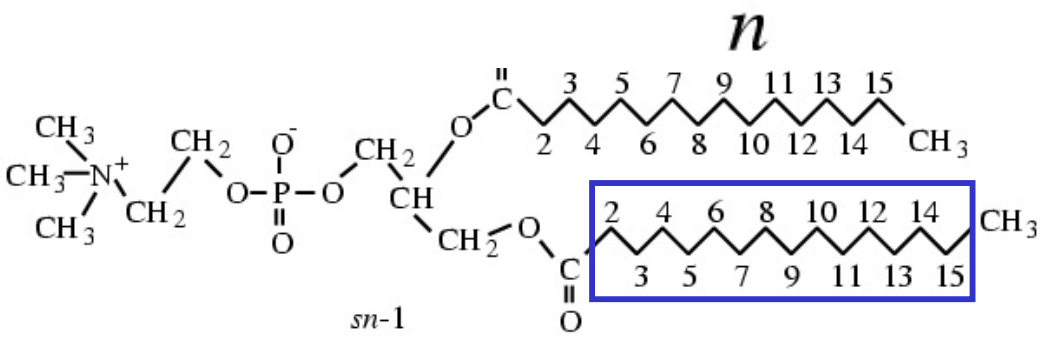
Cholesterol rigidifies the membrane, thus decreasing the area per molecule in agreement with experiments and previous theoretical studies.

[Falck et al., Biophys J 87, 1076 (2004)]

NMR order parameter of acyl chains

Ordering of lipid acyl chains by cholesterol

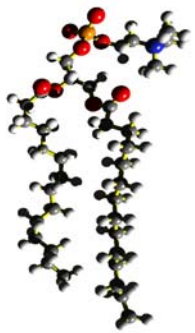


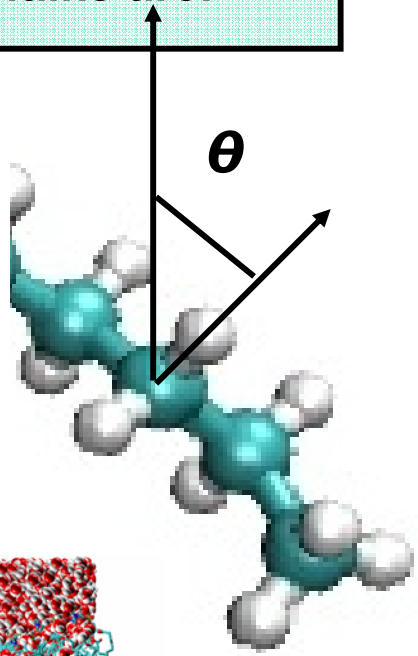


Results fully consistent with NMR

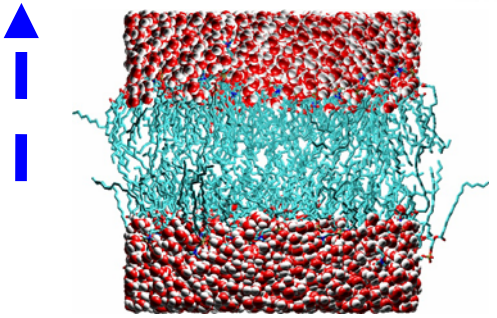
$$S = \frac{3 < \cos^2 \theta > - 1}{2}$$

The larger S, the more ordered the chains are.



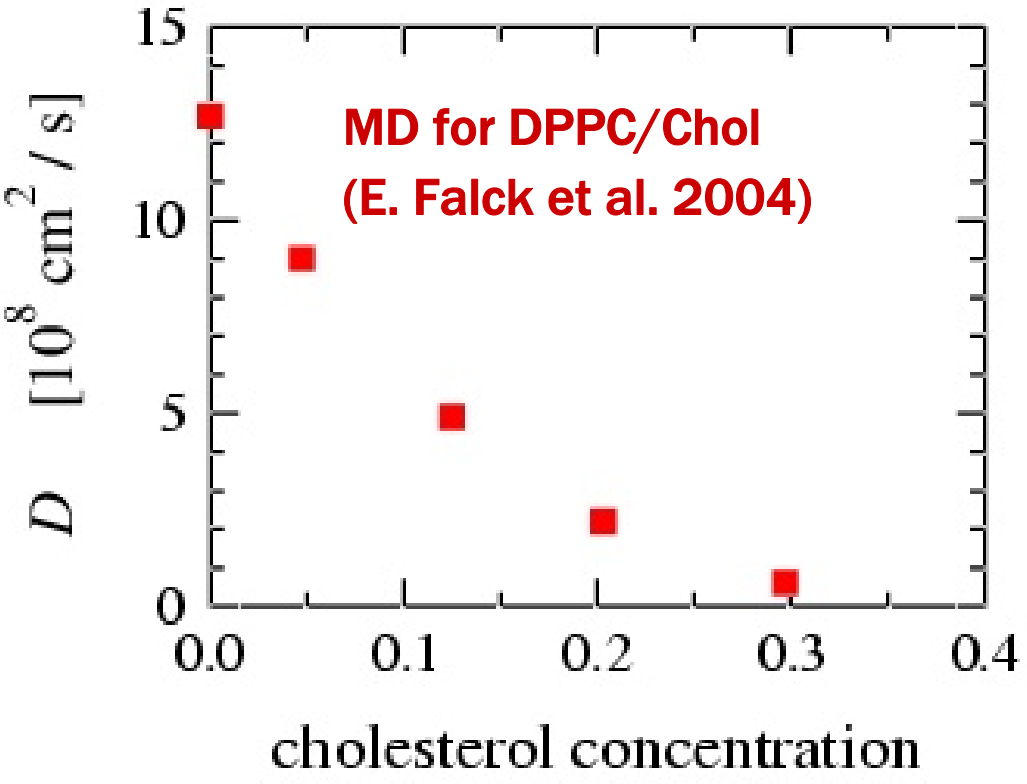


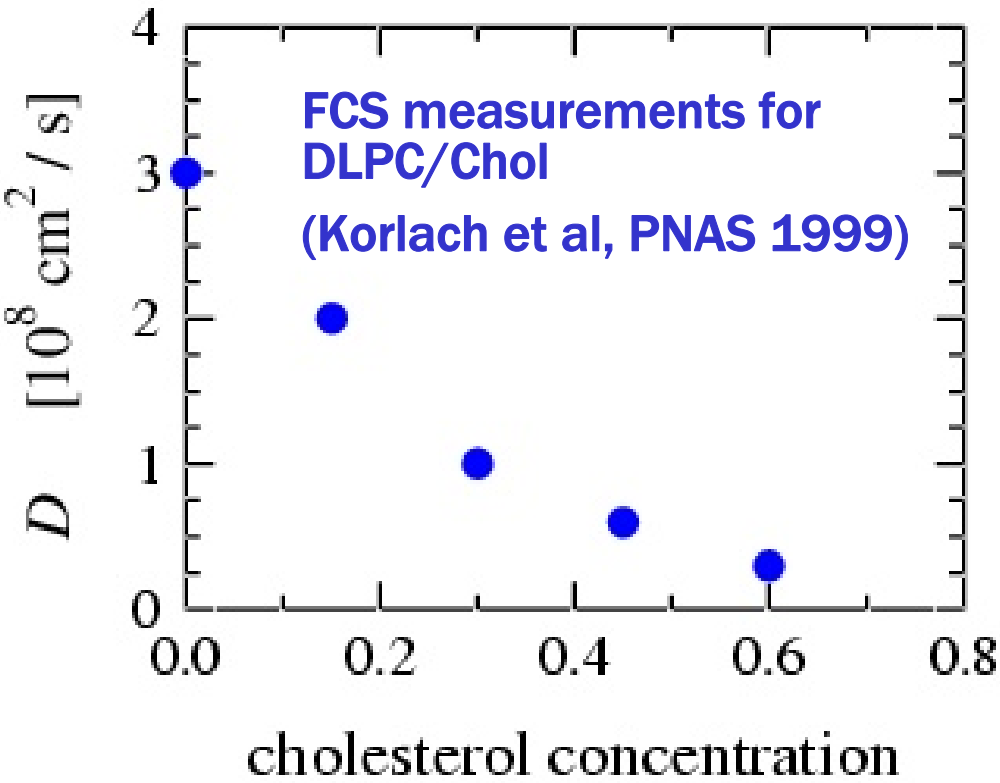
Bilayer normal



Lateral Diffusion Coefficients

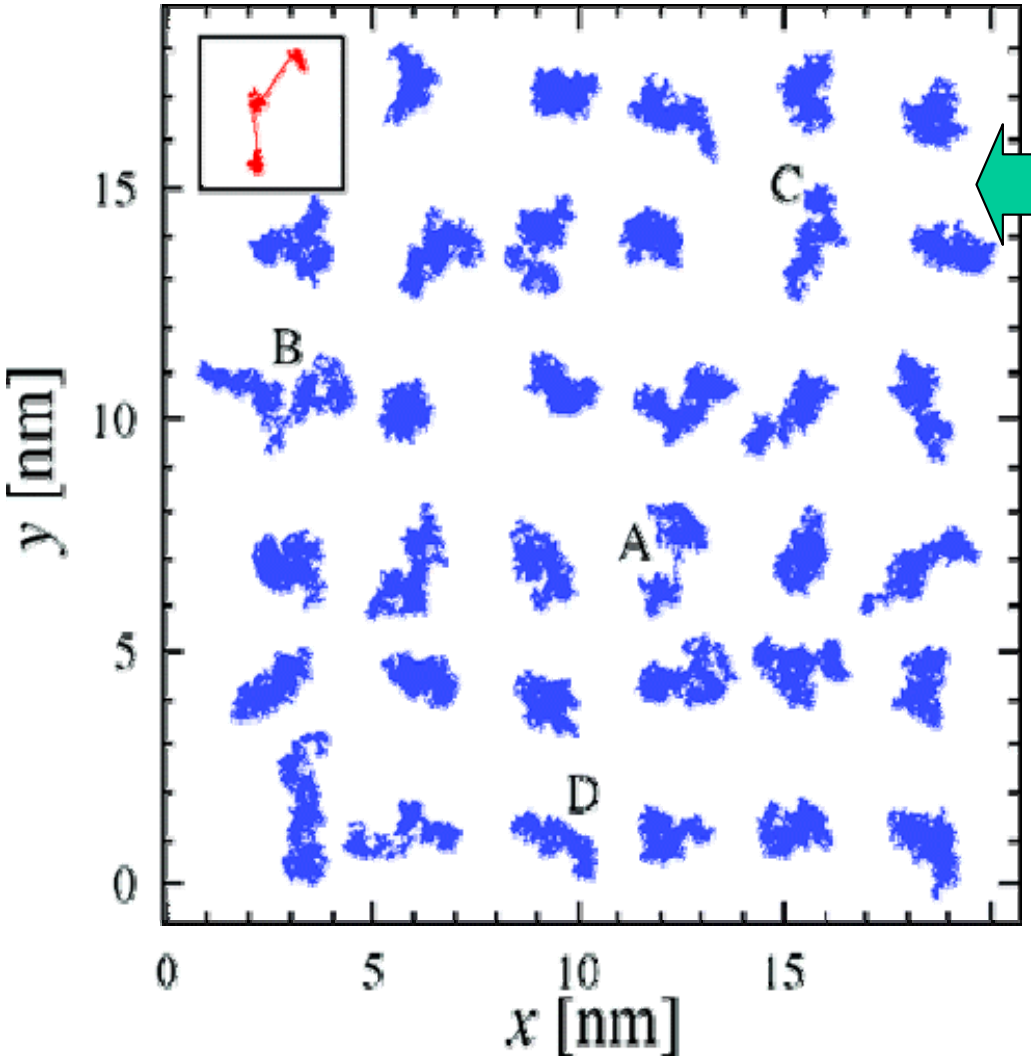
$$D \equiv \lim_{t\to\infty} \frac{\langle [\vec{r}(t) - \vec{r}(0)]^2 \rangle}{2dt}$$





[Falck et al., BJ 87, 1076 (2004)]

Lateral Lipid Diffusion Mechanism



Lateral lipid trajectories in a DPPC bilayer of 1152 lipids over a period of 30 ns

- 4 systems with number of lipids ranging between 128 – 4096
- Time scale 10 – 100 ns

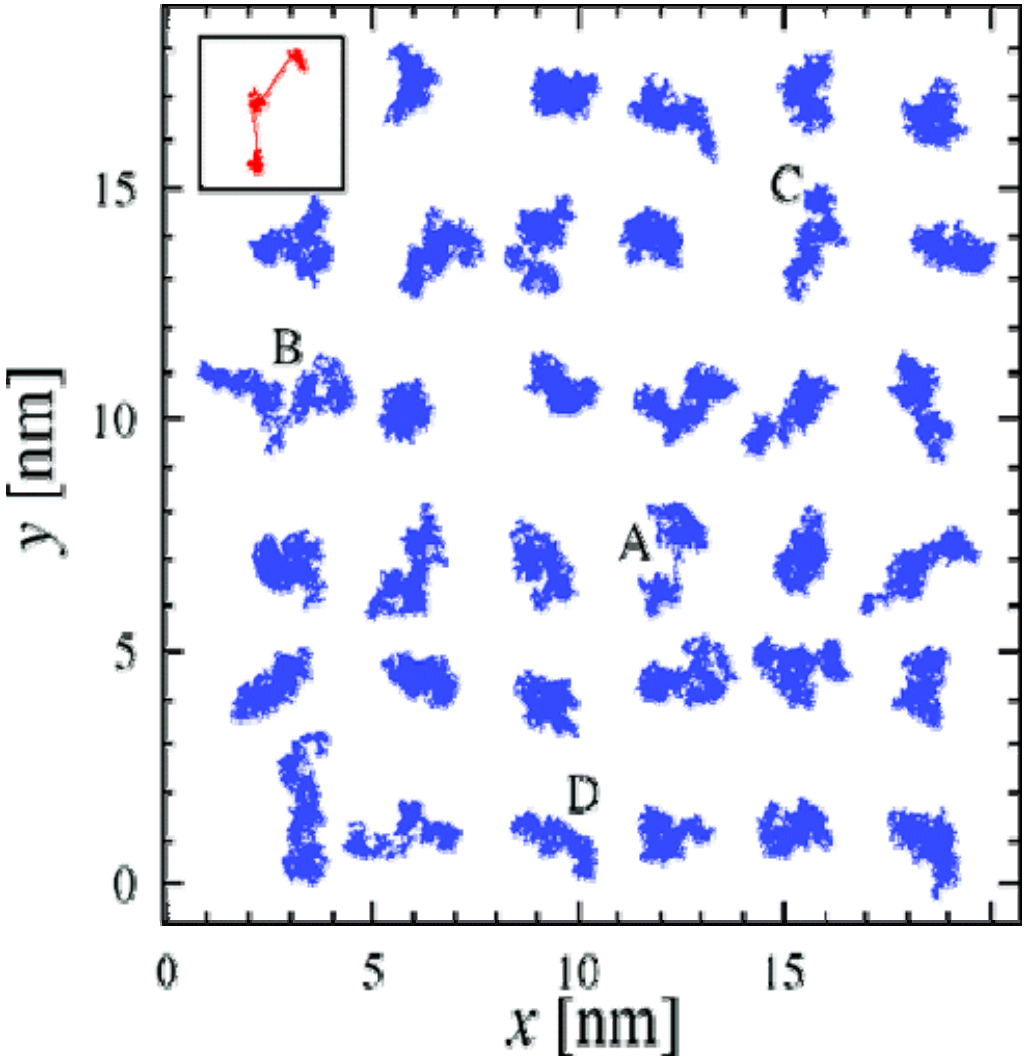
Less than 10 events observed where a lipid moves ~0.7 nm in a short period of ~100 ps.

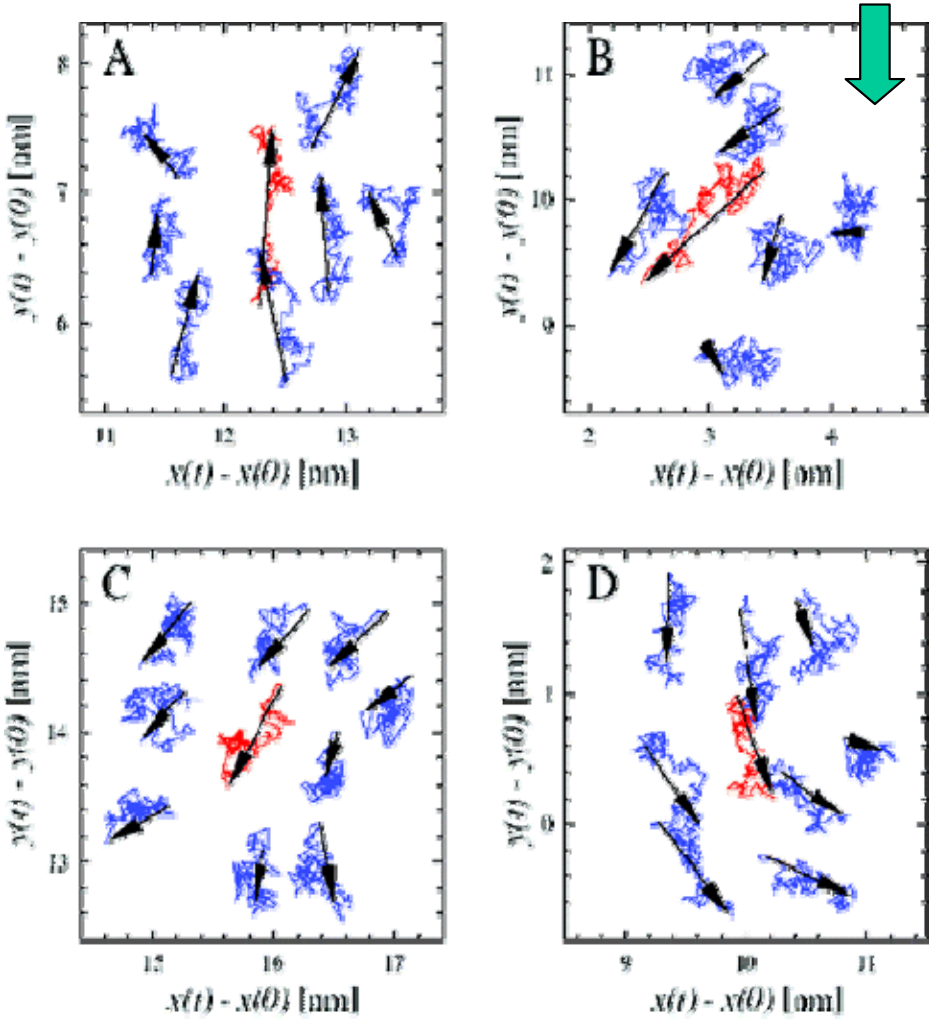
That is, the simulations indicate that there are no single-particle jumps

Falck, Rog, Karttunen, Vattulainen, J Am Chem Soc 130, 44 (2008)

Lateral Lipid Diffusion Mechanism

Lateral lipid displacements over Δt = 1 ns

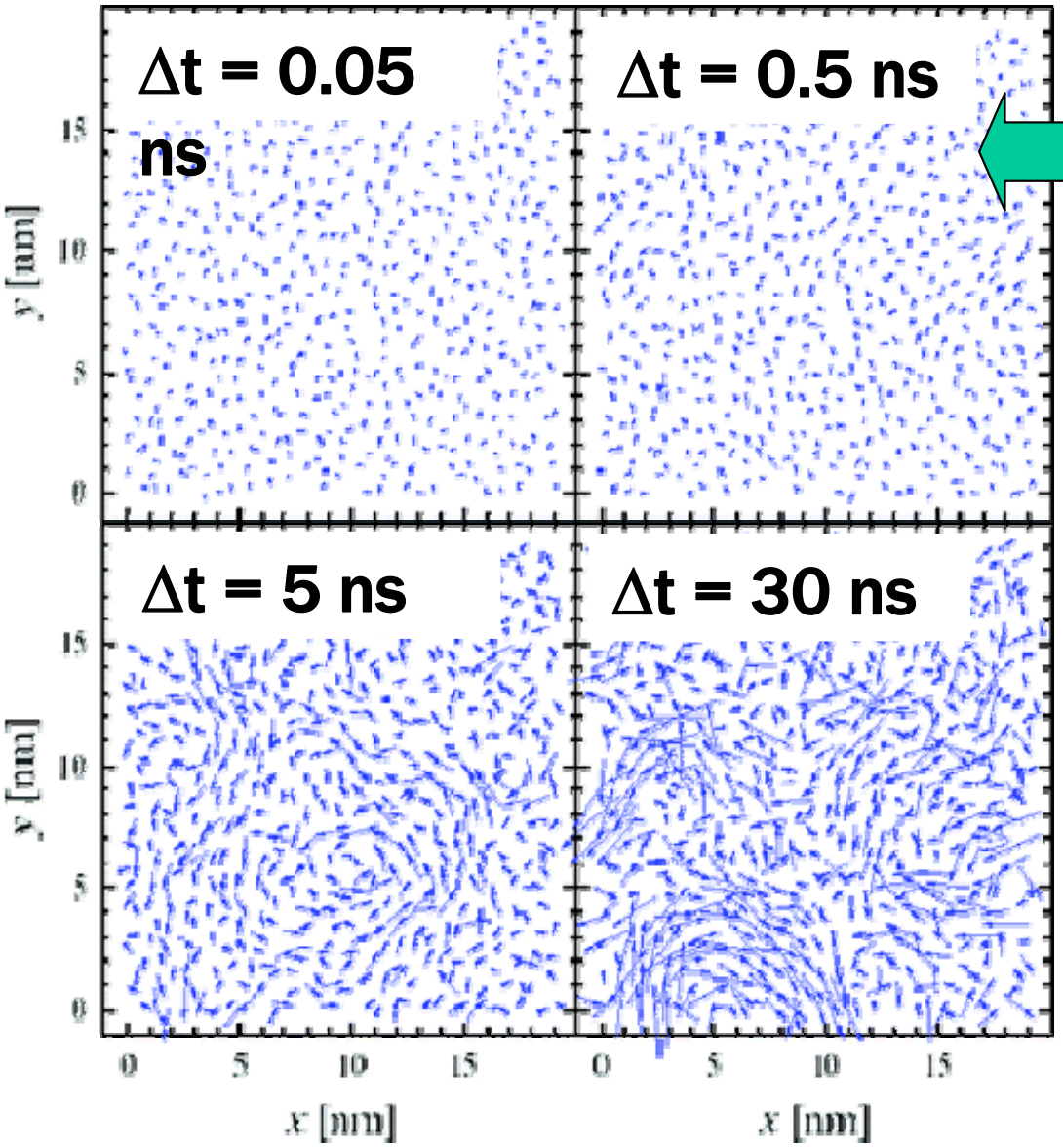




A more detailed consideration reveals that all diffusive motions are collective ones, as nearby lipids move in unison as loosely defined clusters.

Falck, Rog, Karttunen, Vattulainen, J Am Chem Soc 130, 44 (2008)

Collective Diffusive Large-Scales Flows



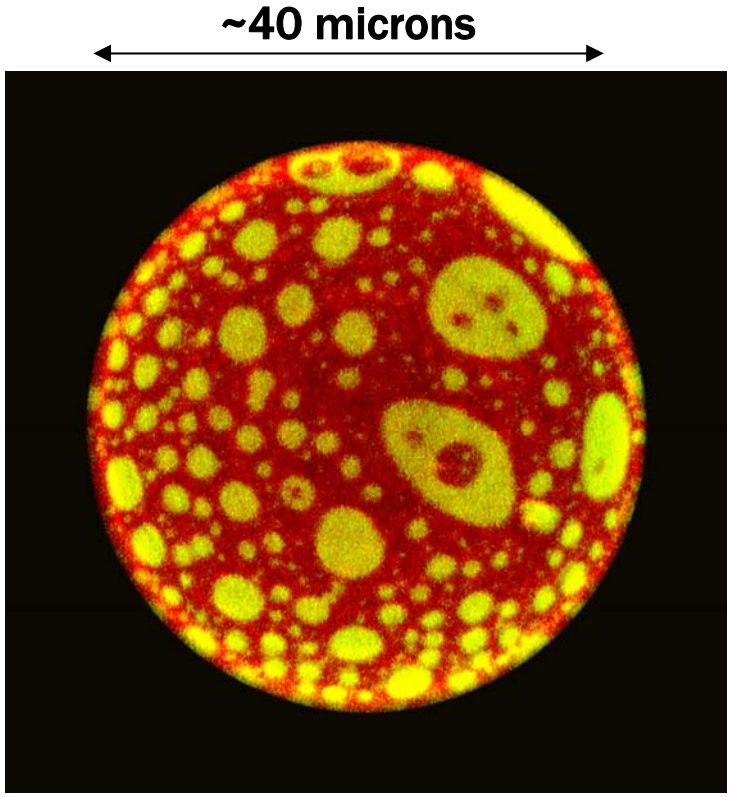
Lateral displacements of individual lipids during a period of Δt

On a molecular scale, lipids move in unison as loosely defined clusters.

On larger scales, the intimately correlated motions of neighboring lipids manifest themselves as *2D flow patterns*

Falck, Rog, Karttunen, Vattulainen, J Am Chem Soc 130, 44 (2008)

Time Scales of Lateral Diffusion



www.memphys.sdu.dk

Time scale for diffusion over a domain whose radius is L

$$t = L^2 / 4D$$

In the fluid phase, $D \approx 1 \times 10^{-7}$ cm^2/s. Then the time scale t is at least

t = 2.5 μs for L = 10 nm (nanorafts)
25 ms for L = 1 μm (large domains)

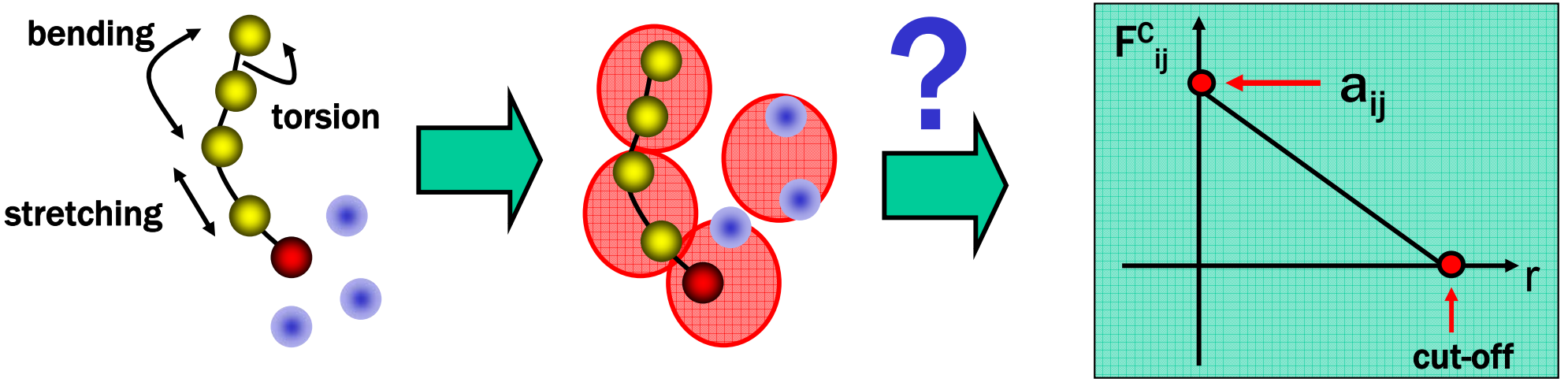
State-of-the-art atomistic simulations are limited to ~0.1 μs and 10 nm.

Long time scales & the large system sizes call for coarse-grained models.

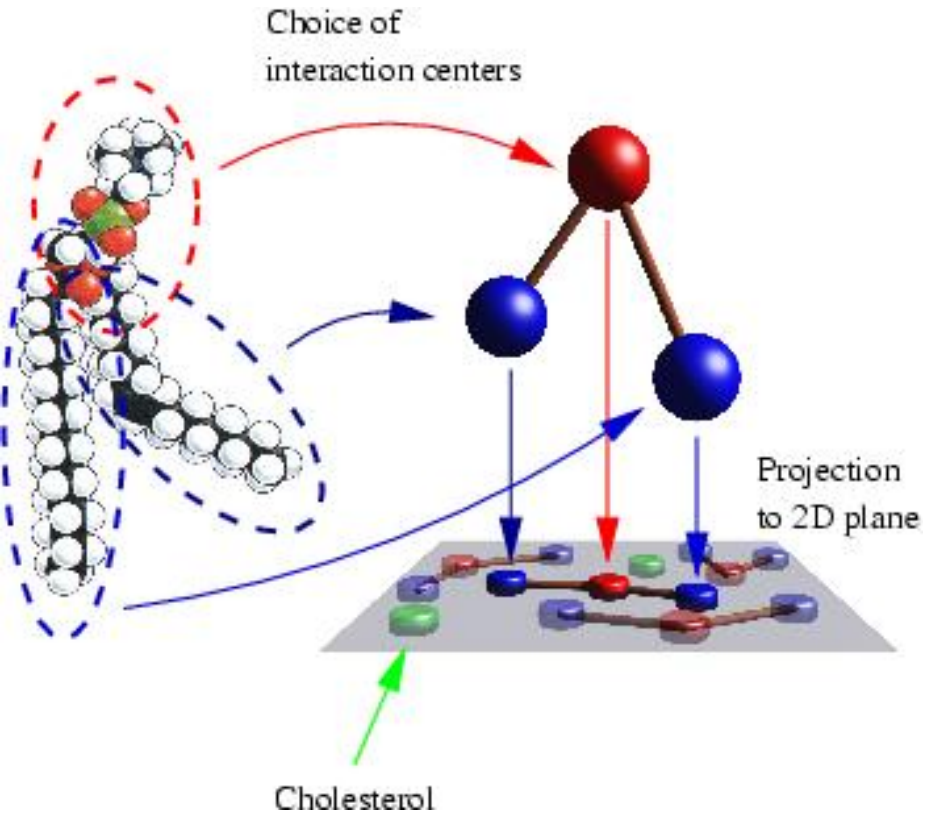
Effective Interactions?

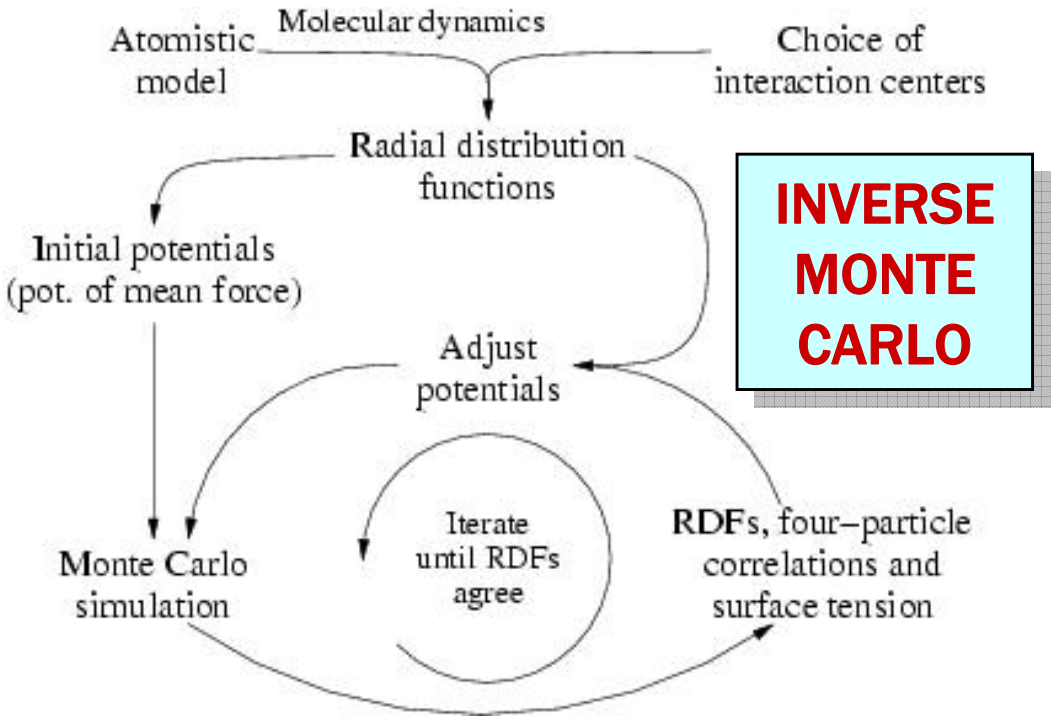
How to find effective interactions for the CG model?

Systematic coarse graining through Inverse Monte Carlo (IMC)



Coarse Grained Model: DPPC/Chol





INVERSE MONTE CARLO

For *Inverse Monte Carlo* (IMC), see Lyubartsev and Laaksonen, PRE 52, 3730-3737 (1995).

Coarse-grained model system:

DPPC + Chol

No explicit water

Time: ~ms

x_{chol} = 0 – 50 mol%

Speed-up: ~ 10^8

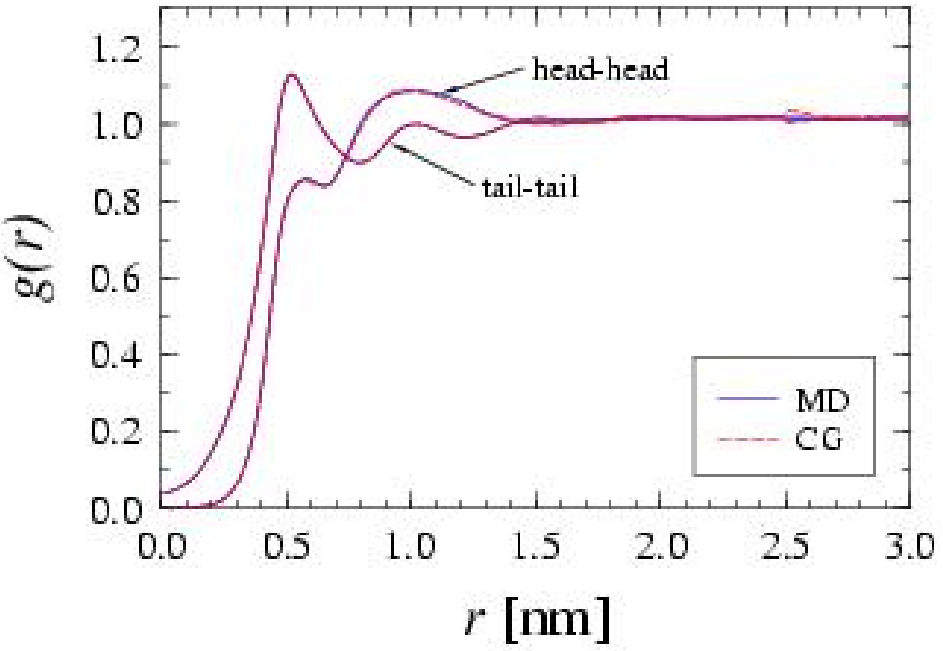
Main features:

1. 3-particle CG representation for DPPC
2. 1-particle CG representation for Chol
3. Surface tension included via Lagrange multipliers to match the area compressibility to the experimental value

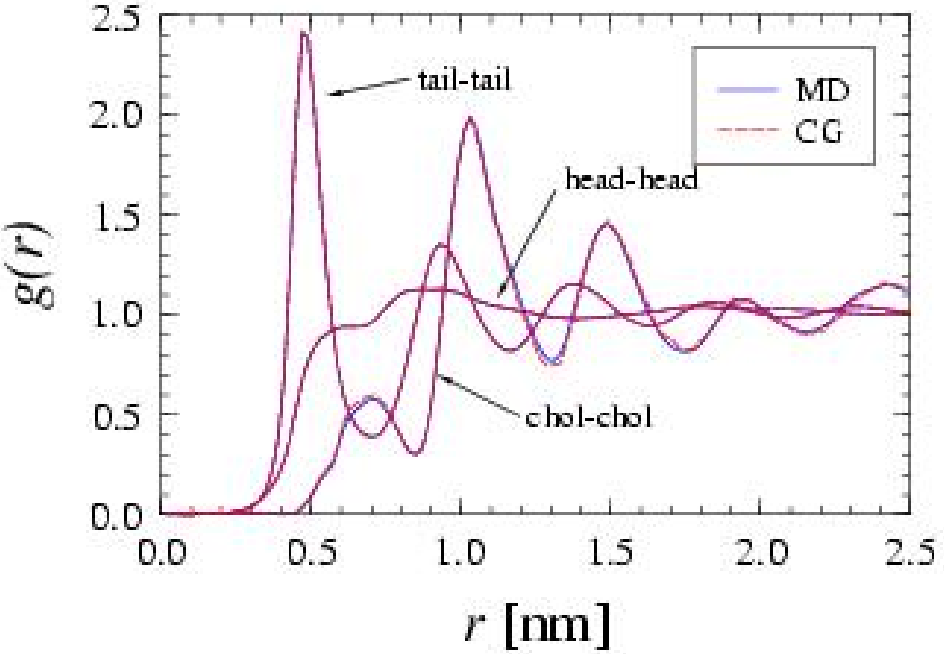
T. Murtola et al., J Chem Phys 126, 075101 (2007)

g(r) from MD → Effective potentials

Chol concentration 0%



Chol concentration 30%



Radial distribution functions of the atom-scale and CG model match, as expected

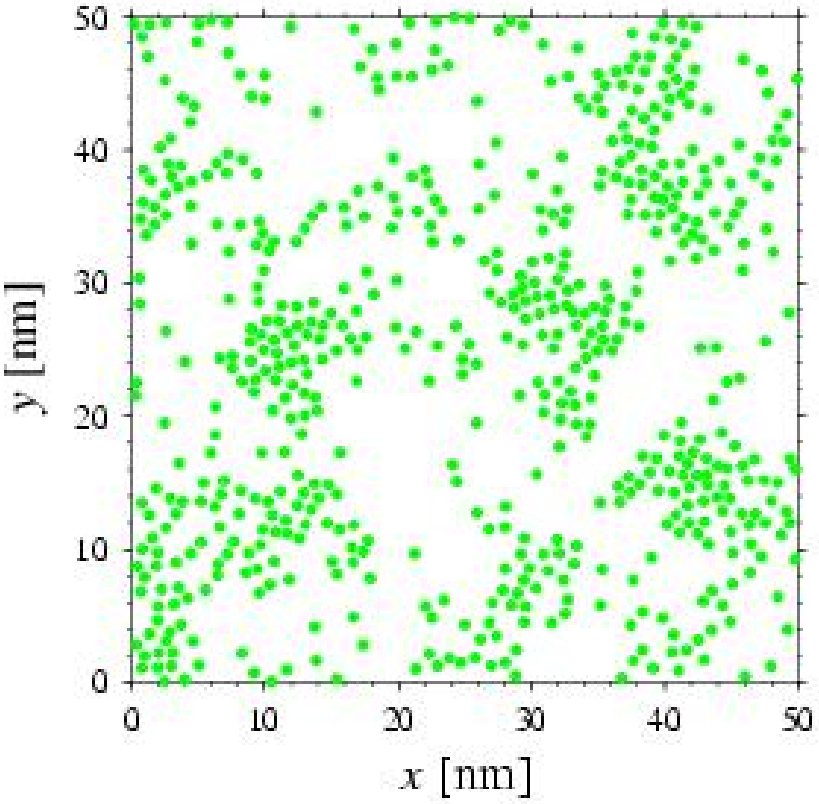
T. Murtola et al., J Chem Phys 126, 075101 (2007)

Large-Scale Structures by CG Model

Snapshots from above: only positions of cholesterol molecules are shown here by green

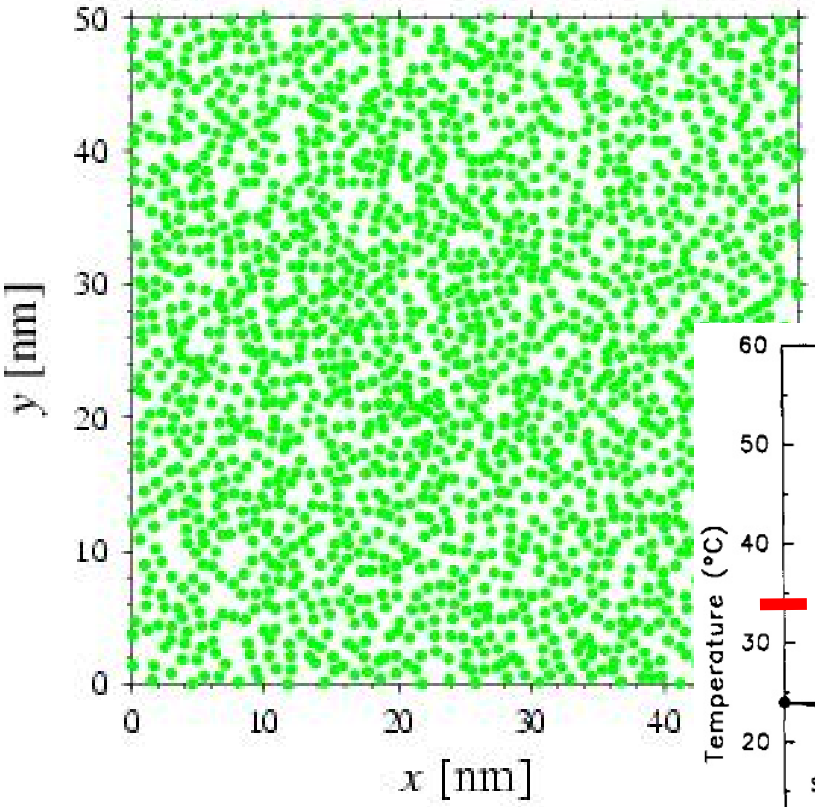
Experiments predict coexistence of chol-rich and chol-poor domains

Chol concentration 13%

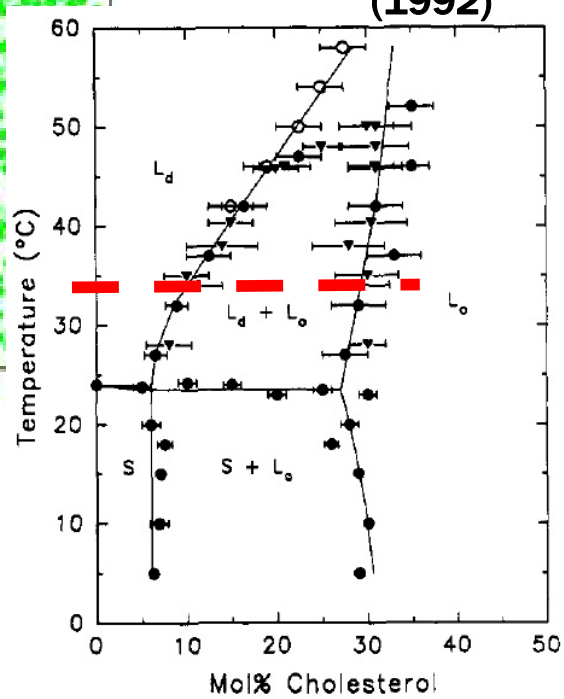


Experiments predict homogeneous distribution of cholesterol

Chol concentration 30%

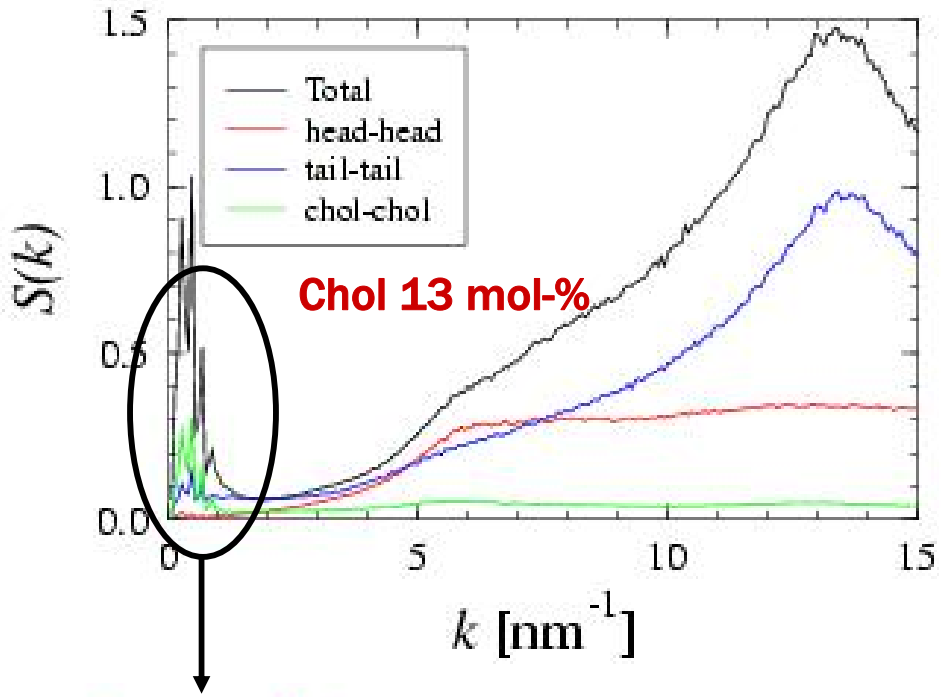


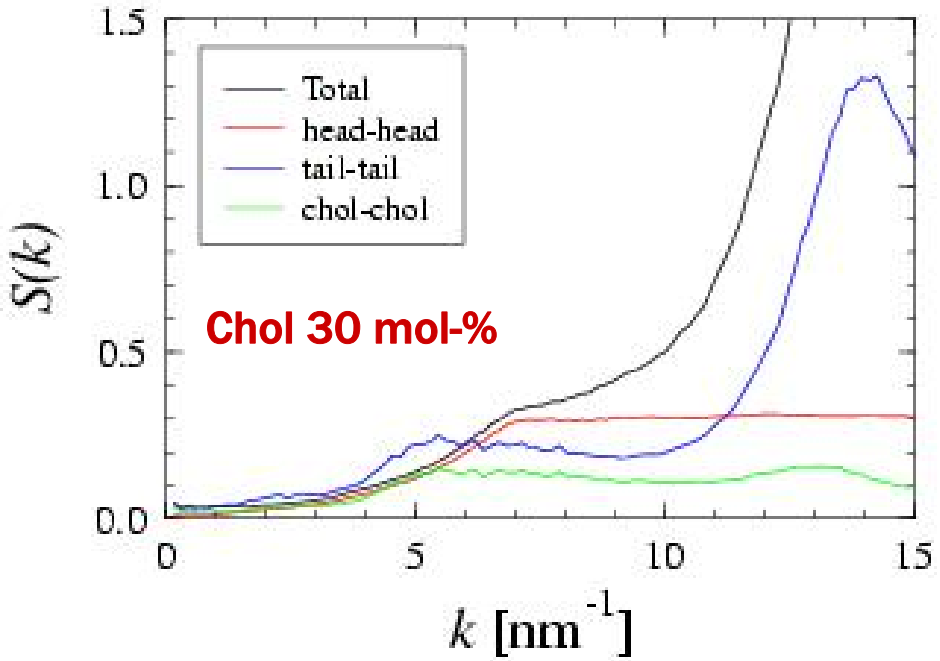
Almeida et al. (1992)

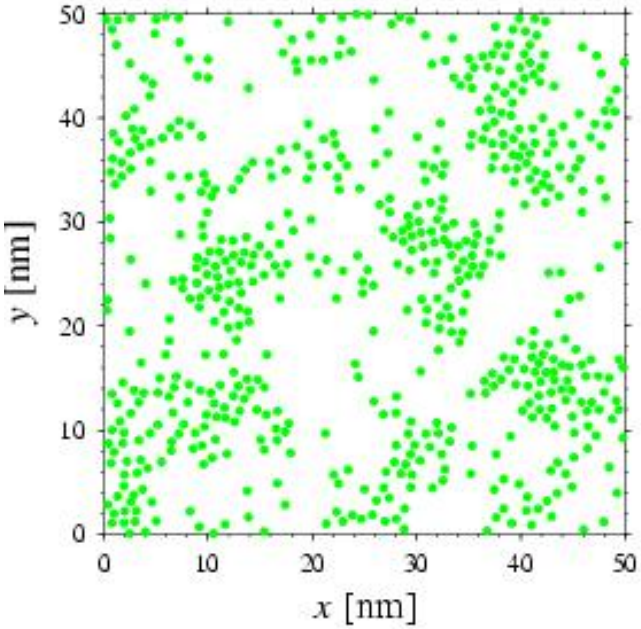


T. Murtola et al., J Chem Phys 126, 075101 (2007)

Static Structure Factors S(k)







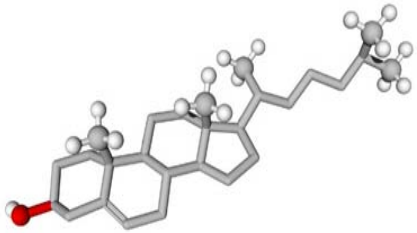
Main advantage of the CG model:

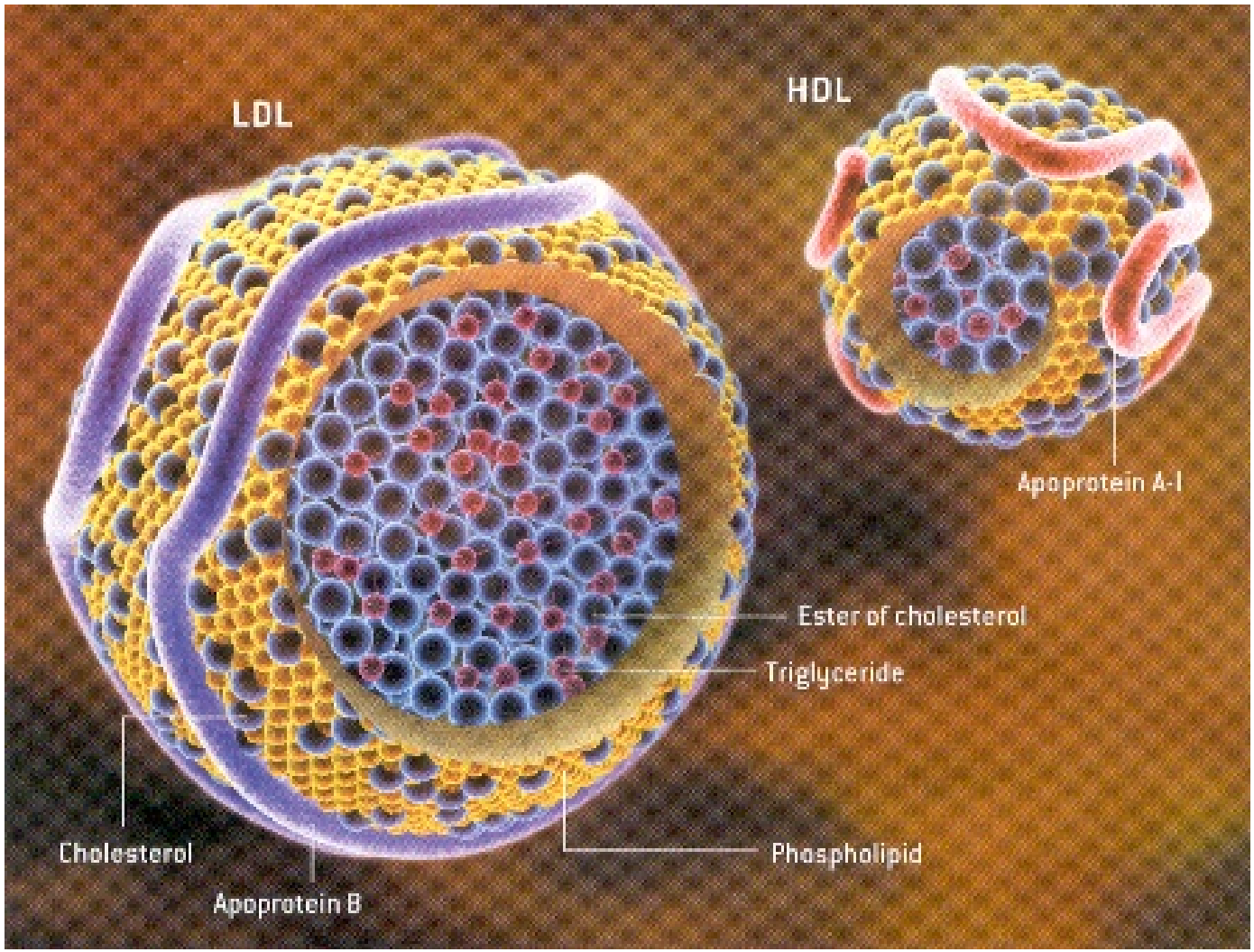
Elastic behavior in terms of area compressibility can be incorporated properly.

Large-scale domain ordering can be predicted

T. Murtola et al., J Chem Phys 126, 075101 (2007)

Lipoproteins, carriers of Chol





Suggestive views **for the structure have been proposed, but the bottom line is that the structures of lipoproteins are not known**

Functions of lipoproteins are not understood either

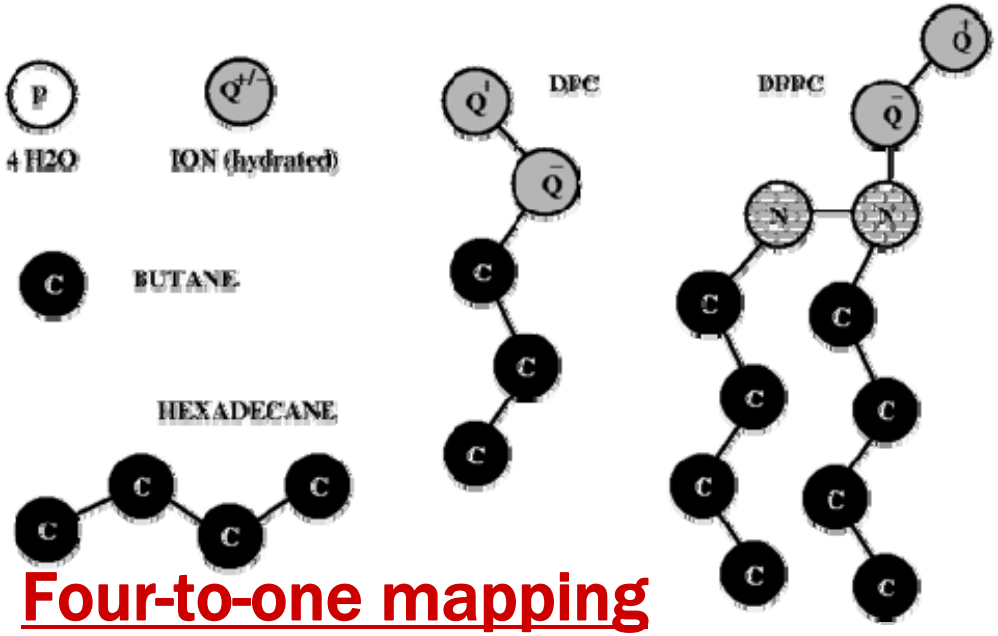
Scientific American (2004)

Coarse-Grained MD – MARTINI Model

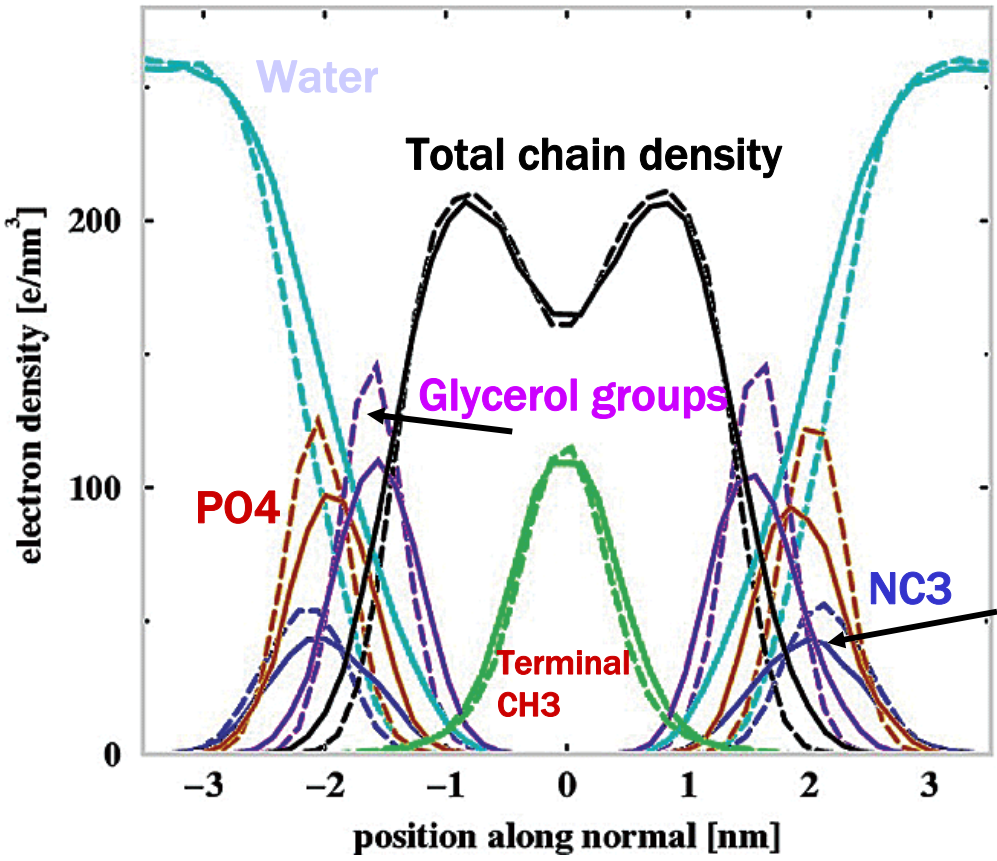
Classical Molecular Dynamics but now with coarse-grained beads and interactions instead of atomistic descriptions

Marrink et al., JPCB 108, 750 (2004)

Marrink et al., JPCB 111, 7812 (2007); & In press.



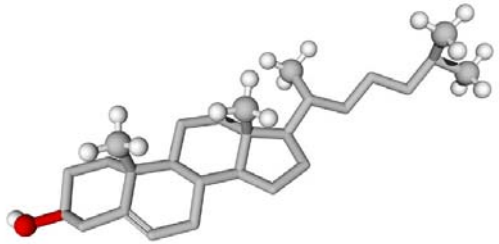
Four-to-one mapping



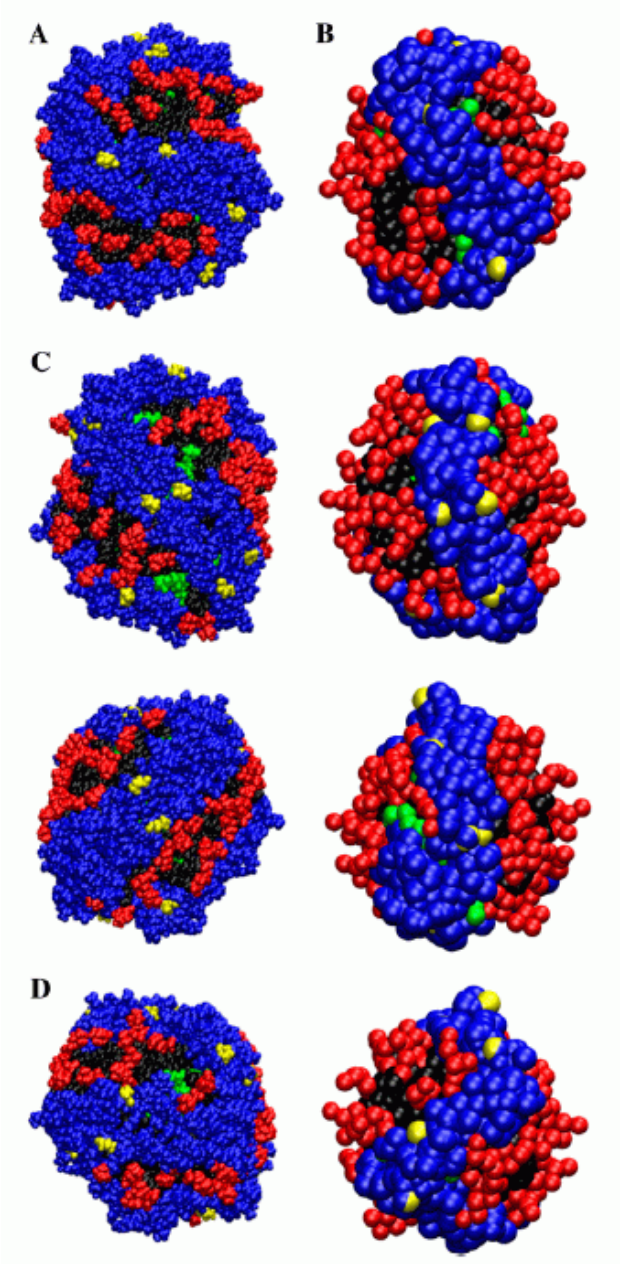
Interaction parameters are chosen such that oil-water partitioning free energies are described properly by the CG model with respect to experimental data.

Density profiles of different components across the lipid membrane – comparison between atomistic and CG model results.

HDL – ”Good” cholesterol



Atomistic **CG**



Model:

2 ApoA-I –proteins

56 POPC

16 Cholesterol oleates

Atomistic simulations:

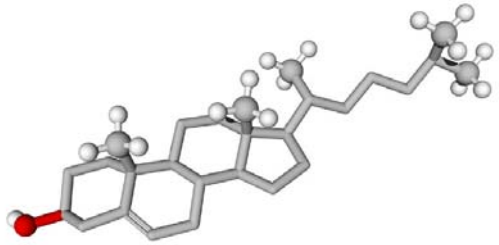
~10 ns, CHARMM force fields

CG simulations

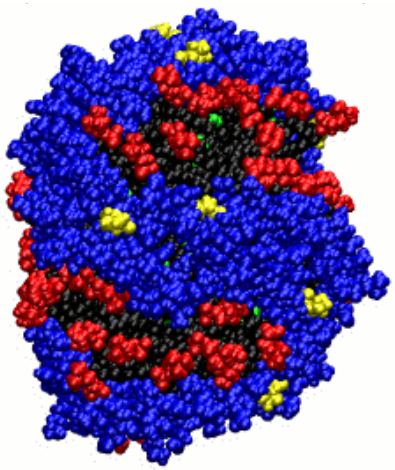
~1 microsecond, MARTINI model by Siewert-Jan Marrink, Luca Monticelli et al.

Structure of spheroidal HDL particles revealed by Combined Atomistic and Coarse Grained Simulations.
A. Catte et al., Biophys. J. 94, 2306 (2008).

HDL – "Good" cholesterol

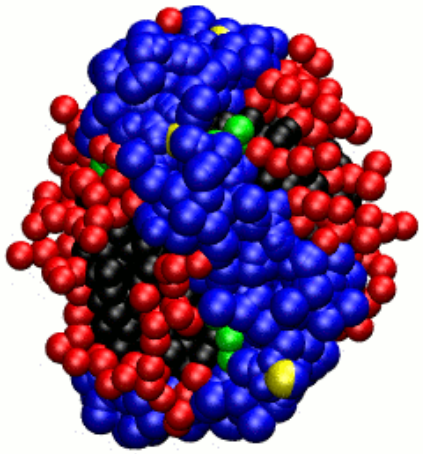


AA
10 ns at 310K



Atomistic model for High Density Lipoprotein

CG
1 μs at 310K



Coarse Grained model for High Density Lipoprotein

TABLE 1 Components of the moments of inertia (I) and values of semiaxes (a–c) of ms-HDL particles from atomistic and CG MD simulations

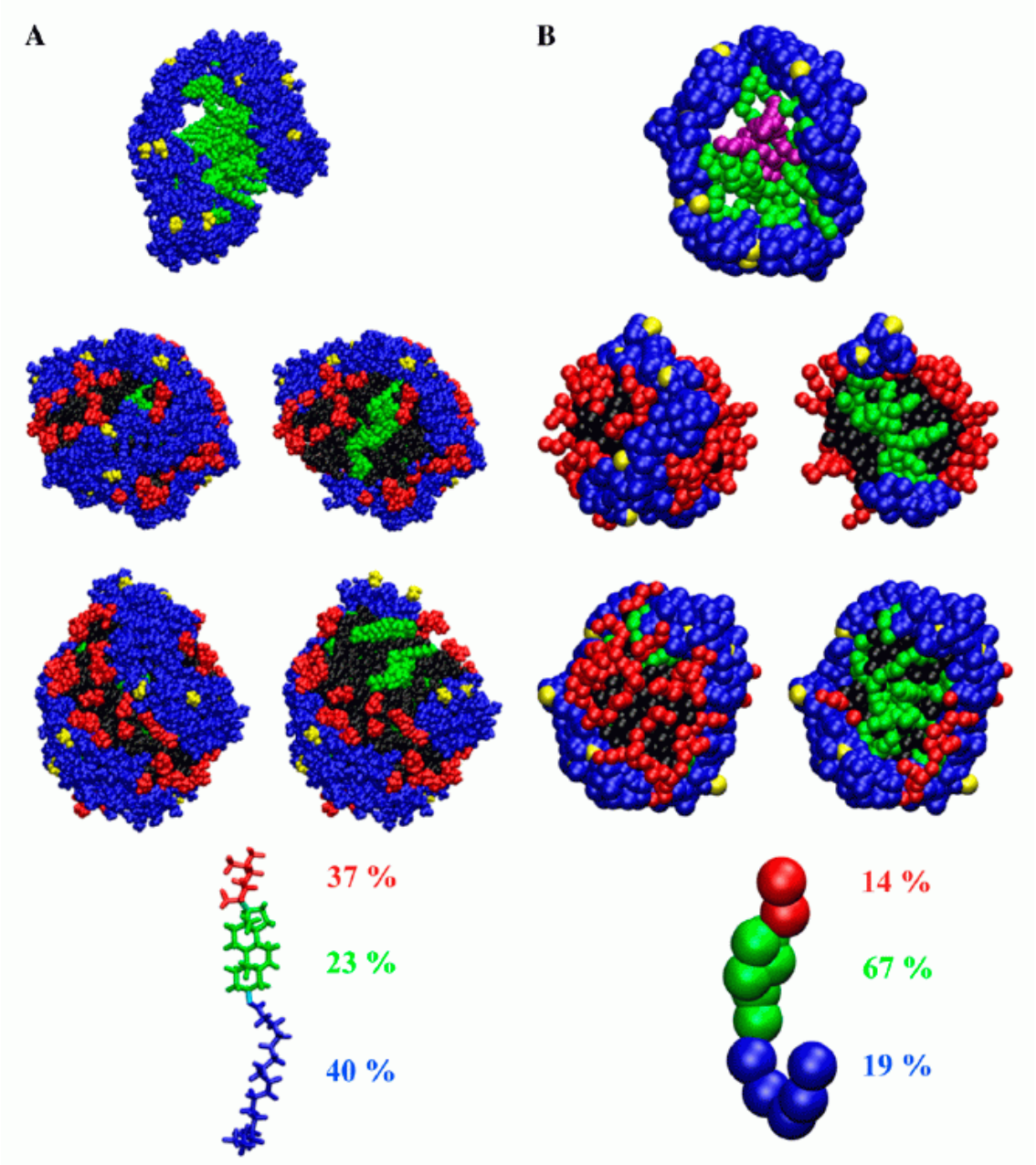
	Particle	
I (kg/Å^2/10^{-3})*	10 ns at 310 K	
a, b, and c (Å)*	(10 ns at 410 K)	1 μs at 310 K
I_{xx}	61.1 ± 0.6	23.3 ± 0.8†
I_{yy}	55.6 ± 0.6	17.8 ± 0.4†
I_{zz}	43.5 ± 0.5	14.2 ± 0.4†
a	31.0 ± 0.3	26.4 ± 0.9
b	35.2 ± 0.3	39.8 ± 1.3
c	42.9 ± 0.4	46.5 ± 0.8

Coarse Grained model describes HDL shape and size very well

Structure of spheroidal HDL particles revealed by Combined Atomistic and Coarse Grained Simulations.
A. Catte et al., Biophys. J. 94, 2306 (2008).

Novel Changes in Discoidal High Density Lipoprotein Morphology: A Molecular Dynamics Study.
A. Catte et al., Biophys. J. 90, 4345 (2006).

HDL – ”Good” cholesterol



A. Catte et al., Biophys. J. 94, 2306 (2008).

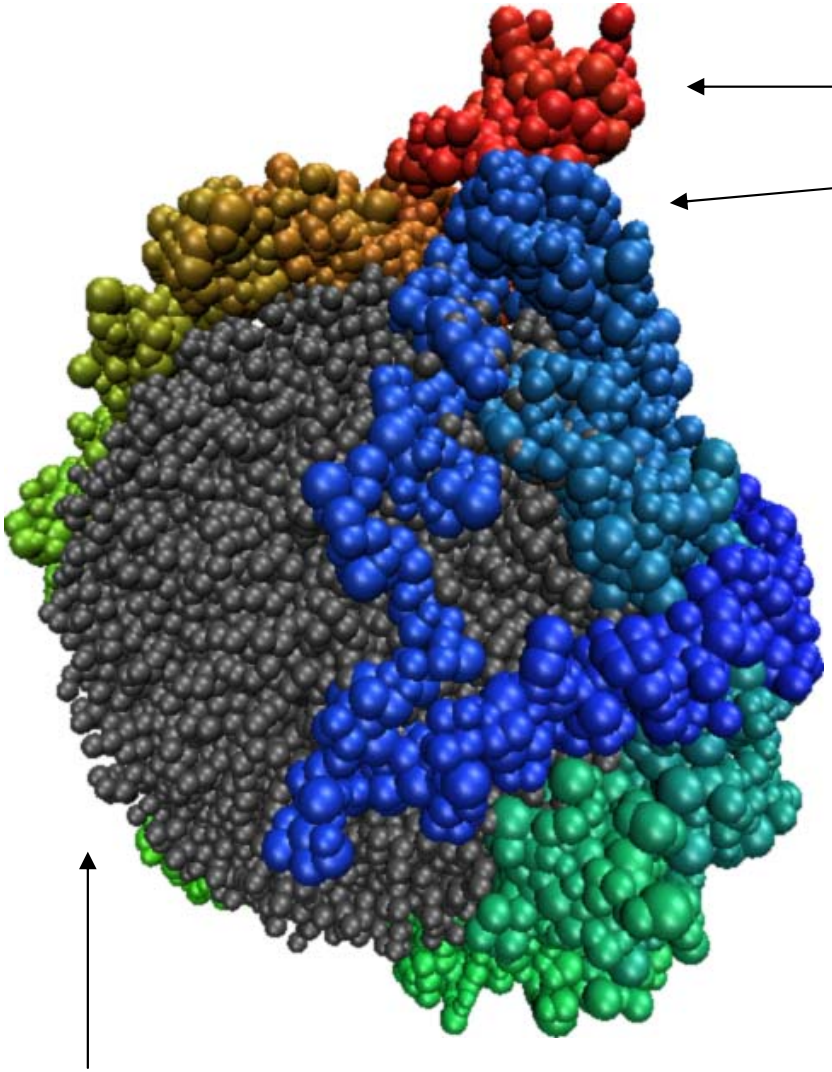
Annular cholesterol esters (green) in contact with apoA-I: Almost 100%

Packing of cholesterol esters (green) within POPCs

Chol esters stabilizing apoA-I and thus HDL

Almost 100% of chol esters are annular.
Atomistic and CG models roughly consistent regarding contacts, the differences due to the CG nature of beads

LDL – ”Bad” Cholesterol



N-terminal of apoB-100

C-terminal

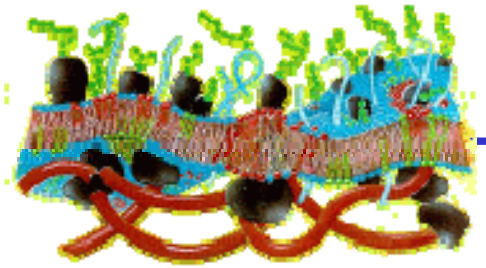
Complex lipid droplet (gray)

Coarse-grained modeling of LDL-sized lipid droplets with molecular composition consistent with experimental data – model designed bottom-up using extensive atomistic simulation data of our own.

T. Murtola, T. Vuorela et al., *work in progress* (2007-2008).

Why coarse-grained simulations?

- **Atomistic simulations for LDL over 1 μs would take ~100 CPU-years**
- **We need time scales > 10 μs...**



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