



Parameterizing Martini molecules

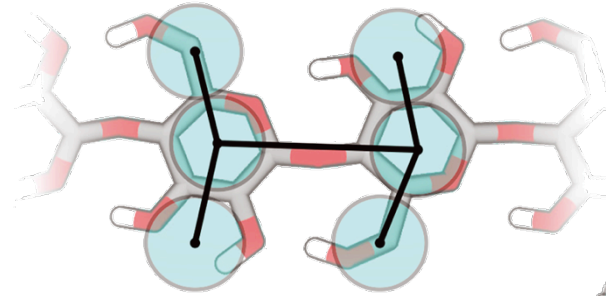
A new topology: what do we need?

Mapping (center of mass)

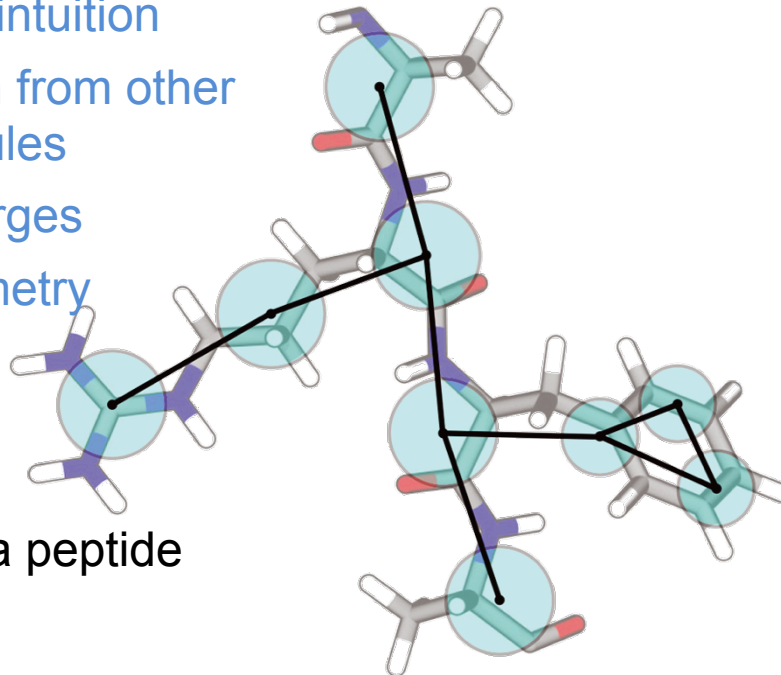
4 heavy atoms to 1 bead
(can be finer or coarser)

Not unique

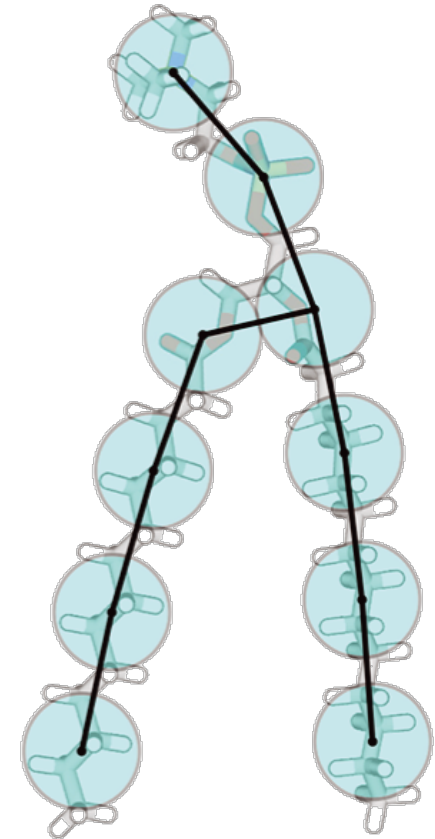
- Use chemical intuition
- Get inspiration from other Martini molecules
- No partial charges
- Respect symmetry
- Be consistent



Cellulose



AlaArgPheAla peptide



Dilauroyl-PC

A new topology: what do we need?

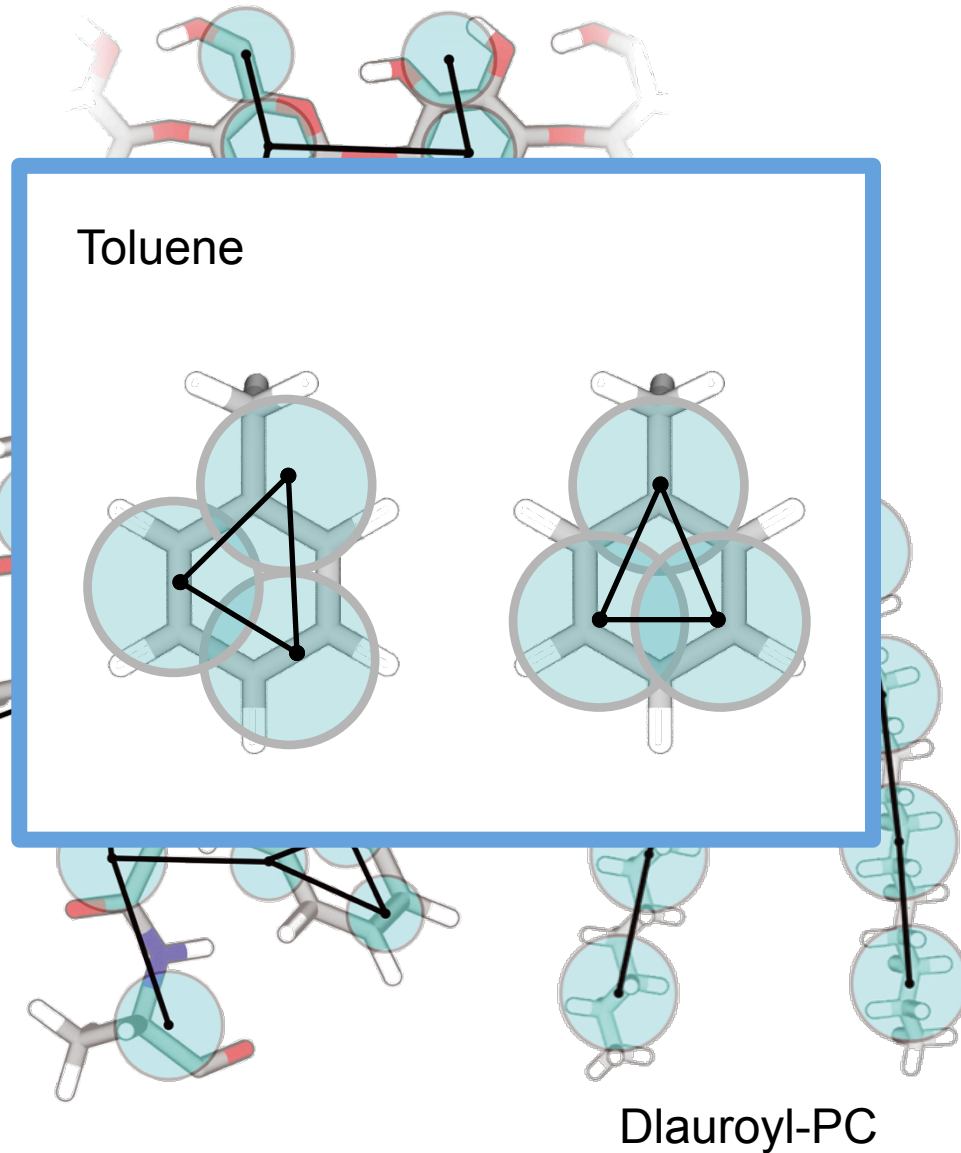
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4 heavy atoms to 1 bead
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AlaArgPheAla peptide



A new topology: what else do we need?

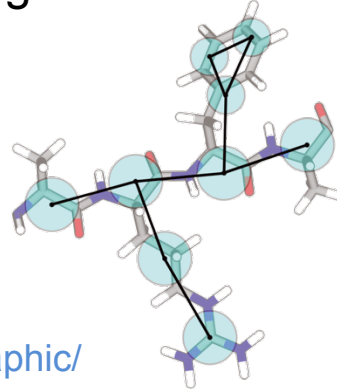
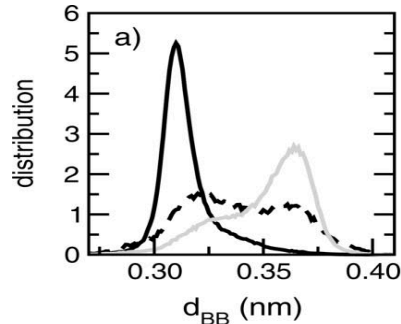
$$U(\vec{r}) = \sum U_{bonded}(\vec{r}) + \sum U_{nonbonded}(\vec{r})$$

A set of intramolecular potentials that recreate the correct distribution of relative configurations

A set of interparticle potentials that recreate the correct partitioning behavior (and density, surf. tension, etc.)

Where do the target distributions/partitions come from?

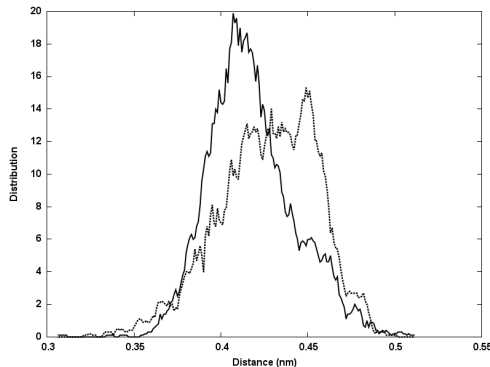
Experiments



Partition data

CG-mapped PDB crystallographic/
NMR coordinates

Simulations with
finer models



Bond stretching
mapped from a
GROMOS 54a6
simulation

ΔG , typically from thermodynamic
integration (TI) simulations

Getting the right potentials

$$U_{\text{bonded}}(\vec{r})$$

$$U_{\text{nonbonded}}(\vec{r})$$

Which bonded potentials? (besides Boltzmann-inverted ones)

Simple potentials ensure portability across simulation software

Are often optimized

May be insufficient (multimodal distributions, for instance)

Bias towards potentials implemented in GROMACS

Bonds: 

$$U(x) = \frac{1}{2}k(x - x_0)^2$$

Simple

Numerically stable

Symmetric distribution (Gaussian)

Angles: 

$$U(\theta) = \frac{1}{2}k(\cos(\theta) - \cos(\theta_0))^2$$

Numerically stable, unlike

Weak potential towards colinearity

$$U(\theta) = \frac{1}{2}k(\theta - \theta_0)^2$$

Getting the right potentials

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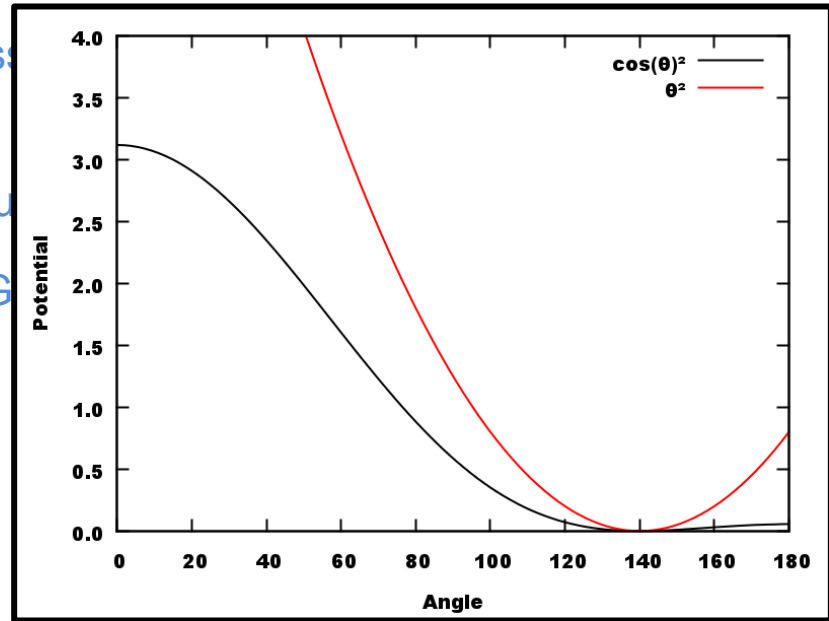
Bias towards potentials implemented in G

Bonds: 

$$U(x) = \frac{1}{2} k (x - x_0)^2$$

Angles: 

$$U(\theta) = \frac{1}{2} k (\cos(\theta) - \cos(\theta_0))^2$$



Numerically stable, unlike

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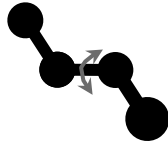
Weak potential towards colinearity

Getting the right potentials

$$U_{bonded}(\vec{r})$$

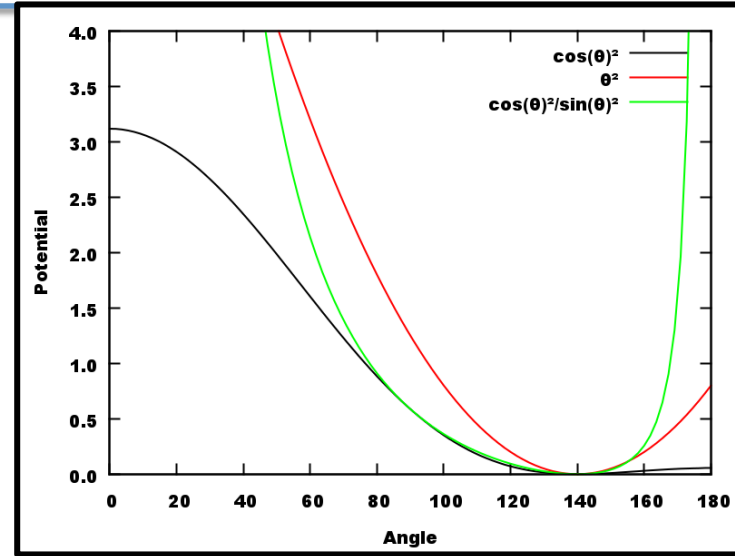
Which bonded potentials?

Dihedral angles:



$$U(\phi) = k(1 + \cos(n\phi - \phi_r))$$

$$U(\phi) = \frac{1}{2}k(\phi - \phi_r)^2$$

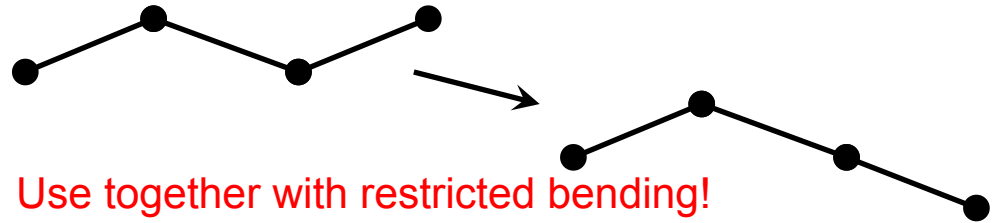


Periodic

Can have multiple minima (n)

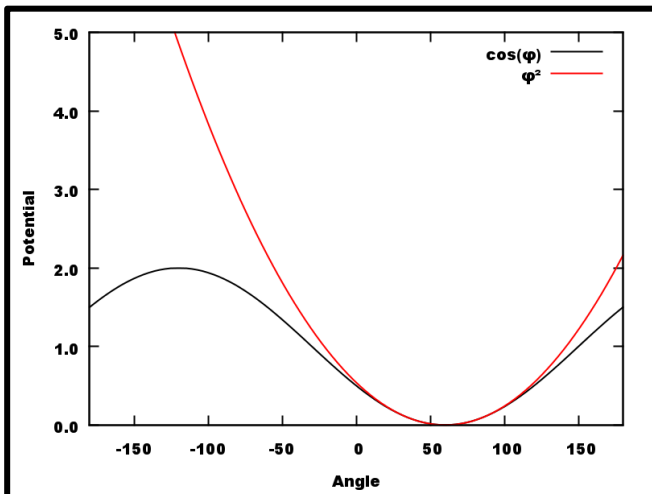
Suitable for keeping torsions that do not flip

Both types become unstable if any two of the constructing bonds become colinear!



Use together with restricted bending!

$$U(\theta) = \frac{1}{2}k \frac{(\cos(\theta) - \cos(\theta_0))^2}{\sin^2(\theta)}$$



Getting the right potentials

$$U_{\text{bonded}}(\vec{r})$$

$$U_{\text{nonbonded}}(\vec{r})$$

Typical Martini approach:

Obtain target distribution

Repeat
until
happy

Assign an analytical potential with
estimated/adjusted parameters

Simulate the tentative CG model

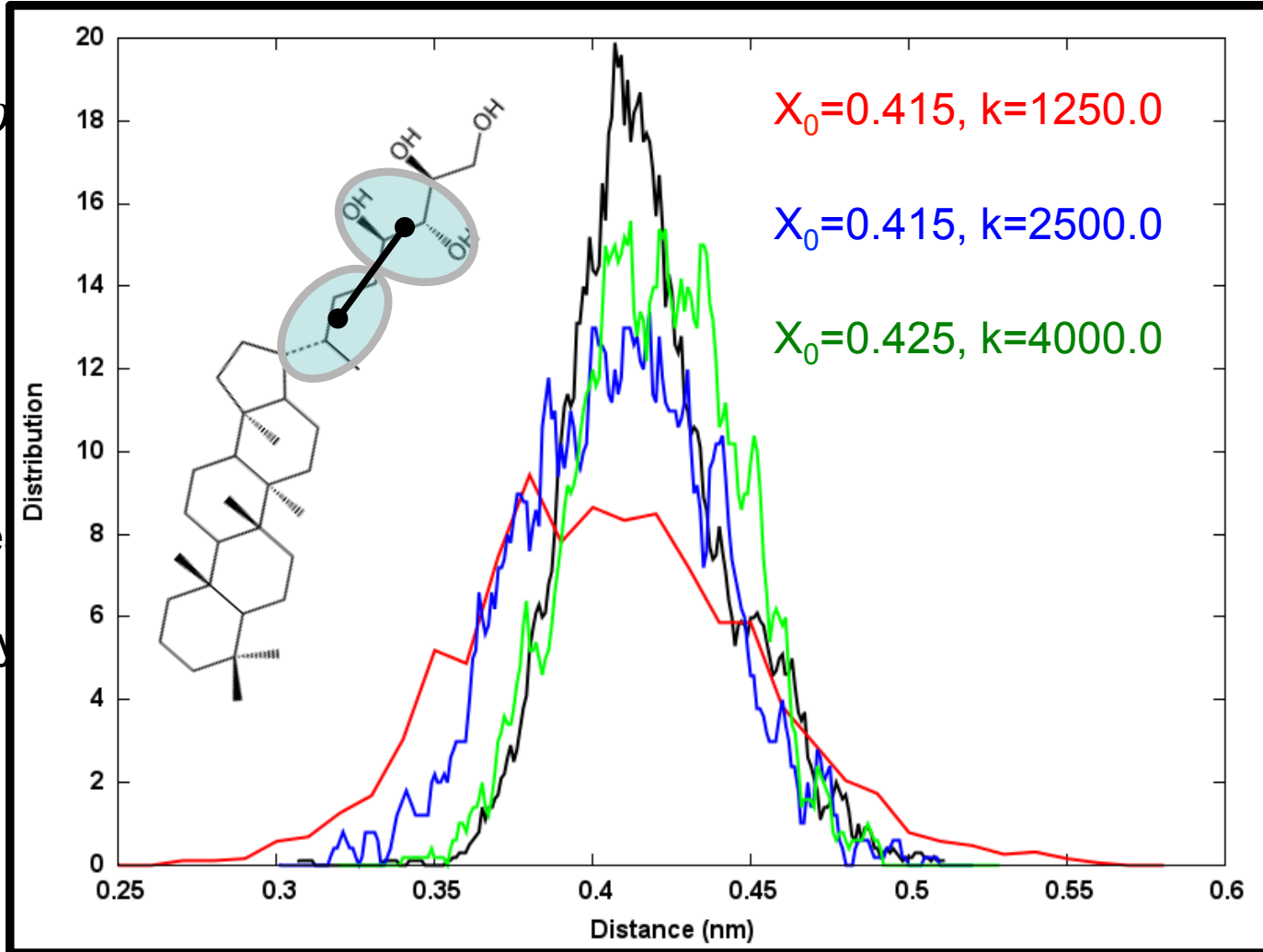
Compare resulting distributions to target ones

$$U(x) = \frac{1}{2} k (x - x_0)^2, \quad (k : \text{kJ/mol} \cdot \text{nm}^2, x : \text{nm})$$

Getting the right potentials

U_{bond}

Repeat until happy



ed (\vec{r})

$$U(x) = \frac{1}{2} k(x - x_0)^2, \quad (k : \text{kJ/mol} \cdot \text{nm}^2, x : \text{nm})$$

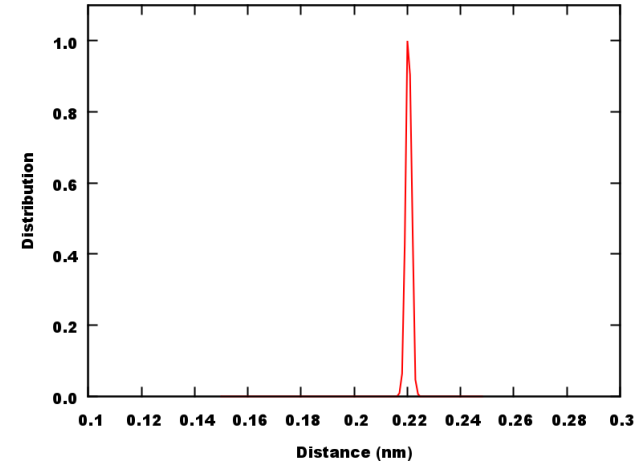
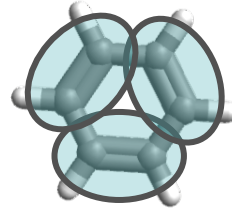
Constraints

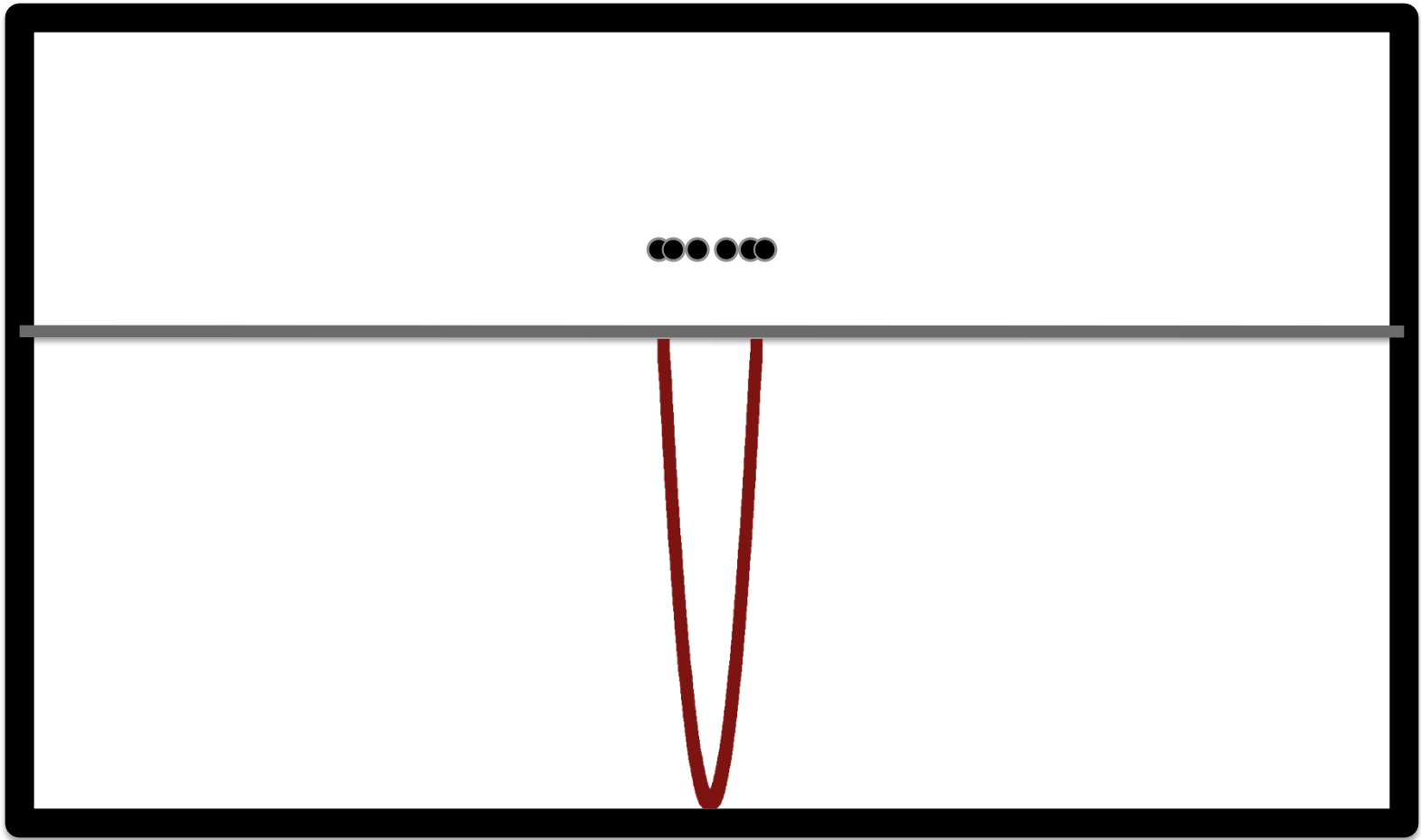
Highly localized distributions

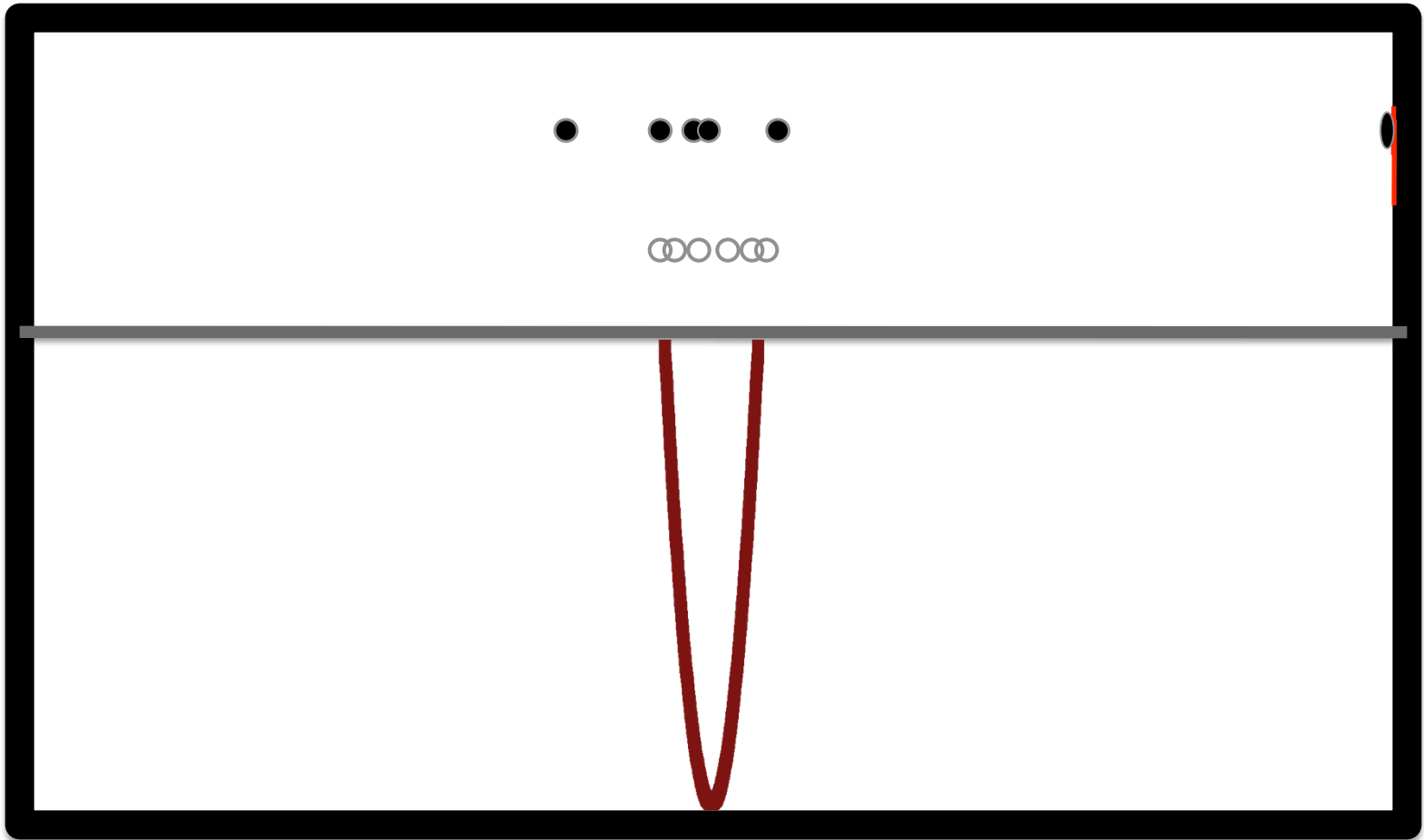
Narrow distributions require stiff potentials

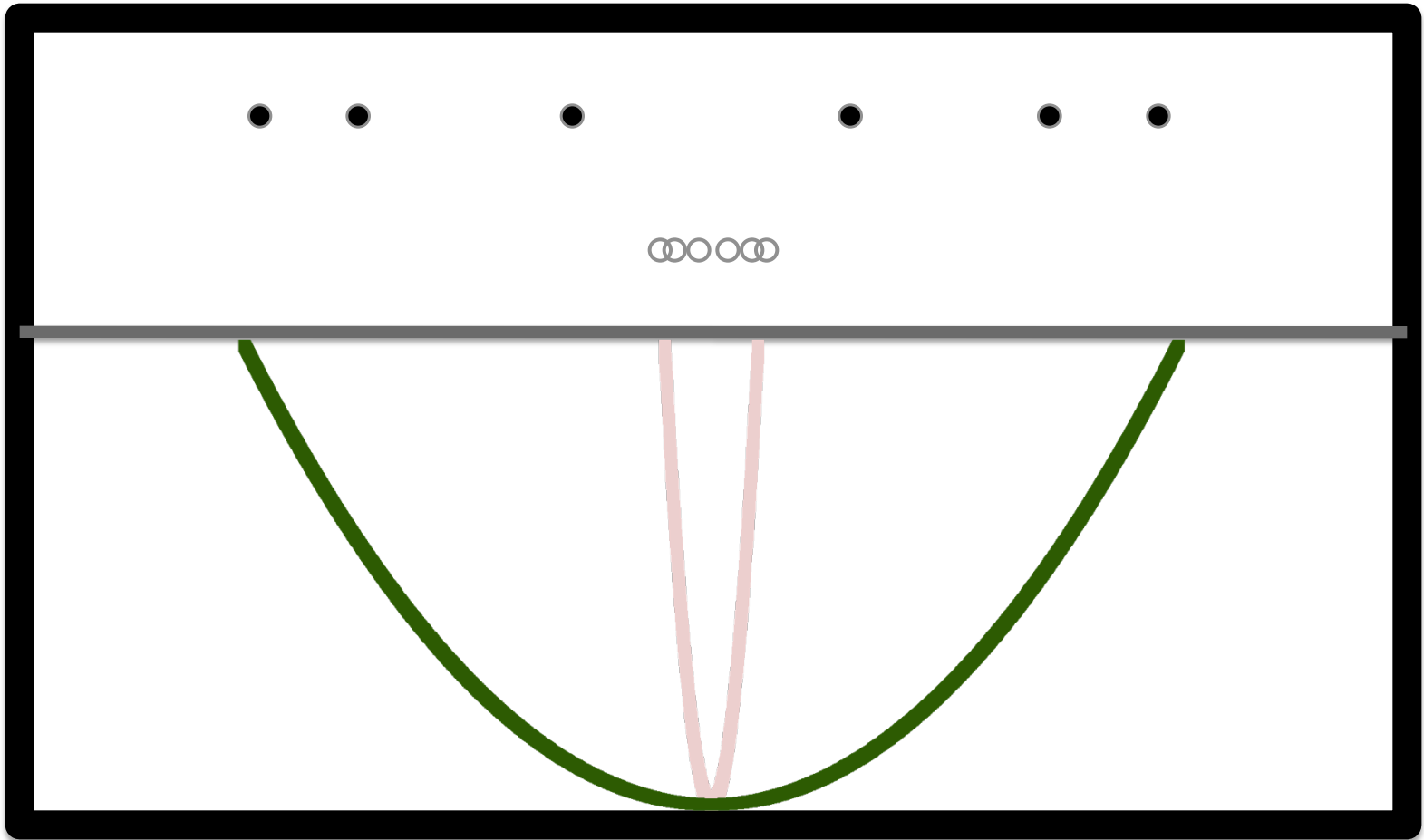
Stiff potentials require short time steps

At the Martini scale the breadth of stiff distributions, and the high oscillation frequencies, become unimportant









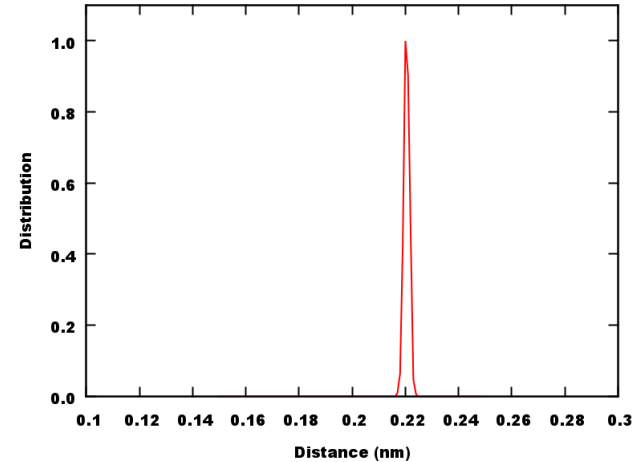
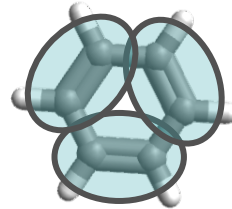
Constraints

Highly localized distributions

Narrow distributions require stiff potentials

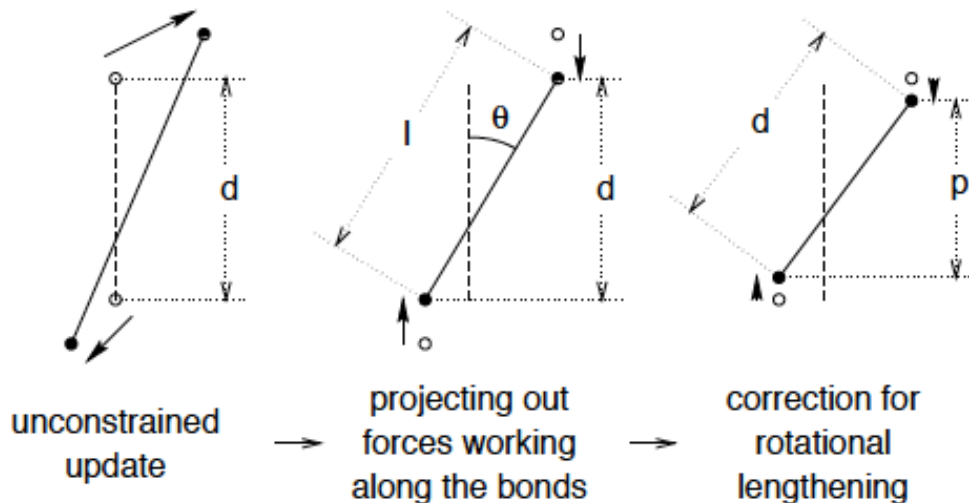
Stiff potentials require short time steps

At the Martini scale the breadth of stiff distributions, and the high oscillation frequencies, become unimportant



Use constraints

Interparticle distance becomes a system constant (1 DOF less)



Getting the right potentials: bead types

$U_{\text{bonded}}(\vec{r})$

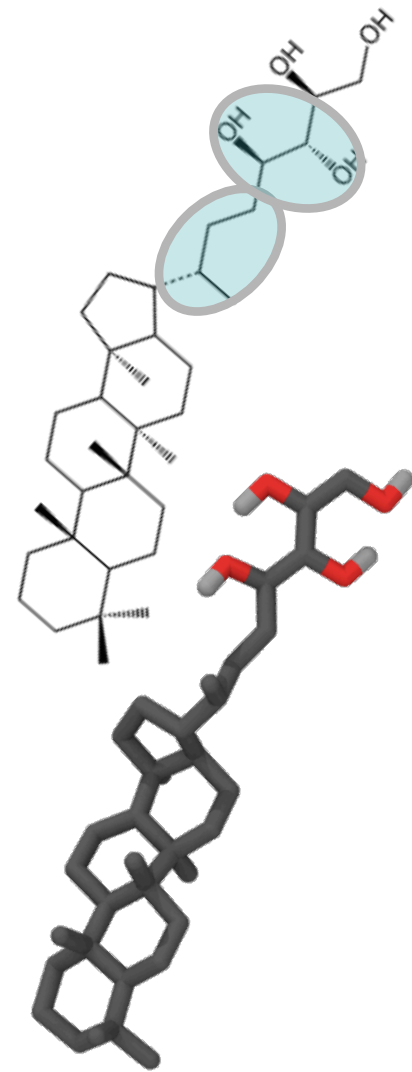
$U_{\text{nonbonded}}(\vec{r})$

7818 *J. Phys. Chem. B*, Vol. 111, No. 27, 2007

Marrink et al.

TABLE 3: Thermodynamic Properties of the CG Particle Types^a

type	building block	examples	ΔG^{vap}		ΔG^{hyd}		$\Delta G_{\text{HW}}^{\text{part}}$		$\Delta G_{\text{CW}}^{\text{part}}$		$\Delta G_{\text{EW}}^{\text{part}}$		$\Delta G_{\text{OW}}^{\text{part}}$	
			exp	CG	exp	CG	exp	CG	exp	CG	exp	CG	exp	CG
Q _{da}	H ₃ N ⁺ -C ₂ -OH	ethanolamine (protonated)			-25		< -30		-18		-13		-18	
Q _d	H ₃ N ⁺ -C ₃	1-propylamine (protonated)			-25		< -30		-18		-13		-18	
	NA ⁺ OH	sodium (hydrated)			-25		< -30		-18		-13		-18	
Q _a	PO ₄ ⁻	phosphate			-25		< -30		-18		-13		-18	
	CL ⁻ HO	chloride (hydrated)			-25		< -30		-18		-13		-18	
Q ₀	C ₃ N ⁺	choline			-25		< -30		-18		-13		-18	
P ₅	H ₂ N-C ₂ =O	acetamide	sol	sol	-40	-25	-27	-28	(-20)	-18	-15	-13	-8	-10
P ₄	HOH (× 4)	water	-27	-18	-27	-18	-25	-23		-14	-10	-7	-8	-9
	HO-C ₂ -OH	ethanediol	-35	-18	-33	-18	-21	-23		-14		-7	-8	-9
P ₃	HO-C ₂ =O	acetic acid	-31	-18	-29	-18	-19	-21	-9	-10	-2	-6	-1	-7
	C-NH-C=O	methylformamide	-35	-18		-18		-21		-10		-6	-5	-7
P ₂	C ₂ -OH	ethanol	-22	-16	-21	-14	-13	-17	-5	-2	-3	1	-2	-2
P ₁	C ₃ -OH	1-propanol	-23	-16	-21	-14	-9	-11	-2	-2	0	1	1	-1
		2-propanol	-22	-16	-20	-14	-10	-11	-2	-2	-1	1	0	-1
N _{da}	C ₄ -OH	1-butanol	-25	-16	-20	-9	-5	-7	2	0	4	2	4	3
N _d	H ₂ N-C ₃	1-propylamine	-17	-13	-18	-9	(-6)	-7	(1)	0	(-3)	2	(3)	3
N _a	C ₃ =O	2-propanone	-17	-13	-16	-9	-6	-7	1	0	-1	2	-1	3
	C-NO ₂	nitromethane	-23	-13	-17	-9	-6	-7		0		2	-2	3
	C ₃ =N	propionitrile	-22	-13	-17	-9	-5	-7		0		2	1	3
	C-O-C=O	methylformate	-16	-13	-12	-9	(-6)	-7	(4)	0	(-1)	2	(0)	3
	C ₂ HC=O	propanal		-13	-15	-9	-4	-7		0	2	2	3	3
N ₀	C-O-C ₂	methoxyethane	-13	-10	(-8)	-2	(1)	-2		6	(3)	6	(3)	5
C ₅	C ₃ -SH	1-propanethiol	-17	-10		1		5		10		10		6
	C-S-C ₂	methyl ethyl sulfide	-17	-10	-6	1	(7)	5		10		10	(9)	6
C ₄	C ₂ =C ₂	2-butyne	-15	-10	-1	5		9		13		13	9	9
	C=C-C=C	1,3-butadiene		-10	2	5	11	9		13		13	11	9
	C-X ₄	chloroform	-18	-10	-4	5	(7)	9	14	13		13	11	9
C ₃	C ₂ =C ₂	2-butene		-10		5		13		13		13	13	14
	C ₃ -X	1-chloropropane	-16	-10	-1	5	12	13		13		13	12	14
		2-bromopropane	-16	-10	-2	5		13		13		13	12	14
C ₂	C ₃	propane	gas	-10	8	10		16		15		14	14	16
C ₁	C ₄	butane	-11 ^b	-10	9	14	18	18		18		14	16	17
		isopropane	gas	-10	10	14		18		18		14	16	17

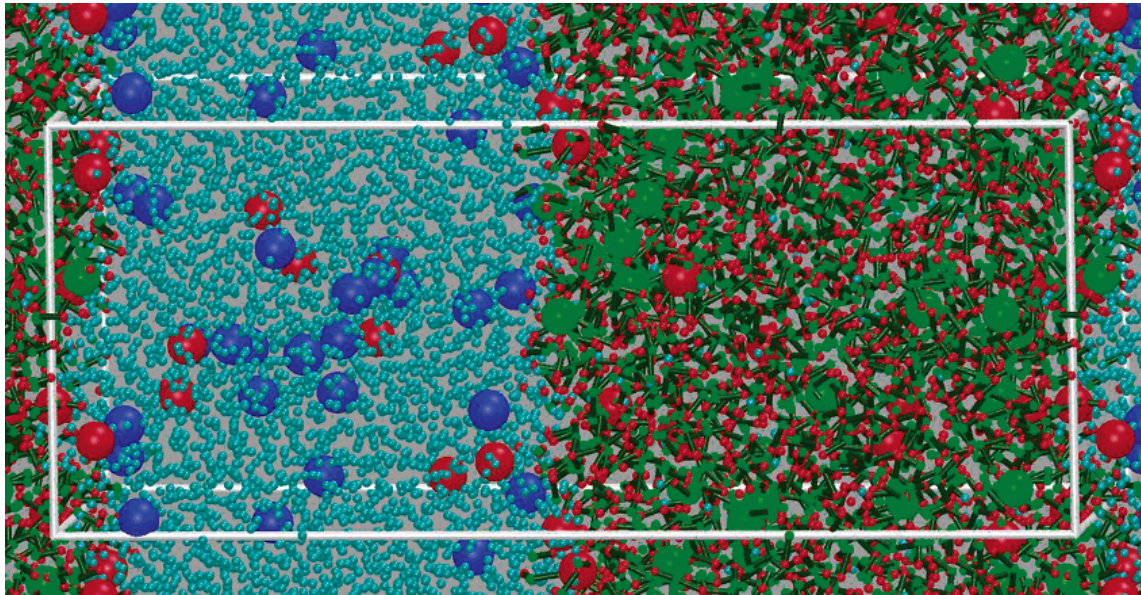


Getting the right potentials: bead types

$$U_{bonded}(\vec{r})$$

$$U_{nonbonded}(\vec{r})$$

Verify the reproduction of partition free energies and adjust bead types accordingly



$$\Delta G_{part} = kT \ln([solute]_w / [solute]_o)$$

Significant counts in both phases must be obtained

The interface may play a role

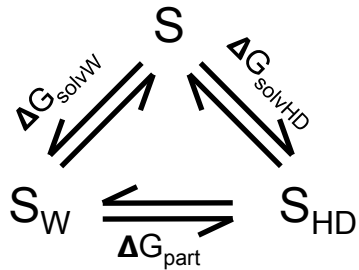
Too expensive to be used atomistically as a source of target free-energy data

Getting the right potentials: bead types

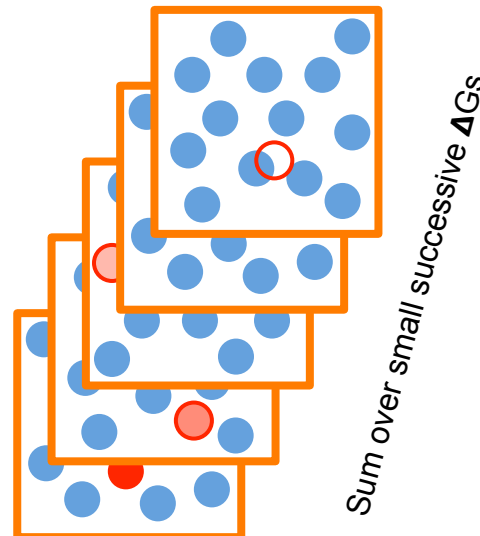
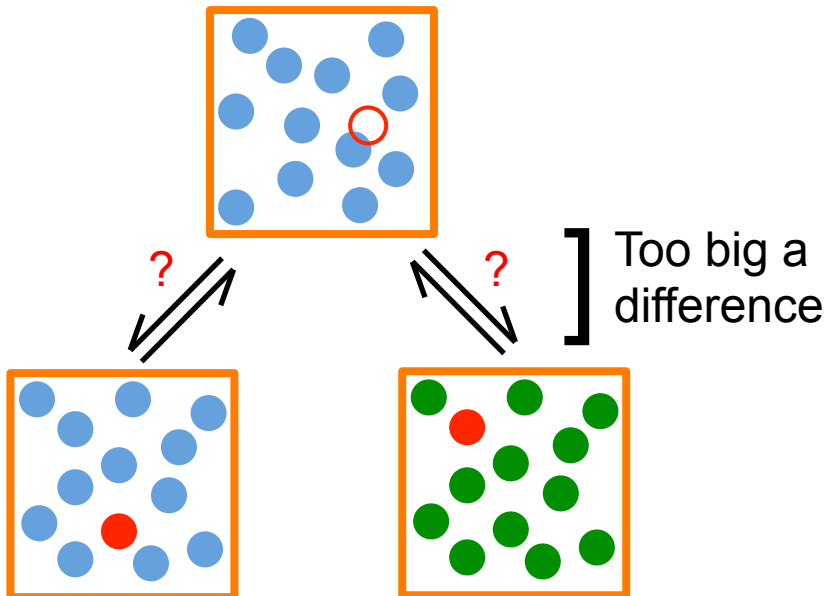
$$U_{bonded}(\vec{r})$$

$$U_{nonbonded}(\vec{r})$$

A more efficient approach through the hydration free-energies



Thermodynamic integration:



Almost always more efficient than running a system with separated phases

Can be used with atomistic systems

Getting the right potentials: bead types

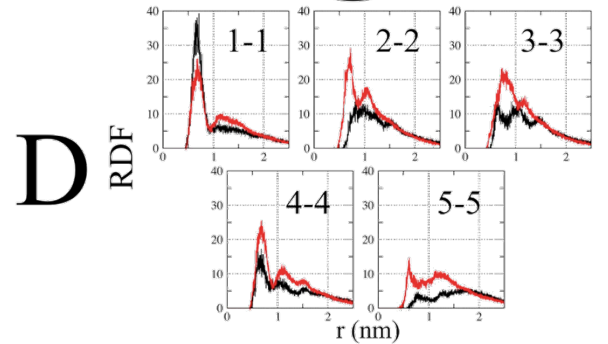
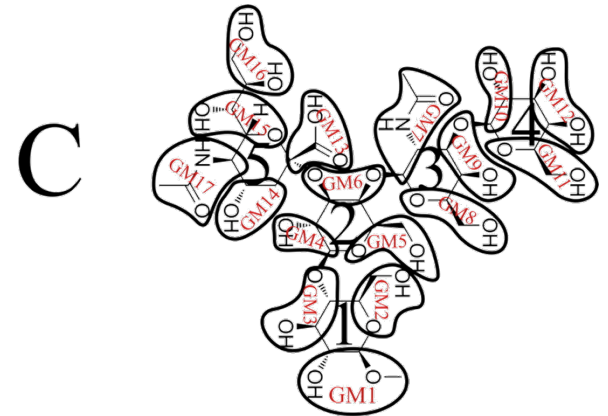
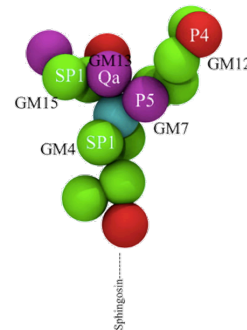
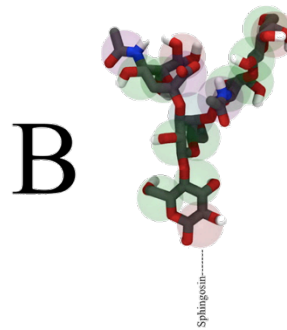
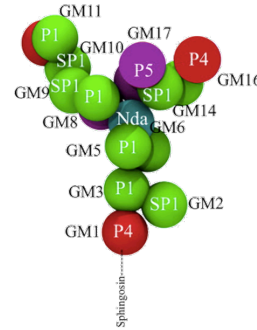
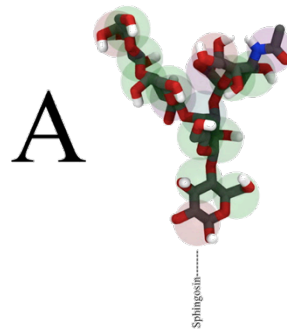
$$U_{bonded}(\vec{r})$$

$$U_{nonbonded}(\vec{r})$$

Important: tailor the matched data to your applications!

Biomolecular applications: hydrophobic/hydrophilic

Not exclusively partitions



Getting the right potentials: bead types

$$U_{bonded}(\vec{r})$$

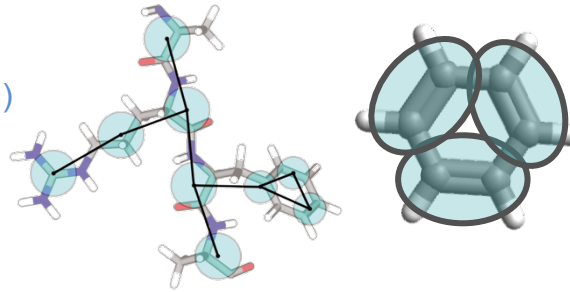
$$U_{nonbonded}(\vec{r})$$

When a finer mapping is needed (to represent planar geometries, for instance)

Very high bead density

Effective very deep energy well (condensation)

Equilibrium distance of ~ 0.52 nm



The S-beads!

25% shallower potentials with shorter equilibrium distance (~ 0.43 nm)

Allow the correct packing of rings

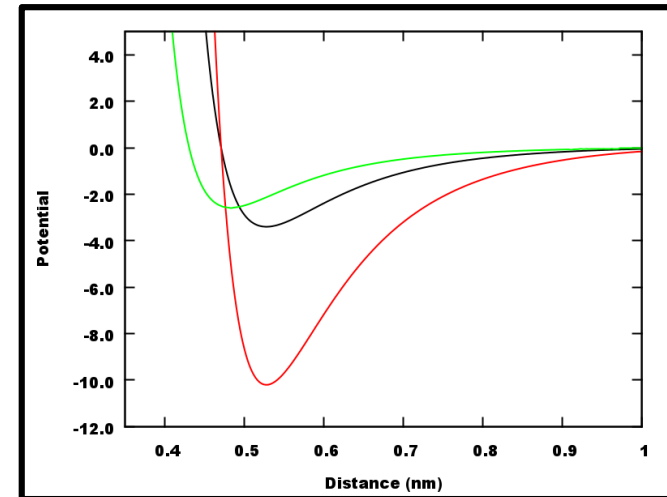
Prevent condensation of the system

Follow the same scale as regular Martini beads (SC1...SP5...SQda)

When to use?

To get correct densities

To get correct packing distances



Interaction with regular beads still follows the regular potential: validate the free energy of interaction!

Important notes

Keep the Martini philosophy in mind but tailor it to your applications

If parameterizing solvents/melts, aim to reproduce bulk properties

For polymers

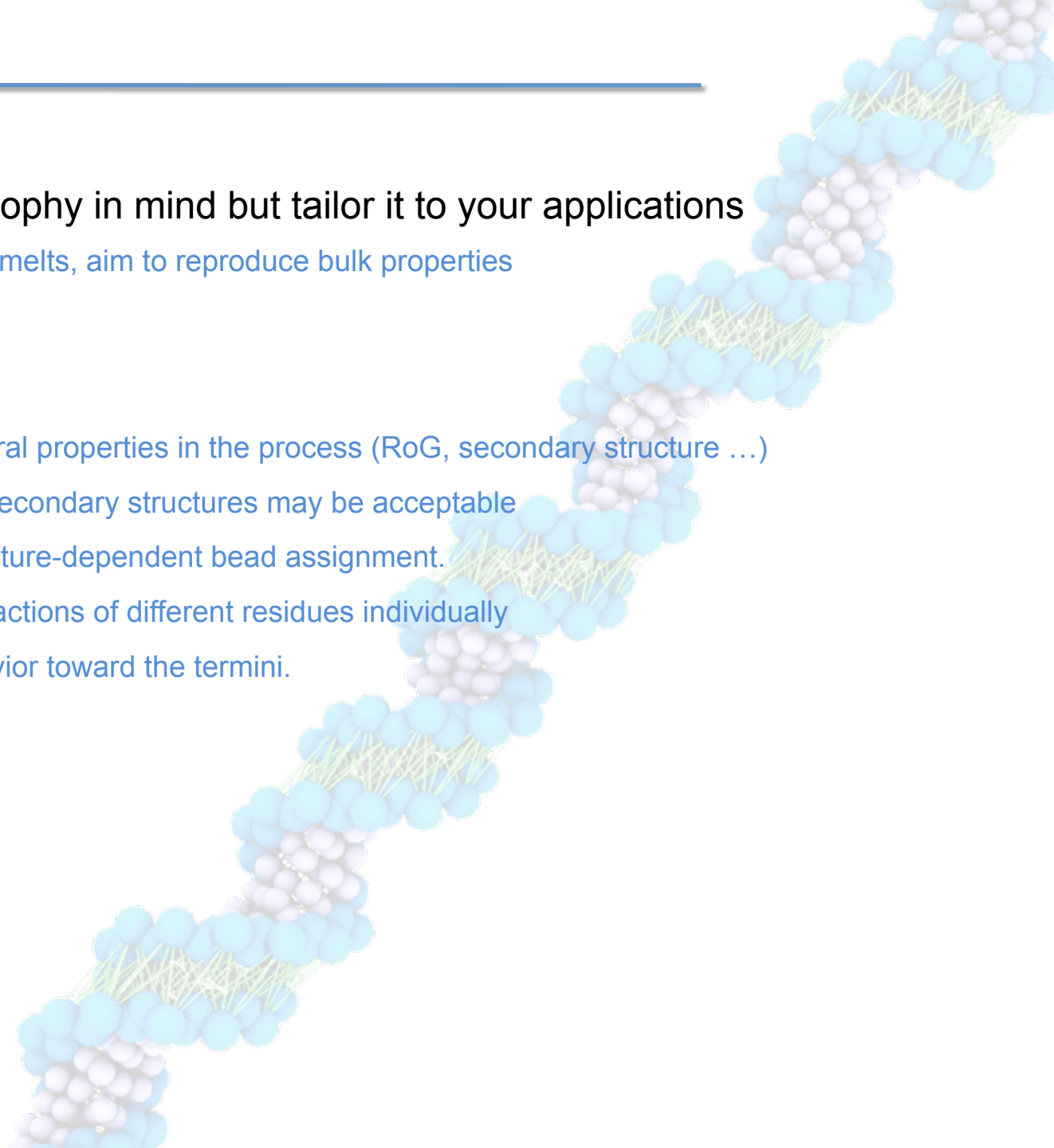
Include long-range structural properties in the process (RoG, secondary structure ...)

Don't give up: restrained secondary structures may be acceptable

But may require structure-dependent bead assignment.

Tune the nonbonded interactions of different residues individually

Beware of divergent behavior toward the termini.

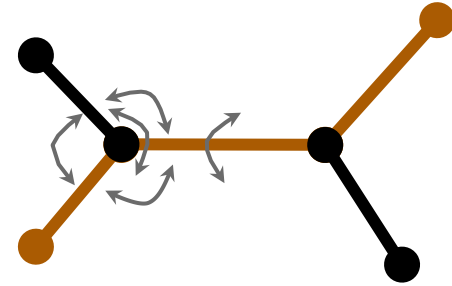


Tips & tricks

Don't over-restrain the bonded interactions

Redundancy makes convergence difficult to achieve

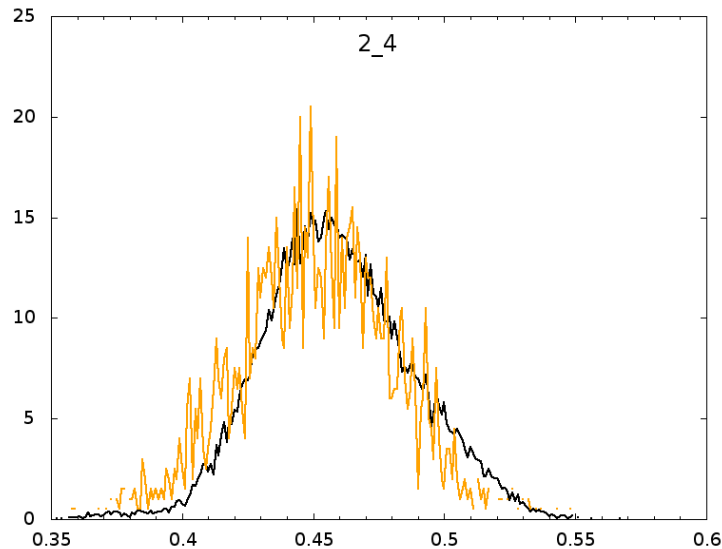
Often the nonbonded interactions push a free angle/dihedral into place



Exclusions and fake bonds between nonbonded particles

Beware of beads at distances below the nonbonded repulsion limit — consider excluding them

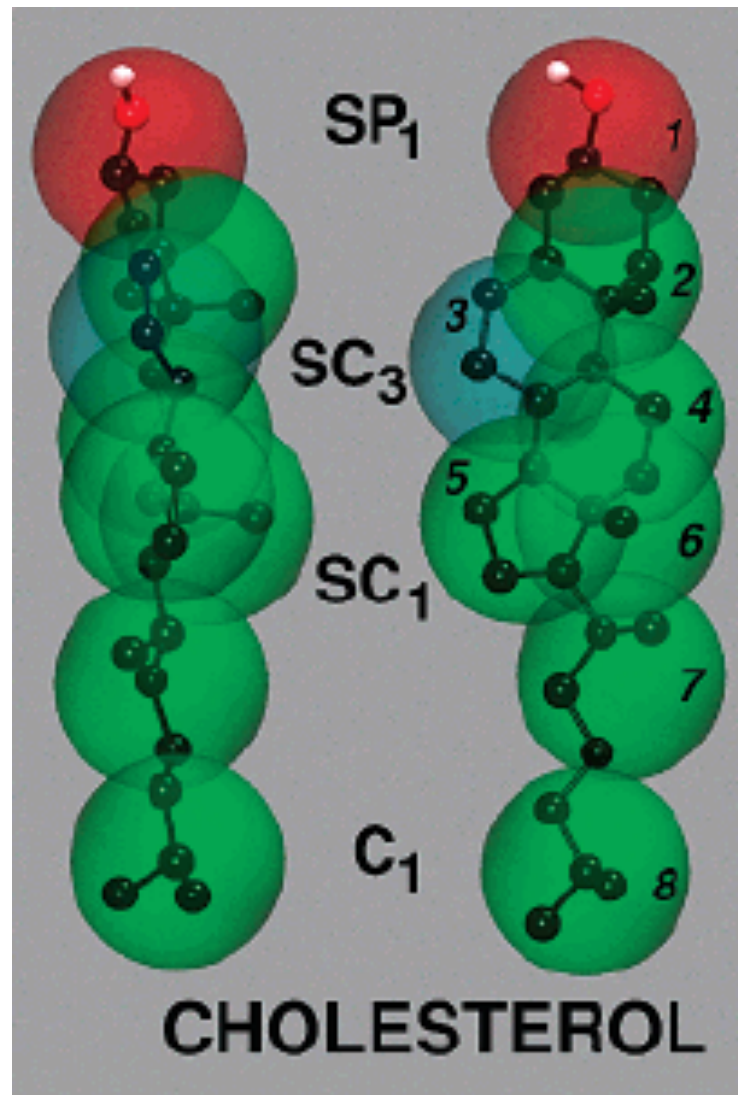
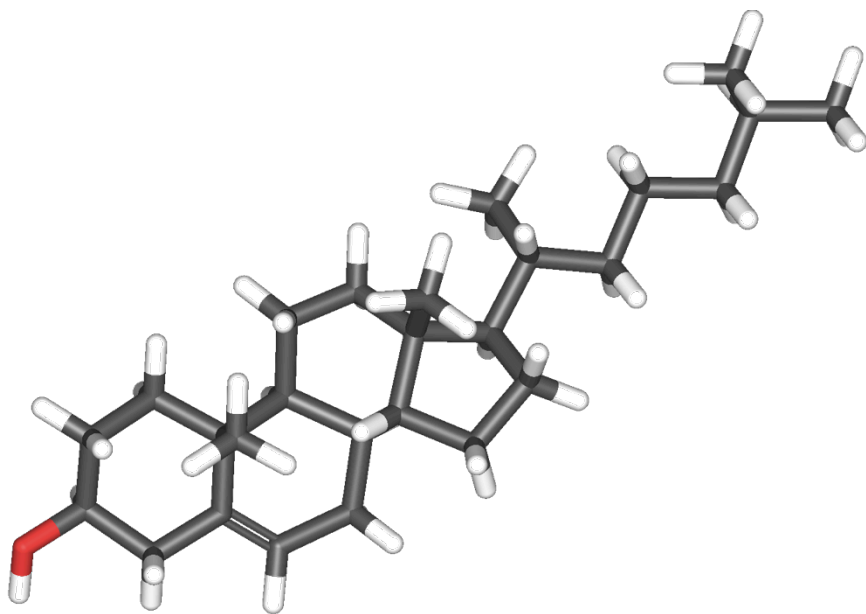
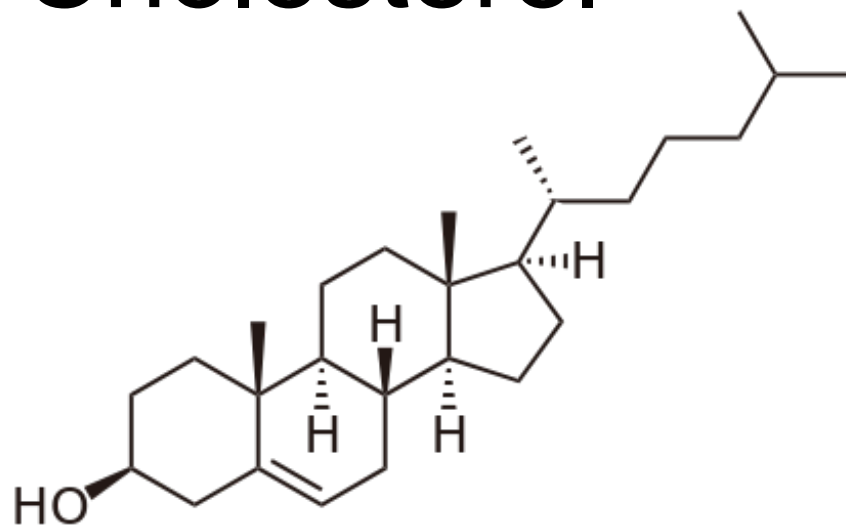
Bonds can be made between nonconsecutive beads



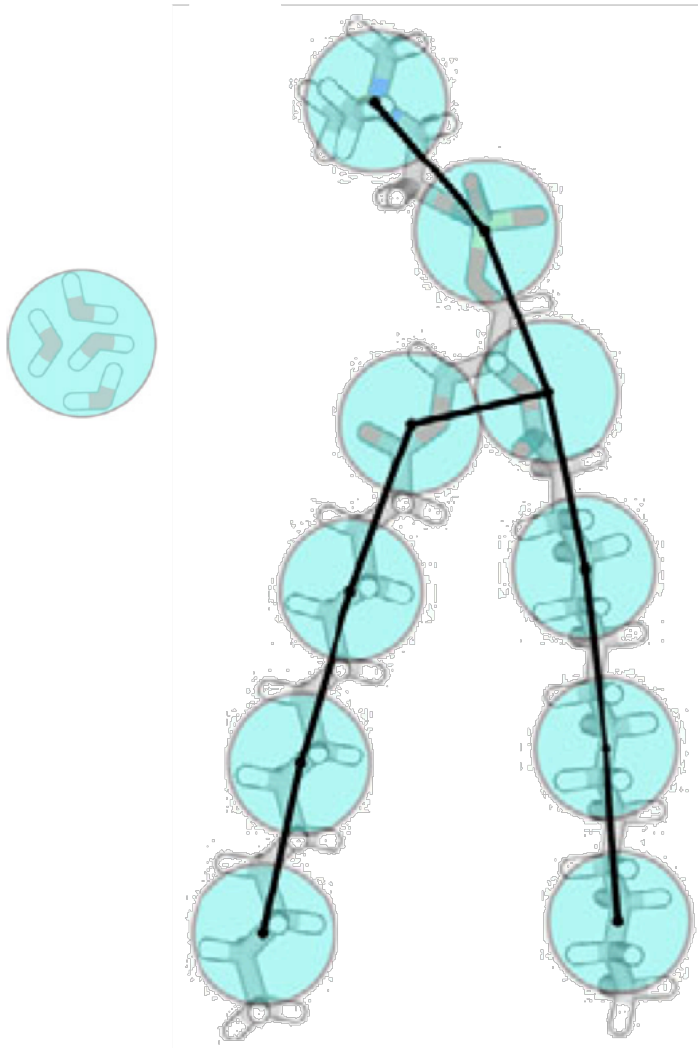


Advanced parameterization

Cholesterol



The Martini model



Fewer particles

Softer potentials

>1000x speedup

up to 40 fs timesteps

(20-40x larger than atomistic)

but...

bonds that rotated more than 30 degrees:

atom 1	atom 2	angle	previous,	current,	constraint length
3	5	33.9	0.4466	0.3470	0.3460
5	7	56.6	0.4478	0.4017	0.4060
4	5	34.9	0.3997	0.2857	0.2940

Step 8073, time 322.92 (ps) LINCS WARNING

relative constraint deviation after LINCS:

rms 0.505886, max 1.177047 (between atoms 5 and 7)

bonds that rotated more than 30 degrees:

atom 1	atom 2	angle	previous,	current,	constraint length
3	4	83.5	0.2731	0.2632	0.2720
3	5	83.8	0.3470	0.4081	0.3460
5	7	117.0	0.4017	0.8839	0.4060
4	5	47.2	0.2857	0.3689	0.2940

Wrote pdb files with previous and current coordinates

Step 8074, time 322.96 (ps) LINCS WARNING

relative constraint deviation after LINCS:

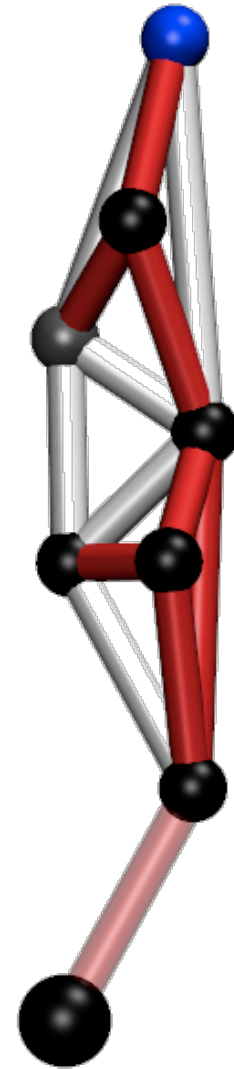
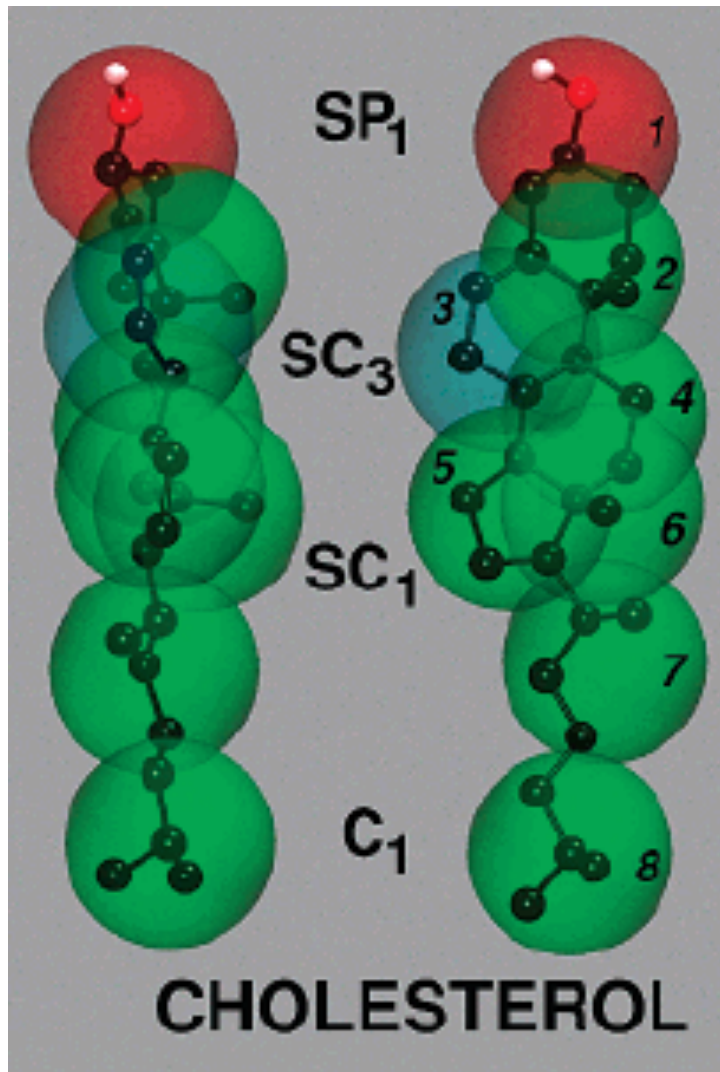
rms 1662.365558, max 4036.032715 (between atoms 5 and 7)

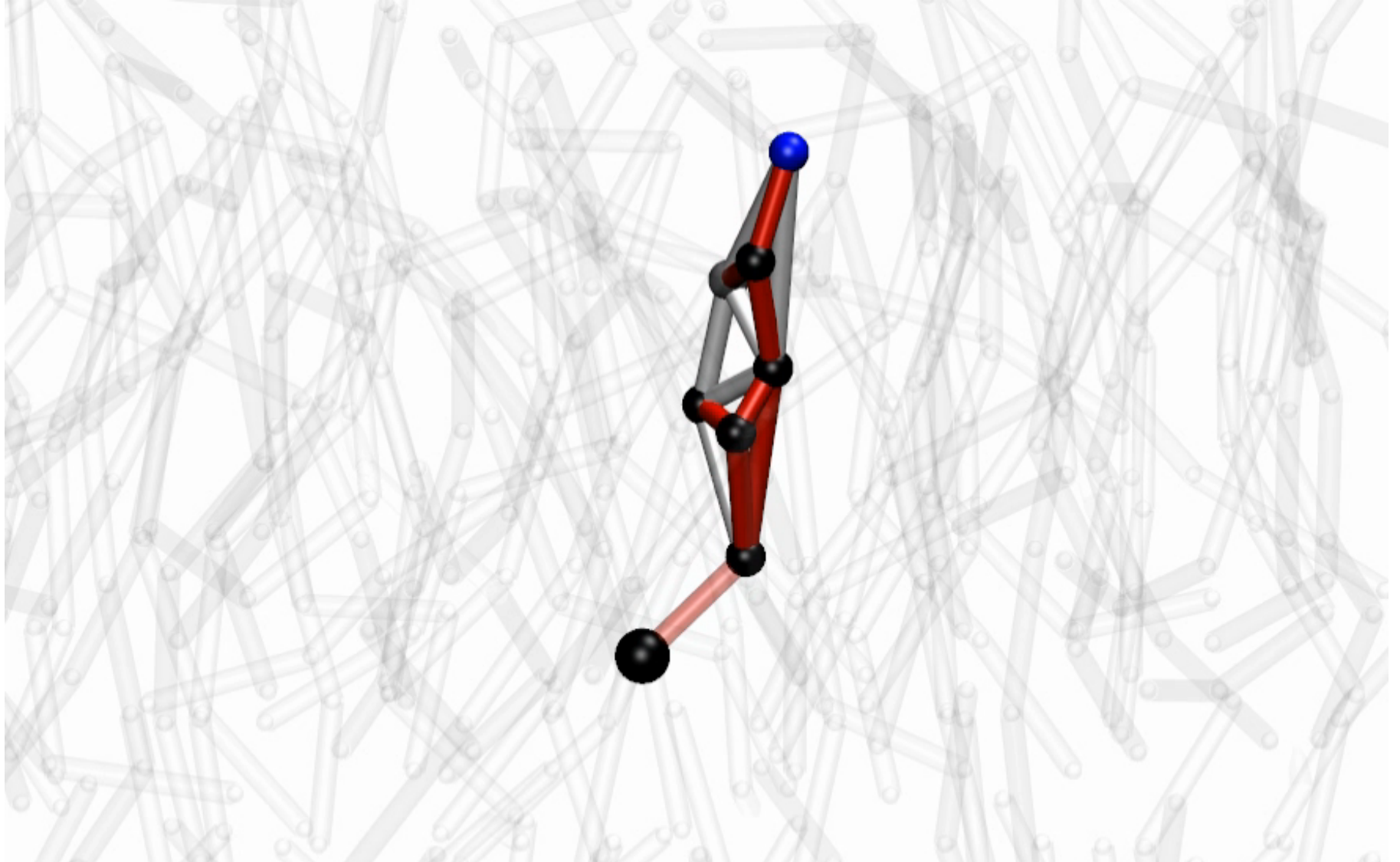
bonds that rotated more than 30 degrees:

atom 1	atom 2	angle	previous,	current,	constraint length
3	4	91.6	0.2632	62.9947	0.2720
3	5	86.5	0.4081	117.0789	0.3460
5	7	89.6	0.8839	1639.0353	0.4060
4	5	94.3	0.3689	101.7266	0.2940
1	3	103.8	0.3853	11.2611	0.4930
1	4	86.7	0.6435	41.9594	0.6040

Wrote pdb files with previous and current coordinates

Segmentation fault (core dumped)





```
#!/bin/bash
while mdrun -v -cpi state.cpt -noappend -maxh 0.05
do
    rm -rf *part*
done
```

What can be done?

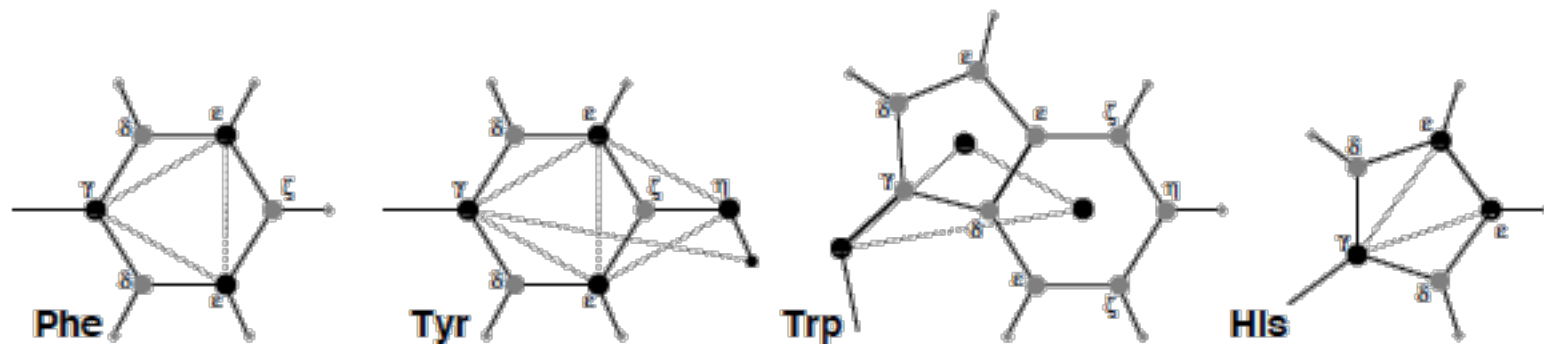
Decrease the time step

Constrain the whole thing

Increase the bead masses

Use virtual interaction sites

Virtual interaction sites?

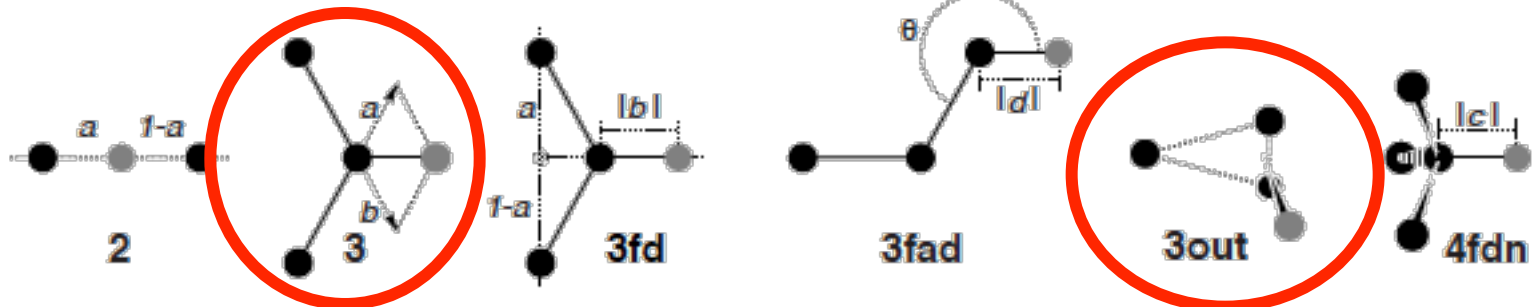
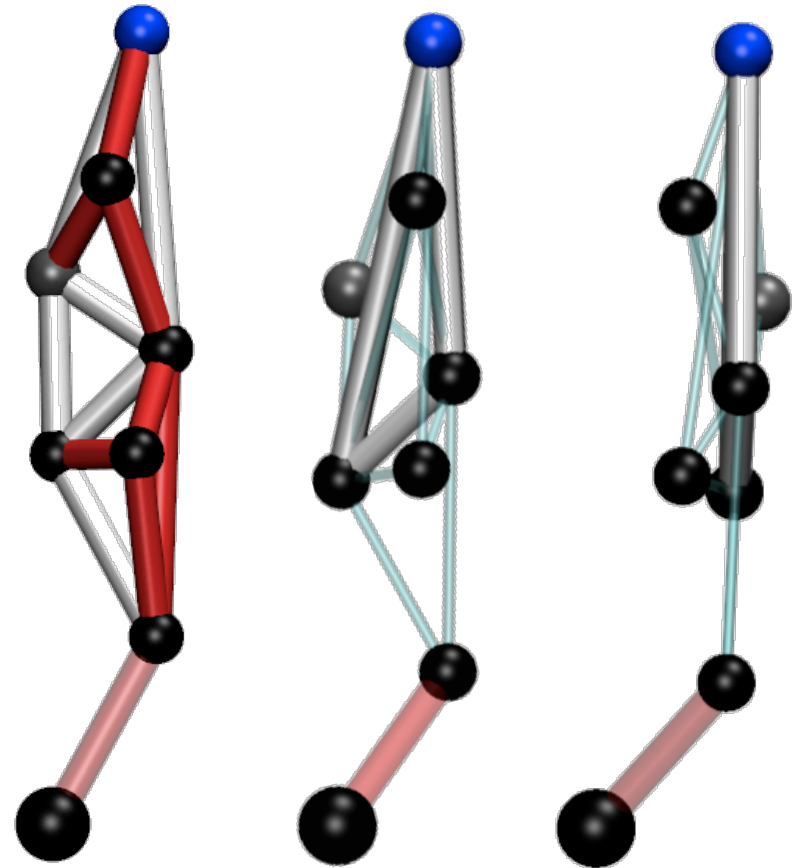


What I did

Chose three atoms for my frame

Obtained the average positions of the remaining four atoms relative to the frame

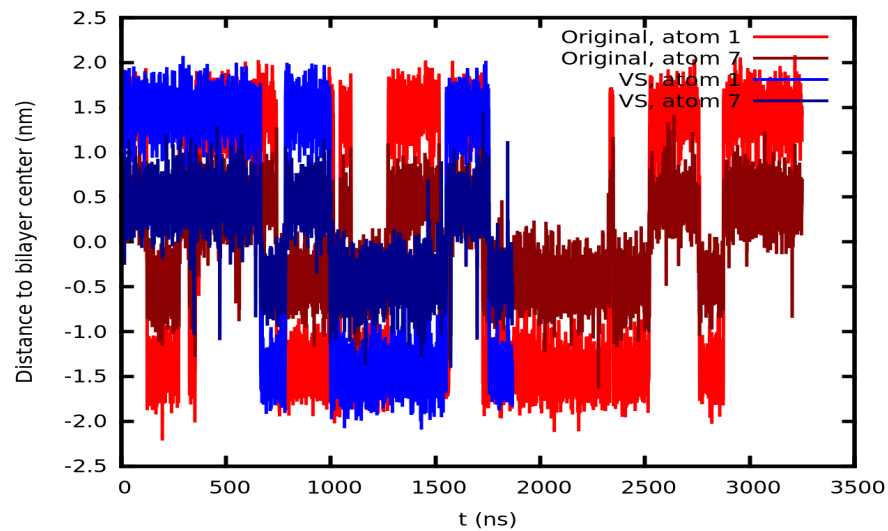
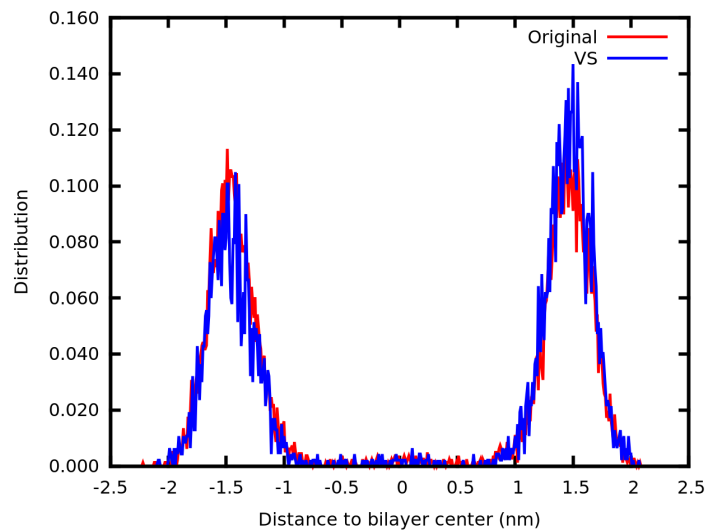
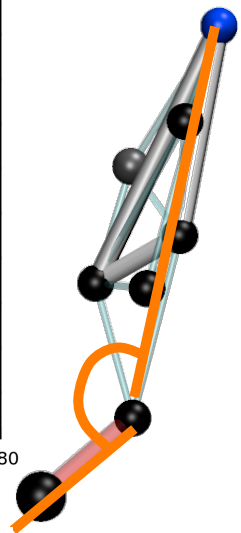
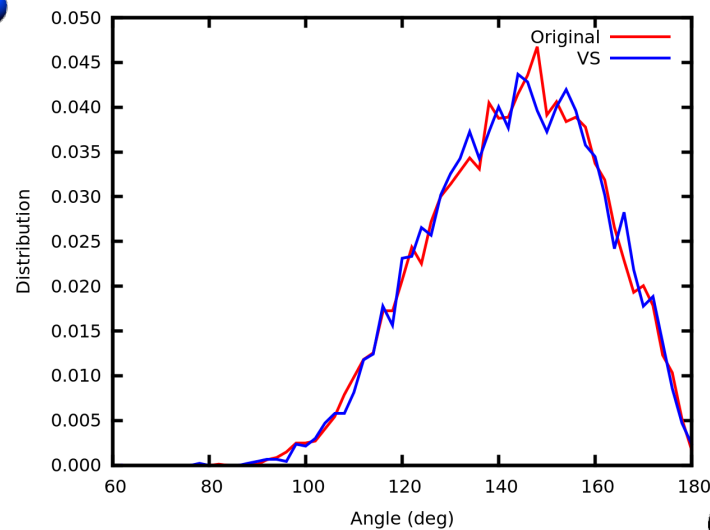
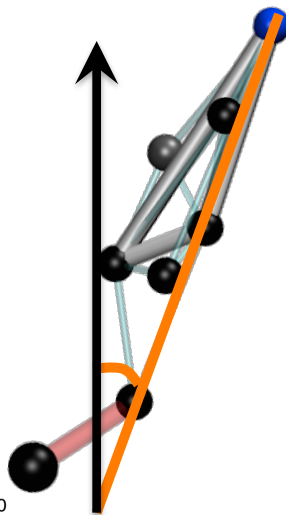
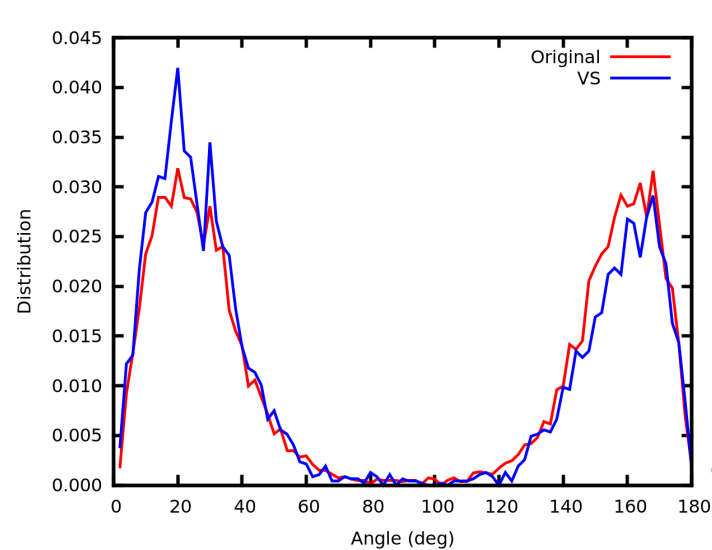
Defined those four atoms as different virtual sites



And it worked!

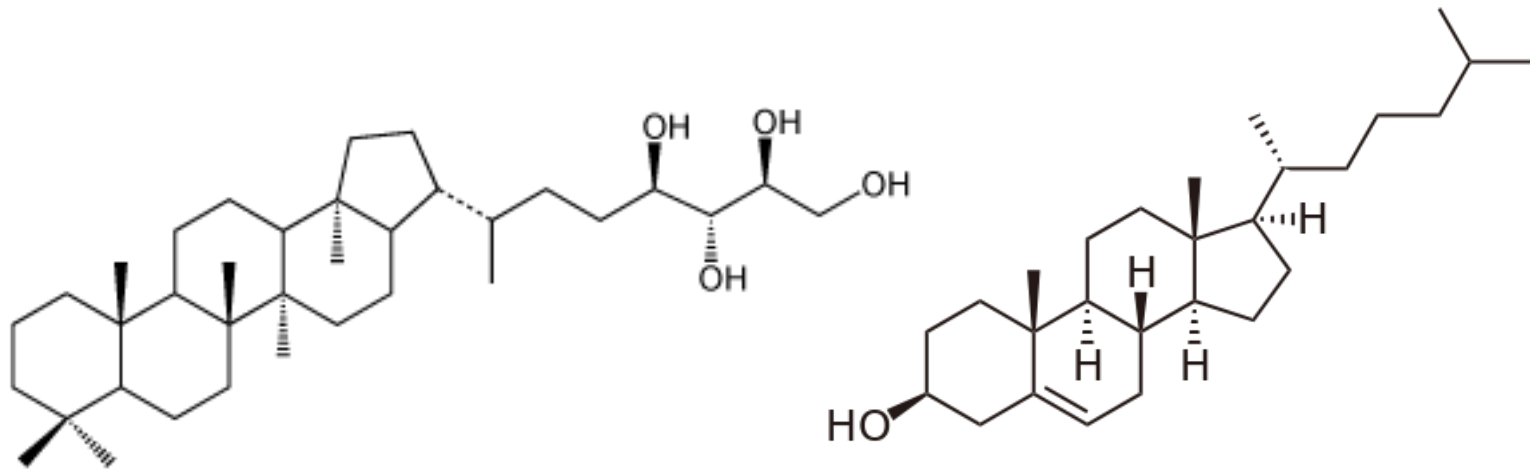
Virtual site version ran stable at 40fs (total 1.6 μ s)

Comparing to a simulation with the original topology ran at 20fs (total 3.5 μ s)



But large systems with many cholesterol
simulated for long times still crashed...

Hopanoids



bacteriohopanetetrol

cholesterol

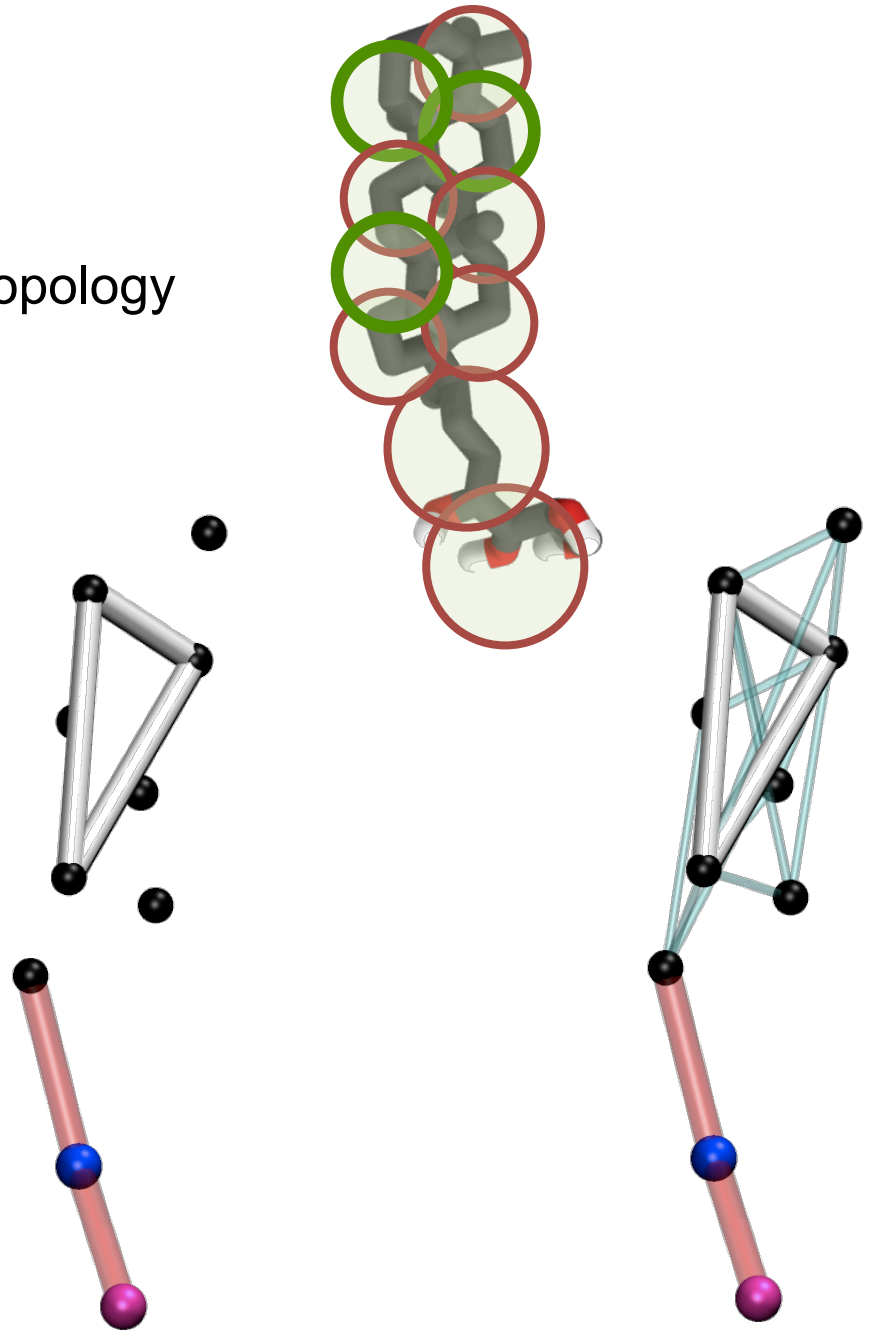
Involved in different kinds of bacterial membrane adaptations

CG parameterization

Started from an existing atomistic topology

Chose a mapping scheme
and a frame for virtual sites

Constructed virtual sites from
the average positions of a
mapped atomistic simulation



Stable?

```
step 6937800, will finish Mon Aug 19 15:15:59 2013imb F 2%
step 6937900, will finish Mon Aug 19 15:15:59 2013imb F 5%
step 6938000, will finish Mon Aug 19 15:15:59 2013imb F 4%
step 6938100, will finish Mon Aug 19 15:15:59 2013imb F 5%
step 6938200, will finish Mon Aug 19 15:15:59 2013imb F 4%
step 6938300, will finish Mon Aug 19 15:15:59 2013imb F 2%
step 6938400, will finish Mon Aug 19 15:15:59 2013imb F 1%
step 6938500, will finish Mon Aug 19 15:15:59 2013imb F 5%
step 6938600, will finish Mon Aug 19 15:15:59 2013imb F 2%
step 6938700, will finish Mon Aug 19 15:15:59 2013imb F 5%
step 6938800, will finish Mon Aug 19 15:15:59 2013imb F 2%
step 6938900, will finish Mon Aug 19 15:15:59 2013imb F 5%
step 6939000, will finish Mon Aug 19 15:15:59 2013imb F 3%
step 6939100, will finish Mon Aug 19 15:15:59 2013imb F 2%
step 6939200, will finish Mon Aug 19 15:15:59 2013
```

A list of missing interactions:

```
      Bond of      2 missing      -1
      Angle of      2 missing      -2
```

Program mdrun, VERSION 4.6.3

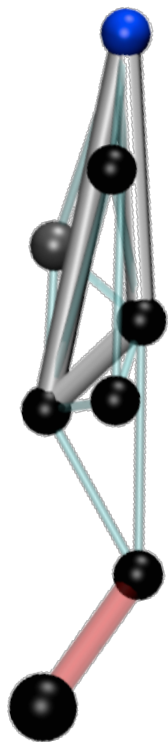
Source code file: /manel/gromacs-4.6.3/src/mdlib/domdec_top.c, line: 389

Software inconsistency error:

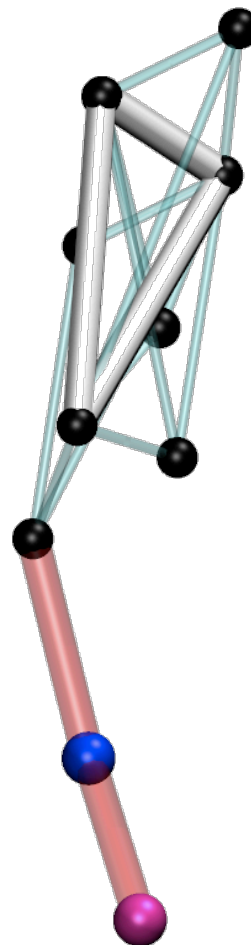
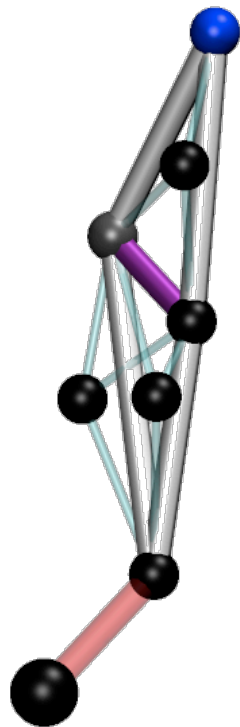
One or more interactions were multiple assigned in the domain decomposition
For more information and tips for troubleshooting, please check the GROMACS
website at <http://www.gromacs.org/Documentation/Errors>

"There's No Room For the Weak" (Joy Division)

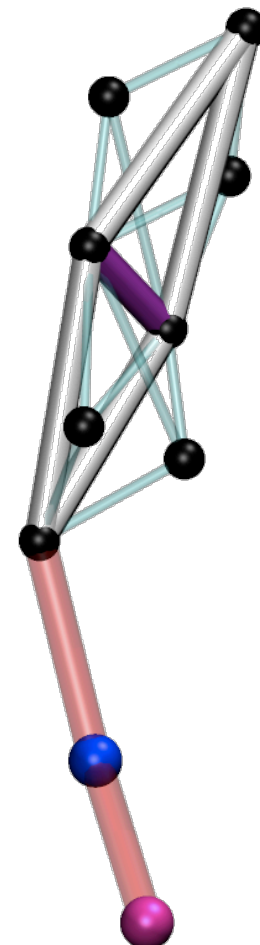
Is the bonded structure too rigid?



cholesterol

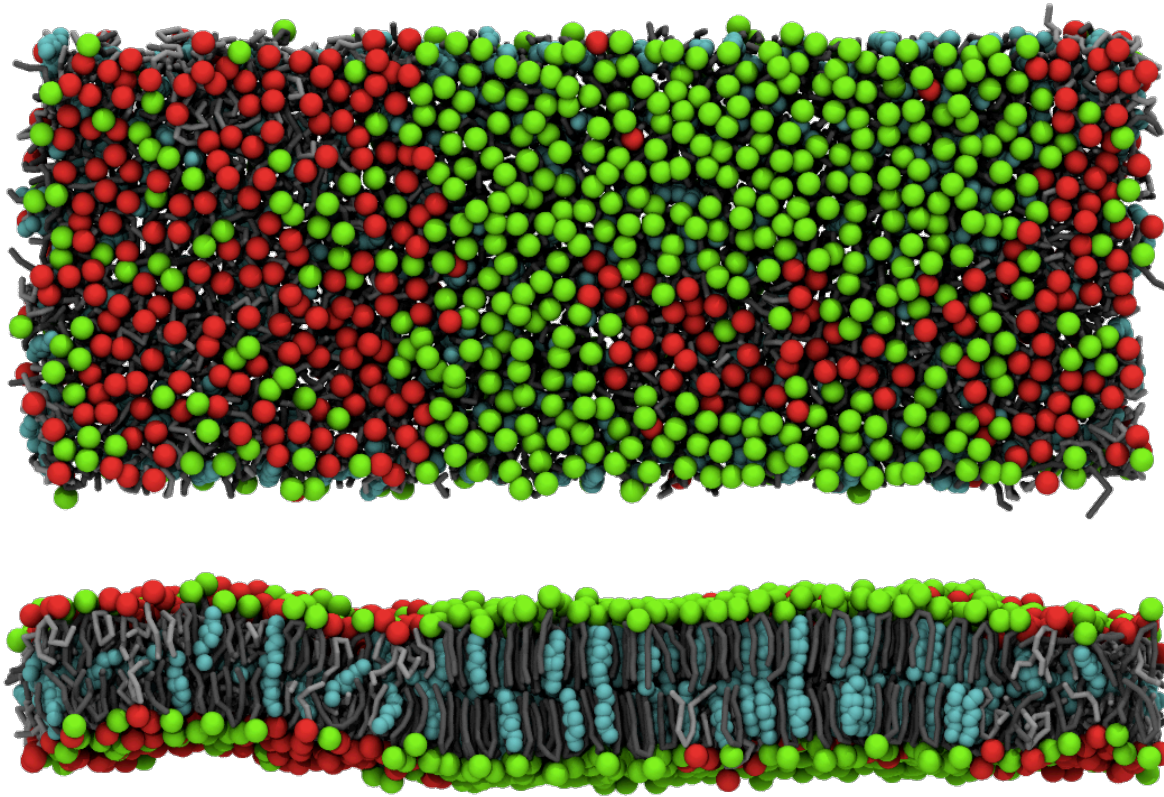


bacteriohopanetetrol



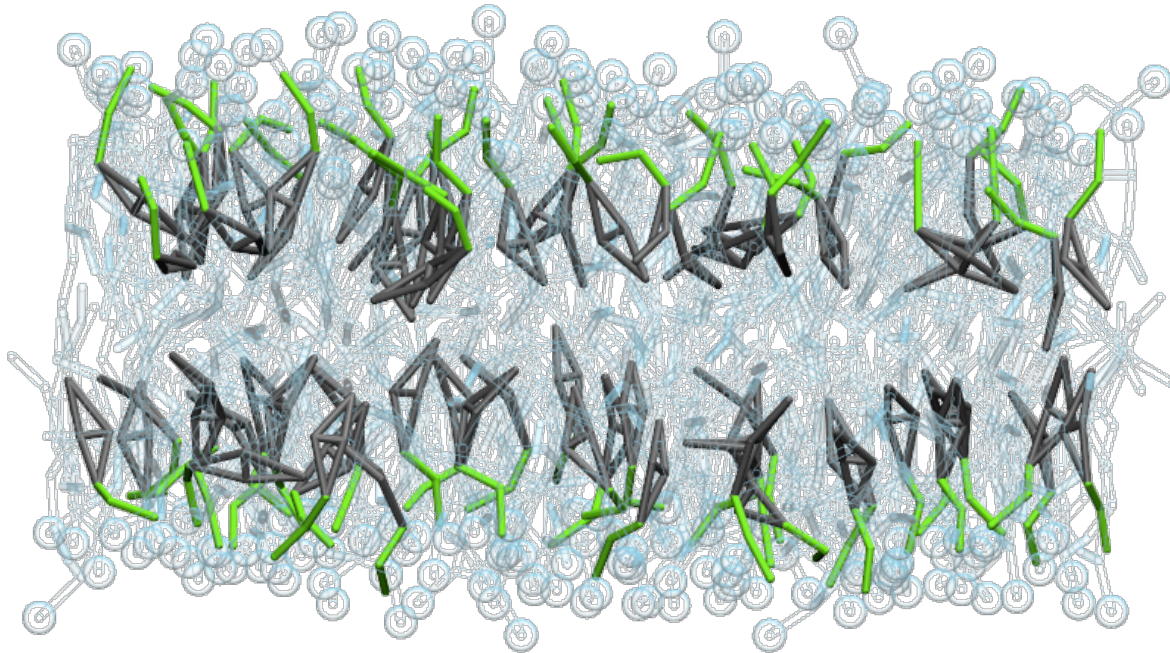
Success!

Cholesterol in bilayer (30 μ s)



Success!

Bacteriohopanetetrol in POPC bilayer
(3 μ s)



3:1 POPC:STEROL