Martini Workshop 2017

“Martini Basics”

Hands on: how to prepare a Martini

“gin and vermouth are combined at a ratio of 2:1,
stirred in a mixing glass with ice cubes,
then strained into a chilled cocktail glass and garnished with an olive”

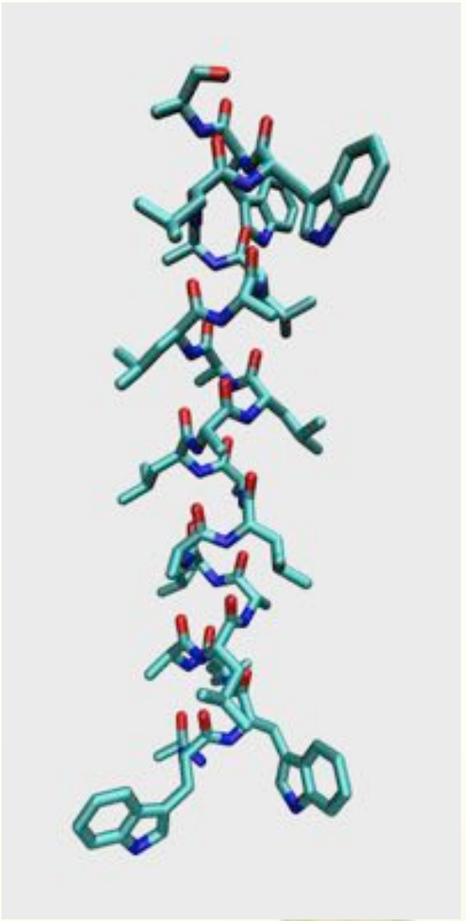
- A **Dry Martini** is made with dry gin and white vermouth
- **Martini Rosso** uses red vermouth (caramel flavor)
- **Vodka Martini** uses vodka instead of gin
- A **Perfect Martini** uses equal amounts of sweet and dry vermouth
- **Zen Martini**: Martini with no gin at all, and no vermouth either

“Martini should be made by filling a glass with gin, then waving it in the general direction of Italy”

Overview of this lecture

How to become a Martini expert in just one week

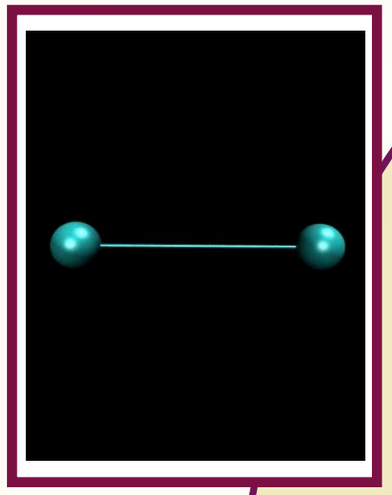
- **Basic modeling principles**
- **Looks of the Martini model**
- **Validation of the Martini model**
- **Limitations of the Martini model**
- ~~**Applications of the Martini model**~~



MARTINI

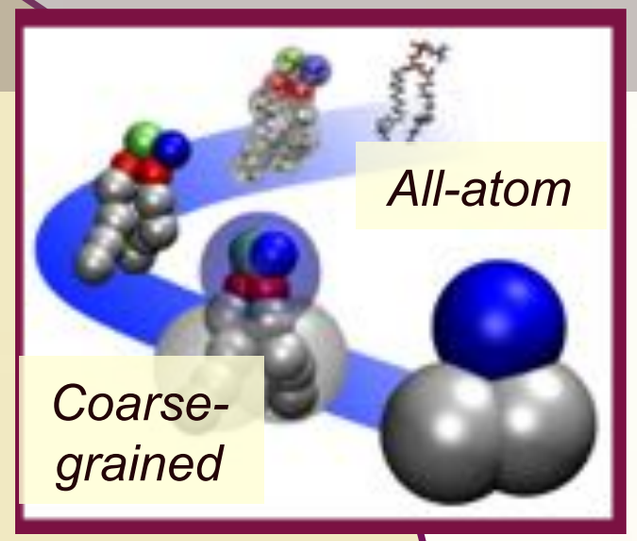
Basic modeling principles

Four essential ingredients



1. Degrees of freedom:

All-atom?
Coarse-grained?
Implicit solvent?



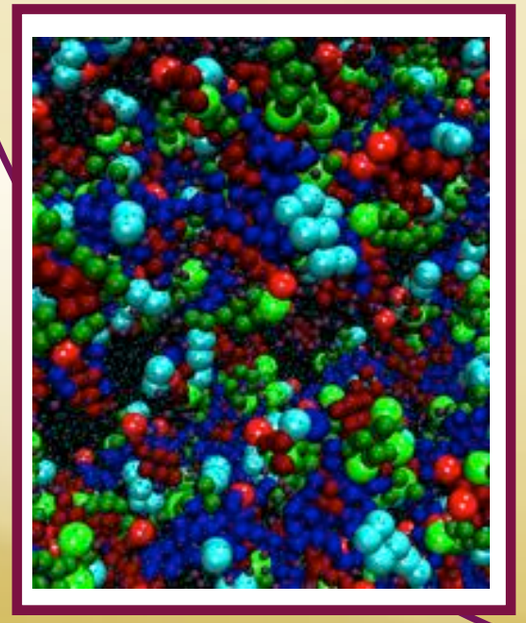
2. Force field:

Bonded,
Electrostatic,
VanderWaals
interactions

Molecular Model

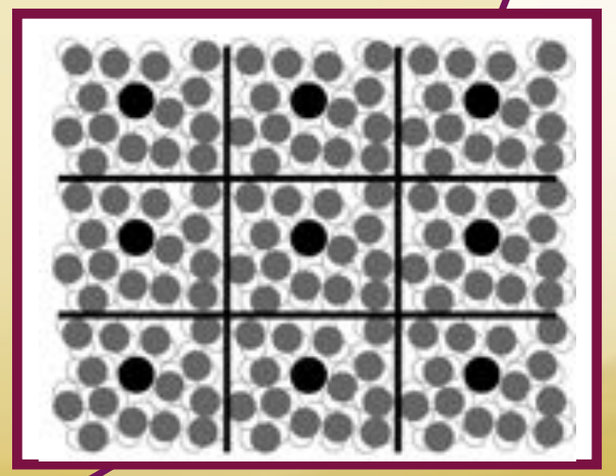
4. Boundary conditions:

Periodic or fixed
Pressure,
Temperature



3. Simulation technique:

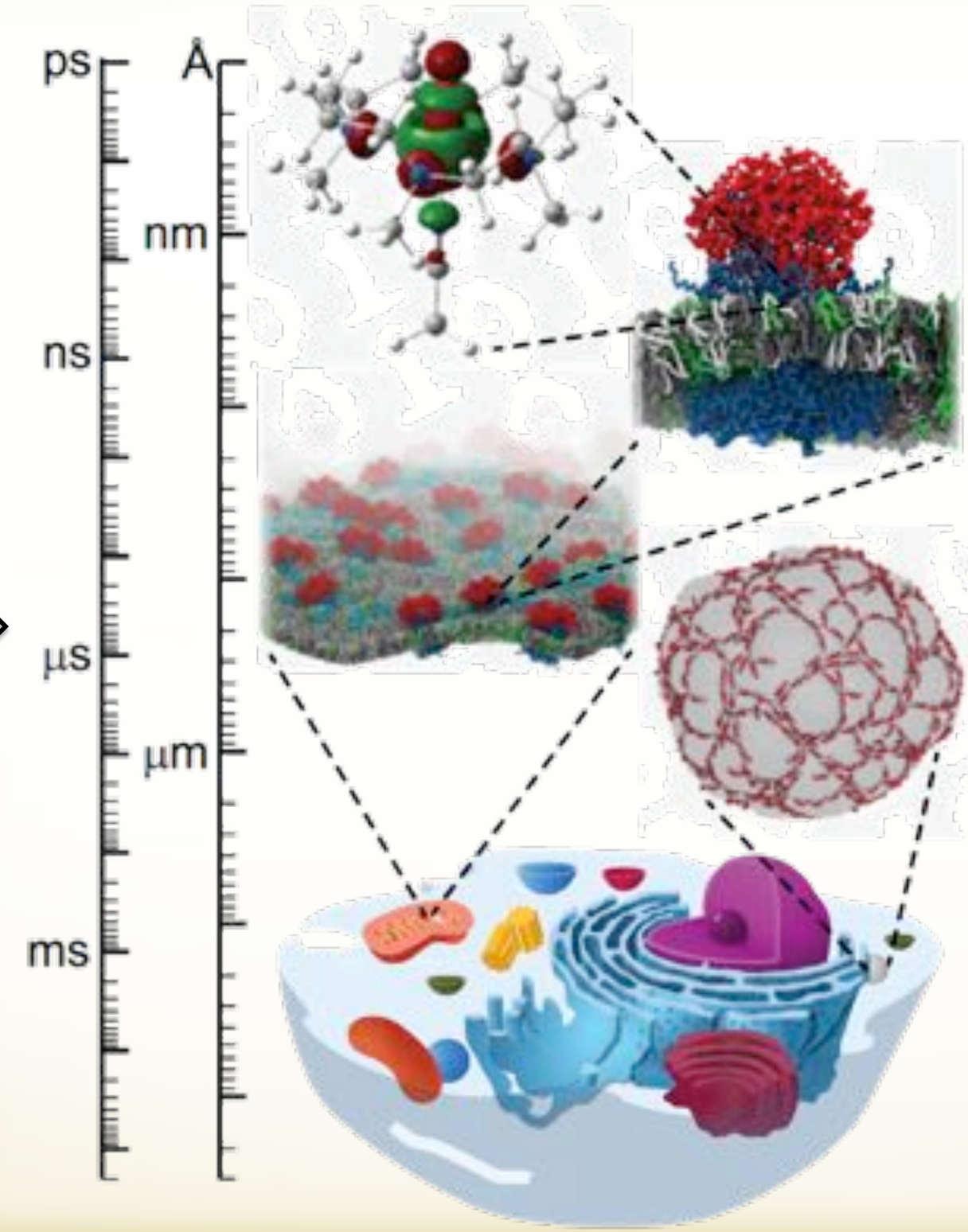
Molecular Dynamics,
Monte-Carlo,
Stochastic Dynamics,
....



Van Gunsteren et al. *Biomolecular modeling: Goals, problems, perspectives.* Angew. Chem. Int. Ed. (2006), 45, 4064.

Basic modeling principles

Coarse-graining: Bridging the all-atom to the continuum scale



Quantum
- atoms, electrons and electron clouds included
- explicit solvent
- quantum mechanics

All-atom
- all or most atoms present
- explicit solvent
- molecular dynamics

Coarse-grained
- beads comprising a few atoms
- explicit or implicit solvent
- molecular dynamics

Supra-coarse-grained
- interaction sites comprising many atoms, protein parts or proteins
- implicit solvent
- stochastic dynamics

Continuum
- materials as a continuous mass
- implicit solvent
- continuum mechanics

Basic modeling principles

Different ways of coarse-graining

HIERARCHICAL COARSE-GRAINING (BOTTOM UP)

- Interactions at less detailed level are the result of the collective interactions at more detailed level
- General method applicable to any system (like an algorithm)

Iterative Boltzmann inversion potentials

Force matching

PRO:
UNBIASED
• Physics follows through the hierarchy of models
• Entirely general approach

CON:
LARGE WORKLOAD
• Need detailed level simulations to derive CG potentials
• Complicated numerical potentials
LIMITED VALIDiTY
• Strictly valid for one state point only (new system, new potentials)

PRAGMATIC COARSE-GRAINING (TOP DOWN)

- Reproduce faithfully certain chosen (experimental) proper
- Developed with certain application area in mind

Go models

Martini model

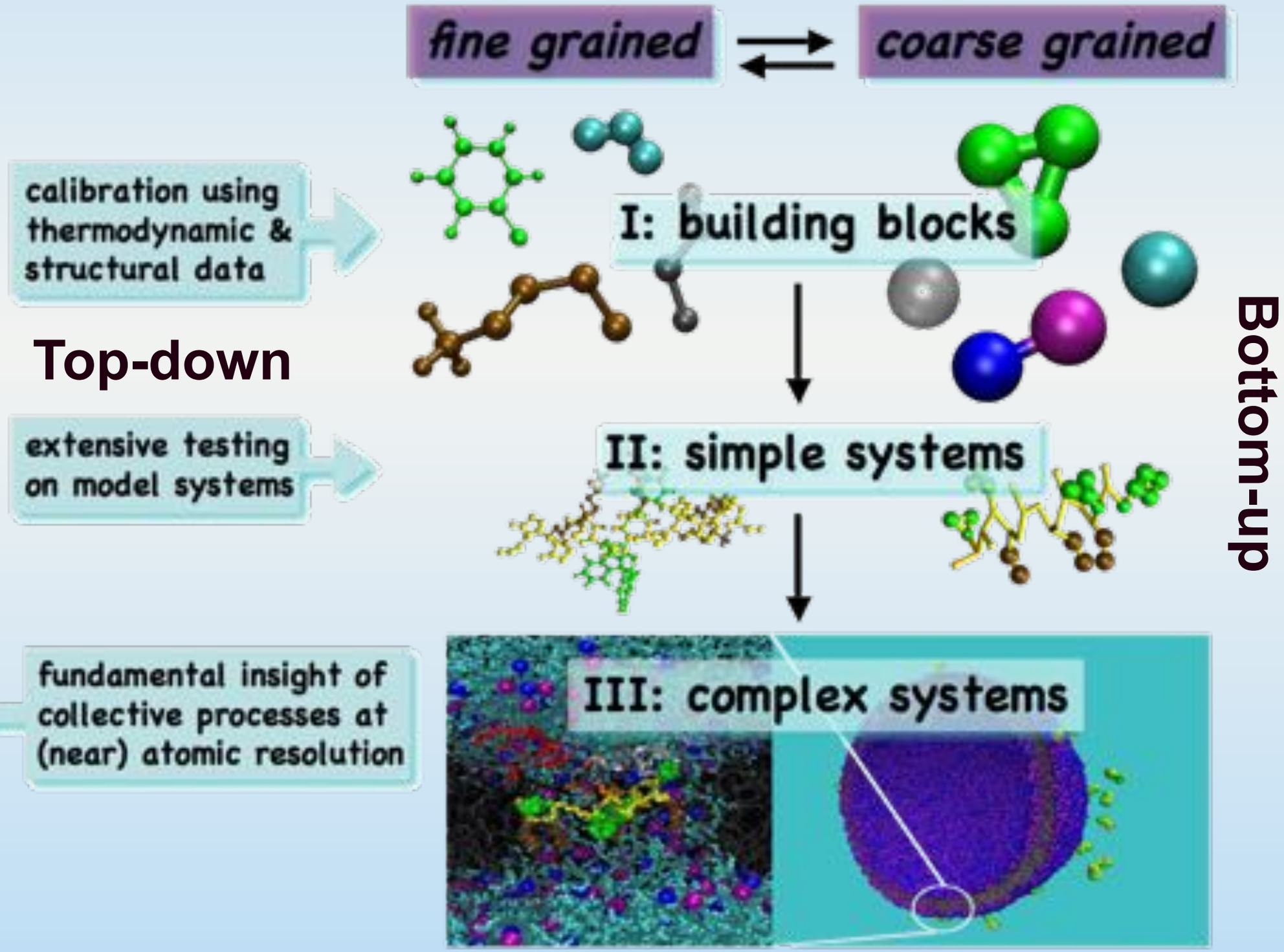
PRO:
CHEAP
• Parameterize on empirical data available
• Simple analytical potentials
• TRANSFERABLE
• After parameterizing building blocks, many similar systems can be treated straightforwardly

CON:
BIASED
• Toward parameterized properties
LIMITED ACCURACY
• Suboptimal representation of underlying detailed resolution

Noid, WG (2013) J. Chem. Phys. 139, 090901; Saunders, MG & Voth, GA (2013). Annu. Rev. Biophy
Ingolfsson HI et al, (2013) WIRES Comput. Sci. 4, 225–248

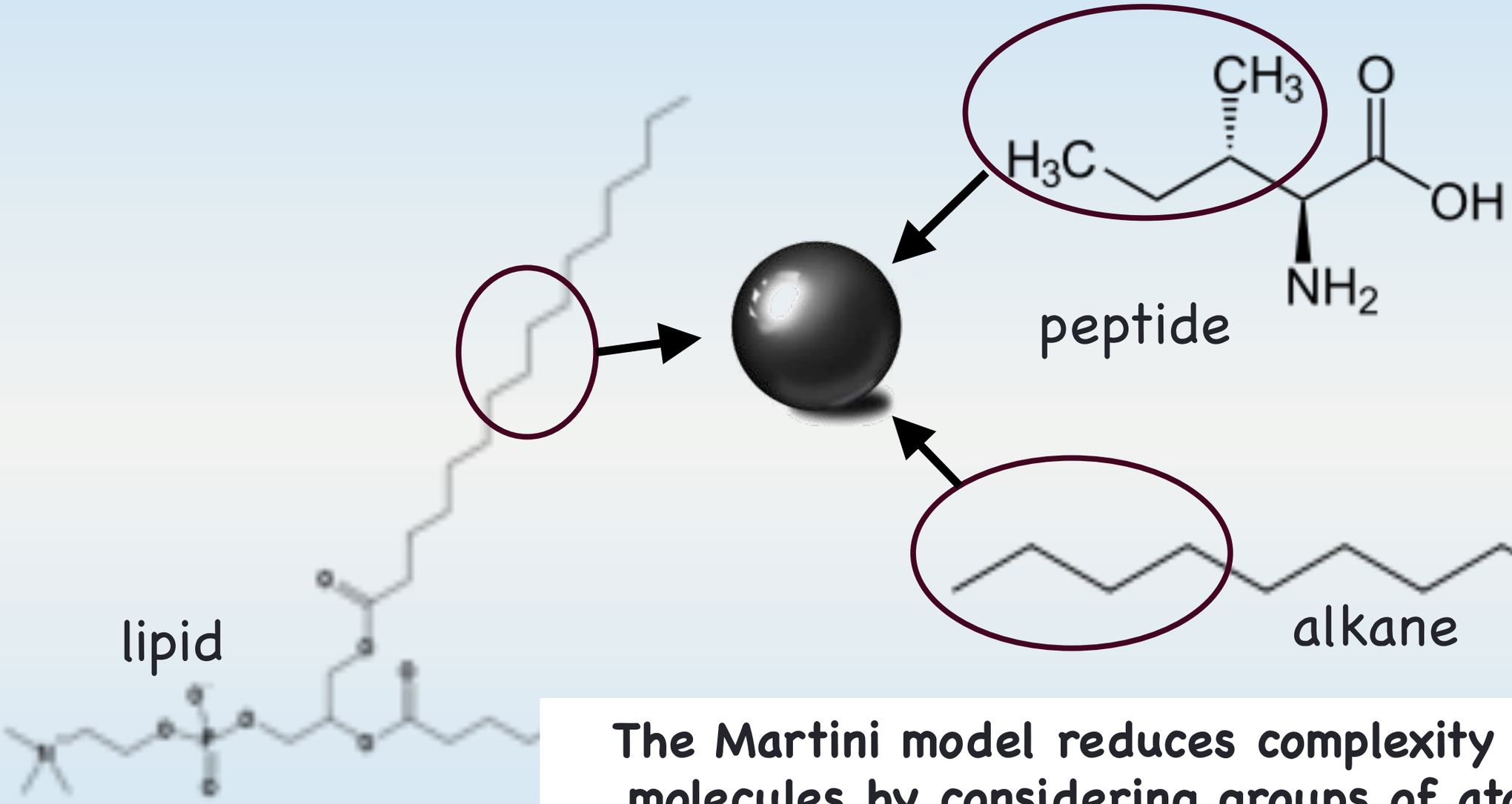
Looks of the Martini model

Systematic parameterization combining top-down and bottom-up approaches



Looks of the Martini model

Mapping of atoms to building blocks



The Martini model reduces complexity of real molecules by considering groups of atoms as building blocks – the "Lego" principle

On average 4 heavy atoms (and associated hydrogens) are considered as building block and mapped to a coarse-grain bead

Looks of the Martini model

The building block principle

Building block types

C1
C2
C3
C4
C5

Apolar

N0
Nd/a
Nda

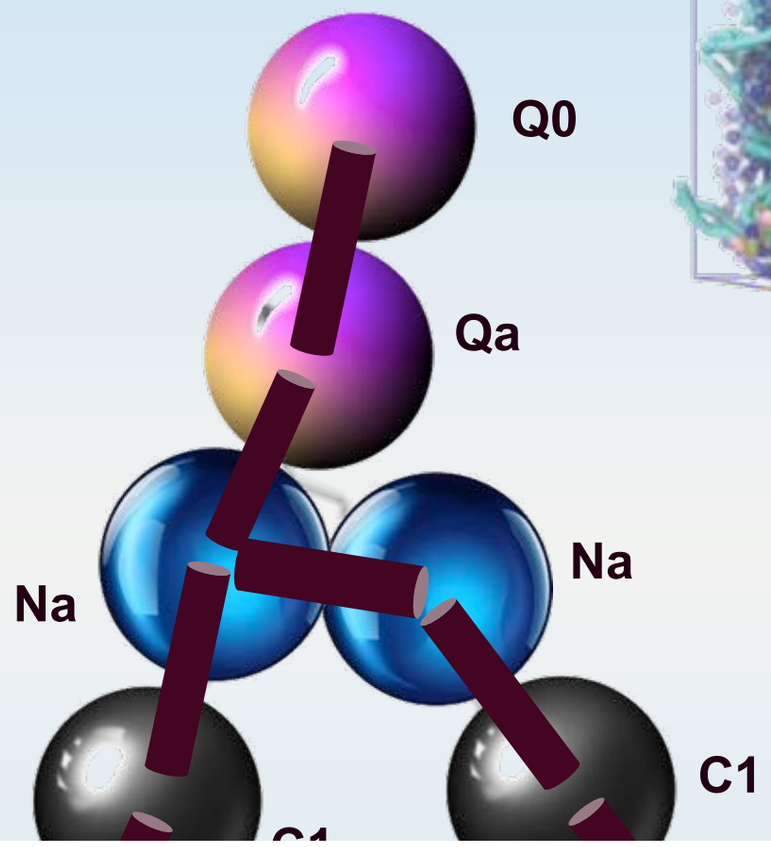
Intermediate

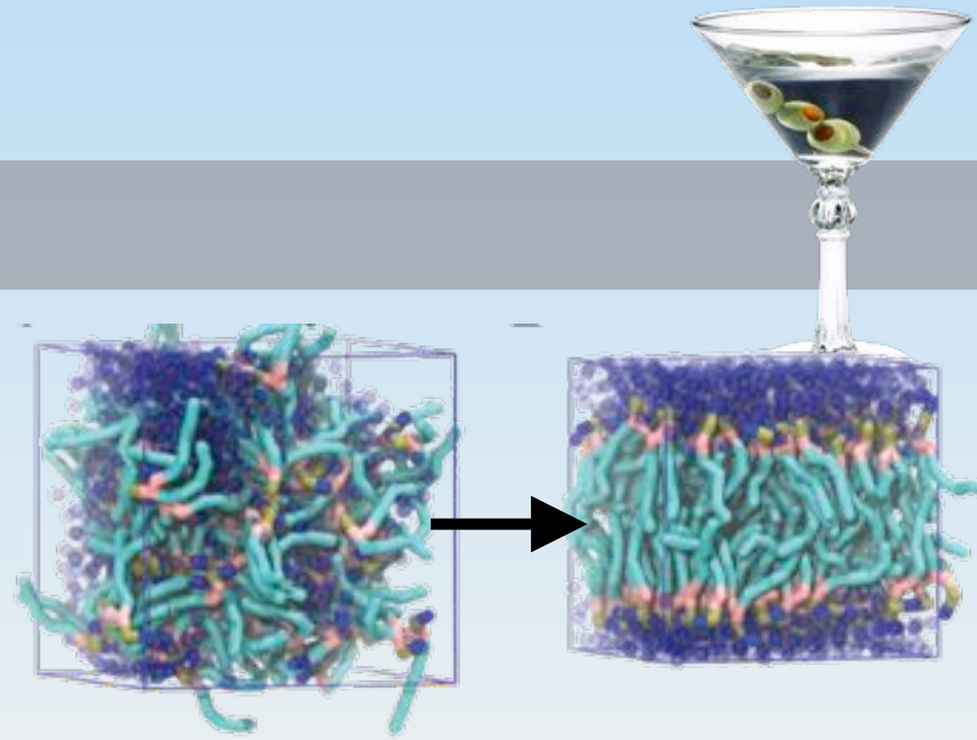
P1
P2
P3
P4
P5

Polar

Q0
Qd/a
Qda

Charged





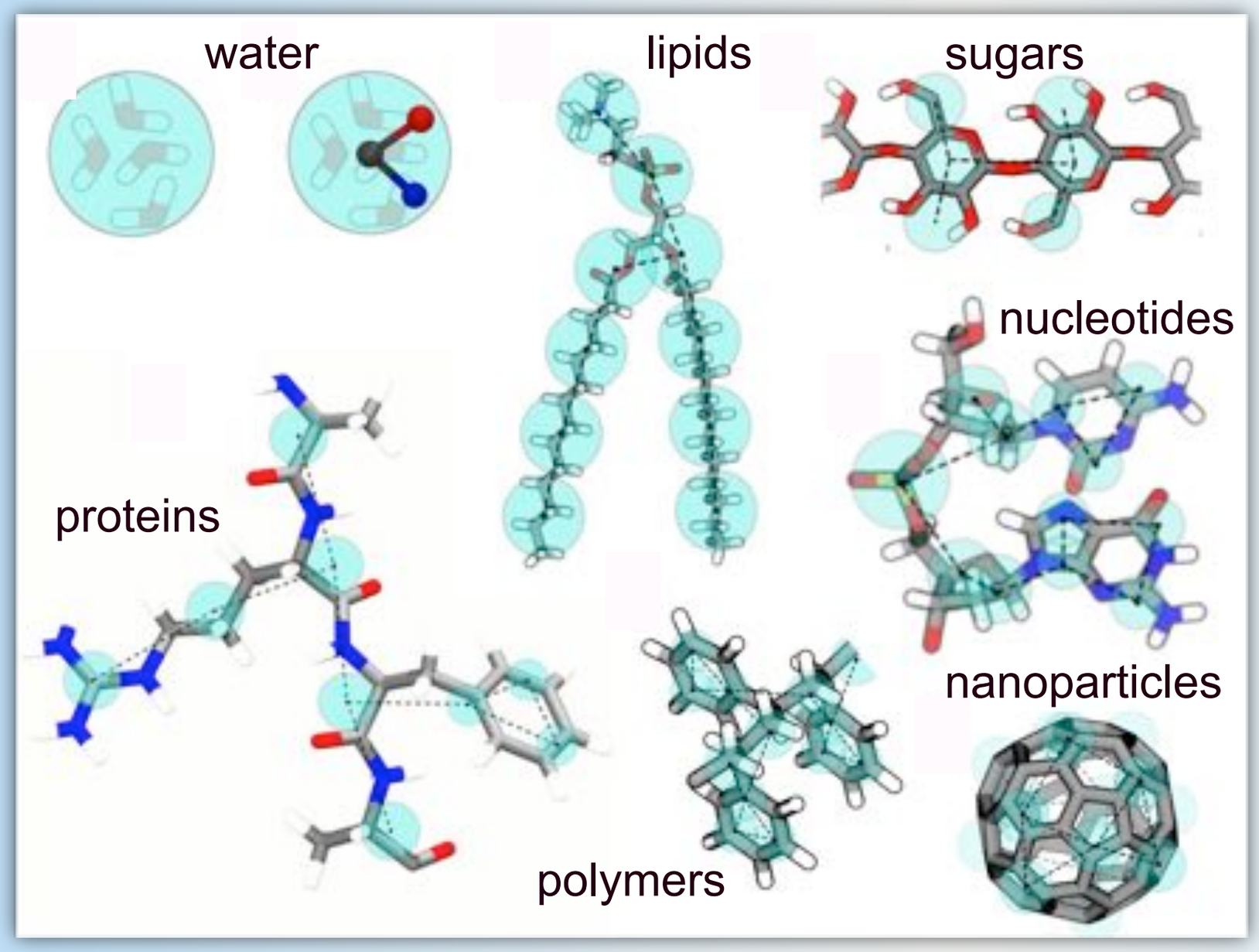
TUTORIAL
Lipids self-assemble into a bilayer, reproducing known membrane properties

Non-bonded interactions of building blocks parameterized based on reproducing experimental thermodynamic data

Bonded interactions parameterized to match conformations of all-atom simulations (or structural databases)

Looks of the Martini model

Welcome to the Martinidome



Key features:

- Chemical specificity
- Fast (10^3 speed-up)
- Compatibility
- Versatility

Parameterization:

TOP DOWN
Thermodynamic data
BOTTOM UP
Atomistic simulations
"TOP UP"

SJ Marrink & DP Tieleman, *Chem. Soc. Rev*. (2013)

Looks of the Martini model

What's in a name?

The Martini force field is developed in Groningen
and named after **Saint Martin**, patron saint of Groningen

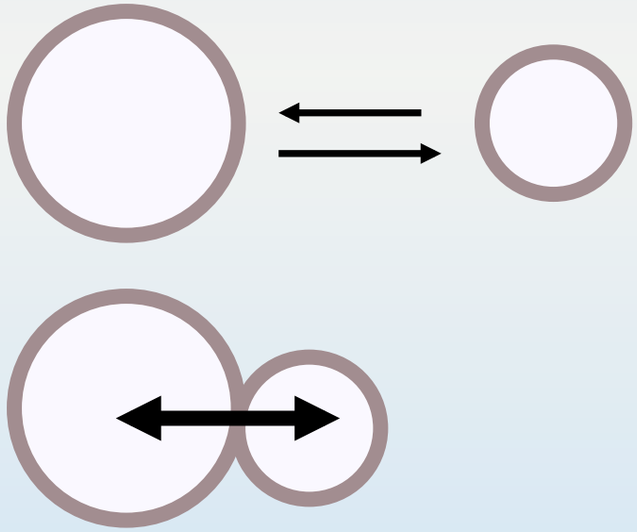
(any association with cocktails is entirely coincidental)

Looks of the Martini model

Non-bonded interactions: LJ & Coulomb

- **Non-bonded interactions** described by standard LJ and Coulombic energy functions

electrostatic — *Coulomb*



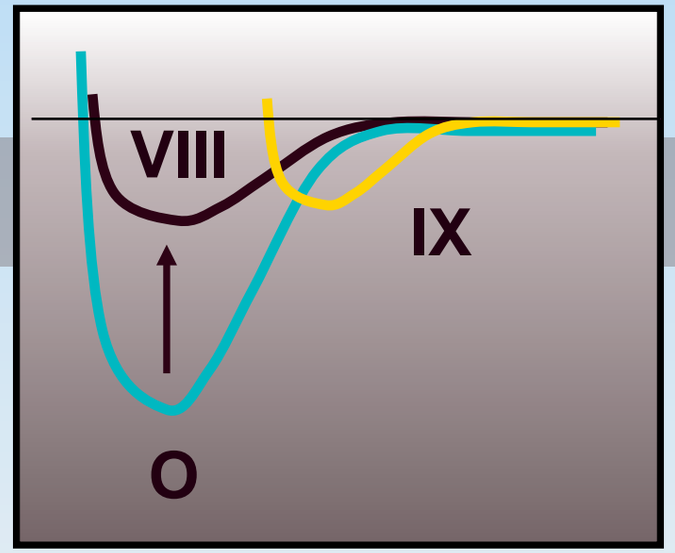
dispersion

overlap

} *Lennard-Jones*

- Potentials are **short-ranged** by use of *cut-off* (1.1 nm, 2-3 neighbors)
- Cut-off artefacts prevented by using potential/force modifiers (so potentials/forces vanish at cut-off)

Looks of the Martini model



LJ interaction matrix for Martini beads

- LJ interactions depend on hydrophilicity of CG bead
  nine levels with 2.0 < ε < 5.6 kJ/mol ; σ = 0.47 nm
  tenth level with ε = 2.0 ; σ = 0.62 nm

- LJ cross interactions explicitly parameterized (*no combination rule!*)

		charged (Q)					polar (P)					intermediate (N)					apolar (C)				
		da	d	a	0	5	4	3	2	1	da	d	a	0	5	4	3	2	1
Q	da	O	O	O	II	O	O	O	I	I	I	I	I	IV	V	VI	VII	IX	IX
	d	O	I	O	II	O	O	O	I	I	I	III	I	IV	V	VI	VII	IX	IX
	a	O	O	I	II	O	O	O	I	I	I	I	III	IV	V	VI	VII	IX	IX
	0	II	II	II	IV	I	O	I	II	III	III	III	III	IV	V	VI	VII	IX	IX
P	5	O	O	O	I	O	O	O	O	O	I	I	I	IV	V	VI	VI	VII	VIII
	4	O	O	O	O	O	I	I	II	II	III	III	III	IV	V	VI	VI	VII	VIII
	3	O	O	O	I	O	I	I	II	II	II	II	II	IV	IV	V	V	VI	VII
	2	I	I	I	II	O	II	II	II	II	II	II	II	III	IV	IV	V	VI	VII
	1	I	I	I	III	O	II	II	II	II	II	II	II	III	IV	IV	IV	V	VI
N	da	I	I	I	III	I	III	II	II	II	II	II	II	IV	IV	V	VI	VI	VI
	d	I	III	I	III	I	III	II	II	II	II	III	II	IV	IV	V	VI	VI	VI
	a	I	I	III	III	I	III	II	II	II	II	II	III	IV	IV	V	VI	VI	VI
	0	IV	IV	IV	IV	IV	IV	IV	III	III	IV	IV	IV	IV	IV	IV	IV	V	VI
C	5	V	V	V	V	V	V	IV	IV	IV	IV	IV	IV	IV	IV	IV	IV	V	V
	4	VI	VI	VI	VI	VI	VI	V	IV	IV	V	V	V	IV	IV	IV	IV	V	V
	3	VII	VII	VII	VII	VI	VI	V	V	IV	VI	VI	VI	IV	IV	IV	IV	IV	IV
	2	IX	IX	IX	IX	VII	VII	VI	VI	V	VI	VI	VI	V	V	V	IV	IV	IV
	1	IX	IX	IX	IX	VIII	VIII	VII	VII	VI	VI	VI	VI	VI	V	V	IV	IV	IV

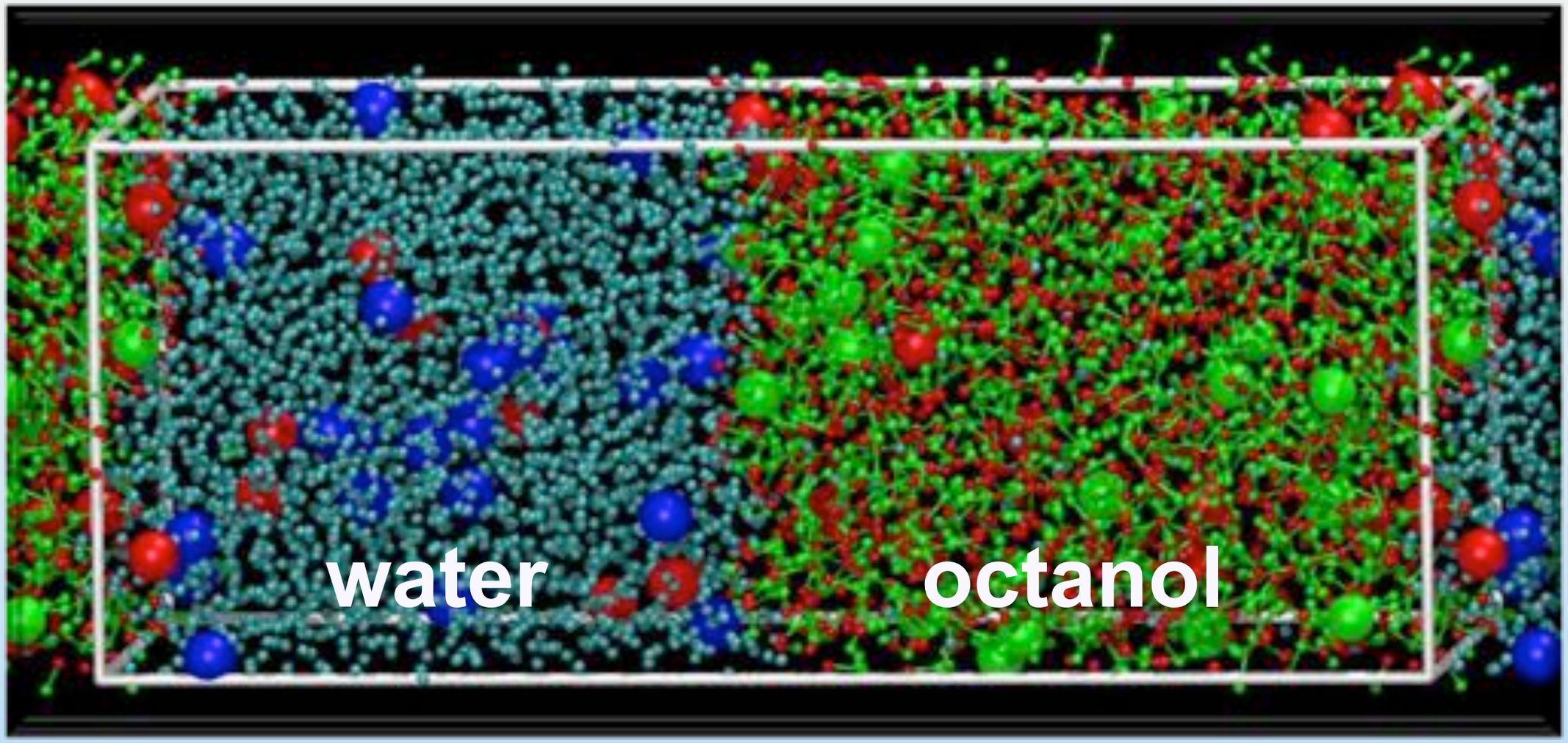
Looks of the Martini model

Top-down: reproducing experimental partitioning data

- LJ interactions are mainly parameterized based on reproducing experimental partitioning free energies

- Free energies obtained from direct counting

Polar (P) **Intermediate (N)** **Apolar (C)**



Looks of the Martini model

The Martini bible: mapping CG bead types to chemical buildin

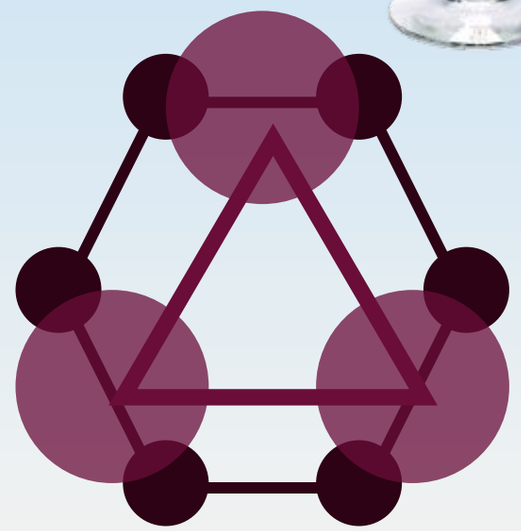
type	building block	examples	$\Delta G^{hex}_{ir/w}$ exp	$\Delta G^{hex}_{ir/w}$ CG	$\Delta G^{hex}_{c/w}$ exp	$\Delta G^{hex}_{c/w}$ CG	$\Delta G^{oct}_{c/w}$ exp	$\Delta G^{oct}_{c/w}$ CG	$\Delta G^{oct}_{o/w}$ exp	$\Delta G^{oct}_{o/w}$ CG
Q_{da}	$H_3N^+-C_2-OH$	ethanolamine (protonated)		≤ -30		-18		-13		-18
Q_d	$H_3N^+-C_3$	1-propylamine (protonated)		≤ -30		-18		-13		-18
	NA^+OH	sodium (hydrated)		≤ -30		-18		-13		-18
Q_a	PO_4^-	phosphate		≤ -30		-18		-13		-18
	CL^-HO	chloride (hydrated)		≤ -30		-18		-13		-18
Q_0	C_5N^+	choline		≤ -30		-18		-13		-18
P_5	$H_2N-C_2=O$	acetamide	-27	-28	(-20)	-18	-15	-13	-8	-10
P_4	HOH ($\times 4$)	water	-25	-23		-14	-10	-7	-8	-9
	$HO-C_2-OH$	ethanediol	-21	-23		-14		-7	-8	-9
P_3	$HO-C_2=O$	acetic acid	-19	-21	-9	-10	-2	-6	-1	-7
	$C-NH-C=O$	methylformamide		-21		-10		-6	-5	-7
P_2	C_2-OH	ethanol	-13	-17	-5	-2	-3	1	-2	-2
P_1	C_3-OH	1-propanol	-9	-11	-2	-2	0	1	1	-1
		2-propanol	-10	-11	-2	-2	-1	1	0	-1
N_{da}	C_4-OH	1-butanol	-5	-7	2	0	4	2	4	3
N_d	H_2N-C_3	1-propylamine	(-6)	-7	(1)	0	(-3)	2	(3)	3
N_a	$C_3=O$	2-propanone	-6	-7	1	0	-1	2	-1	3
	$C-NO_2$	nitromethane	-6	-7		0		2	-2	3
	$C_2=N$	propionitrile	-5	-7		0		2	1	3
	$C-O-C=O$	methylformate	(-6)	-7	(4)	0	(-1)	2	(0)	3
	$C_2HC=O$	propanal	-4	-7		0	2	2	3	3
N_0	$C-O-C_2$	methoxyethane	(1)	-2		6	(3)	6	(3)	5
C_5	C_3-SH	1-propanethiol		5		10		10		6
	$C-S-C_2$	methyl ethyl sulfide	(7)	5		10		10	(9)	6
C_4	$C_2=C_2$	2-butyne		9		13		13	9	9
	$C=C-C=C$	1,3-butadiene	11	9		13		13	11	9
	$C-X_4$	chloroform	(7)	9	14	13		13	11	9
C_3	$C_2=C_2$	2-butene		13		13		13	13	14
	C_3-X	1-chloropropane	12	13		13		13	12	14
		2-bromopropane		13		13		13	12	14
C_2	C_3	propane		16		15		14	14	16
C_1	C_4	butane	18	18		18		14	16	17
		isopropane		18		18		14	16	17

	EXP	CG
P_5	-27	-28
P_4	-25	-23
	-21	-23
P_3	-19	-21
		-21
P_2	-13	-17
P_1	-9	-11
	-10	-11
N_{da}	-5	-7
N_d	(-6)	-7
N_a	-6	-7
	-6	-7
	-5	-7
	(-6)	-7
	-4	-7
N_0	(1)	-2
C_5		5
	(7)	5
C_4		9
	11	9
	(7)	9
C_3		13
	12	13
		13
C_2		16
C_1	18	18
		18

Looks of the Martini model

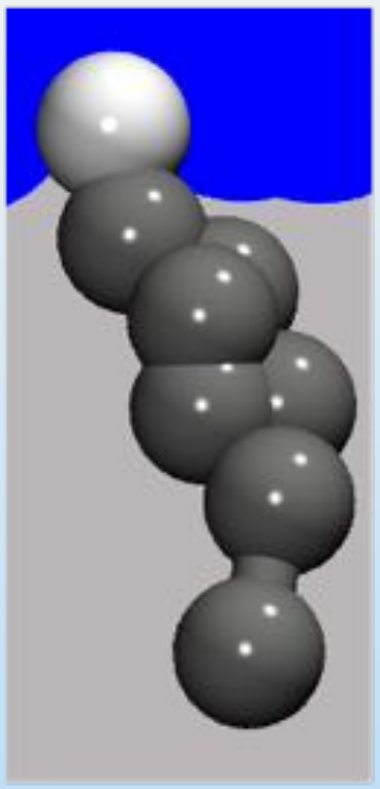
Lord of the rings

Rings: Four-to-one mapping inadequate



- Two/three-to-one mapping
- Reduction of interaction size and strength

$$\sigma = 0.7 * \sigma_{standard}$$
$$\varepsilon = 0.75 * \varepsilon_{standard}$$



- Densities & partitioning free energies for benzene and cyclohexane reproduced
- Condensing behavior of cholesterol in membranes similar to all-atom results

Looks of the Martini model

Implicit screening of Coulomb potentials

- CG beads that represent charged groups interact through standard Coulomb potential

E.g. ions, charged amino acids, ...

- Relative dielectric constant = 15 for implicit screening

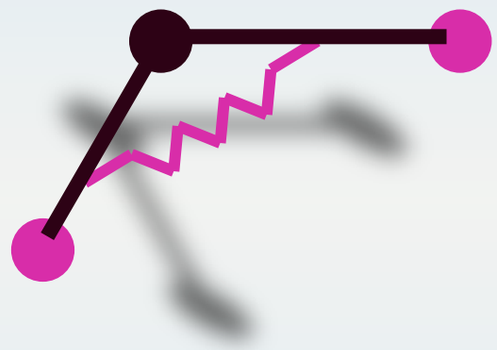
Effectively distant-dependent due to cutoff at 1.1 nm in combination with a Reaction Field approach

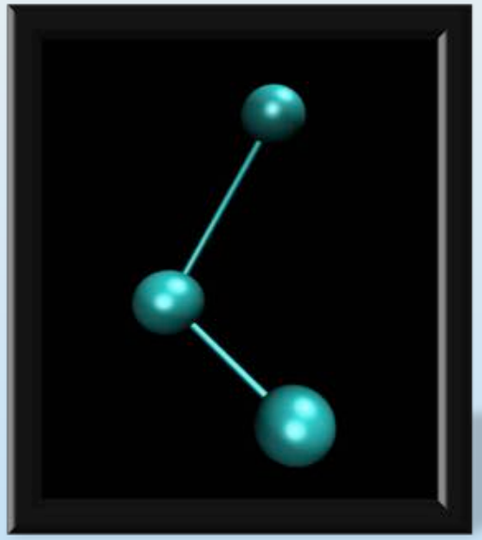
Looks of the Martini model

Simple harmonic forms for bonded interactions

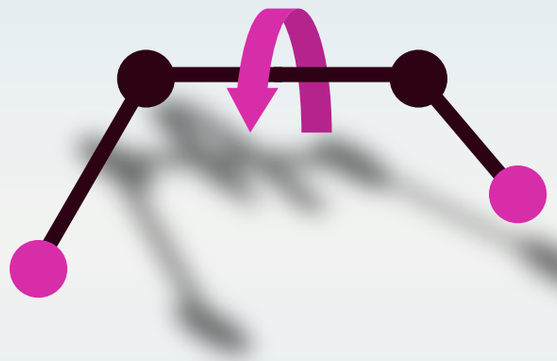
Bonds

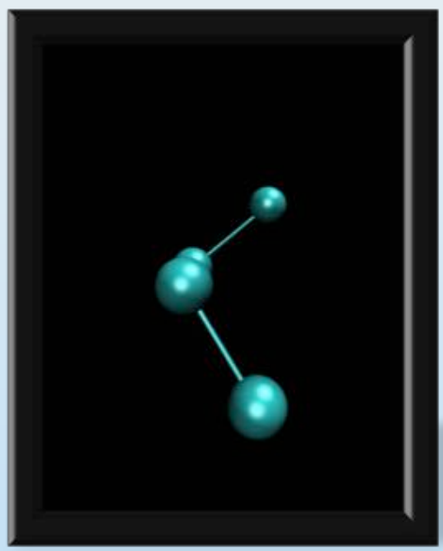
Angles





Dihedrals

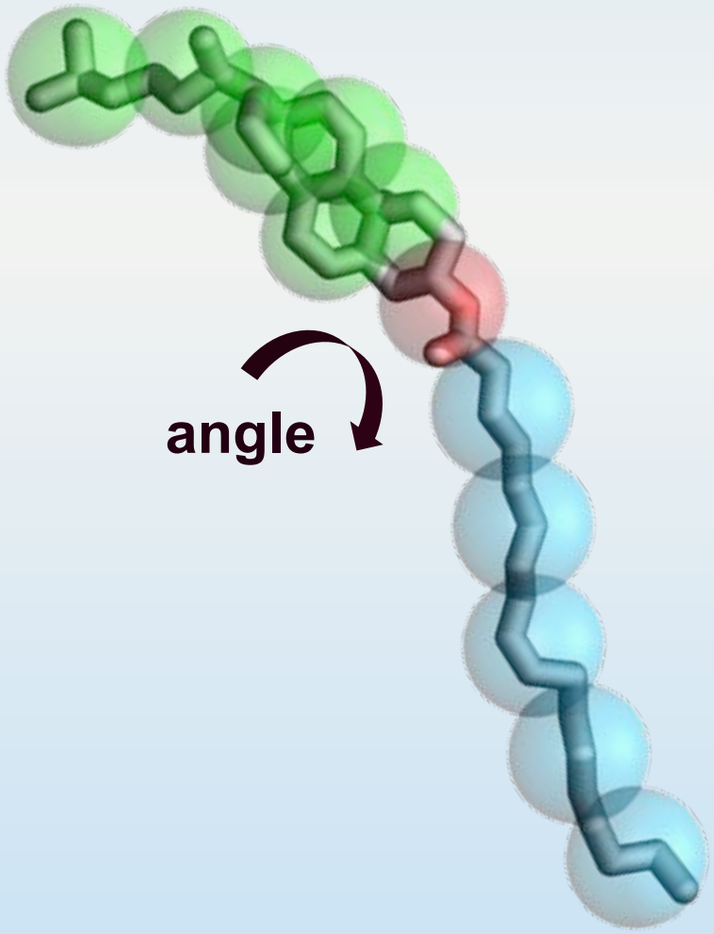


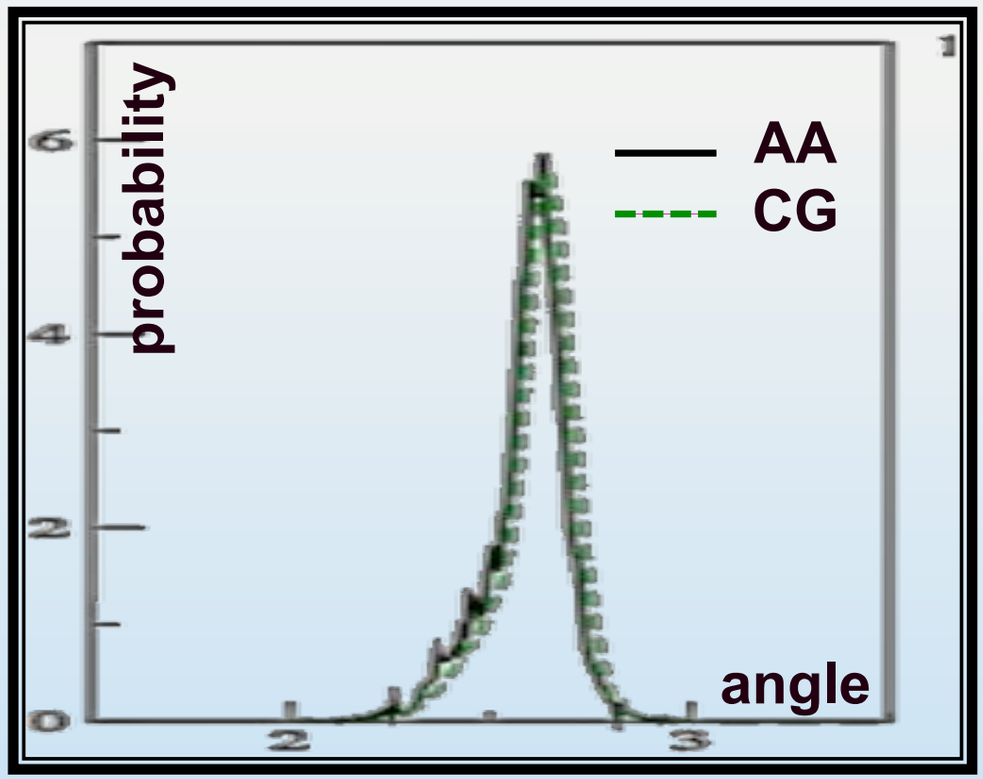


Looks of the Martini model

Bottom-up approach for bonded interactions

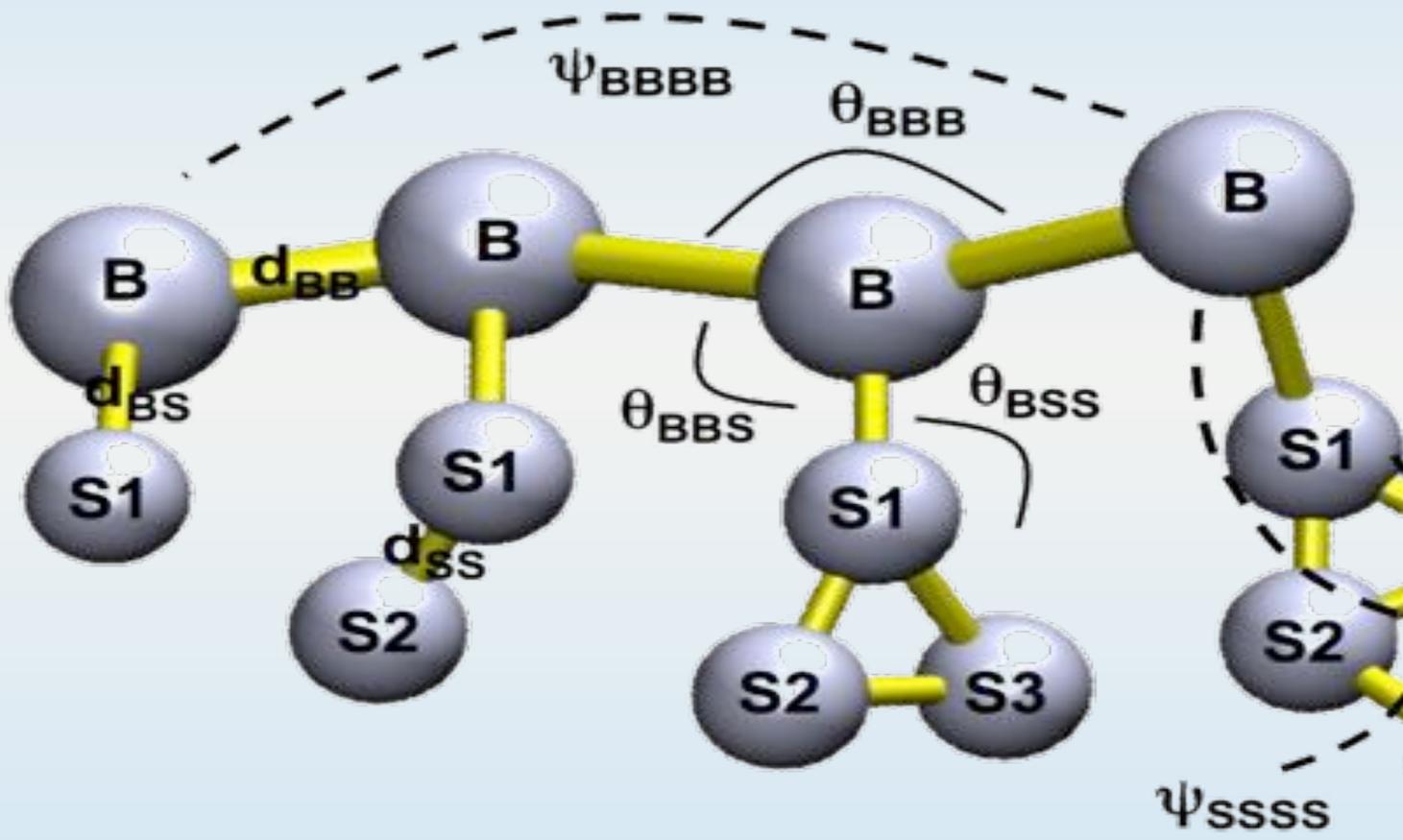
- **Bonded interactions** are parameterized by mapping to all-atom simulations

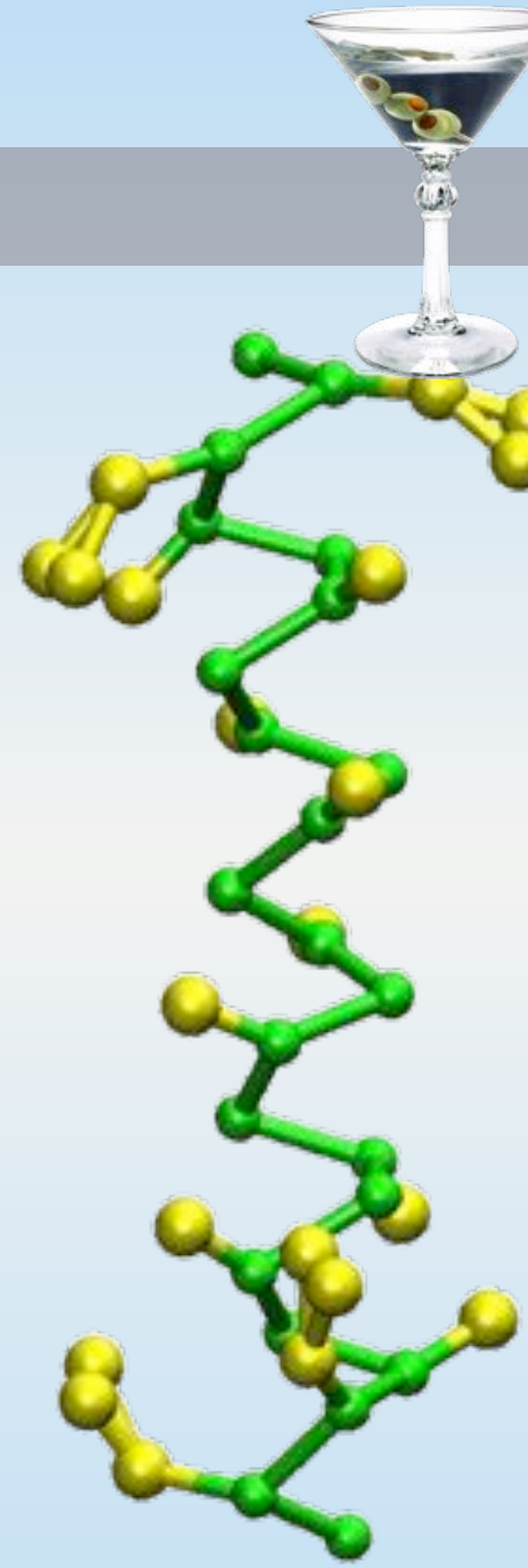




Looks of the Martini model

Bonded potentials provide peptides with 2ndary structure

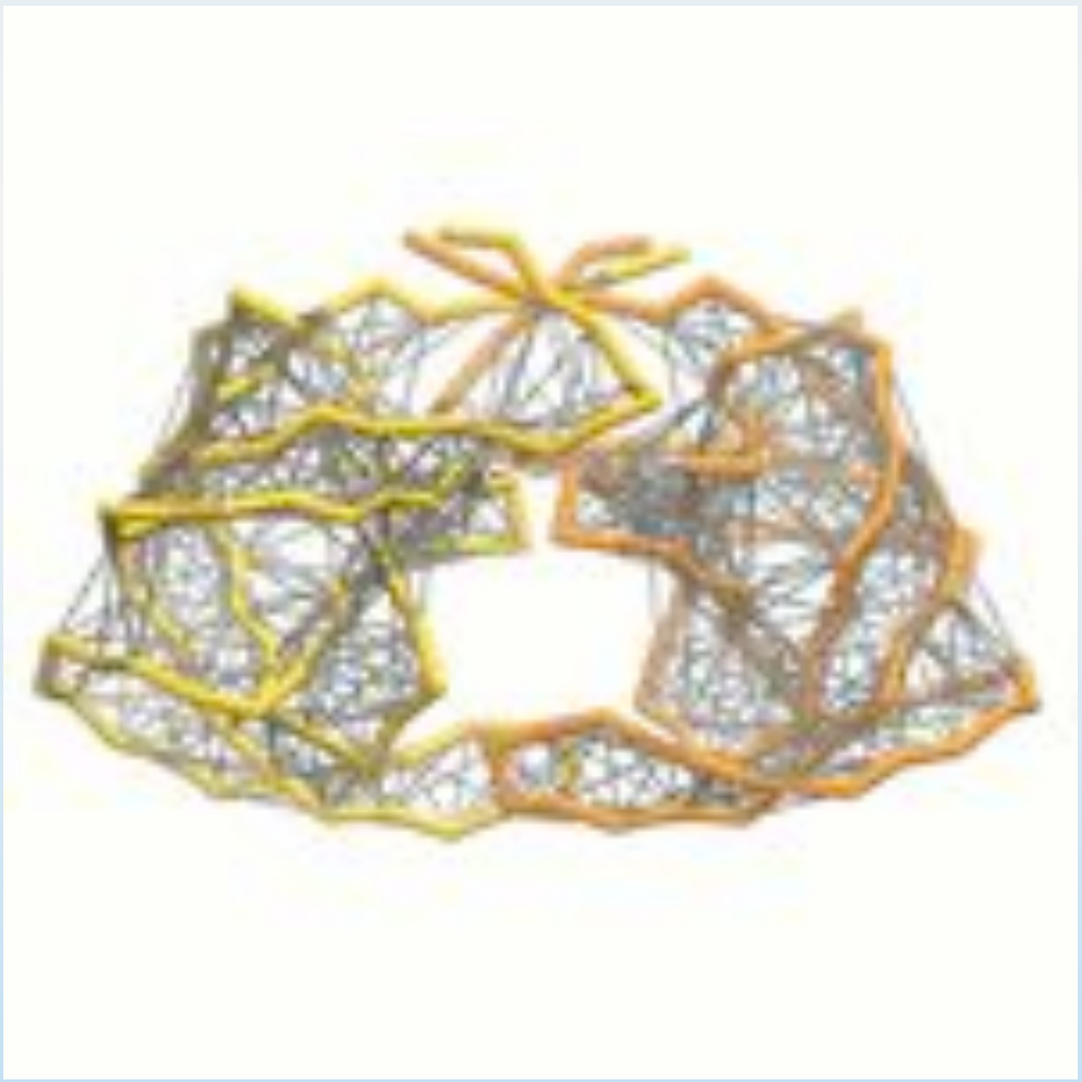




Looks of the Martini model

Proteins require elastic network

- **Elastic network approach (ElNeDyn)** required to maintain 2ndary structure of proteins (Directional H-bonds are missing in Martini !)



ElNeDyn:

Harmonic potentials between

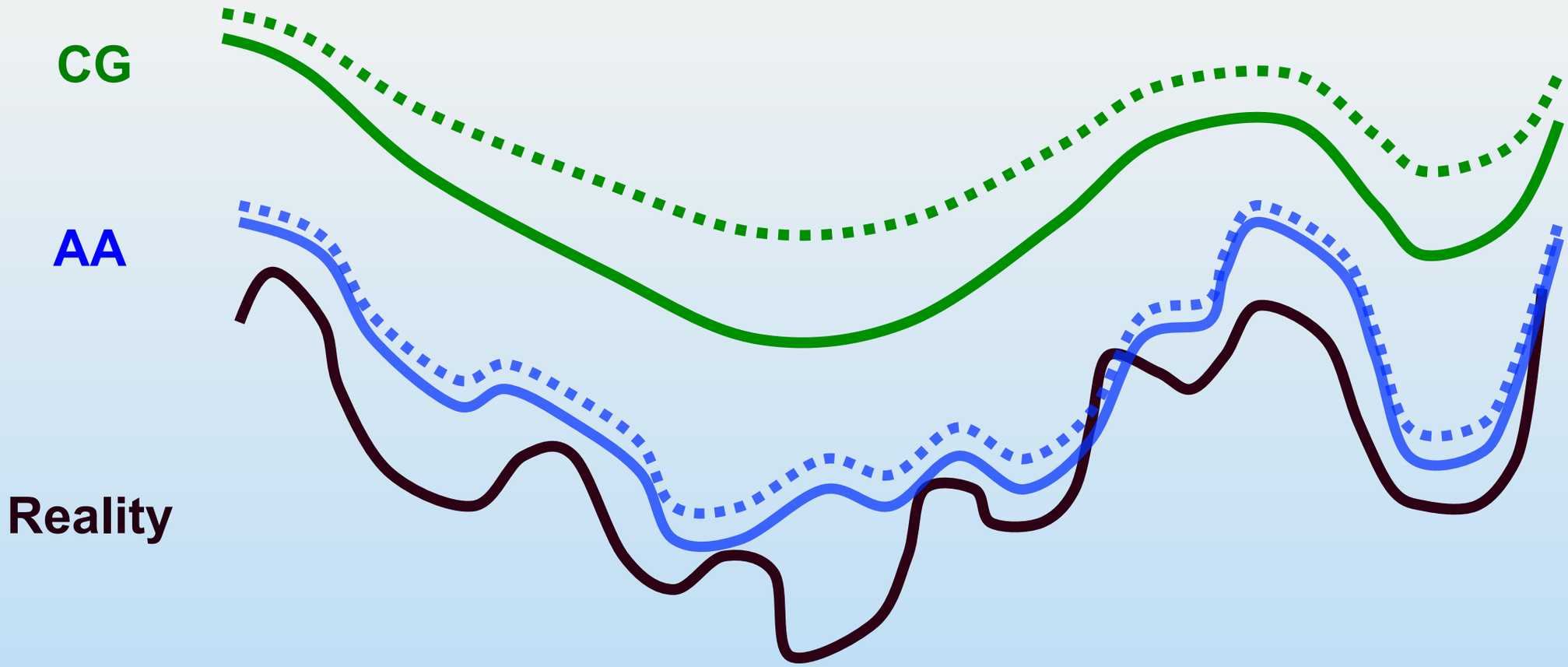
all Cα beads within a cut-off

Looks of the Martini model

Why is Martini so fast (1000 x speedup)

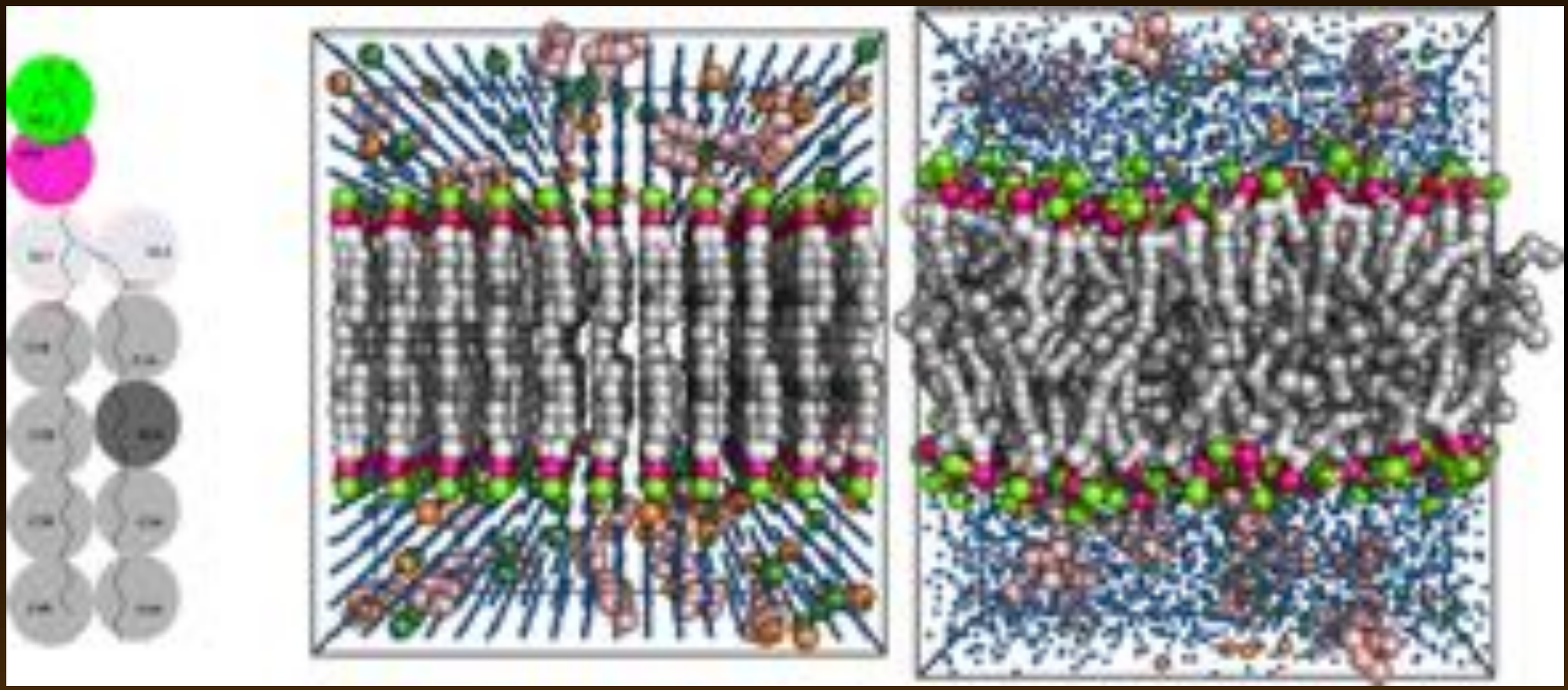
- **Less particles, so less interactions to compute**
- **Short range potentials only**
- **Less friction, so faster sampling**
- **Time steps of 20-30 fs can be used**

(accurate sampling is less critical)



Martini tools

INSANE: membrane packing tool



Martini tools

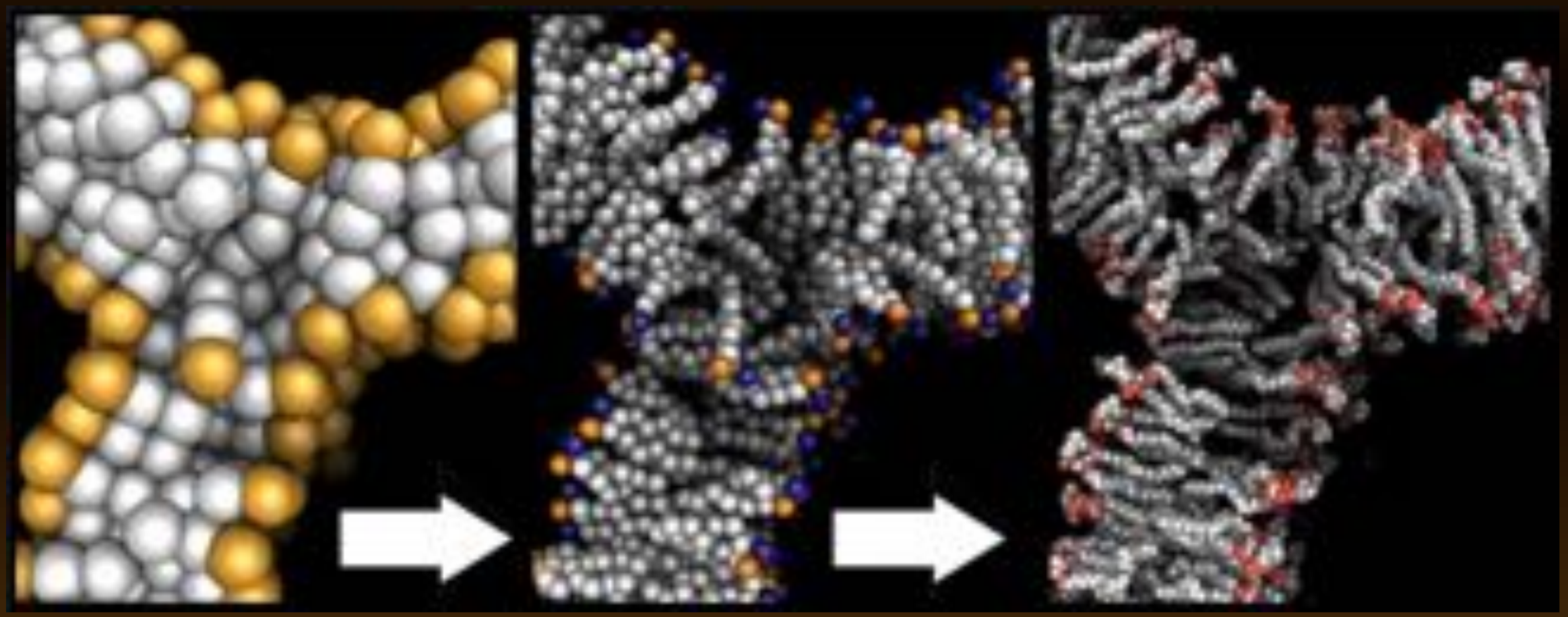
MARTINIZE: tool to make protein topologies

"Martinize is a python script to generate Martini protein topology and structure files based on an atomistic structure file"

- can handle different flavors of Martini force fields
- can add elastic networks using EINeDyn
- can assign 2ndary structure in multiple ways
- can add cys bridges, change charged states …
- .. and much much more …

Martini tools

BACKWARD: tool to obtain all-atom configurations



Break time

Examples of validation

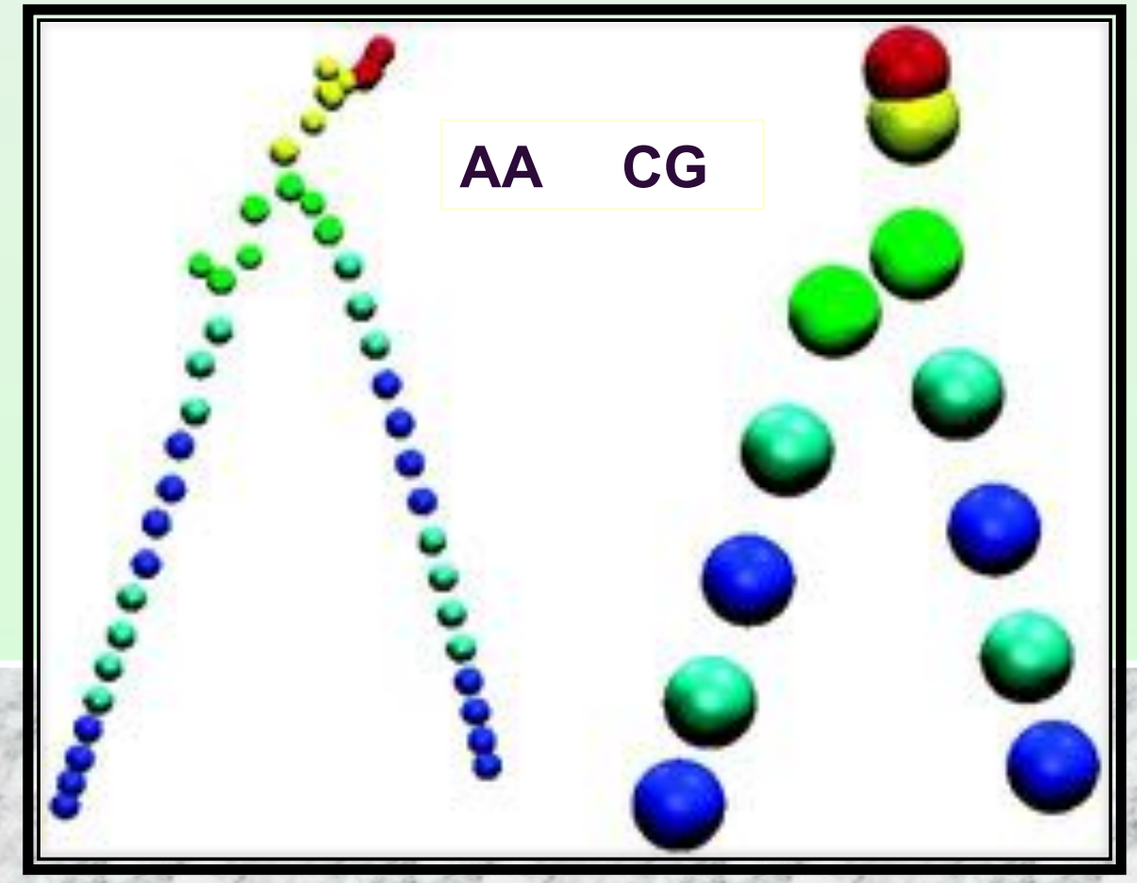
Properties of lipid membranes match experimental data

		Martini CG	Experimental
Structural			
	Area/lipid (nm^2)		
	DPPC	0.66	0.64
	DPPE	0.62	0.60
	DSPC	0.66	0.65
Elastic			
	Bending rigidity (J)	8×10^{-20}	6×10^{-20}
	Area compress. (mN m^{-1})	260	230
Thermodynamical			
	Phase transition T (K)	300	315
	Line tension (pN)	30	10-20
Dynamical			
	Lipid diffusion coeff. (cm^2 s^{-1})	2.5×10^{-7}	10^{-7}-10^{-8}
	Water permeation rate (cm s^{-1})	1.5×10^{-3}	~ 10^{-3}

Examples of validation

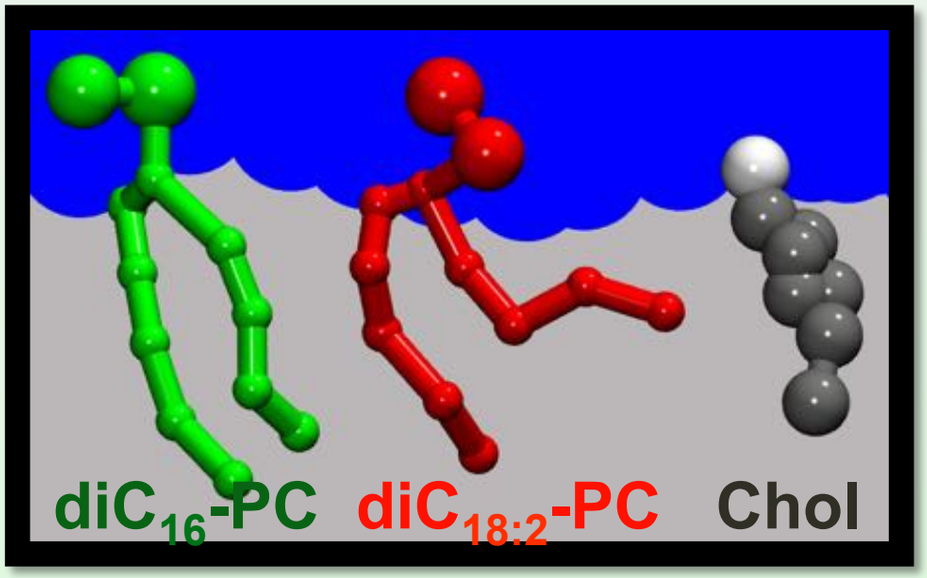
Lipid conformations match all-atom results

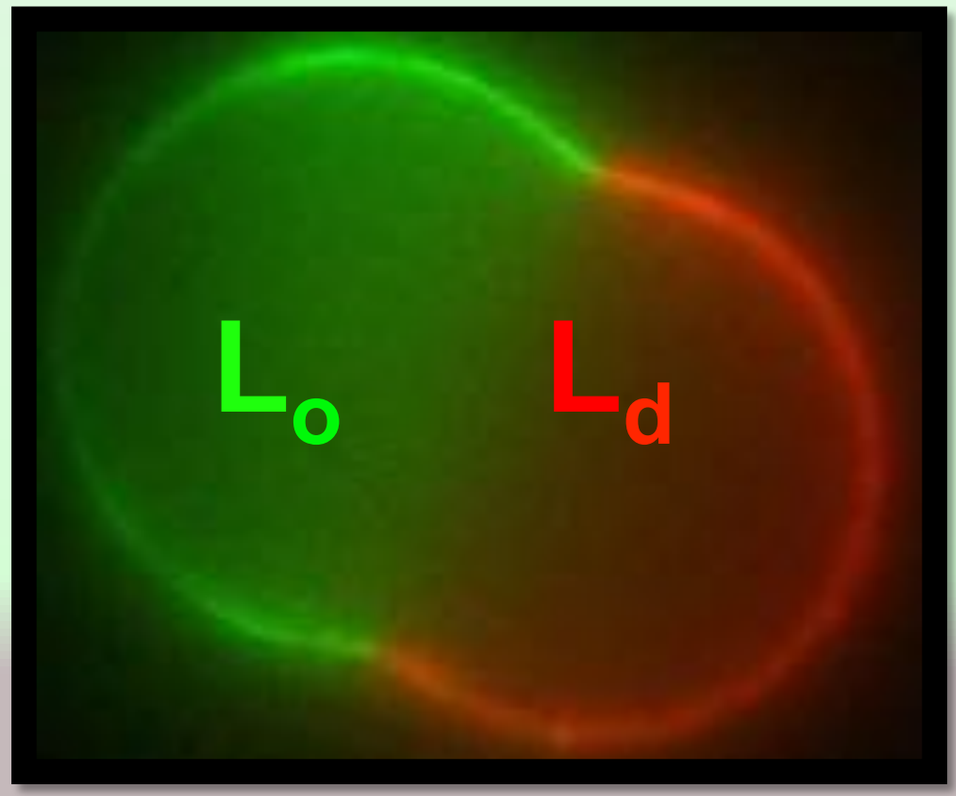
Averaged configurational space sampled by a lipid in a bilayer



Examples of validation

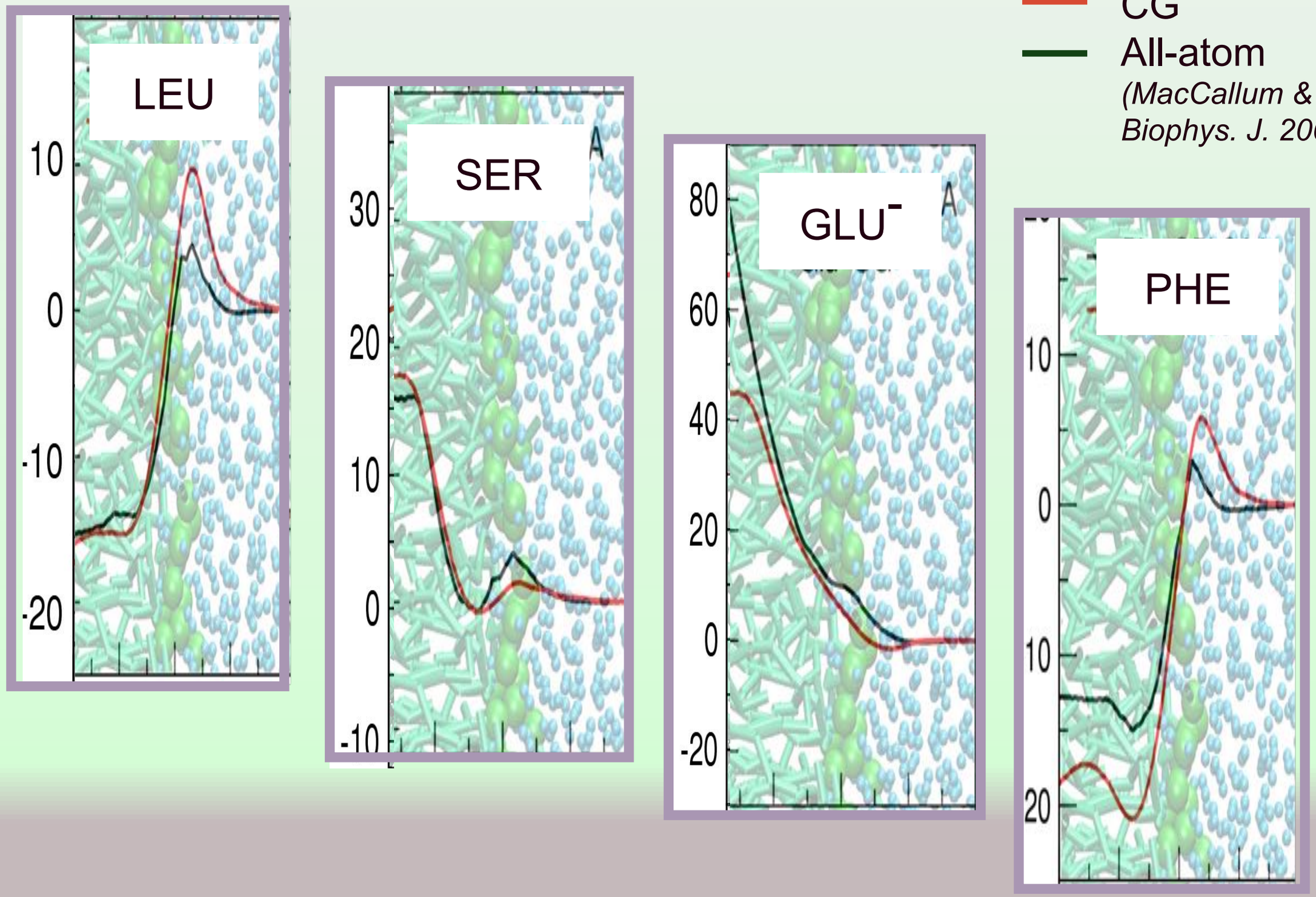
Reproducing experimental lipid phase behavior





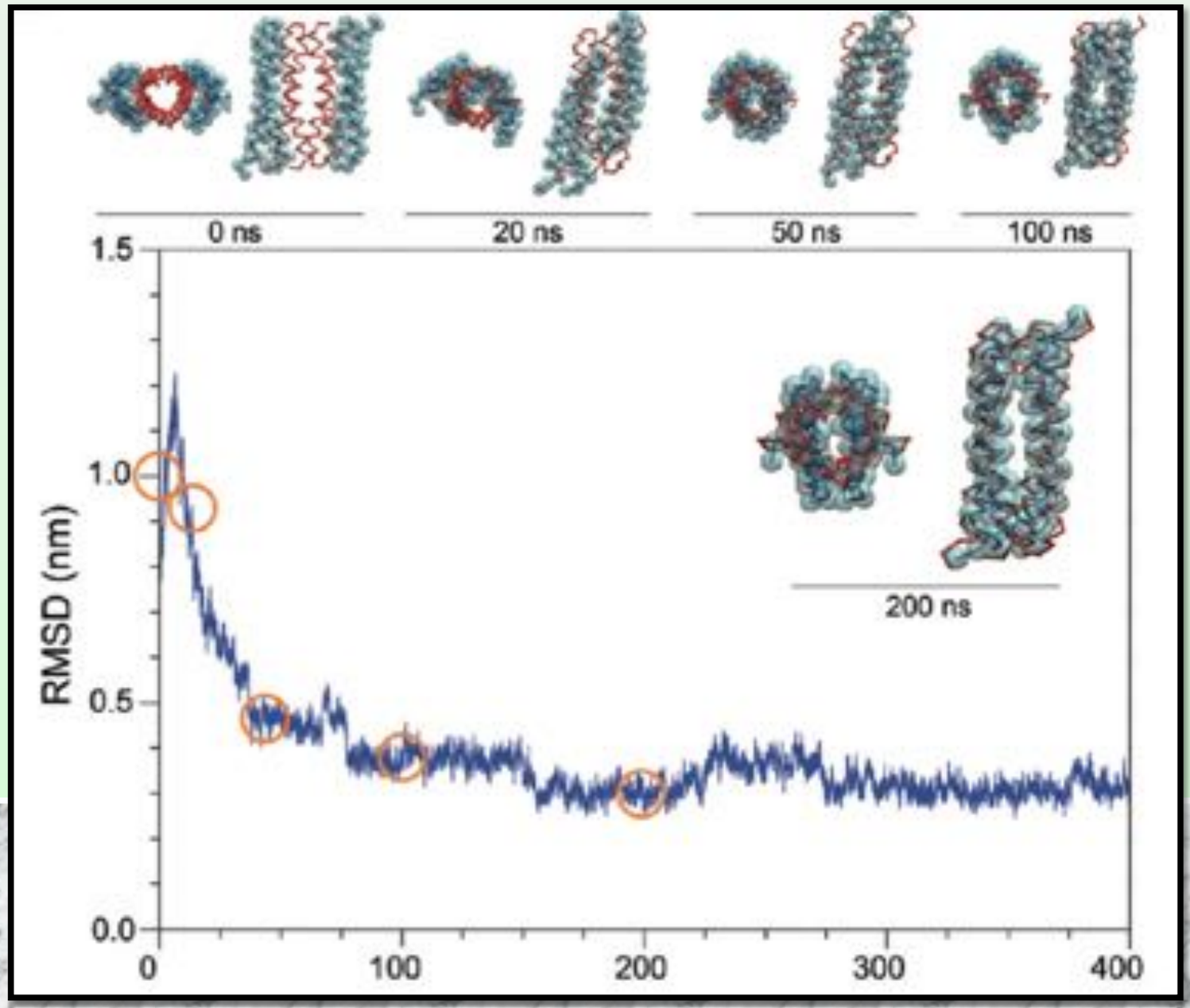
Examples of validation

Partitioning of amino acid residues in lipid bilayers



Examples of validation

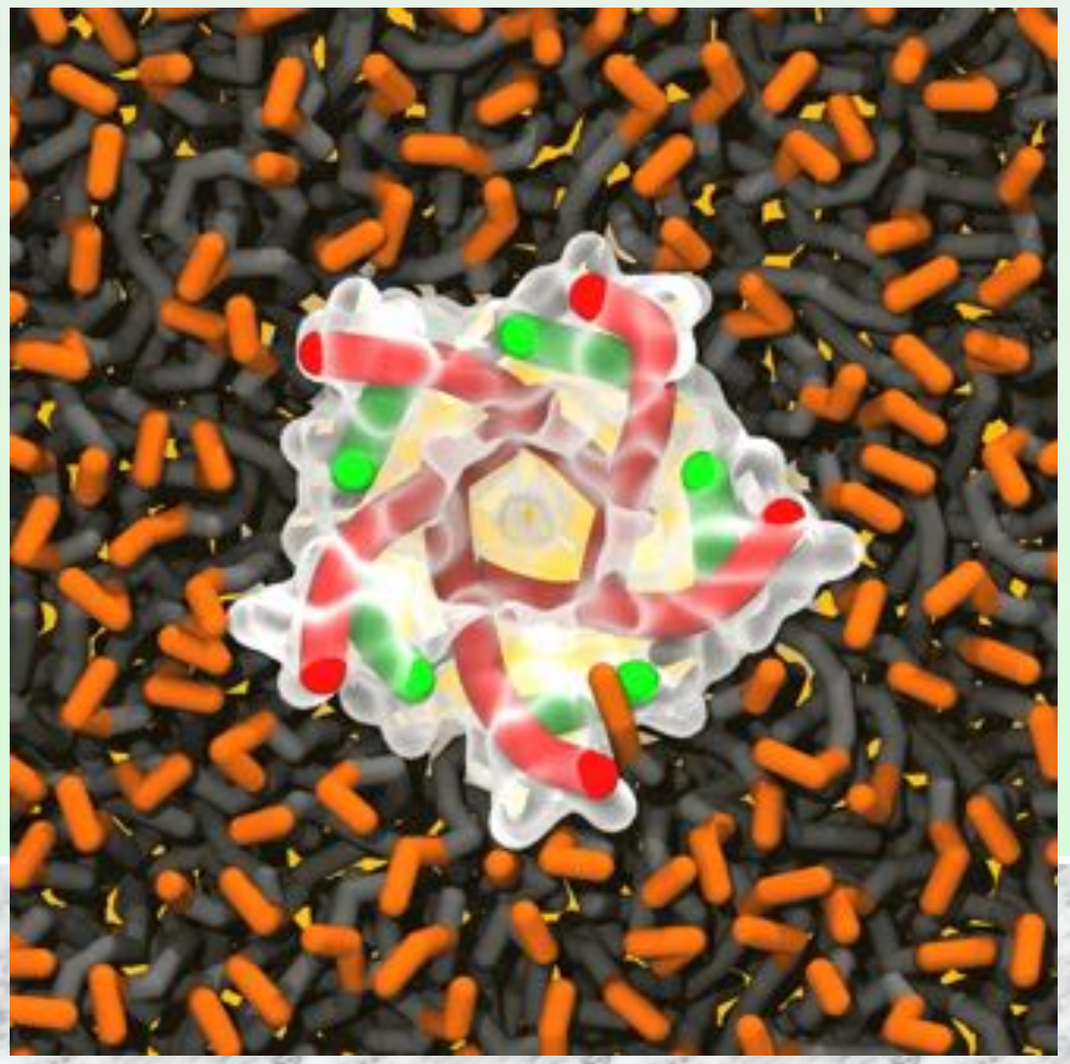
Reproducing known structure of protein-protein complexes



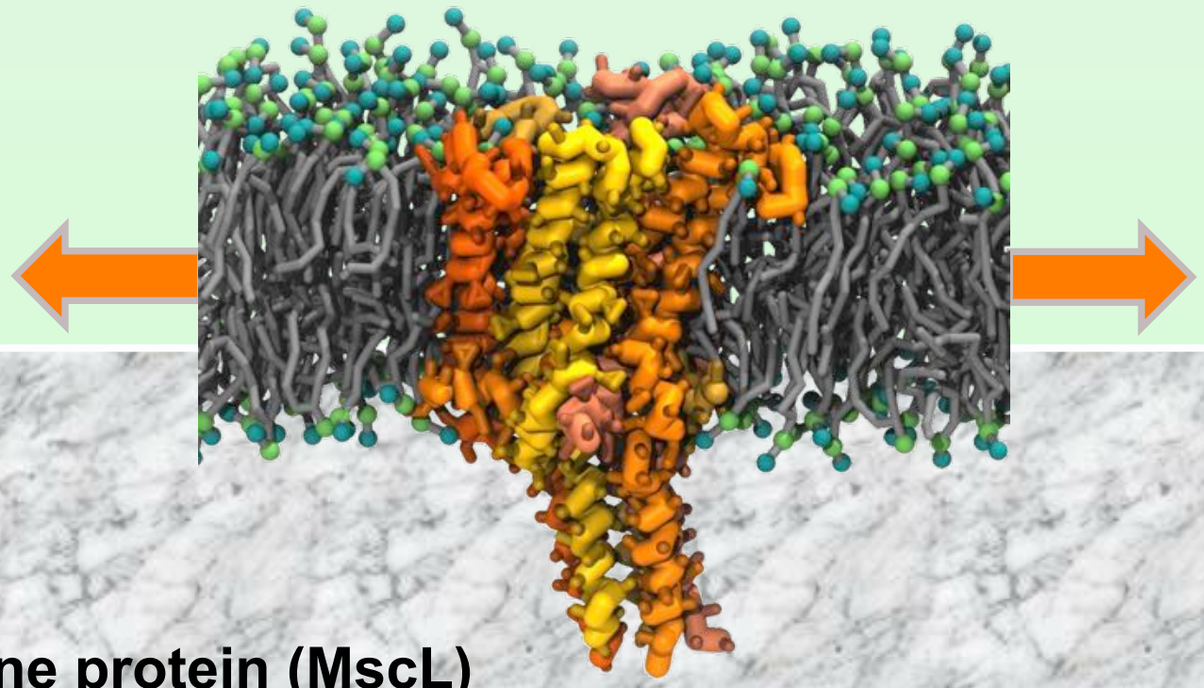
repressor of primer (ROP) protein

Examples of validation

Tertiary structure changes



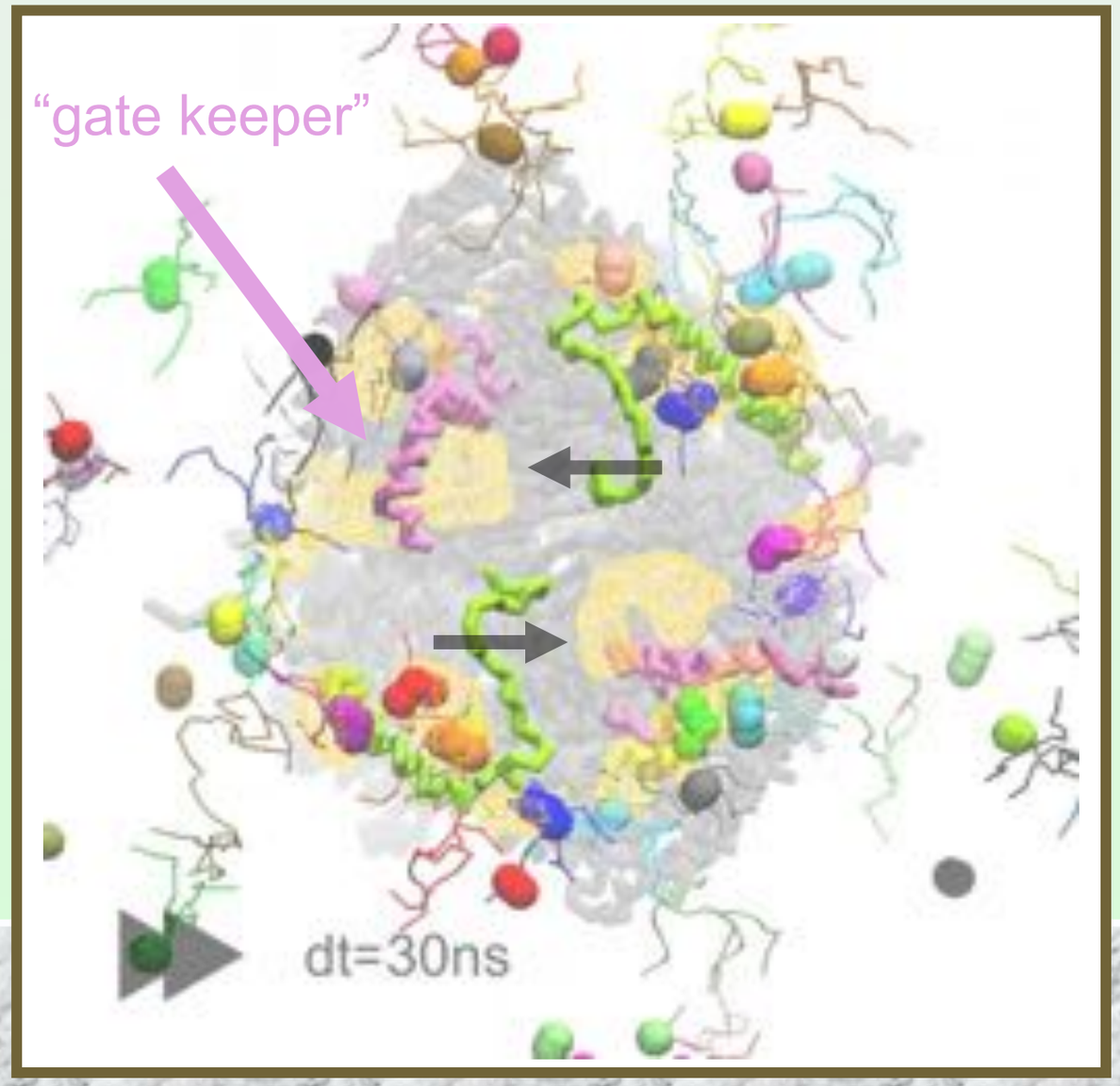
- 1 *Tb*-MscL protein
- 256 DOPC lipids
- 2 μs simulation
- bilayer under tension
- Martini forcefield

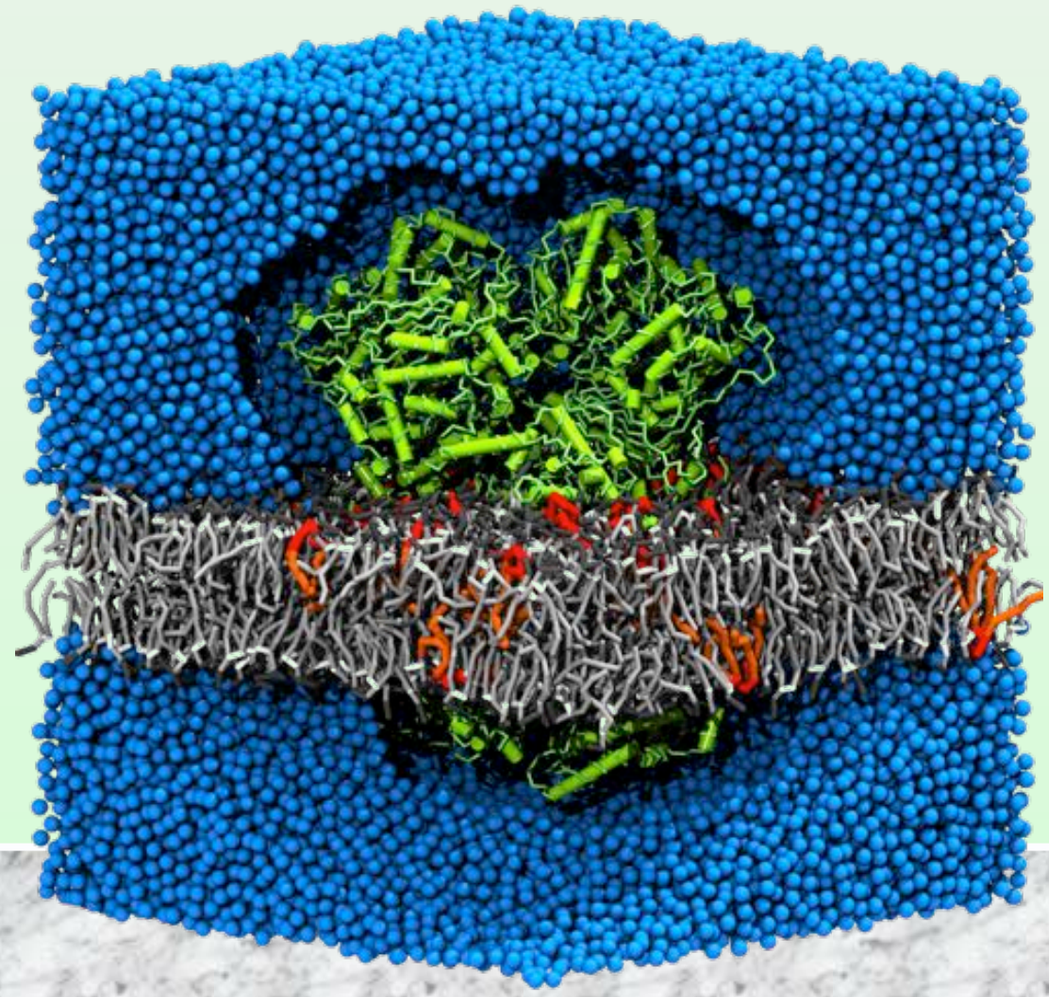


Gating of a mechanosensitive membrane protein (MscL)
Yefimov et al., Biophys. J., 2008; Melo et al., JACS, 2017

Examples of validation

Reproducing co-crystallized lipid binding sites





Binding of cariolipins to cytochrome *bc1*
Arnarez et al., JACS., 2013

Limitations of the Martini model

Limited resolution

- *Martini is 'fuzzy', semi-quantitative nature*

	Martini 4-bead	Martini 3-bead	Experimental DMPC
Bilayer Thickness [nm]	4.8	4.2	4.3
Melting Temperature [K]	295	280	295

Limitations of the Martini model

Limited resolution

- *Martini is 'fuzzy', semi-quantitative nature*

Solution:

Realize fuzzy character, and use to your advantage

Martini person:

"My DPPC bilaye melts at 295K"

Annoying referee:

"That is 20K too low!"

Martini person:

"Excuse me, I me to say DMPC"

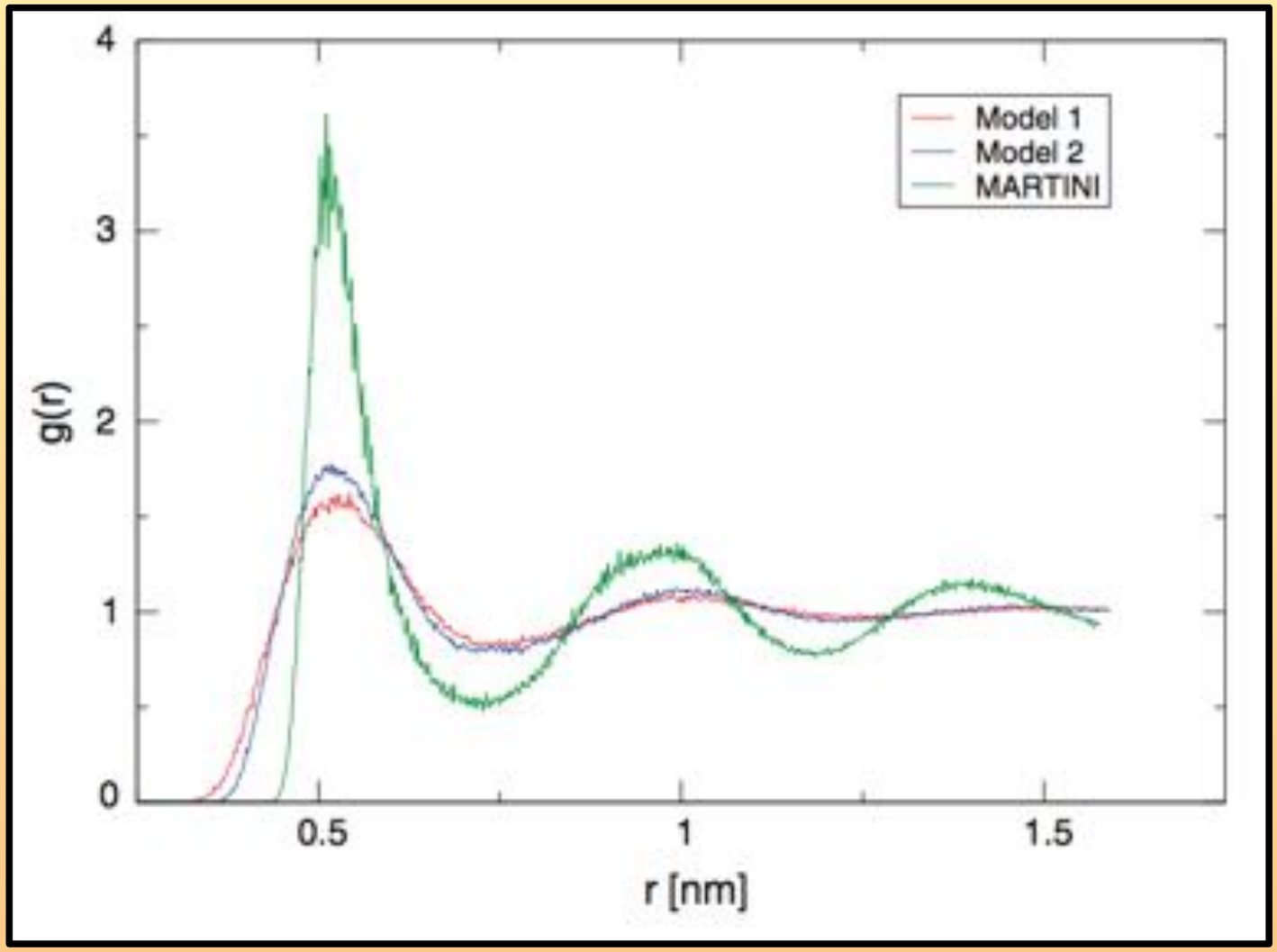
Convinced referee:

"Happy to accept your publication"

Limitations of the Martini model

Limited fluid range of LJ interactions

➢ *Martini solvents are too structured*



- *Water freezes too easily*
- *Solvation free energies not reproduced*

Limitations of the Martini model

Limited fluid range of LJ interactions

➢ *Martini solvents are too structured*

Solution:

(future) Use a softer form of the non-bonded potential
(now) Use anti-freeze particles to prevent freezing

Anti-freeze particles (BP4) can be added at 5-10 mol% to prevent freezing
To disturb the lattice packing of the uniformly sized solvent particles,
the LJ parameter σ for BP4-P4 interactions is scaled up to 0.57 nm instead of 0.47 nm.
To avoid phase separating of antifreeze and solvent particles,
the strength of the BP4-P4 interaction is raised one level

Limitations of the Martini model

Directionality of H-bonds is missing

- *Secondary structure of protein and DNA is fixed*

*Martini uses **elastic networks***
to keep biomacromolecules in
the desired configuration

- *Protein folding cannot be simulated*

Limitations of the Martini model

Directionality of H-bonds is missing

- *Secondary structure of protein and DNA is fixed*

Solution:

Use GO-Martini (?)

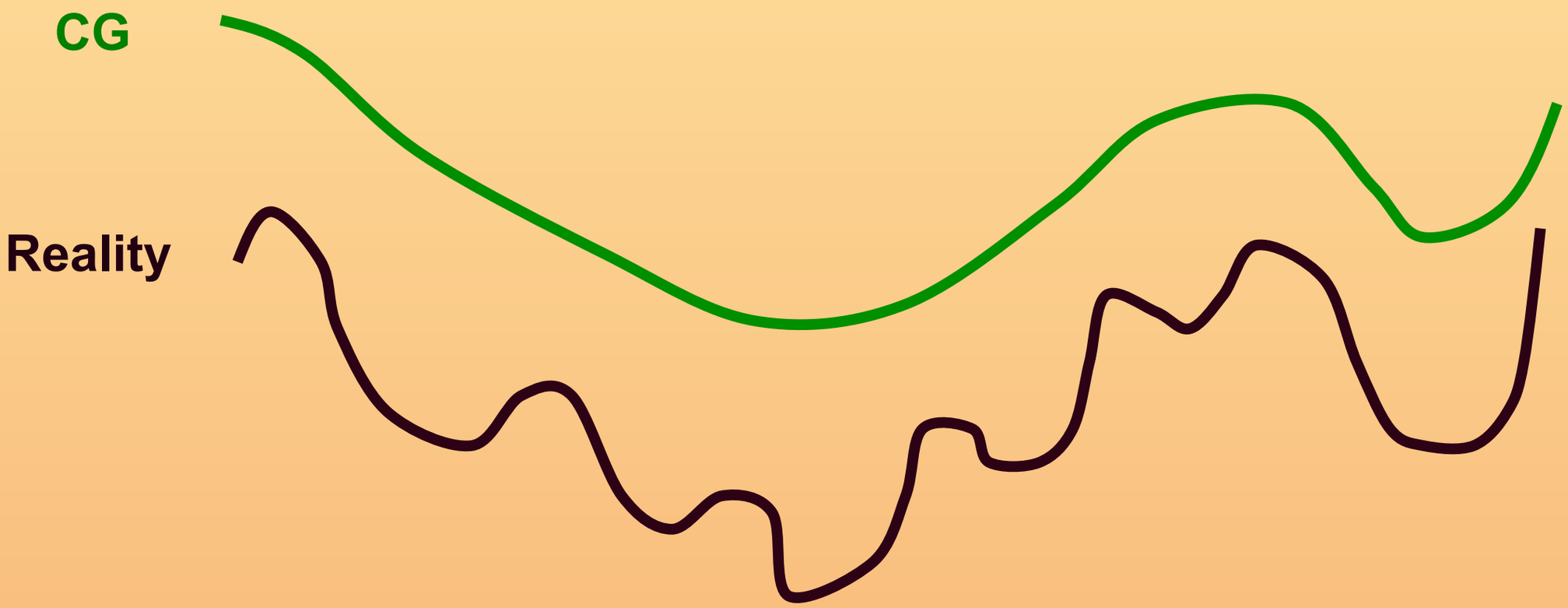
Limitations of the Martini model

Friction from atomistic degrees of freedom is missing

- Time scale should be interpreted with care

Kinetics need to be mapped on real time:

- A mapping factor of 2-8 describes friction dominated processes
  (e.g. lipid diffusion, water permeation)
- Kinetics of more complex processes depend on energy barriers



Limitations of the Martini model

Friction from atomistic degrees of freedom is missing

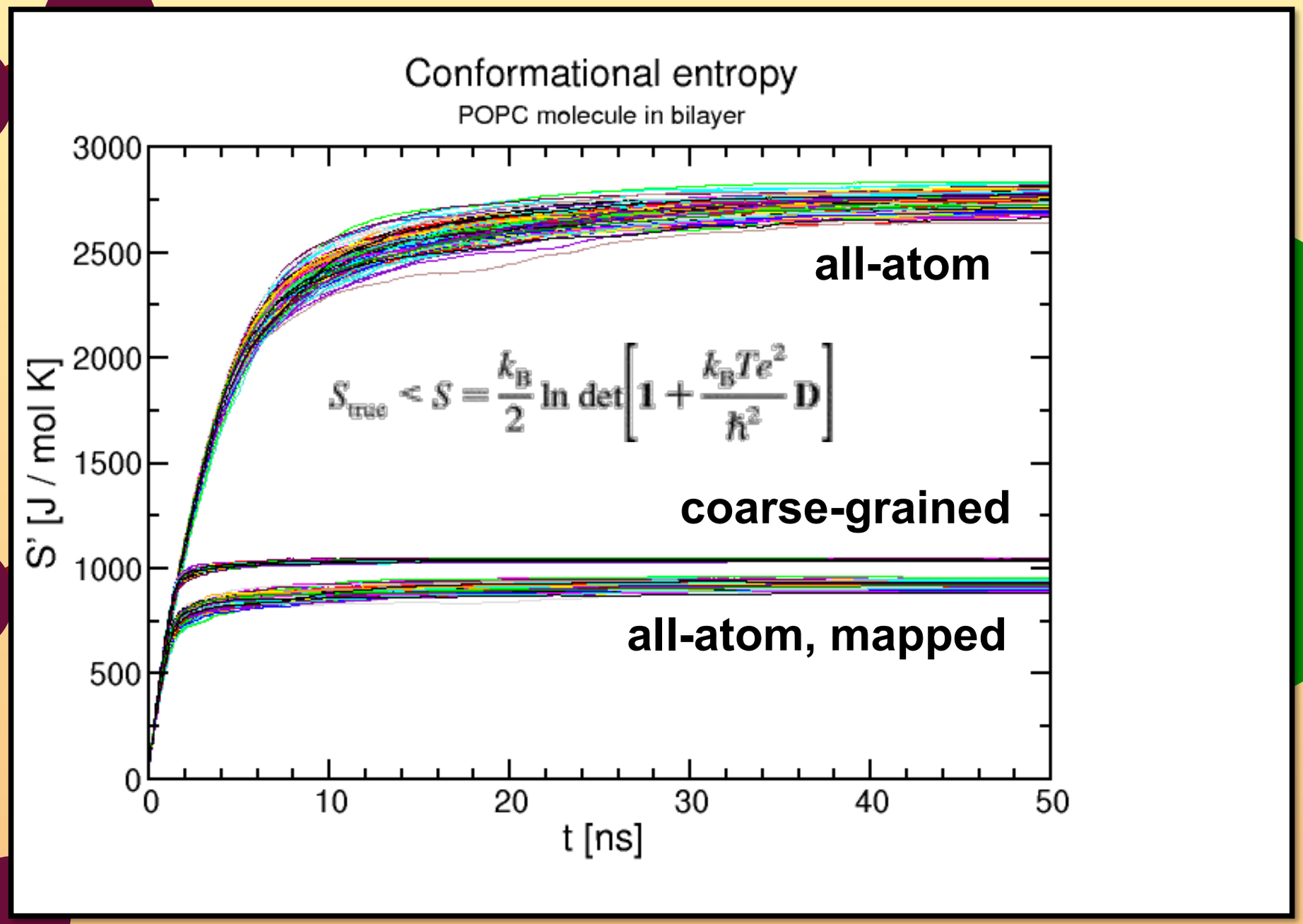
- Time scale should be interpreted with care

Solution (but not recommended):

Apply friction to EOM

Limitations of the Martini model

Missing entropy, compensated by reduced enthalpy



Limitations of the Martini model

Missing entropy, compensated by reduced enthalpy

- *Temperature dependence off*
- *Driving forces wrong*

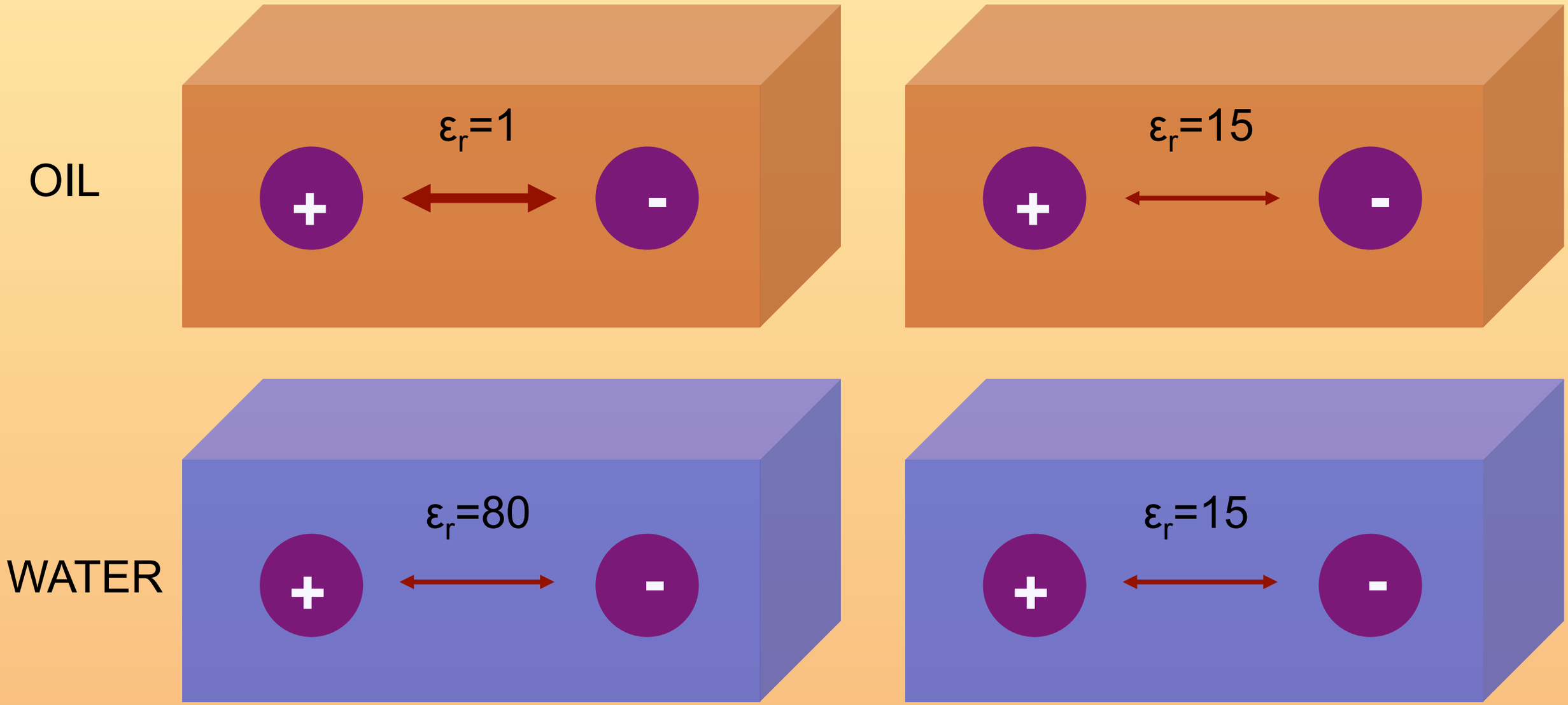
Solution:

Recalibrate parameters for specific temperatures (not very pragmatic), or interpret driving forces with care (certainly useful!)

Limitations of the Martini model

Electrostatic screening of water is only implicit

➢ *Change in environment not felt by charged beads*



Limitations of the Martini model

Electrostatic screening of water is only implicit

- *Change in environment not felt by charged beads*

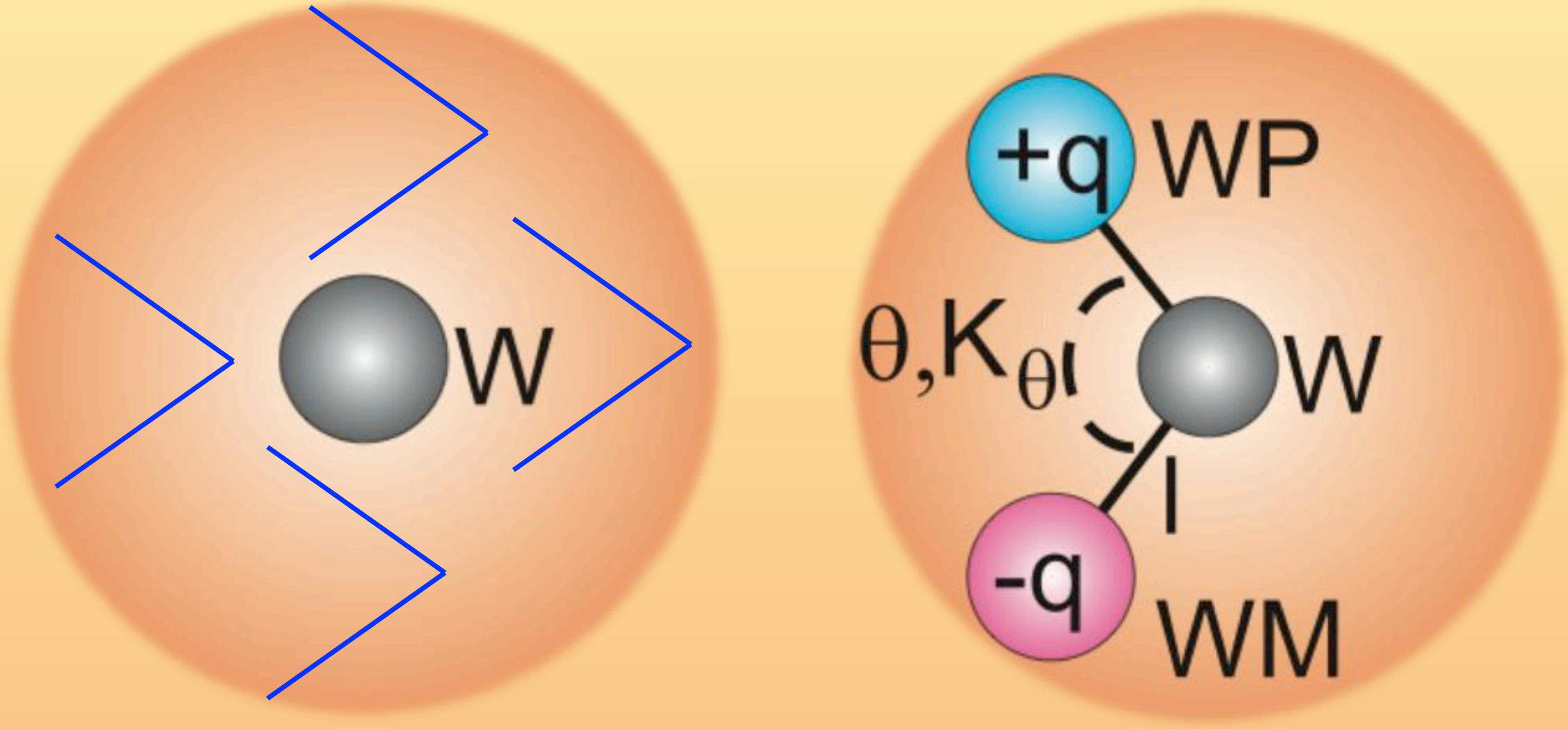
Solution:

Use polarizable water model when charged interactions are important

Limitations of the Martini model

Electrostatic screening of water is only implicit

Explicit screening by polarizable water model:



Standard Martini water

Polarizable Martini water

Limitations of the Martini model

Electrostatic screening of water is only implicit

Parameters & properties of polarizable water model:

Parameters		Properties[a]	
charge WP,WM	$q = \pm 0.46$	density	1043 kg m^{-3}
bond W-WP, W-WM	$l = 0.14$ nm	dielectric constant	75.6
angle WP-W-WM	$\theta = 0$ rad	dipole moment	4.9 Debye
	$K_\theta = 4.2$ kJ mol^{-1} rad^{-2}	self diffusion	2.5 10^{-5} cm^2 s^{-1}
LJ_{W-W}	$\varepsilon = 4.0$ kJ mol^{-1}	hydration free energy	−18.7 kJ mol^{-1}
	$\sigma = 0.47$ nm	freezing temperature	282 ± 3 K
relative screening	$\varepsilon_r = 2.5$	air/water surface tension	30.5 mN/m

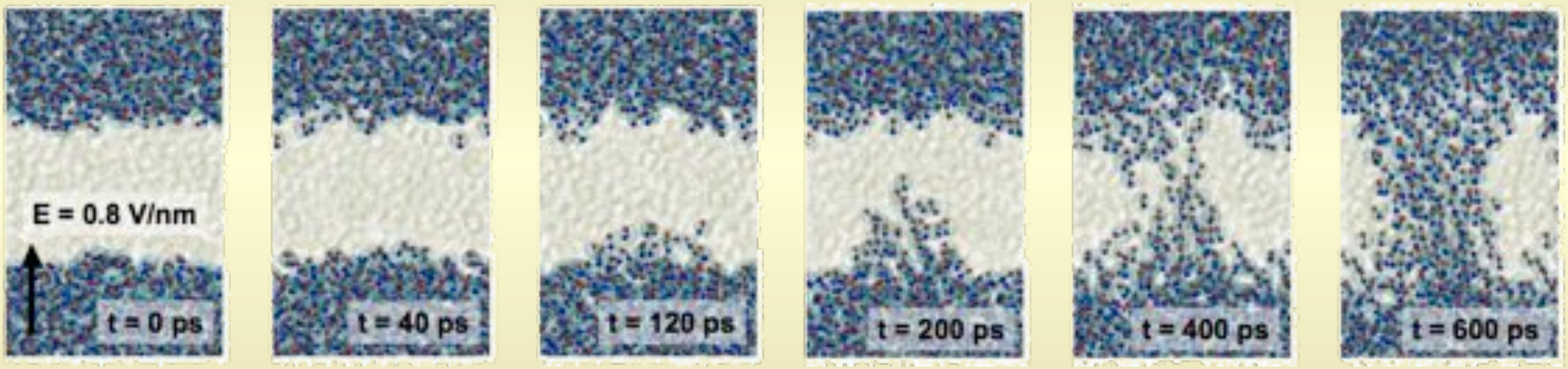
◆ **Dielectric constant of real water reproduced**

Yesylevskyy, Schäfer, Sengupta, Marrink, PLoS Comp. Biol., 2010

Limitations of the Martini model

Electrostatic screening of water is only implicit

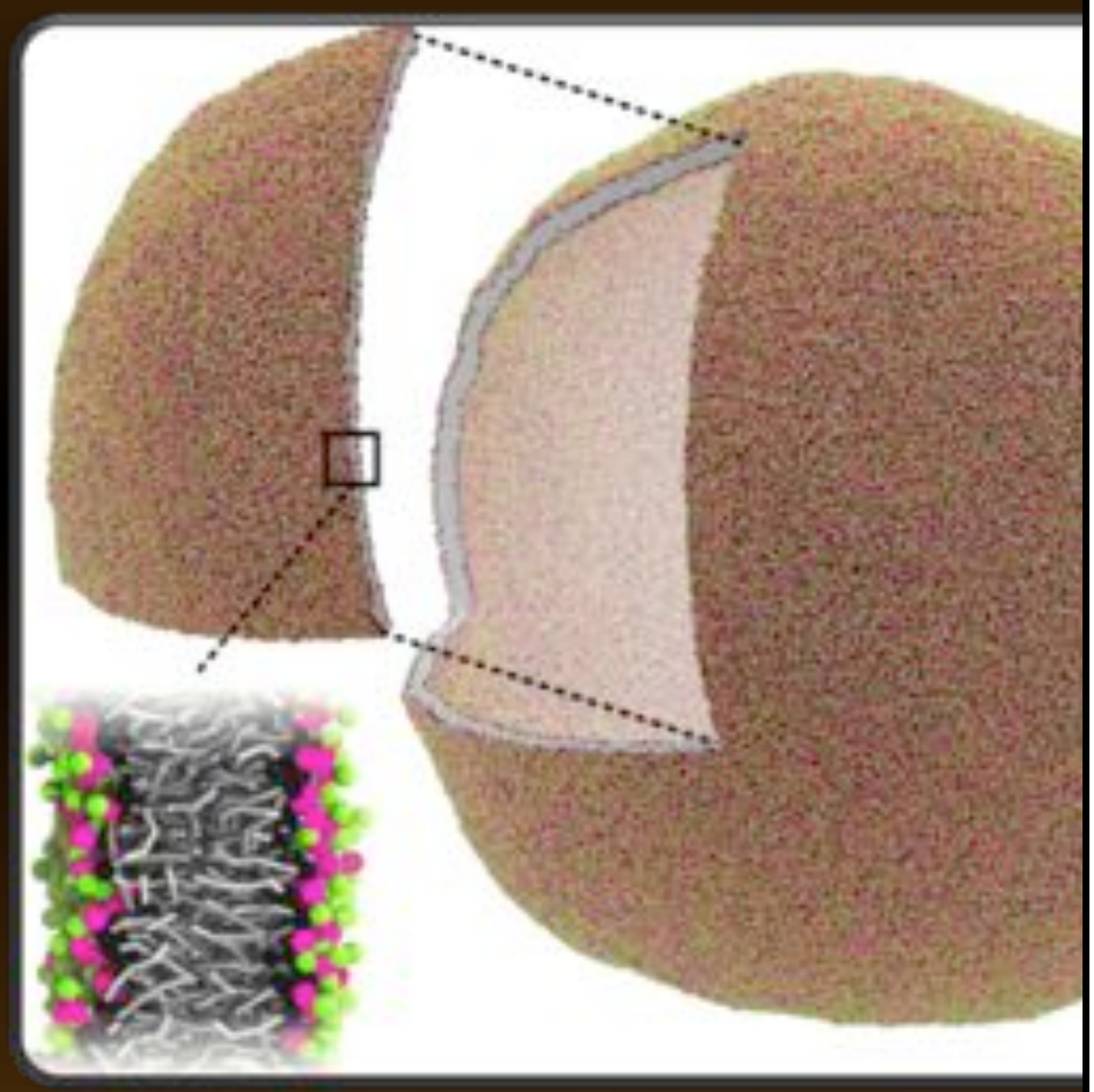
Example of improved behavior with polarizable water: electroporation of an octane slab

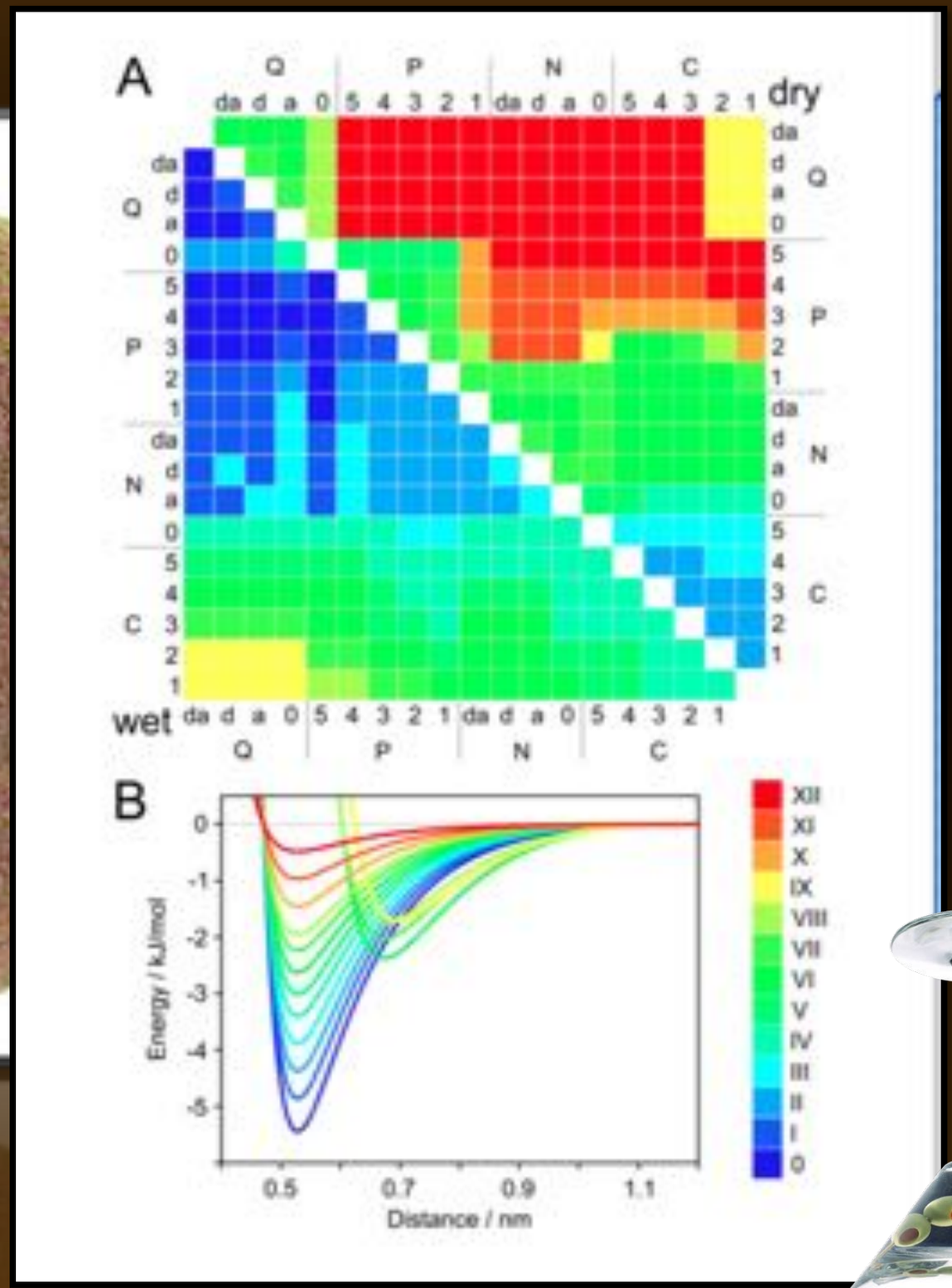


(similar to atomistic simulations by Tieleman)

Dry Martini

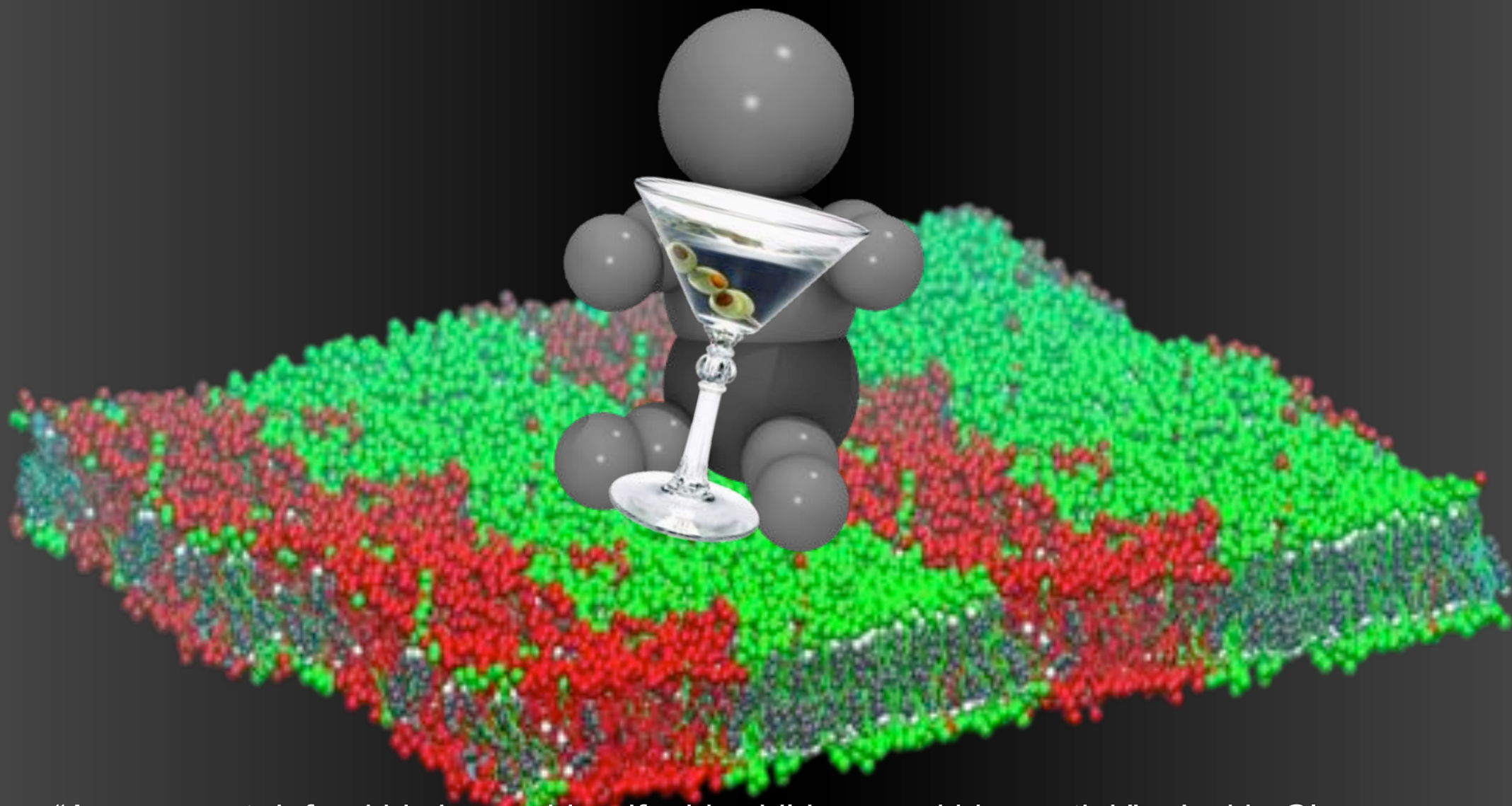
Martini model with implicit solvent





- reshuffled non-bonded interaction matrix

Enjoy Sampling Martinis !!



“A man must defend his home, his wife, his children, and his martini." - Jackie Gleason