

Martini for proteins and application to the Recoverin

Presentation by Giuseppe Gambini

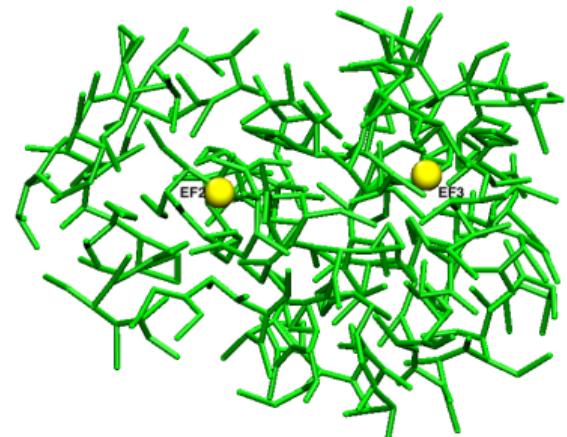
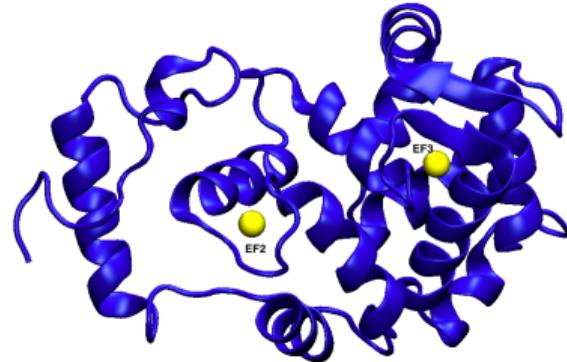
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Outline of the project

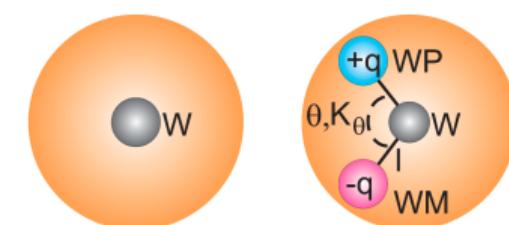
- Basic CG modeling principles of Martini
- Summary of the validations for amino acids
- Simulation of Recoverin in water



Martini mapping

- Specific chemical units can be found irrespective of the larger molecule they belong to
- Four-to-one mapping
- Standard vs polarizable water

type	chemical building block	examples	
		2D	name (mapping)
P2	$\text{CH}_3\text{CH}_2-\text{COOH}$		propanoic acid (P2)
SP2	CH_3-COOH		acetic acid (SP2)
P1	$(\text{CH}_3)_2\text{CH}-\text{OH}$		isopropanol (P1)

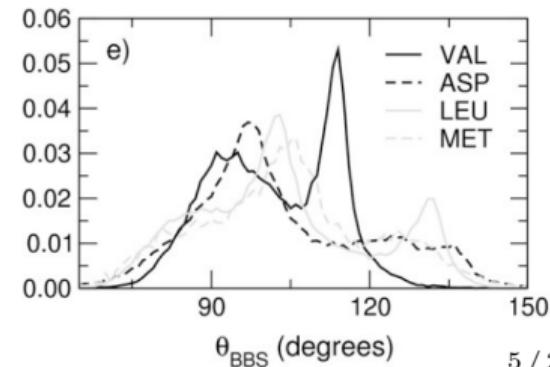
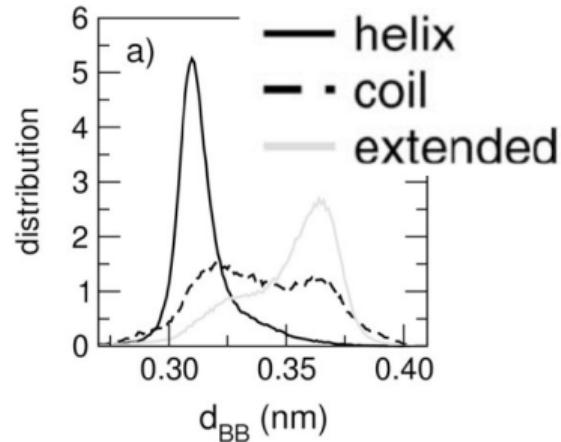
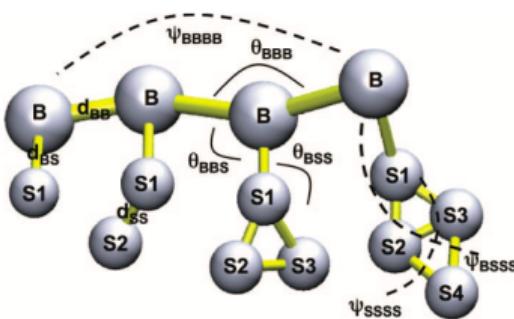


Parametrization philosophy of Martini

Approaches	<i>Top-down</i>	statistics based <i>Bottom-up</i>
Parametrizations	nonbonded interactions	bonded interactions
Methods	partitioning/binding free energies	statistics from PDB

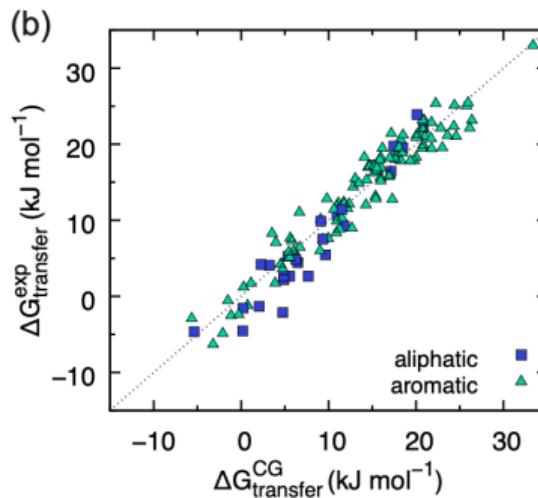
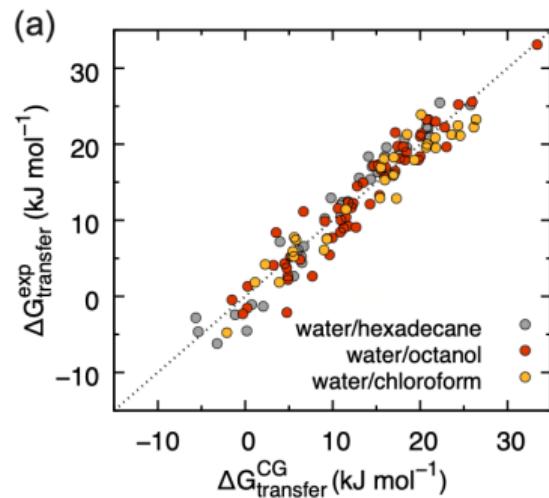
Bonded interactions

$$U_{\text{bonded}}(\mathbf{R}) = \sum_i^{\text{bonds}} \frac{k_{b,i}}{2} (b_i - b_{0,i})^2 + \sum_i^{\text{angles}} \frac{k_{\alpha,i}}{2} (\alpha_i - \alpha_{0,i})^2 \\ + \sum_i^{\text{torsions}} \sum_k^M \frac{V_{ik}}{2} [1 + \cos(n_{ik}\theta_{ik} - \theta_{0,ik})] + \sum_i^{\text{impropers}} \frac{k_{\theta,i}^{\text{imp}}}{2} (\theta_i^{\text{imp}} - \theta_{0,i}^{\text{imp}})^2$$

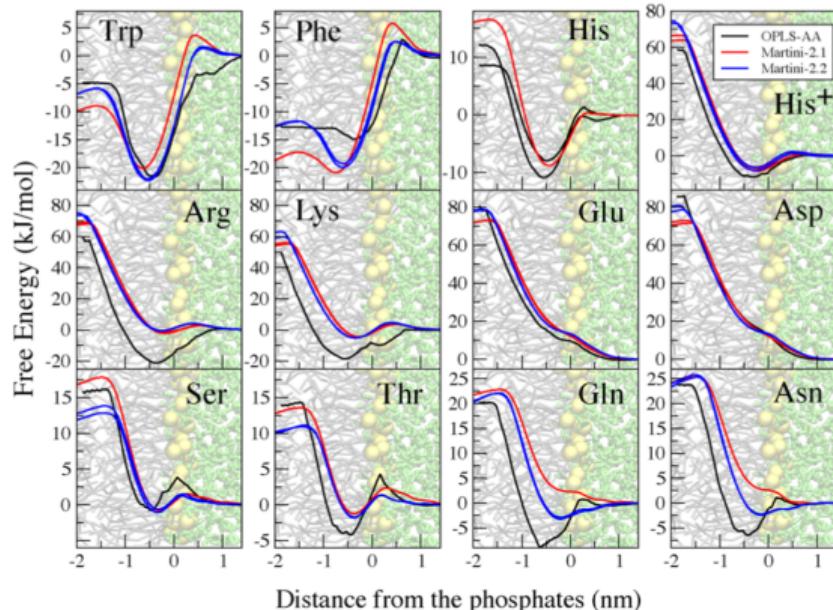


Non-bonded interactions

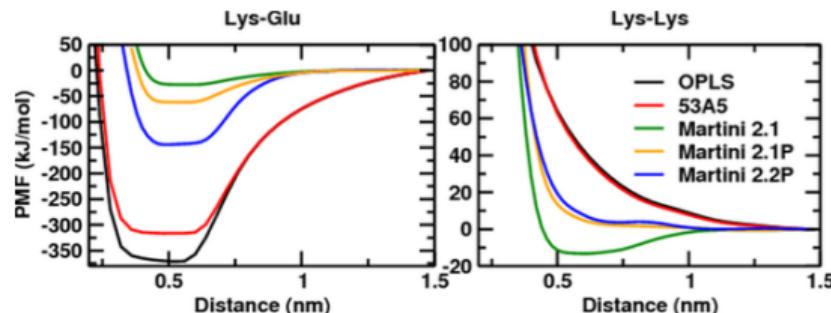
$$U_{\text{nonbonded}}(\mathbf{R}) = \sum_{ij}^{\text{pairs}} 4\varepsilon_{ij} \left[\left(\frac{\sigma_{ij}}{r_{ij}} \right)^{12} - \left(\frac{\sigma_{ij}}{r_{ij}} \right)^6 \right] + \sum_{ij}^{\text{pairs}} \frac{q_i q_j}{4\pi\varepsilon_0\varepsilon_r r_{ij}}$$



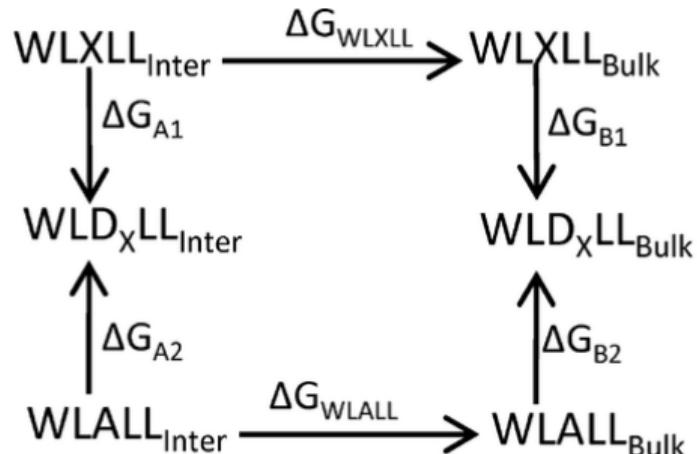
Partitioning and dimerization free energies



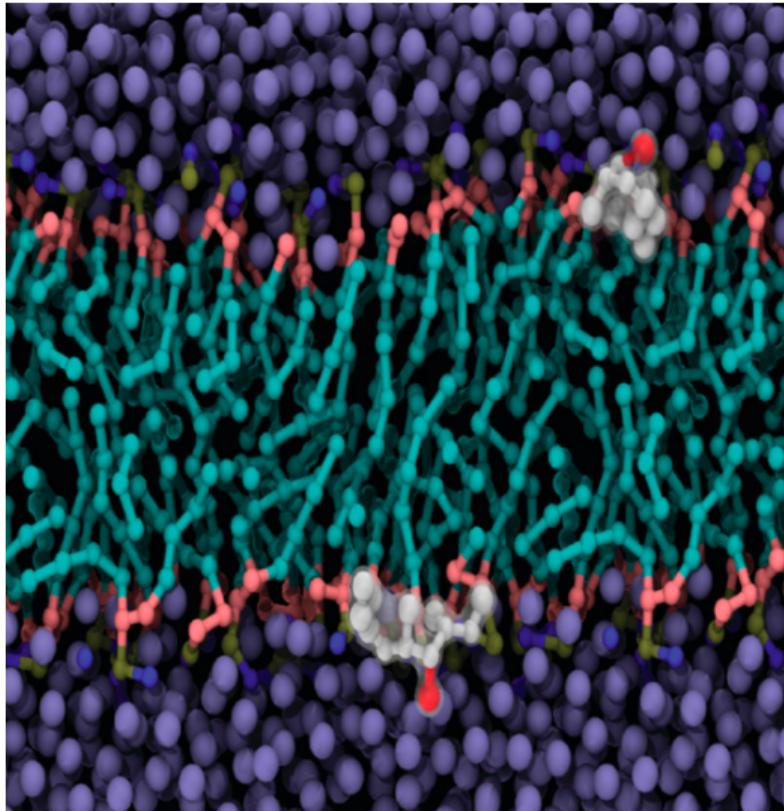
- Water/membrane ΔG^{part} : CG and AA profiles are comparable
- ΔG^{dim} in oil is not well reproduced ($\varepsilon_r = 15$ in standard and $\varepsilon_r = 2.5$ in p)



Whimley-White peptides binding to membranes



$$\begin{aligned}\Delta\Delta G^{\text{residue}} &= \Delta G_{WLXLL} - \Delta G_{WLALL} \\&= \Delta G_{A1} - \Delta G_{A2} - (\Delta G_{B1} - \Delta G_{B2}) \\&= \Delta G_{A1} - \Delta G_{B1} - (\Delta G_{A2} - \Delta G_{B2}) \\&= \Delta G_X - \Delta G_{ALA}\end{aligned}$$



Comparison with reference free energies

SC		type (charge) ^b	$\Delta\Delta G^{\text{WW}}{}^c$	$\Delta G^{\text{part}}{}^d$	$\Delta G^{\text{dim}}_{\text{water}}{}^e$	$\Delta G^{\text{dim}}_{\text{oil}}{}^e$
Phe	ref.		5.4 ± 0.3	12	-1.6	-2.9
	CG	<i>SC4-SC4-SC4</i>	12.2 ± 0.1	21	-4.5	-1.3
		<i>SC5-SC5-SC5</i>	7.7 ± 0.1	10	-3.0	-1.7
Trp	ref.		8.5 ± 0.4	9	-3.3	-3.3
	CG	<i>SC4-SP1-SC4-SC4</i>	9.2 ± 0.1	10	-4.7	-3.0
		<i>SC4-SNd-SC5-SC5</i>	9.4 ± 0.1	8	-4.0	-2.7
Ser	ref.		0.2 ± 0.4	-14	1.6	-5.9
	CG	<i>P1</i>	-1.9 ± 0.1	-12	0.0	-2.3
		<i>N0 (0.40)</i>	-0.5 ± 0.3	-14	-0.2	-5.2
Asn	ref.		-1.0 ± 0.4	-28	-0.1	-17.3
	CG	<i>P5</i>	-2.7 ± 0.1	-31	0.3	-4.2
		<i>Nda (0.51)</i>	1.9 ± 0.7	-28	-0.2	-20.6
		<i>Nda (0.46)</i>	2.0 ± 0.4	-23	-0.4	-13.9
		<i>N0 (0.54)</i>	-1.3 ± 0.3	-27	-0.2	-18.1

Set-up of the system

Mapping and elastic network addition
with *Martinize2*



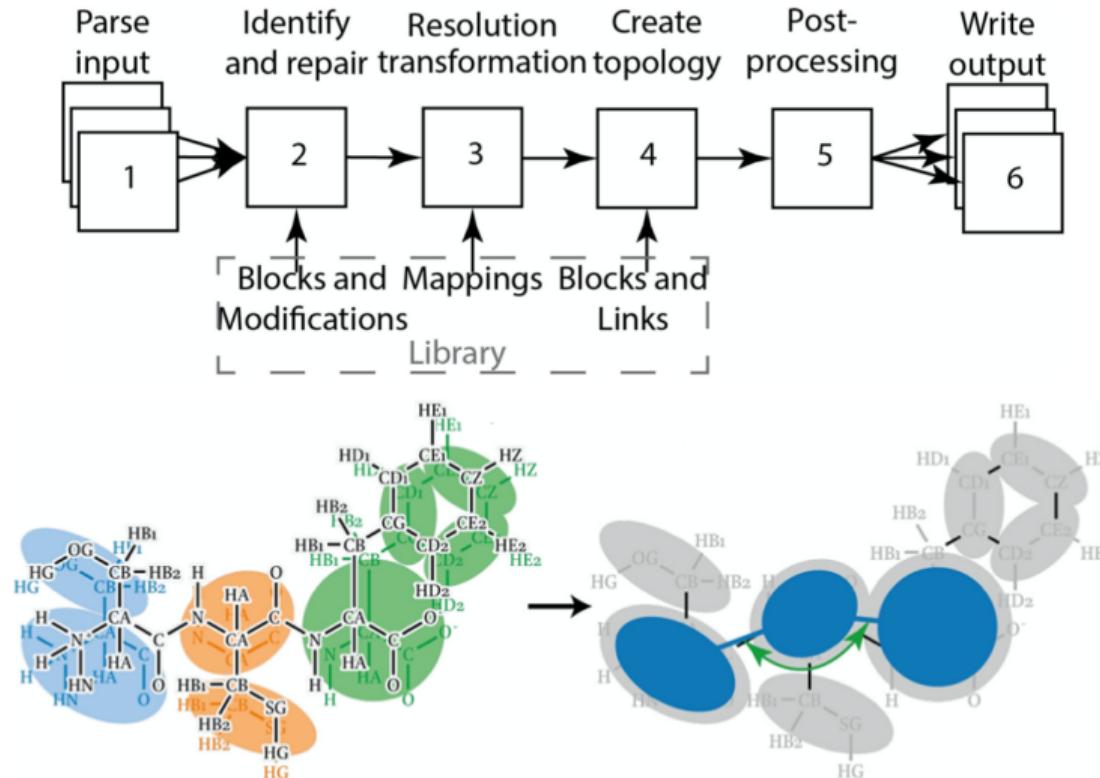
Minimization in vacuum and in solution



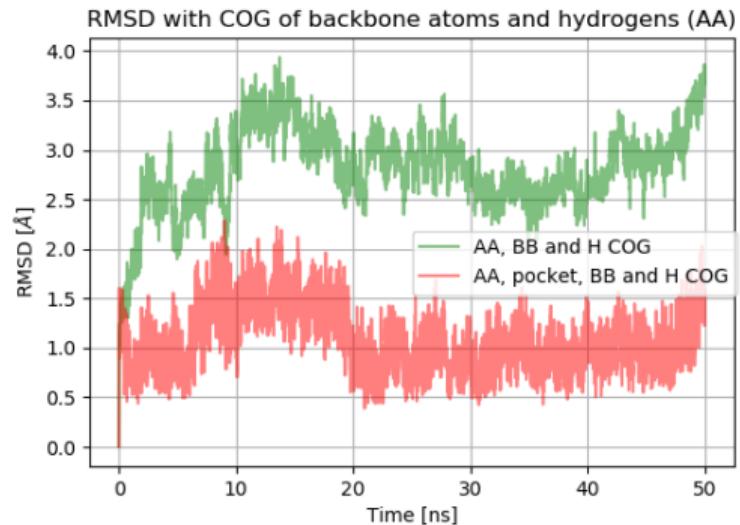
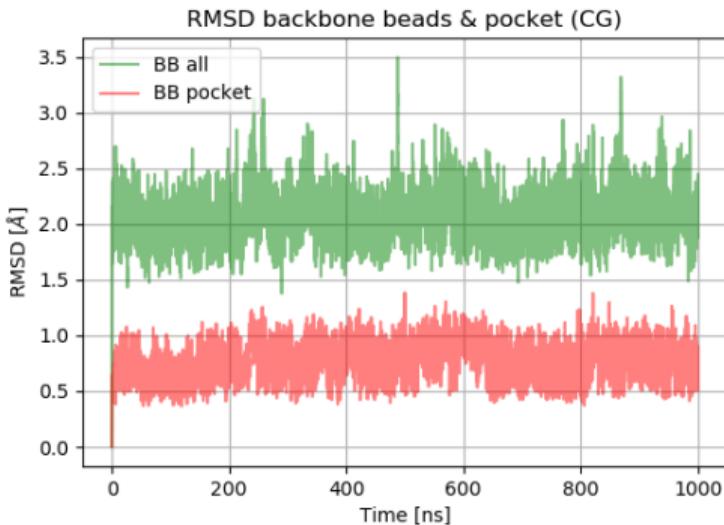
NPT equilibration
and unrestrained run

	parameters
Time step	$\Delta t = 0.02 \text{ ps}$
v-rescale	$\tau_T = 2 \text{ ps}, T_{\text{ref}} = 310 \text{ K}$
Parrinello Rahman	$\tau_P = 12 \text{ ps}, P_{\text{ref}} = 1 \text{ bar}$
Reaction field	$\varepsilon_r = 15, \varepsilon_{RF} = \infty$ $r_c = 1.1 \text{ nm}$
Elastic network	$k = 500 \text{ kJ mol}^{-1}\text{nm}^{-2}$ $r_{\text{low}} = 0.5 \text{ nm}, r_{\text{up}} = 0.9 \text{ nm}$

Martinize2 workflow

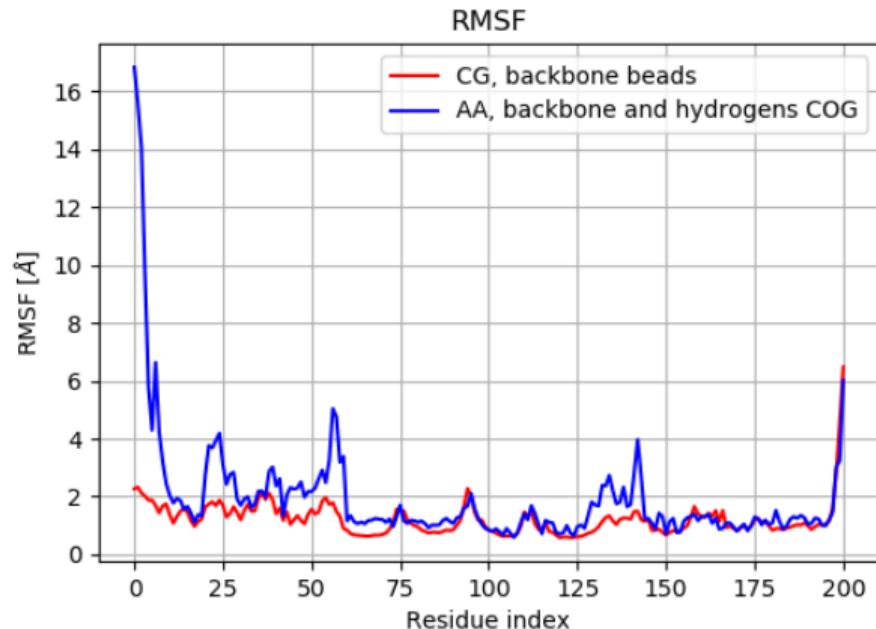


Root Mean Square Deviations

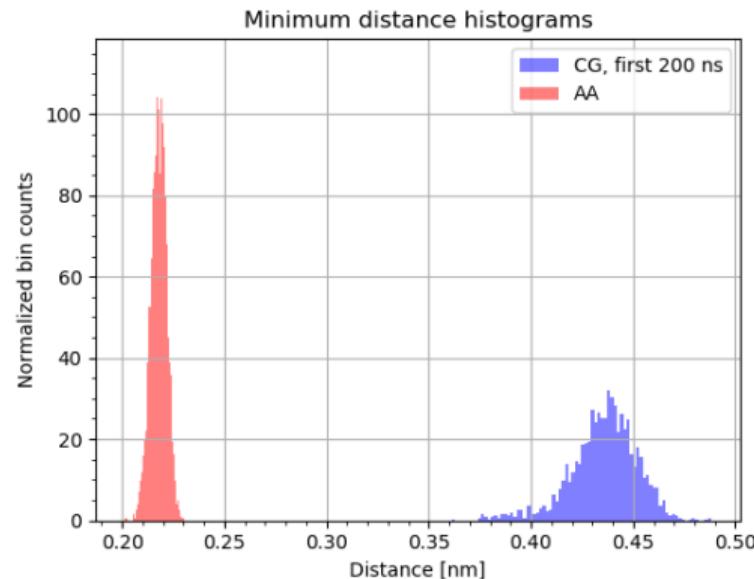
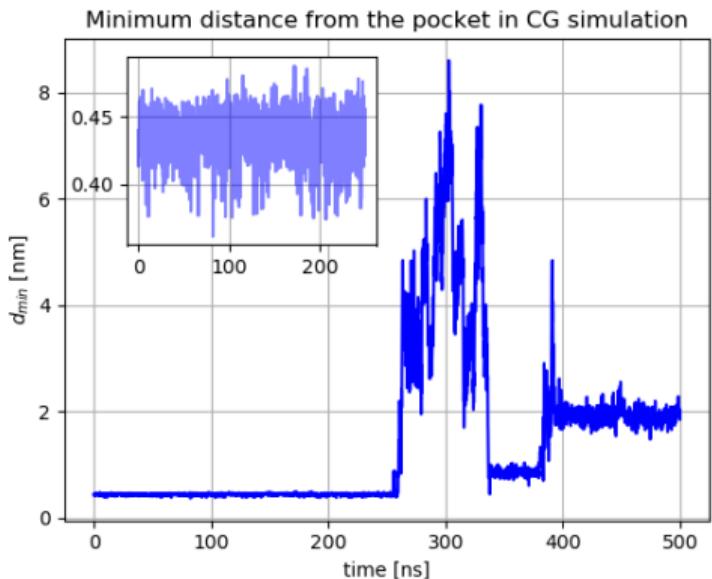


Root Mean Square Fluctuations

- Secondary/tertiary structure
- Elastic network with $k = 500 \text{ kJ mol}^{-1} \text{ nm}^{-2}$

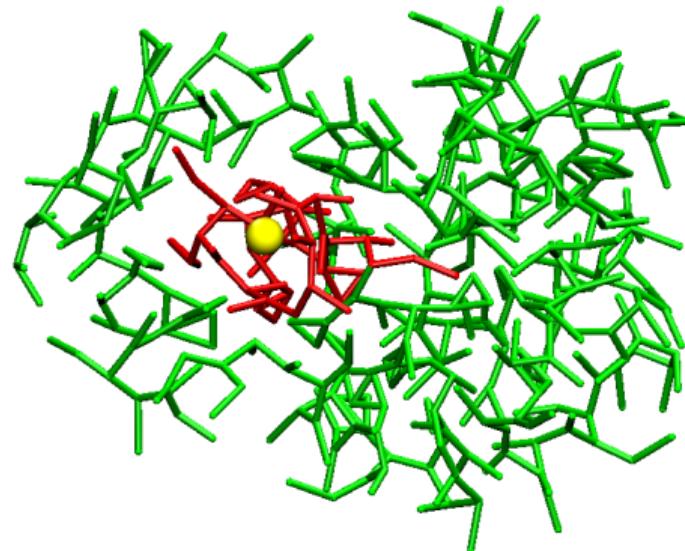


Minimum distance from EF2



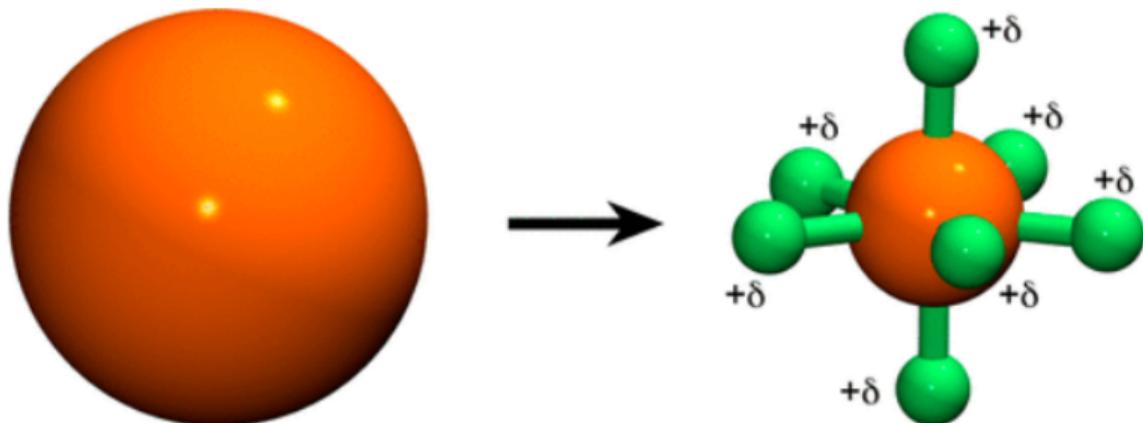
Conclusions

- Overview of Martini for proteins
- Agreement with structural quantities
- Polarizable Martini water and PME for Ca^{2+}

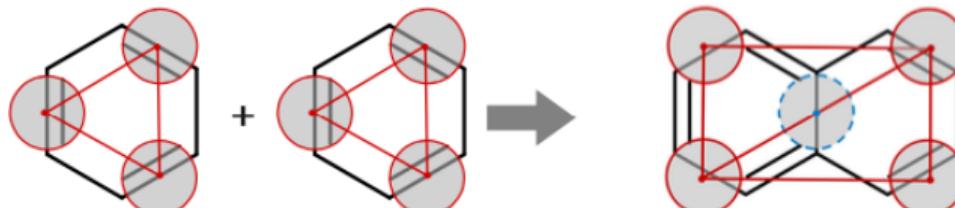
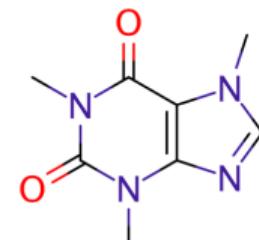
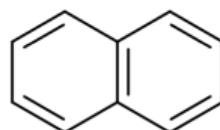
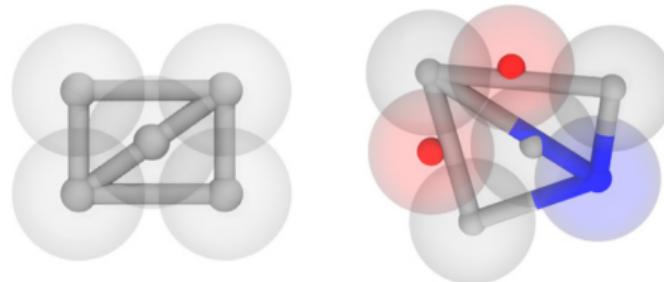


Extra: calcium ion coordination

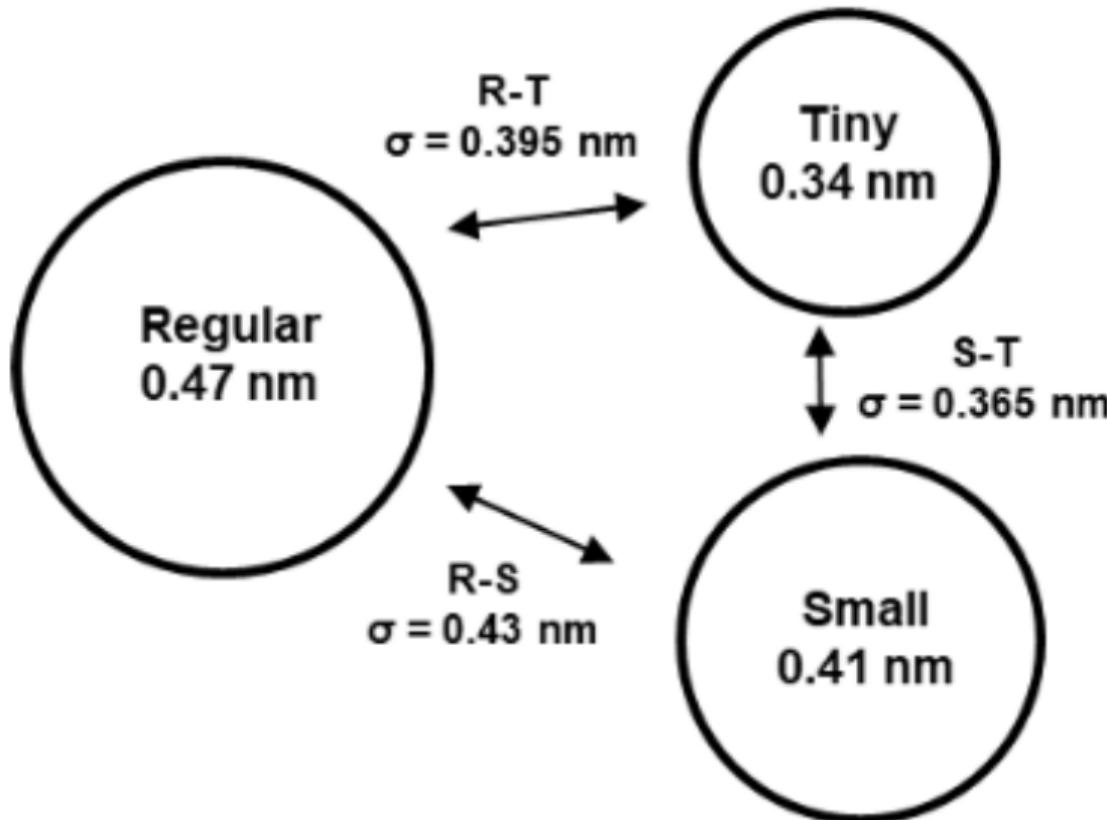
- Calcium can have from 6 to 8 coordinating atoms
- Pentagonal bipyramidal geometry is frequent



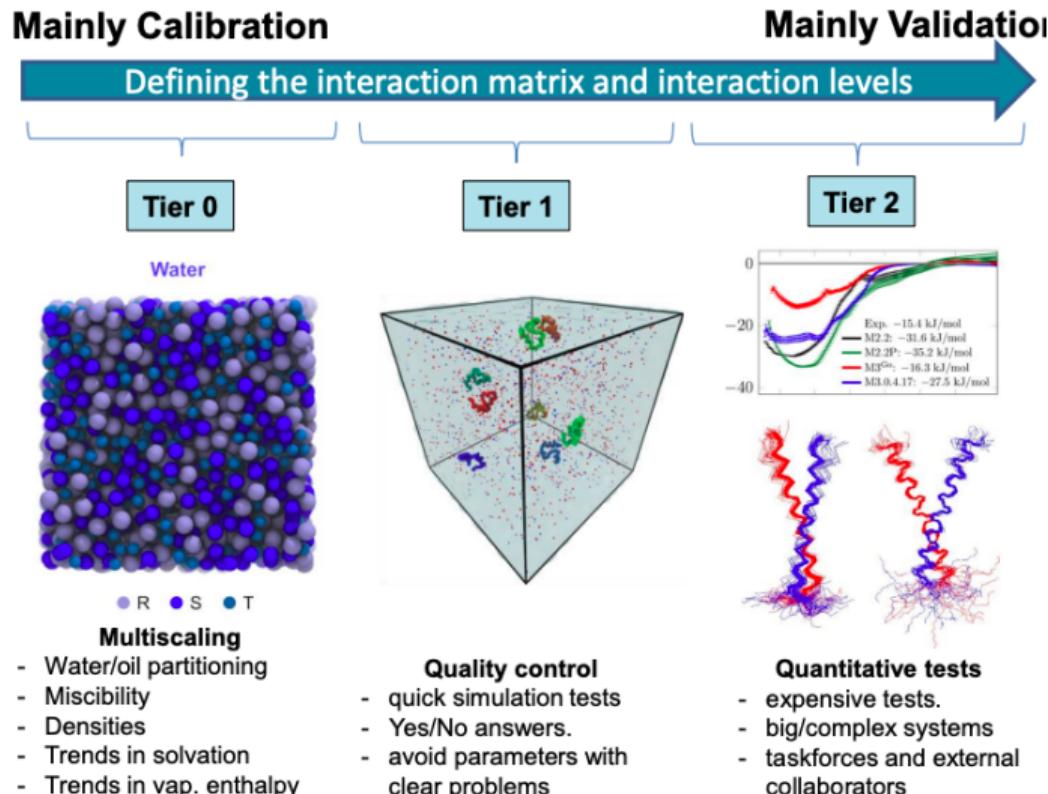
Extra: mapping of aromatic molecules



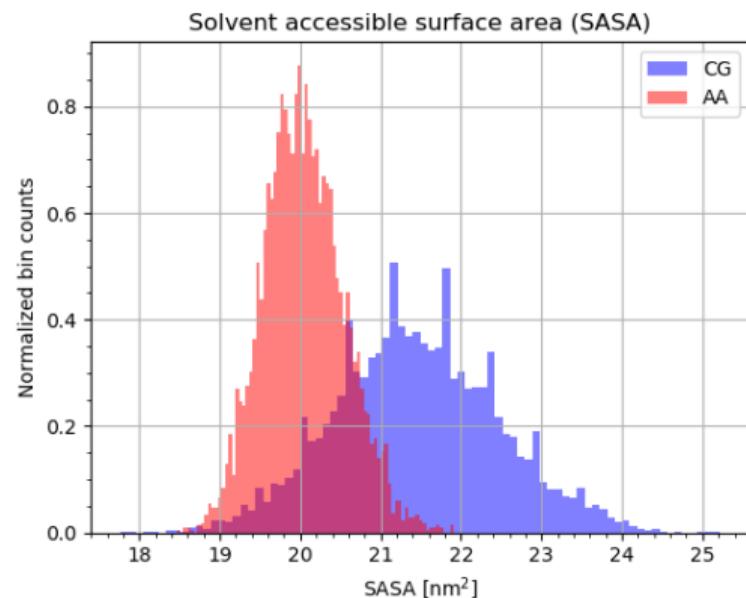
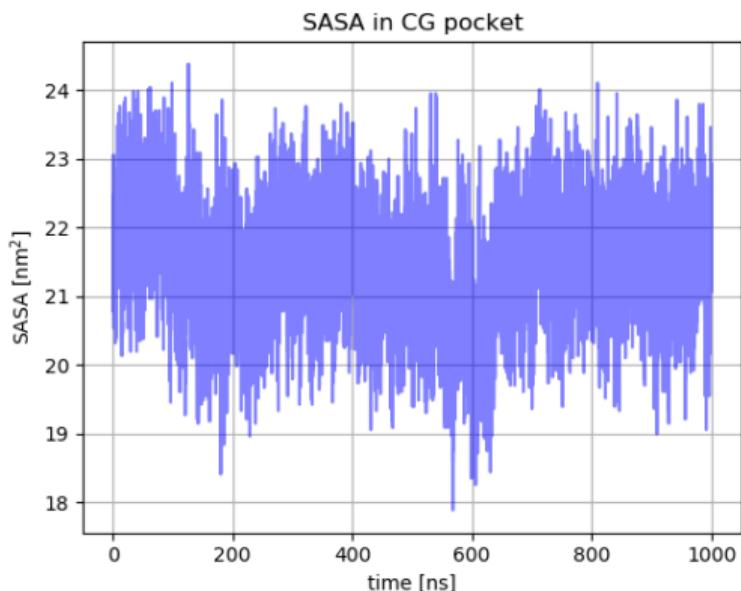
Extra: van der Waals radii



Extra: calibrations and validations

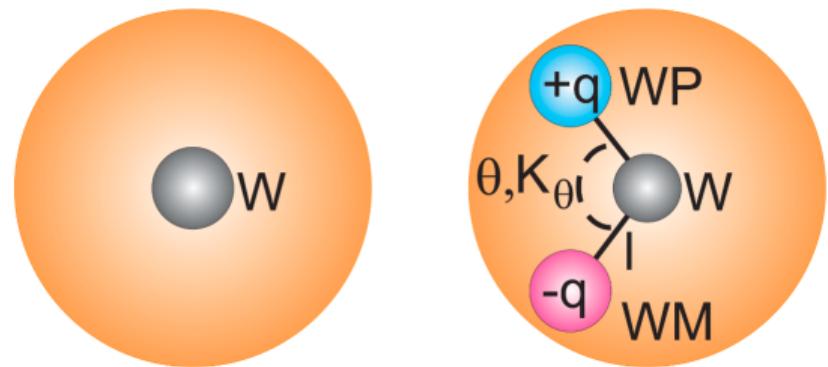


Extra: SASA



lack of explicit screening in polar solvents

- Single bead vs three beads
- Reaction field vs PME



Formulas for the free energies

- Dimerization free energy:

$$\Delta G^{\text{dim}} = -k_B T \ln K_a = -k_B T \ln \frac{4\pi R_{\max}^3 \int_0^{r_c} r^2 g(r) dr}{3v^\emptyset \int_{r_c}^{R_{\max}} r^2 g(r) dr}$$
$$g(r) = \exp \left(-\frac{\text{PMF}(r)}{k_B T} \right) = \left\langle \exp \left(-\frac{W^{\text{dim}}(r)}{k_B T} \right) \right\rangle$$

- Multiple Bennett Acceptance Ratio (MBAR) for WW peptides:

$$\Delta G_{\{\lambda_i\}, \{\lambda_{i+1}\}} = -k_B T \ln \left(\frac{\langle \min(1, \exp [-(U_{\{\lambda_{i+1}\}} - U_{\{\lambda_i\}})/k_B T]) \rangle_{\{\lambda_i\}}}{\langle \min(1, \exp [-(U_{\{\lambda_i\}} - U_{\{\lambda_{i+1}\}})/k_B T]) \rangle_{\{\lambda_{i+1}\}}} \right)$$

$$\Delta G^{\text{WW}} = \sum_i^{M-1} \Delta G_{\{\lambda_i\}, \{\lambda_{i+1}\}}$$