PROTEIN-WATER INTERACTIONS

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PROBLEM

1) The simulations for unfolded state of protein is highly collapsed Molten globule state or non-native trap states

2) The protein-water interactions are not captured properly by the current force-fields

   1) The proteins are not solvated

   2) solvation free energies of side chain analogs are unfavorable

   3) Protein association are slightly more favorable

SOLUTIONS

Parametrization strategy

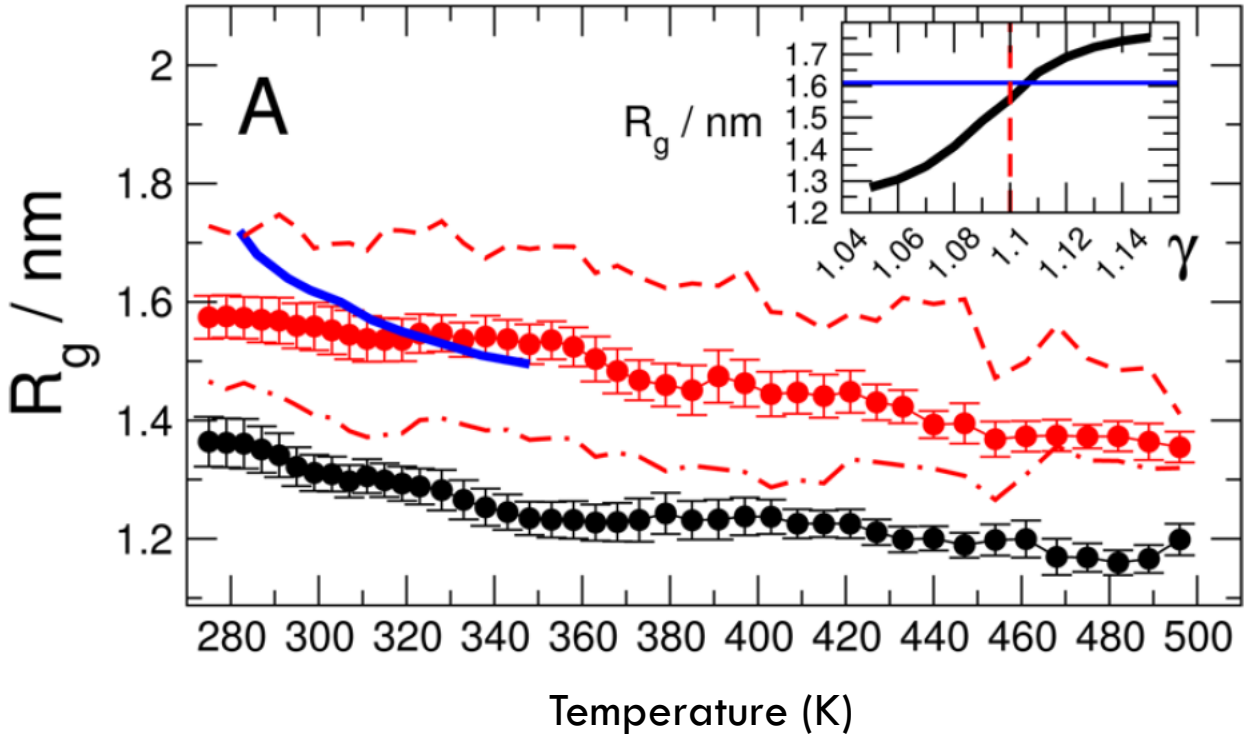
The Lennard-Jones parameters were parametrized to capture the correct unfolded state of the protein without hampering the folded state of the protein

The standard Lorentz-Berthelot mixing rule was scaled

$$\varepsilon_{\mathrm{O}i} = \gamma \varepsilon_{\mathrm{O}i}^{\mathrm{LB}} = \gamma \left(\varepsilon_{\mathrm{O}} \varepsilon_i\right)^{1/2}$$

The γ parameter is the adjustable scaling parameter.

Best, R.B., Zheng, W. and Mittal, J., 2014. Balanced protein–water interactions improve properties of disordered proteins and non-specific protein association. *Journal of chemical theory and computation*, *10*(11), pp.5113-5124.



Black symbols – Radius of gyration with Amber ff03w force field
Red symbols – Radius of gyration with Amber ff03ws force field
Red dot-dashed and dashed lines indicate the results obtained by reweighting at γ = 1.05 and 1.15,respectively.

Amber ff03w- force field with TIP4P/2005 water model
Amber ff03ws- force field with TIP4P/2005 water model with rescaled parameter

The rescaled parameter provided evidence that it correctly characterized the unfolded proteins.

The solvation free energies were calculated for various force fields and error in comparison to experiments were calculated

protein//water force fields	RMSE	MSE	MSE_{PDB}	MSE_{IDP}
OPLS//TIP3P[b]	3.11	2.5	2.11	2.21
Amber9x//TIP3P[b]	3.63	2.42	1.86	1.69
Amber9x//TIP4Pew[b]	4.08	2.87	2.43	2.05
CHARMM//TIP3P[c]	5.63	4.78	3.73	3.59
Amber03*//TIP3P	7.41	4.90	3.81	2.99
Amber03w//TIP4P/2005	8.25	5.32	4.16	3.11
Amber03ws//TIP4P/2005	6.12	1.81	0.95	0.33

$$\mathrm{MSE}_{\mathrm{X}} = \sum_{i} w_{\mathrm{X}}(i)\left(\mu^{\mathrm{ex}}_{\mathrm{sim}}(i) - \mu^{\mathrm{ex}}_{\mathrm{exp\ t}}(i)\right)$$

Global Measures of Deviation from Experimental Solvation Free Energies (kJ/mol)

To validate the protein-protein interaction association of villin HP36 was studied

Villin HP36 is soluble upto concentration of 1.5 mM so K_d > 1.5 mM

force field	k_{on} (M^{-1} ns^{-1})	k_{off} (ns^{-1})	K_d (mM)
Amber ff03*	49.4 (34.9)	0.005 (0.005)	0.10 (0.07)
Amber ff03w	8.3 (2.7)	0.128 (0.043)	15.4 (1.7)
Amber ff03ws	3.5 (1.7)	0.077 (0.034)	21.9 (4.9)

Kinetic and Equilibrium Parameters of Villin HP36 Association

Protein concentration = 8.5 mM

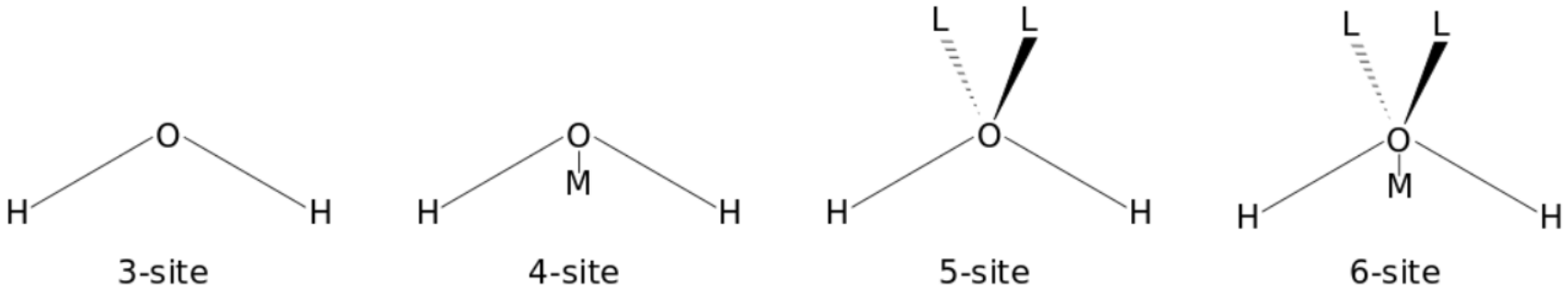
A binding event as when the minimum distance between the molecules falls below 0.2 nm and unbinding when it exceeds 1.0 nm.

WATER MODELS

A water model is defined by its geometry along with its partial charges and interaction parameters such as Lennard-Jones parameters.

Water has a tetrahedral geometry with two lone pairs and V shape.

Water model is characterized by 1) the sites 2) whether the model is rigid or flexible and 3) polarization effects



http://www1.lsbu.ac.uk/water/water_models.html

A new water model (TIP4P-D)

A new, four-point water model, called TIP4P-D, in which the water dispersion coefficient C6 is constrained to be ~50% larger than in current water models, and the remaining nonbonded parameters are optimized with respect to experimental liquid water properties.

Dispersion energy

$$E_{\mathrm{DS}} = -\sum^{n=6,8,10,\ldots} \frac{C_n}{r^n}$$

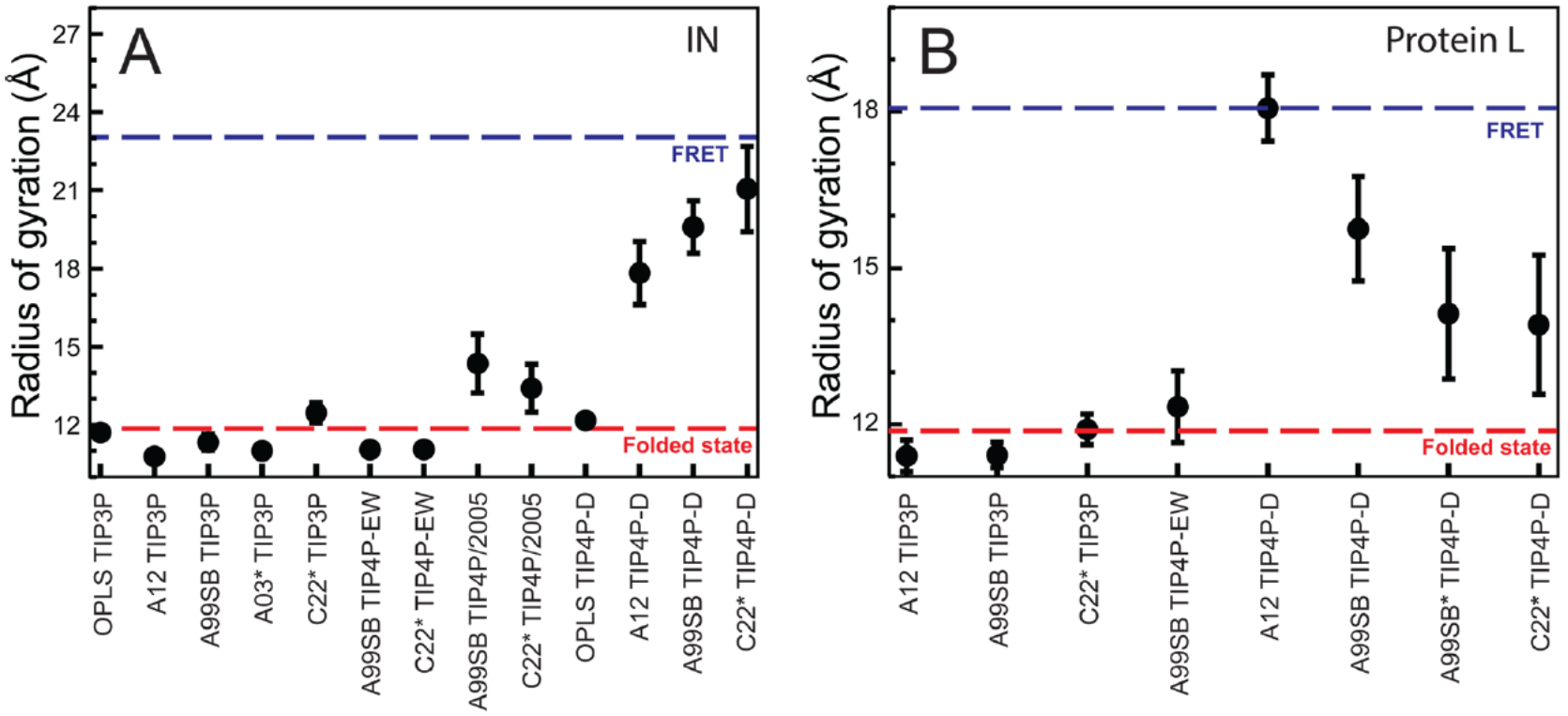
It works accurate only in the asymptotic regime in which r exceeds the molecular sizes.

Short range interactions are not accounted

Various Quantum mechanical approaches and calculated suggests:
At the typical nearest-neighbor distances (~3 Å between the oxygen atoms) observed in liquid water, the cumulative effect of the higher-order C_8/r^8 and C_{10}/r^{10} terms is no longer a small correction and can even exceed the C_6/r^6 contribution to $E_{DS.}$

Piana, S., Donchev, A.G., Robustelli, P. and Shaw, D.E., 2015. Water dispersion interactions strongly influence simulated structural properties of disordered protein states. *The journal of physical chemistry B*, *119*(16), pp.5113-5123.

Increasing the dispersion energy with 50% results in more expanded unfolded protein state



the apo N-terminal zinc-binding domain of HIV-1 integrase (IN)
the immunoglobulin-binding domain of protein L

CONCLUSION

- $\gamma = 1.1$ parametrization works optimally in capturing the true unfolded state of the protein in context to solvation free energy and protein association

- Changing/increasing the dispersion coefficient could enhance the protein water interaction.