Introduction to Martini

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“Martini Basics”

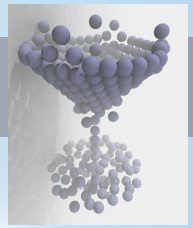
Hands on: how to prepare a Martini

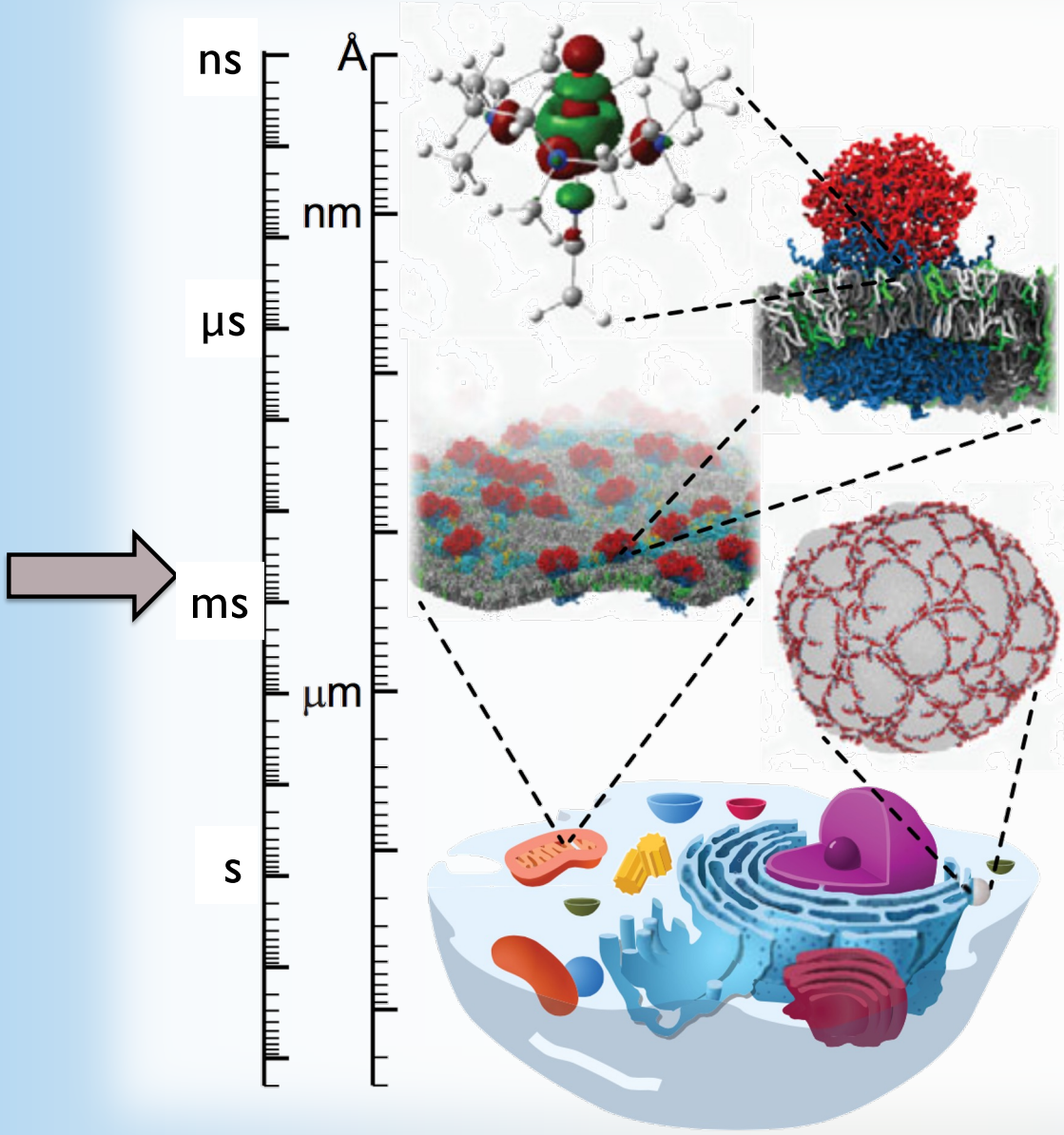
“gin and vermouth are combined at a ratio of 2:1,
stirred in a mixing glass with ice cubes,
then strained into a chilled cocktail glass and garnished with an olive”

- 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”

Bridging the all-atom to the continuum scale





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

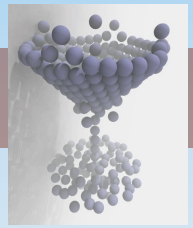
All-atom
- all or most atoms present
- explicit solvent
- molecular dynamics

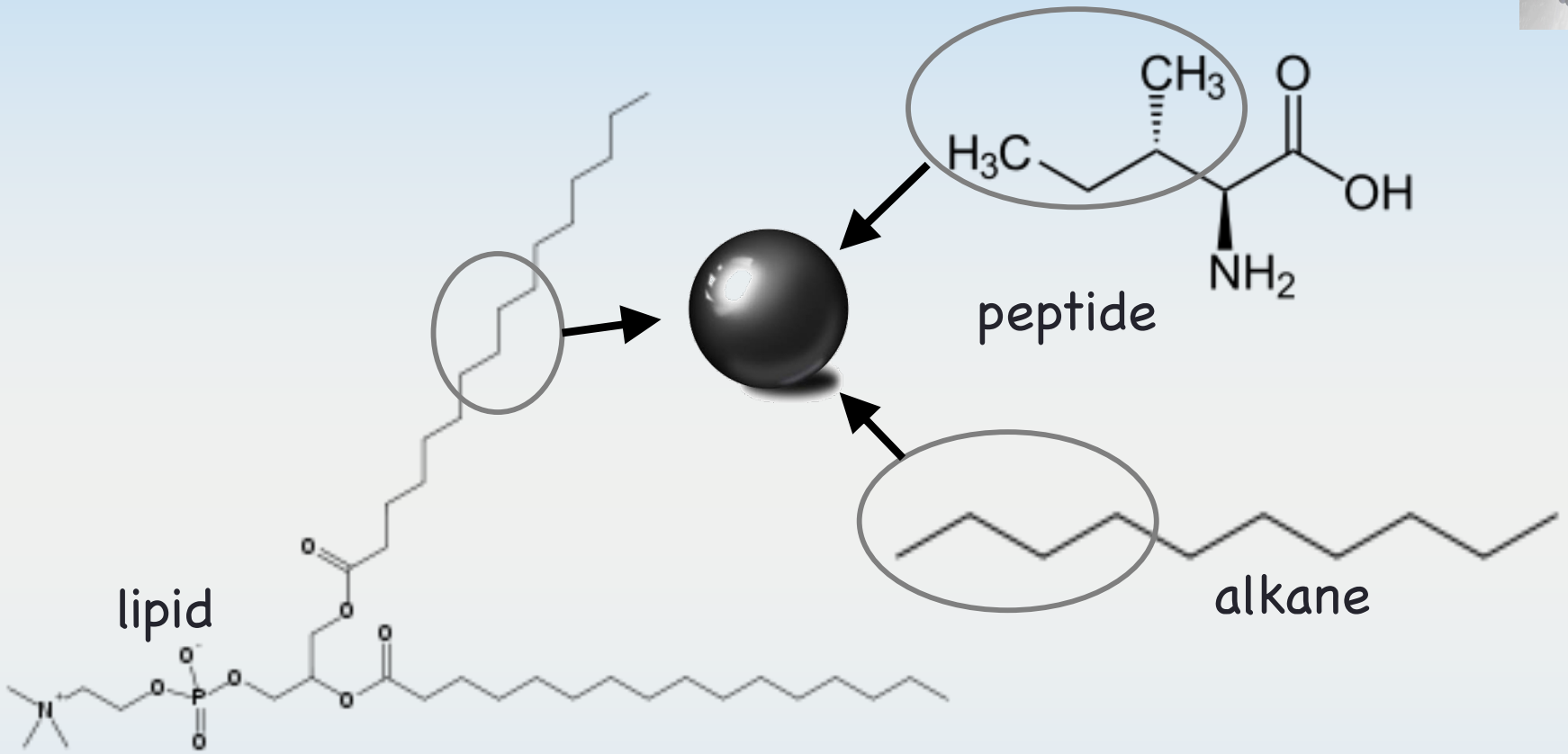
Coarse-grained
- beads comprising a few atoms
- explicit or implicit solvent
- molecular dynamics

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

Mapping of atoms to building blocks

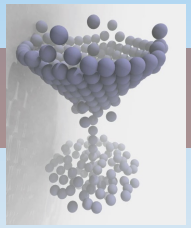




The Martini model reduces complexity of real molecules by considering groups of atoms as building blocks – the "Lego" principle

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

The building block principle



Building block types

C1
C2
C3
C4
C5

Apolar

N0
Nd/a
Nda

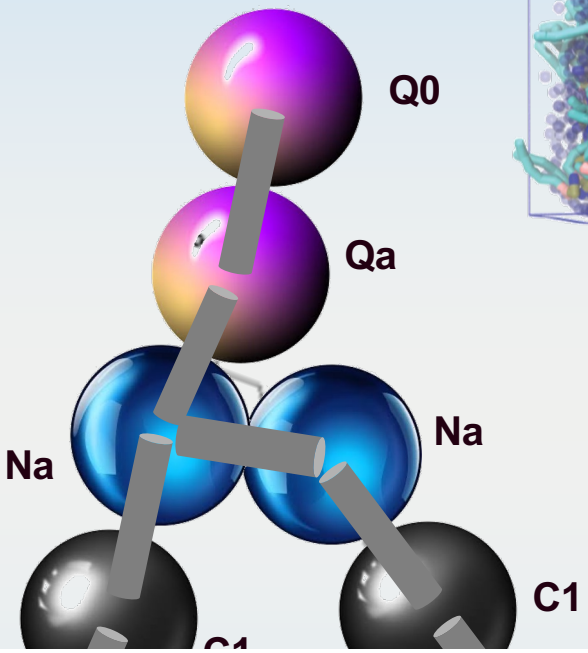
Intermediate

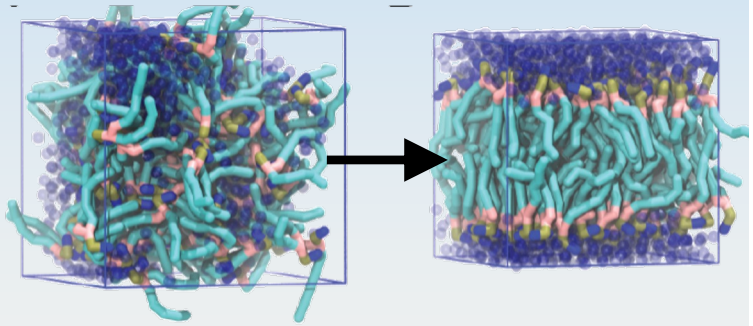
P1
P2
P3
P4
P5

Polar

Q0
Qd/a
Qda

Charged



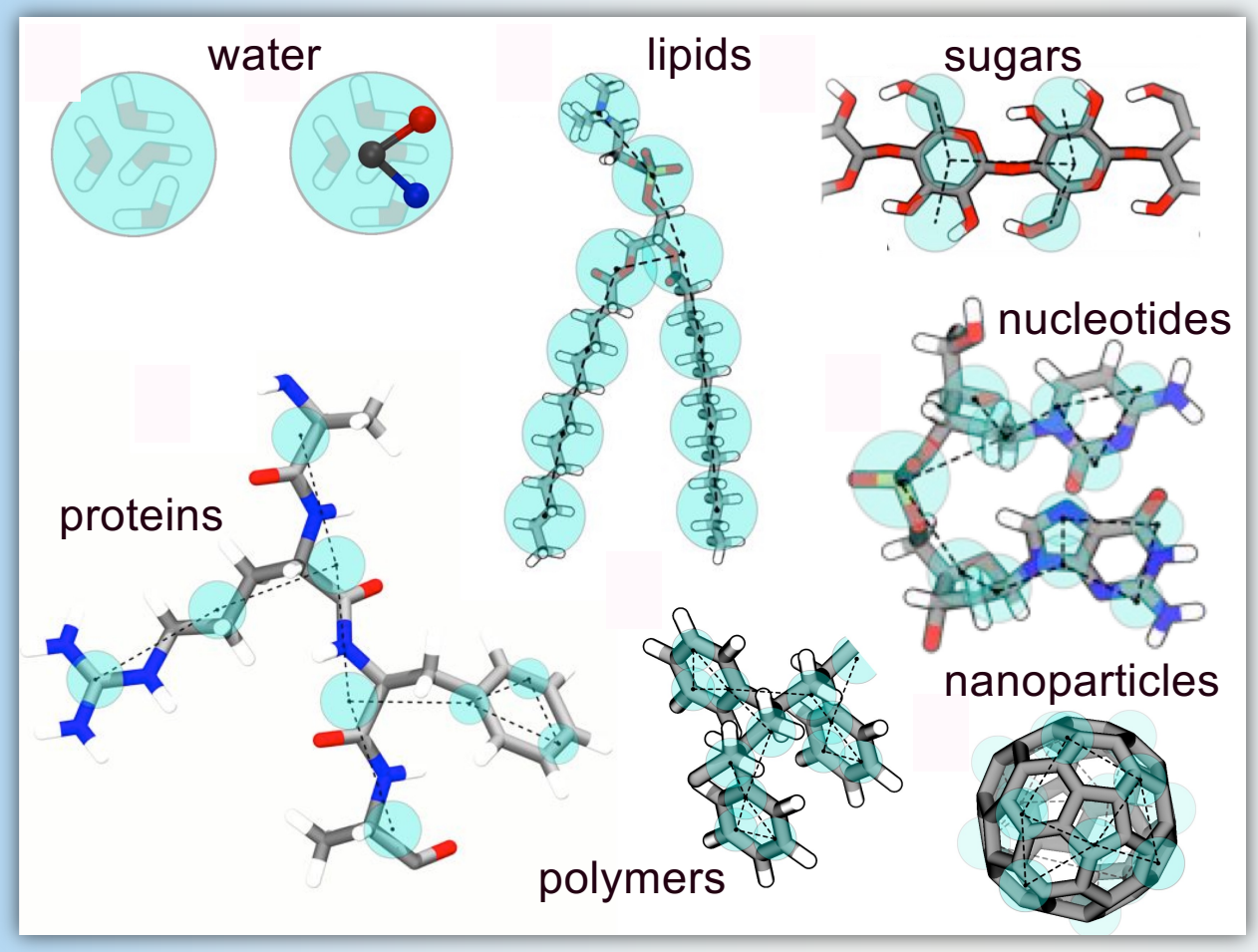


Lipids self-assemble into a bilayer, reproducing known membrane properties

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)

Welcome to the Martinidome



Key features:

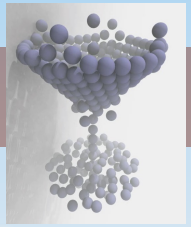
- Chemical specificity
- Fast (10^3 speed-up)
- Compatibility
- Versatility

Parameterization:

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

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

What's in a name?

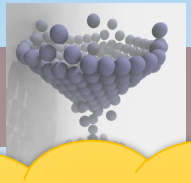


The Martini force field is developed in Groningen
and named after **Saint Martin**, patron saint of Groningen

(any association with cocktails is entirely coincidental)

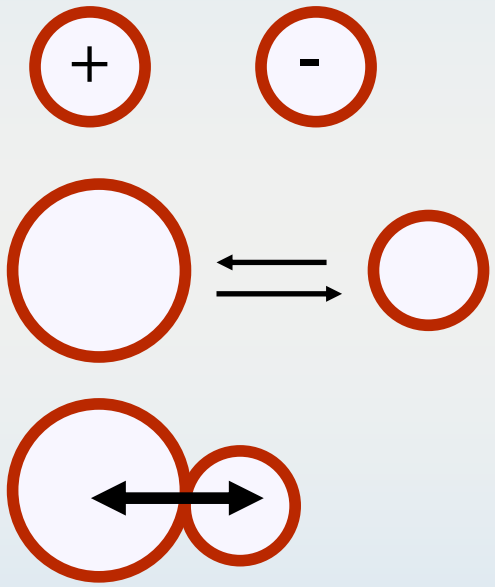
Non-bonded interactions: LJ & Coulomb

effectively distant-dependent screening, $\varepsilon_R=\infty$ at cut-off



Limitation: change in environment not felt by charges

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



electrostatic — *Coulomb (screened, $\varepsilon_R=15$)*

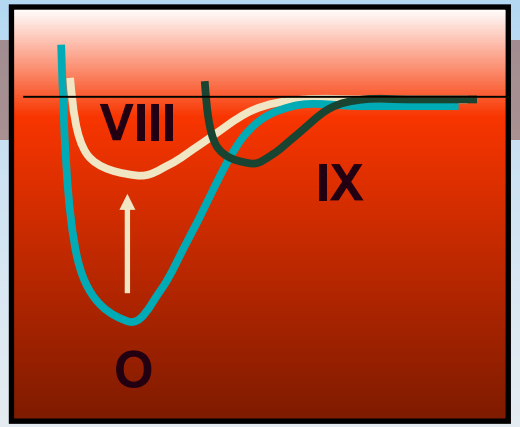
dispersion

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)

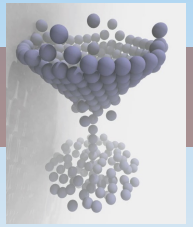
LJ interaction matrix for Martini beads



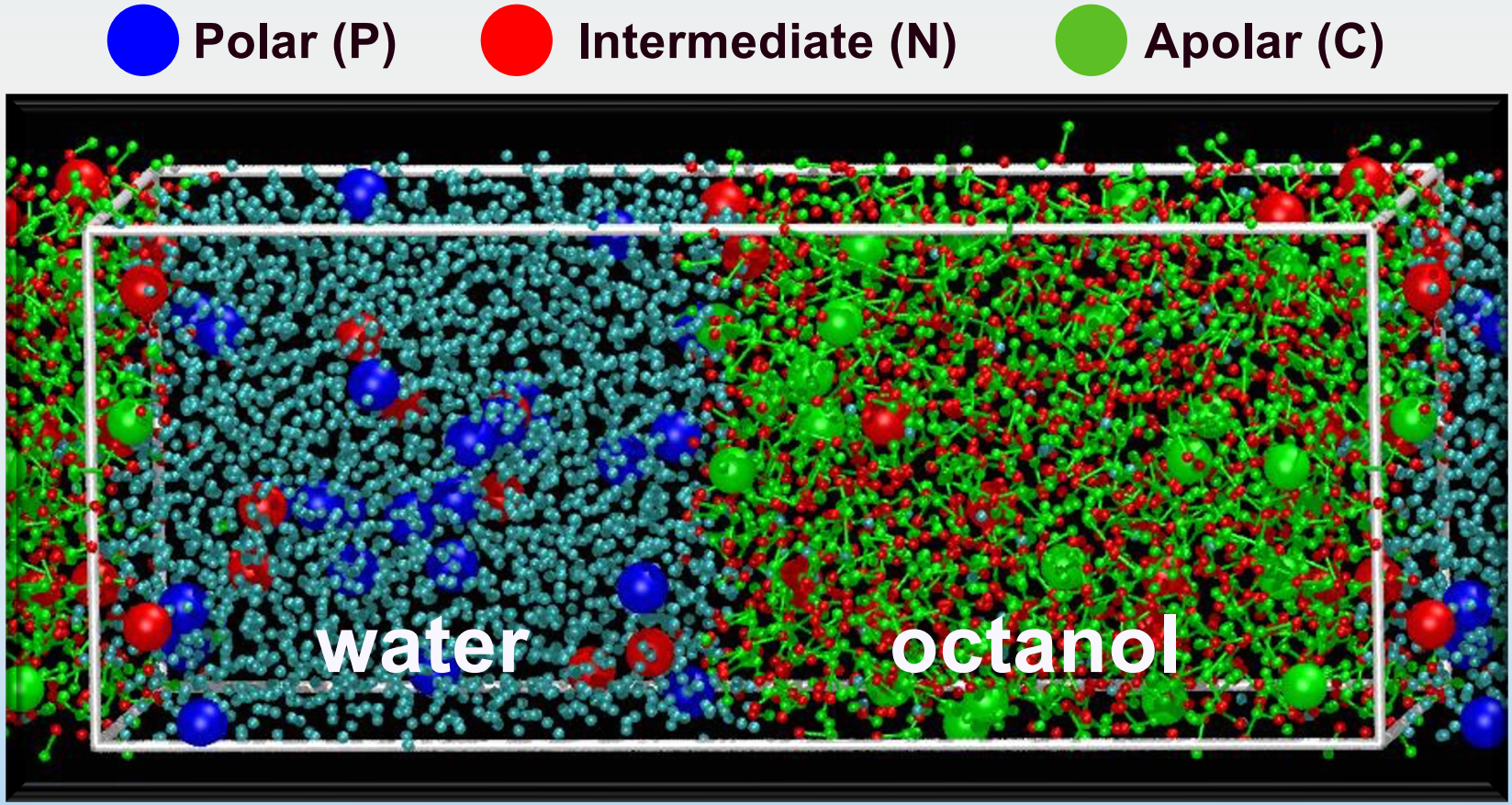
- LJ interactions depend on type of CG bead
- Beads have fixed size (Regular, Small, Tiny)
- LJ cross interactions explicitly parameterized (*no combination rule!*)

		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

Top-down: reproducing experimental partitioning data



- LJ interactions are mainly parameterized based on reproducing experimental partitioning free energies
- Free energies obtained from “direct counting”: $\Delta G_{wat/oct} = \frac{1}{kT} \ln \frac{\rho_{wat}}{\rho_{oct}}$

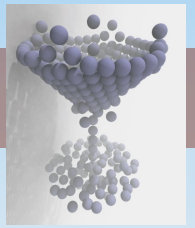


The Martini bible: mapping CG bead types to chemical build

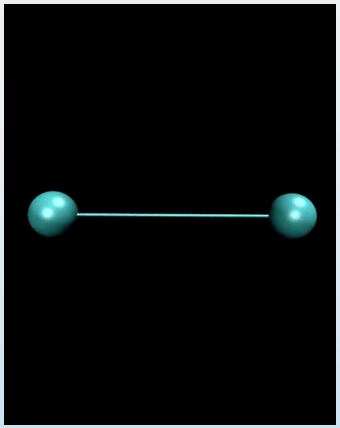
type	building block	examples	ΔG^{part}_{HW} exp	ΔG^{part}_{HW} CG	ΔG^{part}_{CW} exp	ΔG^{part}_{CW} CG	ΔG^{part}_{EW} exp	ΔG^{part}_{EW} CG	ΔG^{part}_{OW} exp	ΔG^{part}_{OW} CG
Q_{da}	$H_3N^+—C_2—OH$	ethanolamine (protonated)		< −30		−18		−13		−18
Q_d	$H_3N^+—C_3$	1-propylamine (protonated)		< −30		−18		−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_3N^+	choline		< −30		−18		−13		−18
P_5	$H_2N—C_2=O$	acetamide	−27	−28	(−20)	−18	−15	−13	−8	−10
P_4	HOH (× 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_3=N	proprionitrile	−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

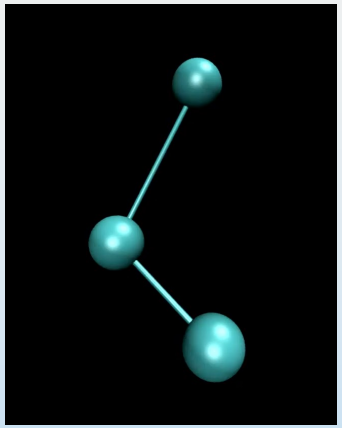
Simple harmonic forms for bonded interactions



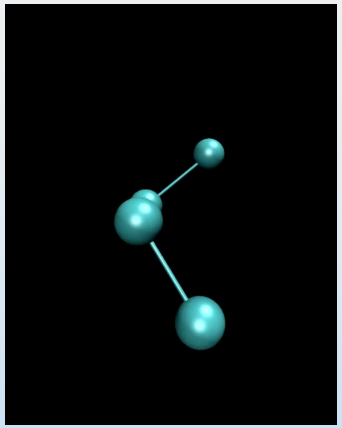
Bonds



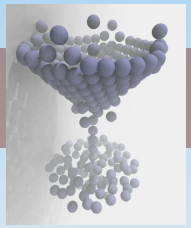
Angles



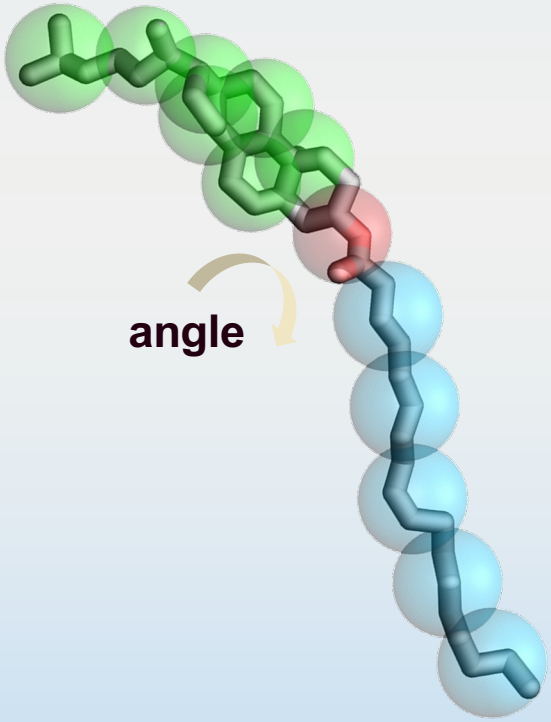
Dihedrals

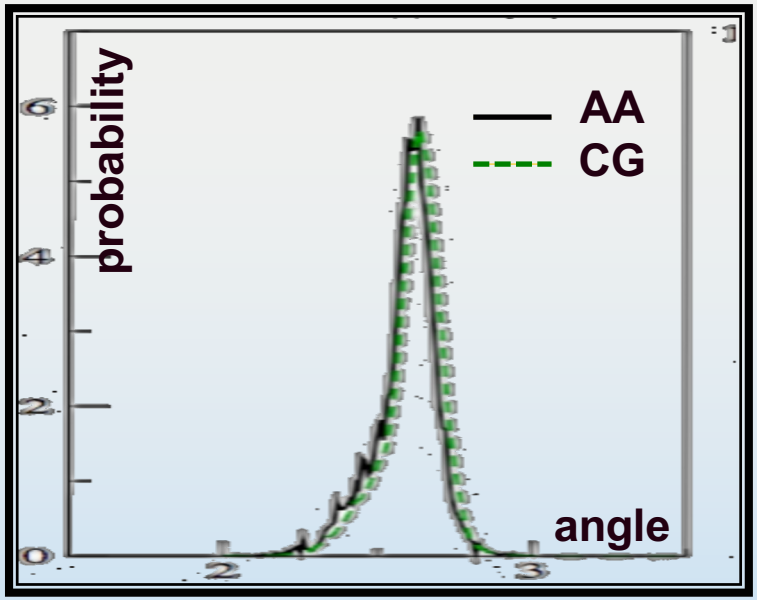


Bottom-up approach for bonded interactions

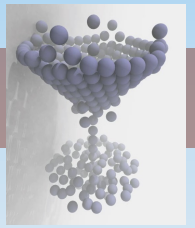


- **Bonded interactions** are parameterized by mapping to all-atom simulations

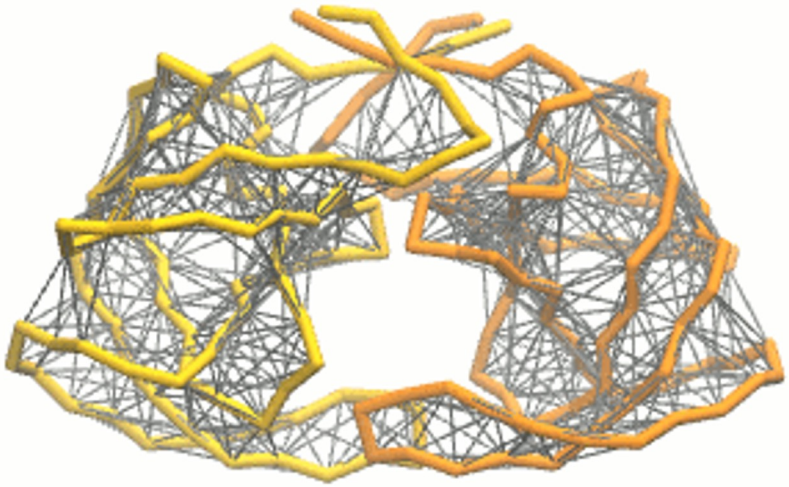




Proteins require elastic network



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



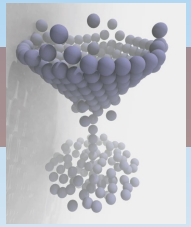
ElNeDyn: harmonic potentials between all Cα beads within a cut-off

Limitation: Folding/unfolding not possible with Martini

However: GoMartini offers some flexibility

Periole et al., JCTC 5:2531-2543, 2009

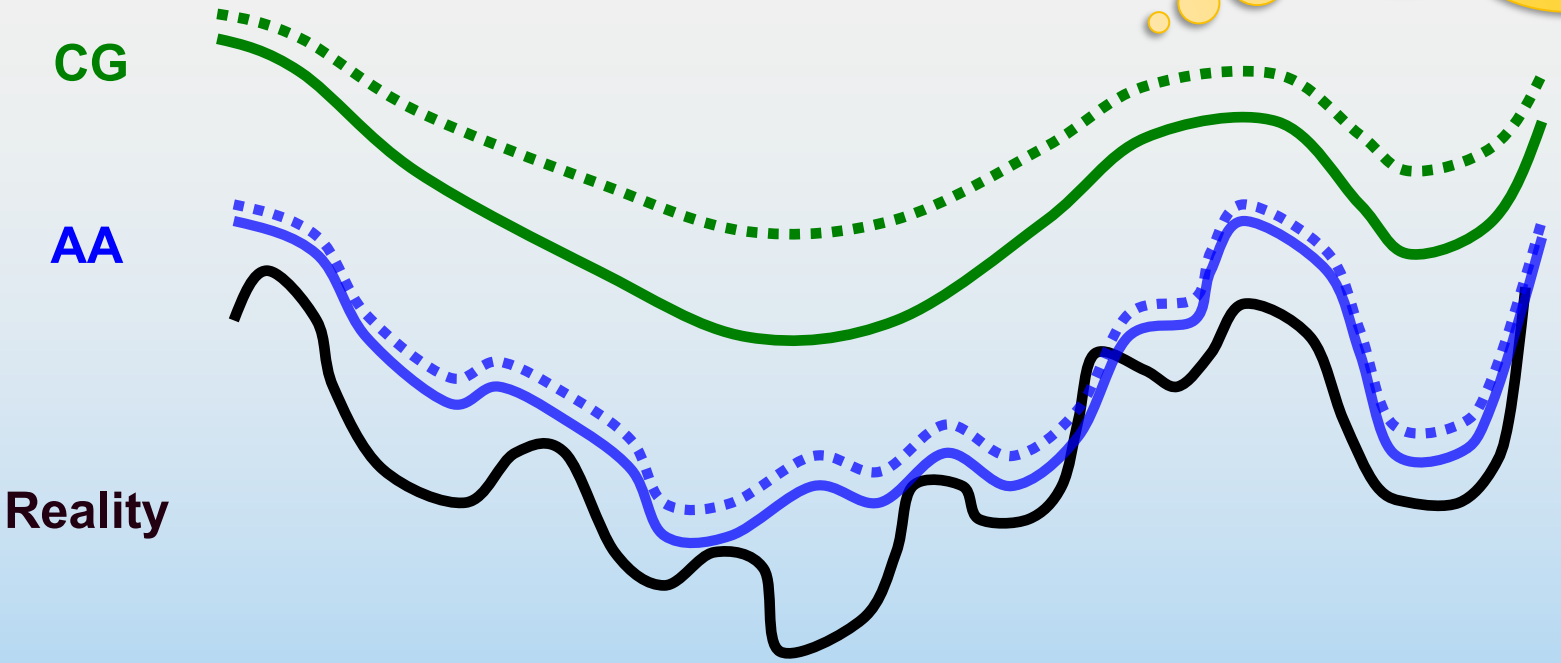
Why is Martini so fast (1000 x speedup)



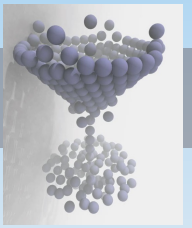
- **Less particles, so less interactions to compute**
- **Short range potentials only**
- **Less friction, so faster sampling**
- **Time steps of 20-30 fs can be used**

(accurate sampling is less critical)

Limitation:
Timescale should be interpreted with care



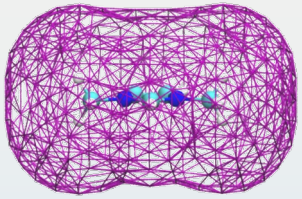
Martini 3



Martini 1: for lipids
Marrink et al. JPCB, 2004

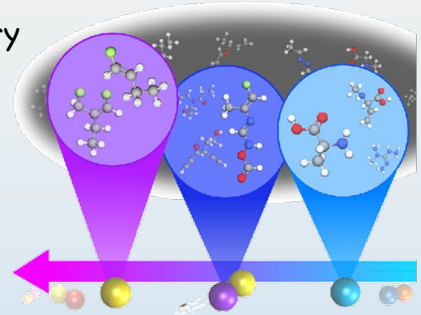
Martini 2: for biomolecules
Marrink et al. JPCB, 2007

Martini 3: for general purpose
Souza et al. Nature Methods, 2021



1) Improved interactions and packing

Reparametrized all bead-bead interactions and bonds using center-of-geometry



2) Better coverage of chemical space

New beads and ways to modify them

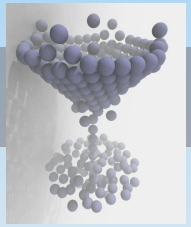
3) Reformulation of charged beads

Including bare ions and double charged ions, Hoffmeister series

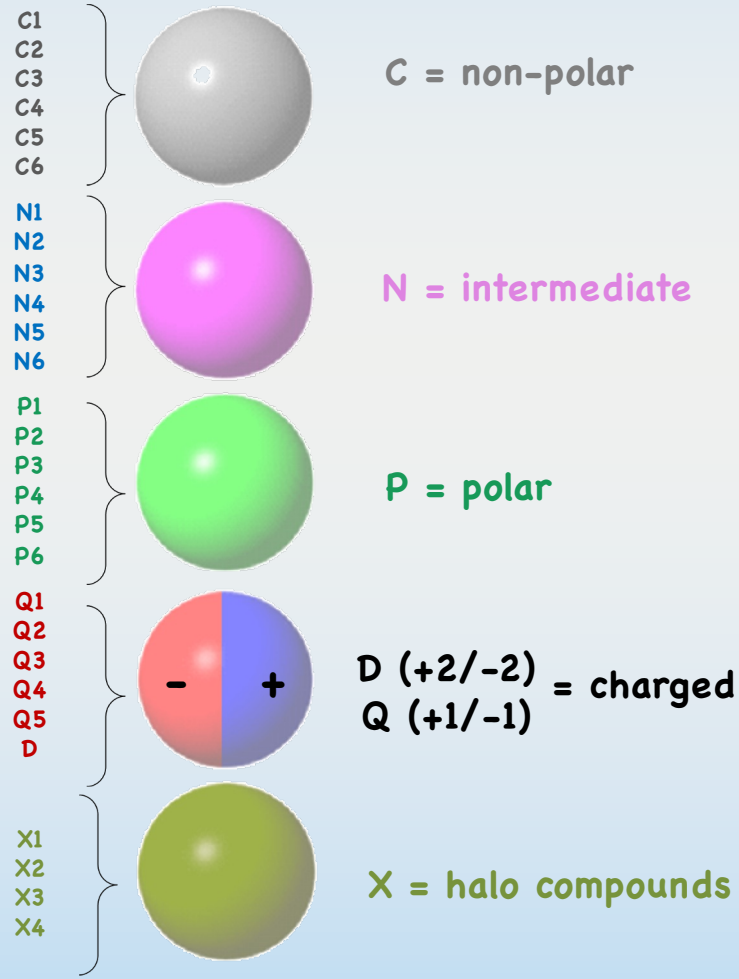
4) Embracing Gō models for proteins

Allowing allostery and folding/unfolding transitions

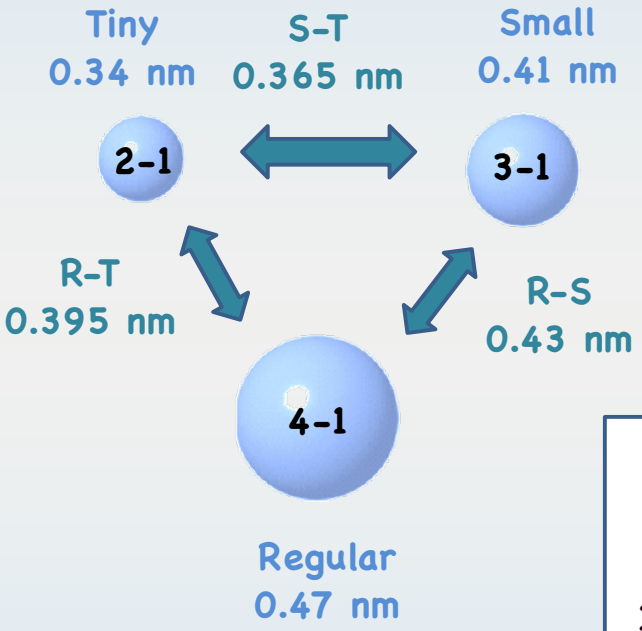
Martini 3: Just bead it …



28 Bead Chemical Types



3 Bead Sizes



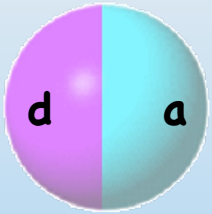
Specific bead for water

W = water

From M2 to M3:

54 → 843 beads
1,485 → 355,746 pairs
60 → 1,301 parameters

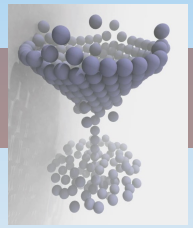
9 Bead Labels



Examples:
H-donor (d) / H-acceptor (a)
Electron rich (e) / Electron poor (v)

Souza et al., *Nature Methods* 2022

Martini 3.0 bead sizes well balanced

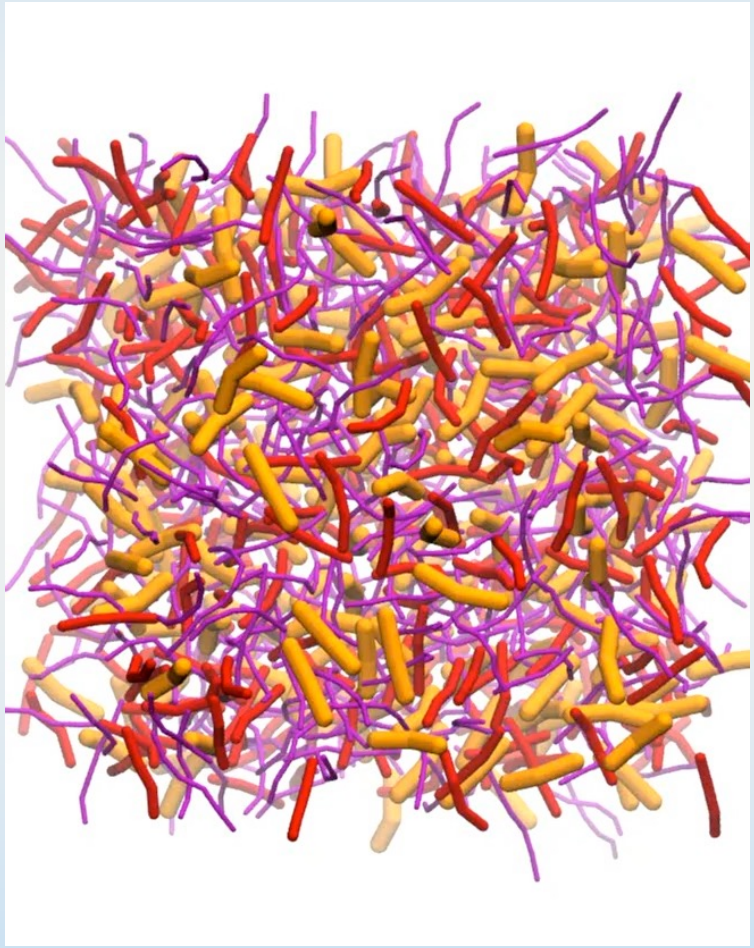


Mixing different resolutions of liquid dodecane with:

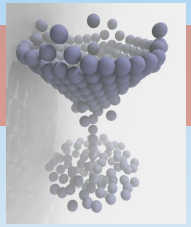
3 N beads (orange),

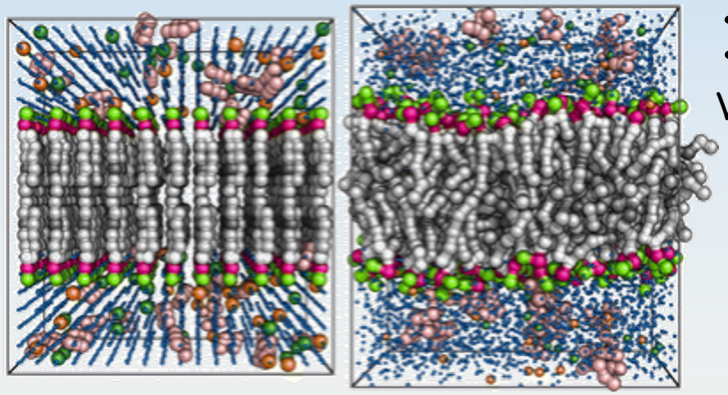
4 S beads (red), and

6 T beads (magenta)



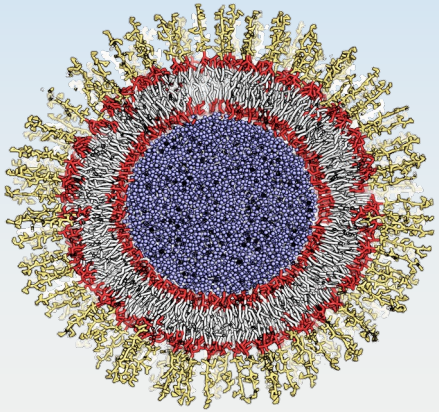
High-throughput tools





Insane

Wassenaar et al., *JCTC* (2015)

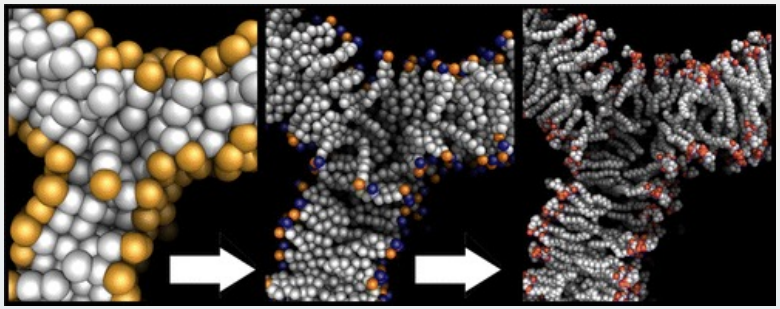


Martini-Maker (Charmm-GUI)

Qi et al., *JCTC* (2015)

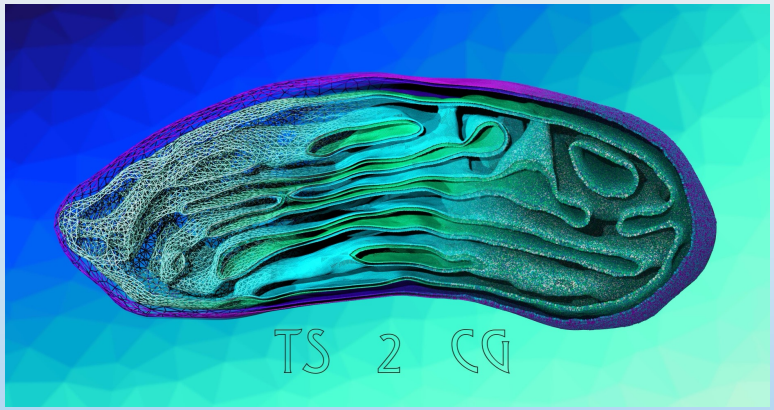
Backward

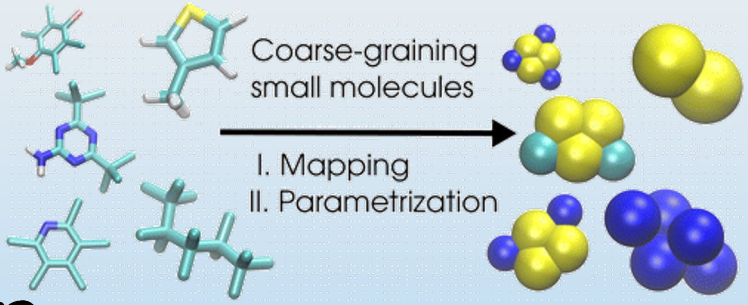
Wassenaar et al., *JCTC* (2014)



TS2CG

Pezeshkian et al., *Nature Comm* (2020)

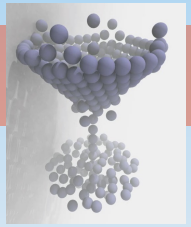




ATB

Bereau & Kremer, *JCTC* (2015)

More high-throughput tools



Total inputs	87084		

Martinize step	#	Fraction of total	
Success	64134	73.6	
Missing side chain beads	21730	25.0	
Unrecognized residues	331	0.4	
Missing backbone atoms	889	1.0	

Grompp step	#	Fraction of total	Fraction of previous step
Success	64134	73.6	100.0
Errors	0	0.0	0.0

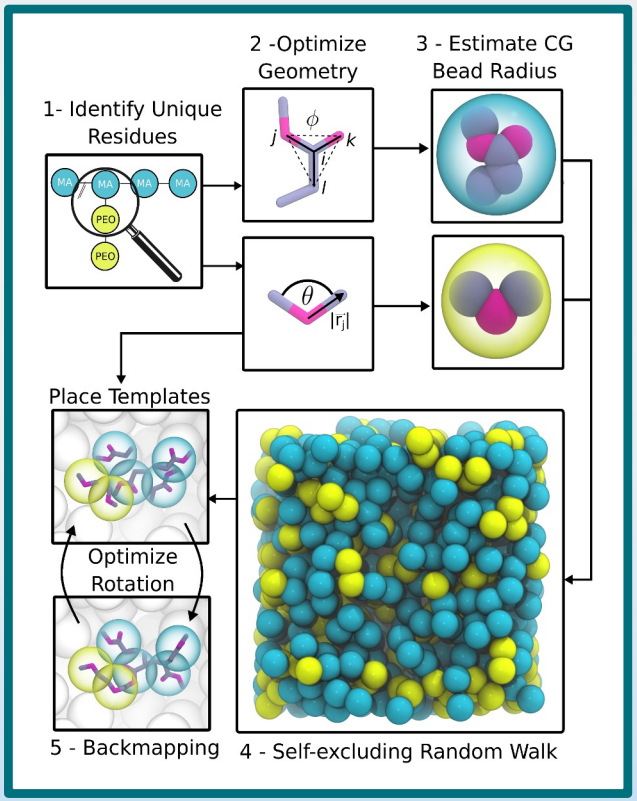
Mdrun step	#	Fraction of total	Fraction of previous step
Success	63784	73.2	99.5
Errors	350	0.4	0.5

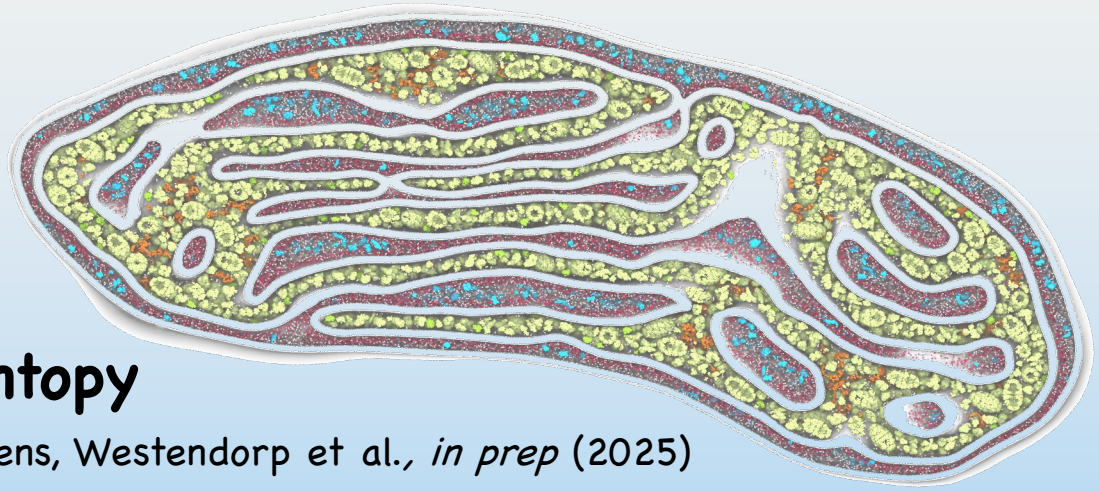
Martinize2

Kroon et al., *eLife* (2023)

Polyply

Grünewald et al., *Nat. Comm.* (2022)

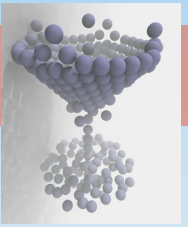


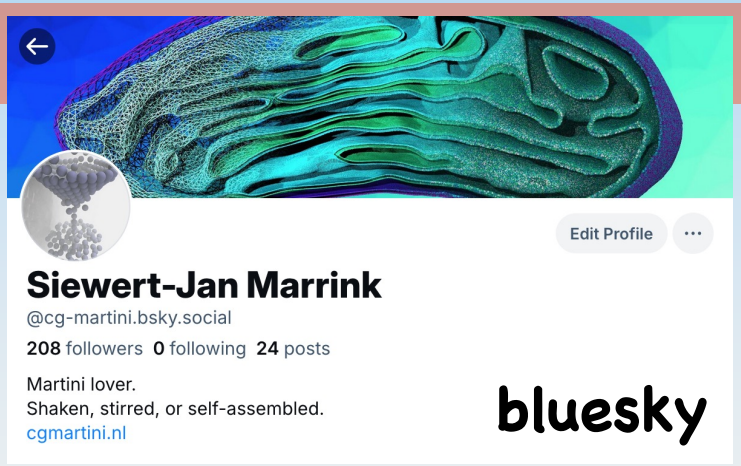


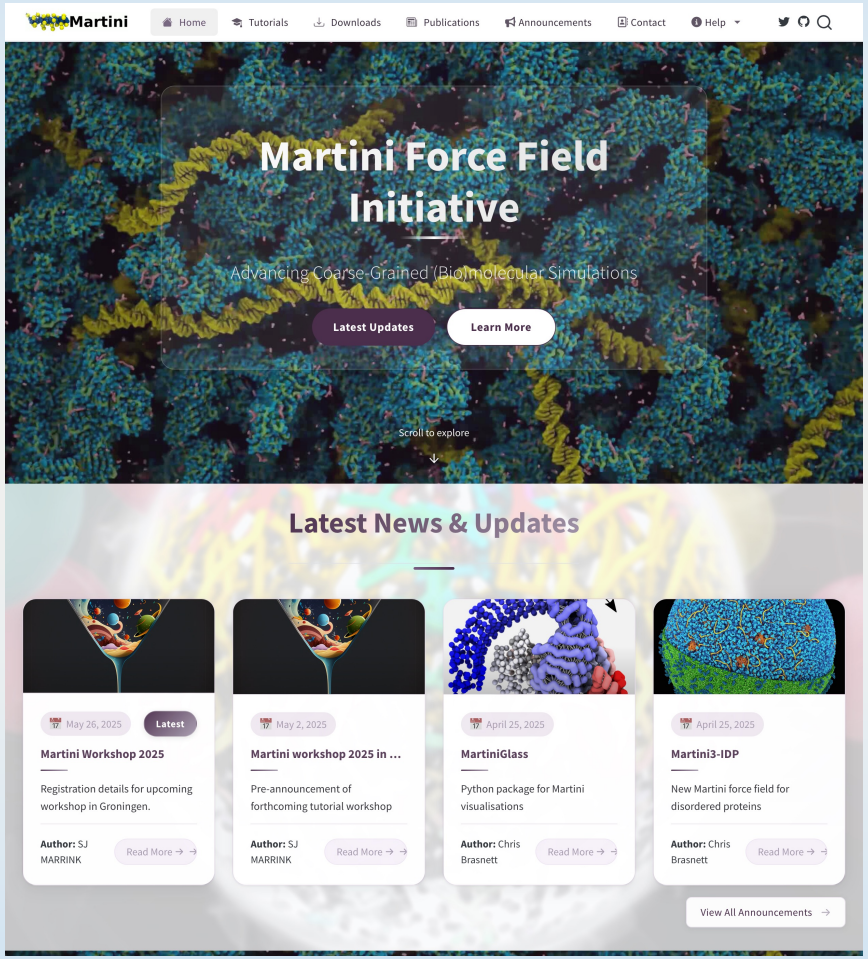
Bentopy

Stevens, Westendorp et al., *in prep* (2025)

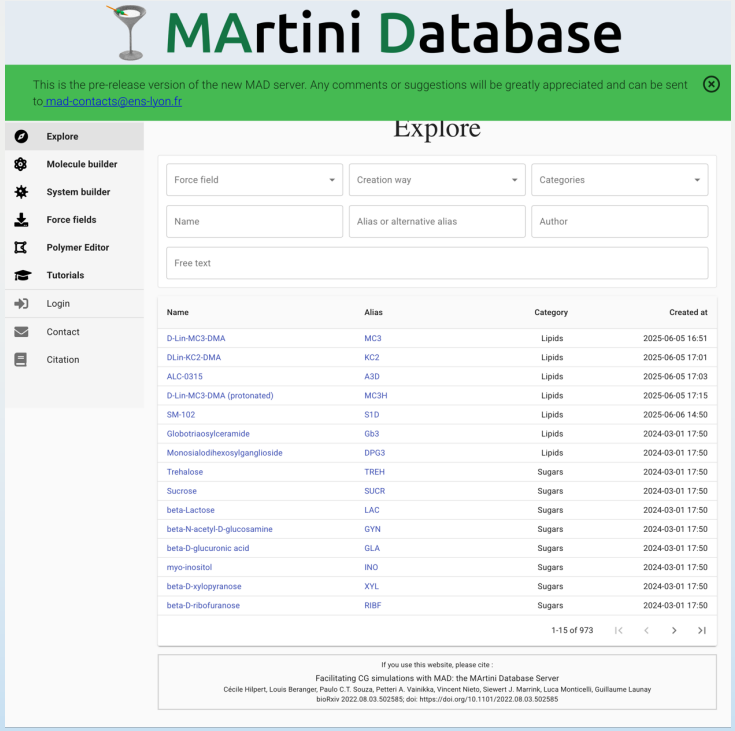
Open science





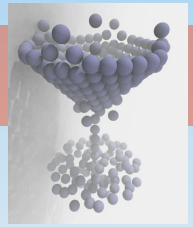


cgmartini.nl



mad.ens-lyon.fr

The schedule



Day 1: Lipids
Morning lectures
Afernoon tutorial

Day 2: Proteins
Morning lectures
Afernoon tutorial
Evening poster session

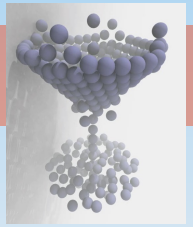
Day 3: Parameterization
Morning lectures
Afernoon tutorial

Day 4: Complex Systems
Morning lectures
Afernoon tutorial
Evening conference dinner

Day 5: Your Own
Morning tutorial

Note: tutorials available at both beginner and advanced levels

The workshop team



Lecturers
Tsjerk Wassenaar
Helgi Ingolfsson
Manel Melo
Sebastian Thallmair
Adolfo Poma
Riccardo Alessandri
Fabian Grünewald
Linus Grünewald
Weria Pezeshkian
Chris Brasnett
Luis Borges
Daniel Ramirez
Jan Stevens
Chelsea Brown

TAs
Abby Dommer
Bart Bruininks
Rubi Zarmiento
Pietro Sillano
Wietske Nauta
Marieke Westendorp
...

Support
Alex de Vries
Jannet Nijhuis

Supervision
Me

Enjoy Sampling Martinis !!

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