

Coarse-Graining of Lipid Micelles and Bilayers

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Abstract

For both fundamental and technological reasons, there is strong desire to understand the overall behavior of **complex macromolecular** and **biological soft-matter** systems.

From theoretical point of view, this task is highly nontrivial since processes in these systems occur over a wide range of **length and time scales**, while current modeling and analytical techniques are feasible over relatively limited scales only.

To fill this gap, one has to develop ways to link different methods, an idea which has led to concepts known as **multiscale modeling** and **coarse-graining**.

The idea of multiscale modeling gives rise to the fundamental problem that there is no unique way to perform coarse-graining. We employ a method that allows us to perform **controlled spatial coarse-graining** followed by corresponding **temporal coarse-graining** in a systematic well-defined fashion.

Problem

The **diffusion constant** for typical lipids is about

$$D = 3 \cdot 10^{-7} \text{cm}^2/\text{s}$$

The time needed to diffuse around the sample shown in the centre is thus:

$$t = 1 \mu\text{s}$$

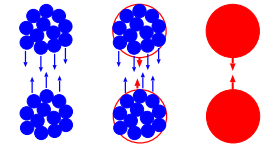
A modern microscopic MD simulation takes about one week per nanosecond \Rightarrow It would take about **20 years** to see a particle exploring the entire sample.

How can we speed up our simulation by at least a factor of 100?

Answer: coarse-graining in **space** and **time**.

Spatial coarse-graining

Aim: Reduce the number of particles



We can describe the collision of two billiard balls by just two particles — instead of 10^{23} atoms.

N particles $\Rightarrow N^2$ interactions

Reduction of particle number leads to quadratic increase in simulation speed!

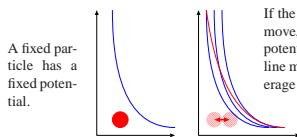
We replace a group of several “microscopic” atoms by a larger “effective” particle.

Temporal coarse-graining

The integration time step in a MD simulation is limited by the slope of the internal potentials.

We want softer potentials!

A potential can be softened by coarse-graining (=averaging) over time. All particles fluctuate somewhat so their potential does, too.



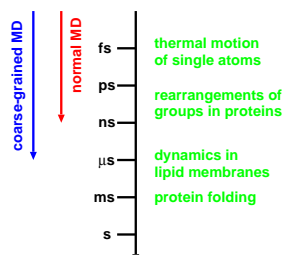
Outlook

Dynamics in biophysical systems has characteristic time scales. The kind of dynamics that can be investigated depends on the power of the molecular-dynamics methods.

Past: Traditional MD can “see” the movement of only small groups of atoms.

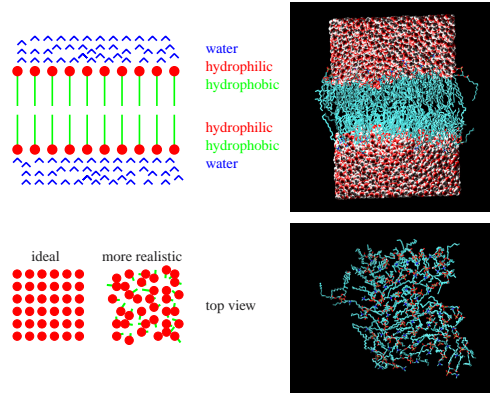
Now: Coarse-grained dynamics brings the dynamics in lipid membranes into the reach.

Future: Better coarse-graining techniques might be able to solve the protein folding problem \Rightarrow “holy grail” of theoretical biophysics



DPPC-Cholesterol bilayers

Lipids possess a **hydrophilic** head and a **hydrophobic** tail. To minimize the interaction of the tails with the surrounding water a bilayer is formed:



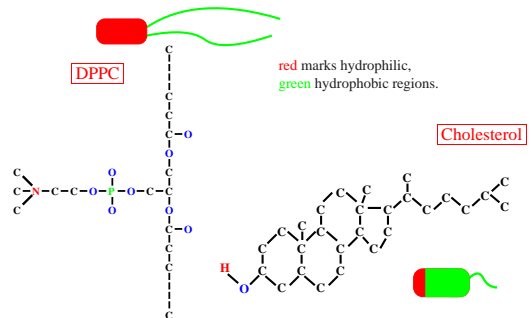
What molecules are we interested in?

Our simulations involve two different lipids, **Cholesterol** and **DPPC** (di-palmitoyl-phosphatidylcholine):

Cholesterol has a relatively large rigid body and small flexible tail. Only the front part of the body is polar (=hydrophilic).

DPPC has a relatively small but flexible body. In addition, it has two almost identical long tails.

Function: The bilayer consists mainly of DPPC. The addition of cholesterol stiffens the bilayer \Rightarrow too much cholesterol is unhealthy!



Spatial coarse-graining

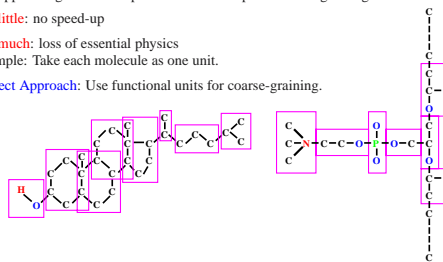
How much coarse-graining do we want?

Our approach gives us complete freedom for spatial coarse-graining.

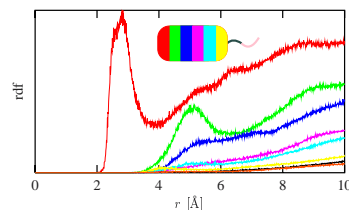
Too little: no speed-up

Too much: loss of essential physics
Example: Take each molecule as one unit.

Correct Approach: Use functional units for coarse-graining.



Do we capture the specificity?

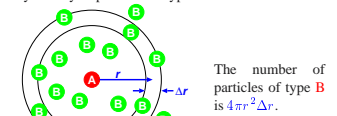


The curves vary monotonically starting from the head to the tail \Rightarrow the interaction is **specific** and **agrees with physical intuition** (for hydrophilic region peak at small distance, for hydrophobic residues no such peak).

We divide each Cholesterol molecule into eight regions and compute the radial-distribution function between water and each of those regions.

Radial distribution functions

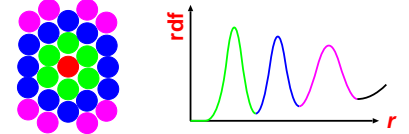
Pair correlation function $g_{AB}(r)$: Probability (density) of finding a particle of type **B** in a distance r of a particle of type **A**, divided by density of particles of type **B**.



Radial distribution function: Divide pair correlation function by $4\pi r^2$.

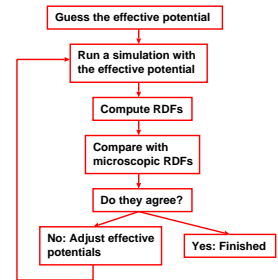
The radial correlation function goes to 1 for large r . If there is an excluded volume, it goes to 0 for small r .

Example: radial-distribution function of the red particle:



Computation of effective potentials

We **demand** that the effective potentials yield the correct radial-distribution function, i.e., the correct **two-particle correlation** function. Typically **higher correlation** functions will then be well approximated as well.



Initial guess: Use potential of mean force
Extract it from the two-particle correlation function $g(r)$ using the Boltzmann factor:

$$g(r) \propto \exp[-\beta V(r)]$$

Adjust potential using

$$\Delta g(r) = \int dr' \frac{\partial g(r)}{\partial V_{eff}(r')} \Delta V_{eff}(r') + \dots$$

\Rightarrow allows iterative improvement by solving a linear equation because we know

$$\frac{\partial g(r)}{\partial V_{eff}(r')} = -\frac{(g(r)g(r')) - (g(r))g(r')}{k_B T}$$

Summary

- run a microscopic simulation for a short time
- divide the molecules in units, guided by knowledge of the system (**spatial coarse-graining**)
- compute the radial distribution functions for the spatially coarse-grained particles from the microscopic simulation
- compute the effective potentials in a systematic well-defined way (**temporal coarse-graining**)
- run a coarse-grained simulation for a much longer time

If a **coarse-grained simulation** is done in this way

- all pair-correlation functions are guaranteed to be correct
- higher correlation functions are very well approximated if the spatial coarse-graining was sensibly chosen

References

- A. P. Lyubartsev & A. Laaksonen, *Calculation of effective interaction potentials from radial distribution functions*, PRE 52, 3730 (1995)
- M. Karttunen, I. Vattulainen, A. P. Lyubartsev & A. Laaksonen, *Coarse-Graining of Lipid Micelles and Bilayers*, submitted to PRL
- M. Patra, M. Karttunen, M. Hyvönen & I. Vattulainen, in preparation

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