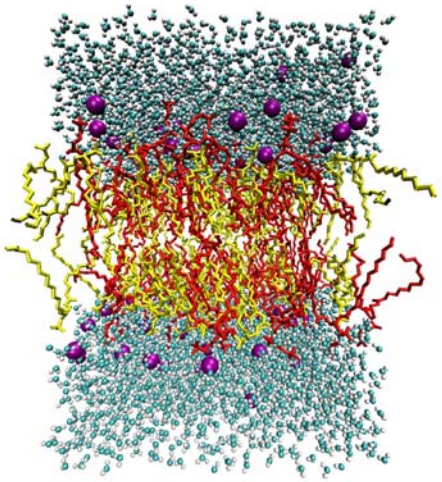
Perspectives in the Computational Modeling of Biosystems



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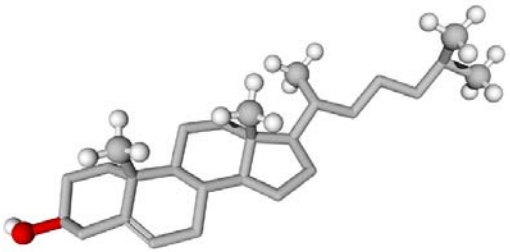
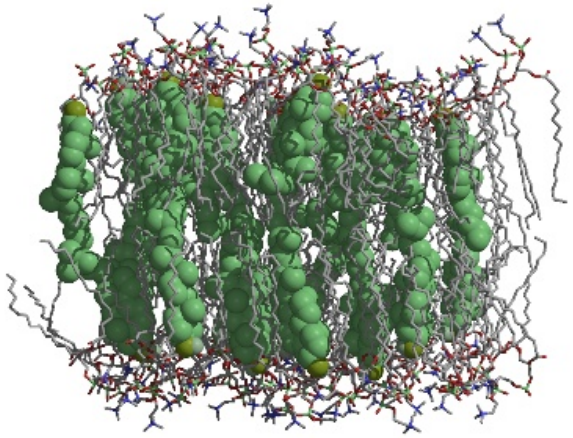
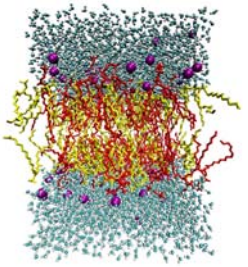
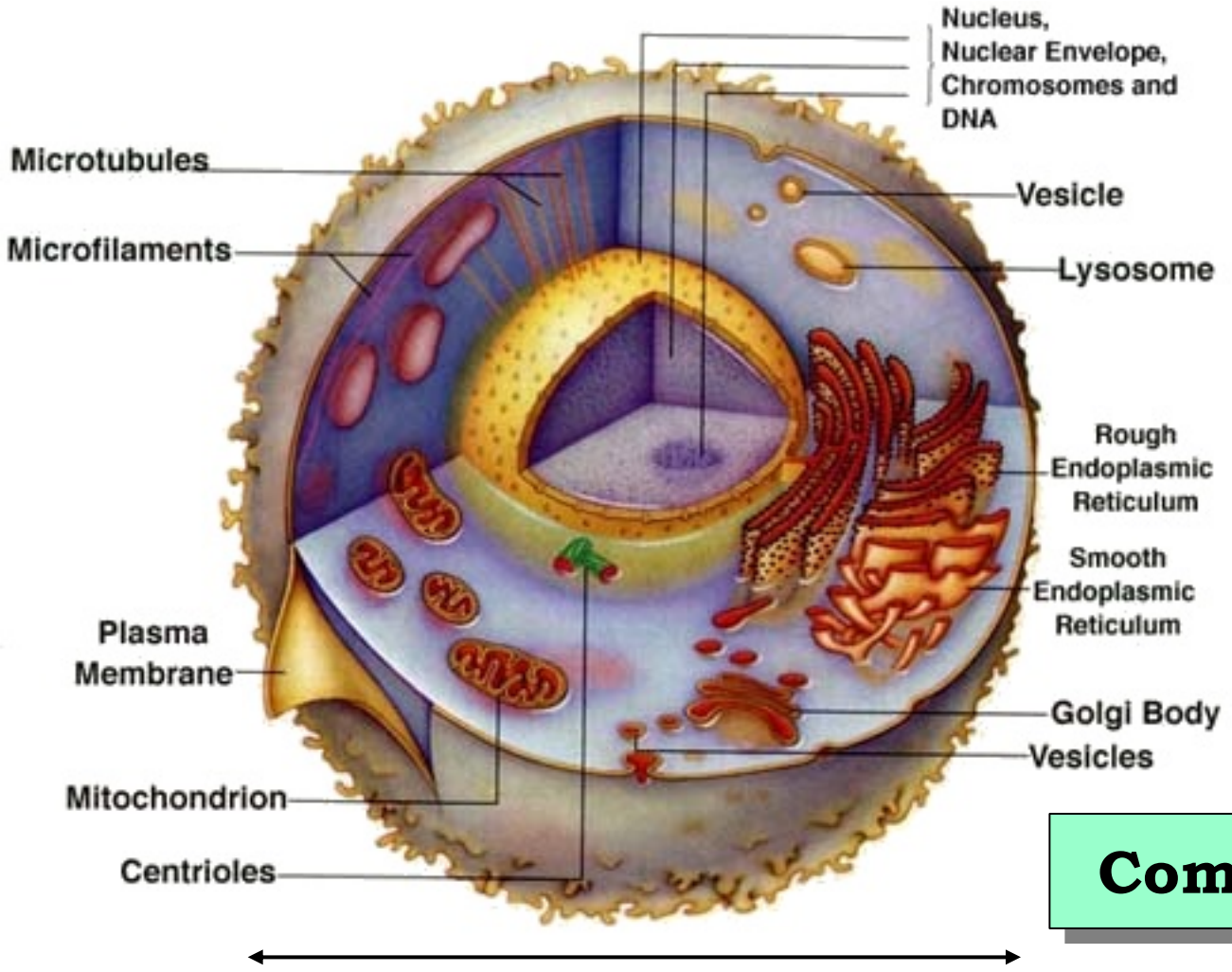
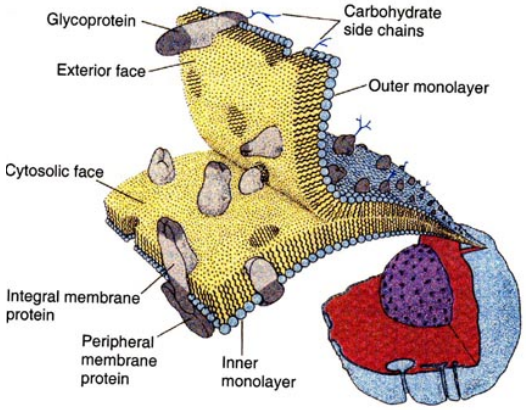




Challenge: modeling cells



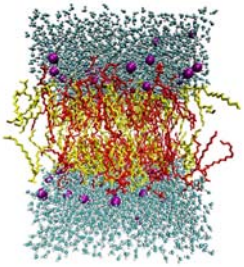




Complexity, scales

~20 μm

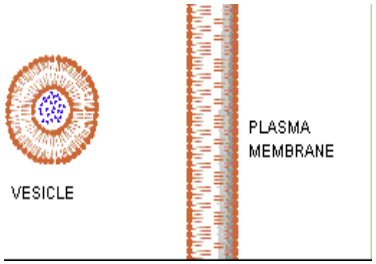
Modeler's toolbox



Various scales, various methods

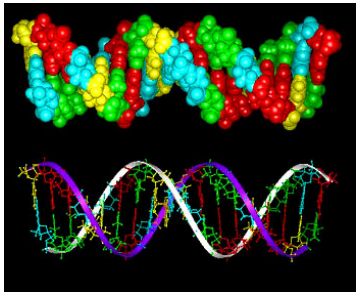
Macroscale:

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



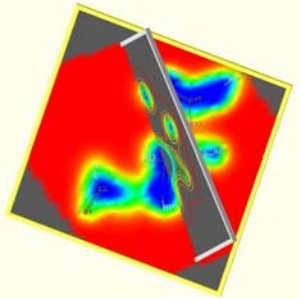
Mesoscale:

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



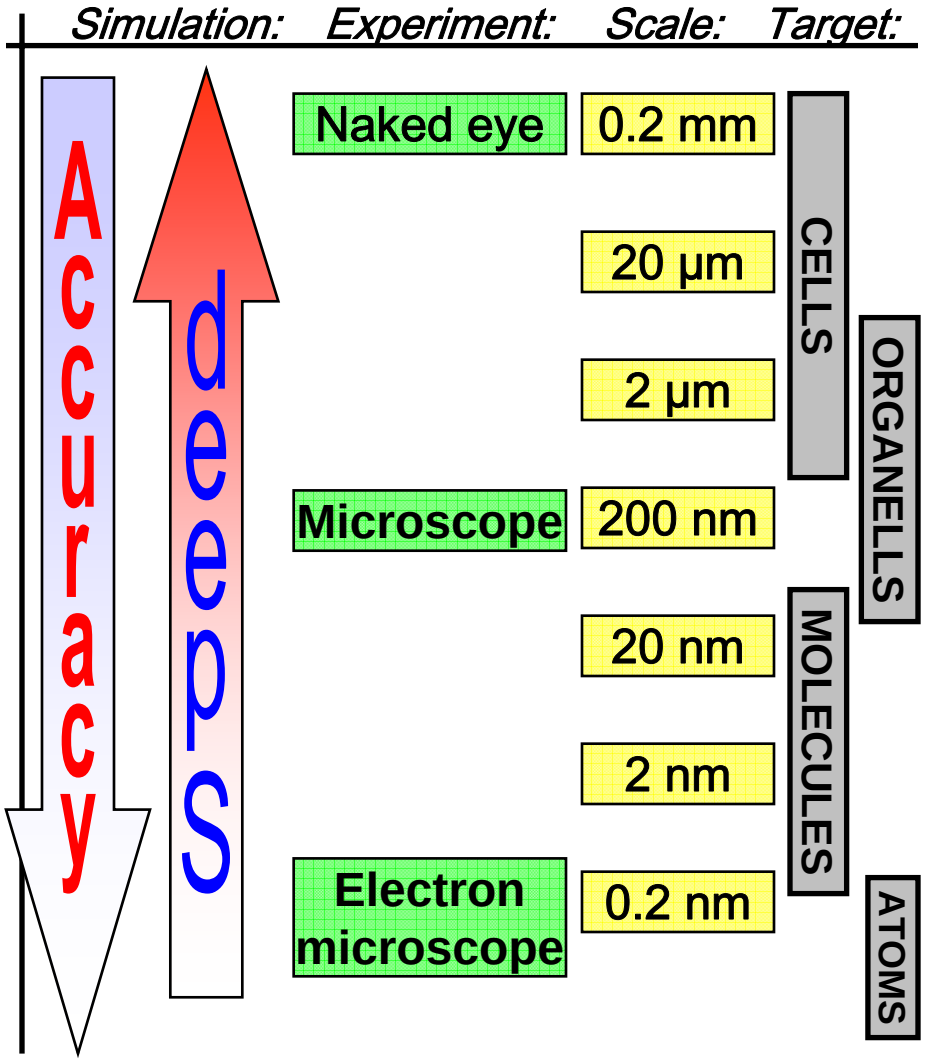
Atomistic scale:

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

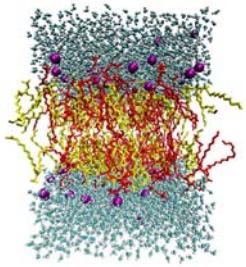


Subatomistic scale:

- electronic structure
- ab initio
- Green's functions

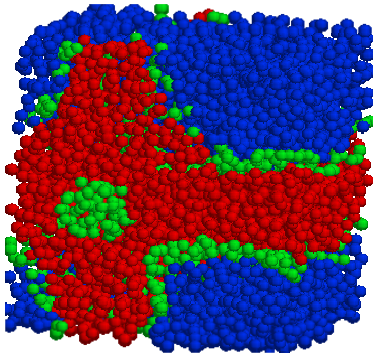


Towards multi-scale modeling



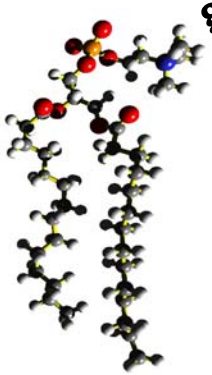
Mesoscale:

- effective interactions
- collective phenomena
- long-range effects



Macroscale:

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



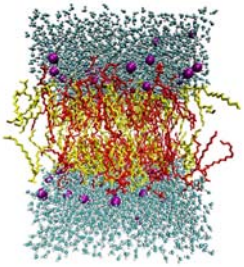
Coarse graining

- Different methods for different scales
- Main question is how to bridge them in a controlled and reliable fashion

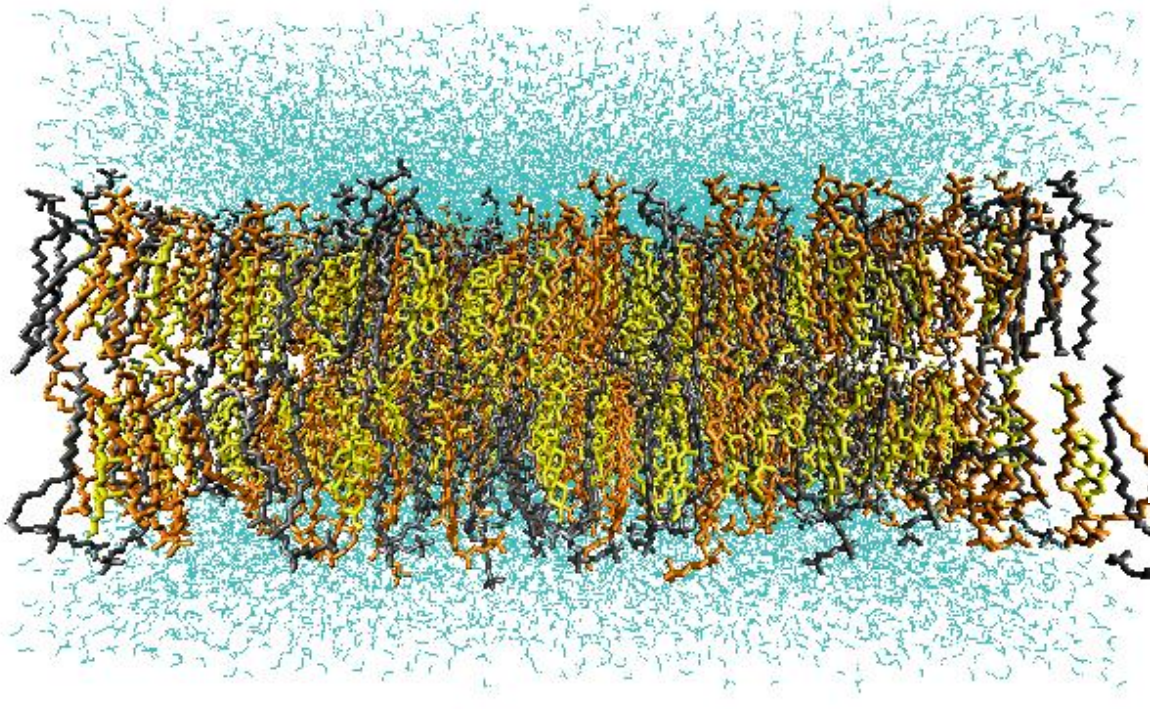
Atomistic picture:

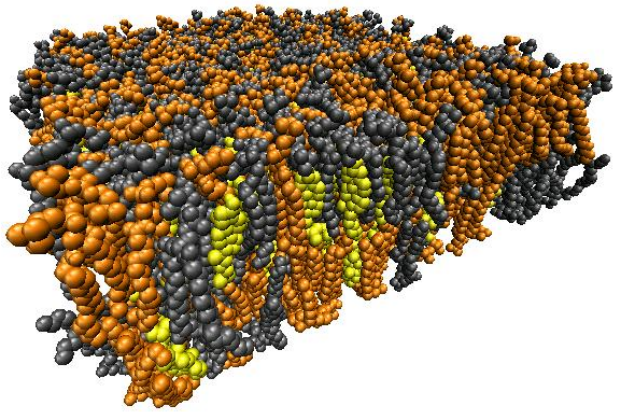
- microscopic accuracy
- interatomic forces
- intermolecular interactions

What is doable at the moment?



Lipid rafts: ordered membrane domains

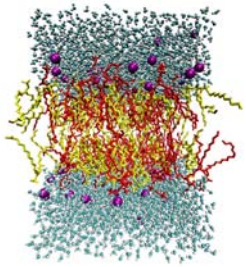




- About 300,000 atoms
- About 100 ns
- Takes about 2-4 CPU-years on the IBMSC using RF for electrostatics

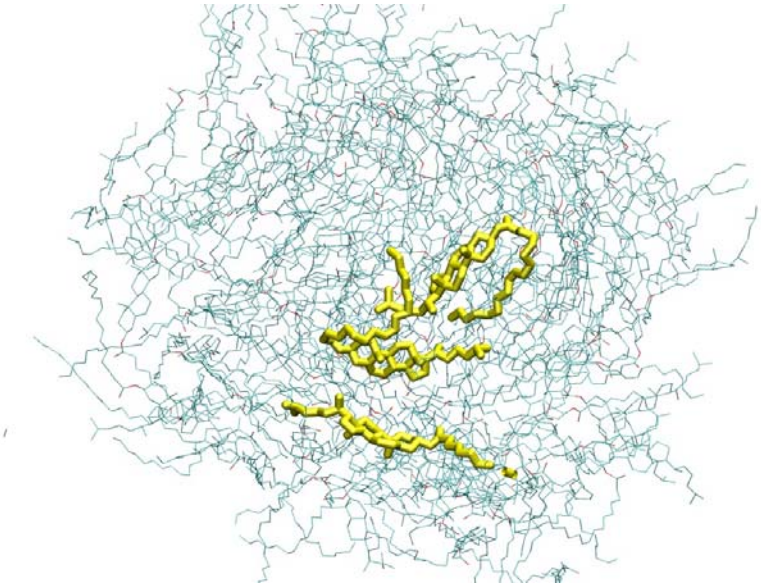
Large-scale atomistic simulations of lipid rafts.
P. Niemelä, M. T. Hyvönen, M. Karttunen, I. Vattulainen (to be submitted);
E. Falck, M. Patra, M. Karttunen, M. T. Hyvönen, I. Vattulainen, Biophys. J. 87, 1076 (2004);
P. Niemelä, M. T. Hyvönen, I. Vattulainen, Biophys. J. 87, 2976 (2004).

What is doable at the moment?

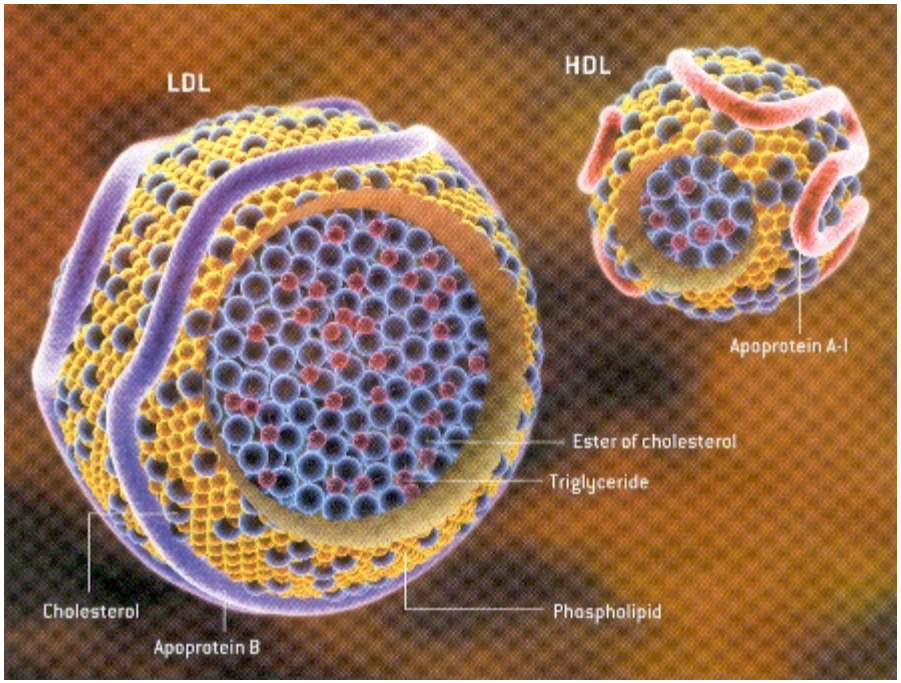


Lipoproteins: carriers of cholesterol

- About 20,000 atoms
- About 300 ns
- Takes about 1 CPU-year

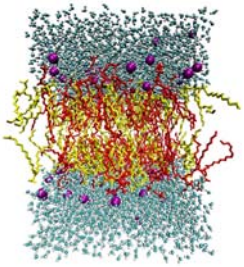


Cholesteryl esters in the interior of LDL.
M. Heikelä, I. Vattulainen, M.T.Hyvönen, Biophys. J. 90 (2006) 2247.

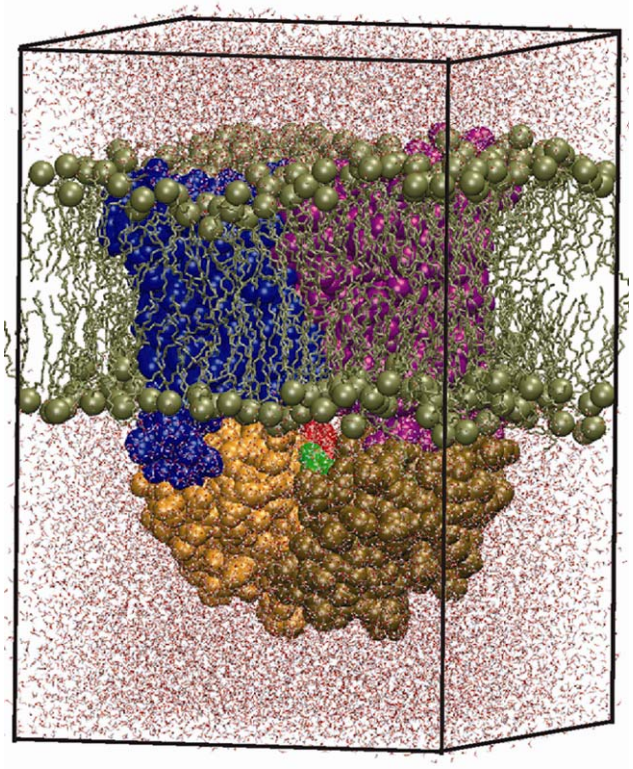


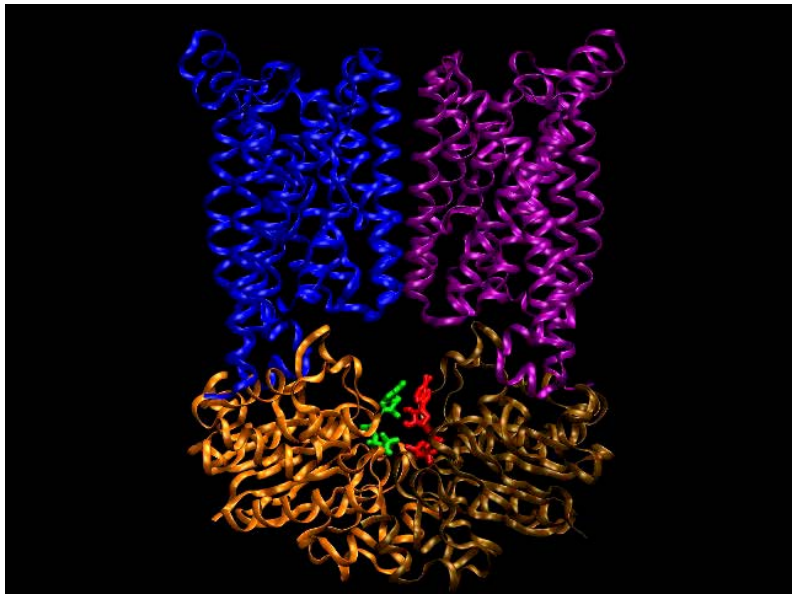
LDL and HDL particles carrying cholesterol.
Work in progress for HDL-sized particles: M. Heikelä et al.

What is doable at the moment?



ABC Transporter protein BtuCD



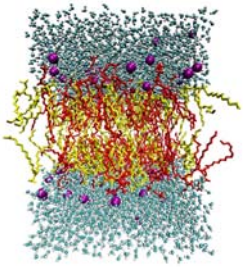


- About 100,000 atoms
- About 15 ns
- Complexity of protein conformational space

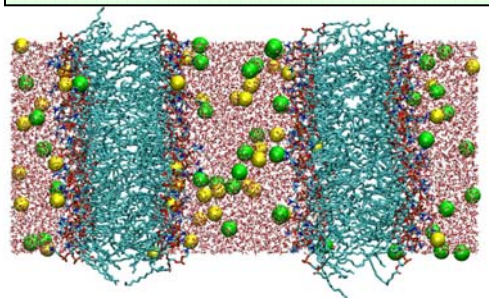
Understanding ATP hydrolysis and its coupling to functions of ABC transporters, such as nutrient uptake in bacteria, regulation of processes in diabetes.

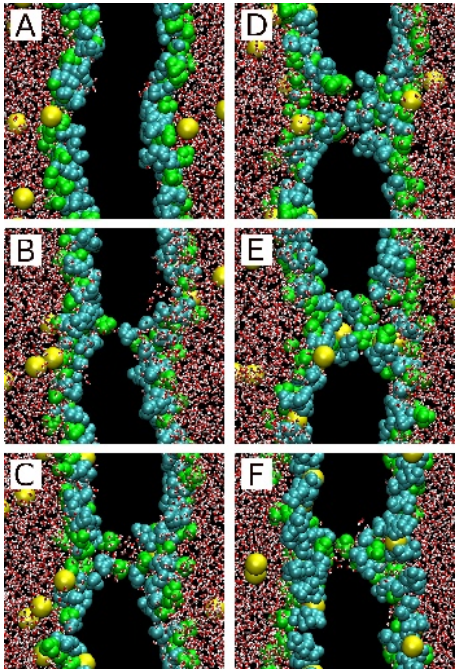
P. Tieleman et al. (Calgary)

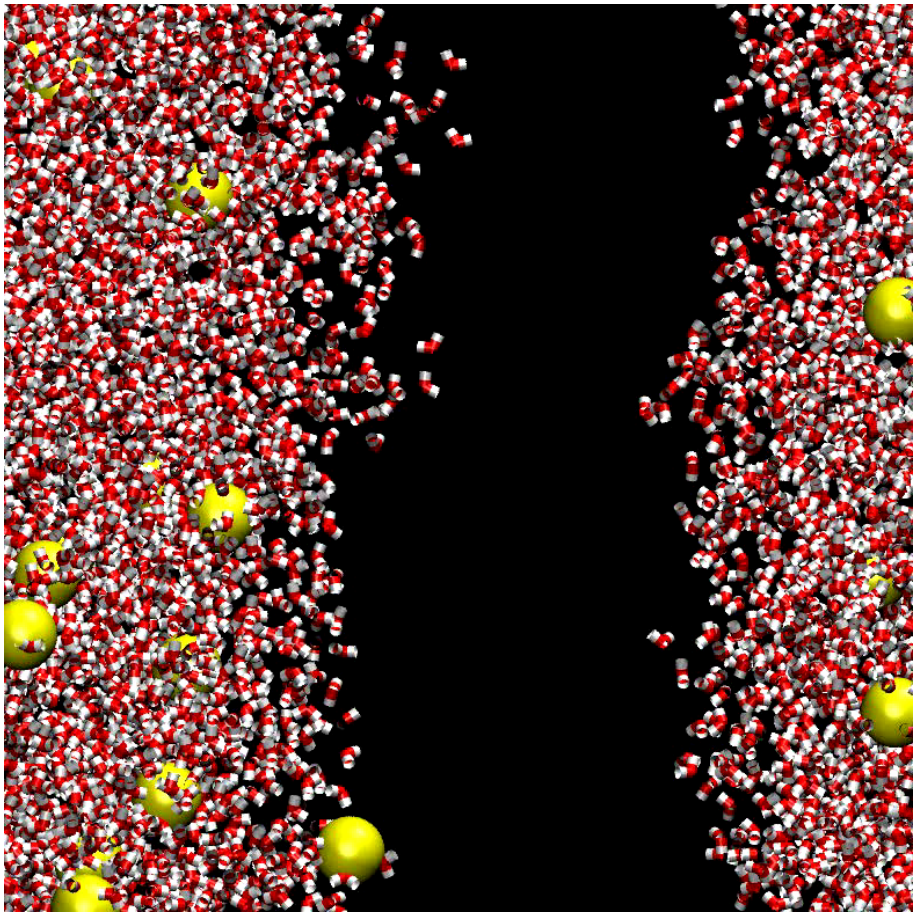
What is doable at the moment?



Pore formation and translocation due to a (physiological) salt concentration gradient across a membrane



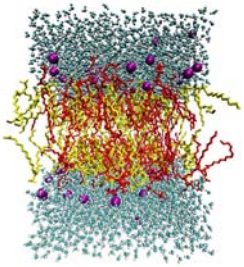




- ***Computational load ~ the same as before***
- ***That is, about 40,000 atoms and times up to about 100 ns***

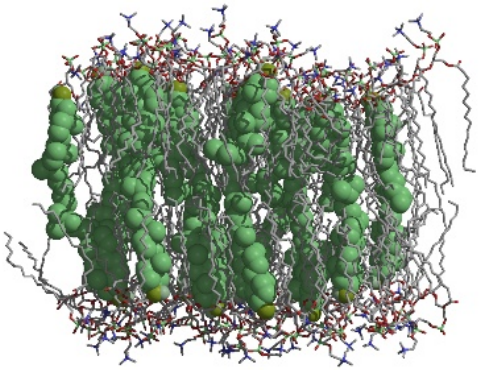
A. A. Gurtovenko and I. Vattulainen, JACS 127 (2005) 17570.

What is doable at the moment?



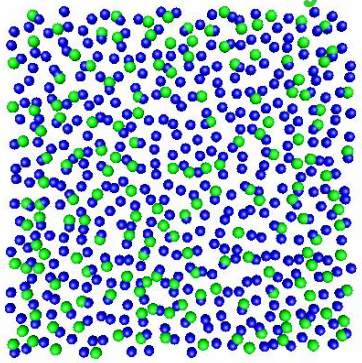
Coarse-grained modeling of membranes

Coarse-Grained Model for Phospholipid/Cholesterol Bilayer



Systematic coarse graining: Inverse Monte Carlo

Speed-up: ~ 10^8

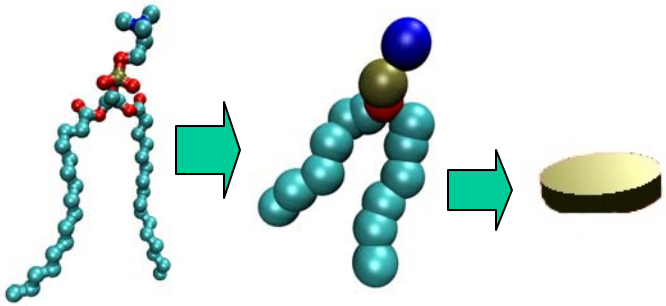


Matches experimental data

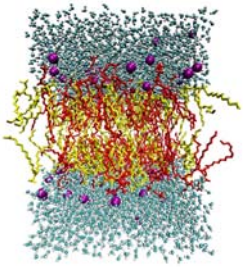
Atomistic modeling:
- **128 molecules plus water, 100 ns**
- **1 CPU-year of computing time**

Coarse-grained model:
- **150,000 molecules over millisecs.**
- **1 week of computing time**

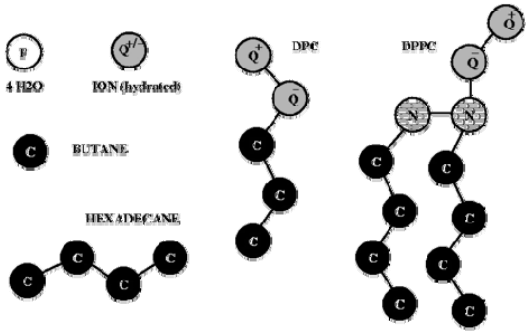
T. Murtola et al., J. Chem. Phys. 121, 9156 (2004);
A. Lyubartsev et al., Soft Materials 1, 121 (2003);
Novel Methods in Soft Matter Simulations (Springer, Berlin, 2004), edited by M. Karttunen, I. Vattulainen, A. Lukkarinen.



What is doable at the moment?

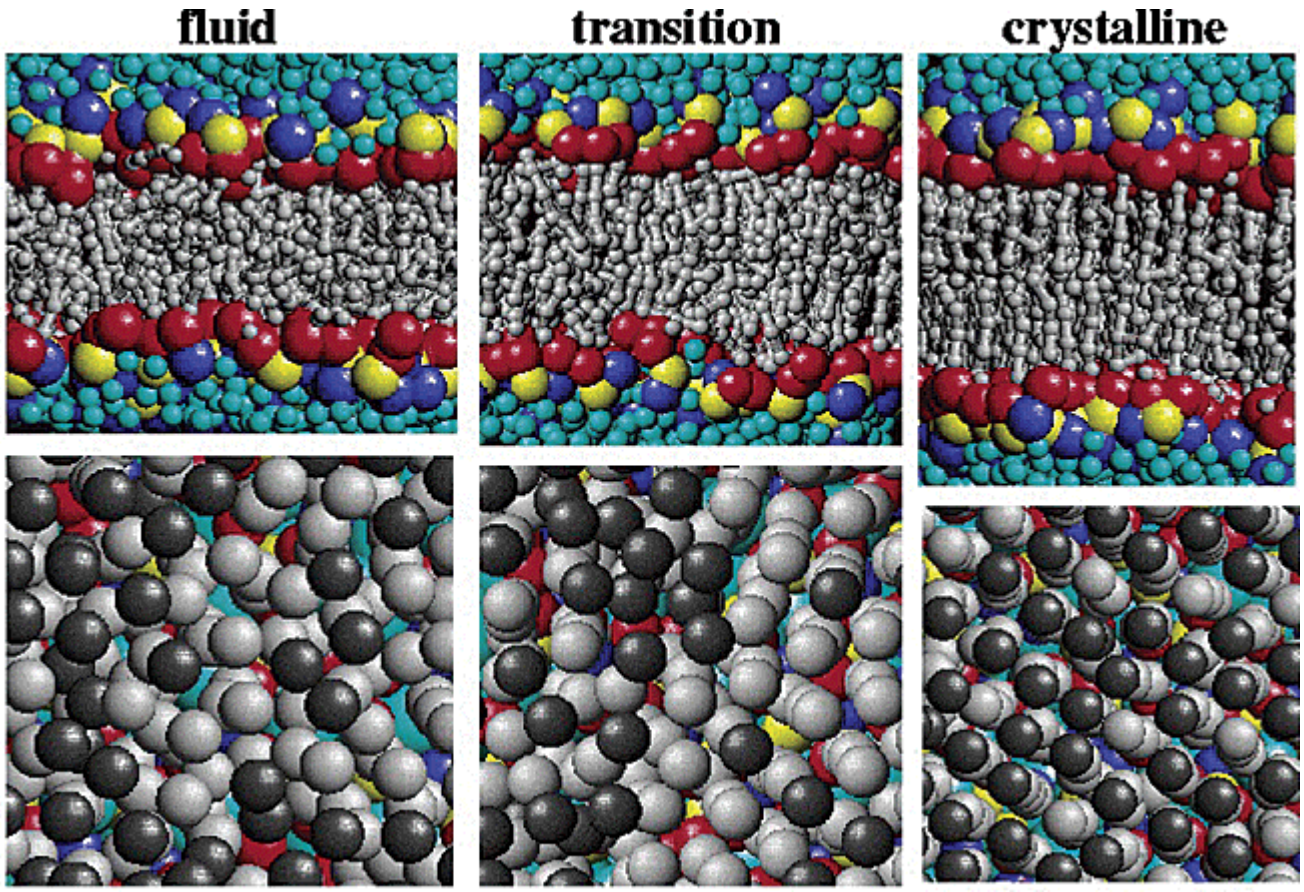


Coarse-grained modeling of membranes



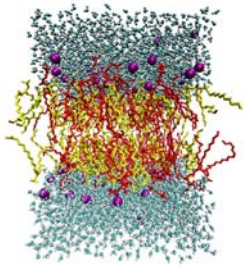
- *Coarse graining by a factor of about 4.*
- *Includes water.*
- *Speed-up by a factor of ~100 compared to atomistic simulations.*

Phase transitions, e.g.



Semi-quantitative CG model for lipid membranes.
S. J. Marrink et al. JPCB 108 (2004) 750.

Present limits: Atomistic models



Limits of present atomistic models ?

Doable at the moment:

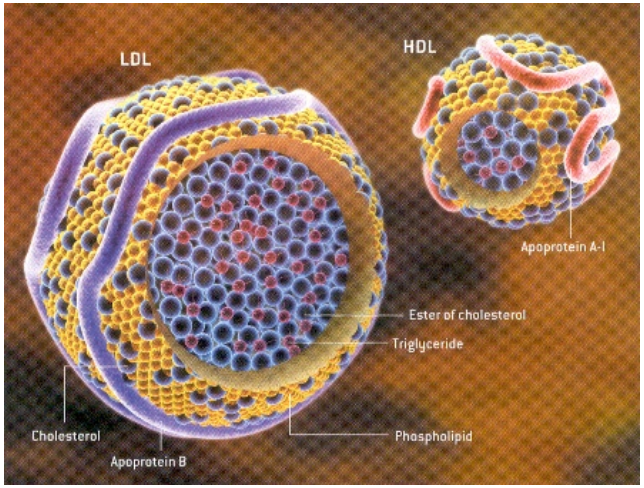
- *No of atoms: ~300,000*
- *Time scale: ~100 ns*
- *Requires a few CPU-years*

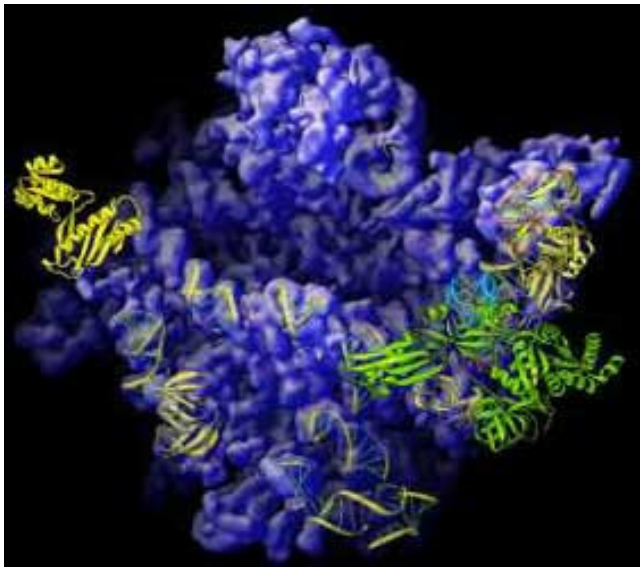
What one would like to do?

- *Full LDL particle*
  Requires ~100 CPU-years
  for 100 ns. ***Doable.***

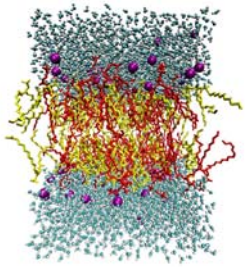
- *Ribosome*
  Requires ~ too much. ***Doable?***

- *Protein folding*
  Requires ~ too much. ***Doable?***





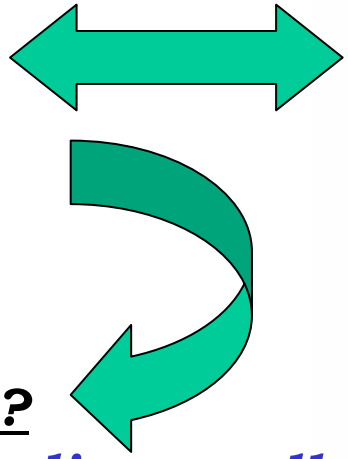
Present limits: CG models

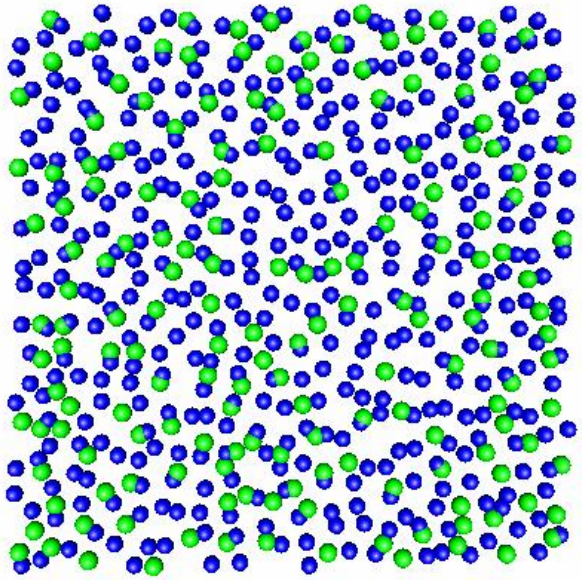


Limits of present CG models ?

Doable at the moment:

- *No of atoms: 4,000,000*
  *(1 μ x 1 μ, **no water**)*
- *Time scale: 1 ms*
- *Requires ~ 1 CPU-year*



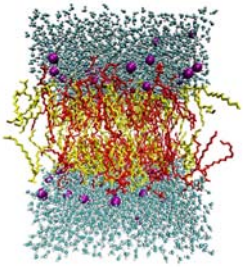


T. Murtola et al. (2004, 2006)

What one would like to do?

- *Whole membrane surrounding a cell*
  (substantial coarse graining)
- *Requires ~ 300 CPU-years for 1 ms*

Needs



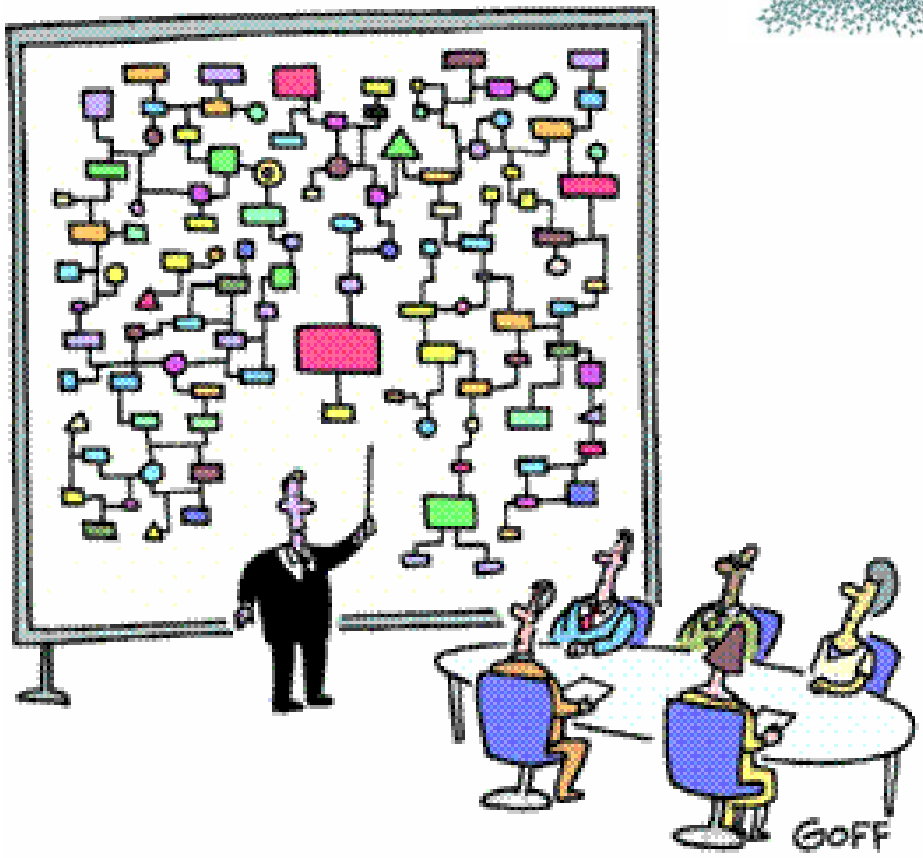
Computational resources

Storage problem

- **Data intensive nature**
- **Studies usually based on post-analysis, each simulation yielding ~ 1 Gb**
- **Coupling to bioinformatics, systems biology, and of course experiments**

Algorithms, methods

Support services



"And that's why we need a computer."