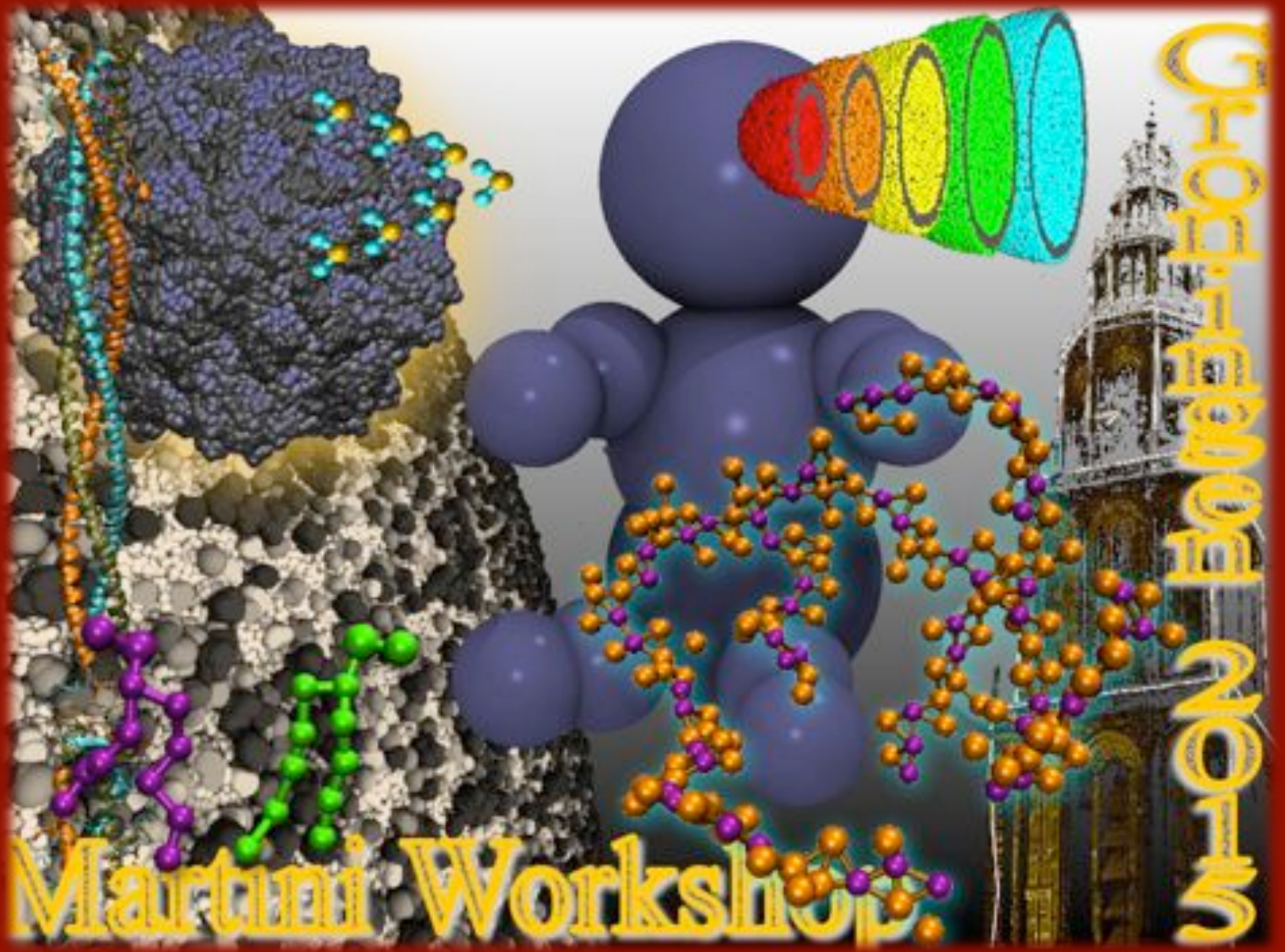

Martini Workshop
Cambridge 2015

“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

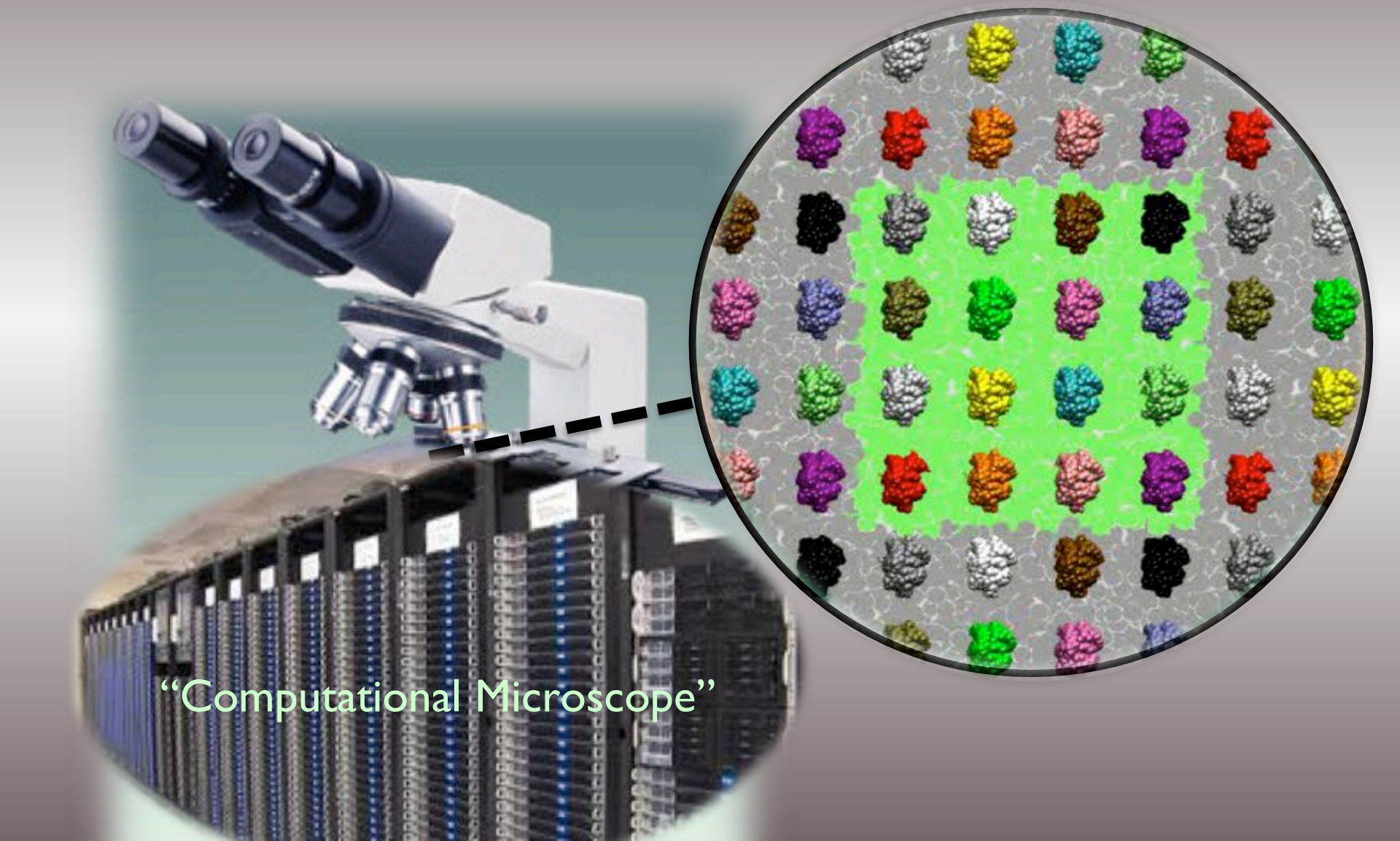
“Martini should be made by filling a glass with gin, then waving it in the general direction of Italy”

Overview of this lecture
"Martini Basics"

- The power of coarse-graining
- Looks of the Martini model
- Validation of the Martini model
- Limitations of the Martini model
- Applications of the Martini model

The power of coarse-graining

Vast range of time and length scales of biomolecular processes

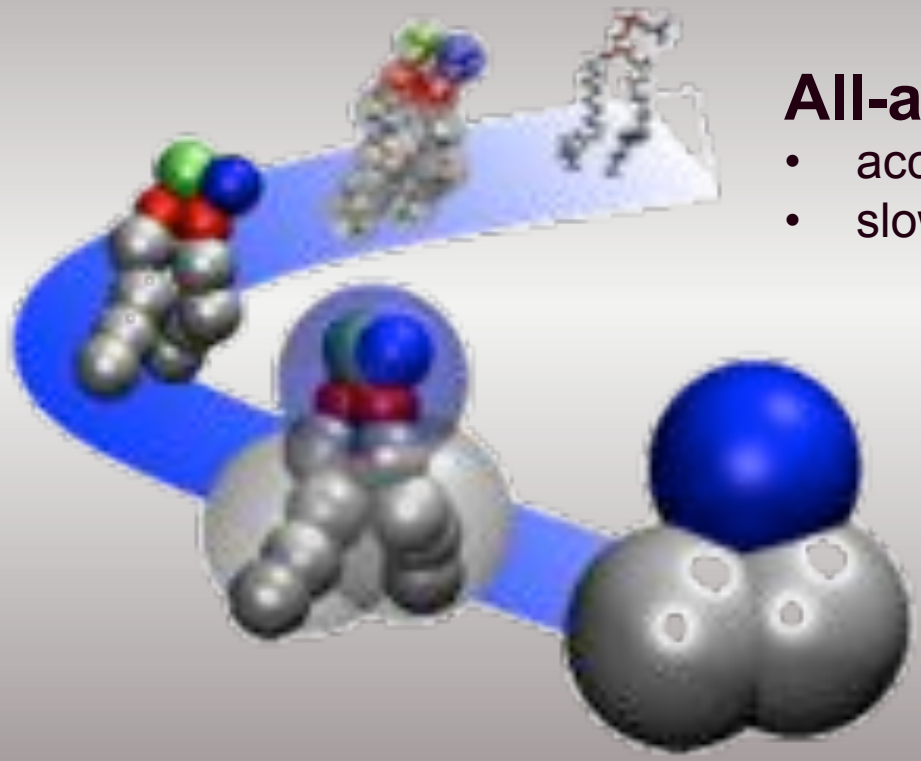


The power of coarse-graining

Different problems require different levels of resolution

Martini

Coarse-grain
- fast
- chemical specificity

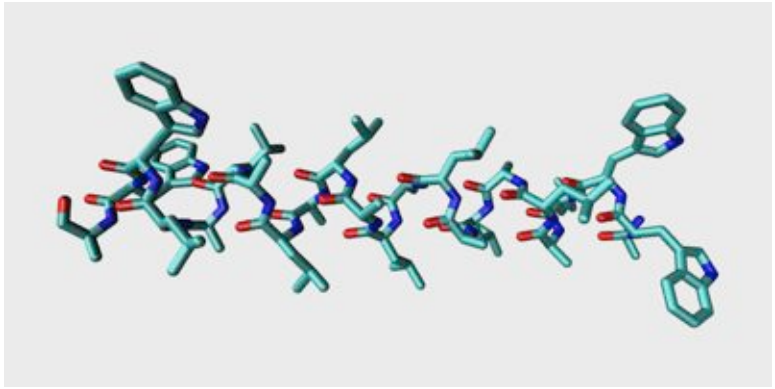


All-atom
- accurate
- slow

Supra CG
- very fast
- not specific

Looks of the Martini model

Four-to-one mapping principle



MARTINI

Biomolecular Forcefield for Coarse-Grained Simulations

http://cgmartini.nl

"One martini is all right. Two are too many, and three are not enough." - James Thurber

Looks of the Martini model

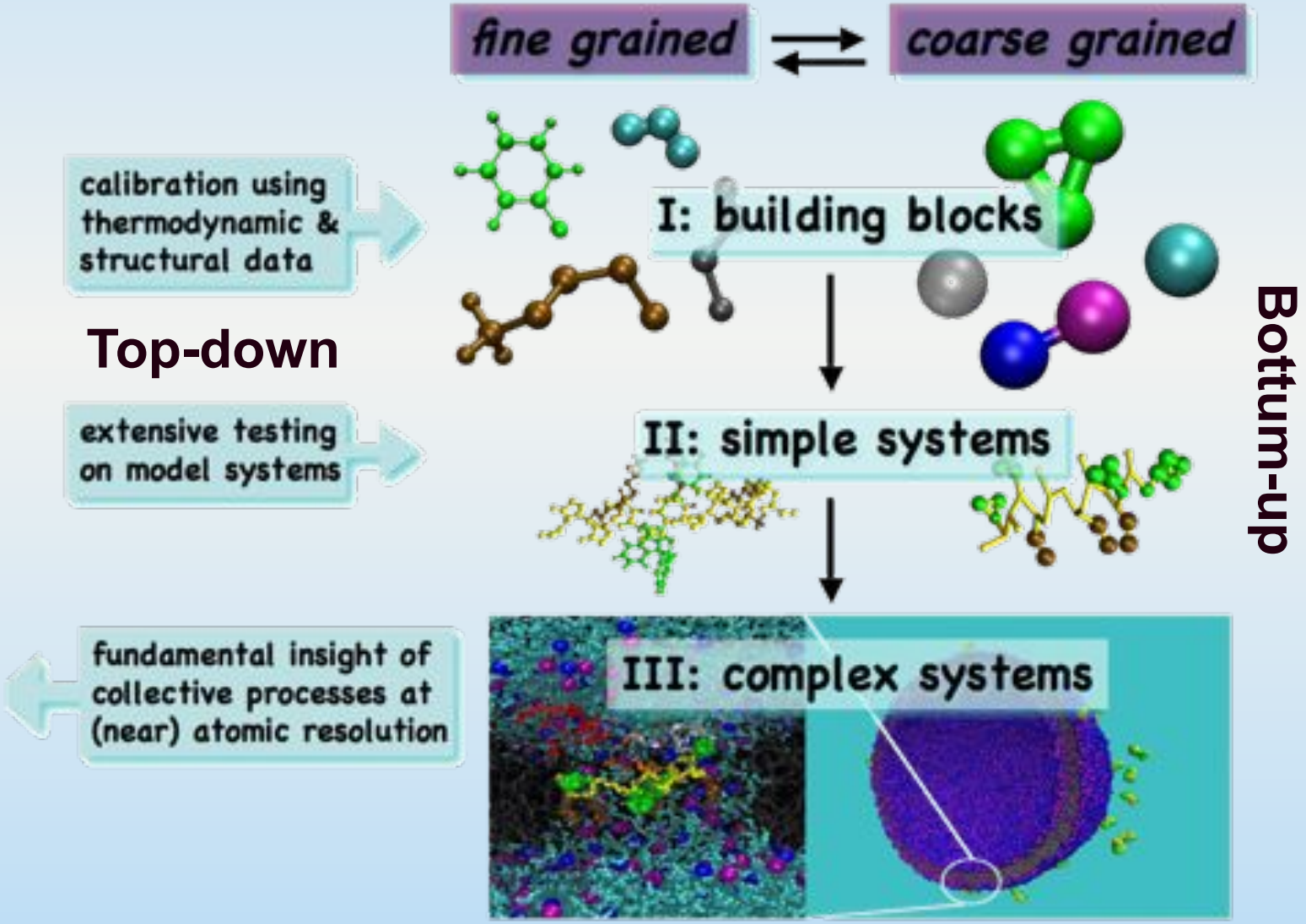
What's in a name?

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

(any association with cocktails is entirely coincidental)

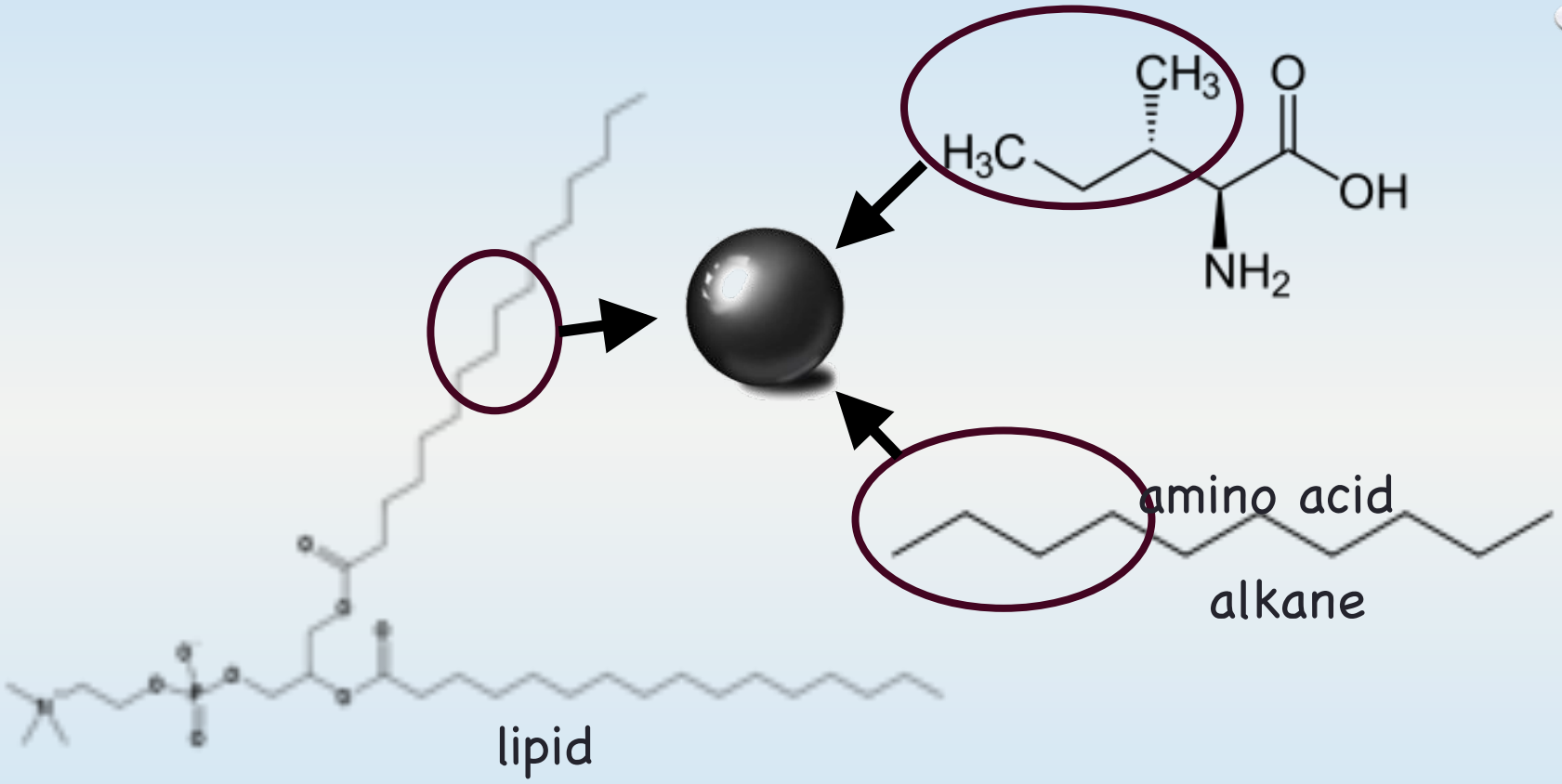
Looks of the Martini model

Systematic parameterization combining top-down and bottum-up approaches



Looks of the Martini model

The building block principle



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

Looks of the Martini model

The building block principle

Building block types

C1
C2
C3
C4
C5

Apolar

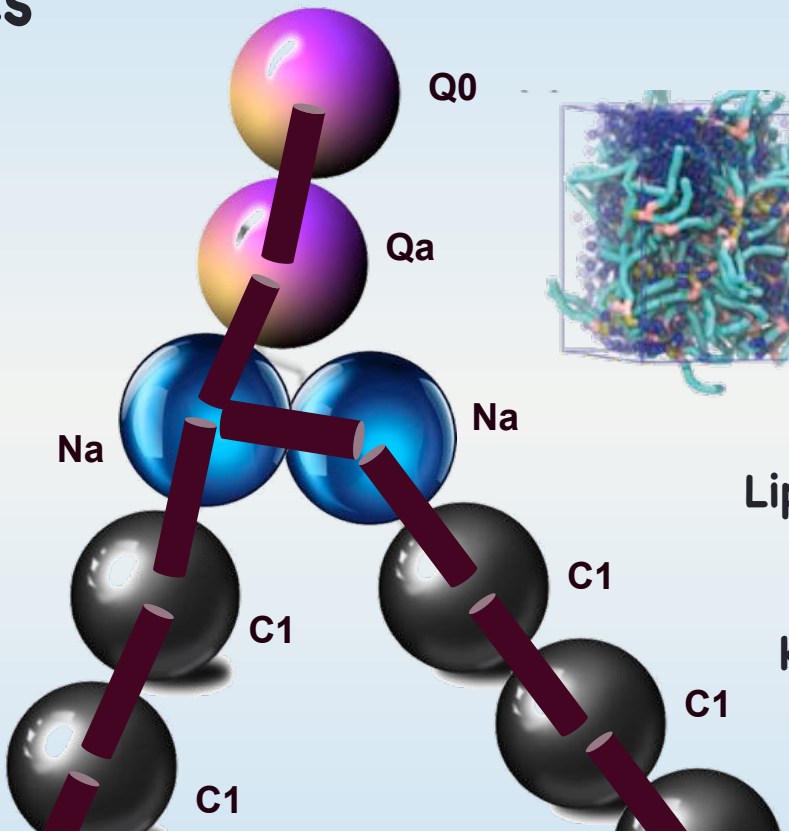
N0
Nd/a
Nda

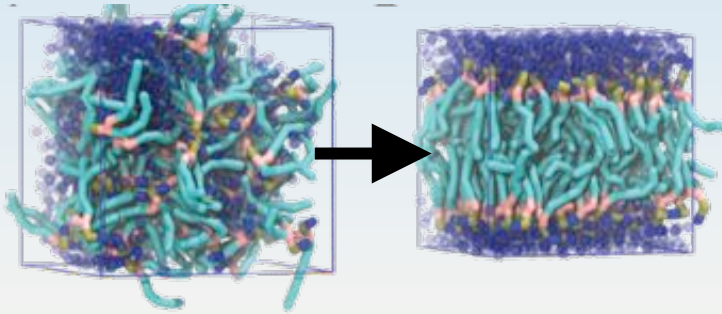
Intermediate

P1
P2
P3
P4
P5

Polar

Q0
Qd/a
Qda



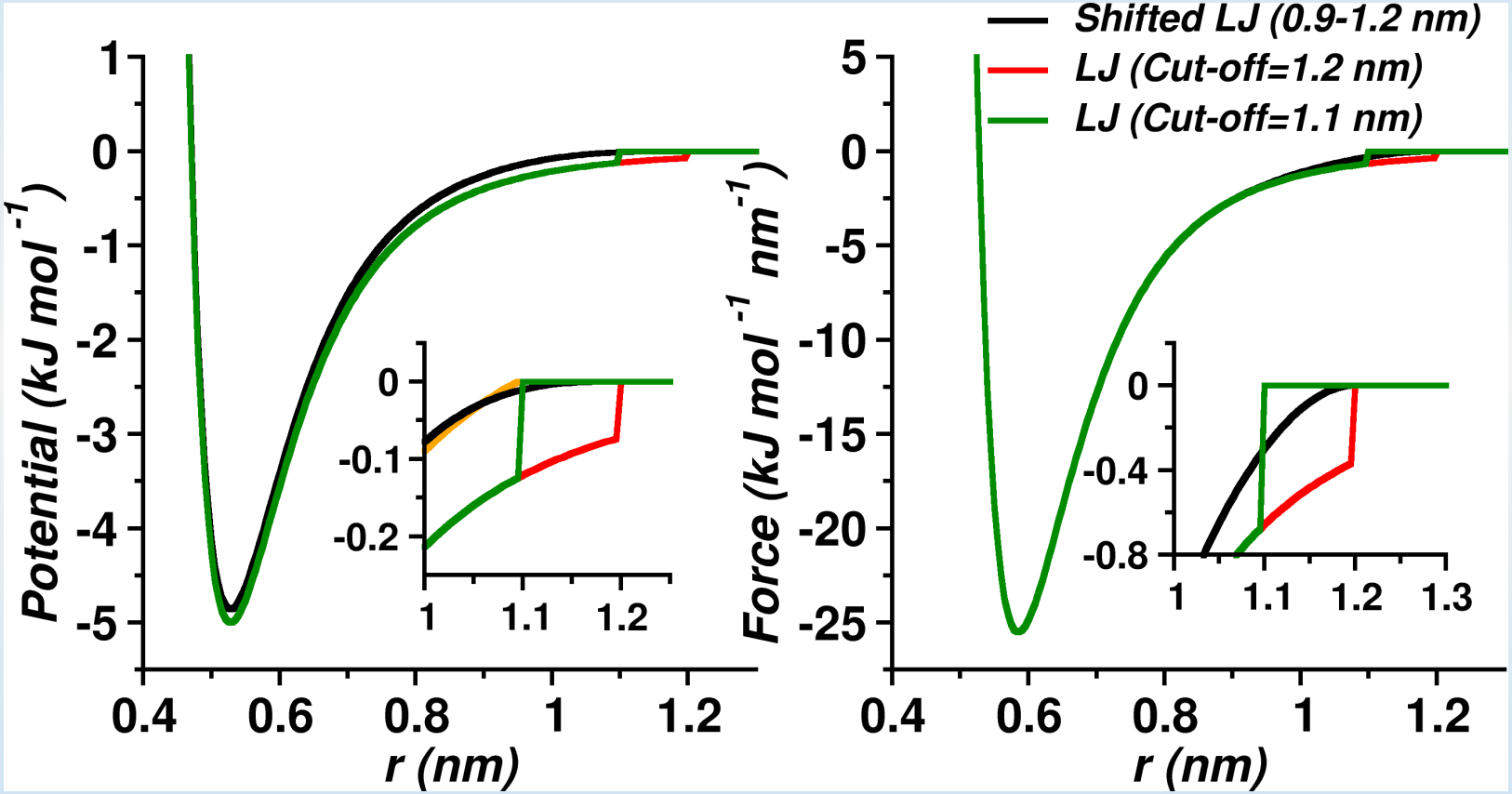


TUTORIAL
Lipids self-assemble into a bilayer, reproducing known membrane properties

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

Looks of the Martini model

Non-bonded interactions: LJ & Coulomb

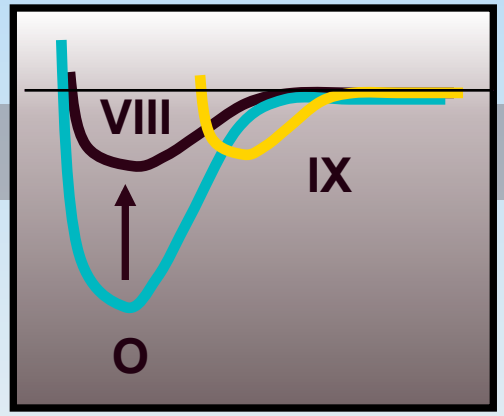


.... however: **short-ranged** by use of shifted functions

(cut-off 1.2 nm, 2-3 neighbors)

Looks of the Martini model

Hocus-pocus with LJ balls



- 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

- Four main classes of CG beads, 18 classes in total:

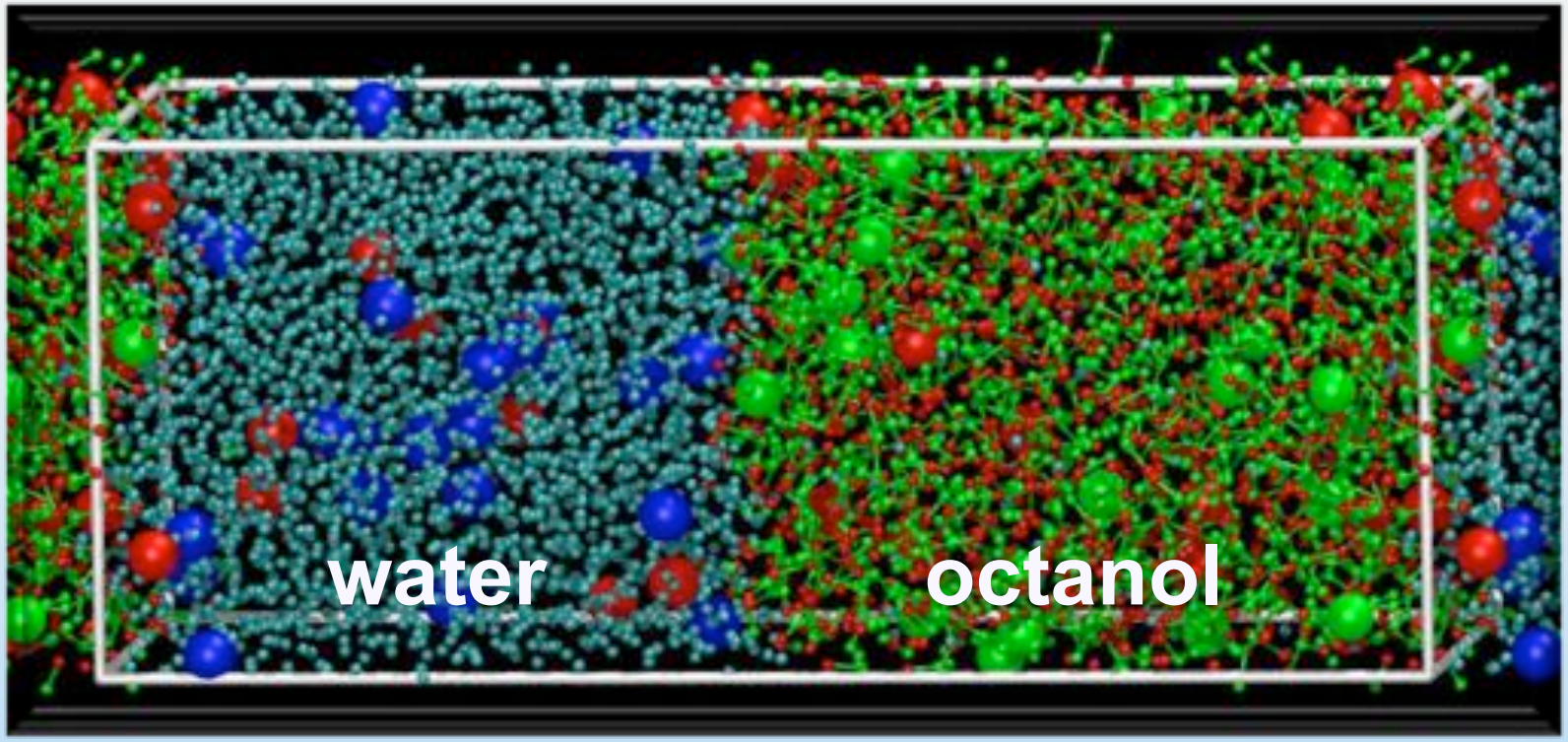
		charged (Q)				polar (P)					intermediate (N)				apolar (C)				
		da	d	a	0	5	4	3	2	1	da	d	a	0	5	4	3	2	1
Q	da	O	O	O	II	O	O	O	I	I	I	I	I	IV	V	VI	VII	IX	IX
	d	O	I	O	II	O	O	O	I	I	I	III	I	IV	V	VI	VII	IX	IX
	a	O	O	I	II	O	O	O	I	I	I	I	III	IV	V	VI	VII	IX	IX
	0	II	II	II	IV	I	O	I	II	III	III	III	III	IV	V	VI	VII	IX	IX
P	5	O	O	O	I	O		O	O	O	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	I	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 parameterized based on reproducing experimental partitioning free energies (and densities)

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



Looks of the Martini mod

The Martini bible: mapping CG bead ty

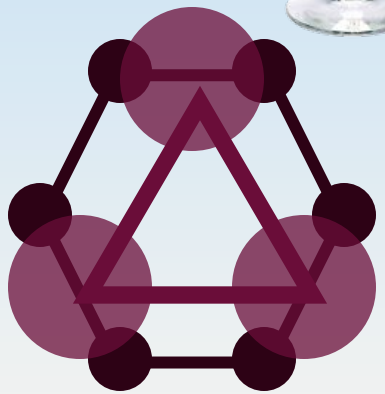
type	building block	examples	ΔG° exp	ΔG° CG	ex
Q_{da}	$H_3N^+-C_2-OH$	ethanolamine (protonated)			
Q_d	$H_3N^+-C_3$	1-propylamine (protonated)			
	NA^+OH	sodium (hydrated)			
Q_a	PO_4^-	phosphate			
	CL^-HO	chloride (hydrated)			
Q_0	C_5N^+	choline			
P_5	$H_2N-C_2=O$	acetamide	sol	sol	−4
P_4	HOH (× 4)	water	−27	−18	−2
	$HO-C_2-OH$	ethanediol	−35	−18	−3
P_3	$HO-C_2=O$	acetic acid	−31	−18	−2
	$C-NH-C=O$	methylformamide	−35	−18	
P_2	C_2-OH	ethanol	−22	−16	−2
P_1	C_3-OH	1-propanol	−23	−16	−2
		2-propanol	−22	−16	−2
N_{da}	C_4-OH	1-butanol	−25	−16	−2
N_d	H_2N-C_3	1-propylamine	−17	−13	−1
N_a	$C_3=O$	2-propanone	−17	−13	−1
	$C-NO_2$	nitromethane	−23	−13	−1
	$C_2=N$	proprionitrile	−22	−13	−1
	$C-O-C=O$	methylformate	−16	−13	−1
	$C_2HC=O$	propanal		−13	−1
N_0	$C-O-C_2$	methoxyethane	−13	−10	(−4
C_5	C_3-SH	1-propanethiol	−17	−10	
	$C-S-C_2$	methyl ethyl sulfide	−17	−10	
C_4	$C_2=C_2$	2-butyne	−15	−10	
	$C=C-C=C$	1,3-butadiene		−10	
	$C-X_4$	chloroform	−18	−10	
C_3	$C_2=C_2$	2-butene		−10	
	C_3-X	1-chloropropane	−16	−10	
		2-bromopropane	−16	−10	
C_2	C_3	propane	gas	−10	
C_1	C_4	butane	−11[b]	−10	
		isopropane	gas	−10	

	EXP	
P_5	sol	
P_4	-27	
	-35	
P_3	-31	
	-35	
P_2	-22	
P_1	-23	
	-22	
N_{da}	-25	
N_d	-17	
N_a	-17	
	-23	
	-22	
	-16	
N_0	-13	
C_5	-17	
	-17	
C_4	-15	
	-18	
C_3		
	-16	
	-16	
C_2	gas	
C_1	-11[a]	
	-gas	

	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

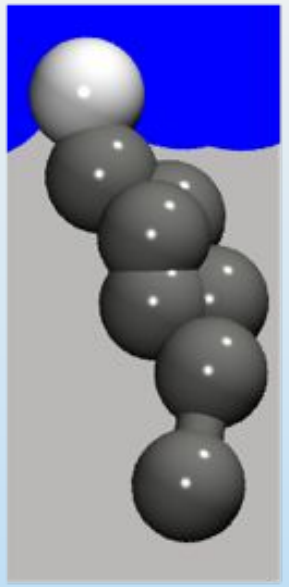


Rings: Four-to-one mapping inadequate

- 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

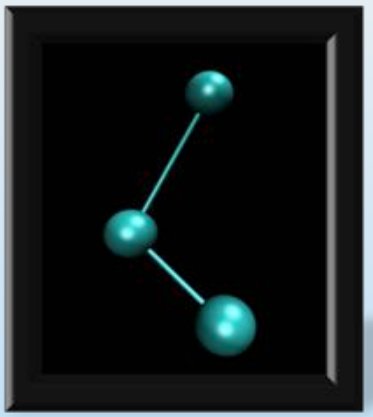


Looks of the Martini model

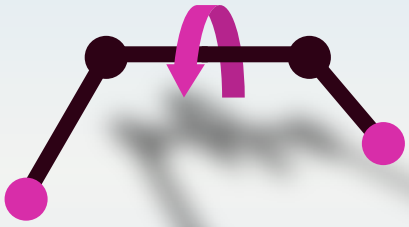
Simple harmonic forms for bonded interactions

Bonds

Angles



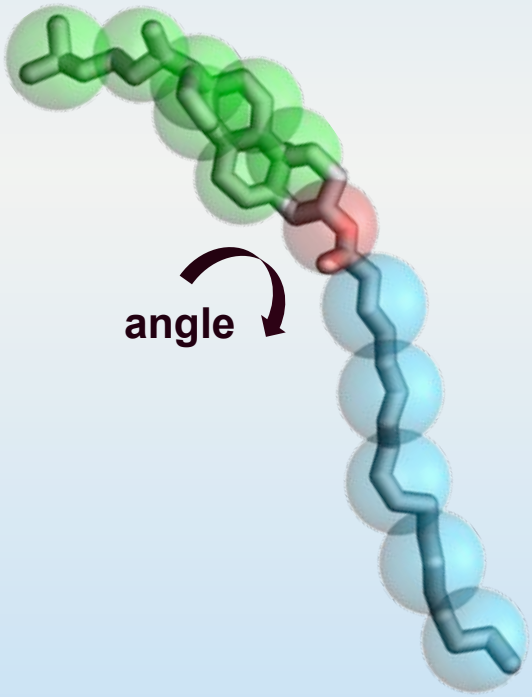
Dihedrals

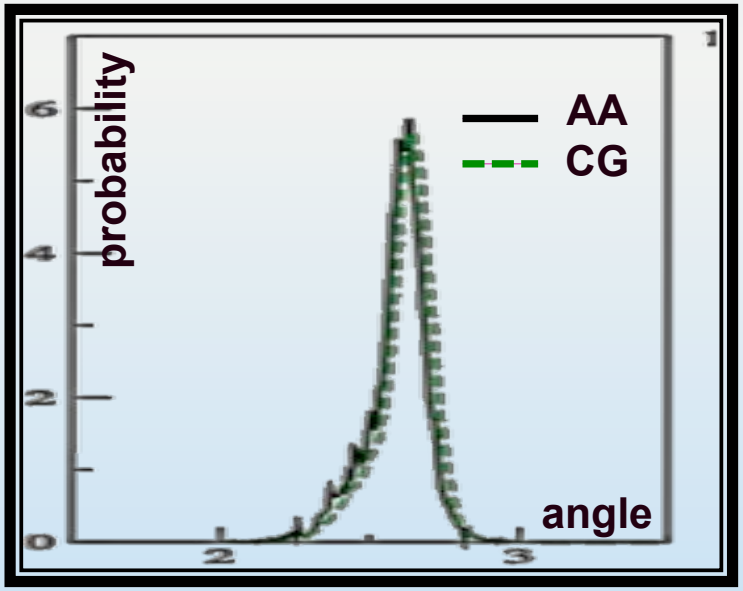


Looks of the Martini model

Bottom-up approach for bonded interactions

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





Looks of the Martini model

Simulation parameters important

- **Simulation parameters** are considered to be part of the force-field!

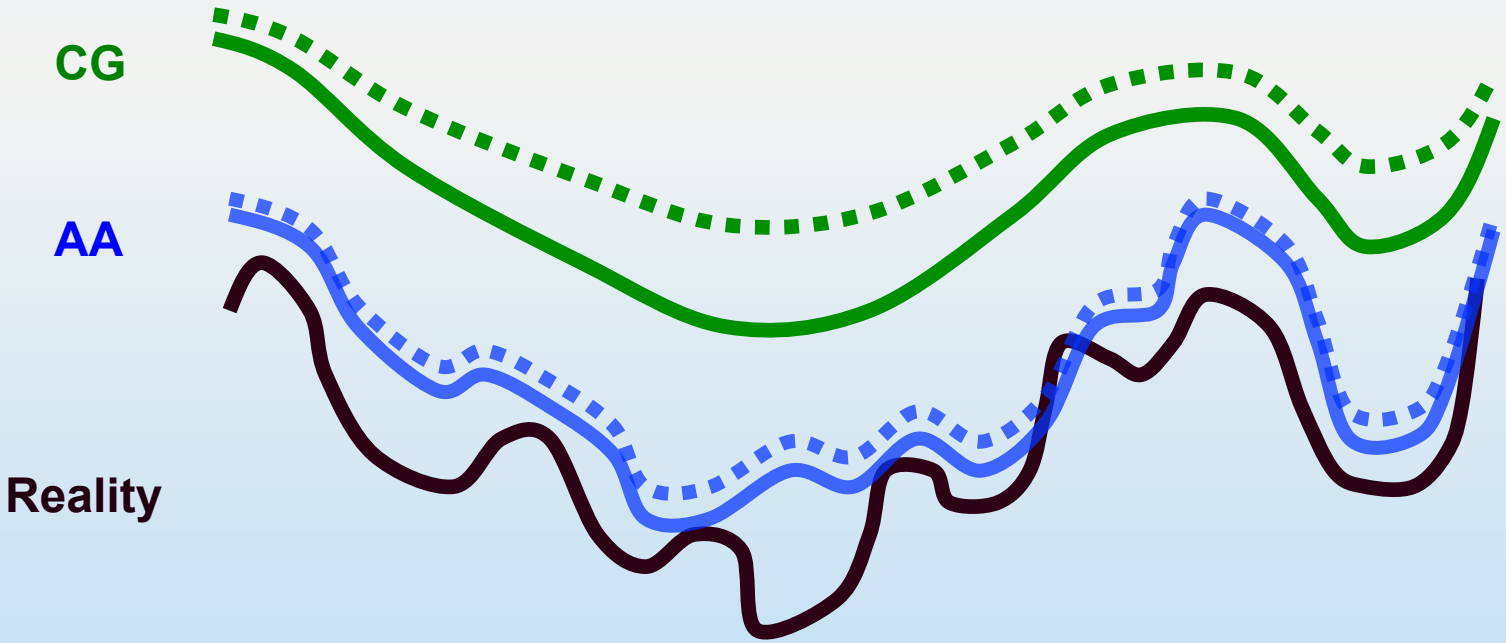
  - Cut-off 1.2 nm (using shifted potentials)

  - Relative dielectric constant = 15 for implicit screening
    Effectively distant-dependent!

Looks of the Martini model

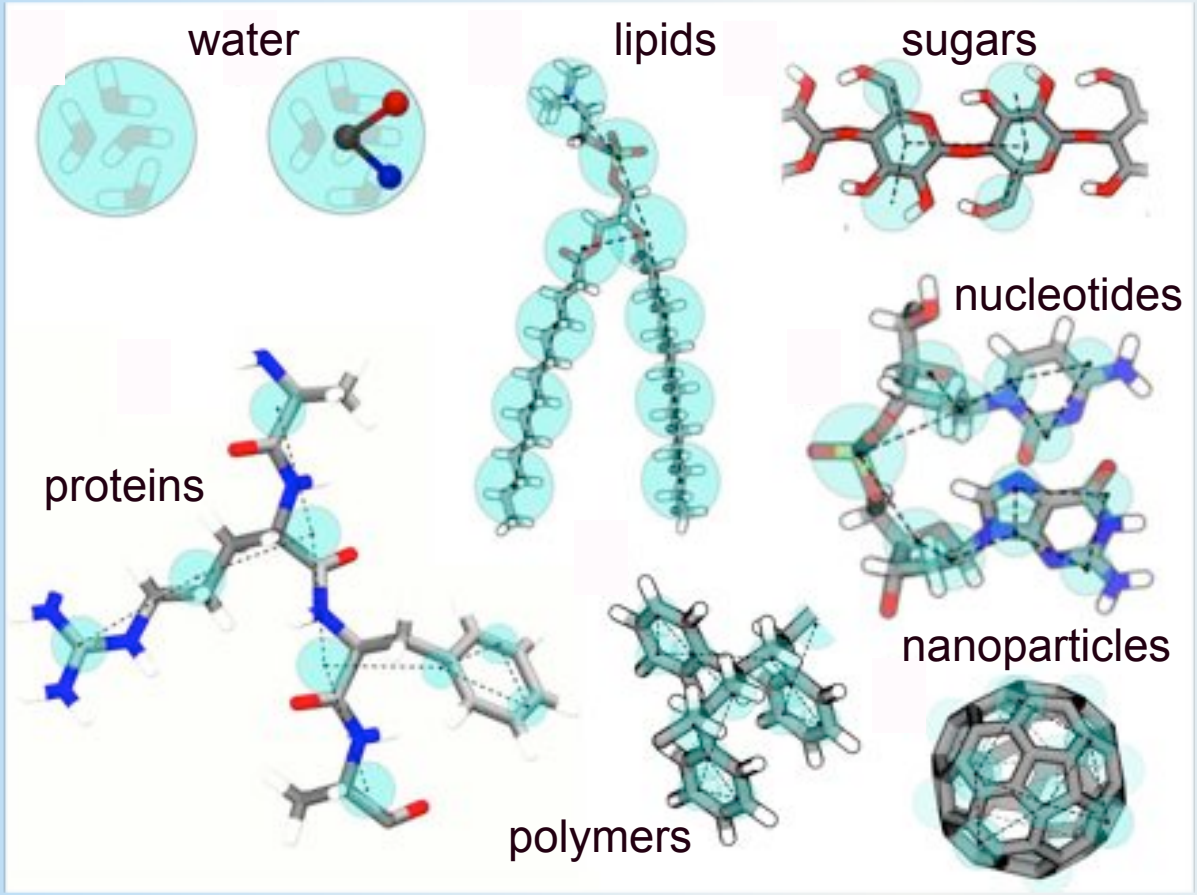
Martini tolerates large time steps

- **Time steps of 20-30 fs can be used**
  (accurate sampling is less critical)



Looks of the Martini model

Welcome to the Martini zoo!



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

Key features:

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

(building block approach)

- Versatility

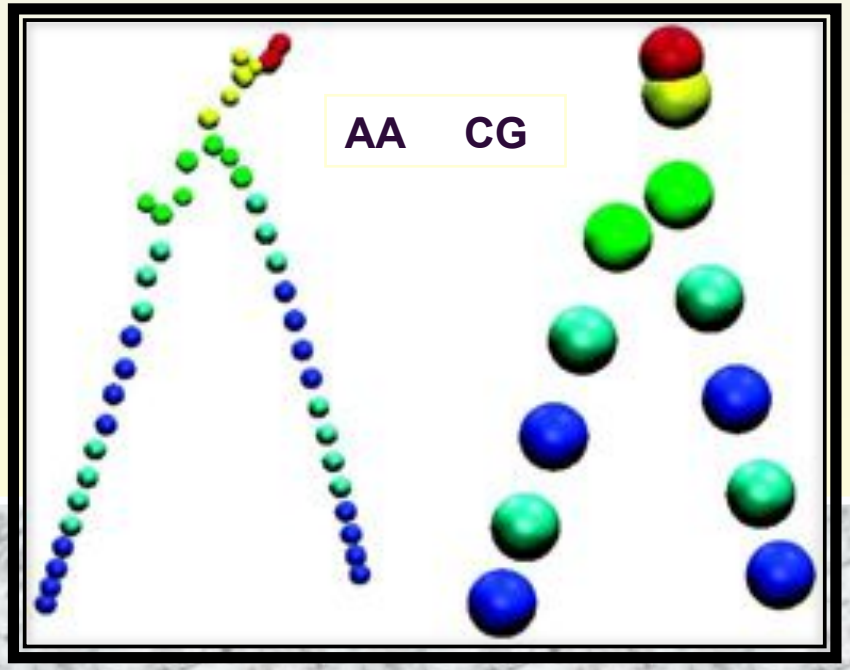
Parameterization:

TOP DOWN
Thermodynamic data
BOTTUM UP
Atomistic simulations

Examples of validation

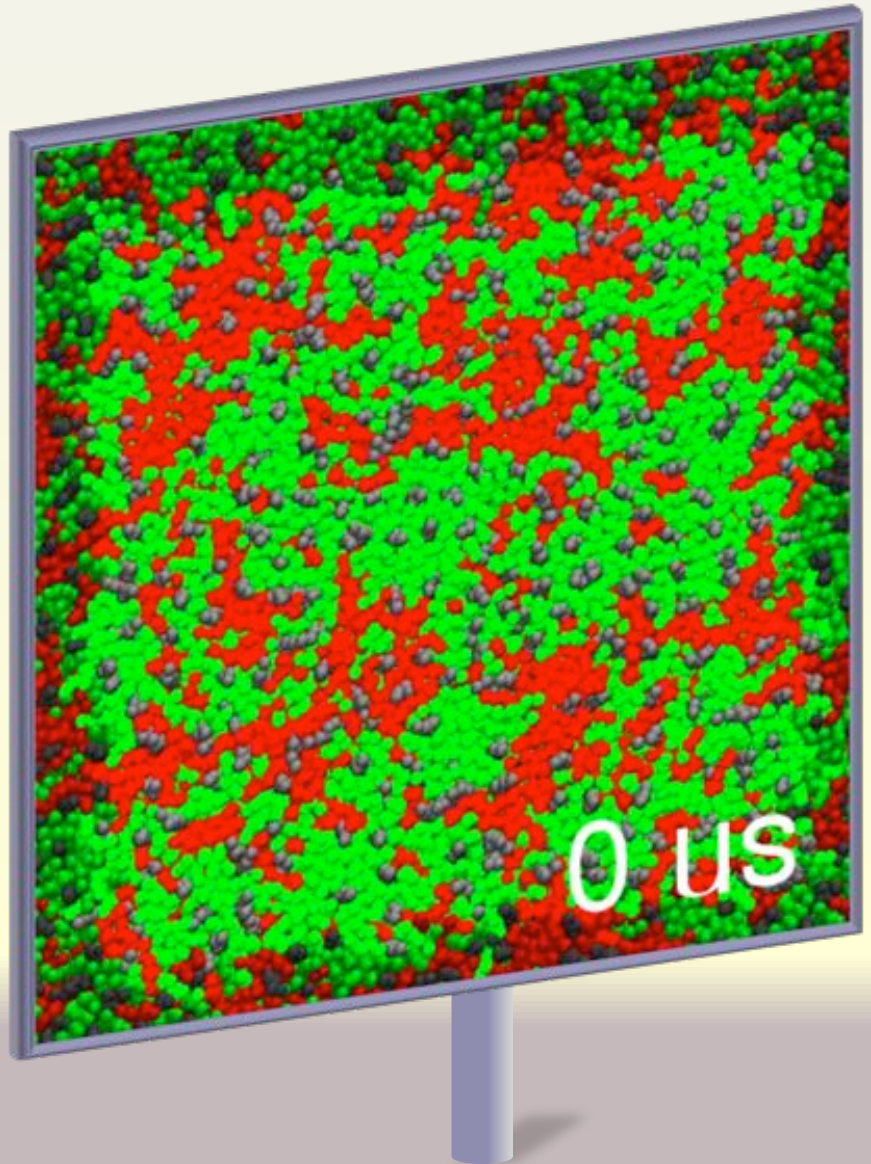
Lipid conformations match all-atom results

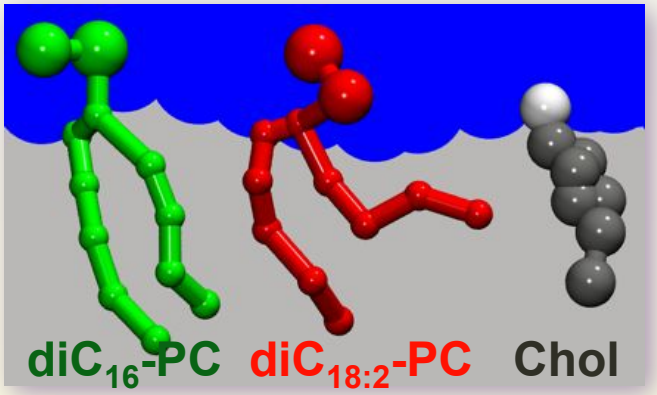
Averaged configurational space sampled by a lipid in a bilayer

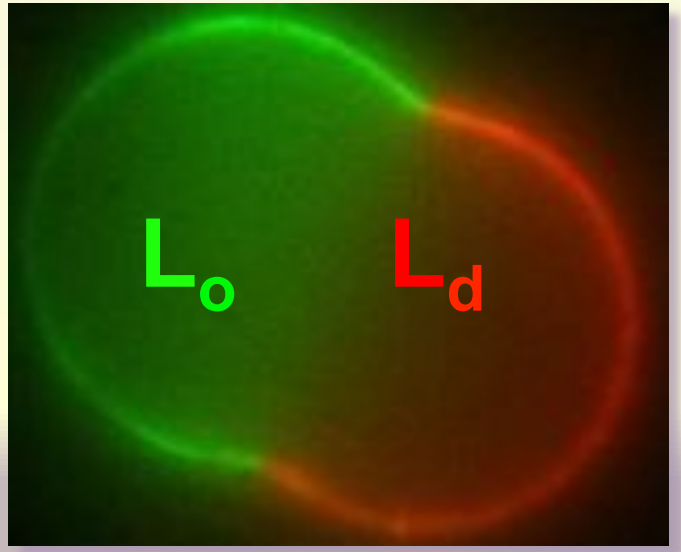


Examples of validation

Reproducing experimental lipid phase behavior

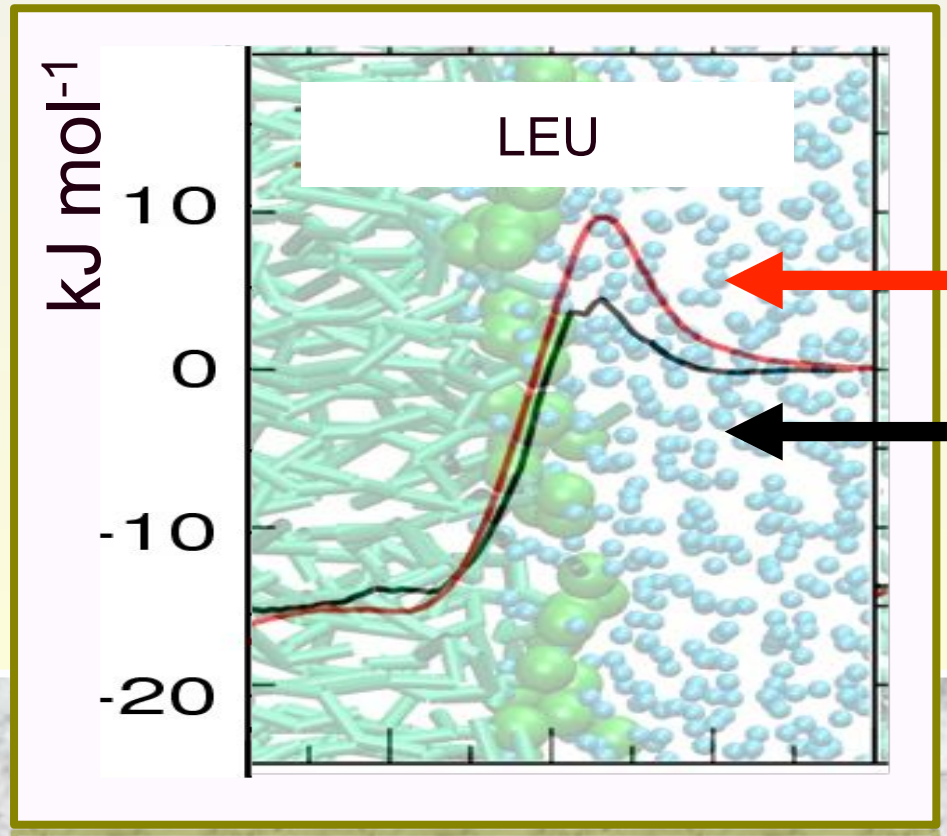






Examples of validation

Matching all-atom partitioning free energies

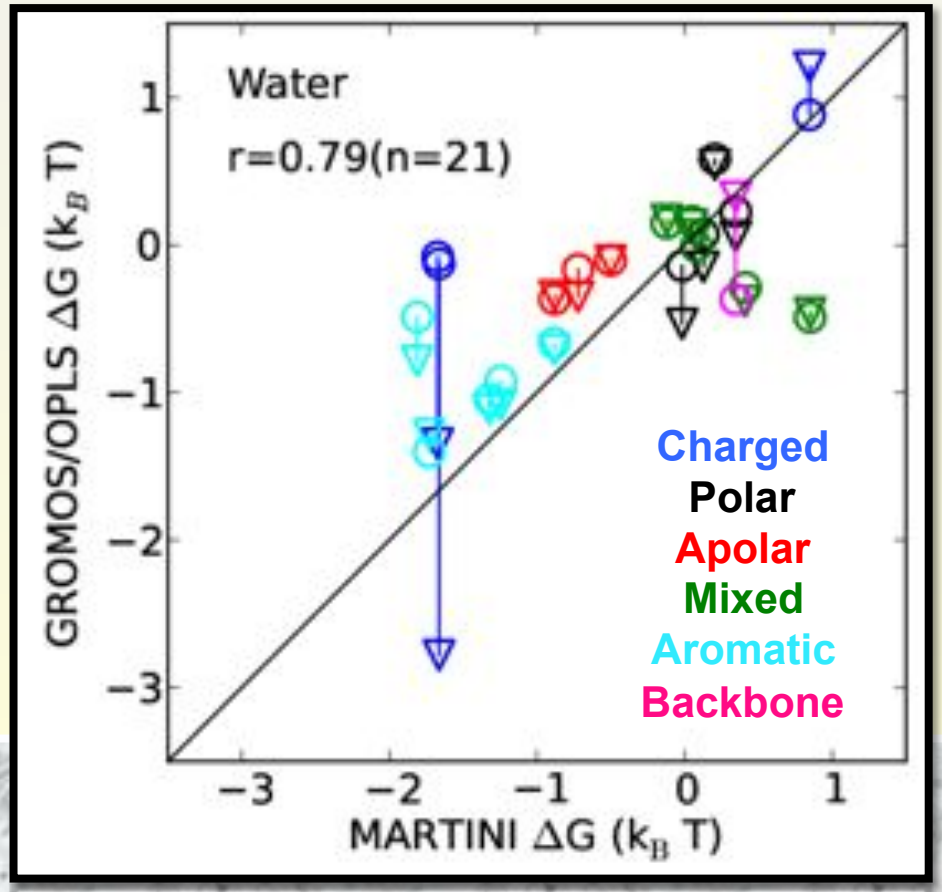


coarse-grain

atomistic

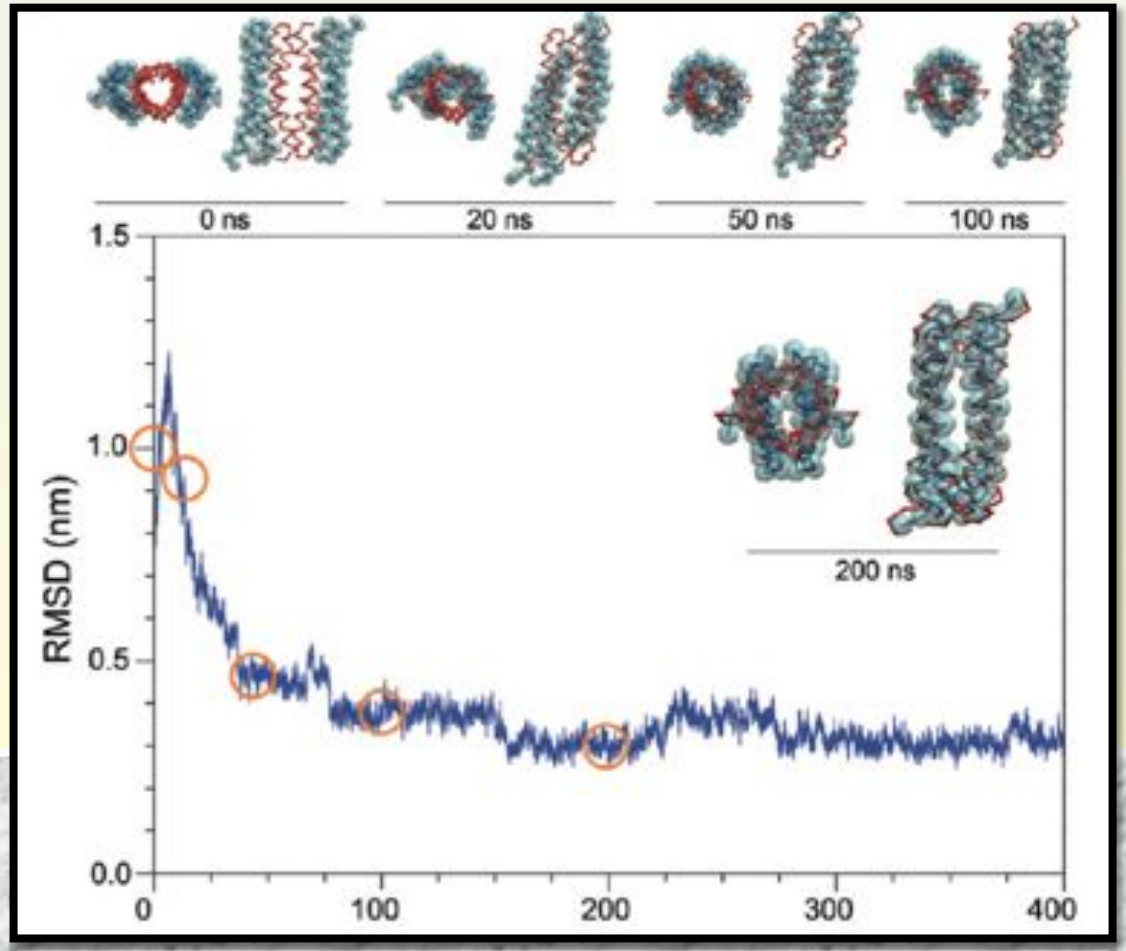
Examples of validation

Matching all-atom dimerization free energies



Examples of validation

Reproducing known structure of protein-protein complexes

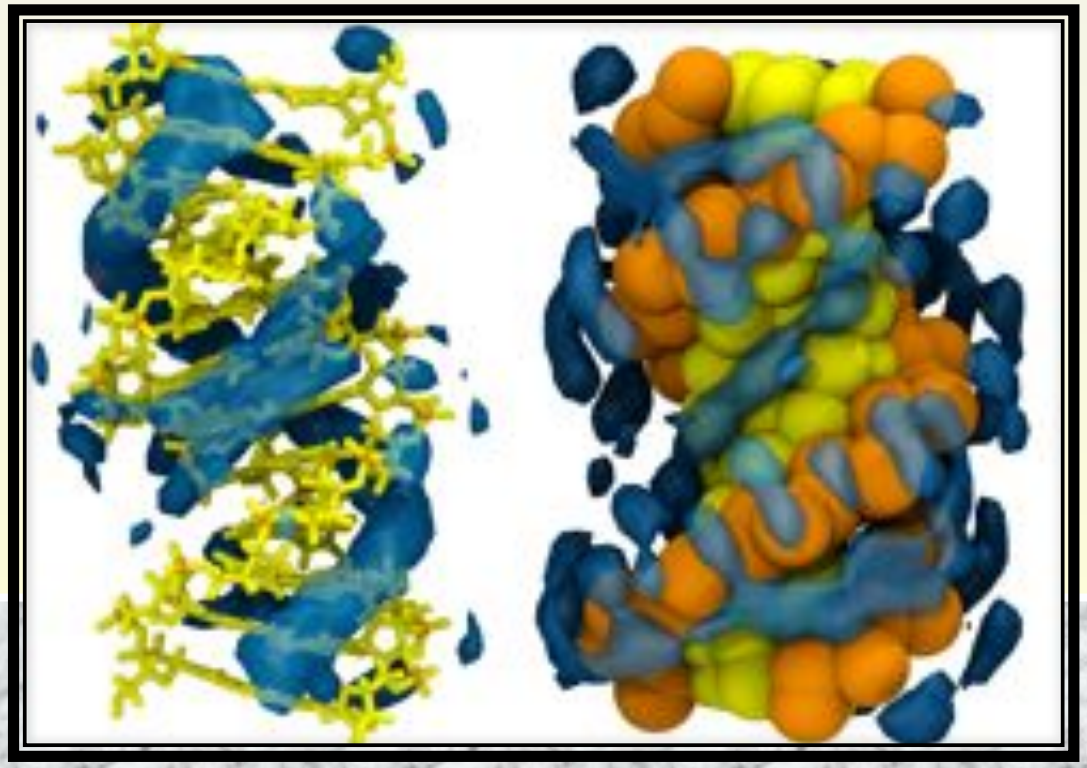


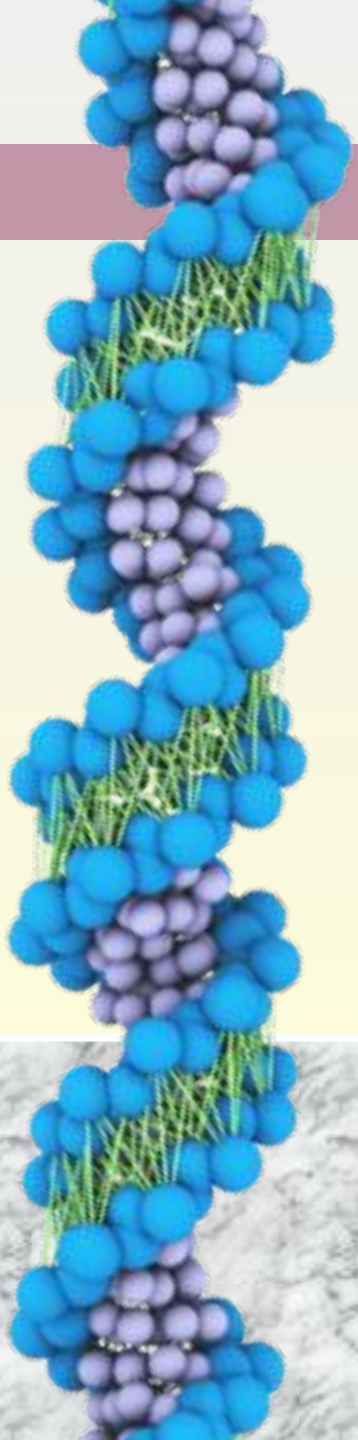
repressor of primer (ROP) protein

Examples of validation

Reproducing counterion condensation of dsDNA

Charmm **Martini**





Limitations of the Martini model

Good to know the limits

- **Limited resolution**
- **Directional h-bonds are missing**
- **Missing entropy, compensated by reduced enthalpy**
- **Electrostatic screening of water is only implicit**
- **Limited fluid range of LJ interactions**
- **Friction from atomistic degrees of freedom is missing**
- **Interdependency of parameters**

"I like to have a martini, two at the very most. After three I'm under the table, After four, I'm under my host." - Dorothy Parker

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"

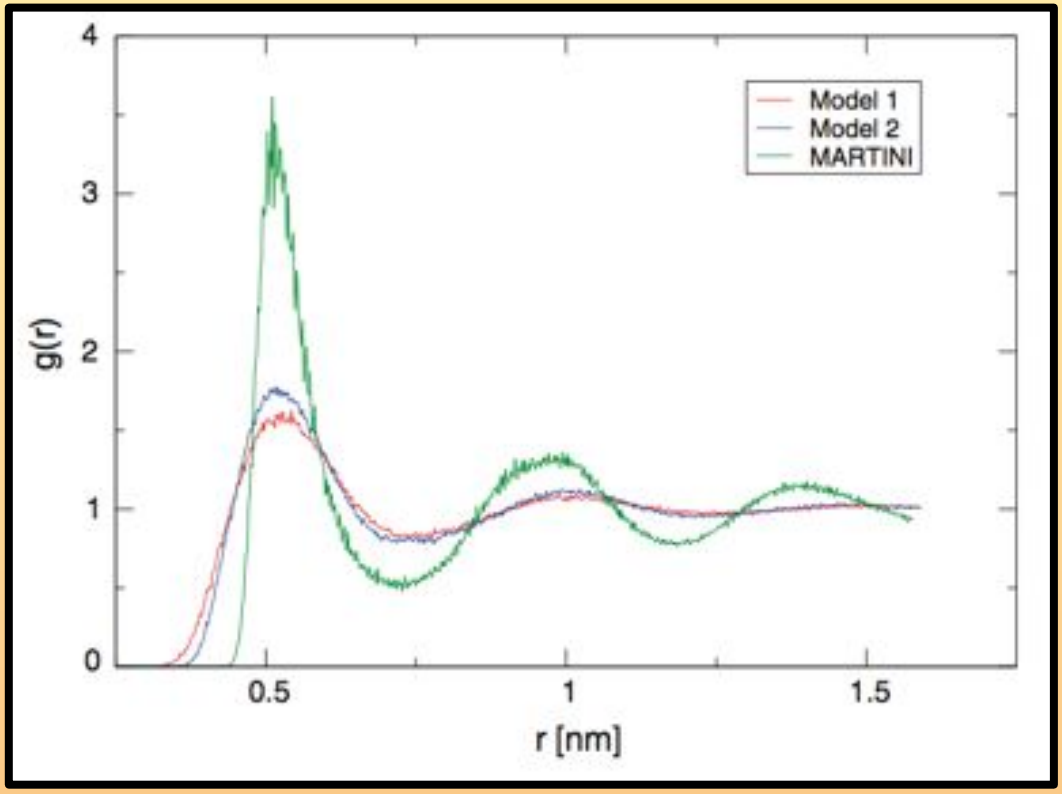
Convinced referee:

"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*

(more details, and possible solutions in following lectures)

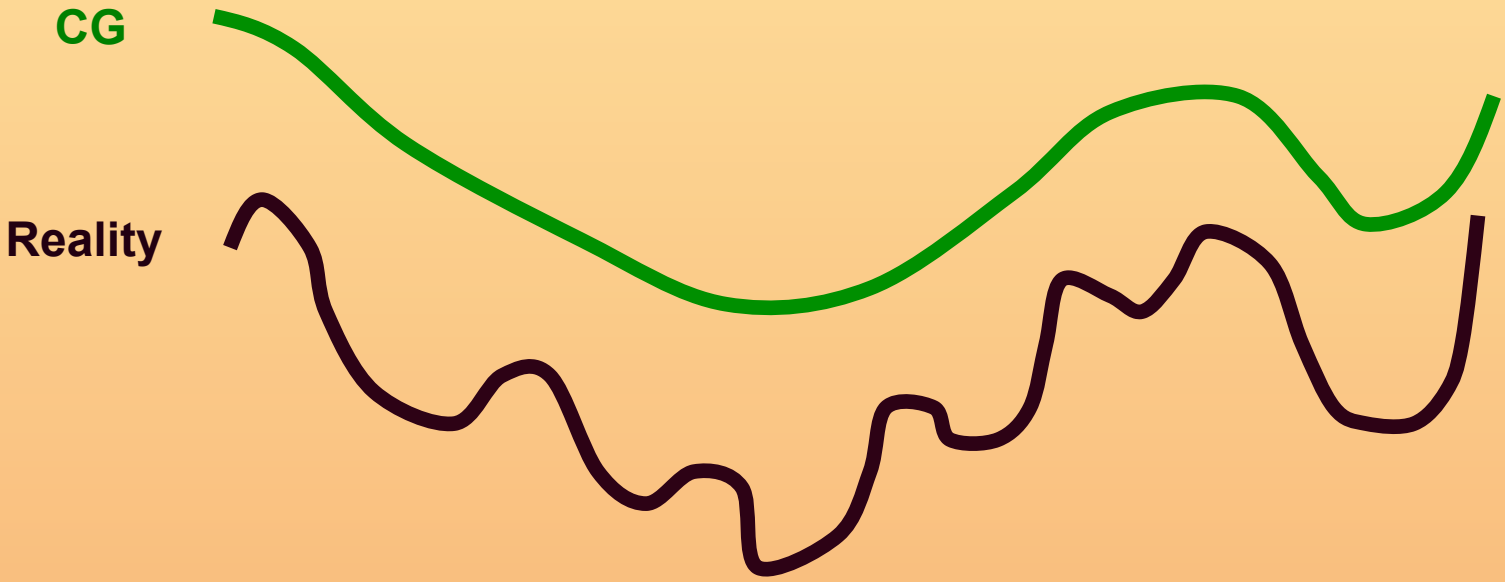
Limitations of the Martini model

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

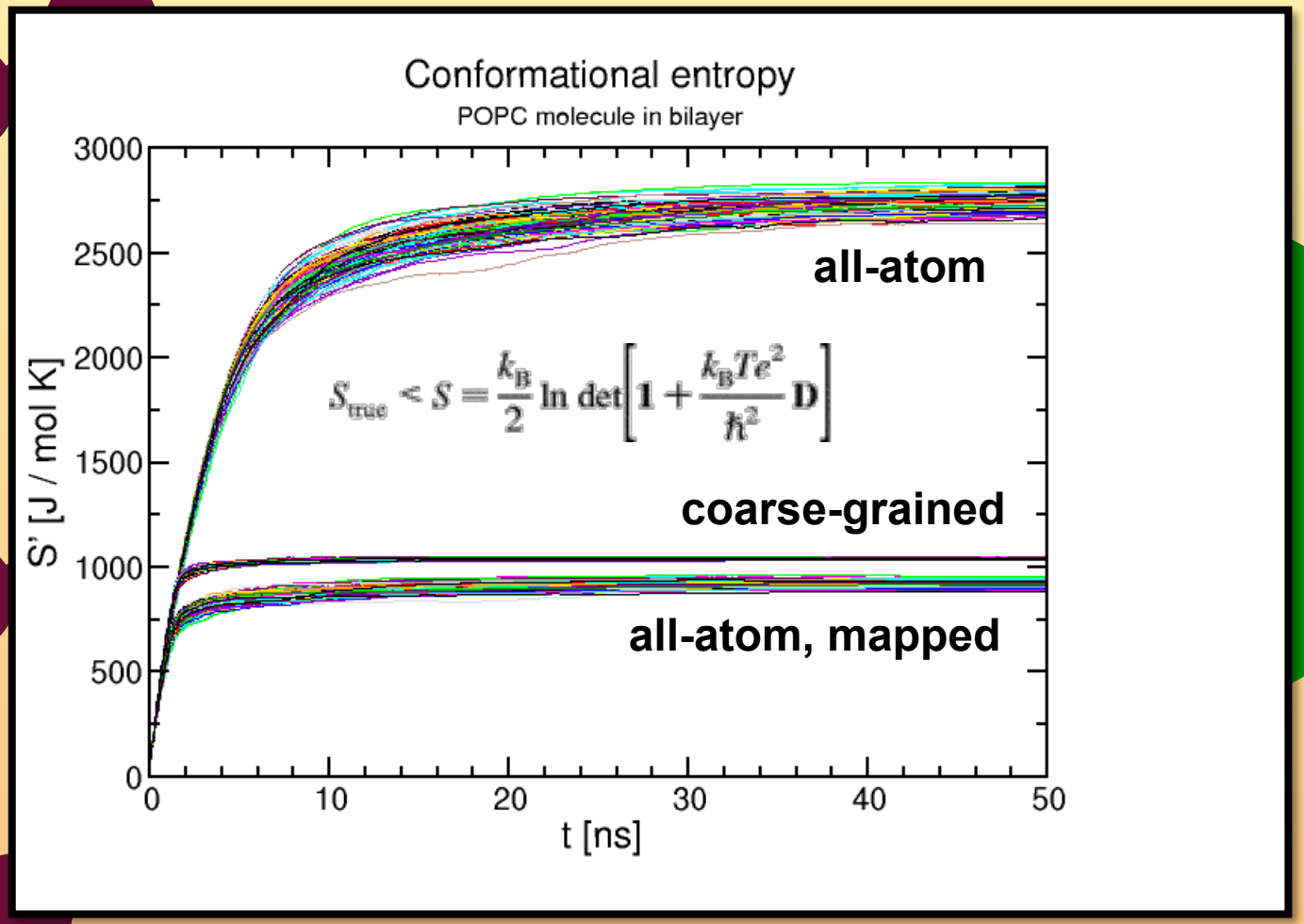
- Time scale should be interpreted with care

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*

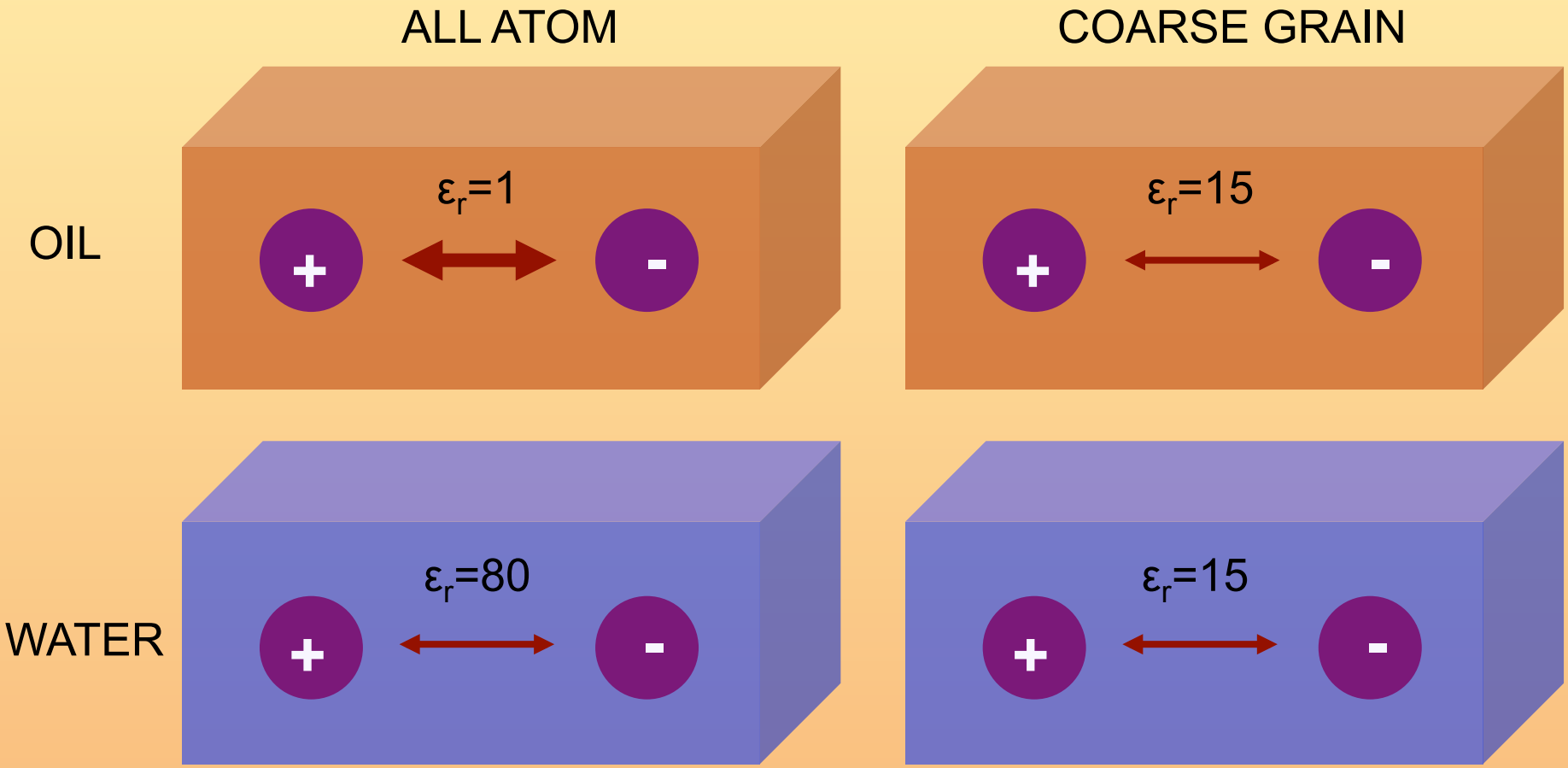
Solution:

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*

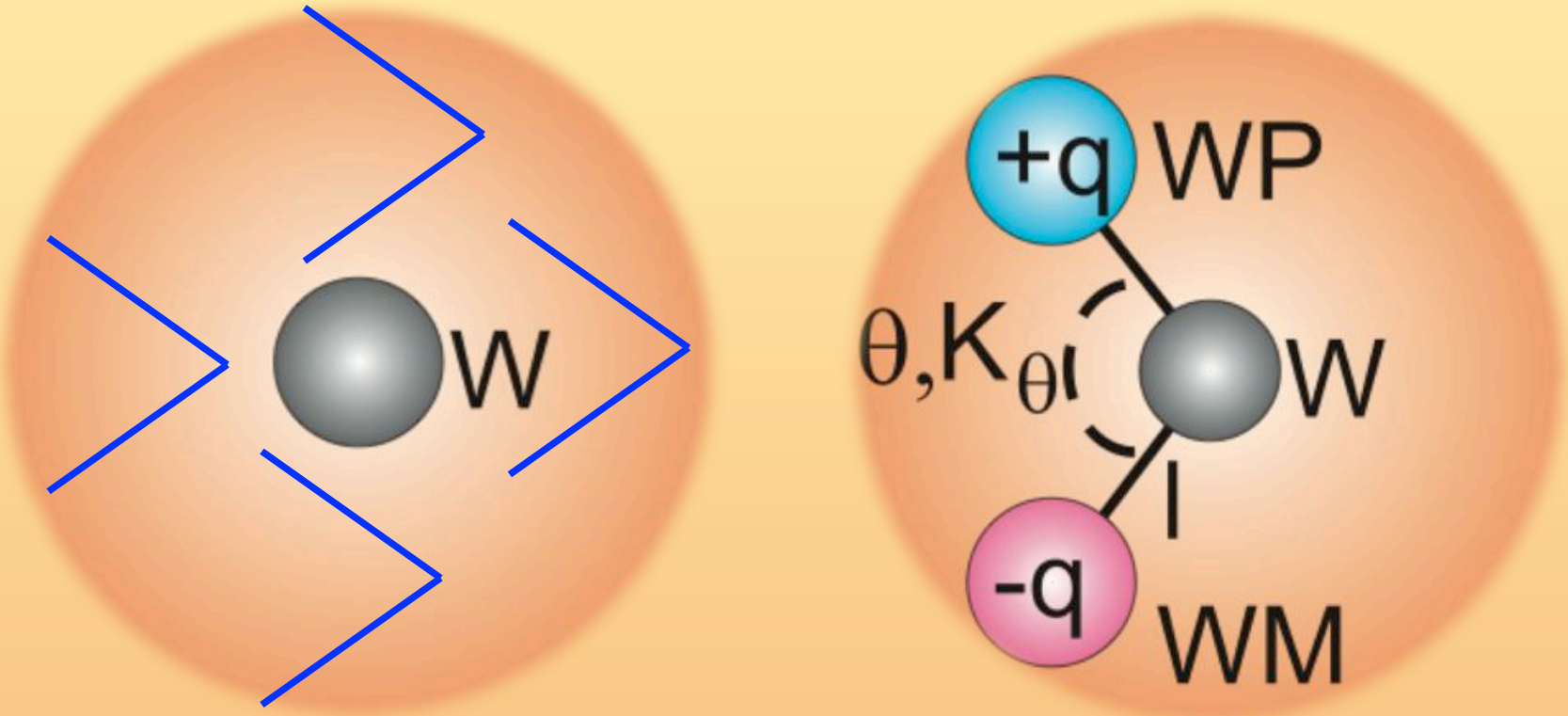
Solution:

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}
$LJ_{W\text{-}W}$	$\varepsilon = 4.0$ 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

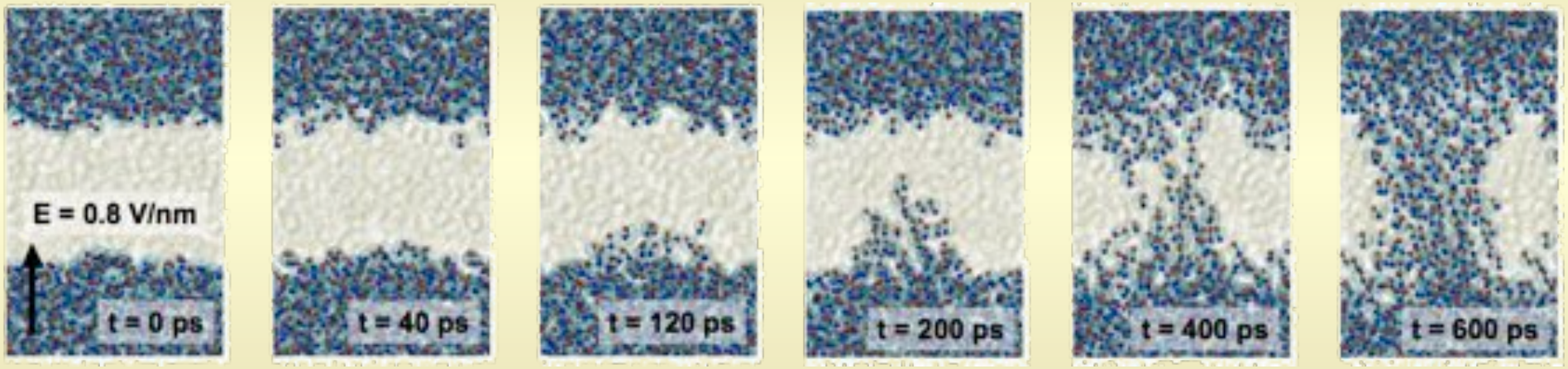
◆ **Dielectric constant of real water reproduced**

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

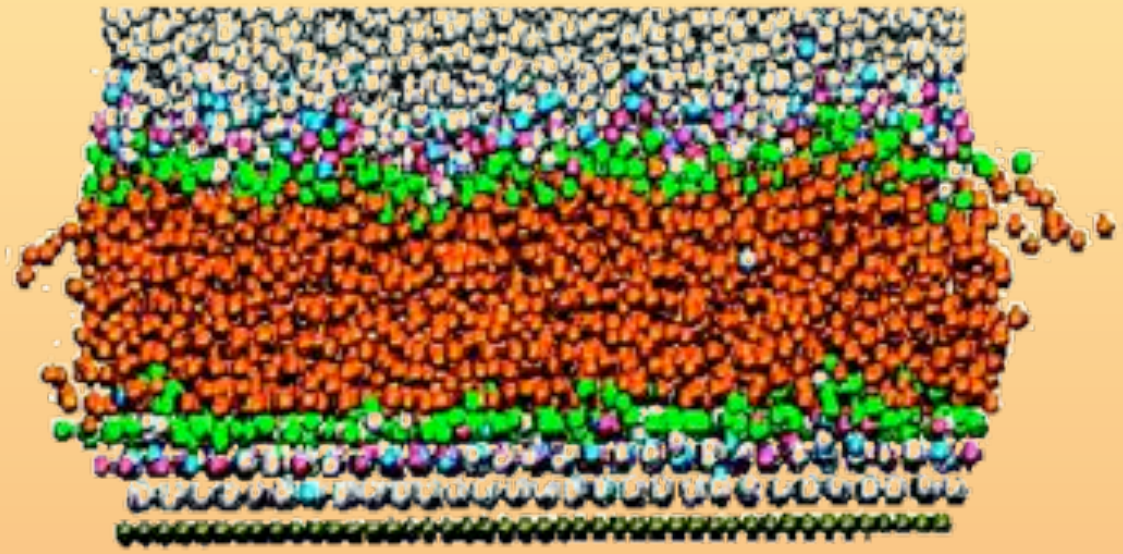


(similar to atomistic simulations by Tieleman)

Limitations of the Martini model

Interdependency of parameters

➢ *Local improvement may lead to global disaster*



- ***Problem:***
  Martini water freezes near solid support
- ***Local improvement:***
  Reduce water-water interactions to 76%
- ***Global disaster:***
  Lipid bilayer now behaves as solvated by ethanol

Limitations of the Martini model

Electrostatic screening of water is only implicit

- *Local improvement may lead to global disaster*

Solution:

Make force field optimizations with care !

Applications of the Martini model

Main areas of research where Martini has been successfully applied

- **Simulation of basic (bio)molecular processes**
- **Unraveling the workings of biomacromolecules**
- **Computational design of advanced (bio-inspired) materials**
- **Simulation of collective processes**
- **Simulation of the dynamical organization of complex systems**

Long time scales

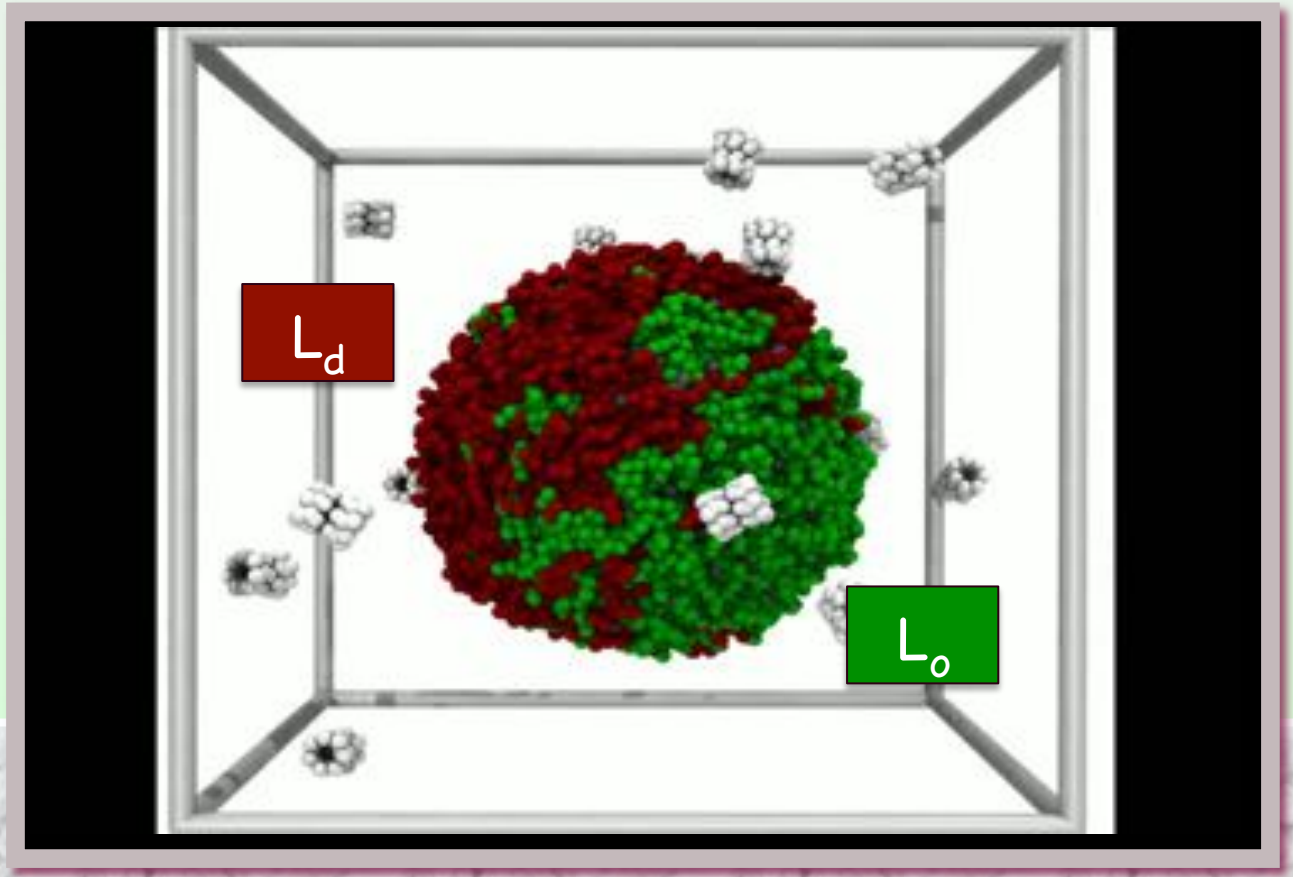
High throughput

Huge systems

Large complexity

Examples of application

Simulation of basic (bio)molecular processes

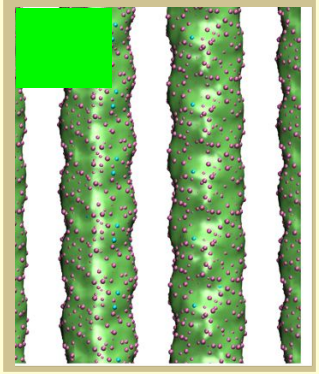


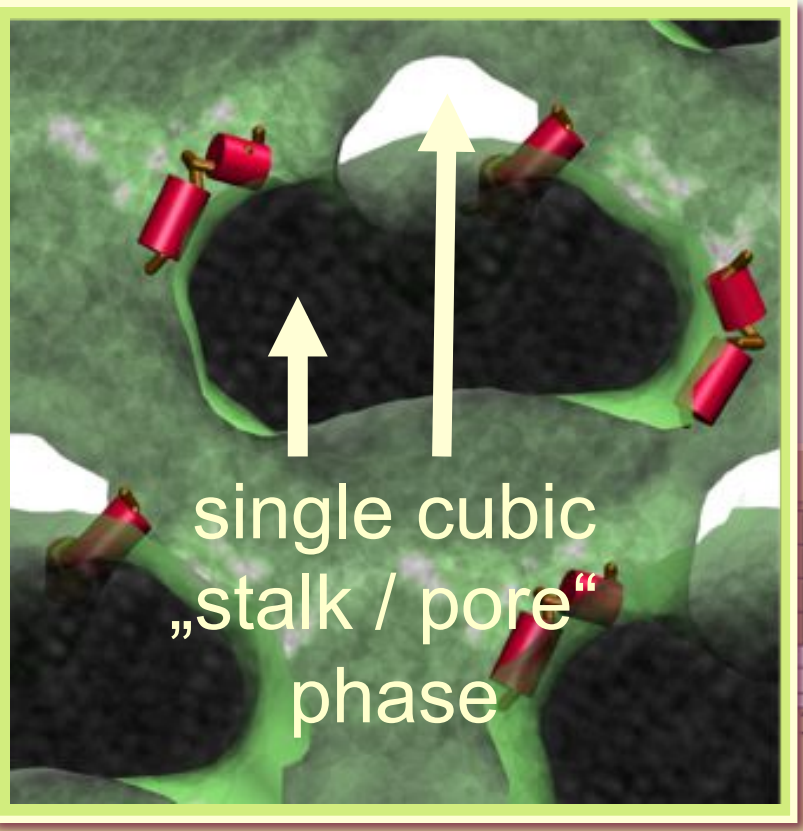
Extraction of cholesterol from Ld domains by cyclodextrin
Lopez et al, Sci Rep, 2013

Examples of application

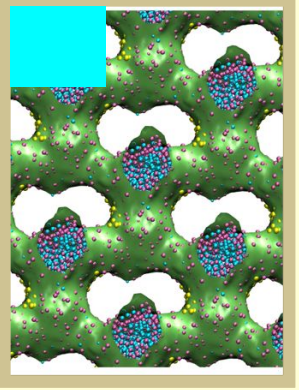
Simulation of collective processes

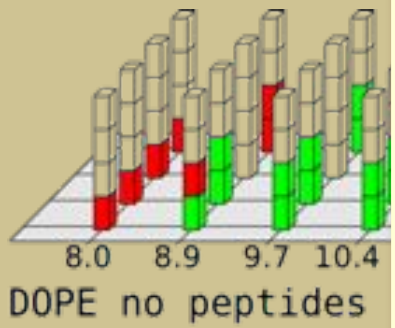
inv hexagonal

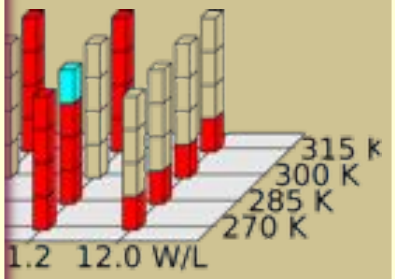




single cubic





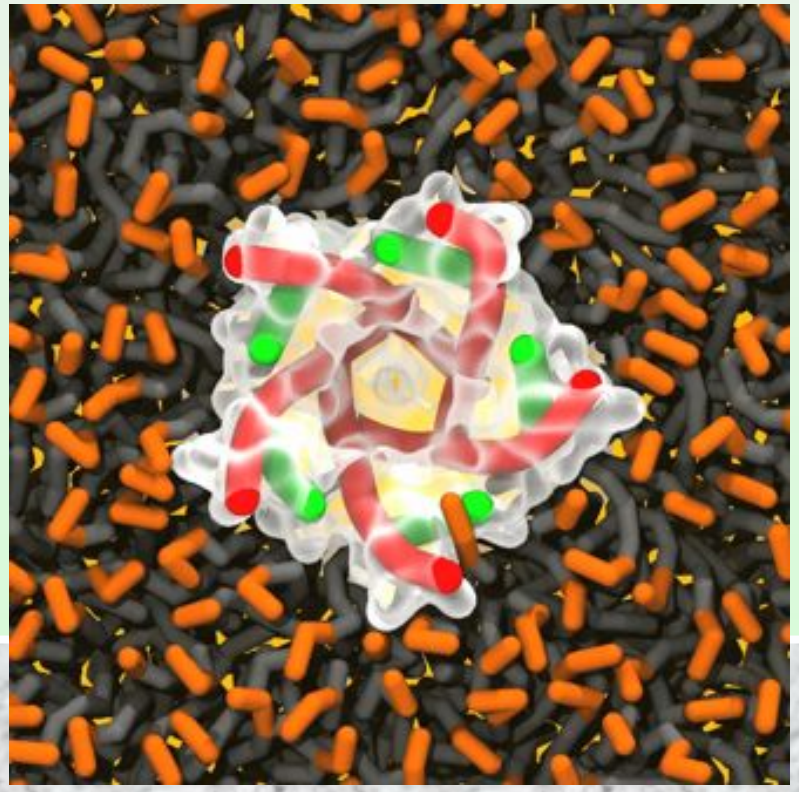


Effect of fusion peptides on lipid phase diagram

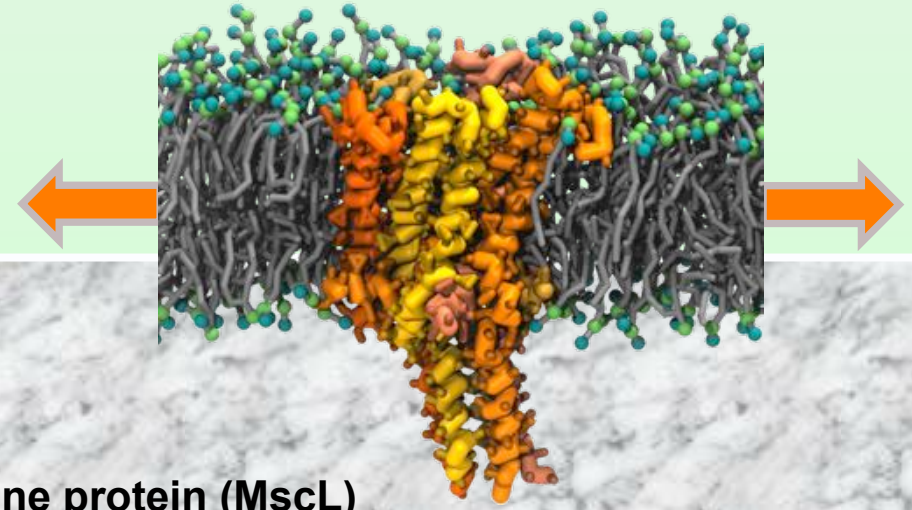
Fuhrmans et al, JACS 2012

Examples of application

Unraveling biomolecular function



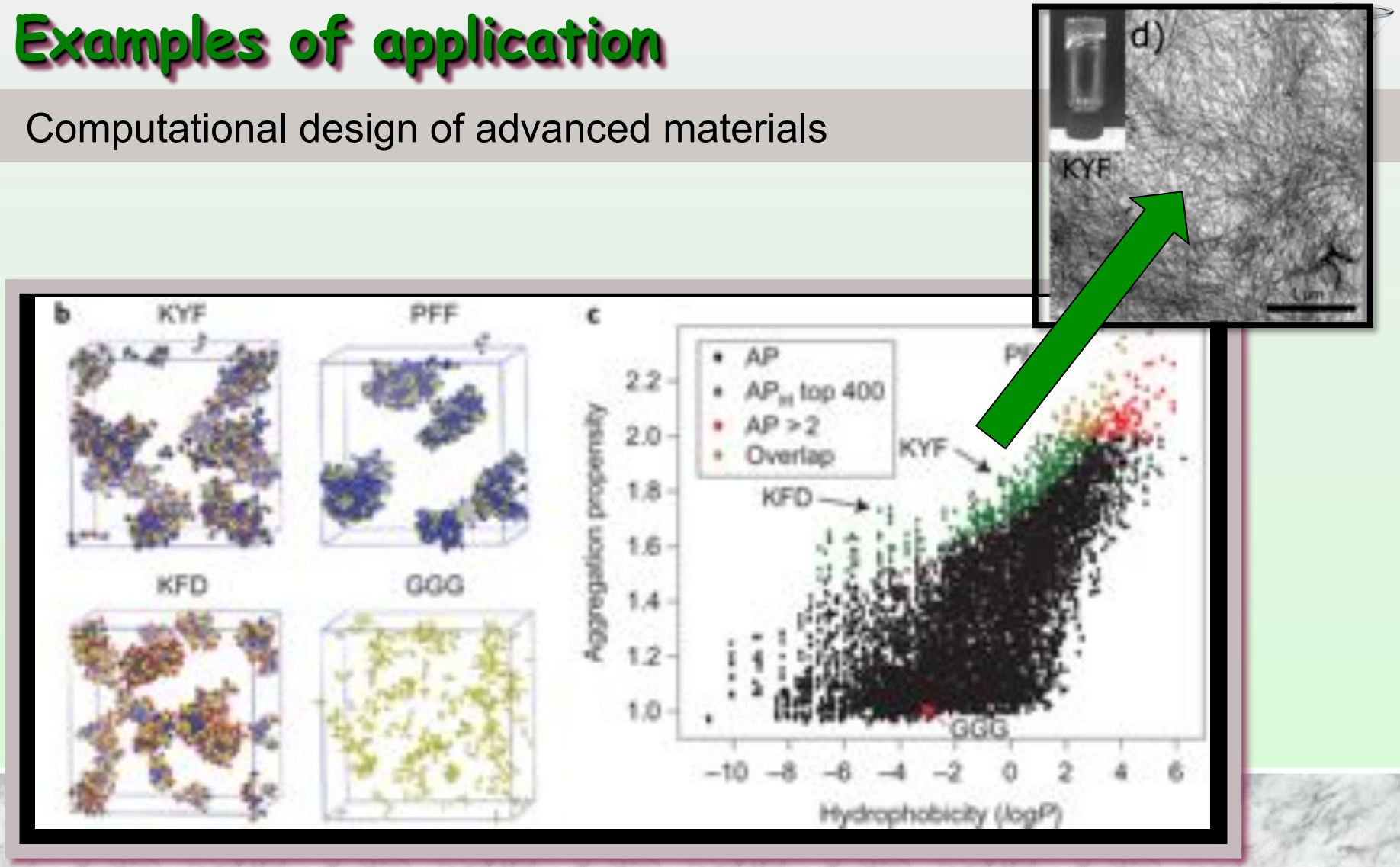
- 1 *Tb*-MscL protein
- 256 DOPC lipids
- 2 μs simulation
- bilayer under tension
- Martini forcefield



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

Examples of application

Computational design of advanced materials



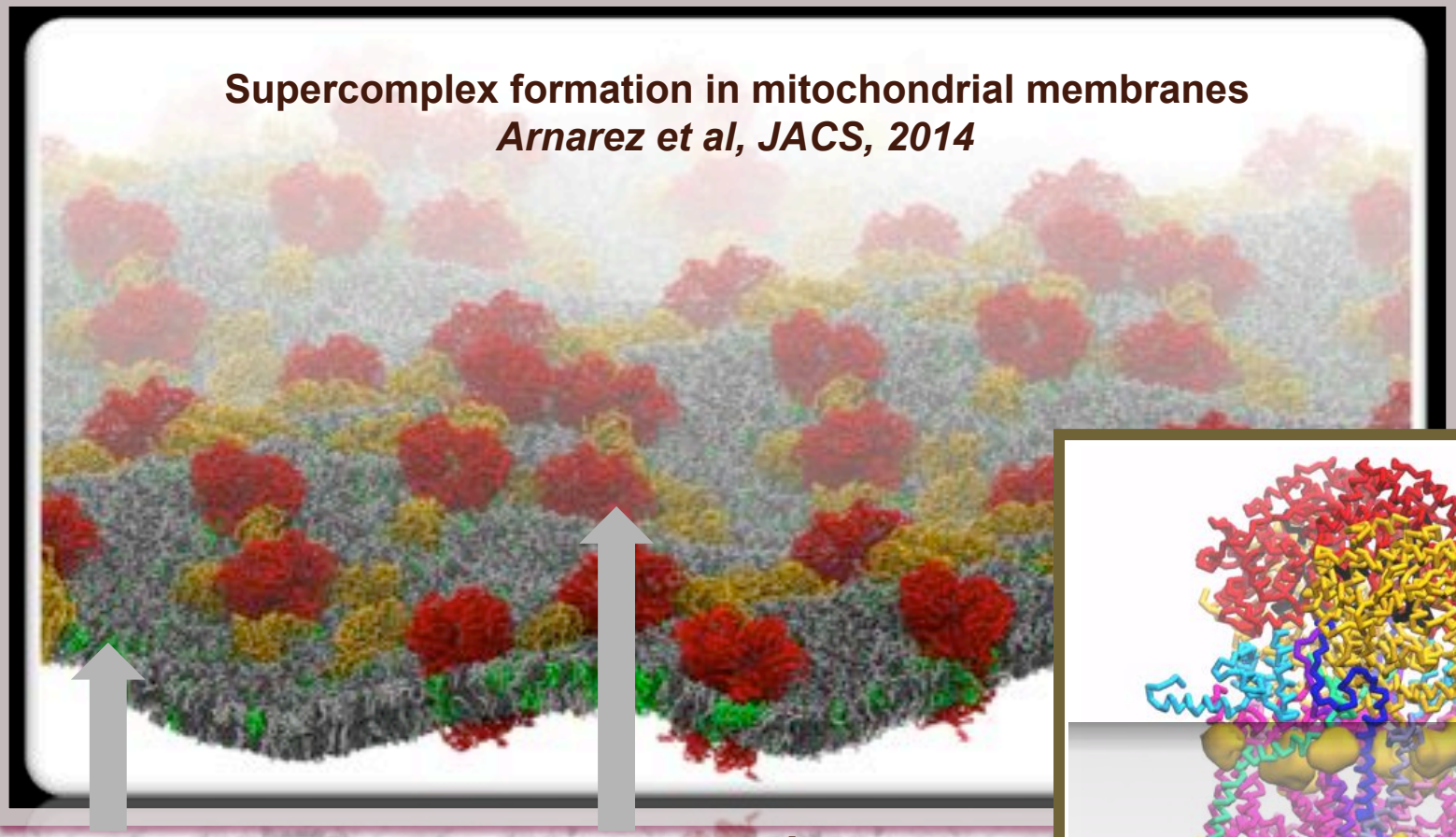
Screening the aggregation behavior of all possible tri-peptides

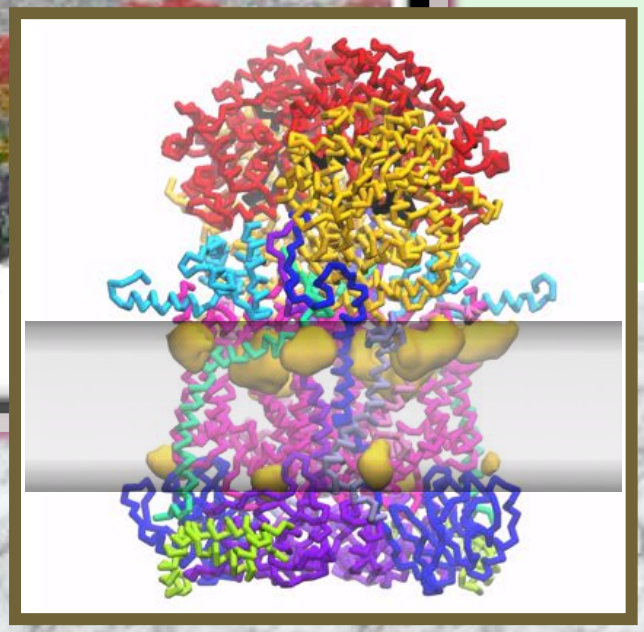
Frederix et al, Nat. Chem., 2015

Examples of application

Simulation of dynamic organization of complex systems

Supercomplex formation in mitochondrial membranes
Arnarez et al, JACS, 2014





lipids
cardiolipin
PC, PE, PG

respiratory chain complexes
cytochrome c oxidase, cytochrome bc1

PhD positions available !

- Multiscale method development
- Design of self-assembling nanotubes
- Modeling complex cell membranes

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

Enjoy Sampling Martinis !!