university of groningen

Martini Workshop 2017

Future of Martini Force Field

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Huge success of Martini 2 during 10 years, but there are some problems

1) Fundamental problems related with CG approach

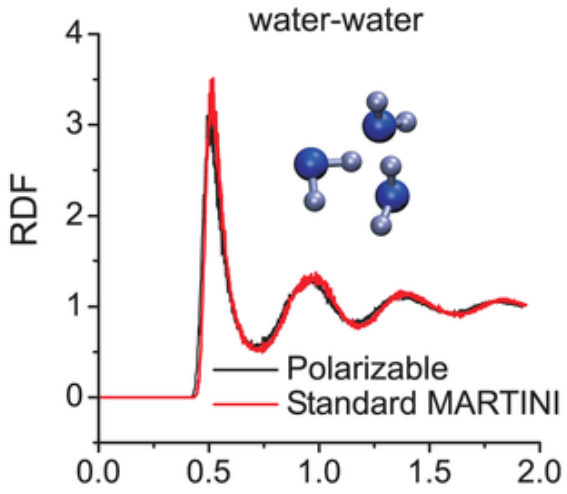
- 1A) Missing entropy, compensated by reduced enthalpy
- 1B) Temperature dependence off
- 1C) Driving forces wrong
- 1D) Time scale

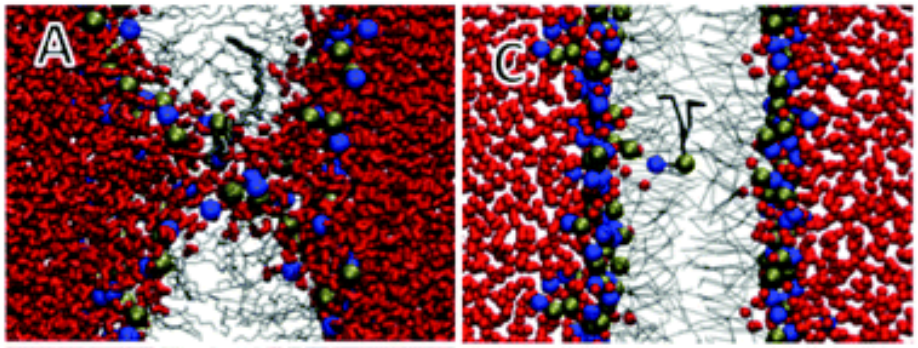
2) Problems that could be solved buy polarizable models and new bonded parameters

- 2A) Protein and DNA/ RNA structures are fixed.
- 2B) Electrostatic screening of water is only implicit
- 2C) Directionality of H-bonds

Huge success of Martini 2 during 10 years, but there are some problems

3) Problems that (potentially) could be solved by softer non-bonded potentials .





Bennett and Tieleman , JCTC, 2011

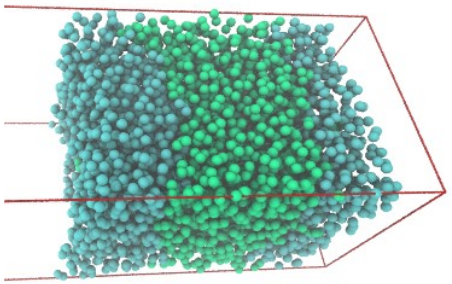
3A) Solvents are too structured and water freezing.

3B) Pores are difficult to be formed in bilayers.

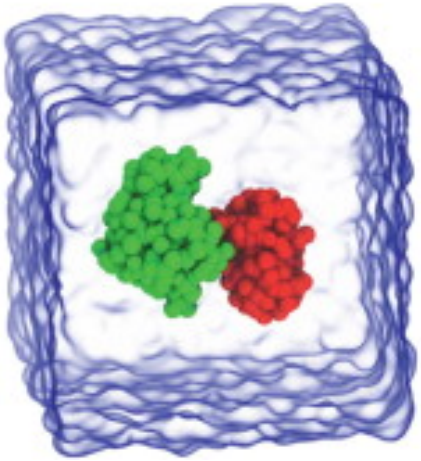
Huge success of Martini 2 during 10 years, but there are some problems …

4) “Sticky” problems: Excessive aggregation of some compounds.

4A- Phase separation of systems that should mix (ex: benzene+cyclohexane)

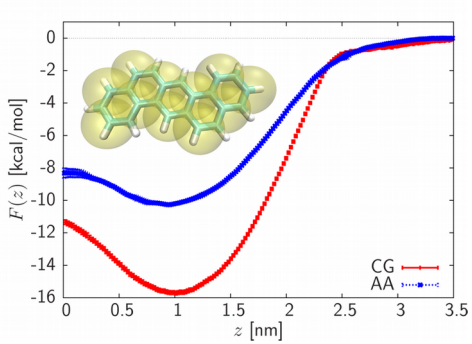


4D- proteins



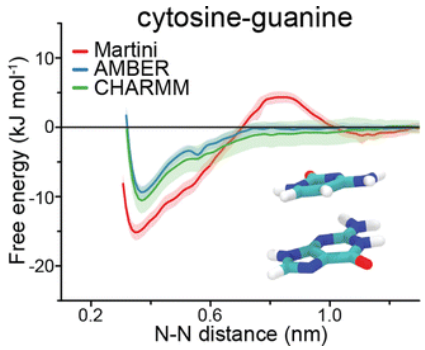
Stark, Andrews, and Elcock, JCTC, 2013

4B- Wrong partitions



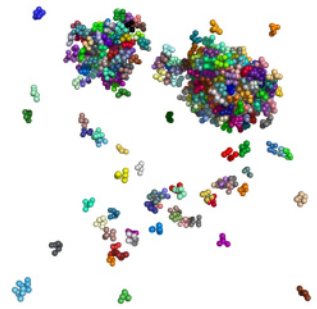
Bereau and Kremer, JCTC, 2015

4C- Big barriers



Uusitalo, JCTC, 2015

4E- sugars

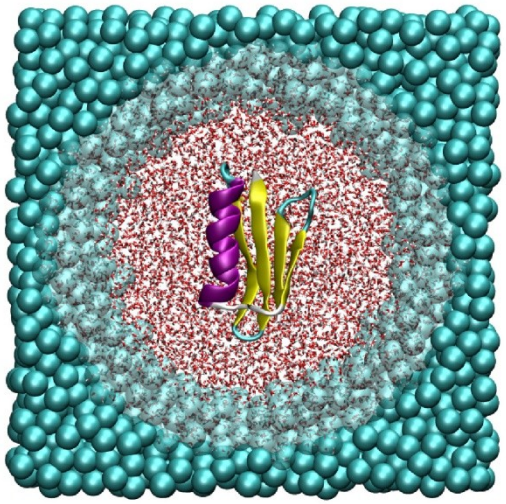


Schmalhorst et al, JCTC, 2017

Current solutions for some problems

1) Improve your model:

- Polarizable models
- Multiresolution approaches
- New bead combinations and bonded parameters.



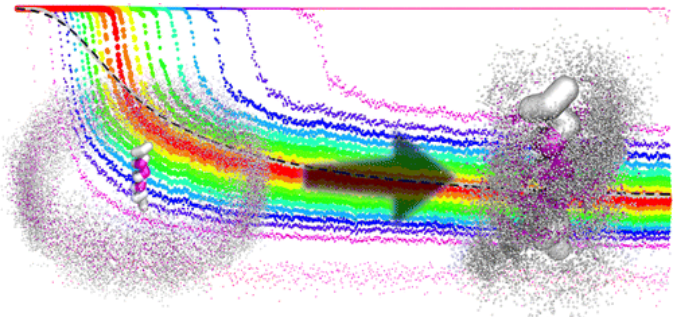
Zavadlav et al, JCP, 2014

Current solutions for some problems

2) Improve your sampling:

- Enhanced sampling methods
- Ensemble simulations (ex: Daft)
- New MD code implementations

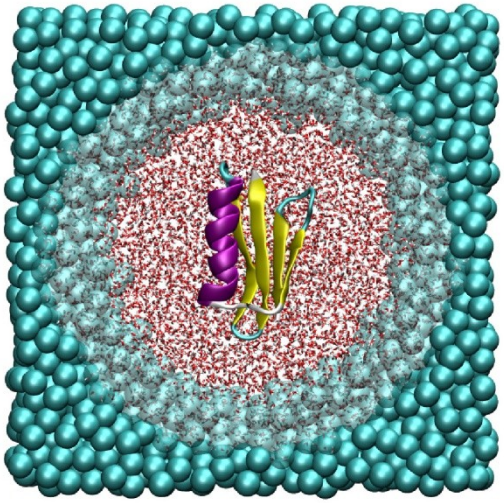
(ex: gromacs/namd/amber + GPUs)



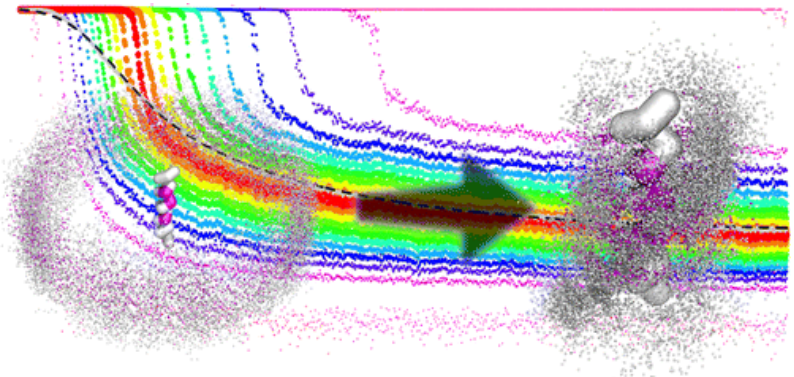
Wassenaar et al, JCTC, 2015

Current solutions for sticky problems

Improved model and Enhanced Sampling



Zavadlav et al, JCP, 2014



Wassenaar et al, JCTC, 2015

Both are computationally expensive and/or mentally demanding!

How could we improve the standard MARTINI 2 ?

Goals of the presentation

- Try to understand the reasons why some problems are happening with the current version of Martini 2 (specially the sticky problems).

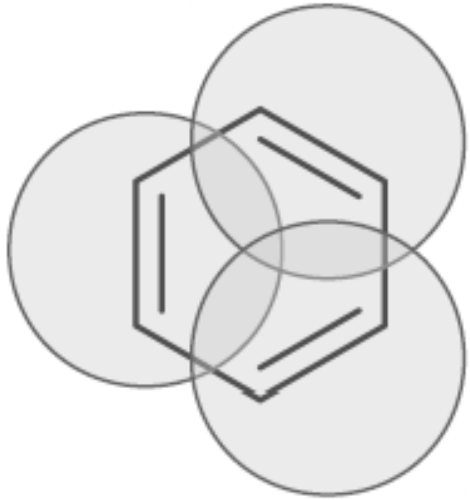
- Show some new improvements that will result in a new Martini (version 3.0).

Reasons for problems in Martini 2

Hypothesis 1: Lack of cross interactions in between normal and small (S)/tiny (T) beads

What are S- an T-beads?

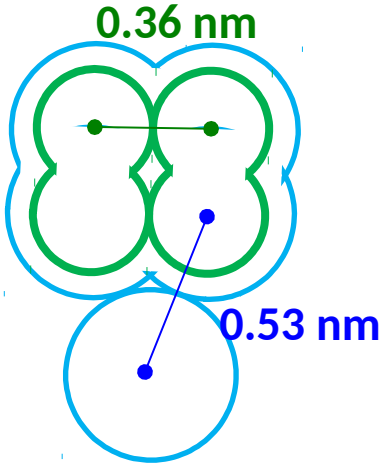
- Special Martini beads types used to model rings.
- Mapping: 2-to-1 (some cases 3-to-1)
- Lennard-Jones interactions

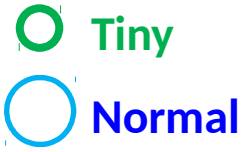


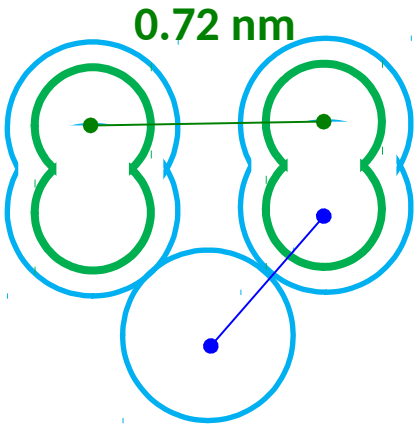
T – T	$\epsilon_T = 1 * \epsilon_N$	$\sigma_{TT} = 0.32$ nm (nucleotides).
S – S/T	$\epsilon_S = 0.75 * \epsilon_N$	$\sigma_{SS} = 0.43$ nm (general rings and some polymers).
N – N/S/T	ϵ_N	$\sigma_{N\,N} = 0.47$ nm (everything else).

Reasons for problems in Martini 2

Hypothesis 1: Lack of cross interactions in between normal and small (S)/tiny (T) beads





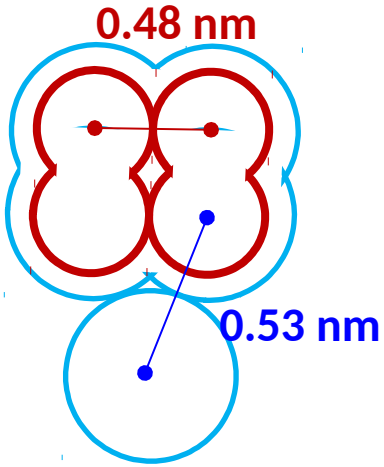


dissociation

Uusitalo, JCTC, 2015

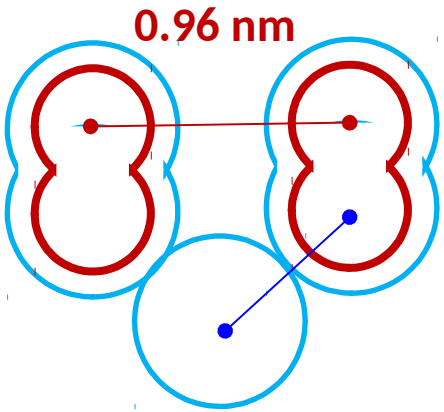
Reasons for problems in Martini 2

Hypothesis 1: Lack of cross interactions in between normal and small (S)/tiny (T) beads



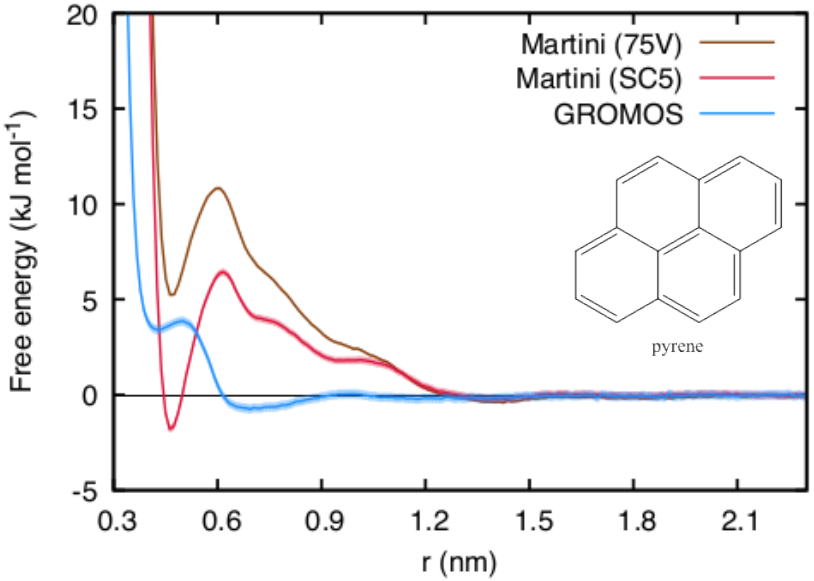
Small

Normal



dissociation ⟶

pyrene –pyrene PMF
in chloroform



Take-home message 1

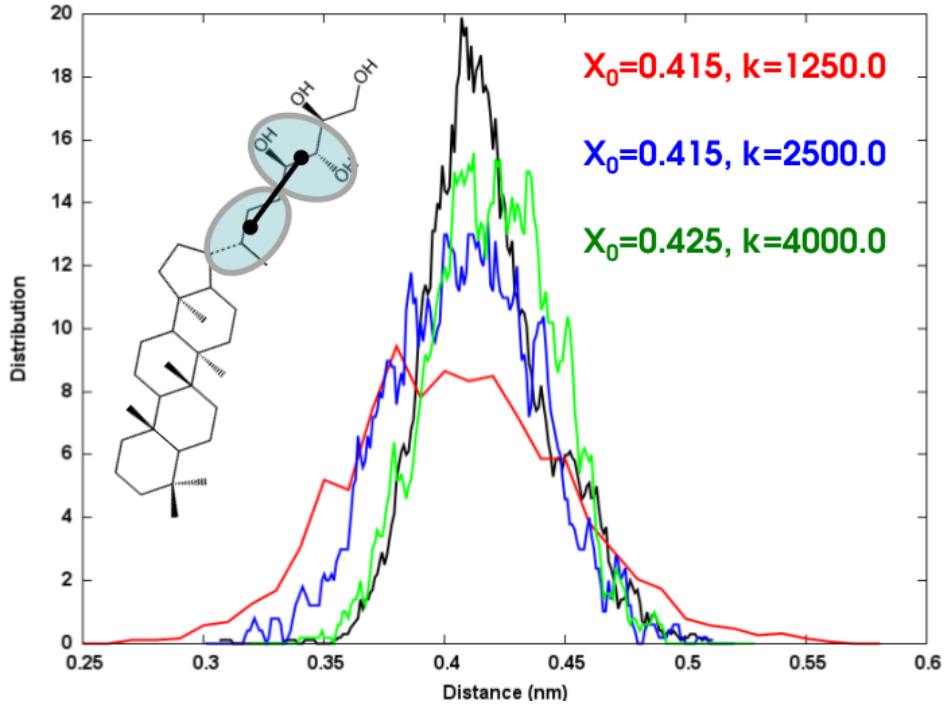
No free lunch with S-/T-beads

- *Advantage*: In relation to the normal bead sizes, they improve the interactions and packing of rings.

- *Disavantage*: can create artifical barriers that could promote aggregation in situations where rings should be soluble.

Reasons for problems in Martini 2
Hypothesis 2: Problems with short bond lengths

How we parametrize bond lenghts in Martini?



- Bond parameters can be obtained from atomistic simulation.

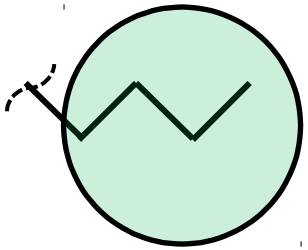
Reasons for problems in Martini 2

Hypothesis 2: Problems with short bond lengths

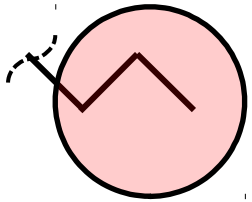
When can I have short bond lengths (< 0.40nm) ?

1) Bead with less than 4 heavy atoms

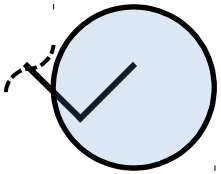
4-heavy atoms



3-heavy atoms

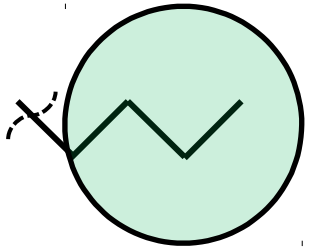


2-heavy atoms

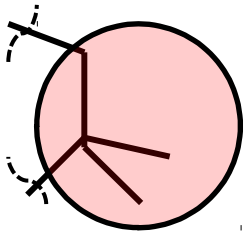


2) Bead with different geometry

linear



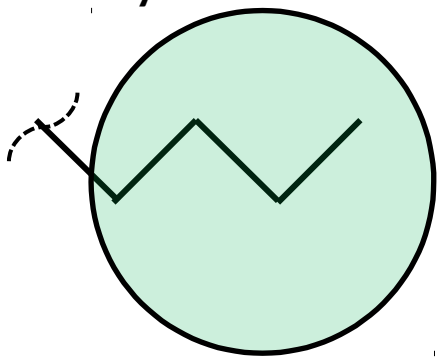
Branched
or part of a ring



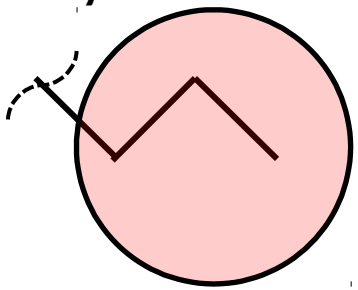
Reasons for problems in Martini 2

Hypothesis 2: Problems with short bond lengths

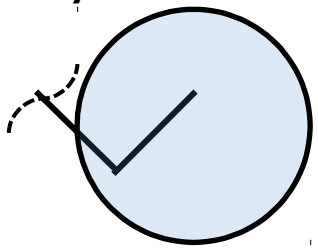
4-heavy atoms



3-heavy atoms



2-heavy atoms



How properties should change as we reduce the bond lengths?

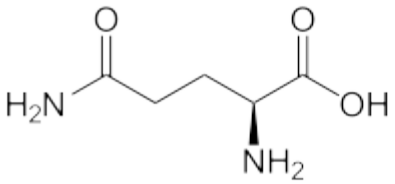
Same chemical group, different number of aliphatic carbons

- reduce the solvent accessible area
- more hydrophilic (↓ ΔG oil/water)
  - -3.0 to -3.5 kj/mol → hydrophobic molecules
  - -2.0 to -2.5 kj/mol → hydrophilic molecules
- interact less with the environment
- ↓ ΔG solvation

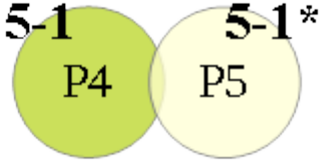
Reasons for problems in Martini 2
Hypothesis 2: Short bond lengths

$\Delta G_{W/HD}$ (kJ/mol)

Gromos Mart22 Eln22

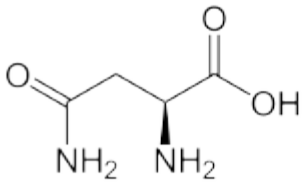


neutral free glutamine



-51.6

0.40 nm; K=5000 (M22)
0.30 nm ; K= 2400 (E22)



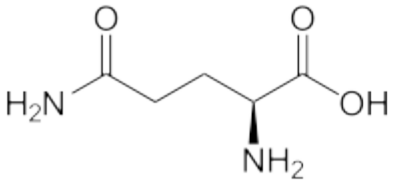
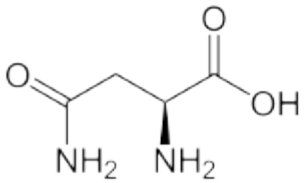
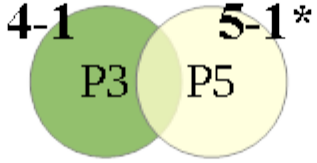
neutral free asparagine

-52.3

0.32 nm, K=5000 (M22)
0.25 nm, const (22)

Too hydrophilic !

Reasons for problems in Martini 2
Hypothesis 2: Short bond lengths

		$\Delta G_{W/HD}$ (kJ/mol)		
		Gromos	Mart22	Eln22
 neutral free glutamine	 0.40 nm; K=5000 (M22) 0.30 nm ; K= 2400 (E22)	-51.6	-52.6	-54.6
 neutral free asparagine	 0.32 nm, K=5000 (M22) 0.25 nm, const (22)	-52.3	-52.0	-52.5

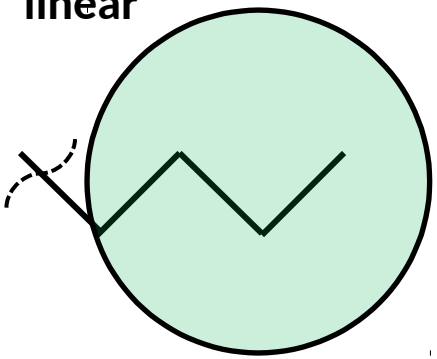
P3 is not used for amide group!

Reasons for problems in Martini 2

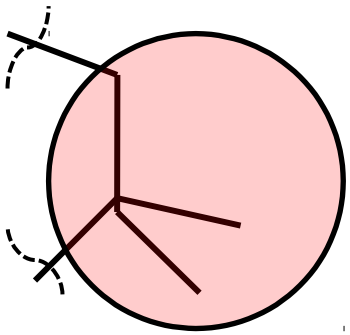
Hypothesis 2: Problems with short bond lengths

How properties should change as we reduce the bond lengths?

linear



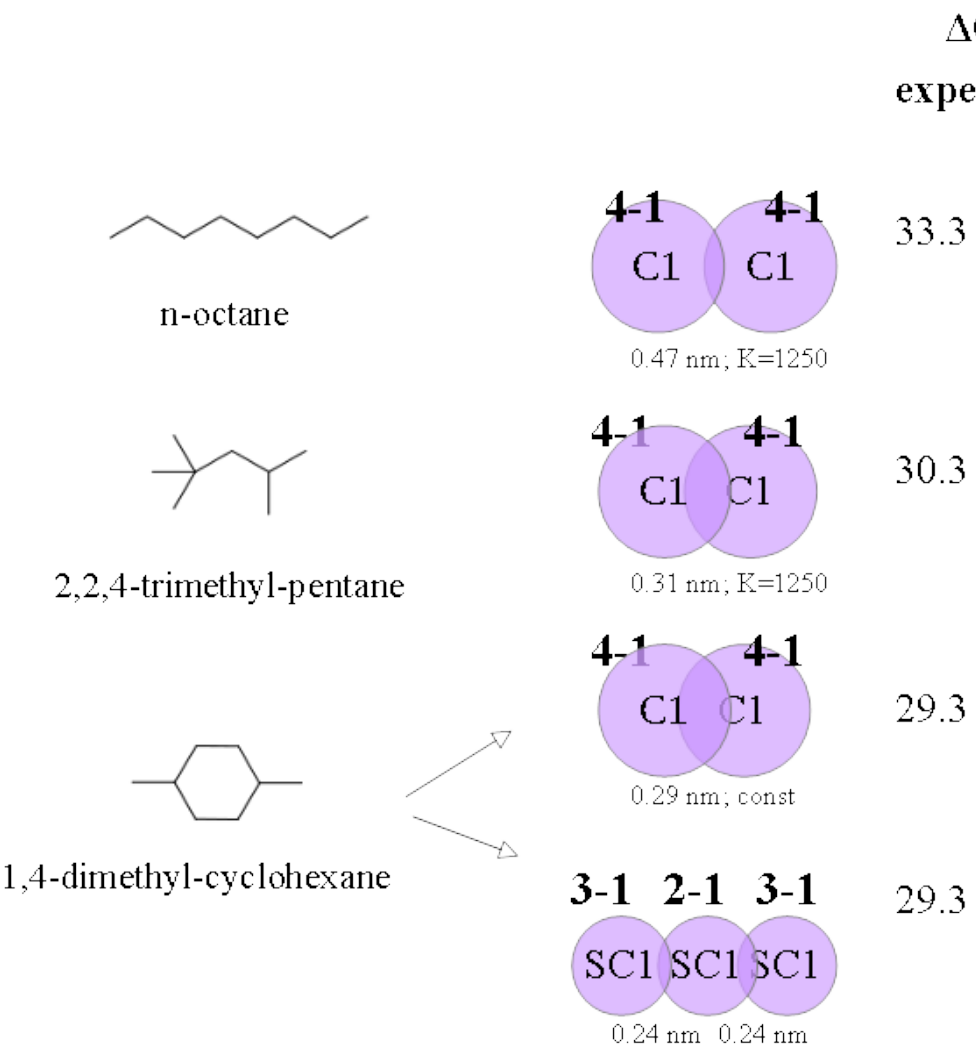
Branched or part of a ring



Same chemical group, same number of heavy atoms but different connectivity

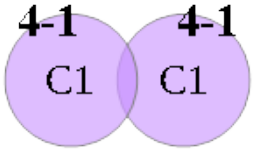
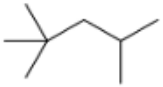
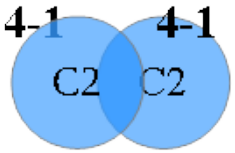
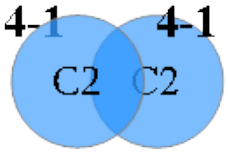
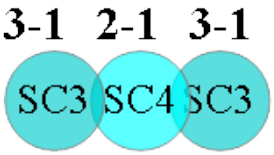
- reduce the solvent accessible area
- more hydrophilic (↓ ΔG oil/water)
  -3.0 kj/mol → branched/ring
- interact less with the environment
- ↓ ΔG solvation

Reasons for problems in Martini 2
Hypothesis 2: Short bond lengths



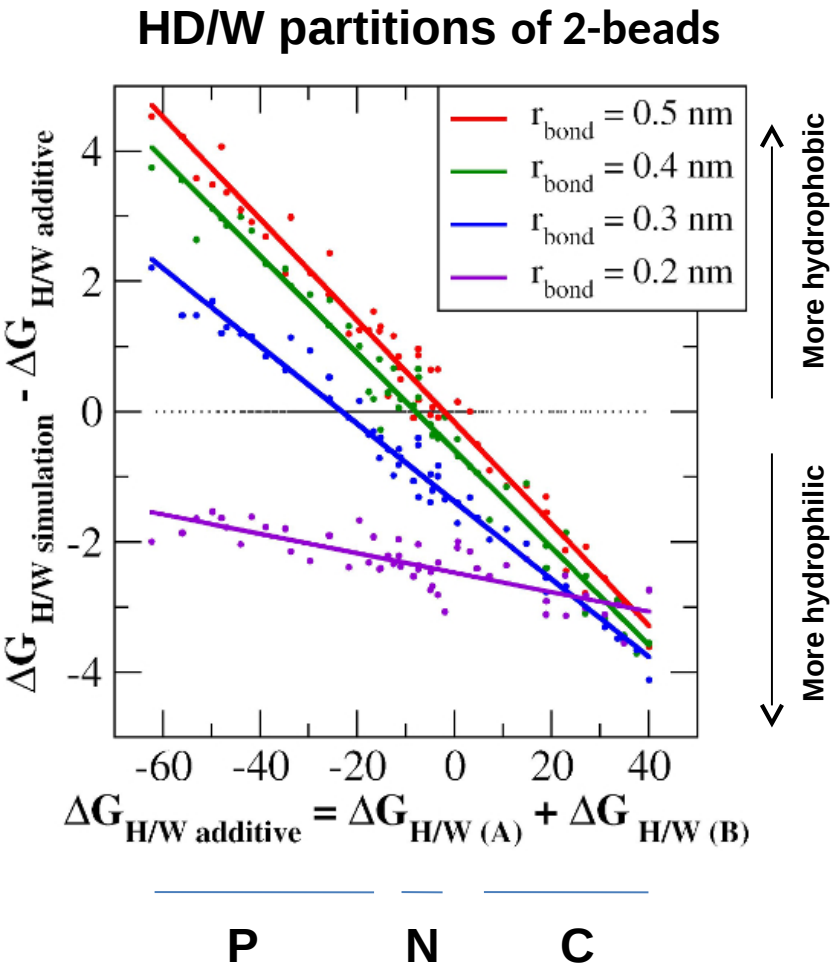
Too hydrophobic!

Reasons for problems in Martini 2
Hypothesis 2: Short bond lengths

		$\Delta G_{W/HD}$ (kJ/mol) experim	Martini
 n-octane	 0.47 nm; K=1250	33.3	36.6
 2,2,4-trimethyl-pentane	 0.31 nm; K=1250	30.3	31.2
 1,4-dimethyl-cyclohexane	 0.29 nm; const	29.3	31.3
	 0.24 nm 0.24 nm	29.3	29.9

Actually, C3 and C4 are not good!
Used for unsaturated compounds

Reasons for problems in Martini 2
Hypothesis 2: Short bond lengths



- Bond lenghts affect the HD/W partition

- **P region:** too hydrophilic

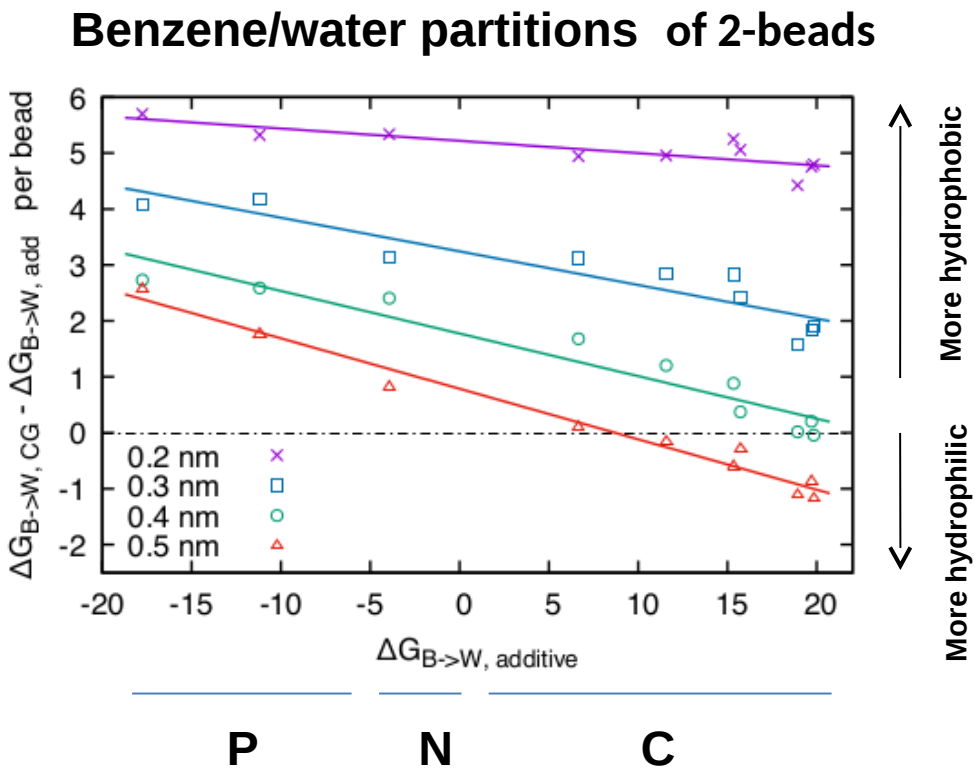
- **C region:** too hydrophobic

- Still can partiallycorrect the effect if you change the bead type.

- problem increase with the number of beads and ring geometries.

- Not intuitive

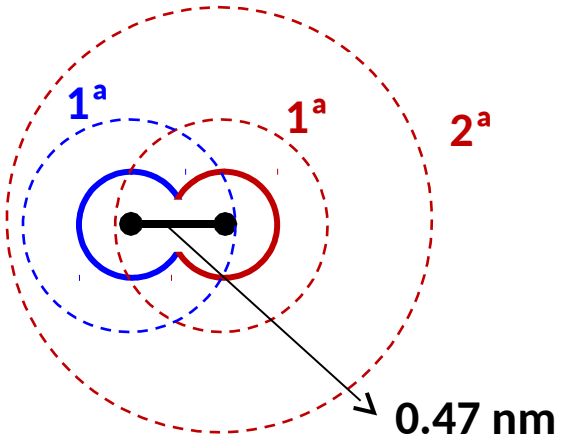
Reasons for problems in Martini 2
Hypothesis 2: Short bond lengths



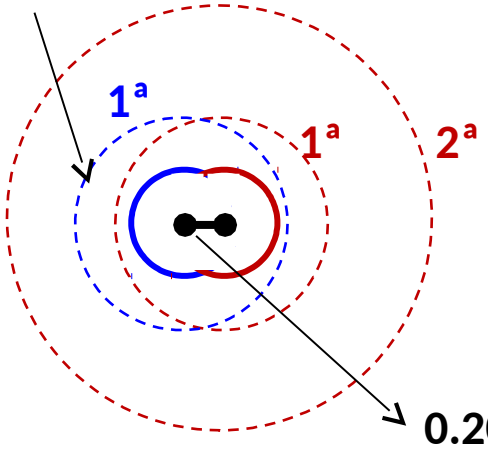
- Shorter bond lenghts make the molecule more hydrophobic.

-Cavity cost higher in benzene than water!

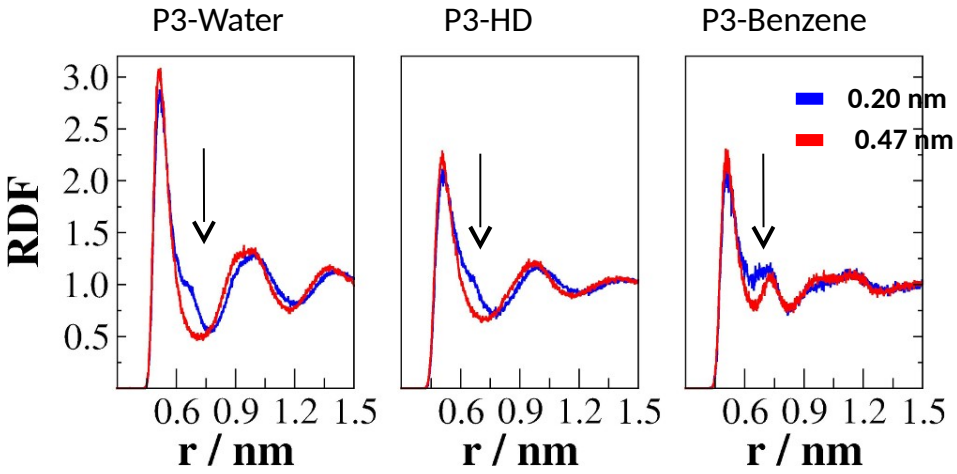
Reasons for problems in Martini 2
Hypothesis 2: Short bond lengths



Intermediate solvation shell for bead red



Why these problems are happening?
Higher interaction energy !



	$\Delta E_{0.20\text{-}0.50\ nm}$ (KJ/mol)		
	H2O	**HD**	**BENZ**
solute-solvent	-5,5	-3,3	-7,3
solvent-solvent	-14,5	-13,6	-25,4
total	-20	-16,9	-32,7

Take-home message 2

No free lunch with short-bond lenghts

- *Advantages:* for branched and ring molecule, you can get the best match between the bond distance distributions of atomistic and CG simulations.

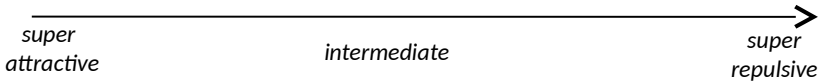
- *Disavantages*: change the partition of your molecules and can also promote aggregation via higher interaction energies.

Reasons for problems in Martini 2

Hypothesis 3: Something wrong or missing in the interaction table

	Qda	Qd	Qa	Q0	P5	P4	P3	P2	P1	Nda	Nd	Na	N0	C5	C4	C3	C2	C1
Qda	0	0	0	2	0	0	0	1	1	1	1	1	4	5	6	7	9	9
Qd	0	1	0	2	0	0	0	1	1	1	3	1	4	5	6	7	9	9
Qa	0	0	1	2	0	0	0	1	1	1	1	3	4	5	6	7	9	9
Q0	2	2	2	4	1	0	1	2	3	3	3	3	4	5	6	7	9	9
P5	0	0	0	1	0	0	0	0	0	1	1	1	4	5	6	6	7	8
P4	0	0	0	0	0	1	1	2	2	3	3	3	4	5	6	6	7	8
P3	0	0	0	1	0	1	1	2	2	2	2	2	4	4	5	5	6	7
P2	1	1	1	2	0	2	2	2	2	2	2	2	3	4	4	5	6	7
P1	1	1	1	3	0	2	2	2	2	2	2	2	3	4	4	4	5	6
Nda	1	1	1	3	1	3	2	2	2	2	2	2	4	4	5	6	6	6
Nd	1	3	1	3	1	3	2	2	2	2	3	2	4	4	5	6	6	6
Na	1	1	3	3	1	3	2	2	2	2	2	3	4	4	5	6	6	6
N0	4	4	4	4	4	4	4	3	3	4	4	4	4	4	4	4	5	6
C5	5	5	5	5	5	5	4	4	4	4	4	4	4	4	4	4	5	5
C4	6	6	6	6	6	6	5	4	4	5	5	5	4	4	4	4	5	5
C3	7	7	7	7	6	6	5	5	4	6	6	6	4	4	4	4	4	4
C2	9	9	9	9	7	7	6	6	5	6	6	6	5	5	5	4	4	4
C1	9	9	9	9	8	8	7	7	6	6	6	6	6	5	5	4	4	4

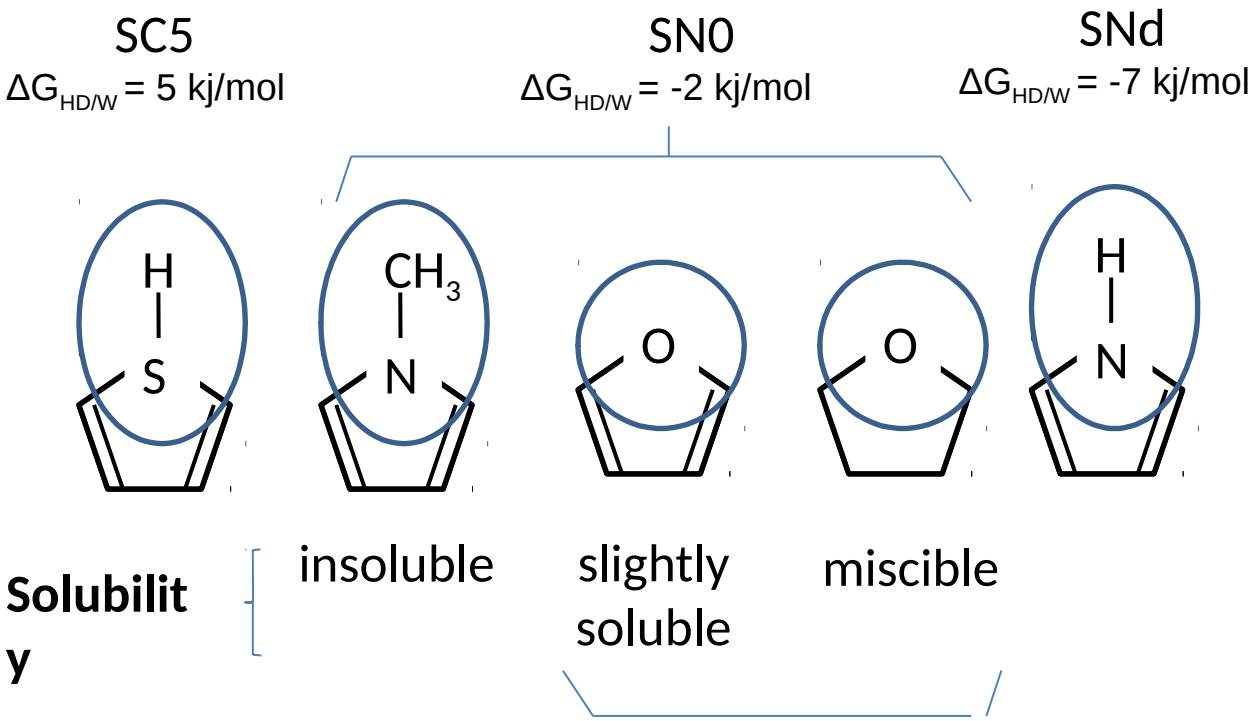
Levels	**0**	**1**	**2**	**3**	**4**	**5**	**6**	**7**	**8**	**9**
Epsilon – kJ/mol	5.6	5.0	4.5	4.0	3.5	3.1	2.7	2.3	2.0	2.0
Sigma – nm	0.47	0.47	0.47	0.47	0.47	0.47	0.47	0.47	0.47	0.62



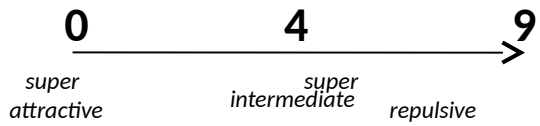
Reasons for problems in Martini 2

Hypothesis 3: Something wrong or missing in the interaction table

Example 1: Solubility of N0 bead



		N0
Qda		4
Qd		4
Qa		4
Q0		4
P5		4
P4		4
P3		4
P2		3
P1		3
Nda		4
Nd		4
Na		4
N0		4
C5		4
C4		4
C3		4
C2		5
C1		6

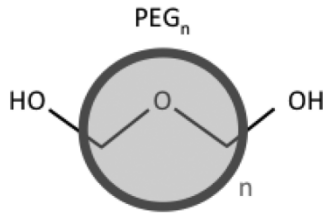


Reasons for problems in Martini 2

Hypothesis 3: Something wrong or missing in the interaction table

Example 1: Solubility of N0 bead

Simulations of PEG chain

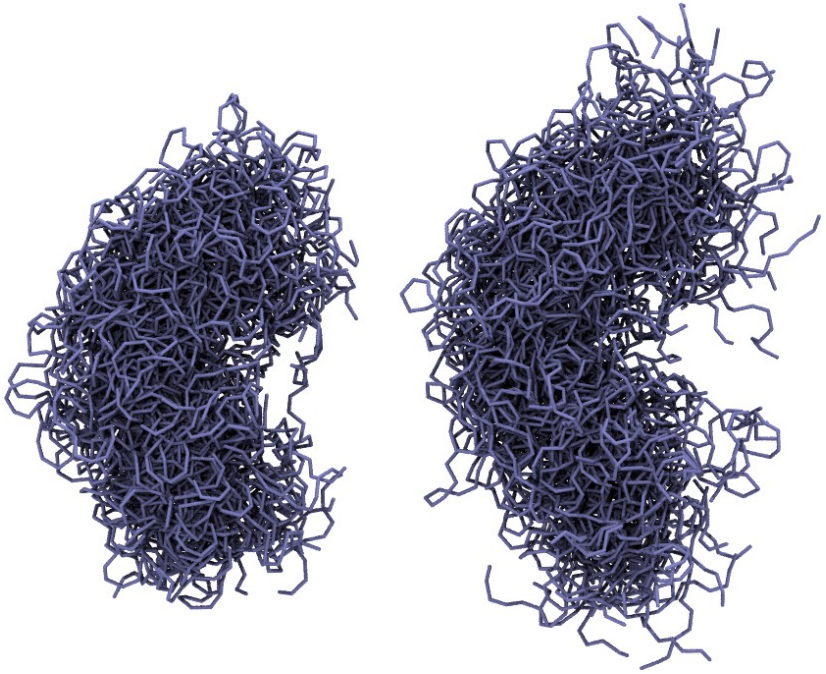


-Size: 100 monomers

- Experimental data:
Gyration radius (R_G)= 2.4 nm

SN0 model
R_G= 1.9 ± 03 nm

"SP0" model
R_G= 2.4 ± 03 nm

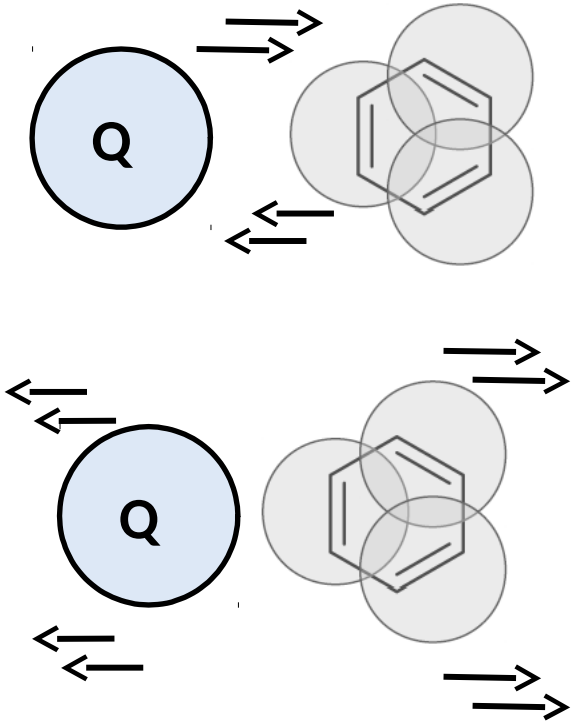


- Rossi el al, JPCB, 2012: develop a new "P0" to model PEG

Reasons for problems in Martini 2

Hypothesis 3: Something wrong or missing in the interaction table

Example 2: Lack of Ion – π interactions



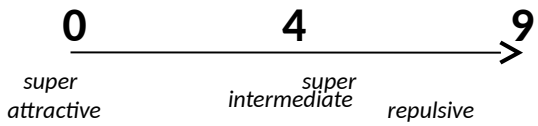
- How should they be?

Attractive or Intermediate (at least for cations)

- How are they in MARTINI 2 ?

Repulsive

		Qda	Qd	Qa	Q0
Qda		0	0	0	2
Qd		0	1	0	2
Qa		0	0	1	2
Q0		2	2	2	4
P5		0	0	0	1
P4		0	0	0	0
P3		0	0	0	1
P2		1	1	1	2
P1		1	1	1	3
Nda		1	1	1	3
Nd		1	3	1	3
Na		1	1	3	3
N0		4	4	4	4
C5		5	5	5	5
C4		6	6	6	6
C3		7	7	7	7
C2		9	9	9	9
C1		9	9	9	9



Take-home message 3

- **No free lunch with fixed bead types and interaction matrix**

Advantage: Each bead type represents a group of molecules/chemical groups (“fuzzy” nature of martini), with their average interaction levels defined in the interaction matrix.

Disavantage 1: some chemical group could be a bit to far from the average behavior described by the bead (N0 example).

Disavantage 2: some interactions were not considered when the interaction matrix were created (ion-pi interactions example).

Reasons for problems in Martini 2

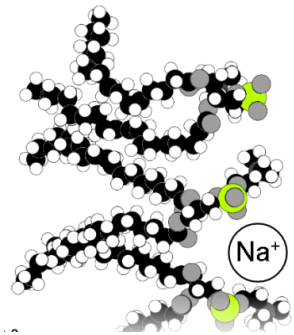
Hypothesis 4: Problems with Q-beads.

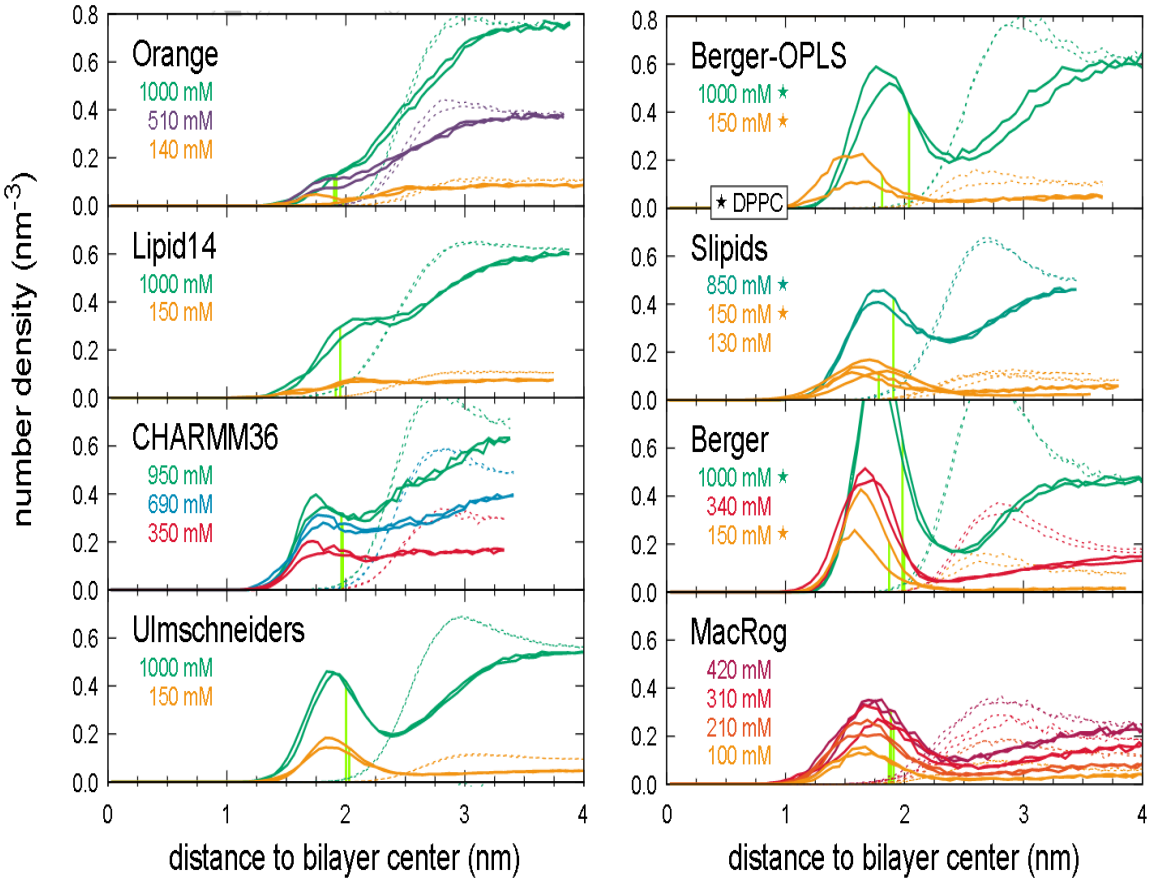
Two main problems to parametrize Q-beads:

- lack or complicated experimental data.
- disagreement between all atomistic force fields.

Example:

POPC





Catte, et al , *Molecular electrometer and binding of cations to phospholipid bilayers.* **Phys. Chem. Chem. Phys.** 18(47):32560-32569, 2016.

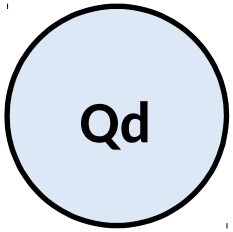
Reasons for problems in Martini 2

Hypothesis 4: Problems with Q-beads.

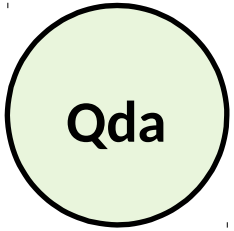
What are Q-beads ?

- Special bead types designed to model ions and charged groups in MARTINI.

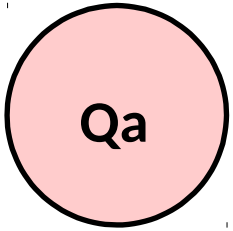
- Four chemical type



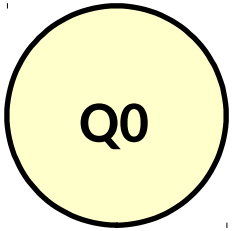
H-donor positive



H-donor and acceptor positive or negative



H-acceptor negative



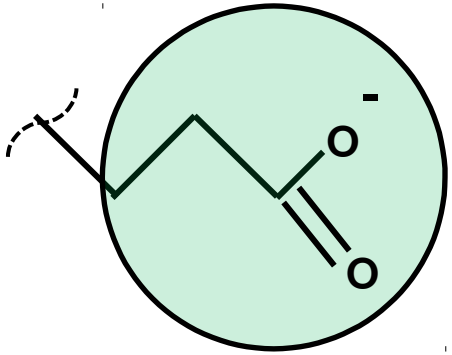
None H-bonds positive or negative

Reasons for problems in Martini 2

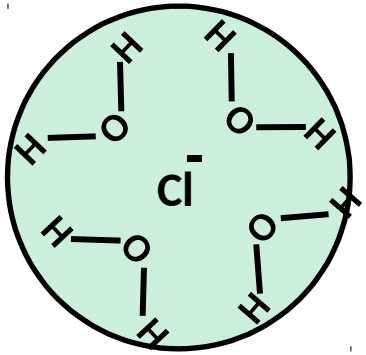
Hypothesis 4: Problems with Q-beads.

- Huge diversity of ions represented by the same beads.

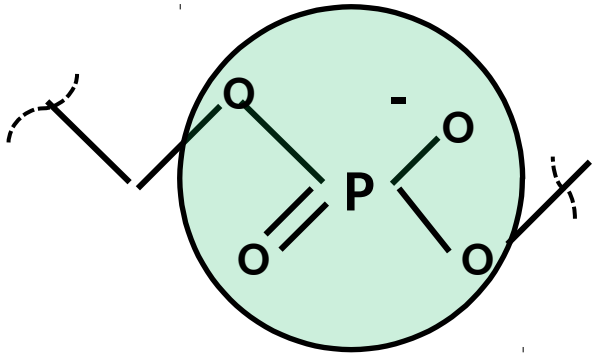
Example: Qa



carboxilate



chloride ion



phosphate

Reasons for problems in Martini 2

Hypothesis 4: Problems with Q-beads.

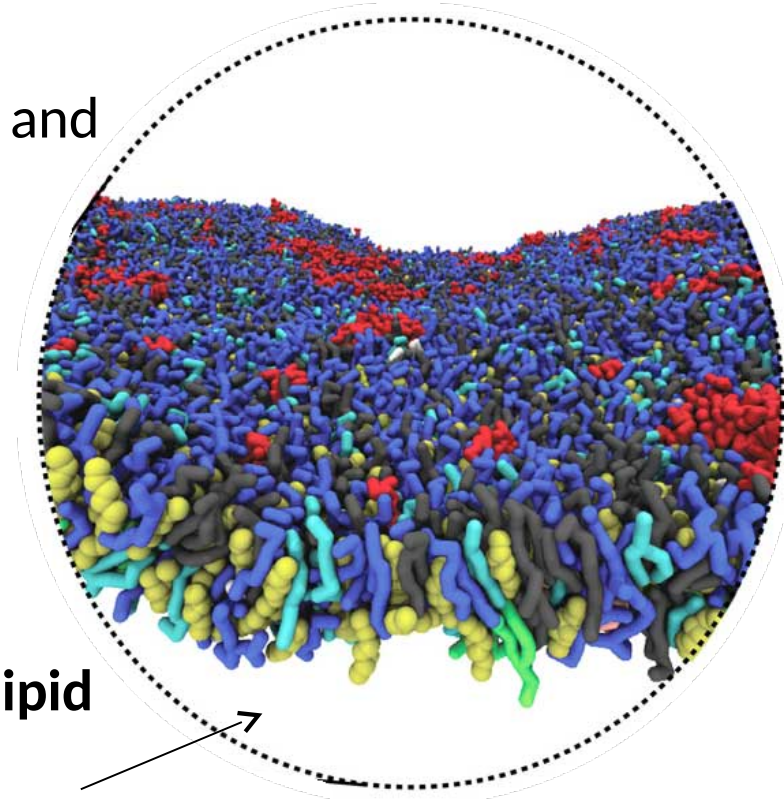
Parametrization of charged beads in Martini 2

- **qualitative** agreement for partition $\Delta G_{w/o}$ and other $\Delta\Delta G$.

- Interactions levels were choosen based in the expected trends.

- Balance consider only +1 and -1 ions.

- **They were balanced to give us very nice lipid properties.**

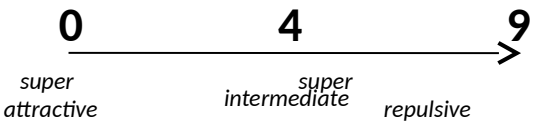


Reasons for problems in Martini 2

Hypothesis 4: Problems with Q-beads.

Interaction matrix

		Qda	Qd	Qa	Q0
Qda		0	0	0	2
Qd		0	1	0	2
Qa		0	0	1	2
Q0		2	2	2	4
P5		0	0	0	1
P4		0	0	0	0
P3		0	0	0	1
P2		1	1	1	2
P1		1	1	1	3
Nda		1	1	1	3
Nd		1	3	1	3
Na		1	1	3	3
N0		4	4	4	4
C5		5	5	5	5
C4		6	6	6	6
C3		7	7	7	7
C2		9	9	9	9
C1		9	9	9	9

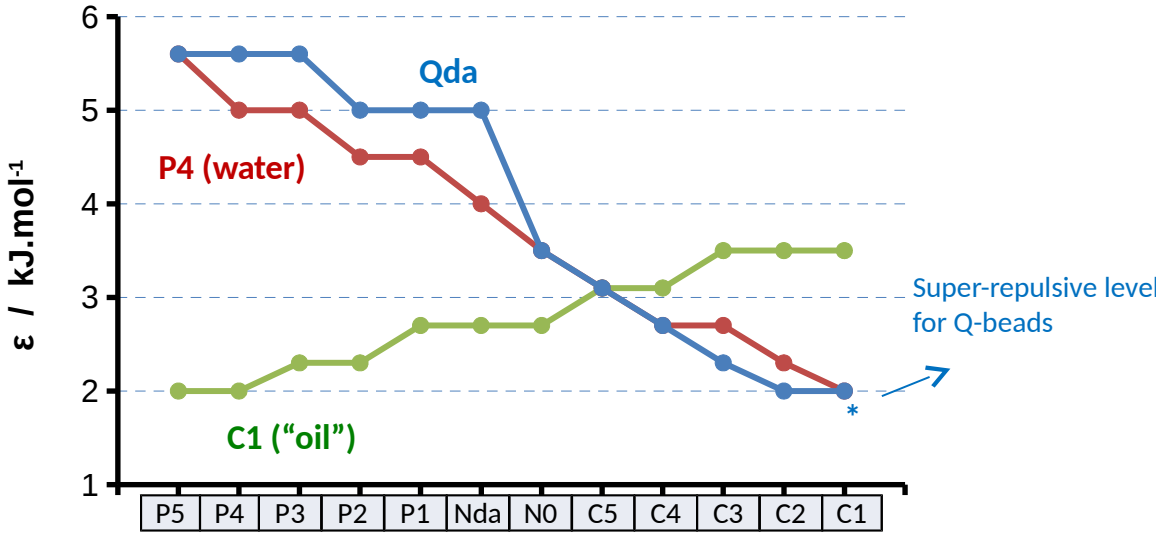


- Q – Q interactions: Lennard-Jones + Coulomb Potentials

$$V(r_1 \ldots r_n) = \sum_{ij} 4\varepsilon \left[\left(\frac{\sigma_{ij}}{r_{ij}} \right)^{12} - \left(\frac{\sigma_{ij}}{r_{ij}} \right)^{6} \right] + \sum_{ij} \frac{1}{4\pi\varepsilon_0} \frac{q_i \cdot q_j}{r_{ij}^2}$$

– 5.6 to -3.5 kJ/mol ± 7 kJ/mol

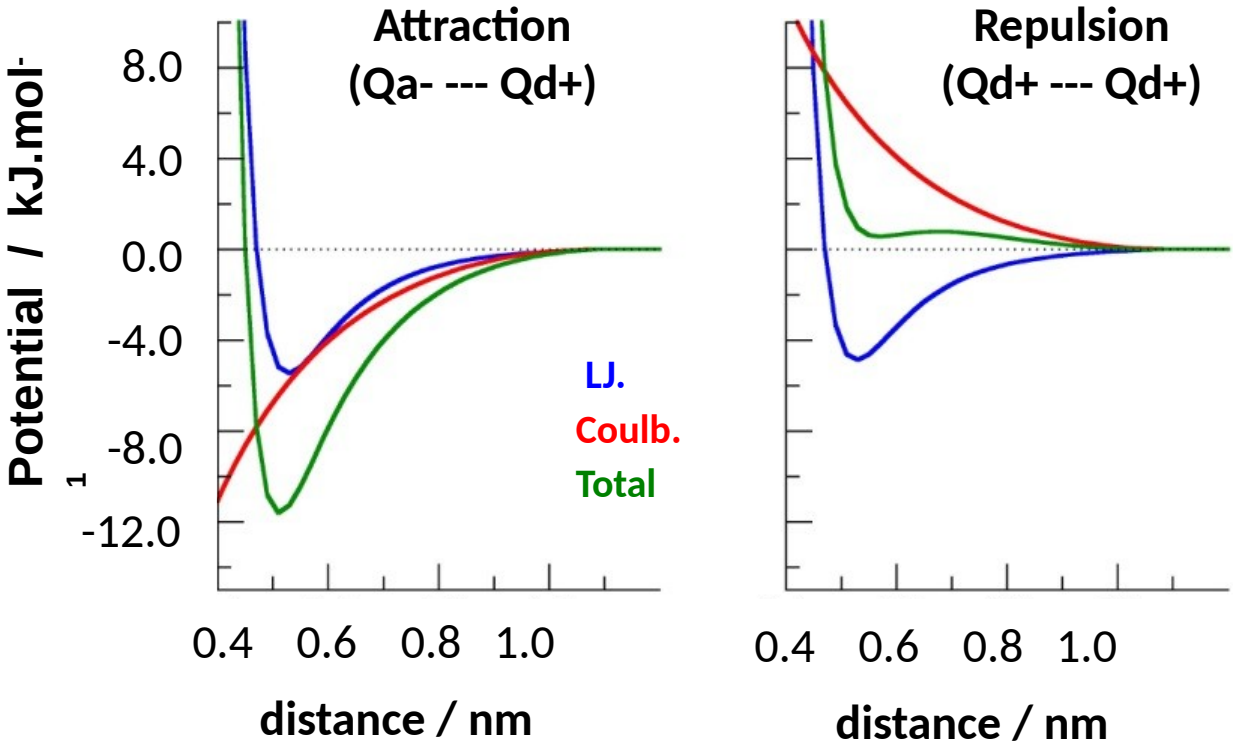
- Q – Other beads interactions: Only Lennard-Jones potential



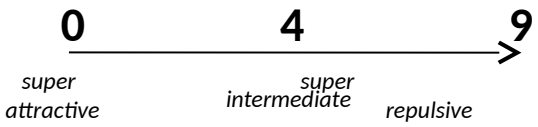
Reasons for problems in Martini 2

Hypothesis 4: Problems with Q-beads.

Hypothesis 4A: Lack of repulsive interactions, specially between Qd-Qd and Qa-Qa (+1/-1)



		Qda	Qd	Qa	Q0
Qda		0	0	0	2
Qd		0	1	0	2
Qa		0	0	1	2
Q0		2	2	2	4
P5		0	0	0	1
P4		0	0	0	0
P3		0	0	0	1
P2		1	1	1	2
P1		1	1	1	3
Nda		1	1	1	3
Nd		1	3	1	3
Na		1	1	3	3
N0		4	4	4	4
C5		5	5	5	5
C4		6	6	6	6
C3		7	7	7	7
C2		9	9	9	9
C1		9	9	9	9

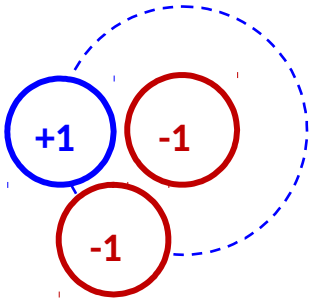


Reasons for problems in Martini 2

Hypothesis 4: Problems with Q-beads.

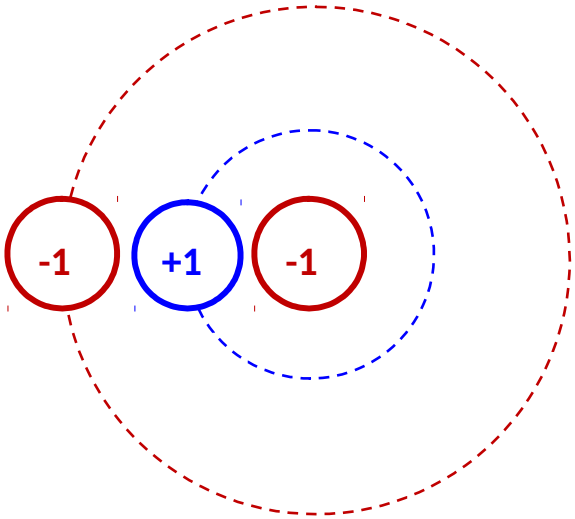
Hypothesis 4A: Lack of repulsive interactions, specially between Qd-Qd and Qa-Qa

- How Q-beads with same charge interact?
  Almost zero kJ/mol !

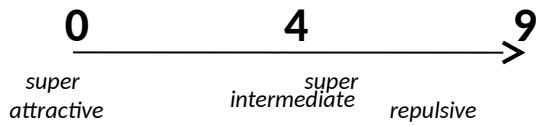


So, they can be together depending of the enviroment.

- How should they be?
  Repulsive



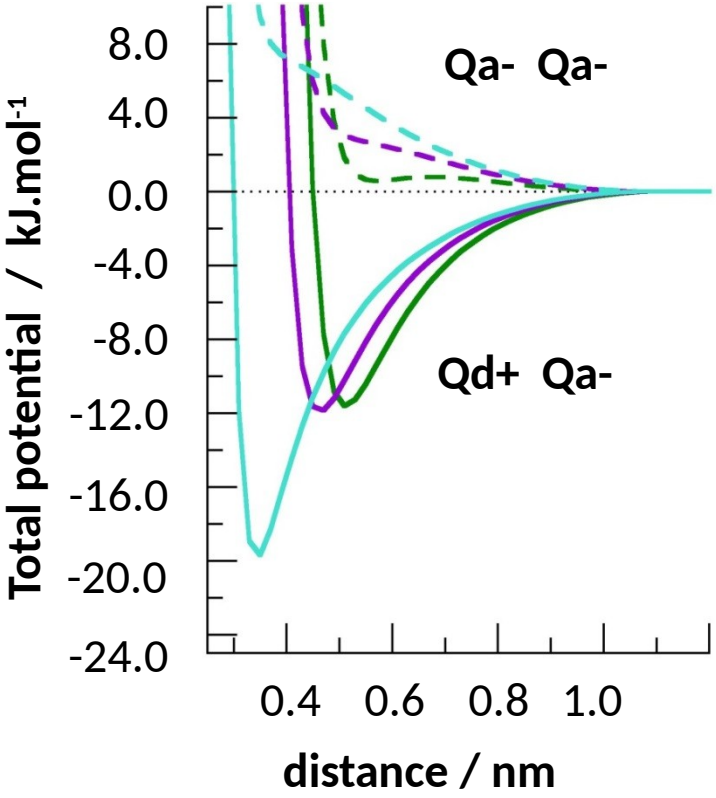
		Qda	Qd	Qa	Q0
Qda		0	0	0	2
Qd		0	1	0	2
Qa		0	0	1	2
Q0		2	2	2	4
P5		0	0	0	1
P4		0	0	0	0
P3		0	0	0	1
P2		1	1	1	2
P1		1	1	1	3
Nda		1	1	1	3
Nd		1	3	1	3
Na		1	1	3	3
N0		4	4	4	4
C5		5	5	5	5
C4		6	6	6	6
C3		7	7	7	7
C2		9	9	9	9
C1		9	9	9	9



Reasons for problems in Martini 2

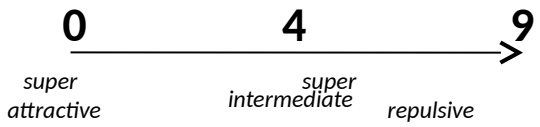
Hypothesis 4: Problems with Q-beads.

Hypothesis 4B: Small and tiny Q-beads are more sticky than normal Q-beads in MARTINI 2.0



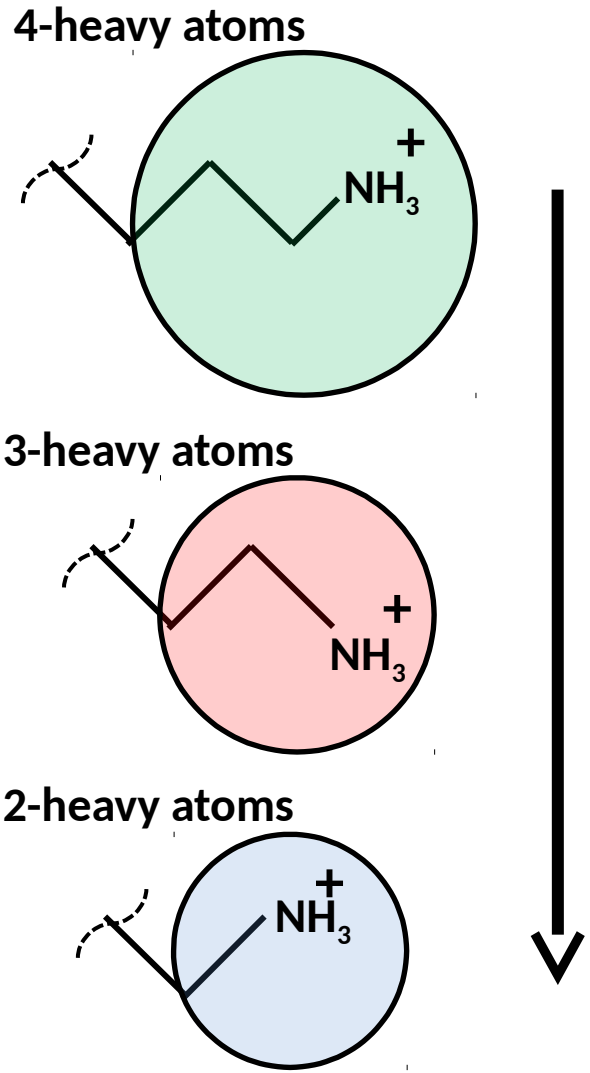
- Current interaction table was balanced for normal Q-beads.
- For now, no application for SQ and TQ in MARTINI 2

		Qda	Qd	Qa	Q0
Qda		0	0	0	2
Qd		0	1	0	2
Qa		0	0	1	2
Q0		2	2	2	4
P5		0	0	0	1
P4		0	0	0	0
P3		0	0	0	1
P2		1	1	1	2
P1		1	1	1	3
Nda		1	1	1	3
Nd		1	3	1	3
Na		1	1	3	3
N0		4	4	4	4
C5		5	5	5	5
C4		6	6	6	6
C3		7	7	7	7
C2		9	9	9	9
C1		9	9	9	9



Reasons for problems in Martini 2

Hypothesis 4: Problems with Q-beads.



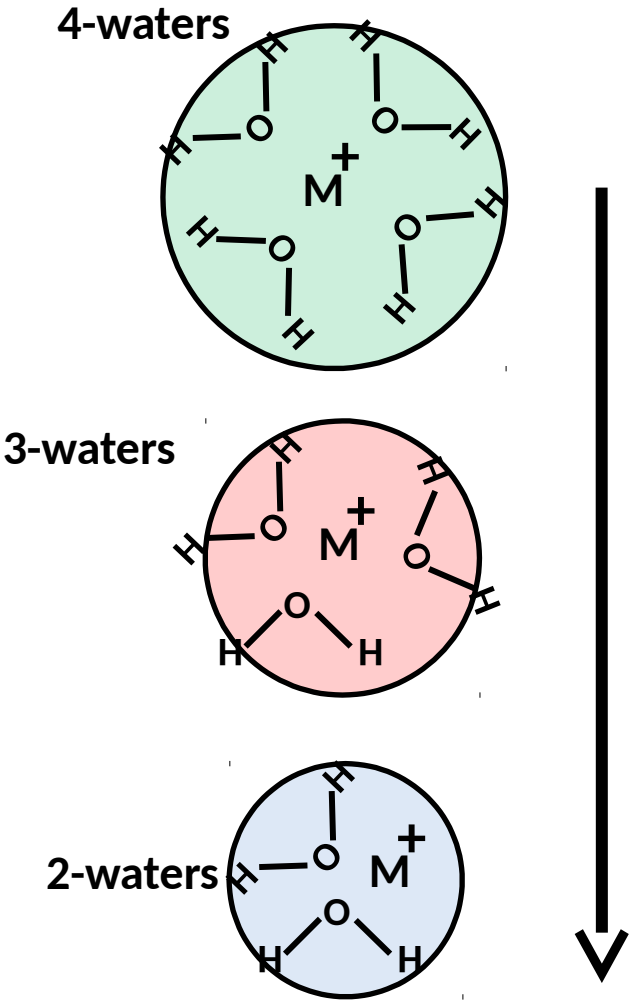
How Q-beads of different sizes should work in a CG model ?

Same charged group, different number of aliphatic carbons

- more hydrophilic (↓ ΔG oil/water)
- more soluble in water.
- Interact more with water and polar beads.

Reasons for problems in Martini 2

Hypothesis 4: Problems with Q-beads.



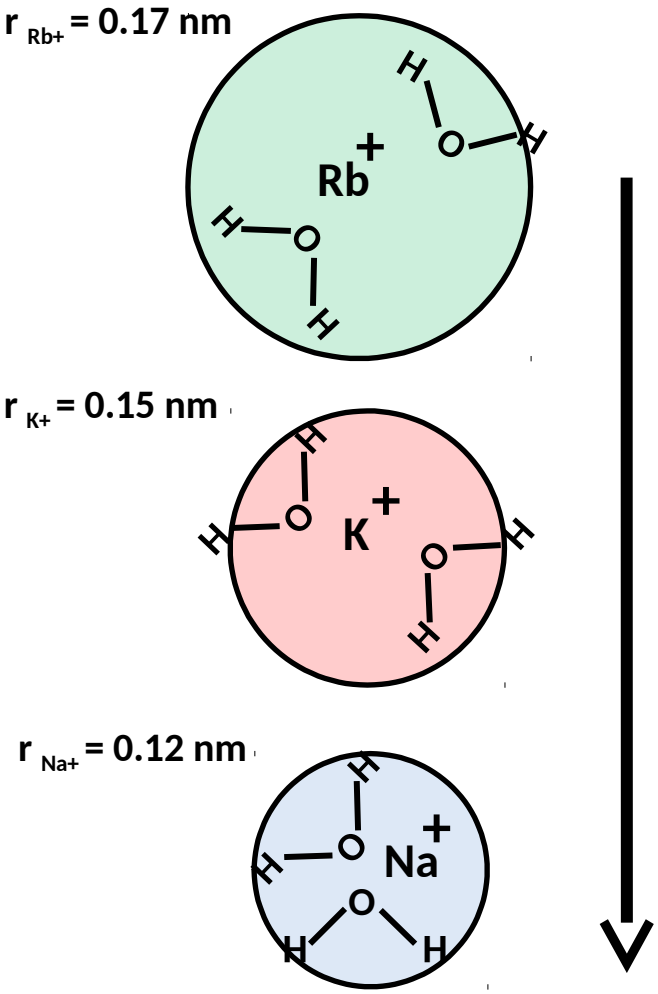
How Q-beads of different sizes should work in a CG model ?

Same charged group, different number of water molecules

- Ion more exposed
- Higher interactions with water
- Probably interact more with water and other polar beads

Reasons for problems in Martini 2

Hypothesis 4: Problems with Q-beads.



How Q-beads of different sizes should work in a CG model ?

Same number of water molecules, but ion group with different sizes

- Lower hydration ΔG
  (More hydrophilic)

- More soluble in water.

- Probably interact more with water and polar beads as well.

Take-home message 4

- Never expect quantitative aggrements for ΔΔG calculations involving Q-beads. We have only qualitative trends here.

- Electrostatic repulsive interactions in Martini 2 are weak. Only good for some applications (specially situations where Q-beads are in contact with water)

- Martini 2 is not balanced to use SQ/TQ-beads or charged groups with net charge different than +1/-1.

Break Time!

MARTINI 3: what do we want to keep from version 2?

- Chemical specificity
- Build block approach (“Lego”)
- Fast (10^3 speed-up)
- Compatibility
- Versatility
- Parameterization:
  - TOP DOWN
    Thermodynamic data
  - BOTTOM UP
    Atomistic simulations

MARTINI 3: what will be new?

- Improvements in the interaction matrix
- New parametrization of S/T beads
- Reformulation of Q-beads
- New water models
- New bead chemical types (including polymer/ material science)
- H-donor and H-acceptor choices for all N- and P-beads (not implemented yet).
- Quality control tests.

New interaction table

	Q2	Q1	Qa	Qd	Q0	P5	P4	P3	P2	P1	Nda	Na	Nd	N0	C6	C5	C4	C3	C2	C1	W
Q2	12	11	11	11	11	0	1	2	3	4	4	4	4	6	11	13	15	16	19	19	0
Q1	11	1	2	2	10	1	2	2	3	4	4	4	4	6	11	13	15	16	19	19	1
Qa	11	2	9	2	10	2	3	3	4	5	5	6	5	7	11	13	15	16	18	18	2
Qd	11	2	2	9	10	2	3	3	4	5	5	5	6	7	10	11	12	14	18	18	2
Q0	11	10	10	10	8	3	4	4	6	7	7	8	8	9	9	10	11	13	18	18	3
P5	0	1	2	2	3	2	3	4	4	5	6	9	9	11	11	12	14	15	16	17	3
P4	1	2	3	3	4	3	4	5	6	7	7	8	8	11	11	12	14	15	16	17	4
P3	2	2	3	3	4	4	5	5	6	7	7	7	7	10	10	11	12	14	15	16	5
P2	3	3	4	4	6	4	6	6	6	7	7	7	7	10	10	11	12	14	14	15	6
P1	4	4	5	5	7	5	7	7	7	7	7	7	7	9	10	11	12	13	14	15	7
Nda	4	4	5	5	7	6	7	7	7	7	7	7	7	9	10	11	11	12	13	14	7
Na	4	4	6	5	8	9	8	7	7	7	7	9	7	10	10	10	11	11	13	14	8
Nd	4	4	5	6	8	9	8	7	7	7	7	7	9	10	10	10	11	11	13	14	8
N0	6	6	7	7	9	11	11	10	10	9	9	10	10	10	10	10	11	11	12	12	8
C6	11	11	11	10	9	11	11	10	10	10	10	10	10	10	9	9	10	10	12	12	10
C5	13	13	13	11	10	12	12	11	11	11	11	10	10	10	9	9	10	10	12	12	12
C4	15	15	15	12	11	14	14	12	12	12	11	11	11	11	10	10	10	10	12	12	14
C3	16	16	16	14	13	15	15	14	14	13	12	11	11	11	10	10	10	10	11	11	15
C2	19	19	18	18	18	16	16	15	14	14	13	13	13	12	12	12	12	11	10	10	16
C1	19	19	18	18	18	17	17	16	15	15	14	14	14	12	12	12	12	11	10	10	17
W	0	1	2	2	3	3	4	5	6	7	7	8	8	8	10	12	14	15	16	17	4

original levels	**0**		**1**		**2**		**3**		**4**		**5**		**6**		**7**	**8**	**9**	
new_levels	0	1	**2**	3	**4**	5	**6**	7	**8**	9	**10**	11	**12**	13	**14**	15	**16**	**17**	18	**19**
	hyper attractive		**supra attractive**		**attractive**		**almost attractive**		**semi attractive**		**intermediate**		**almost intermediate**		**semi repulsive**		**almost repulsive**	**repulsive**	**super repulsive**	

Blocks with different balance when we reduce the bead size:

organic
water
ion
ion-others

Difference in relation to Martini 2

	Q2	Q1	Qa	Qd	Q0
Q2	12	11	11	11	11
Q1	11	1	2	2	10
Qa	11	2	9	2	10
Qd	11	2	2	9	10
Q0	11	10	10	10	8

	P5	P4	P3	P2	P1	Nda	Na	Nd	N0	C6	C5	C4	C3	C2	C1	W
Q2	0	1	2	3	4	4	4	4	6	11	13	15	16	19	19	0
Q1	1	2	2	3	4	4	4	4	6	11	13	15	16	19	19	1
Qa	2	3	3	4	5	5	6	5	7	11	13	15	16	18	18	2
Qd	2	3	3	4	5	5	5	6	7	10	11	12	14	18	18	2
Q0	3	4	4	6	7	7	8	8	9	9	10	11	13	18	18	3

	P5	P4	P3	P2	P1	Nda	Na	Nd	N0	C6	C5	C4	C3	C2	C1	W
P5	0	1	2	2	3	2	3	4	4	5	6	9	9	11	11	3
P4	1	2	3	3	4	3	4	5	6	7	7	8	8	11	11	4
P3	2	2	3	3	4	4	5	5	6	7	7	7	7	10	10	5
P2	3	3	4	4	6	4	6	6	6	7	7	7	7	10	10	6
P1	4	4	5	5	7	5	7	7	7	7	7	7	7	9	10	7
Nda	4	4	5	5	7	6	7	7	7	7	7	7	7	9	10	7
Na	4	4	6	5	8	9	8	7	7	7	7	9	7	10	10	8
Nd	4	4	5	6	8	9	8	7	7	7	7	7	9	10	10	8
N0	6	6	7	7	9	11	11	10	10	9	9	10	10	10	10	8
C6	11	11	11	10	9	11	11	10	10	10	10	10	10	9	9	10
C5	13	13	13	11	10	12	12	11	11	11	11	10	10	9	9	12
C4	15	15	15	12	11	14	14	12	12	12	11	11	11	10	10	14
C3	16	16	16	14	13	15	15	14	14	13	12	11	11	10	10	15
C2	19	19	18	18	18	16	16	15	14	14	13	13	13	12	12	16
C1	19	19	18	18	18	17	17	16	15	15	14	14	14	12	12	17

	P5	P4	P3	P2	P1	Nda	Na	Nd	N0	C6	C5	C4	C3	C2	C1	W
W	0	1	2	2	3	3	4	5	6	7	7	8	8	8	10	12	14	15	16	17	4

original levels	0		1		2		3		4		5		6		7		8		9	
new_levels	0	1	**2**	3	**4**	5	**6**	7	**8**	9	**10**	11	**12**	13	**14**	15	**16**		**17**		18	**19**
	hyper attractive		supra attractive		attractive		almost attractive		semi attractive		intermediate		almost intermediate		semi repulsive		almost repulsive		repulsive		super repulsive	

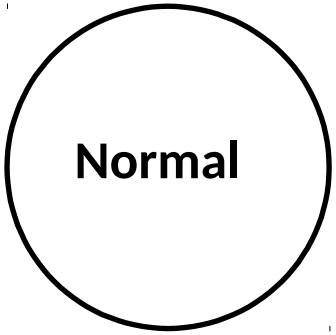
decrease interactions
increase interactions

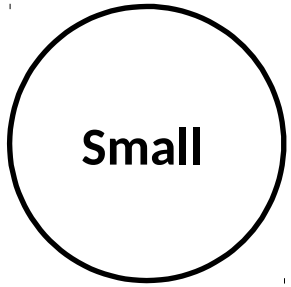
New beads
PS: Q1 bead replaced Qda

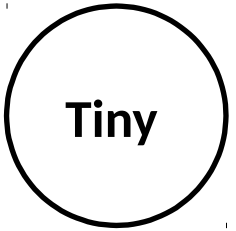
New S and T beads

How are S and T beads now ?

- Bead size ? number of heavy atoms
  geometry/shape
- Different sizes (sigma) for SS, TT, NS, ST and NT interactions.
- S- and T- beads are well-balanced with N-beads.
- Chemical types and size types change the properties.

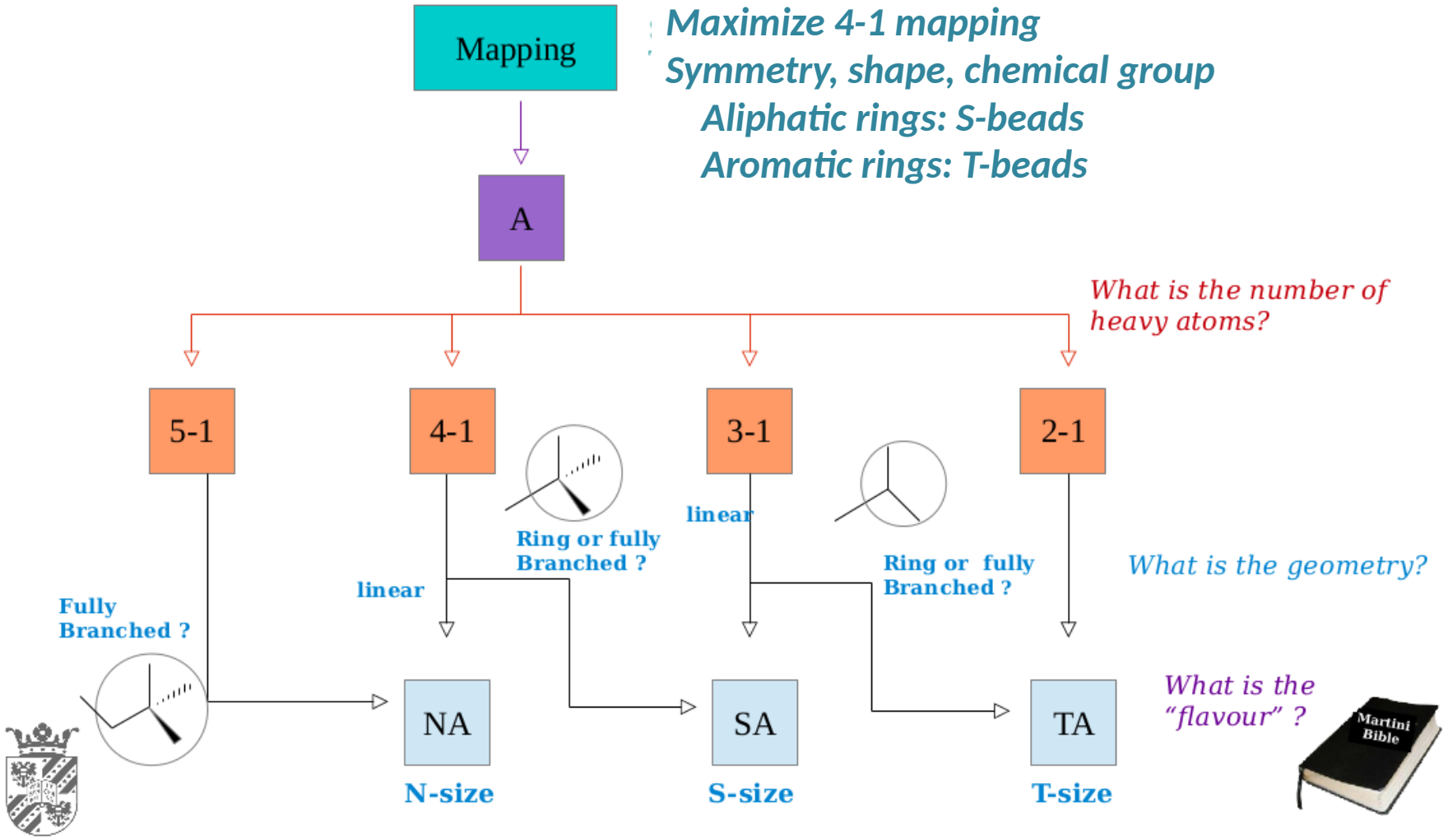






How the beads behave when we reduce their size?			
Block	**Interactions with themselves**	**Interactions with solvents**	**Hydrophobicity**
Organic	reduce	reduce	more hydrophilic
Water	reduce	reduce	more hydrophobic
Ion	increase	increase with polar beads	more hydrophylic

Bead sizes: number of heavy atoms and geometry



How are sigma and epsilon of Lennard-Jones potentials ?

$$V = 4\varepsilon\left[\left(\frac{\sigma}{r}\right)^{12} - \left(\frac{\sigma}{r}\right)^{6}\right]$$

- **Arithmetic averages of σ_{NN} and σ_{TT}**

N	**0.47 nm**		
S	0.44 nm	0.40 nm	
T	0.40 nm	0.36 nm	**0.32 nm**
	N	**S**	**T**

- **Same interaction matrix of N-N interations (ε_{NN})**

- **N-S, N-T, S-S, S-T and T-T are function of ε_{NN}**

$$\varepsilon_{ij} = f(\varepsilon_{NN}) = \alpha + \beta\varepsilon_{NN} + p_{Q_i O_j}$$

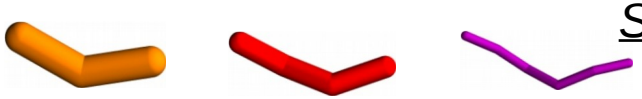
additive factor — scale factor — Polarization induced by Q- bead in O- bead.

- **For some repulsive interactions**

$$\sigma_{ij} = \sigma_{ij}^{0} + s_{ij}$$

Perfecting Epsilon for S- and T-sizes

1) Constructions of system in different resolutions

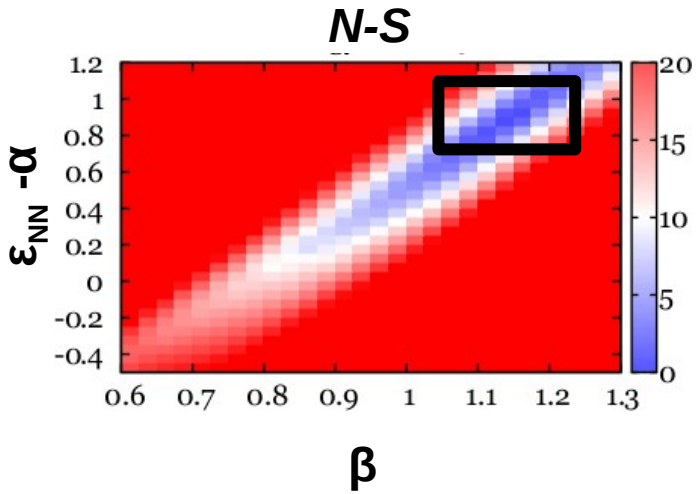


3 N-beads 3 S-beads 6 T-beads

Solvents:
Water
Hexadecane
and others

↓ Check if bead type works with sym. and asym. molecules

2) Refine solute-solvent interactions



Reference:

N-N systems

Balance with N-beads!

↓ Error < 10%

3) Refine the ΔG $_{solvation}$

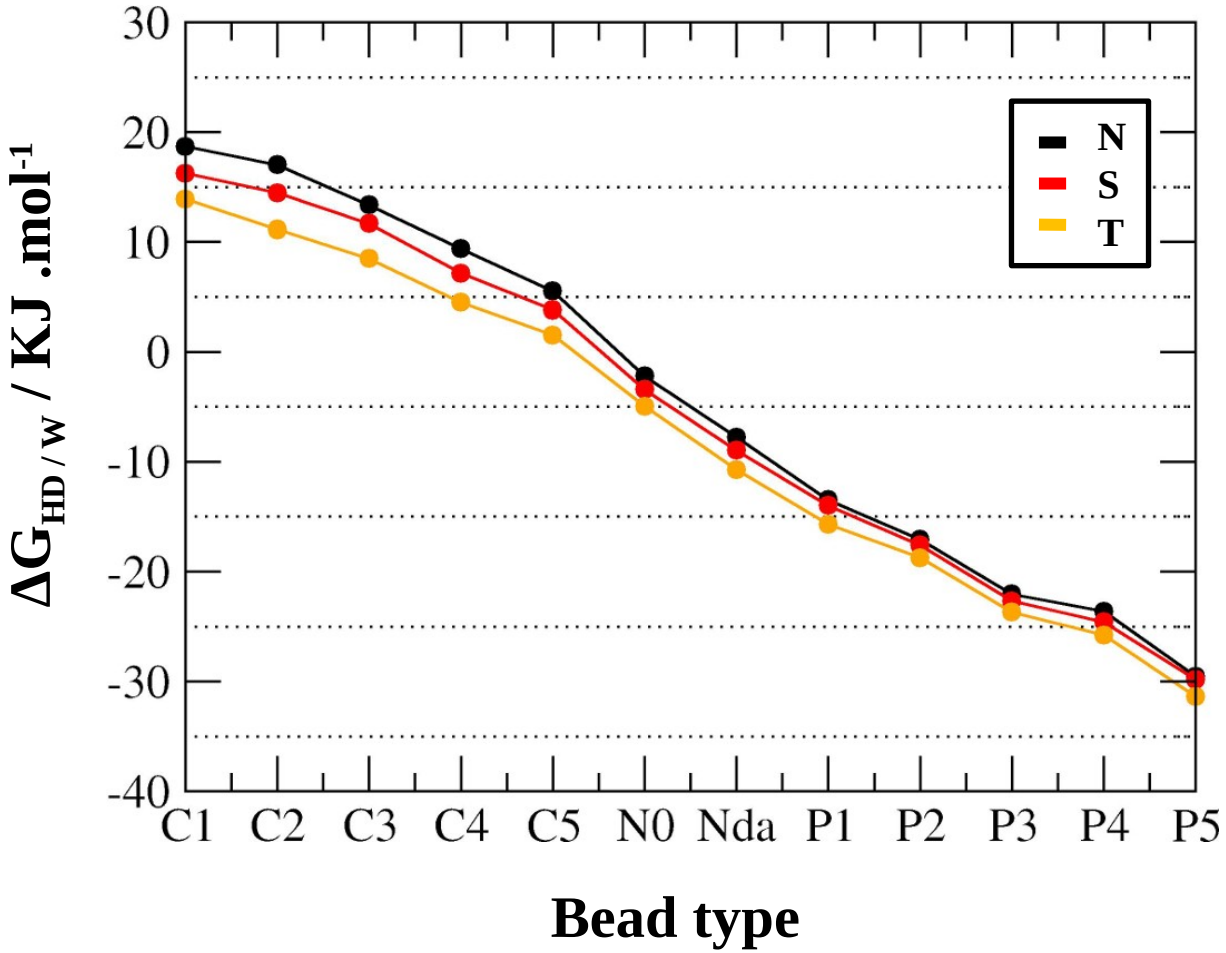
↓ Error < 5 kJ/mol

4) Refine the ΔG $_{oil/water}$

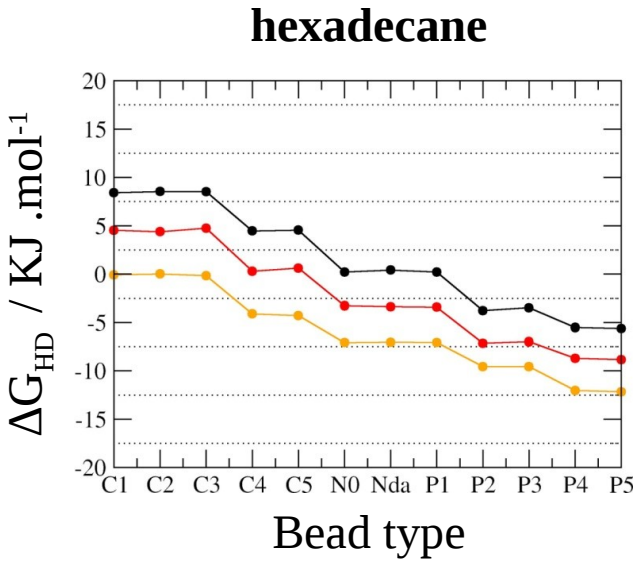
Error < 3 kJ/mol

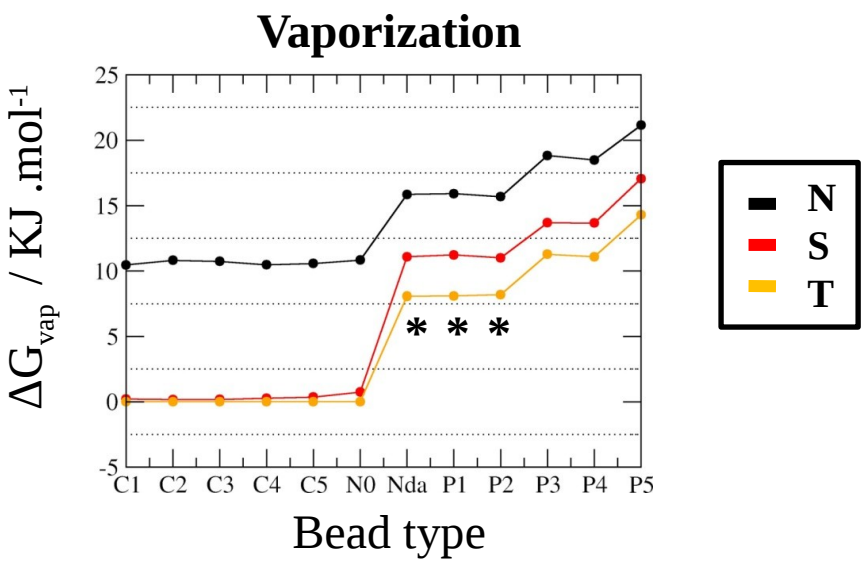
Reference: Experimental data !

Hexadecane/water partitions of 1-bead solutes

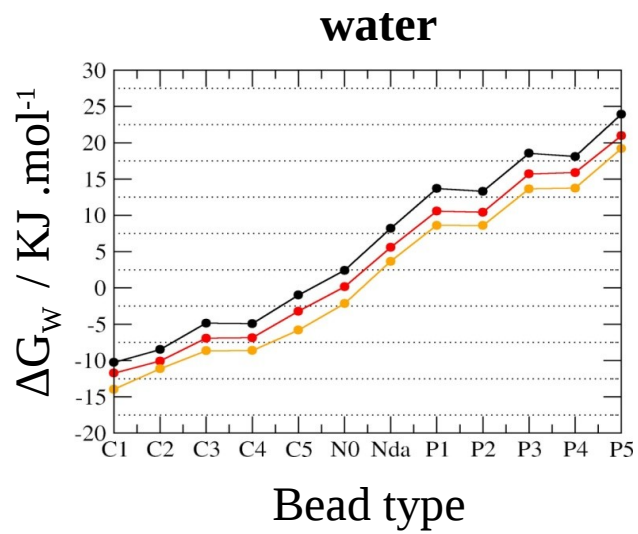


Solvation and Vaporization of 1-bead



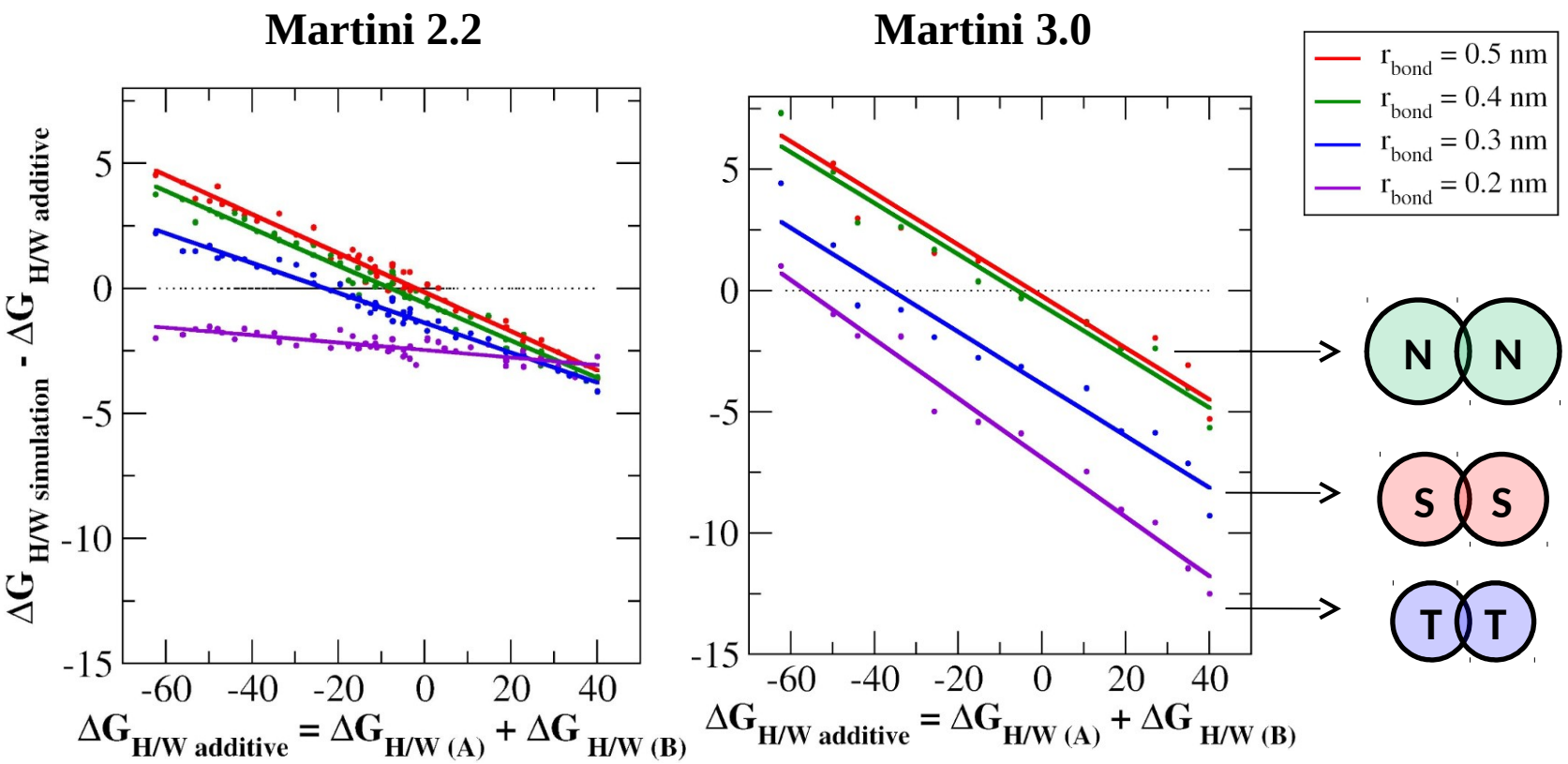


* Maybe these beads are gases



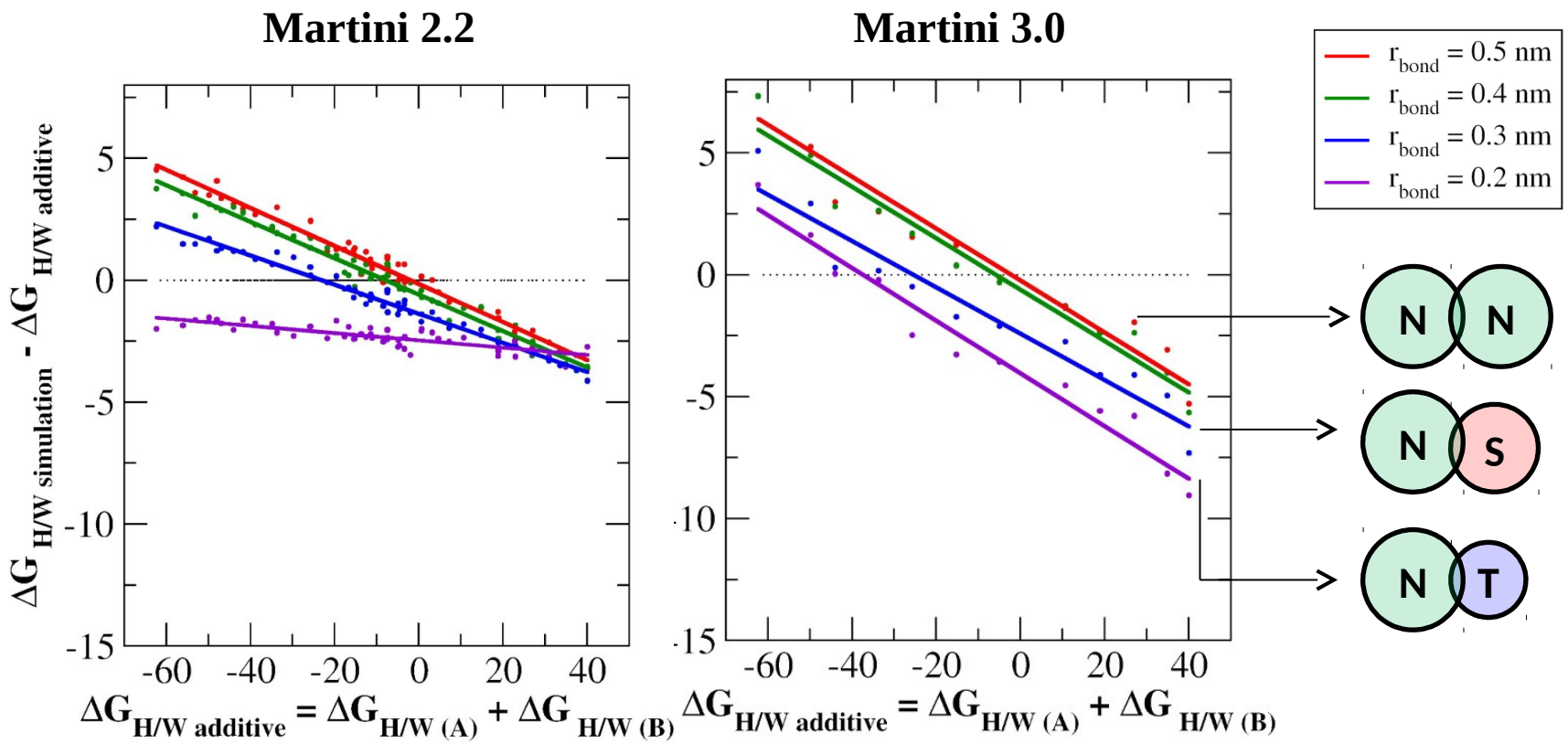
- Correct trends for solvation and vaporization free energies.

Partitions of 2-bead molecules



- Correct trends when reduce the size of the molecule.

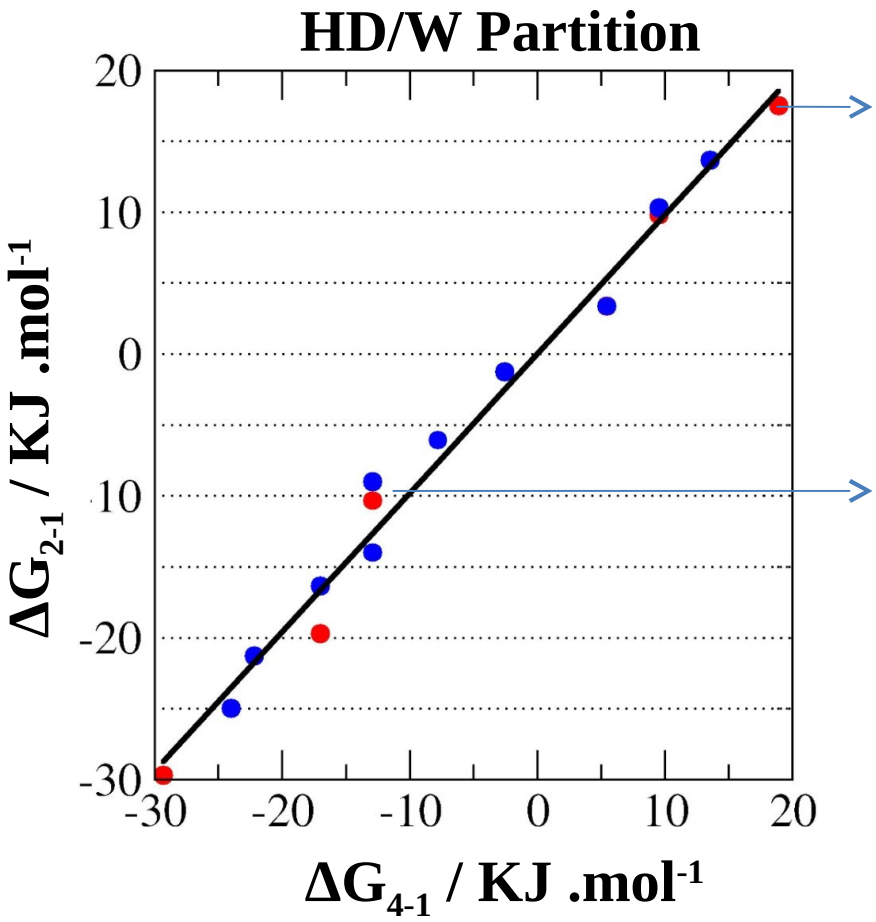
Partitions of 2-bead molecules

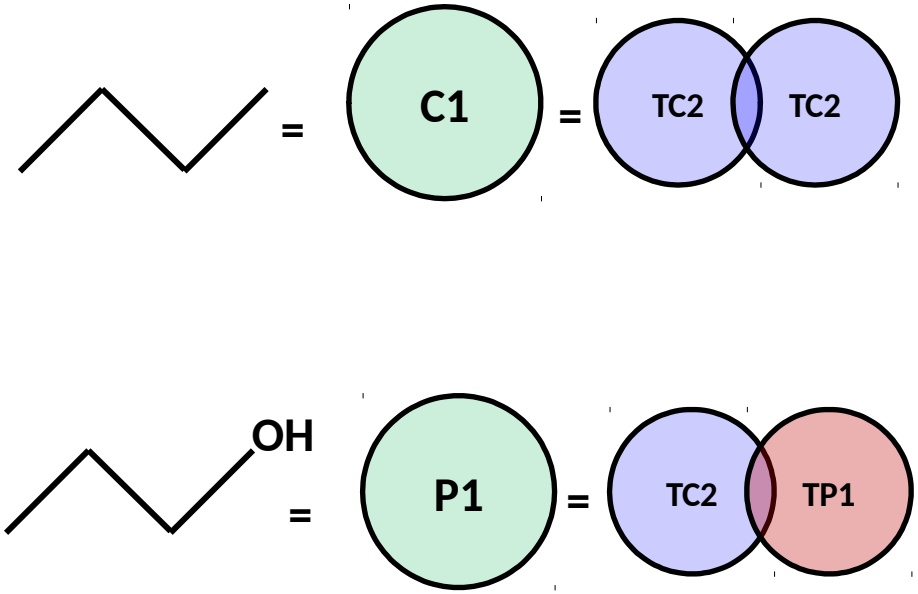


- Correct trends when reduce the size of the molecule.

How balance are the beads?

- Test 1: Build 1 N-bead with 2 T-beads

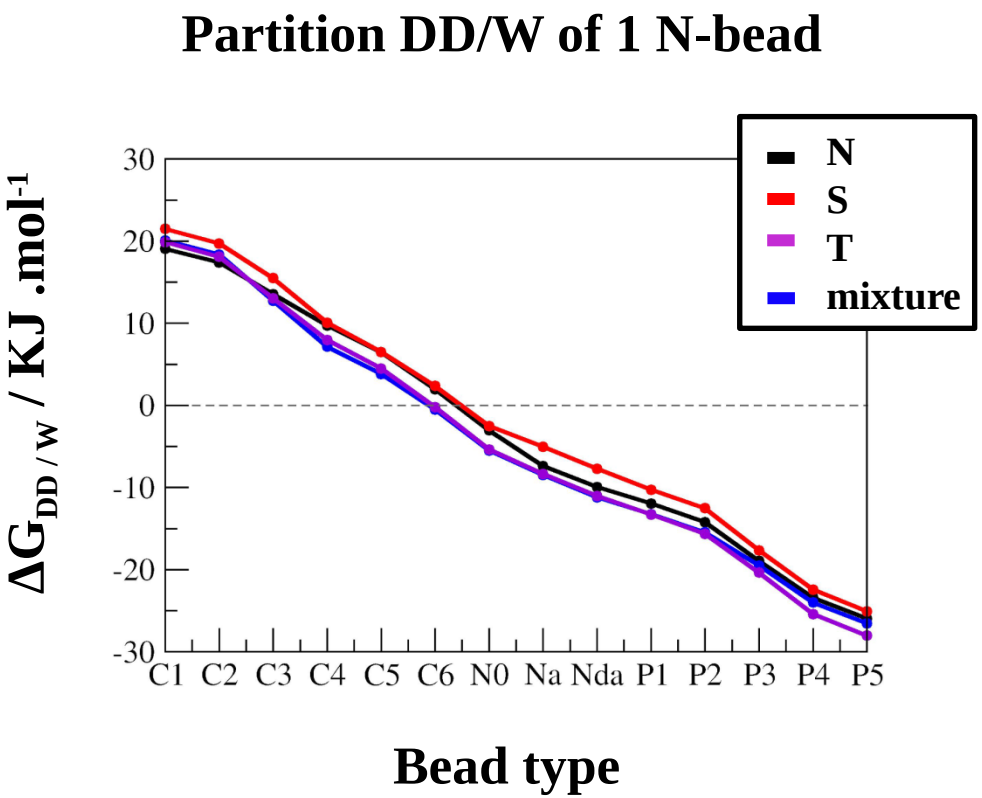


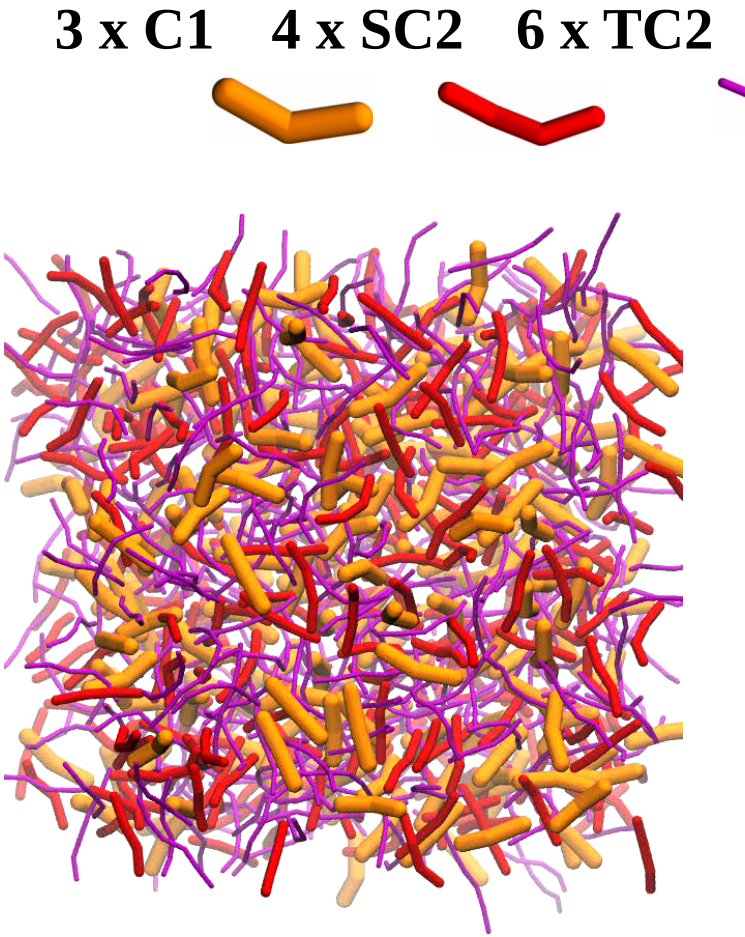


<Error> = 1.5 KJ/mol

How balance are the beads?

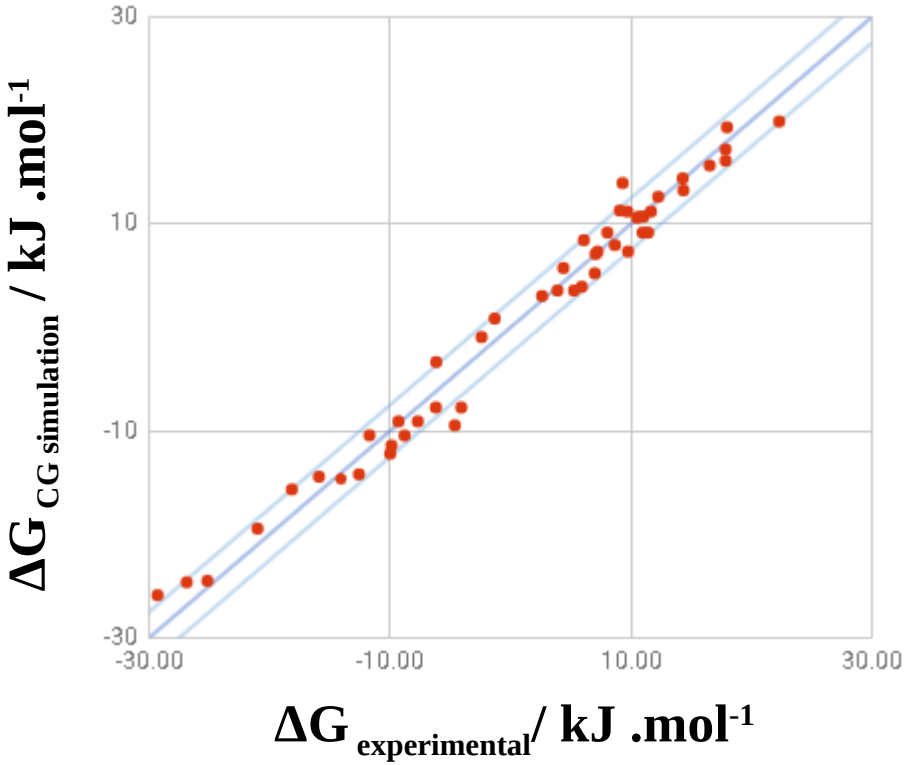
- Test 2: Multi-resolution Dodecane





Water/Oil Partitions

HD/W Partition



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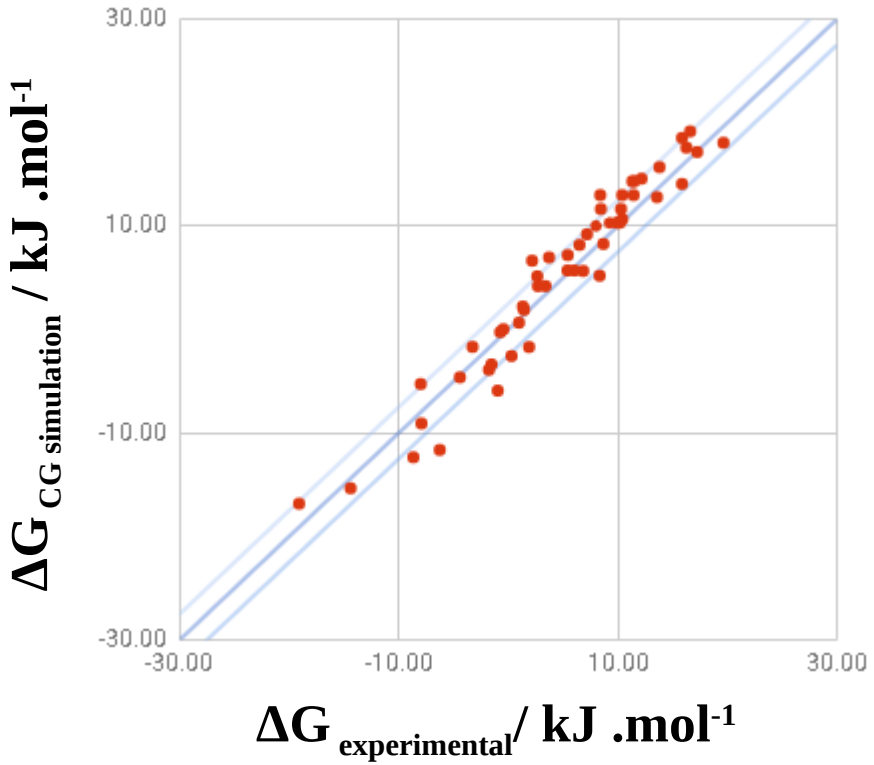
OCO/W Partition



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Results include linear and cyclic molecules (aromatic and aliphatic)

Quality control tests

- quick simulation tests (0.5 to 1 us) in small systems.
- Yes/No answers.
- Check qualitative improvements
- Avoid share itp files with clear problems
- Continuos optmization of the beads after release the force field.

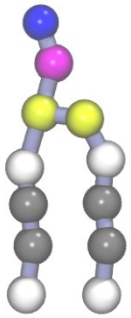
Examples of tests

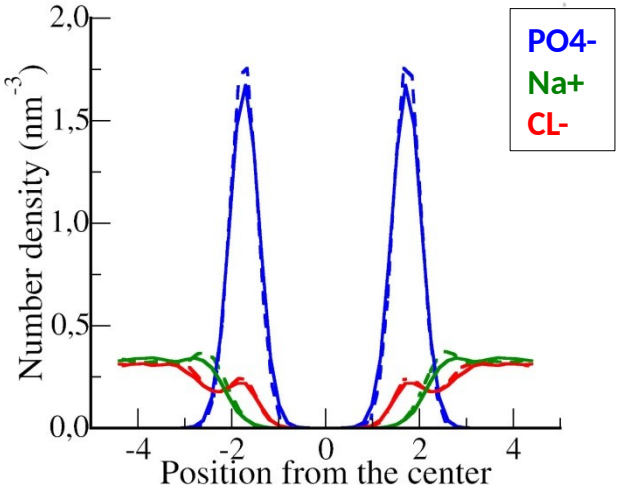
System	Goal	Status
•Standard Lipids	Check bilayer properties	
•Villin Protein	Solubility in water	
•Polyleucines in POPC	Solubility in bilayers	
•Barnase-Barstar dimer	Protein-protein interactions	
•Glycoporin A homodimer		
•Peripheral membrane proteins in POPC	Anchoring PC head Cation-pi interactions	
•Rhodopsin in POPC	Transmebrane protein Protein-lipid interaction	

1) Standard Lipids

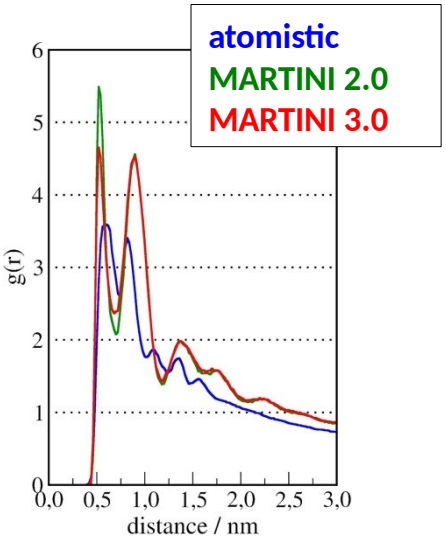
- Good structural properties

DIPC

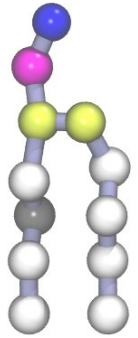




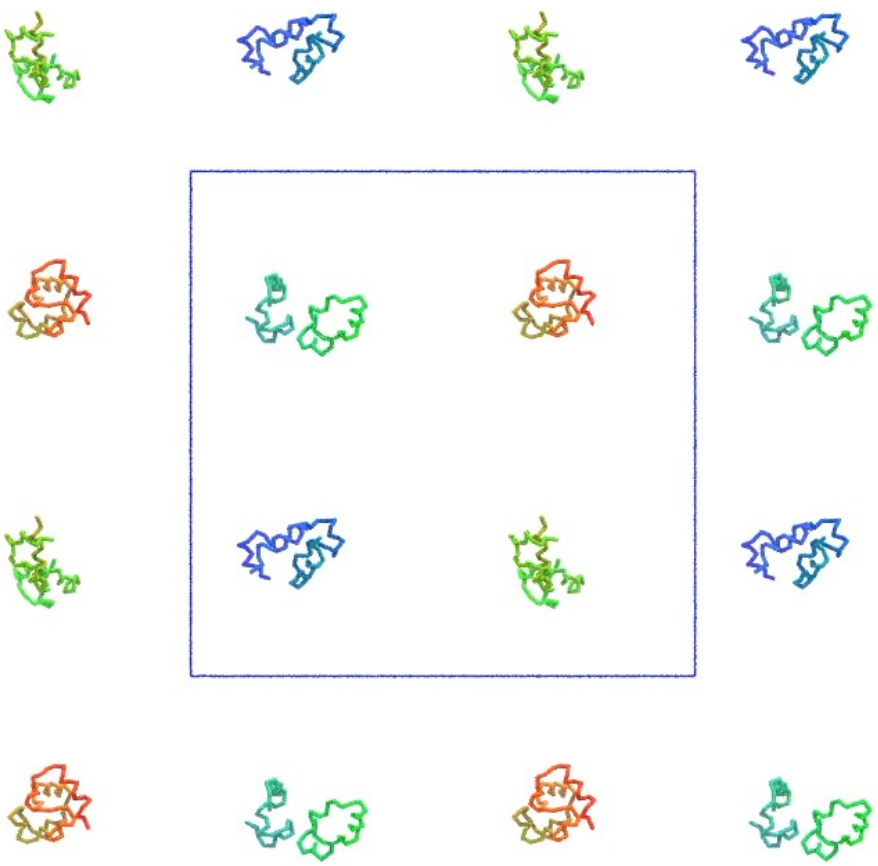
- Small changes in head organization.



POPC



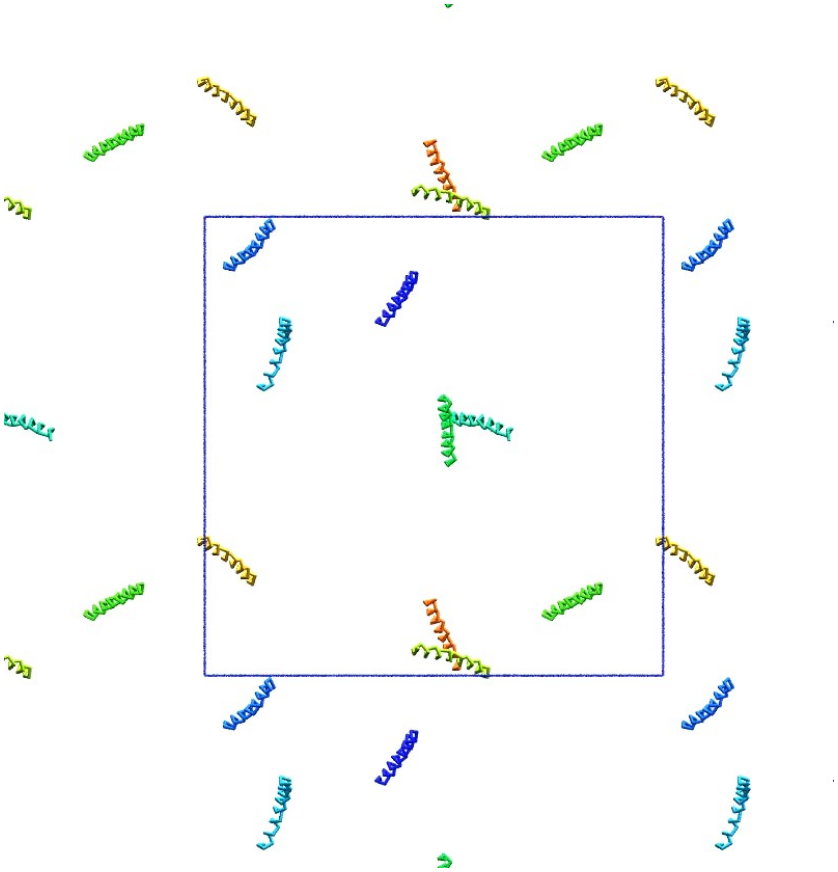
2) Villin: Soluble Proteins



Why soluble now ?

- new S/T beads in the side chains
- New Q-beads
- New water
- Backbone based in the partition (P2 bead)
- Solubility is dependent of ion concentration

3) Polyleucines in POPC



- Dimerizarion/aggregation controlled by:

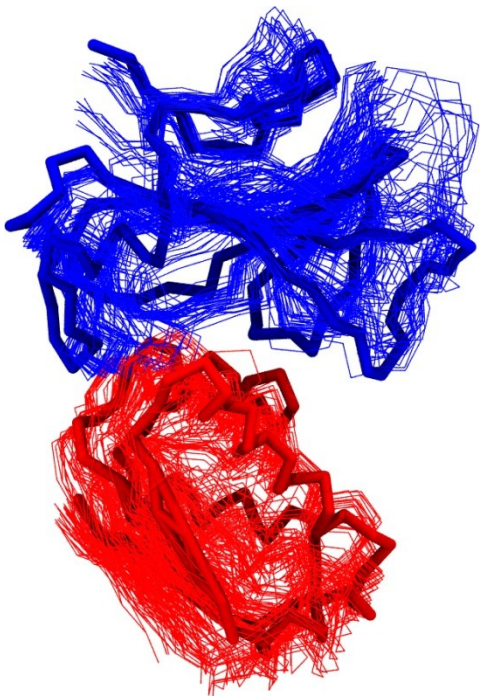
-Mutations in the middle of the chain

-Lipid composition

-Solubility of the domains/motifs in water

- Example: $K_2L_{26}K_2$

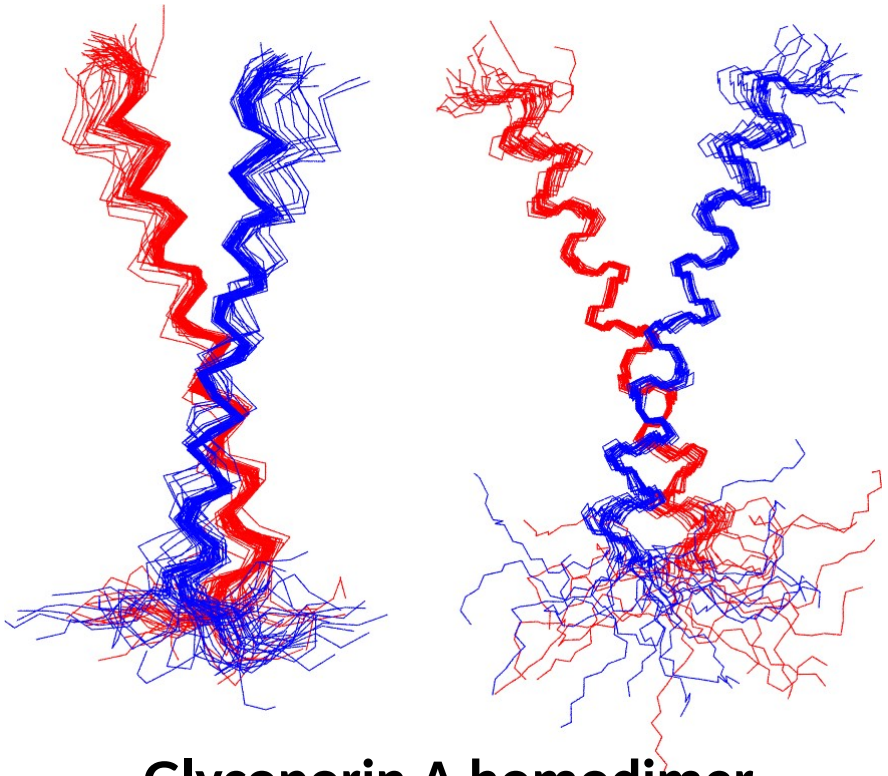
3) Protein dimers in water and bilayer



Barnase-Barstar

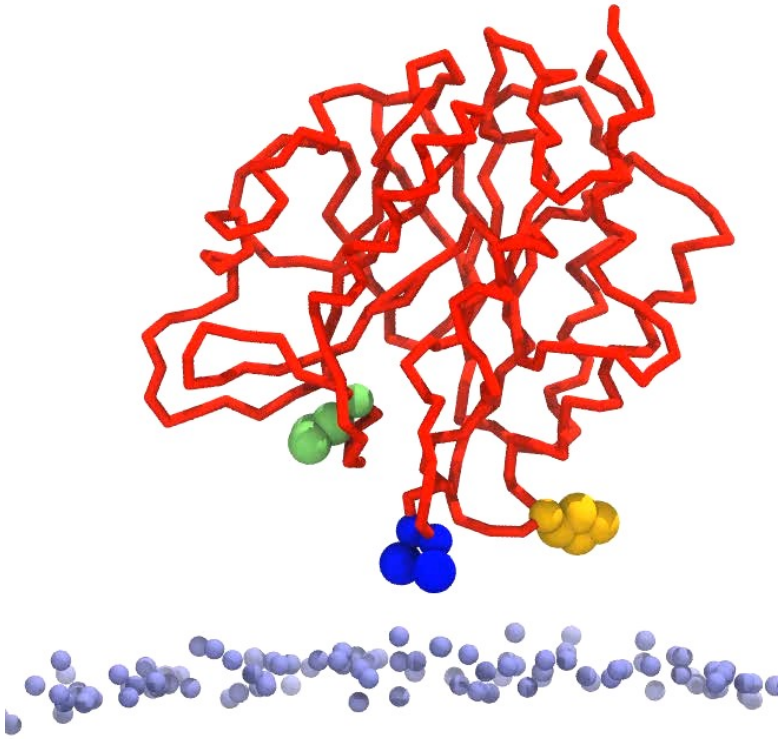
CG Simulations
POPC Bilayer

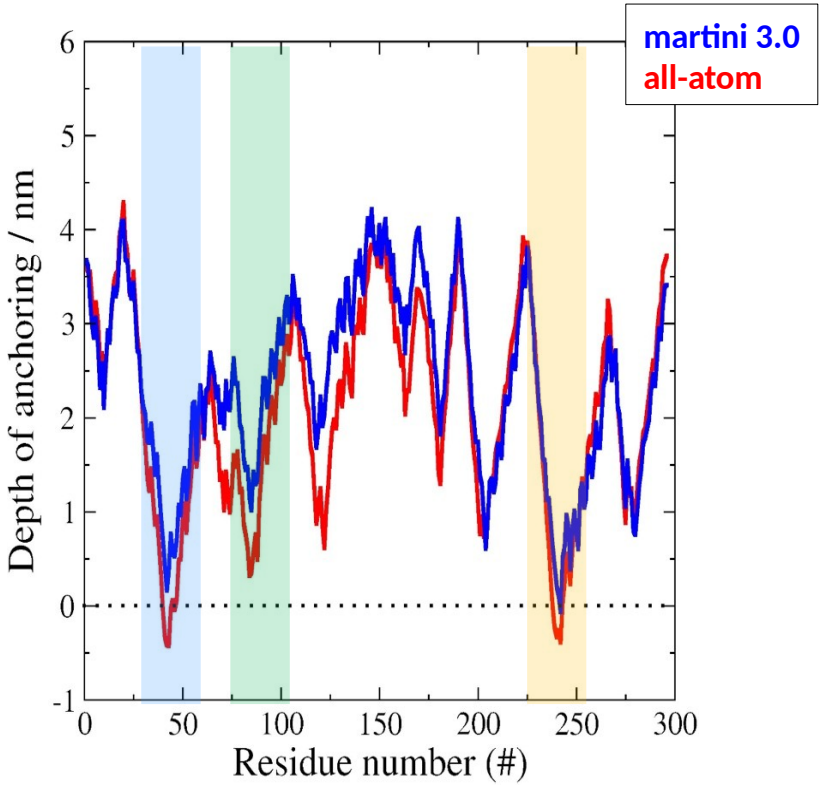
NMR experiment
Detergent micelle



Glycoporin A homodimer

4)Peripheral membrane protein cation- π interactions

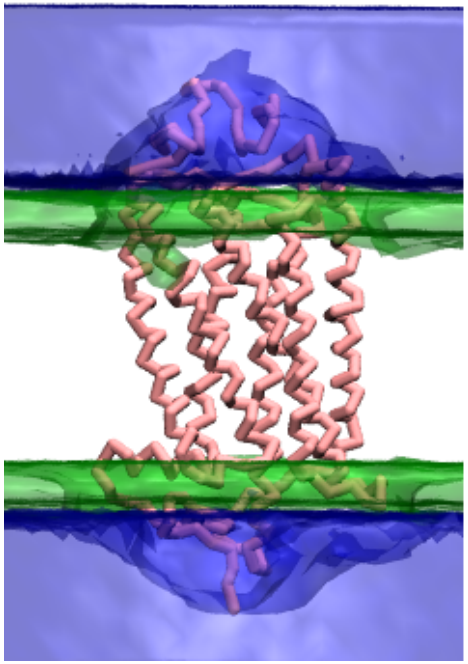




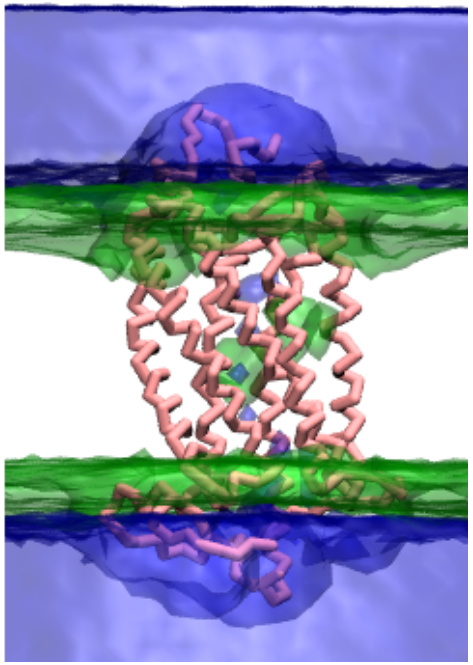
- Example: phospholipase C (BtPI-PLC))

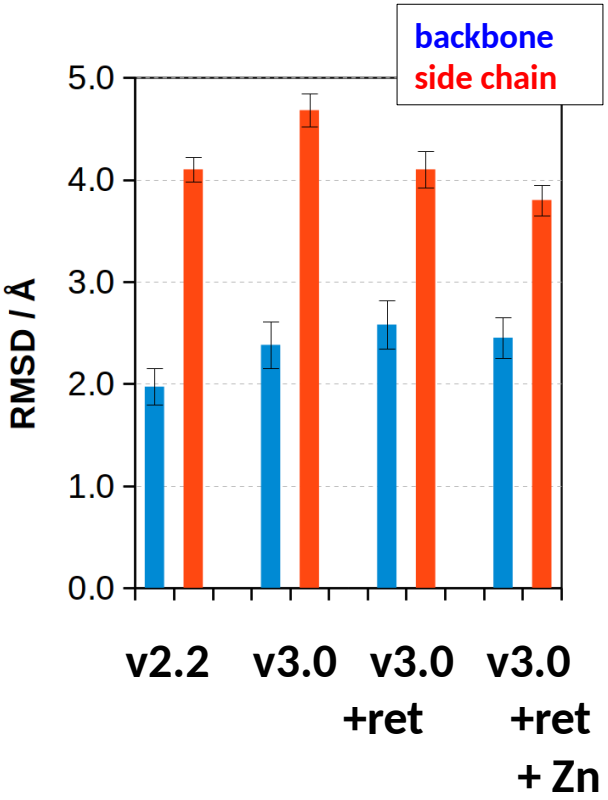
5) Rhodopsin in POPC: Protein-lipid interactions

MARTINI 2.2 + EN



MARTINI 3.0 + EN

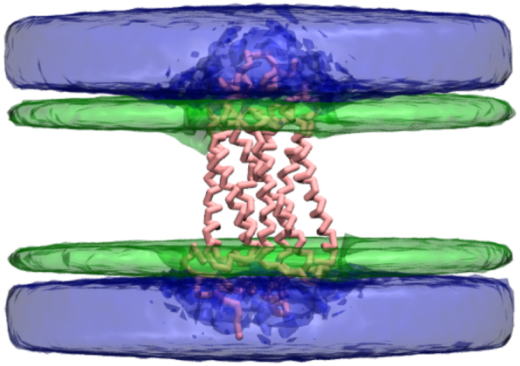




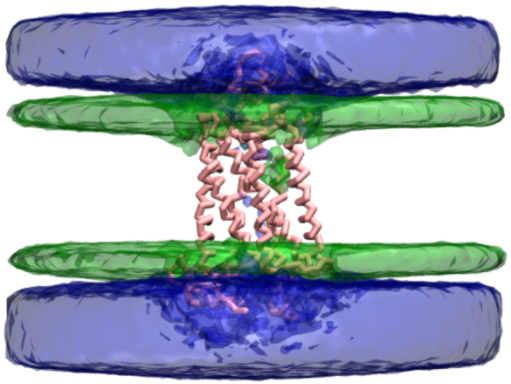
EN = Elastic Network; SC: Side chain dihedrals corrections; cof: cofactors

5) Rhodopsin in POPC: Protein-lipid interactions

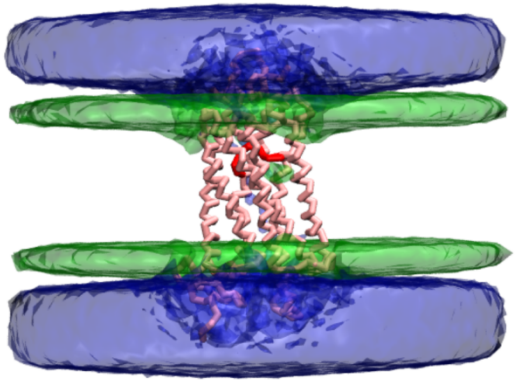
MARTINI 2.2



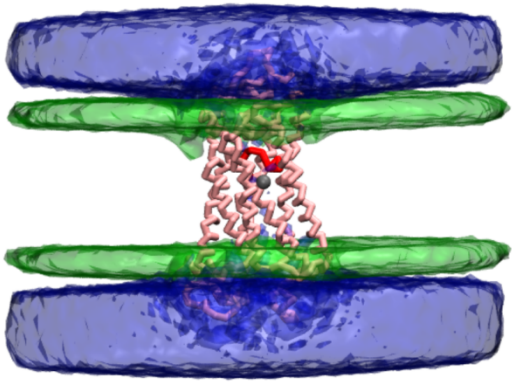
MARTINI 3.0



MARTINI 3.0
(with retinal)

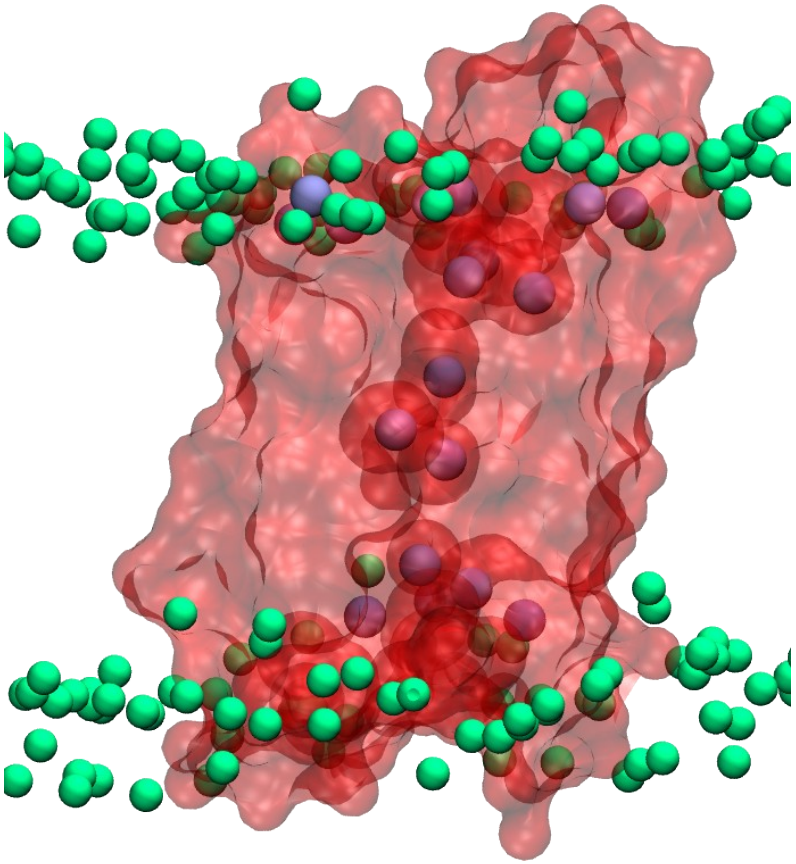


MARTINI 3.0
(with retinal and zinc)

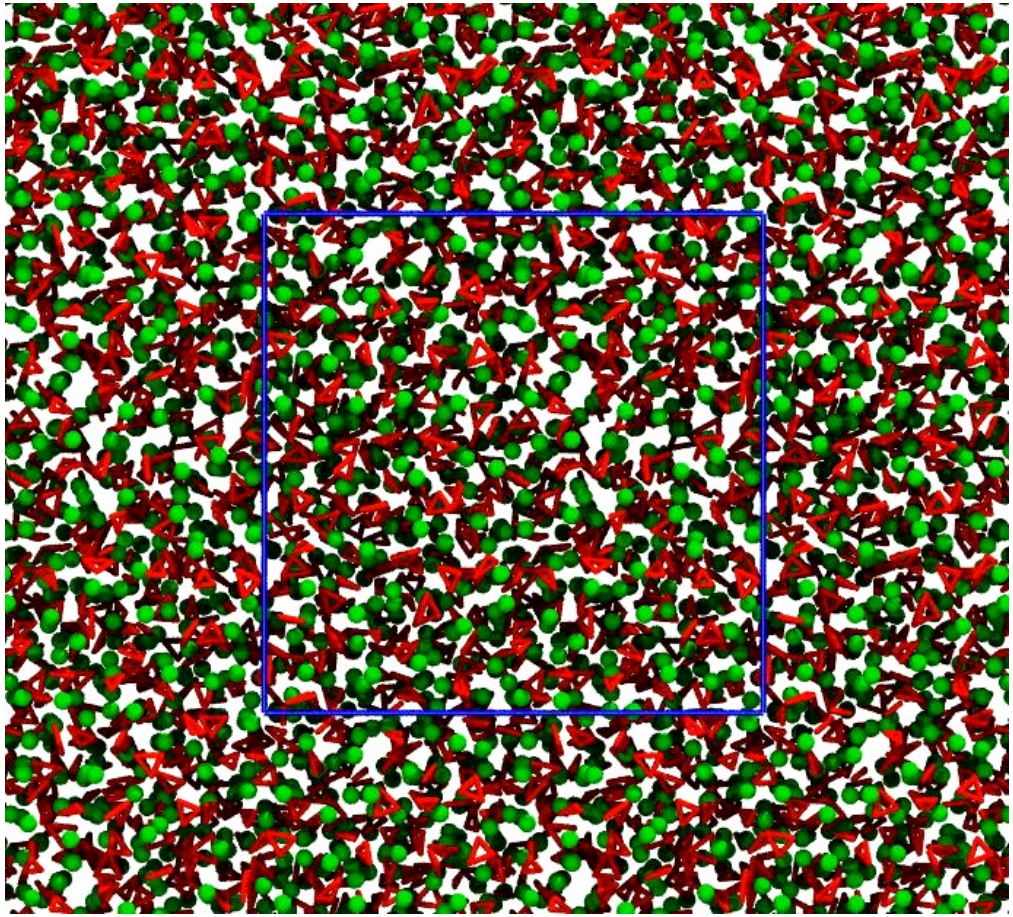


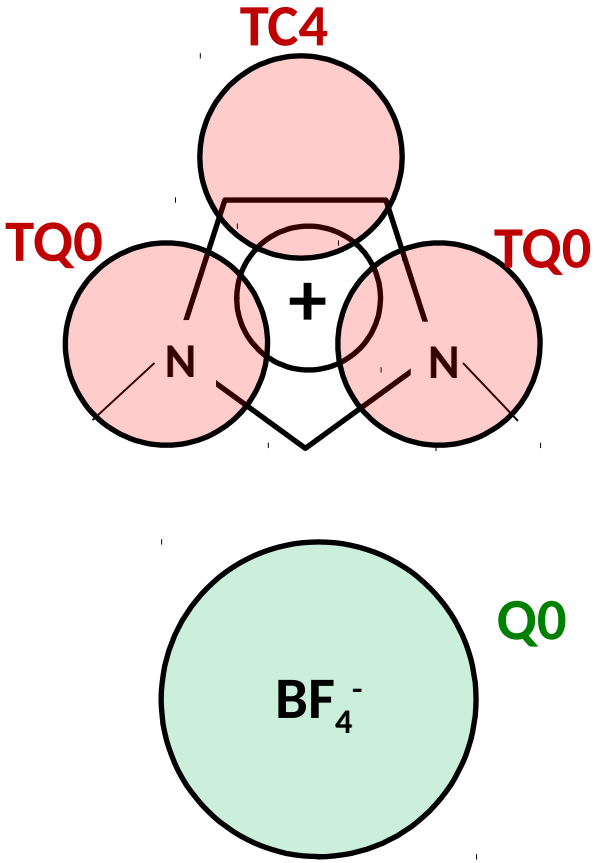
Water PC head Retinal Zinc

6) Aquaporin: proper hydration of proteins



7) Ionic Liquids





Current state of Martini 3.0

“Ready”

- Improvements in the interaction matrix
- Some new beads (C6 and Q2)
- New parametrization of S/T beads.
- New water models

“Final“ refinement in the parameters

- Reformulation of Q-beads

(special Q-X interactions)

- Other new beads (X-beads and new N-beads)

Not implemented yet

- H-donor and H-acceptor choices for all N- and P-beads.
- Improvements in bonded parameters for the most important classes of molecules (lipids, proteins, rings, sugars, dna/rna, etc)
- “Pore taskforce”: add new improvements/beads to facilitate pore formation.

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