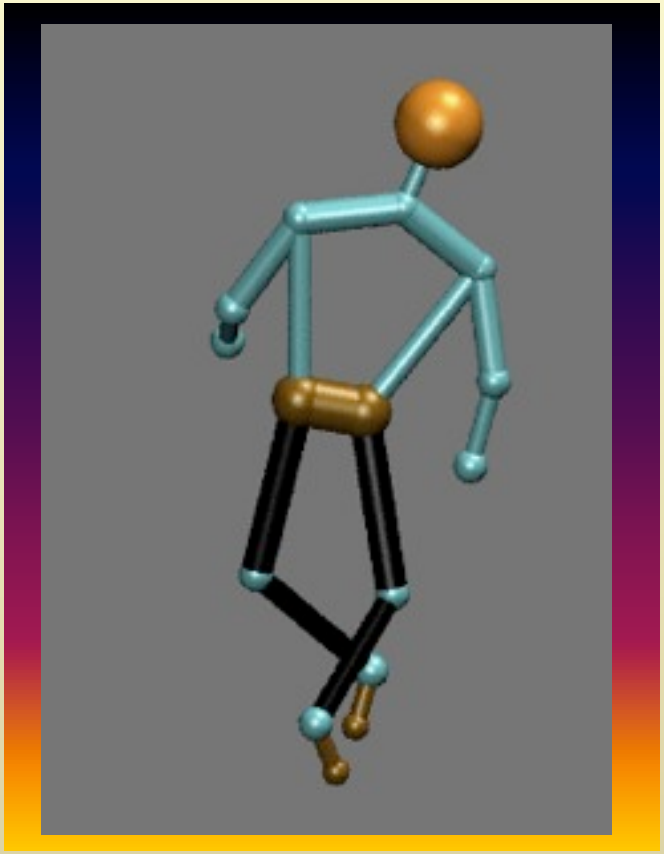
The Art of Coarse Graining



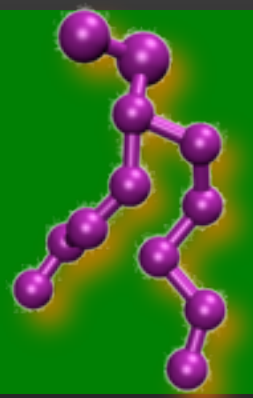
How to become a CG master - part II

Martini forcefield for biomolecular simulations

Martini forcefield for biomolecular simulations

I Lipids

- Basic Martini philosophy
- Parameterization
- Applications



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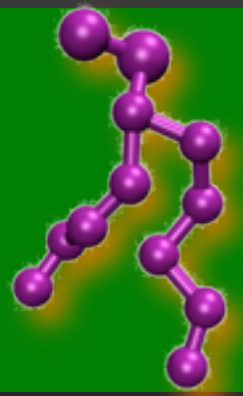
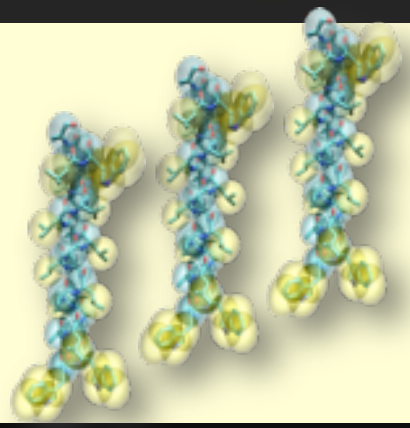


II Proteins & Sugars

- Parameterization
- Elastic networks
- Applications



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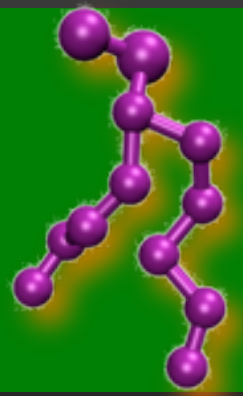

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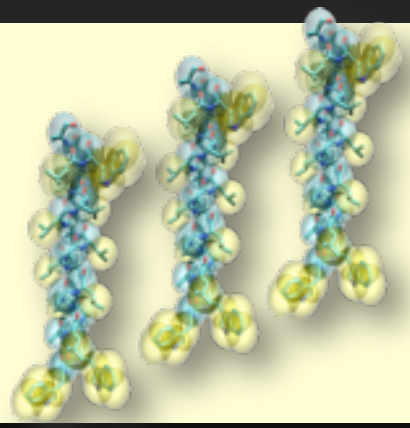


III Future

- Hybrid models
- Polarizable Martini

The Martini forcefield for proteins

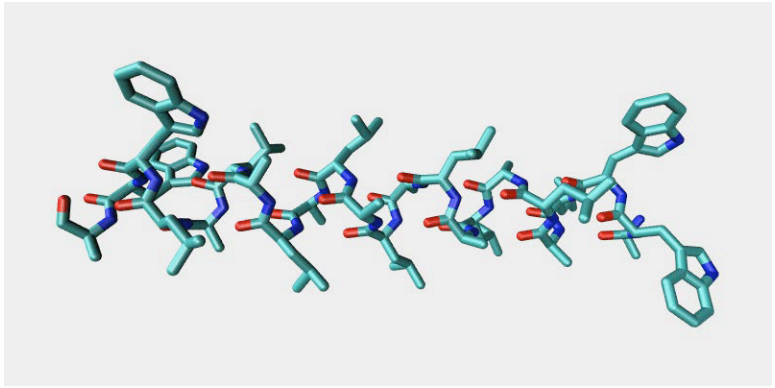
The looks

Biomolecular Forcefield for Coarse-Grained Simulations

New web-pages coming up soon!

The Martini forcefield for proteins

The looks



MARTINI

Biomolecular Forcefield for Coarse-Grained Simulations

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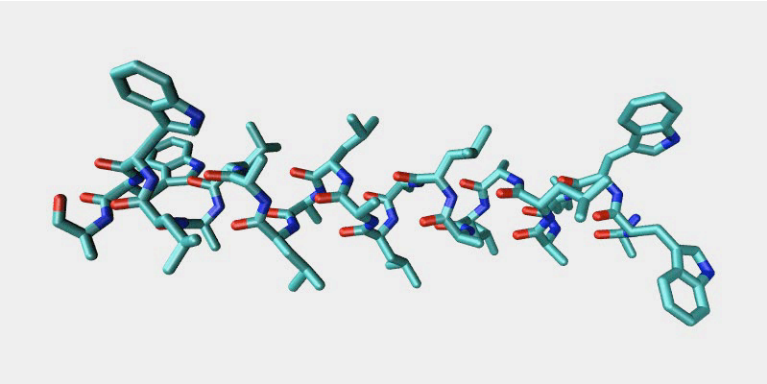
The looks

Luca Monticelli



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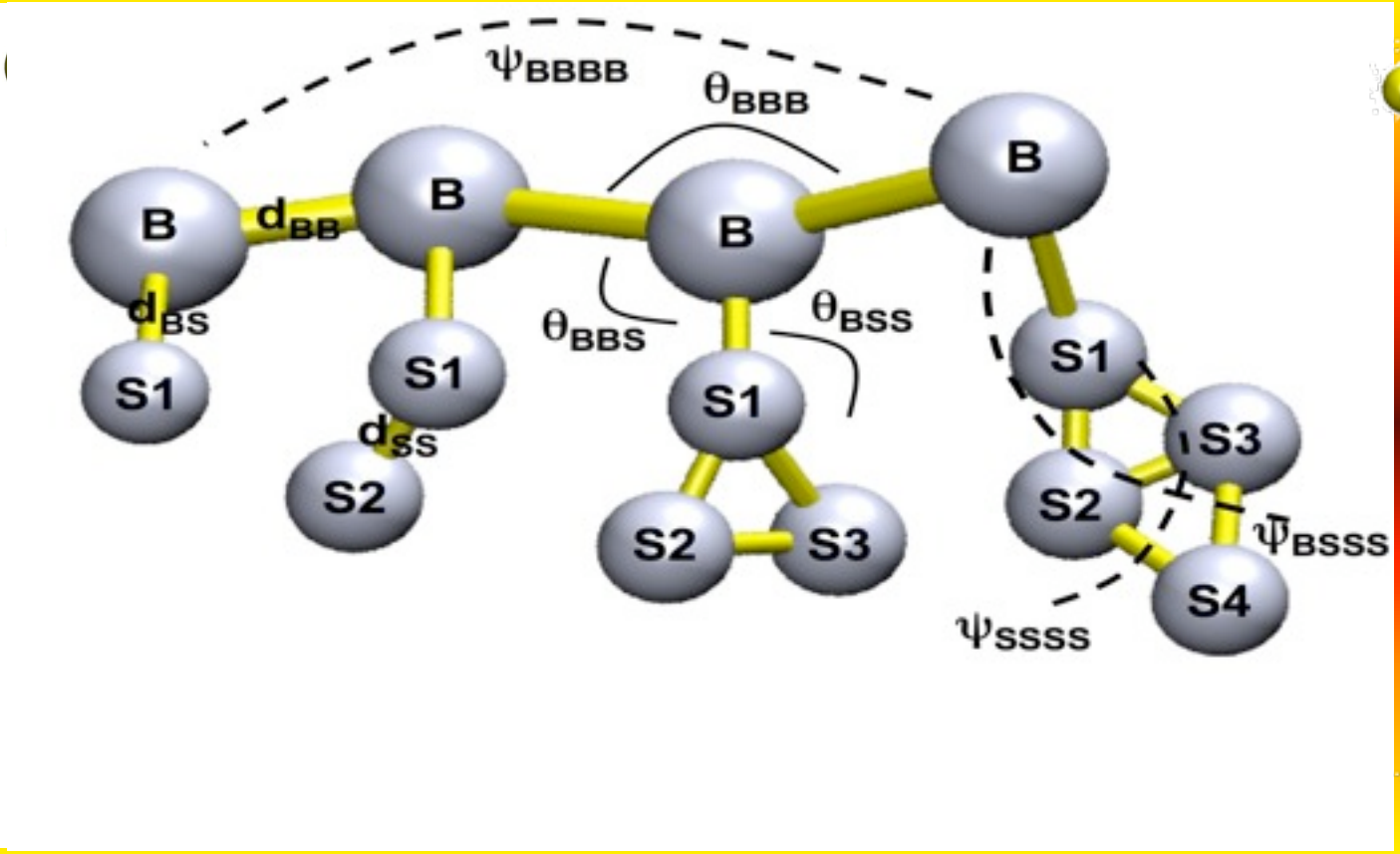
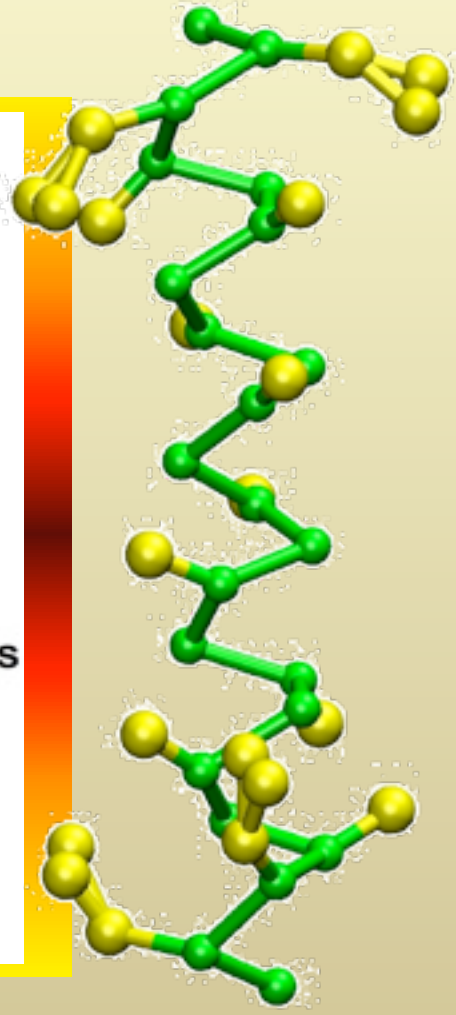
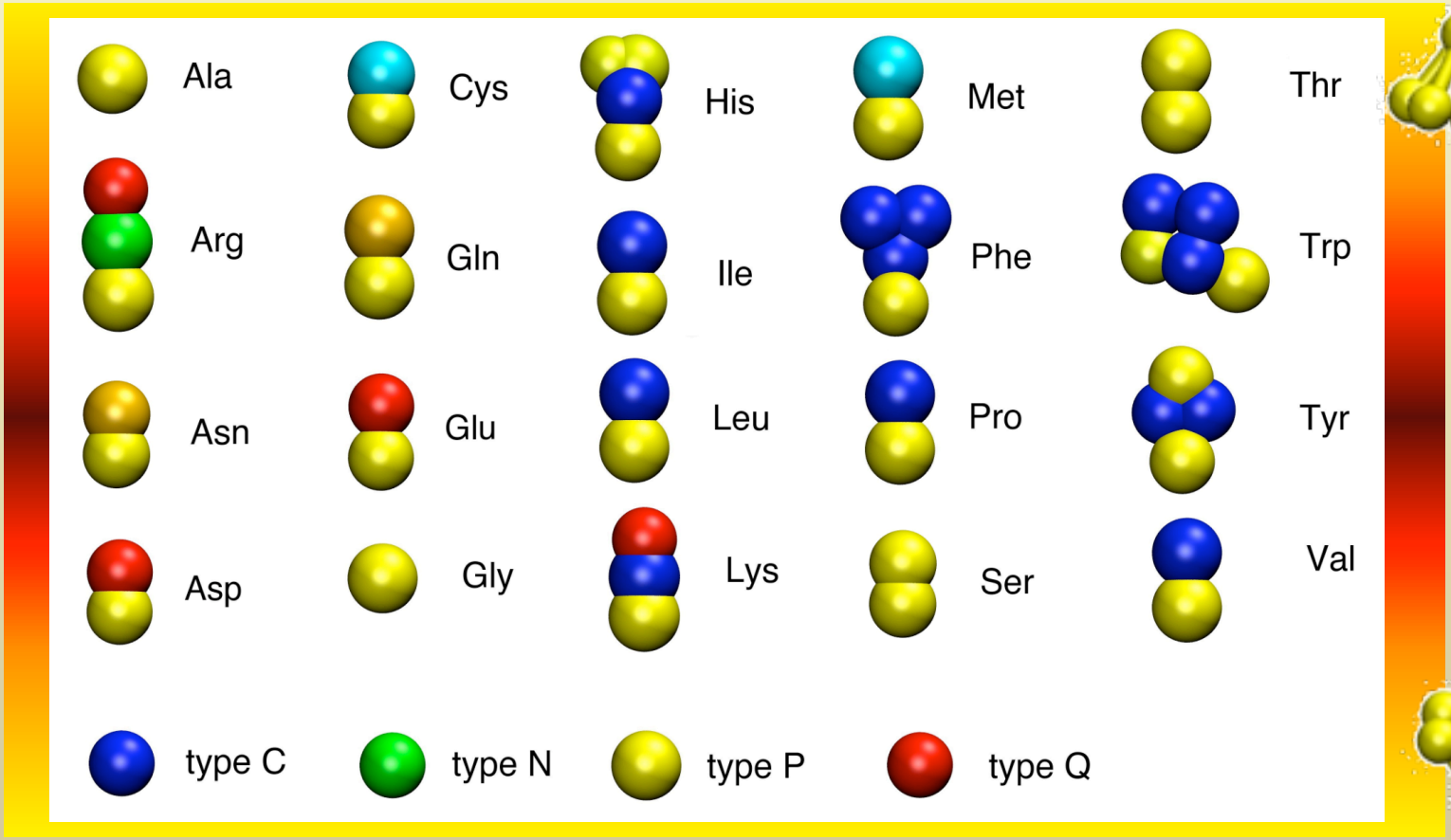
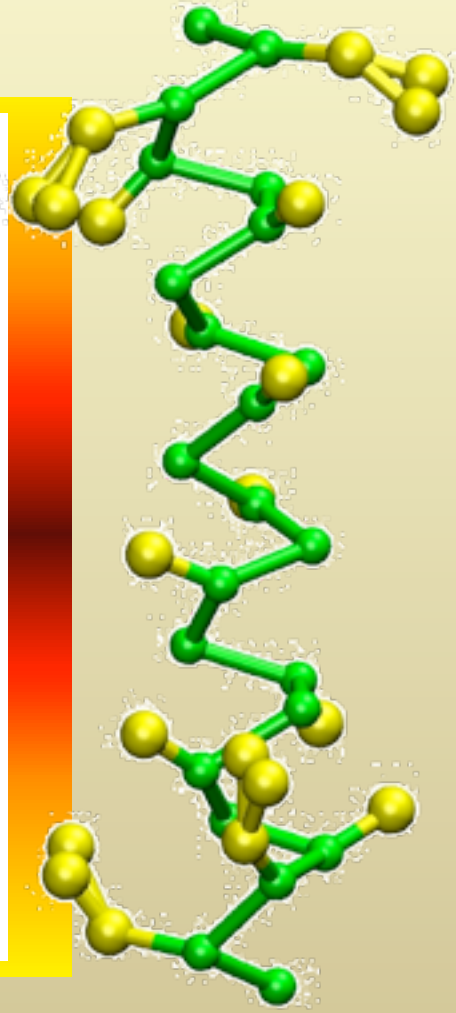




The Martini forcefield for proteins

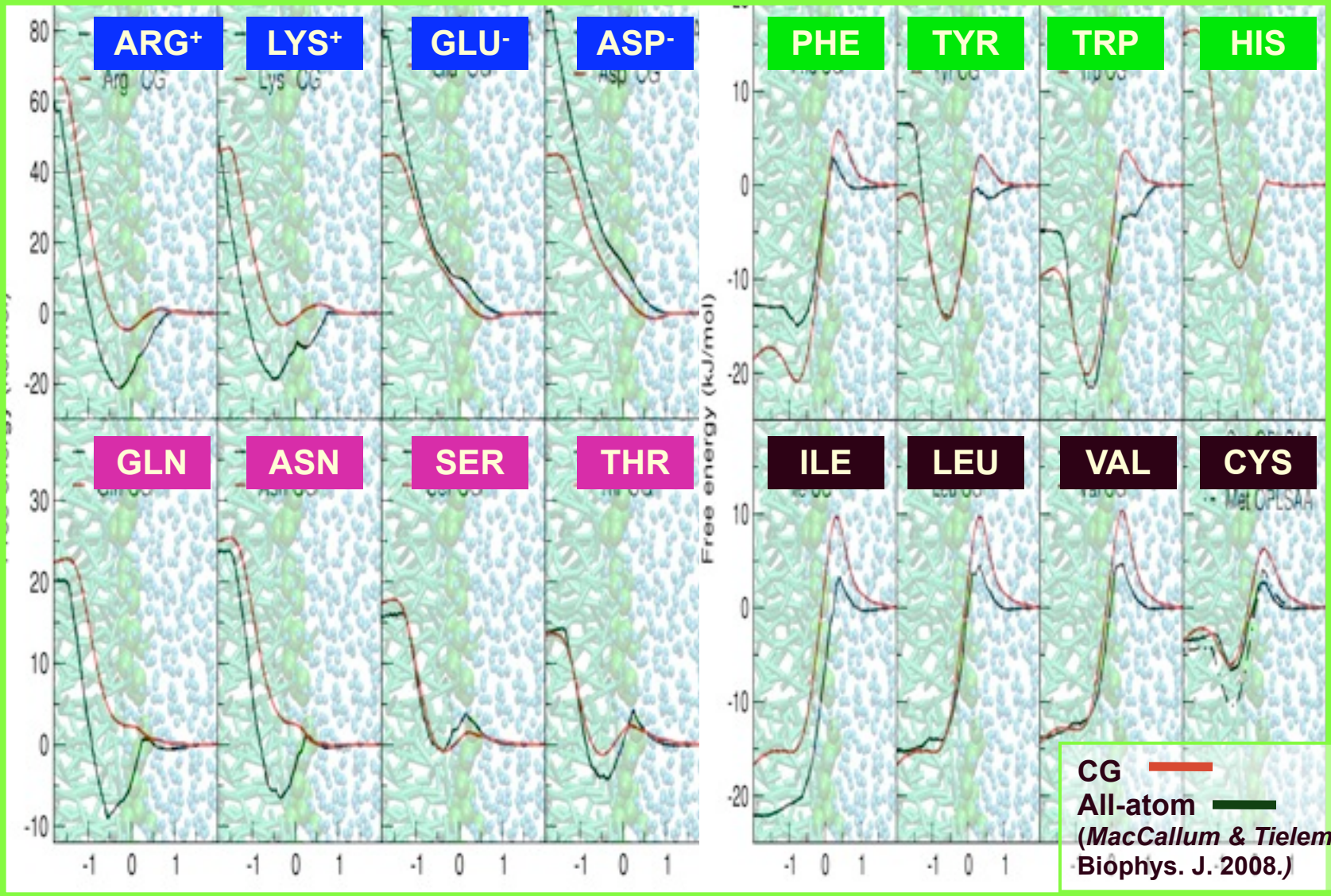
The looks





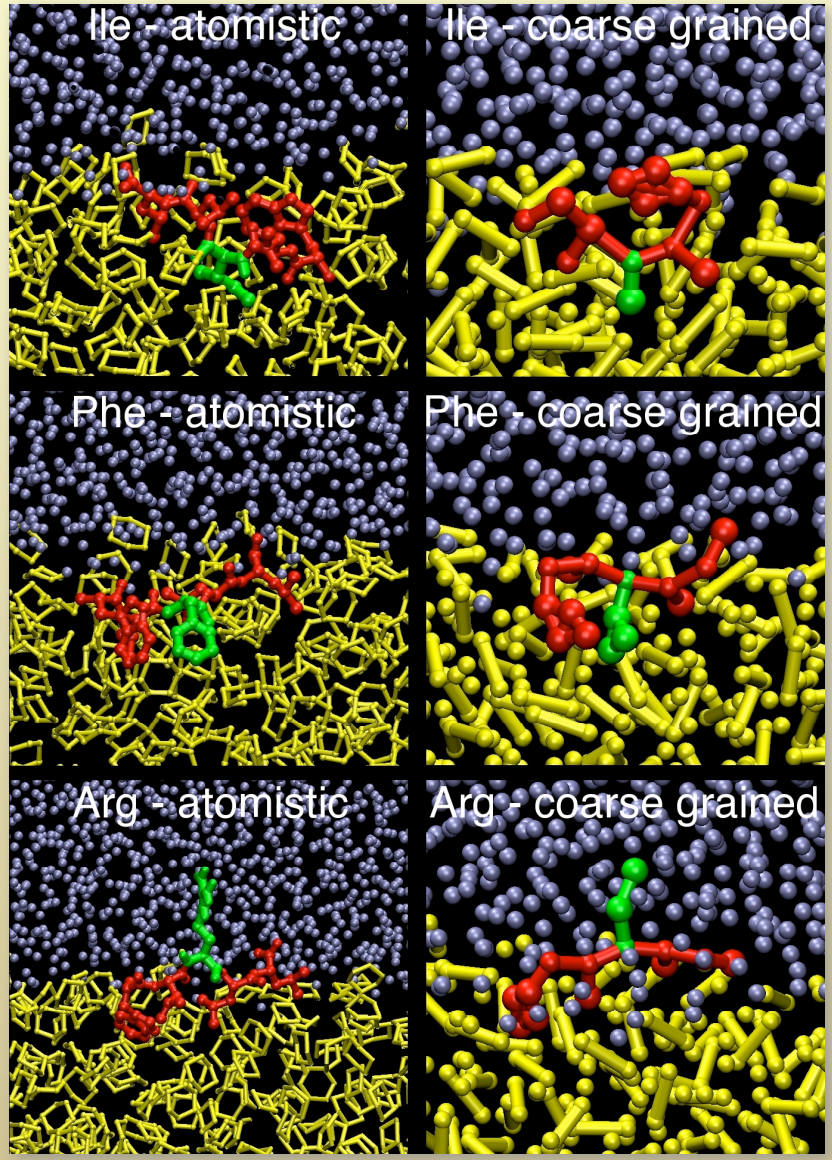
The Martini forcefield for proteins

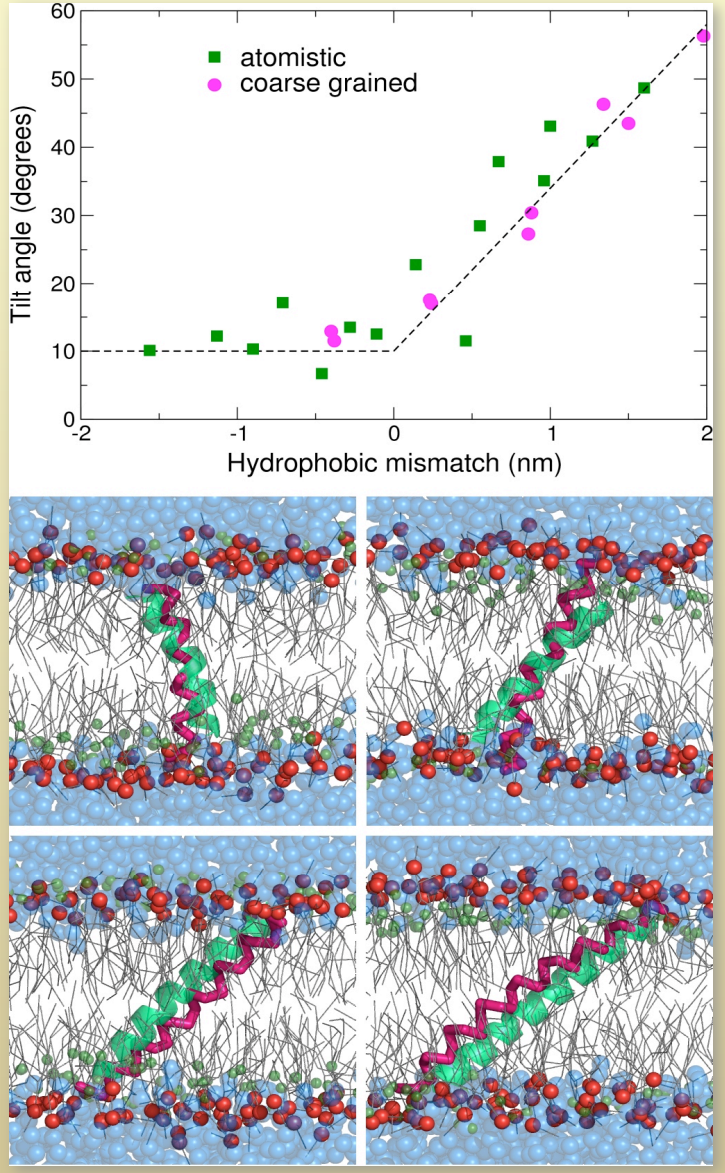
Validation: partitioning of amino acid residues in lipid bilayers



The Martini forcefield for proteins

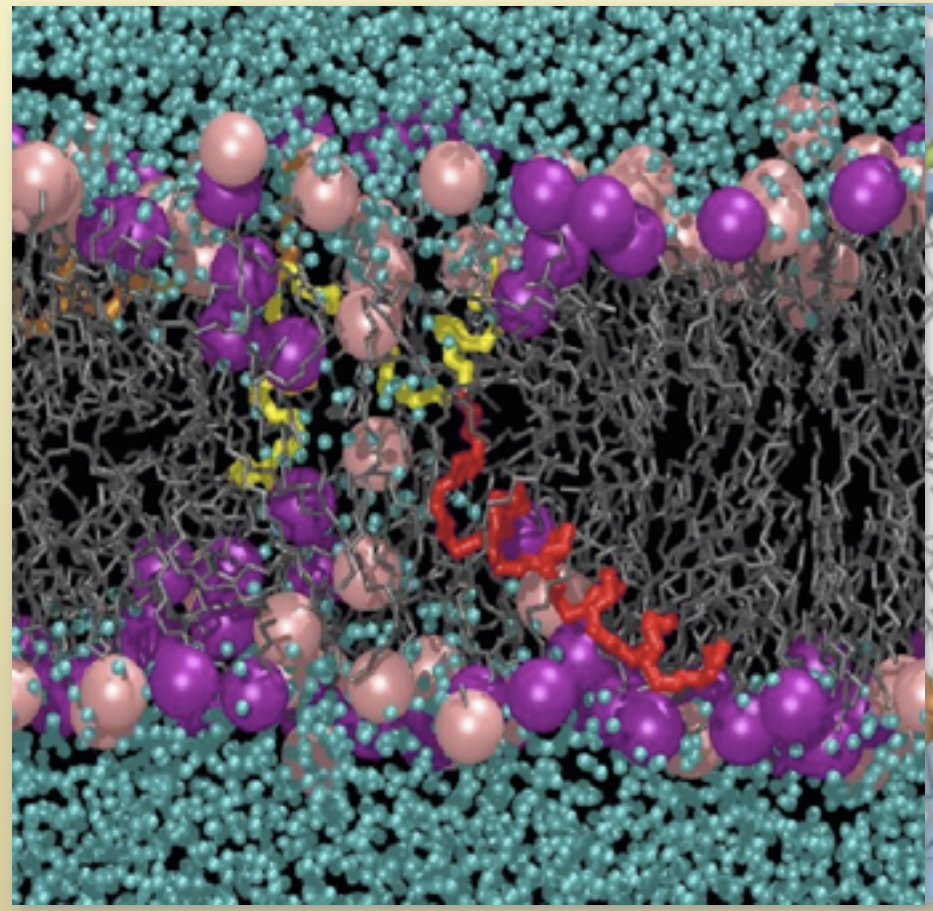
Validation: binding and tilting of peptides

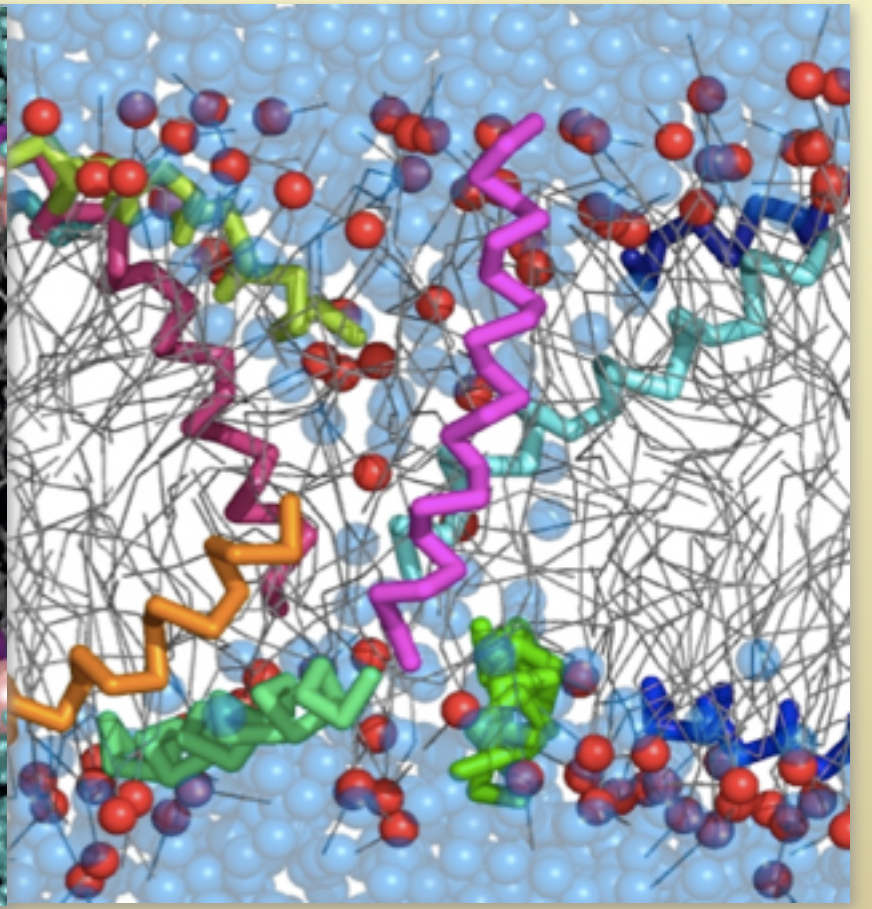




The Martini forcefield for proteins

Validation: pores stabilized by antimicrobial peptides

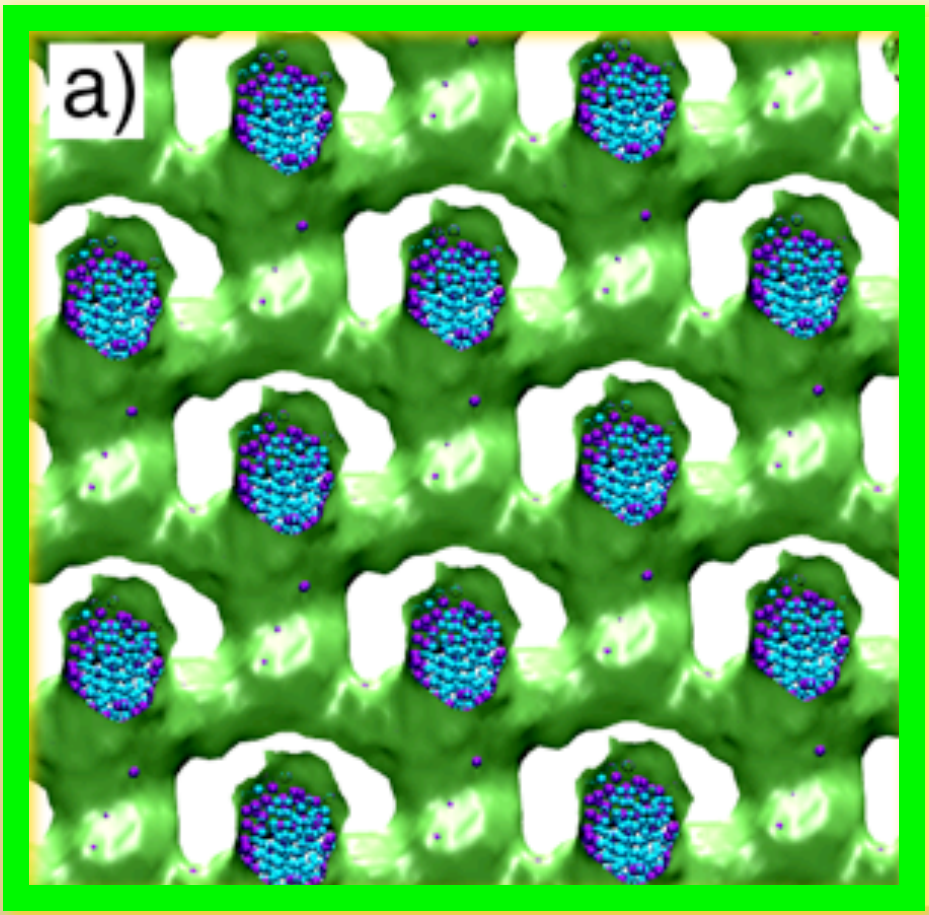


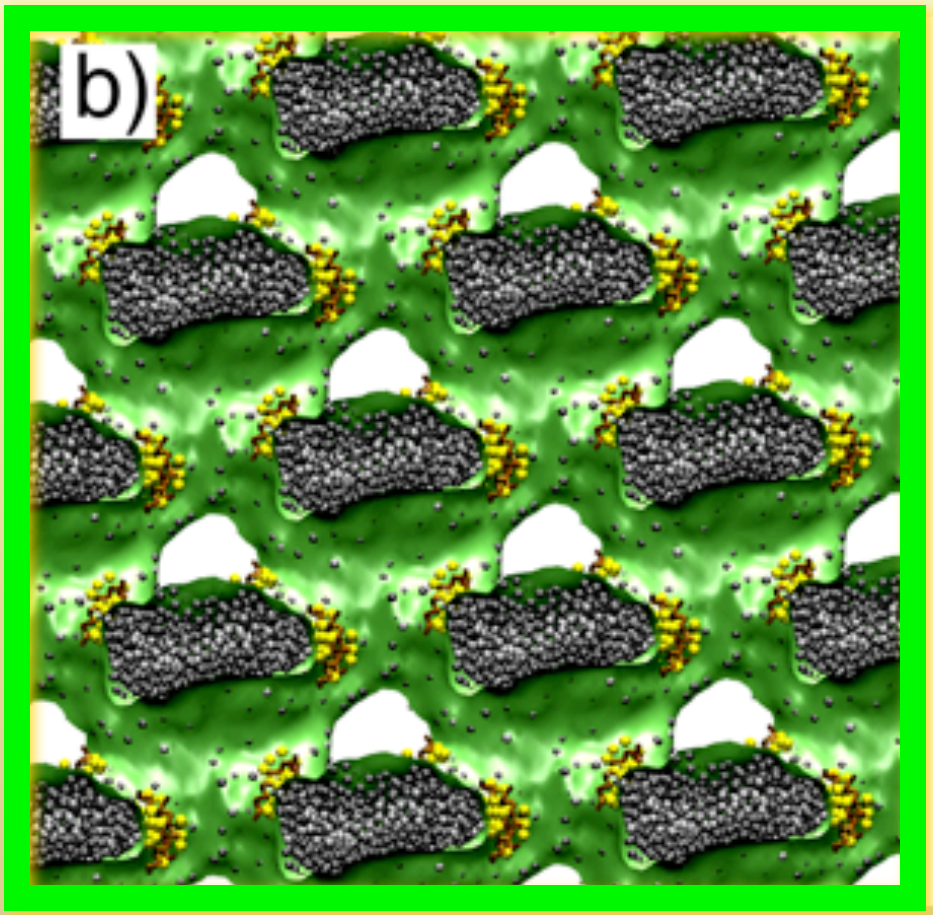


All-atom Martini CG

The Martini forcefield for proteins

Validation: phase behavior of lipid/peptide systems





Cubic phase induced by fusion peptides

The Martini forcefield for proteins

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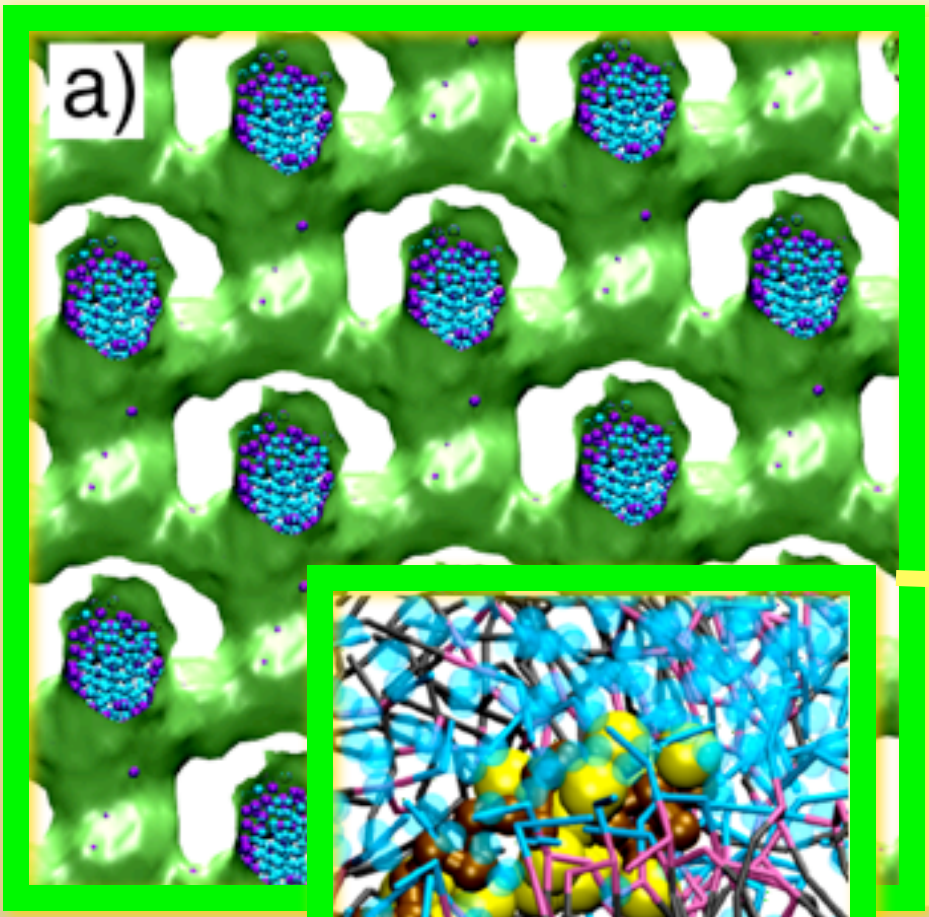

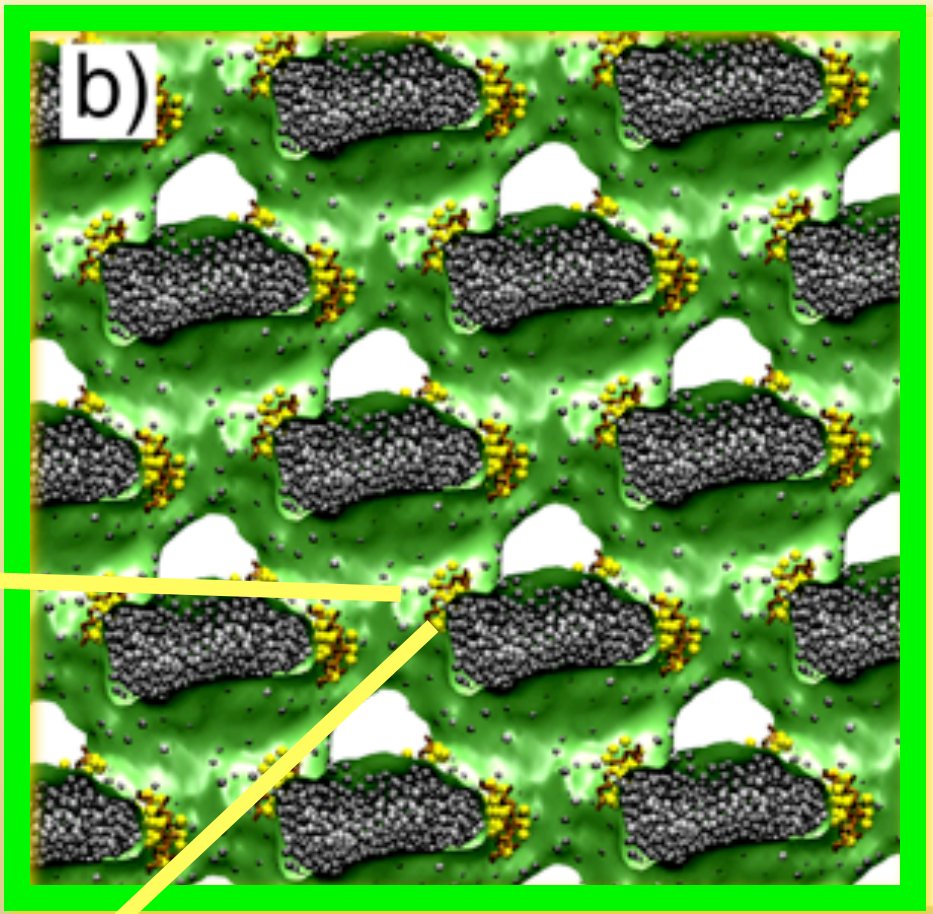

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What you can do and what you should be careful of

DO's **(but be careful)**

DO-NOTs **(or be very careful)**

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(e.g. complex formation, crowding behavior, ligand binding)

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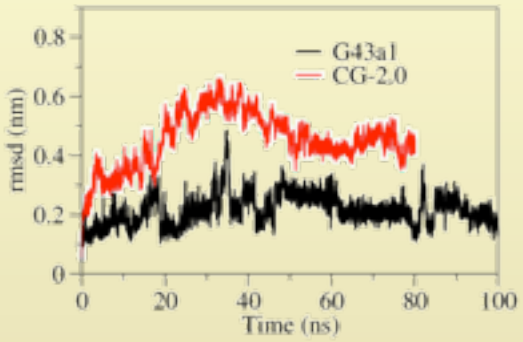
Model → **Elastic Network**

(ElNeDyn)

Three test proteins:

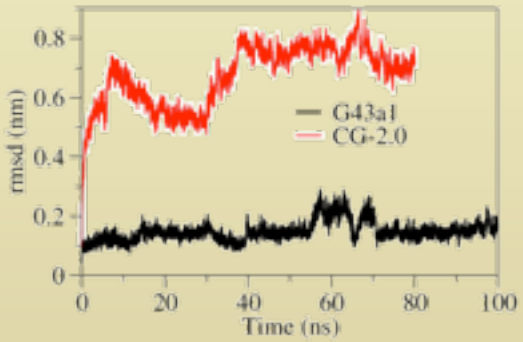
all α

Villin headpiece



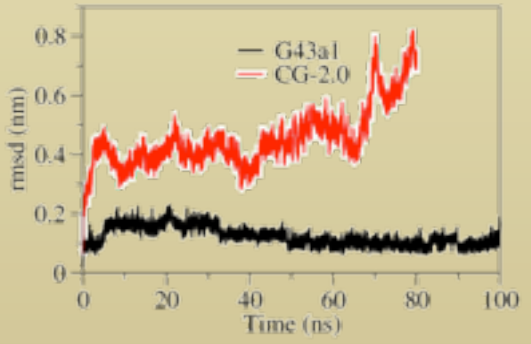
all β

SH3 domain



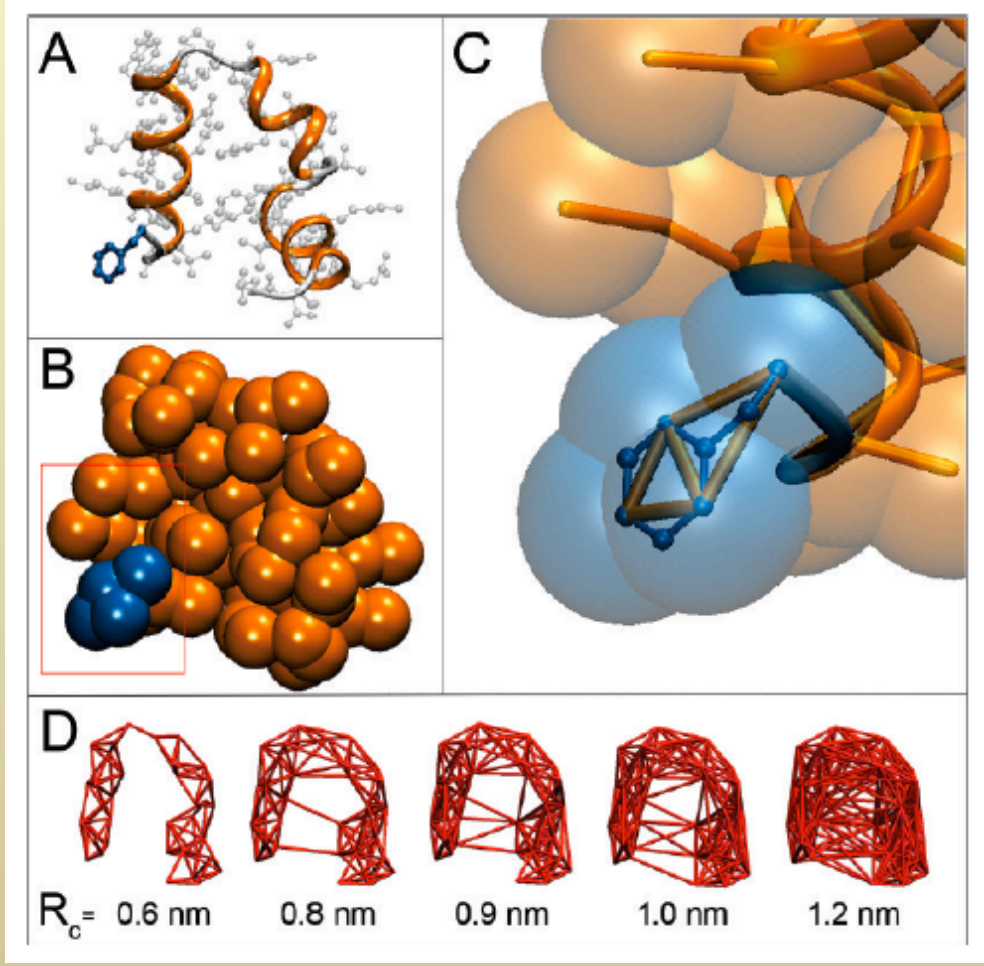
α/β

protein G



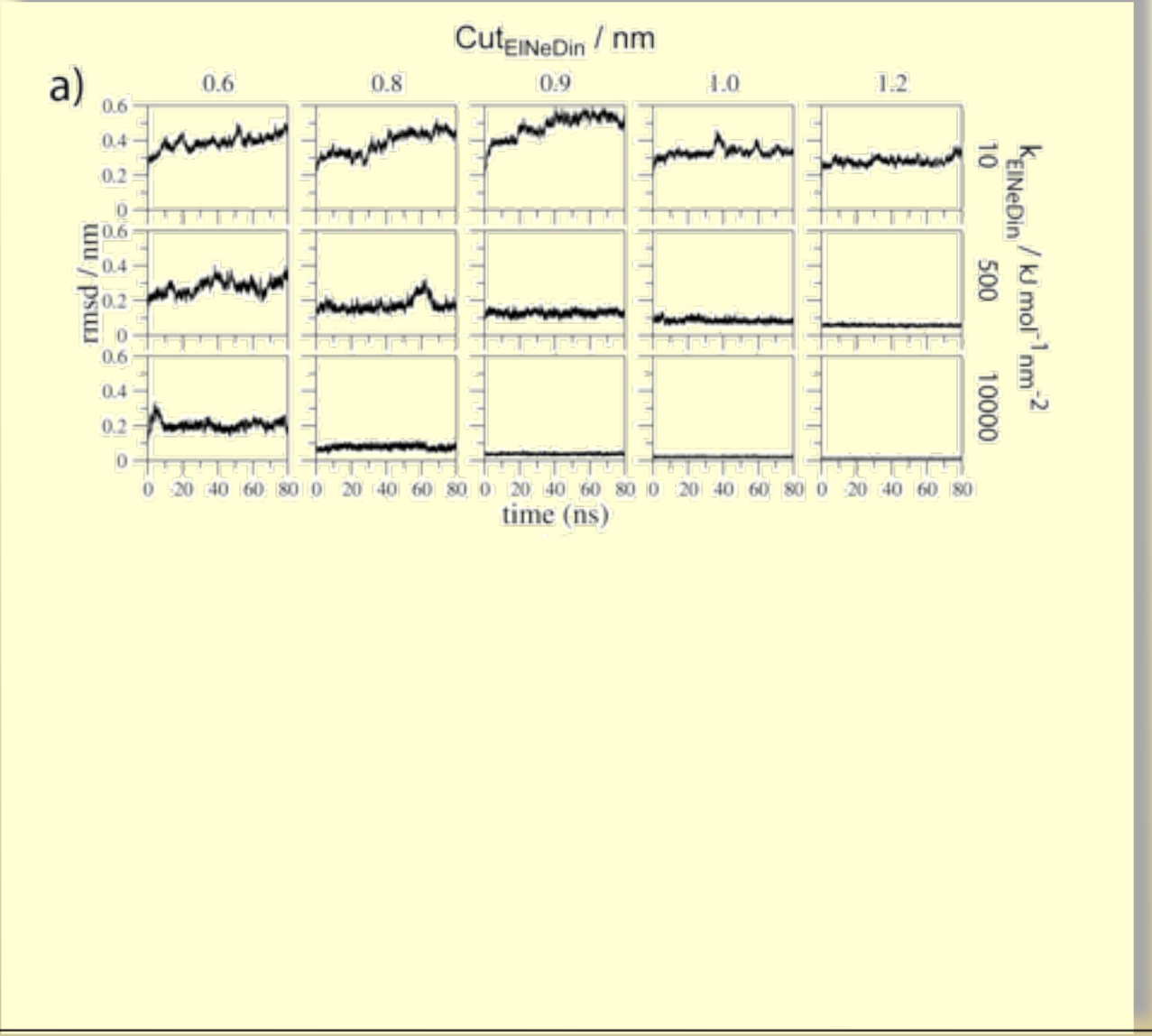
ElNeDyn: Elastic Network in Dynamics

harmonic potentials between all Cα beads within a cut-off



Villin headpiece

Effect of k_{EN} and C_{EN} on the structure and dynamics of the protein



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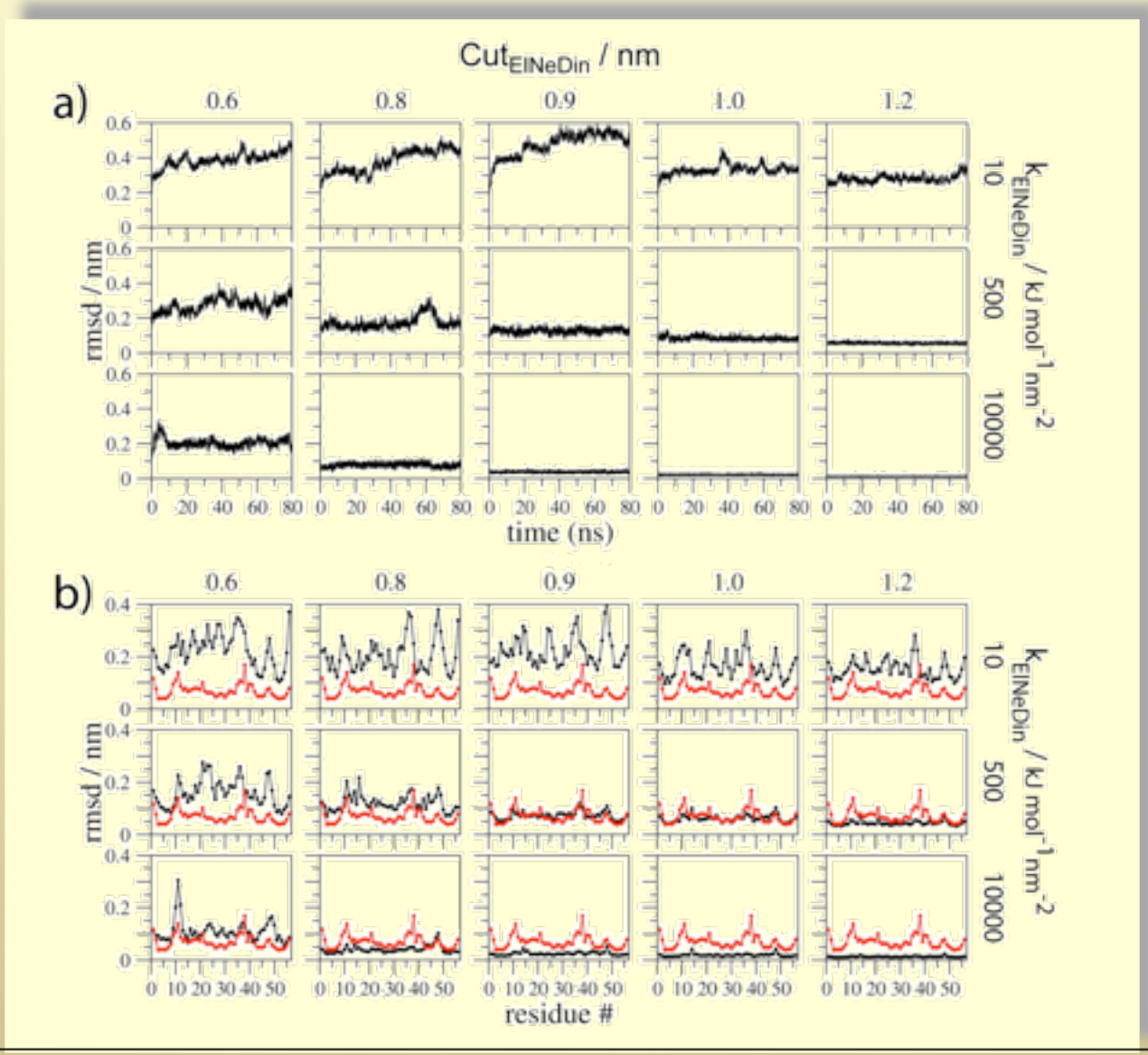
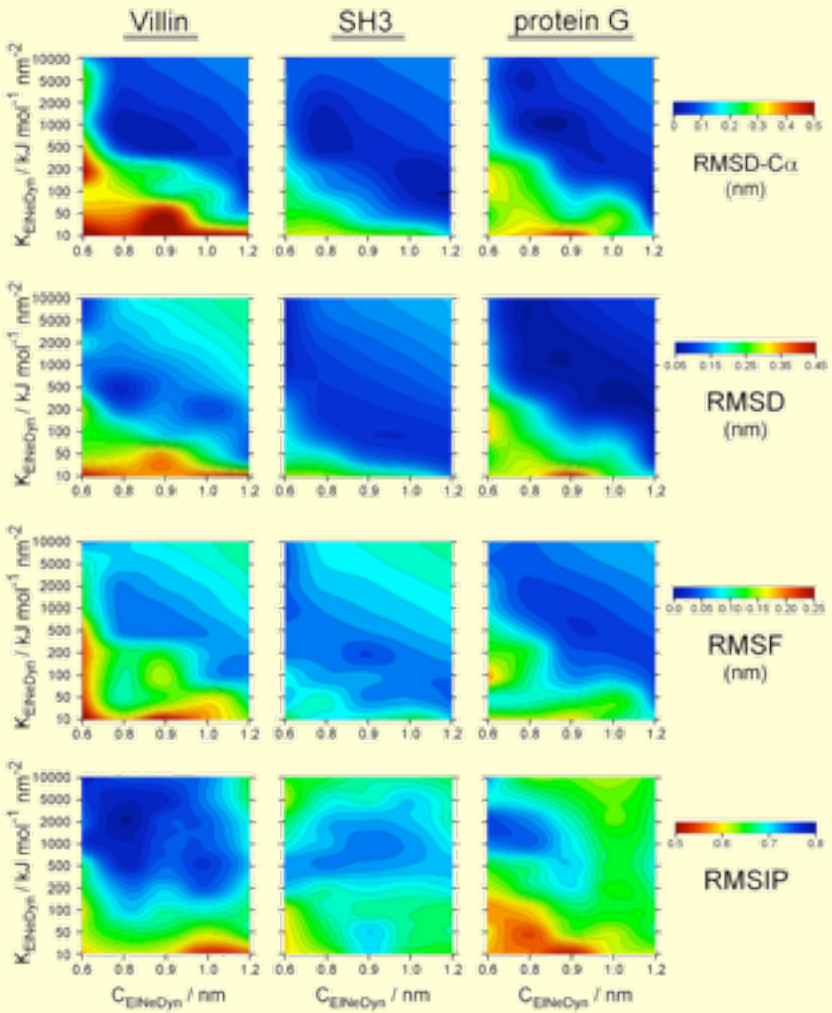


ElNeDyn: C_{EN} and k_{EN} parameterized against *AA* simulations



$$\Delta\mathrm{RMSD} = \left| \langle \mathrm{RMSD} \rangle^{\mathrm{AT}}_{\text{last 60 ns}} - \langle \mathrm{RMSD} \rangle^{\mathrm{ELNEDIN}}_{\text{last 60 ns*}} \right|$$

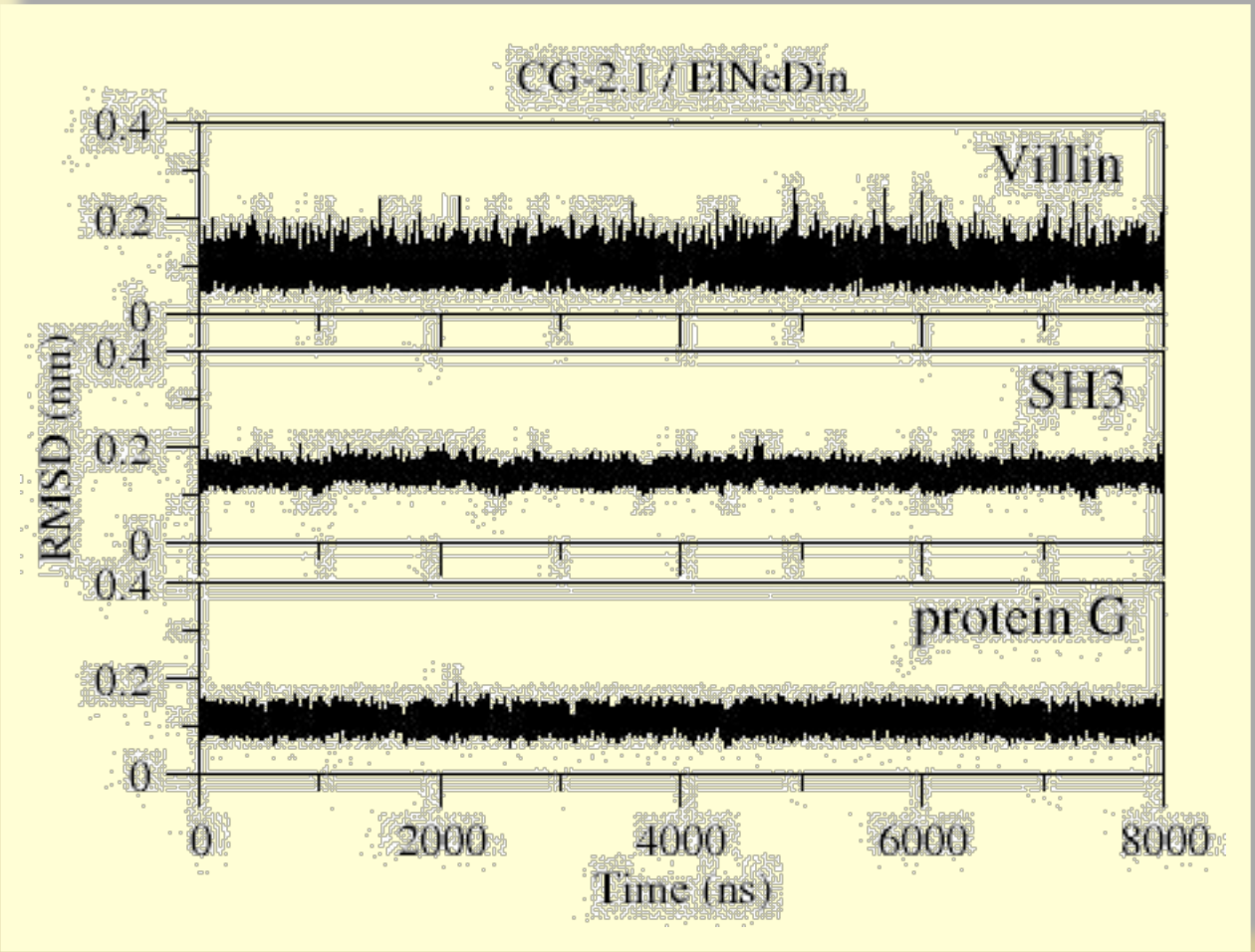
$$\Delta\mathrm{RMSD\_res} = \sqrt{\frac{1}{N}\sum_{i=1}^{N}\left(\mathrm{RMSD\_res}_i^{\mathrm{AT}} - \mathrm{RMSD\_res}_i^{\mathrm{ELNEDIN}}\right)^2}$$

$$\Delta\mathrm{RMSF\_res} = \sqrt{\frac{1}{N}\sum_{i=1}^{N}\left(\mathrm{RMSF\_res}_i^{\mathrm{AT}} - \mathrm{RMSF\_res}_i^{\mathrm{ELNEDIN}}\right)^2}$$

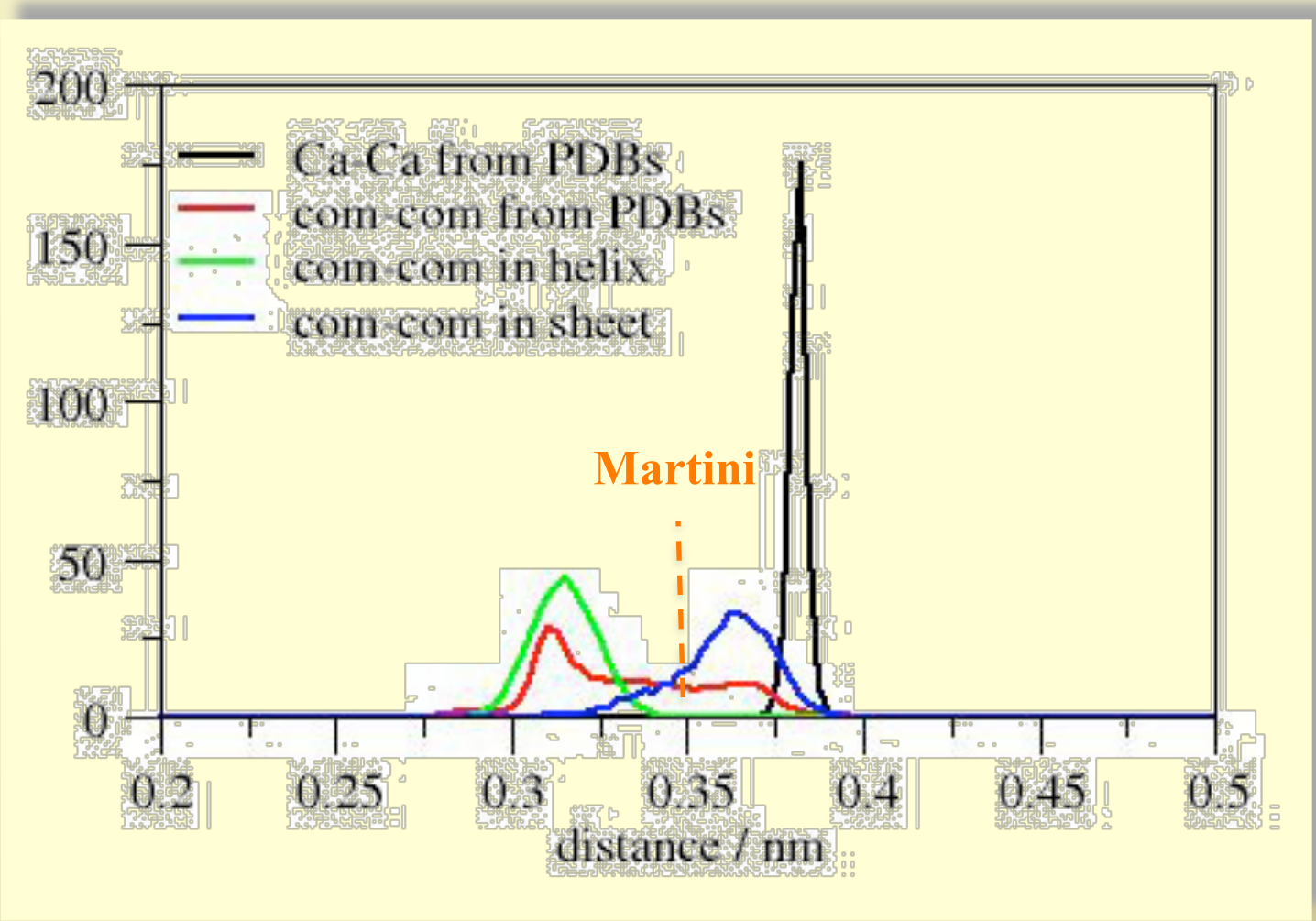
$$\mathrm{RMSIP} = \sqrt{\frac{1}{10}\sum_{i=1}^{10}\sum_{j=1}^{10}\left(\eta_i^{\mathrm{AT}} \cdot \eta_j^{\mathrm{ELNEDIN}}\right)^2}$$

ElNeDyn: useful tool when single (native) state matters

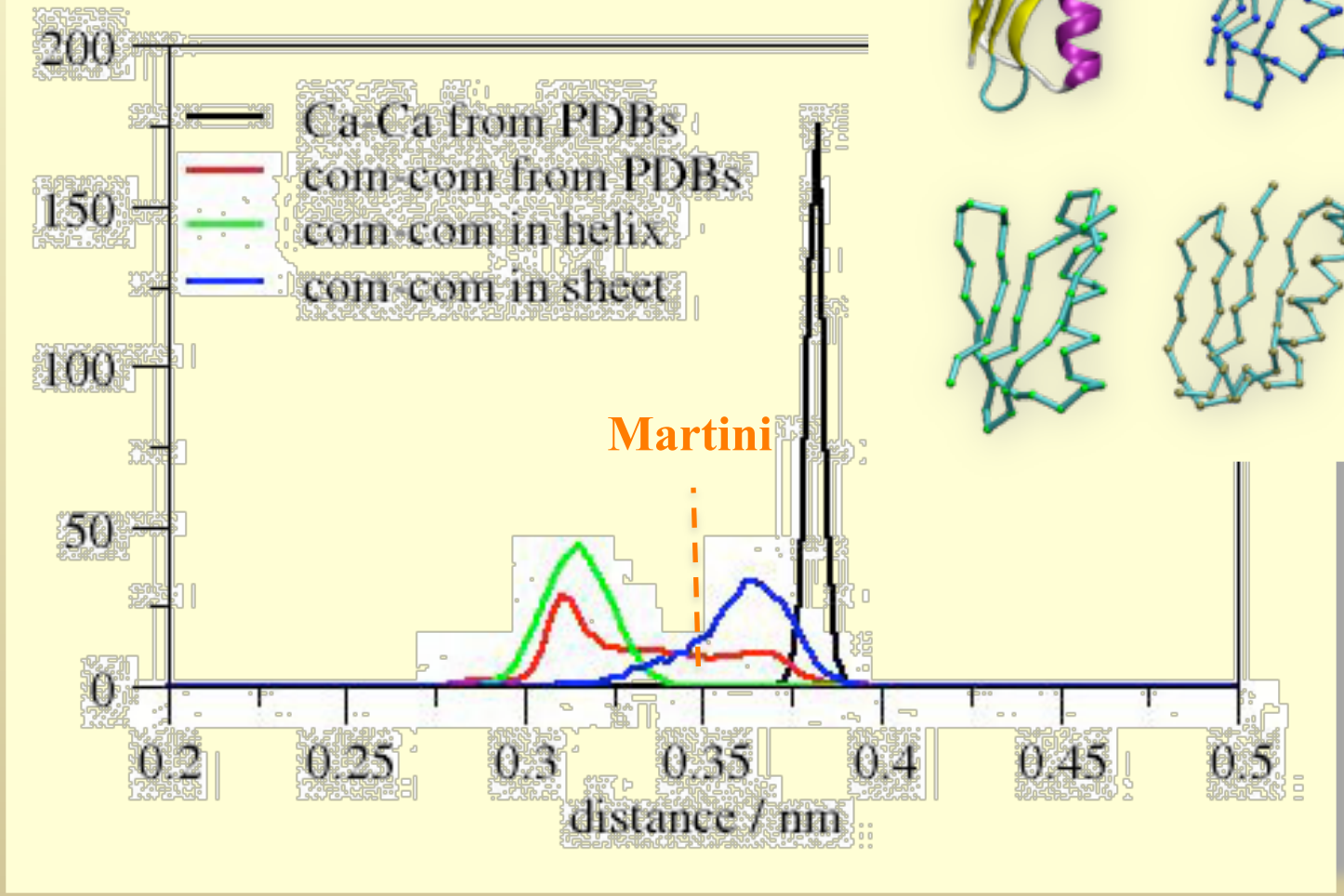
→ **both structure and internal dynamics well represented**

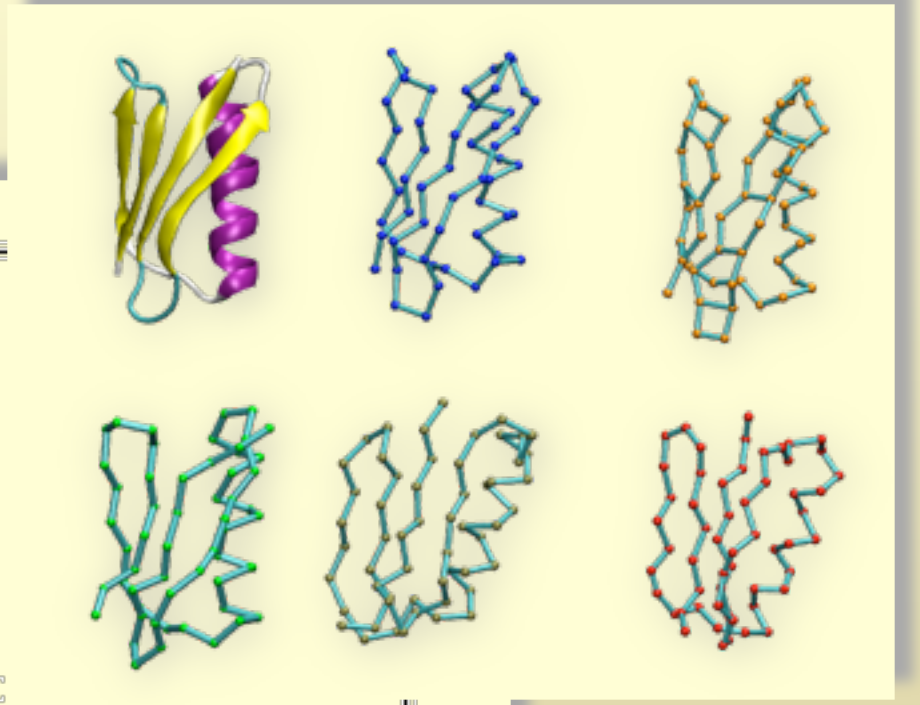


COM vs. Cα


200
150
100
50
0
Ca-Ca from PDBs
com-com from PDBs
com-com in helix
com-com in sheet
Martini
0.2
0.25
0.3
0.35
0.4
0.45
0.5
distance / nm

COM vs. Cα


200
150
100
50
0
Ca-Ca from PDBs
com-com from PDBs
com-com in helix
com-com in sheet
Martini
0.2
0.25
0.3
0.35
0.4
0.45
0.5
distance / nm



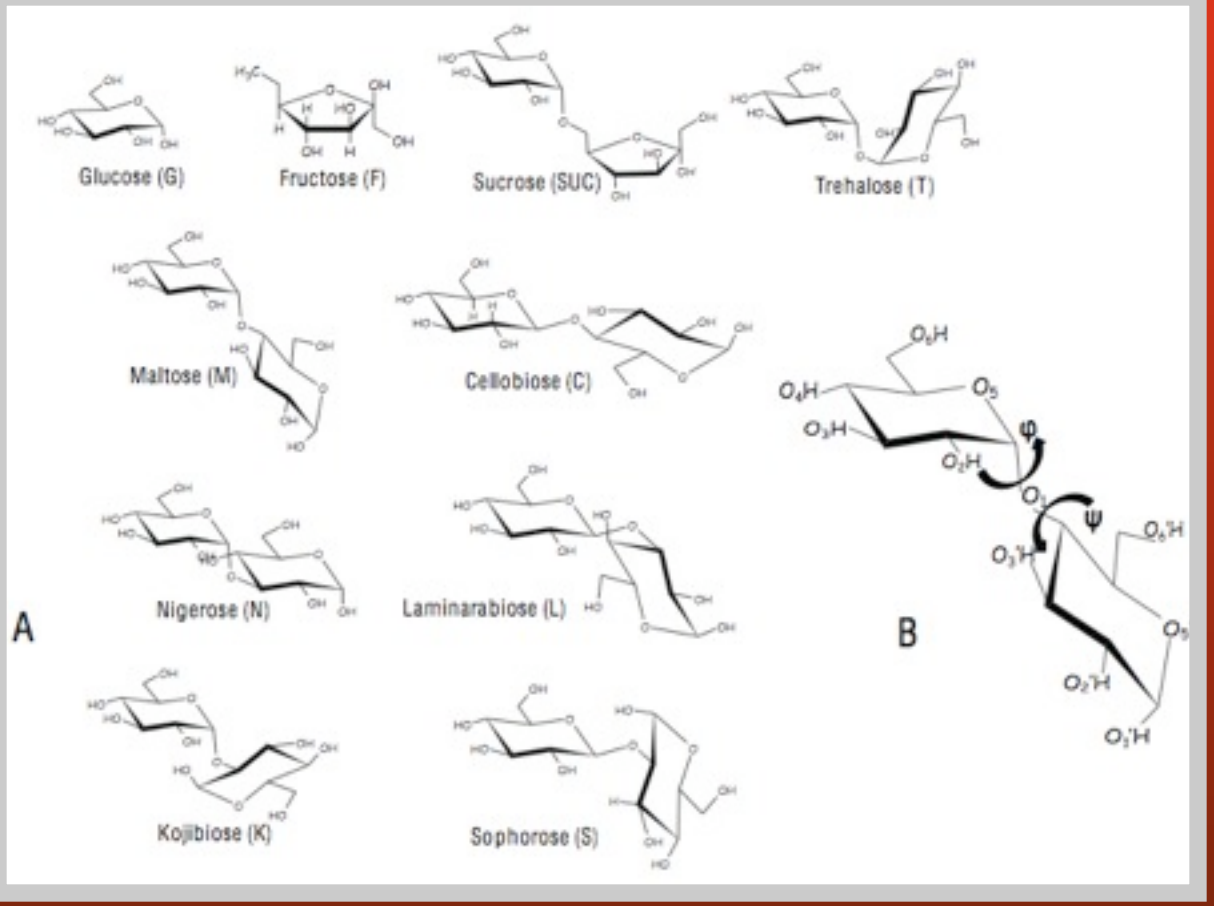
Coarse-graining new molecules:

Sweet MARTINI

extension of Martini force field to carbohydrates

Sweet MARTINI

Choosing the mapping



Sweet MARTINI

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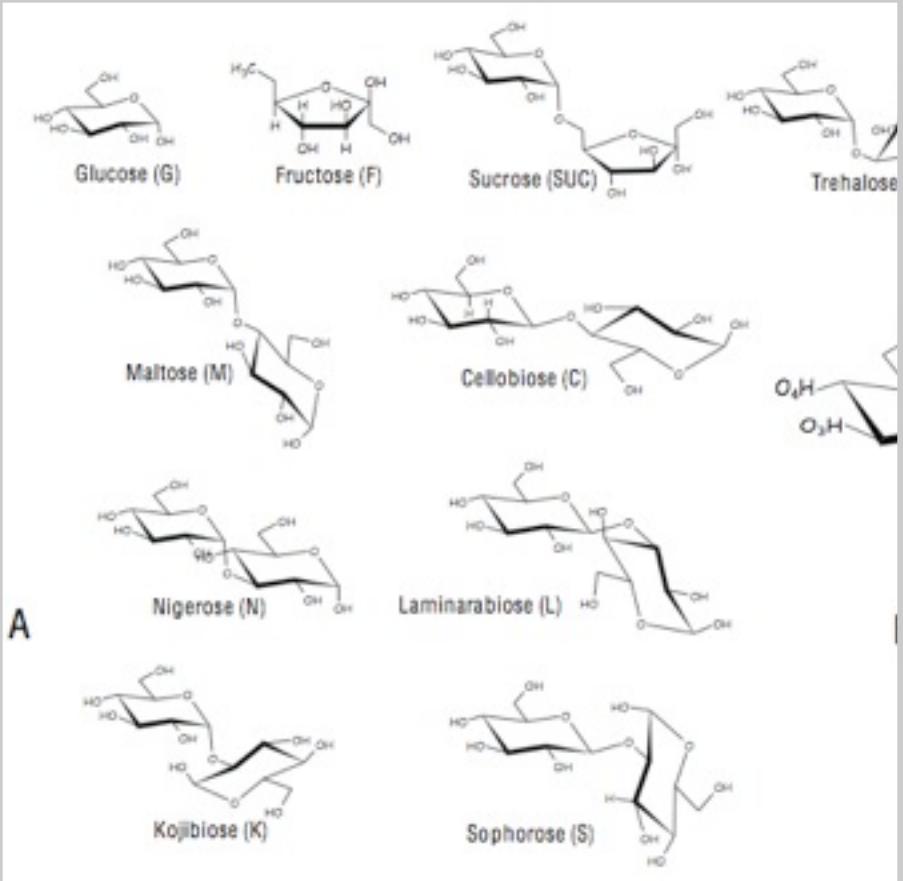
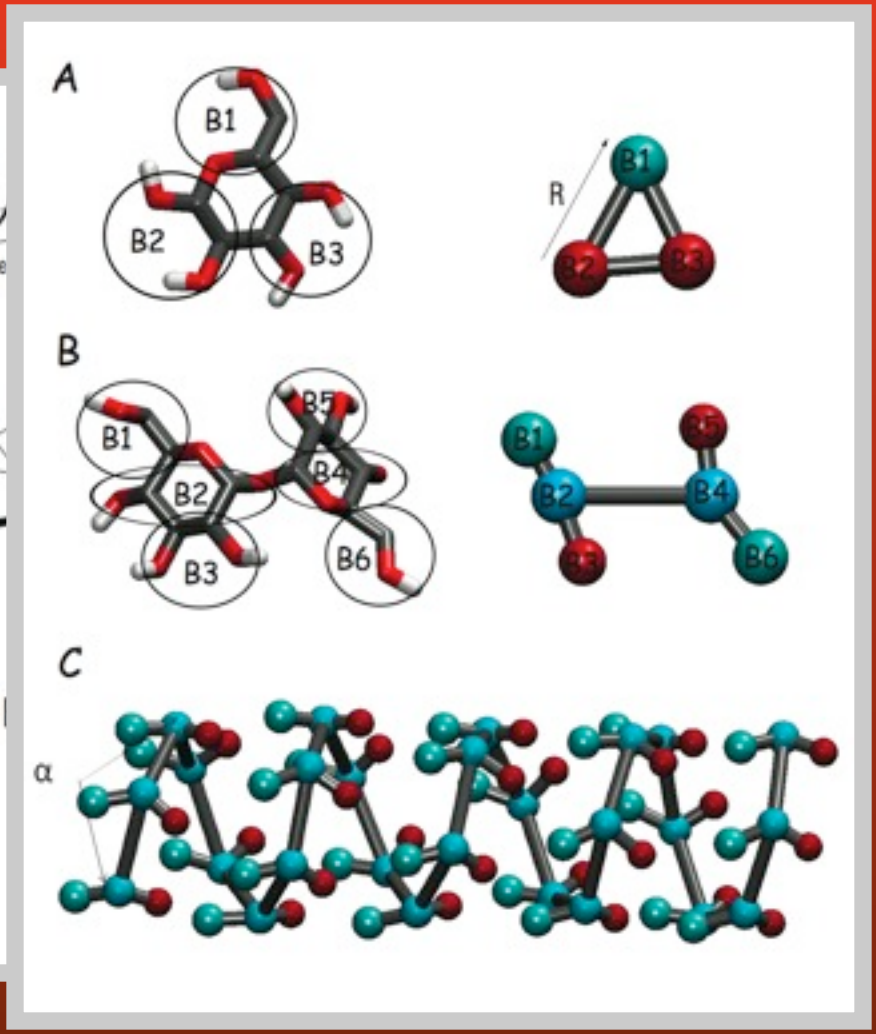
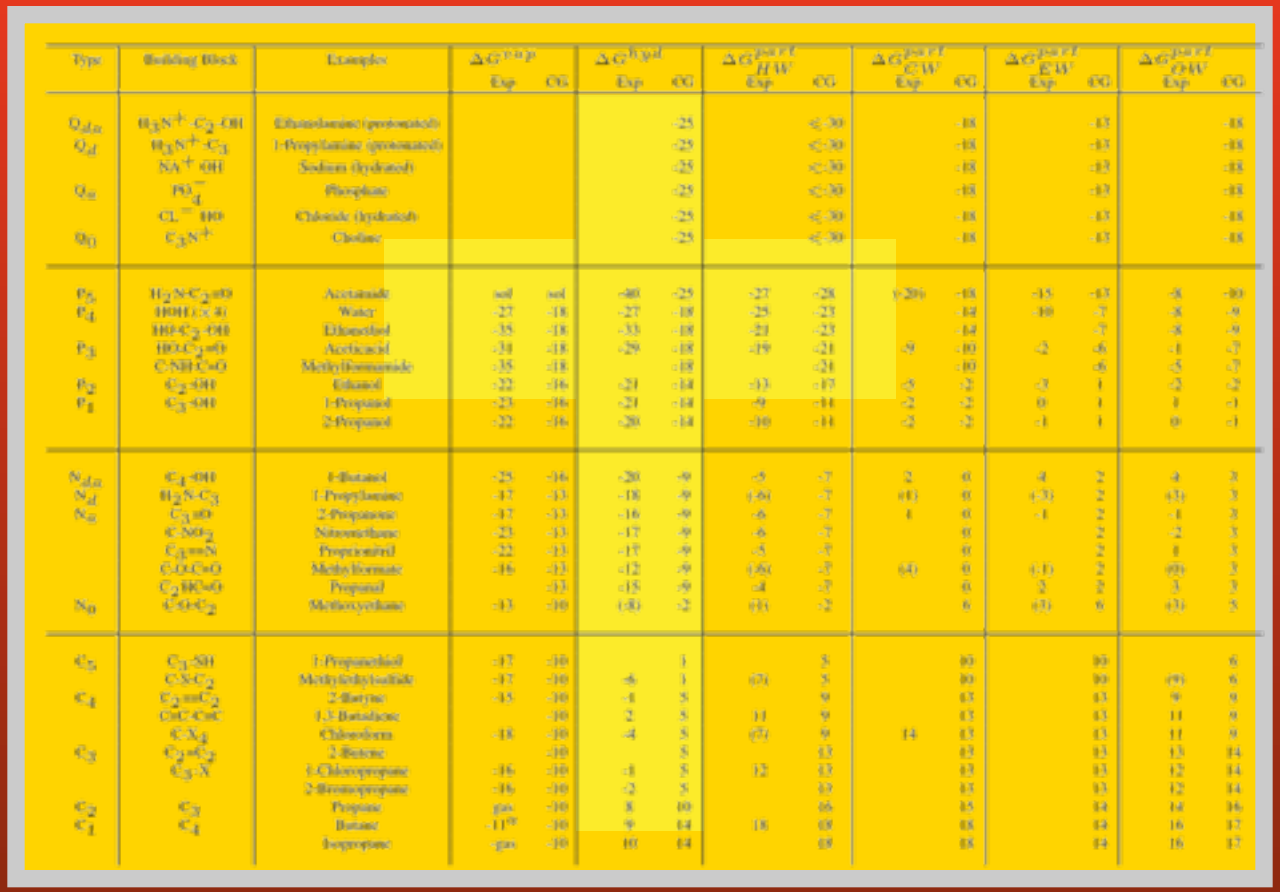




Sweet MARTINI

Parameterization of non-bonded interactions



Type	Building Block	Examples	ΔG^{vap} Exp	ΔG^{vap} CG	ΔG^{hyd} Exp	ΔG^{hyd} CG	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)				-25		≤-30		-18		-13		-18
Q_d	H_3N^+-C_3	1-Propylamine (protonated)				-25		≤-30		-18		-13		-18
	NA^+-OH	Sodium (hydrated)				-25		≤-30		-18		-13		-18
Q_a	PO_4^-	Phosphate				-25		≤-30		-18		-13		-18
	CL^--HO	Chloride (hydrated)				-25		≤-30		-18		-13		-18
Q_0	C_3N^+	Choline				-25		≤-30		-18		-13		-18
P_5	H_2N-C_2=O	Acetamide	sol	sol	-40	-25	-27	-28	(-20)	-18	-15	-13	-8	-10
P_4	HOH (×4)	Water	-27	-18	-27	-18	-25	-23		-14	-10	-7	-8	-9
	HO-C_2-OH	Ethanediol	-35	-18	-33	-18	-21	-23		-14		-7	-8	-9
P_3	HO-C_2=O	Acetic acid	-31	-18	-29	-18	-19	-21	-9	-10	-2	-6	-4	-7
	C-NH-C=O	Methylformamide	-35	-18		-18		-21		-10		-6	-5	-7
P_2	C_2-OH	Ethanol	-22	-16	-21	-14	-13	-17	-5	-2	-3	1	-2	-2
P_1	C_3-OH	1-Propanol	-23	-16	-21	-14	-9	-14	-2	-2	0	1	1	-1
		2-Propanol	-22	-16	-20	-14	-10	-11	-2	-2	-1	1	0	-1
N_{da}	C_4-OH	1-Butanol	-25	-16	-20	-9	-5	-7	2	0	4	2	4	3
N_d	H_2N-C_3	1-Propylamine	-17	-13	-18	-9	(-6)	-7	(0)	0	(+3)	2	(+3)	3
N_a	C_3=O	2-Propanone	-17	-13	-16	-9	-6	-7	1	0	-1	2	-1	3
	C-NO_2	Nitromethane	-23	-13	-17	-9	-6	-7		0		2	-2	3
	C_3≡N	Propiconitril	-22	-13	-17	-9	-5	-7		0		2	1	3
	C-O-C=O	Methylformate	-16	-13	-12	-9	(-6)	-7	(-1)	0	(+1)	2	(0)	3
	C_2-HC=O	Propanal		-13	-15	-9	-4	-7		0	2	2	3	3
N_0	C-O-C_2	Methoxyethane	-13	-10	(-8)	-2	(+1)	-2		0	(+3)	0	(+1)	3
C_5	C_3-SH	1-Propanethiol	-17	-10		1		5		10		10		6
	C-S-C_2	Methylethylsulfide	-17	-10	-6	1	(-1)	5		10		10	(+1)	6
C_4	C_2=C_2	2-Butyne	-15	-10	-1	5		9		13		13	9	9
	C#C-C#C	1,3-Butadiyne		-10	2	5	11	9		13		13	11	9
	C-X_4	Chloroform	-18	-10	-4	5	(-1)	9	14	13		13	11	9
C_3	C_2=C_2	2-Butene		-10		5		13		13		13	13	14
	C_3-X	1-Chloropropane	-16	-10	-1	5	12	13		13		13	12	14
		2-Bromopropane	-16	-10	-2	5		13		13		13	12	14
C_2	C_3	Propane	gas	-10	8	10		16		15		14	14	16
C_1	C_4	Butane	-11*	-10	9	14	18	18		18		14	16	17
		Isopropane	gas	-10	10	14		18		18		14	16	17

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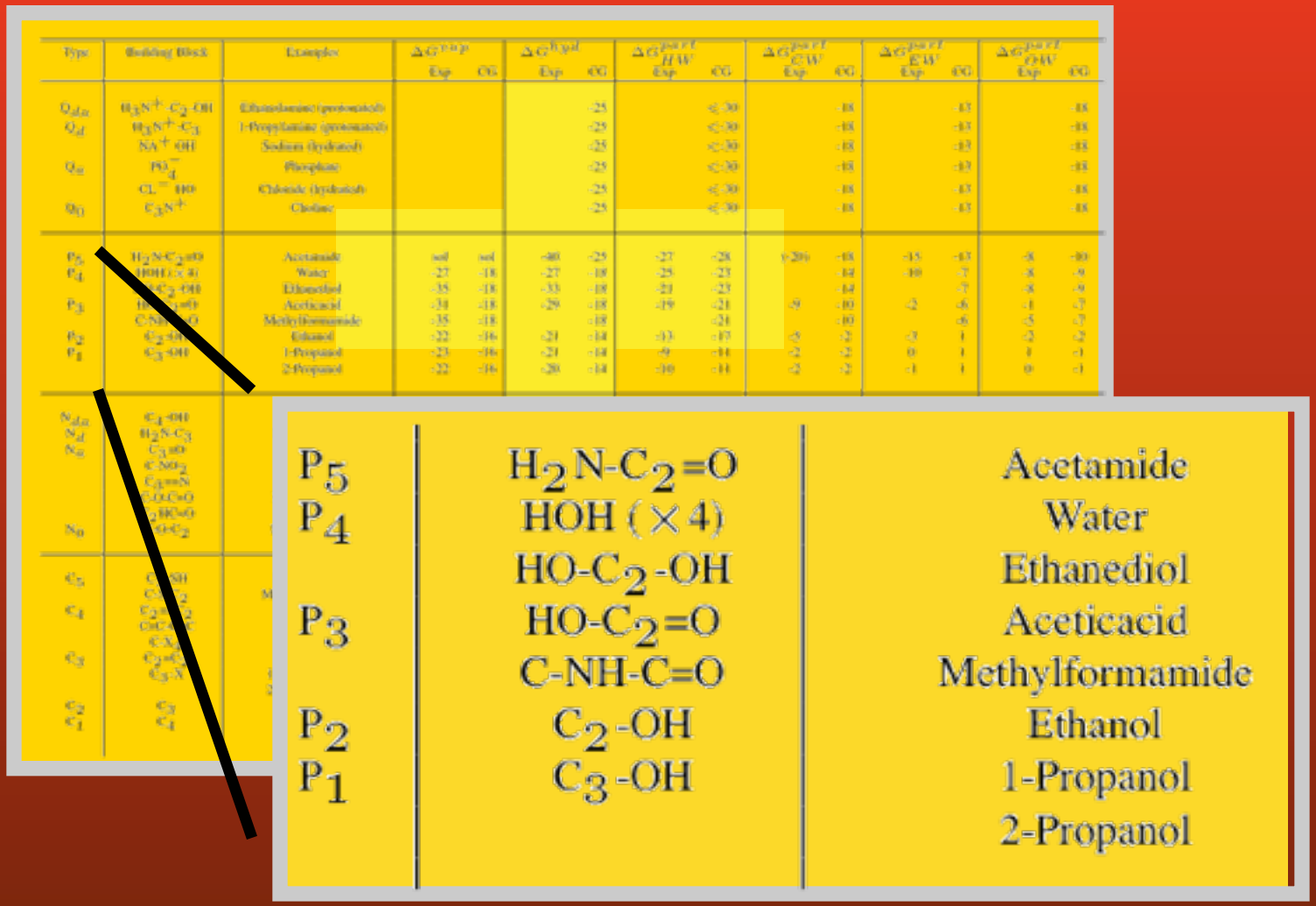
Parameterization of non-bonded interactions



P_5	$H_2N\text{-}C_2=O$	Acetamide
P_4	$HOH\ (\times 4)$	Water
	$HO\text{-}C_2\text{-}OH$	Ethanediol
P_3	$HO\text{-}C_2=O$	Aceticacid
	$C\text{-}NH\text{-}C=O$	Methylformamide
P_2	$C_2\text{-}OH$	Ethanol
P_1	$C_3\text{-}OH$	1-Propanol
		2-Propanol

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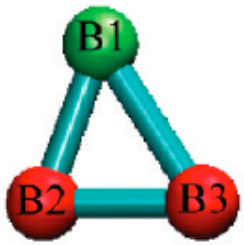
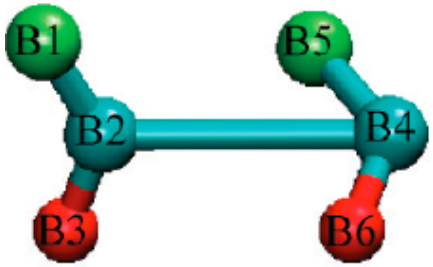
Final particle types





molecule	B1	B2	B3	B4	B5	B6
glucose (G)	P1	P4	P4			
fructose (F)	P1	P3	P4			
sucrose (SUC)	P1	P2	P4	P1	P1	P4
maltose (M)	P1	P2	P4	P2	P1	P4
cellobiose (C)	P1	P2	P4	P2	P1	P4
kojibiose (K)	P1	P2	P4	P2	P4	P1
sophorose (S)	P1	P2	P4	P2	P4	P1
nigerose (N)	P1	P2	P4	P2	P4	P1
laminarabiose (L)	P1	P2	P4	P2	P4	P1
trehalose (T)	P1	P2	P4	P2	P1	P4

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Parameterization of bonded interactions

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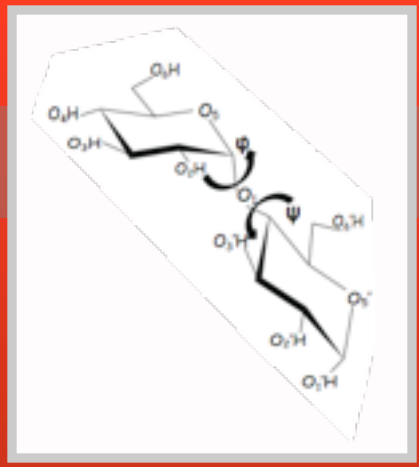
Parameterization of bonded interactions



o Angles and dihedrals should account for rotameric states

Sweet MARTINI

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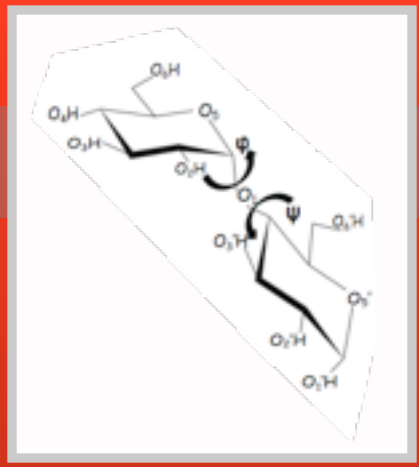

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- Bonded parameters fitted to mapped atomistic simulations

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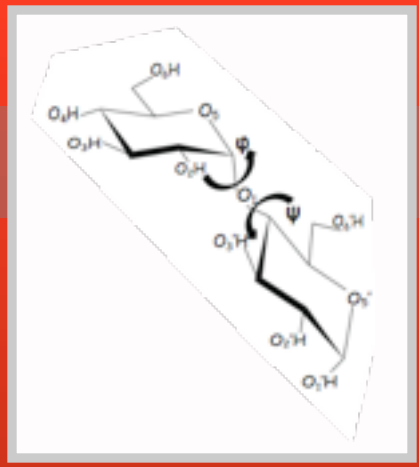

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Sweet MARTINI

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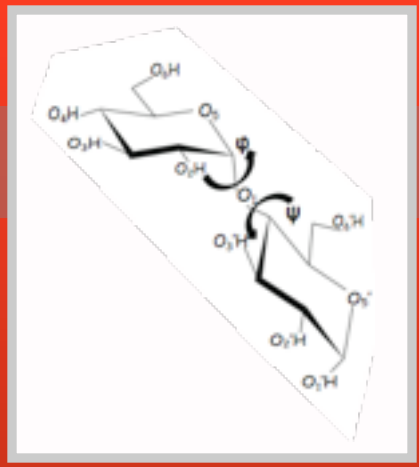

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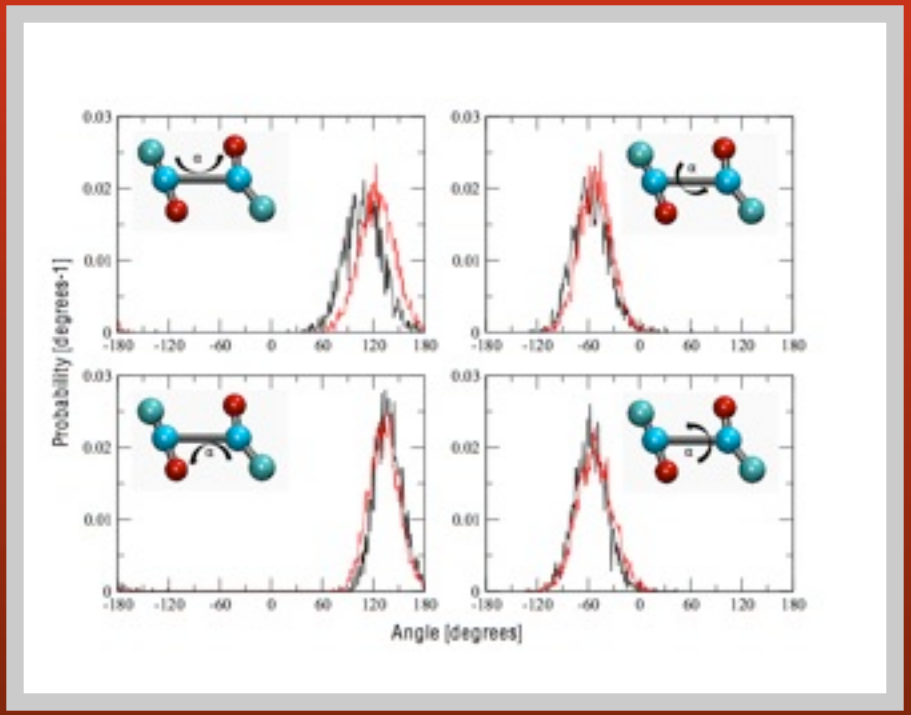

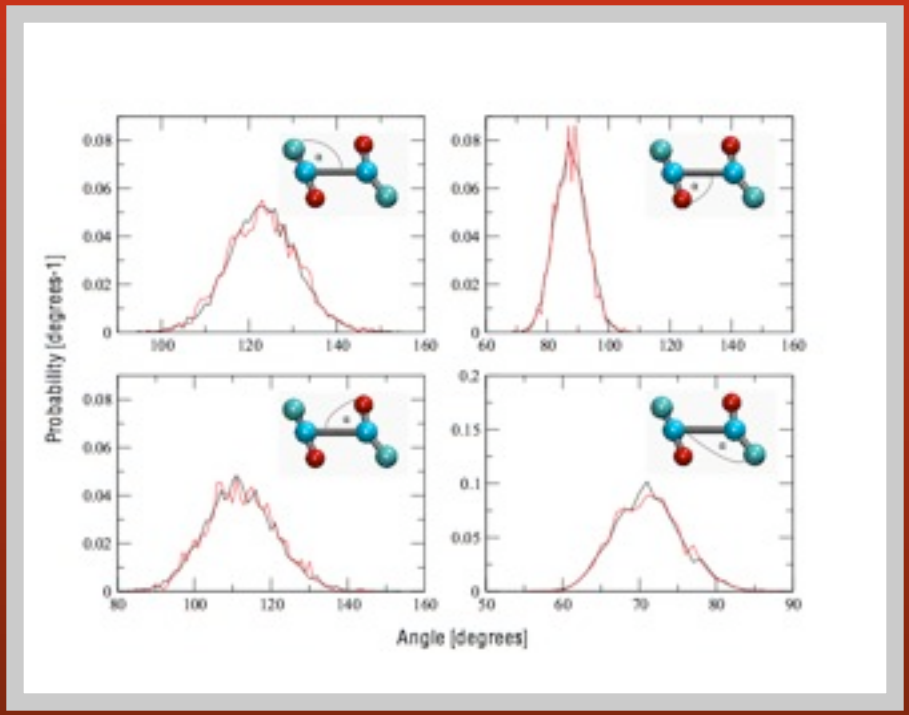

Sweet MARTINI

Testing: partitioning free energy

			All-atom (Gromos)				Martini		Exp
molecule	ΔG^{W} (AA) (kJ mol^{-1})	ΔG^{O} (AA) (kJ mol^{-1})	$\Delta\Delta G_{OW}$ (AA) (kJ mol^{-1})	log P_{OW}(AA)	ΔG^{W} (CG) (kJ mol^{-1})	ΔG^{O} (CG) (kJ mol^{-1})	$\Delta\Delta G_{OW}$ (CG) (kJ mol^{-1})	log P_{OW}(CG)	log P_{OW} (exp)
glucose (G)	−89	−74	15	−2.5	−60	−43	17	−2.9	−2.8
fructose (F)	−80	−69	11	−2.0	−60	−44	16	−2.7	
sucrose (SUC)	−107	−89	18	−3.0	−103	−83	20	−3.4	−3.3
maltose (M)	−121	−96	25	−4.2	−120	−96	24	−4.0	
cellobiose (C)	−114	−90	24	−4.0	−120	−96	24	−4.0	
kojibiose (K)	−121	−93	28	−4.7	−120	−96	24	−4.0	
sophorose (S)	−120	−88	32	−5.4	−120	−96	24	−4.0	
nigerose (N)	−119	−89	30	−5.0	−120	−96	24	−4.0	
laminarabiose (L)	−120	−91	29	−5.0	−120	−96	24	−4.0	
trehalose (T)	−120	−92	28	−5.0	−120	−96	24	−4.0	−3.78

Sweet MARTINI

Testing on oligosaccharides: amylose

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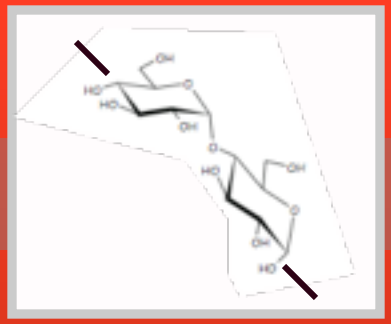

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Sweet MARTINI

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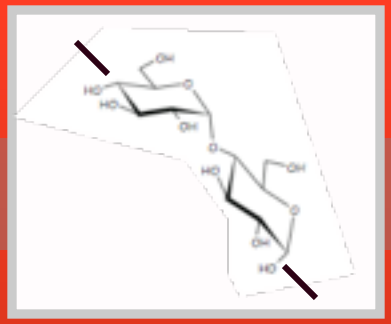

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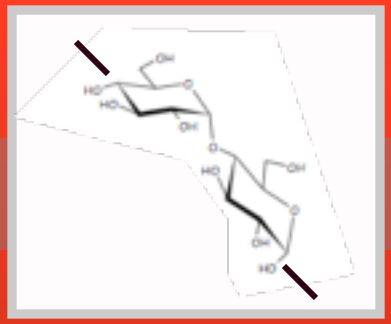

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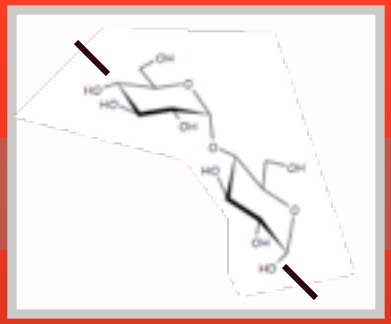

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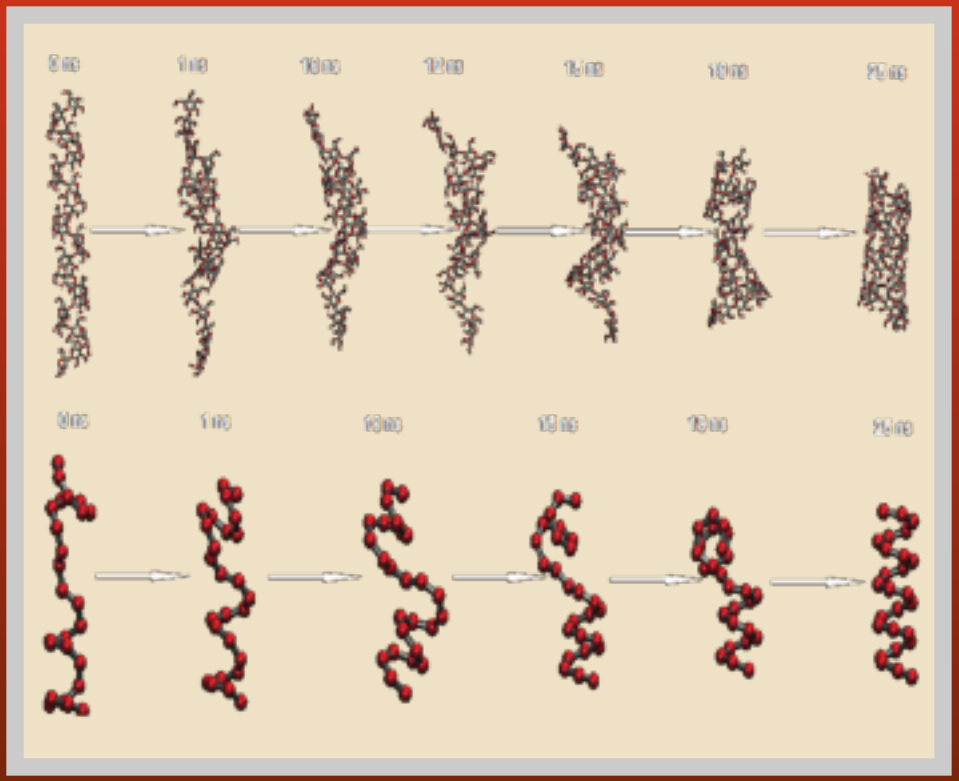

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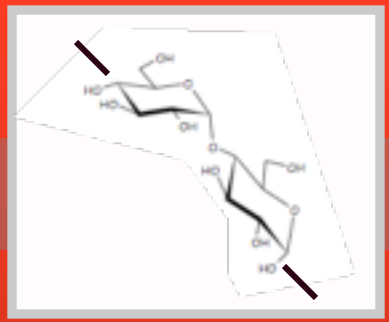
Testing on oligosaccharides: amylose



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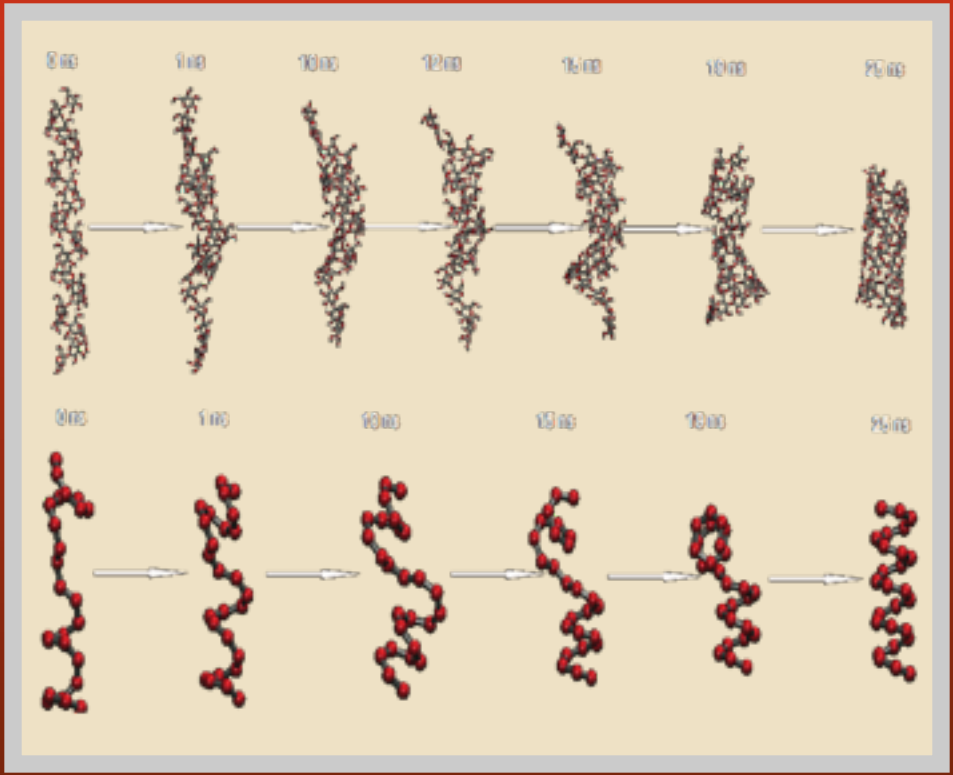

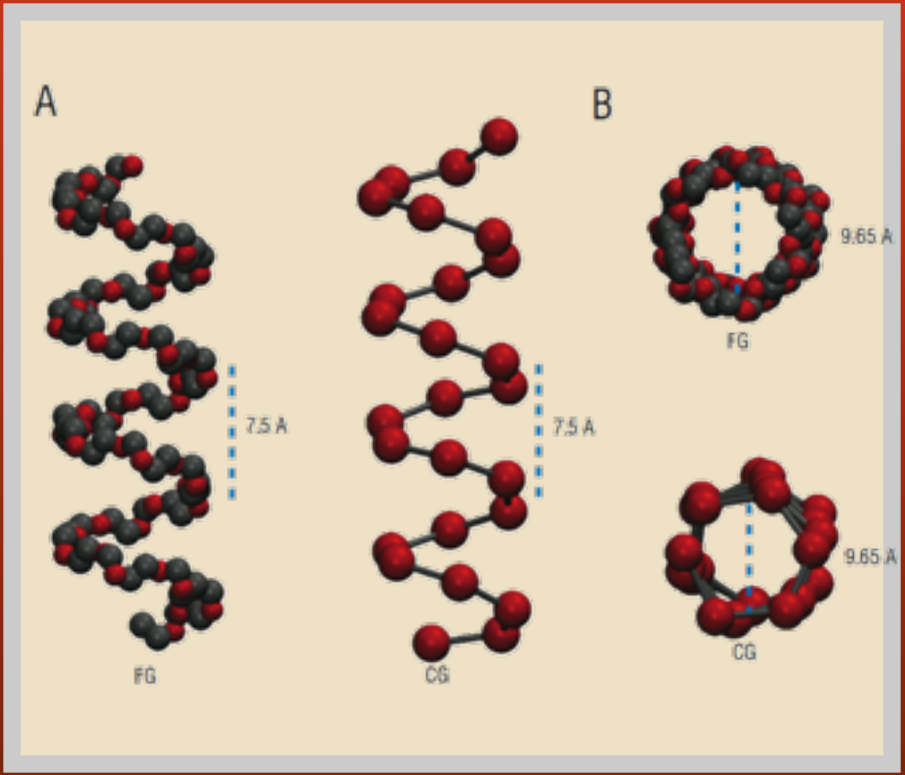

Sweet MARTINI

General recipe for CGing your own molecule

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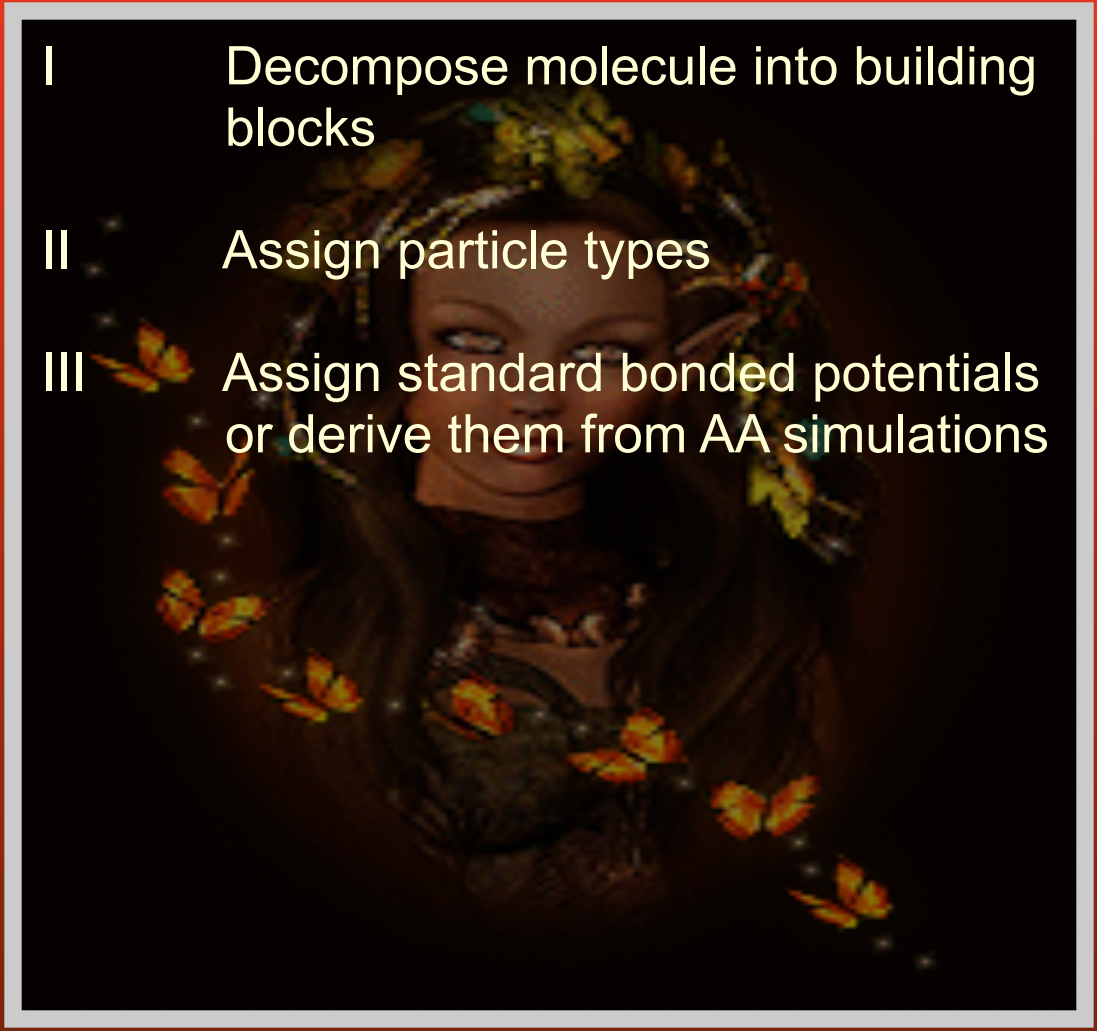

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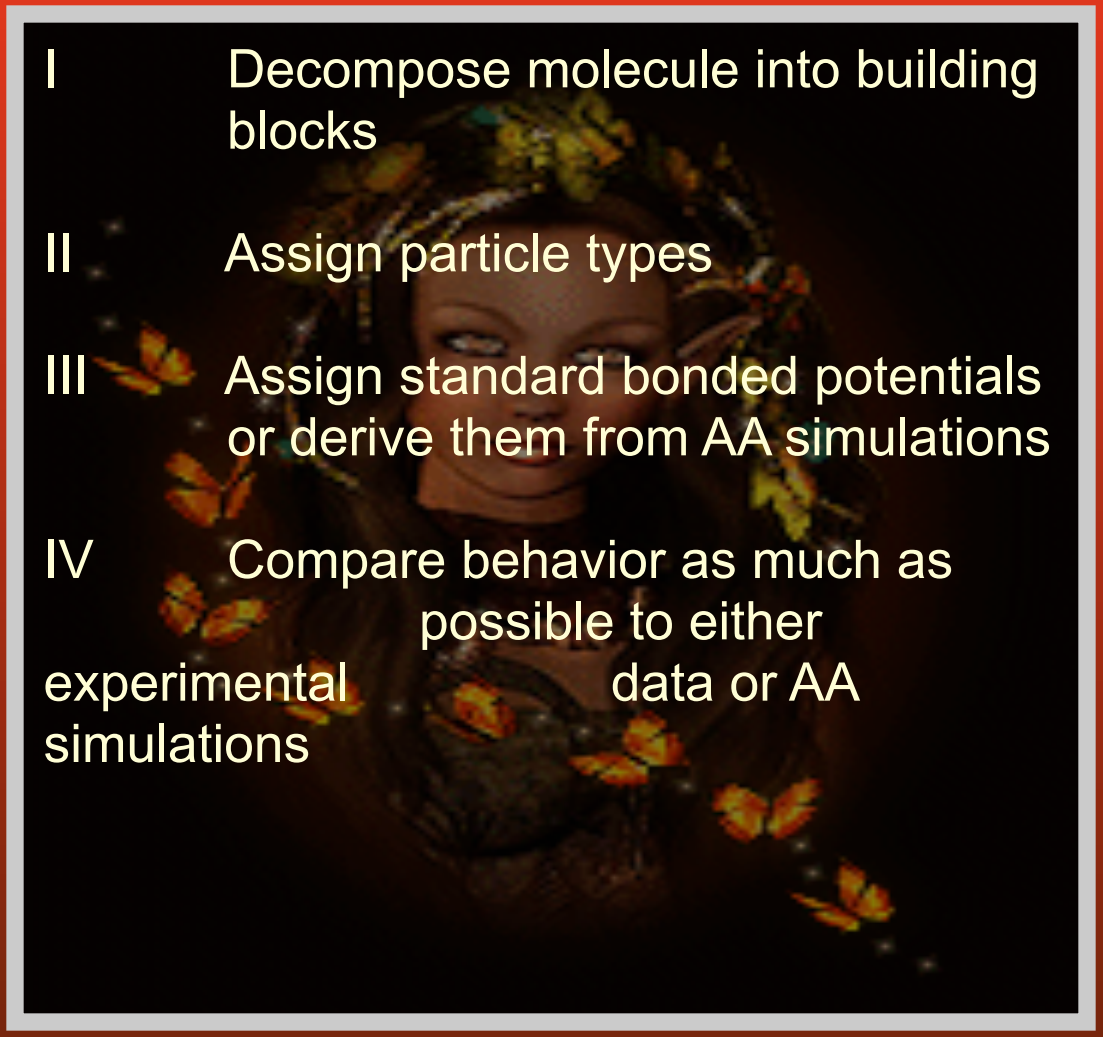

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General recipe for CGing your own molecule

I Decompose molecule into building blocks

II Assign particle types

III Assign standard bonded potentials or derive them from AA simulations

IV Compare behavior as much as possible to either experimental data or AA simulations

V Optimize model going back to step I, II or III

Overview of Martini force field

Key features of the MARTINI model

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- Four-to-one mapping

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Lipid force field

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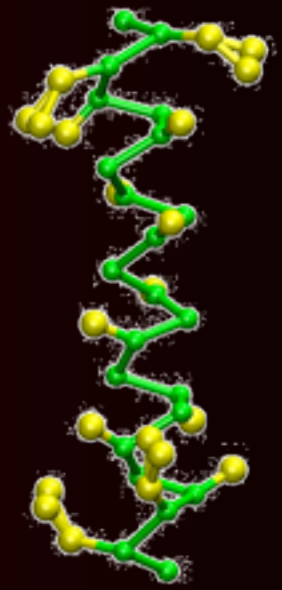

Protein force field

Monticelli, Kandasamy, Periole, Larson, Tieleman, Marrink JCTC (2008)

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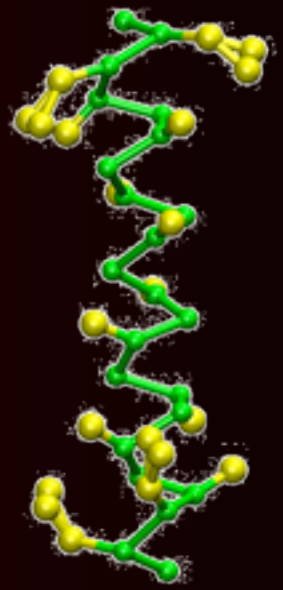

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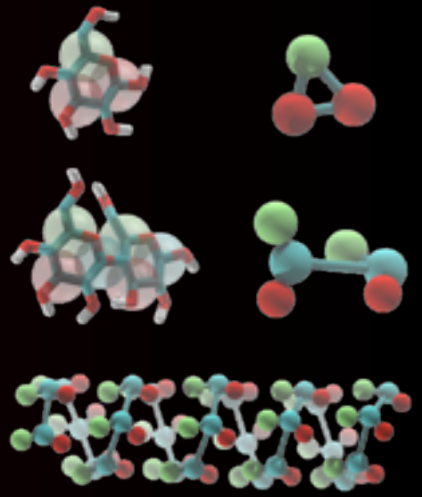

Carbohydrate force field

Lopez, Rzepiela, de Vries, Dijkhuizen, Huenenberger, Marrink JCTC (2009)

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Same particle type for similar building blocks e.g. O-C-C-OH group

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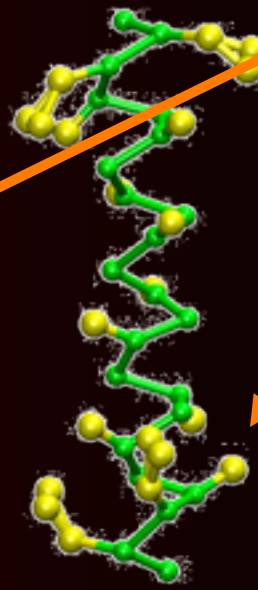

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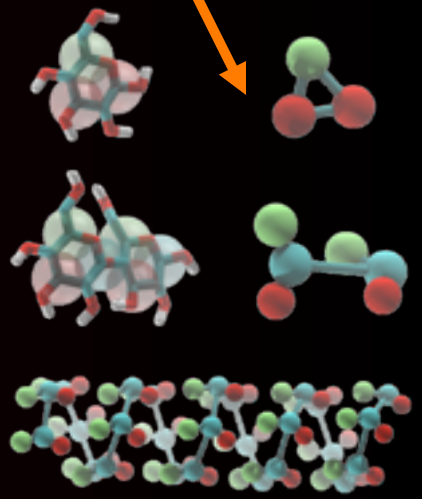

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Human force field

(not yet released ...)

Lipid force field

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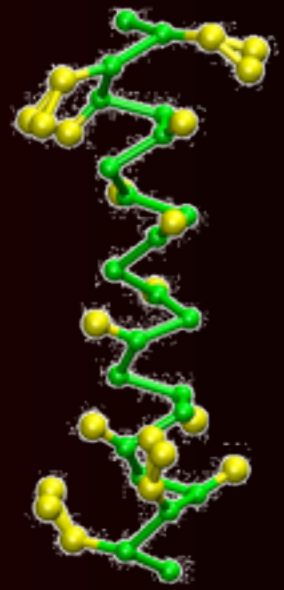

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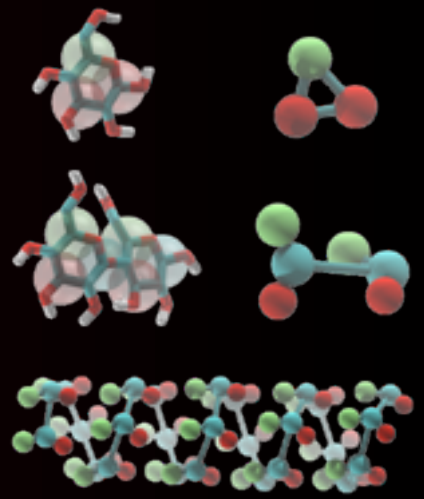

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