Towards a Greater Transferability of Water Models in Biomolecular Simulations

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Water Models in Classical Biomolecular Simulations

- water model chosen at the start of force-field parameterisation
- plays a fundamental role in the parameterisation procedure
- most force-fields originally developed in the late 70s – early 80s
- little effort been made to use newer water models

TTM2.1-F — Fanourgakis and Xantheas, JCPA 2006

Accurate, *ab initio*, flexible water model

Nada — Nada and van der Eerden, JCP 2003

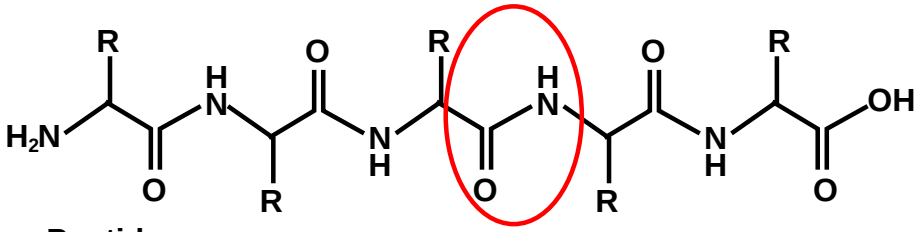
Empirical six-point model, designed for ice–water coexistence

GCPM — Paricaud *et al.*, JCP 2005

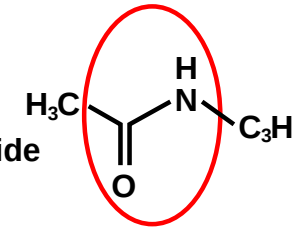
Empirical polarisable model, works well for a wide range of fluid phases

Water and Biomolecular Simulations : The CHARMM Force Field

1. mTIP3P model chosen (Jorgensen *et al.*, JCP 1983)
2. N-methyl acetamide (NMA)···water non-bonded interactions parameterised to reproduce *ab initio* data



Peptide

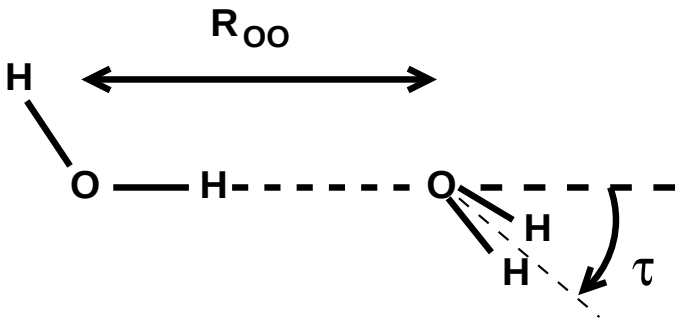


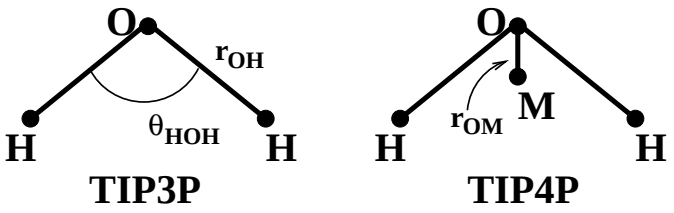
N−methyl acetamide

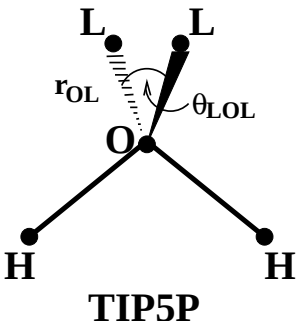
3. solvated NMA properties were calculated

... substituting the water model may lead to an unbalanced potential

Illustration of an Unbalanced Potential : The Water Dimer

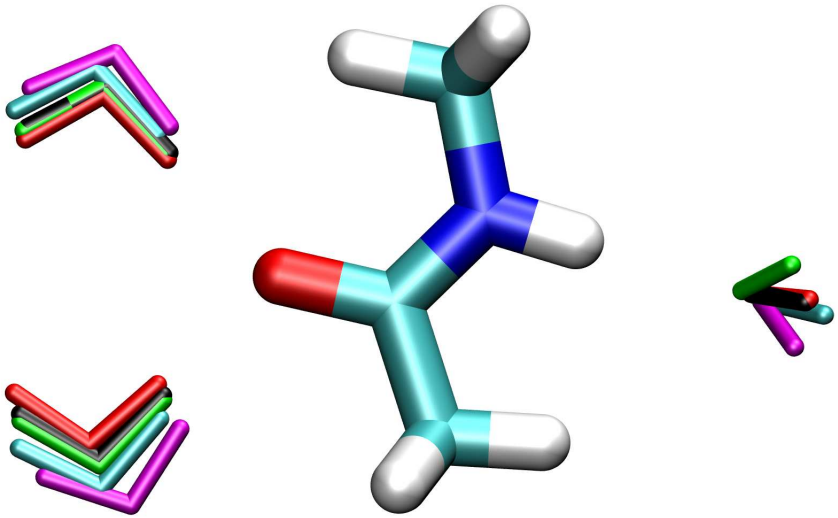






Donor	Acceptor	$R_{OO}/\text{Å}$	$\tau/^\circ$	$\Delta E/\text{kcal/mol}$
Homo-dimers				
TIP3P	TIP3P	2.75	27.3	-6.50
mTIP3P	mTIP3P	2.77	27.4	-6.55
TIP4P	TIP4P	2.75	46.2	-6.23
TIP5P	TIP5P	2.68	51.4	-6.78
Hetero-dimers				
mTIP3P	TIP4P	2.79	50.3	-5.88
TIP4P	mTIP3P	2.72	21.0	-7.05
mTIP3P	TIP5P	2.63	51.7	-9.06
TIP5P	mTIP3P	2.80	30.3	-5.27
TIP4P	TIP5P	2.53	51.4	-10.60
TIP5P	TIP4P	2.83	48.8	-4.74
HF/6-31G*		2.98	56.2	-5.65
Experiment		2.98 ± 0.02	$57. \pm 10$	-5.4 ± 0.5

Properties of Water—NMA complexes



➥ mTIP3P and TIP4P similar

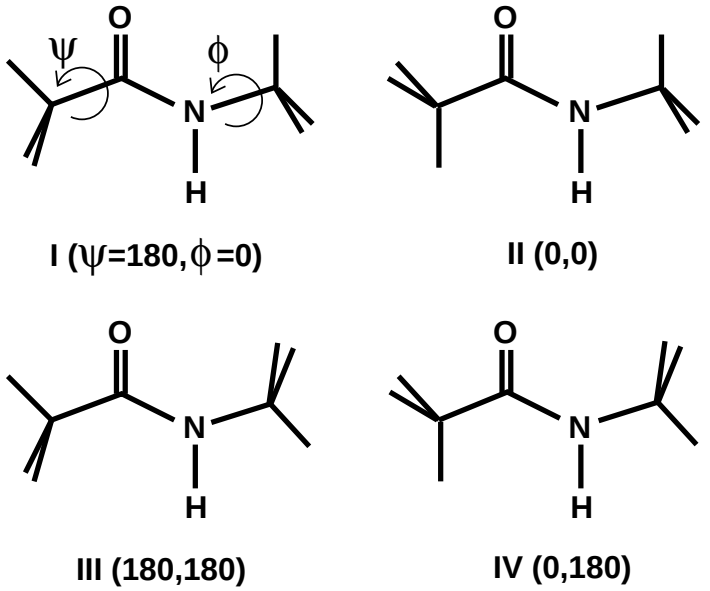
➥ TIP5P slightly different

mTIP3P TIP4P TIP5P HF/6-31G* MP2/6-31G*

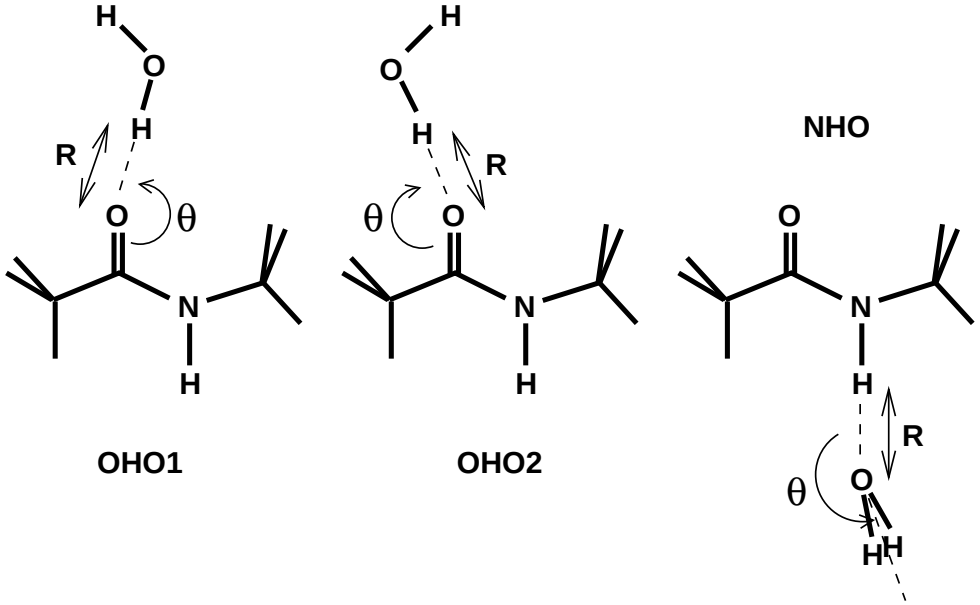
Is there a general way of "correcting" a water model for use with CHARMM *?*

➥ Parameter adjustment : ε, $r_{\min}$ . . . **for the interface only !**

Parameter Adjustment



4 rotamers of NMA



3 hydrogen-bonding conformations

- Optimisation of 2 intermolecular degrees of freedom (R, θ)
- HF/6-31G*, $\Delta E = E_{\text{complex}} - E_{\text{water}} - E_{\text{NMA}}$
- $\Delta E, R, \theta$ used to determine optimal ε and $r_{\min}$

Determining New van der Waals Parameters for NMA–TIP4P

- Evaluate $(\Delta E, R, \theta)$ on a grid $(\varepsilon, r_{\min})$
- Find the best choice of parameters using a merit function :

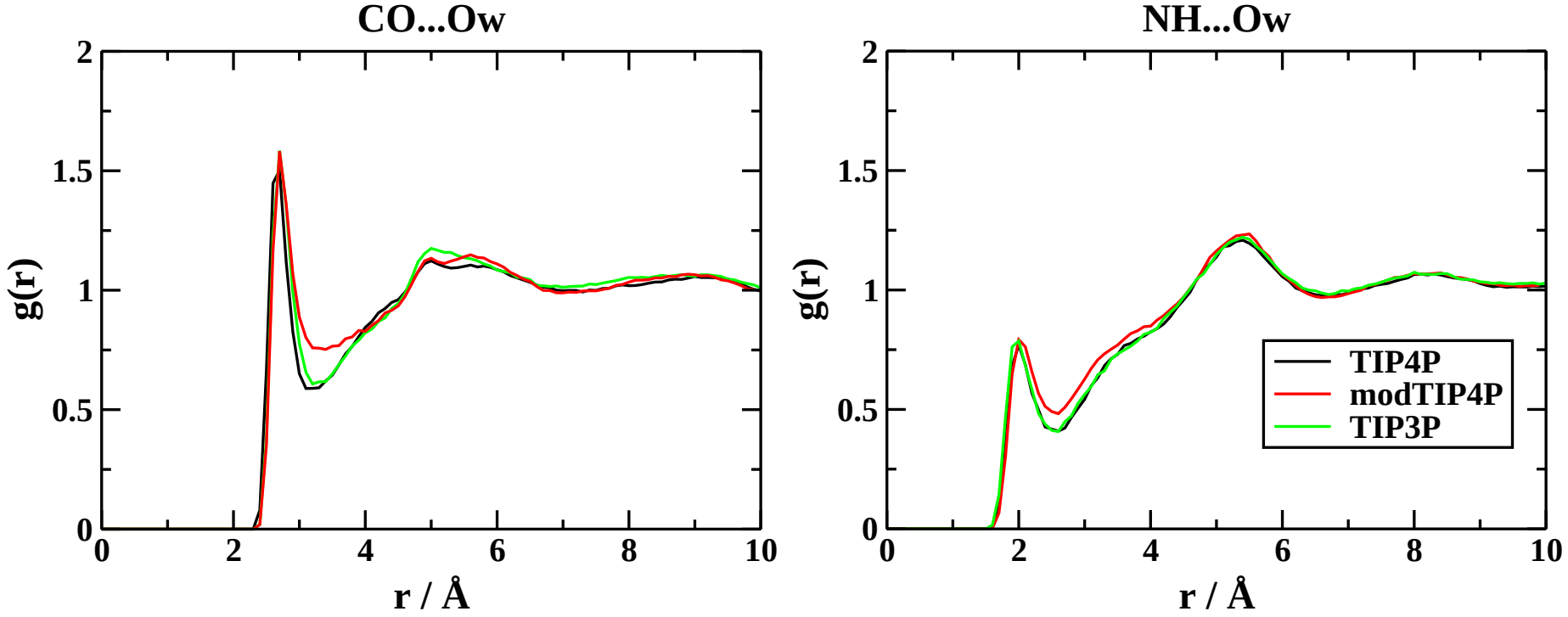
$$M = \sum_{\text{obs.}i} w_i (p_{\text{fit}} - p_{\textit{ab initio}})^2 \qquad \text{where} \qquad w_i = w_{i,\text{rel}} \left(\frac{\text{maxrange}}{\text{range}_i} \right)^2$$

			OHO1			OHO2			NHO		
	ε/kcal/mol	$r_{\min}$/Å	E	R	θ	E	R	θ	E	R	θ
ab initio			−7.54	1.79	145	−7.98	1.79	122	−5.68	1.94	175
original	−0.155	1.77	−7.94	1.72	147	−7.43	1.73	129	−5.53	1.95	171
fit	−0.490	1.67	−8.19	1.76	146	−7.66	1.77	126	−6.02	1.97	171

E in kcal/mol, R in Å, θ in degrees ; data for NMA rotamer I with equal weighting

Assessment of the New Parameters

Local Radial Distribution Functions



Solvation Free Energy

TP = Thermodynamic Perturbation

TI = Thermodynamic Integration

ΔA /kcal/mol	TP	TI
Original	-10.22 ± 0.07	-9.94 ± 0.06
Modified	-18.93 ± 0.06	-18.63 ± 0.06
Expt. (ΔG)	-10.1	

Evaluation of Neutron Structure Factors

Direct calculation of $S(k)$:

$$S(k) = \frac{1}{N}\sum_{\alpha}^{N}\sum_{\beta}^{N} b_\alpha b_\beta \left\langle \exp i\mathbf{k}\cdot(\mathbf{r}_\alpha - \mathbf{r}_\beta)\right\rangle$$

Calculation *via* pair correlation function, $g_{\alpha\beta}$:

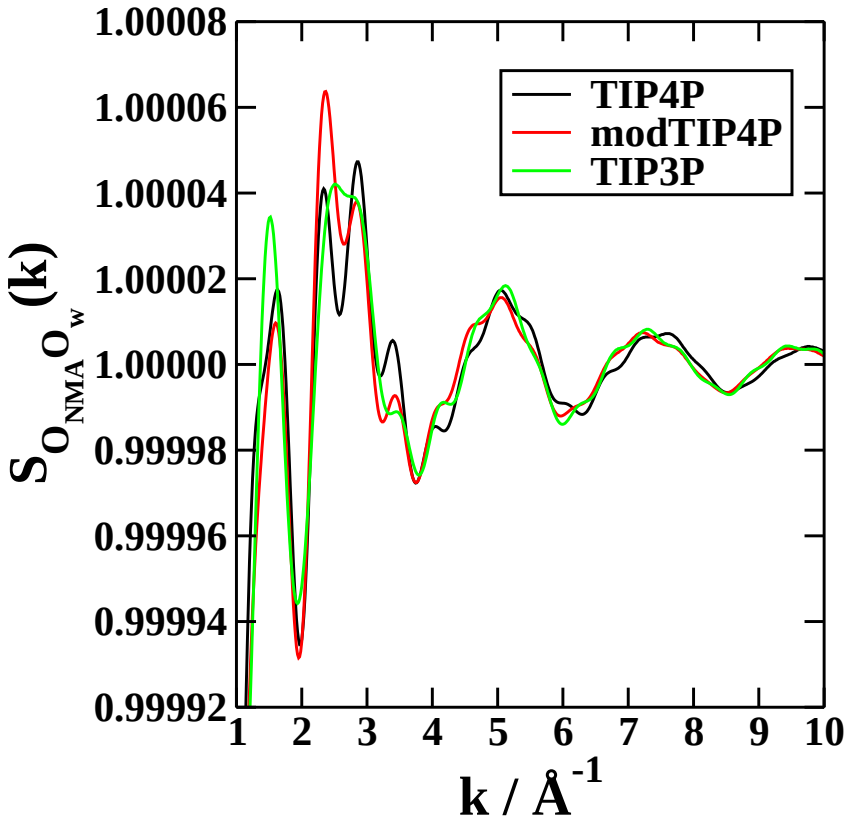
$$S(k) = \sum_{\alpha}^{N}\sum_{\beta\geq\alpha}^{N}(2-\delta_{\alpha\beta})c_\alpha c_\beta b_\alpha b_\beta S_{\alpha\beta}$$

$$S_{\alpha\beta}(k) = 4\pi\rho\int_0^\infty r^2[g_{\alpha\beta}(r)-1]\frac{\sin(kr)}{kr}\mathrm{d}r$$

$b_\alpha =$ coherent scattering length of atom α

$c_\alpha =$ mole-fraction for atom α

$\mathbf{k} =$ scattering vector



Conclusions

- A general method has been developed to enable additional water models to be used with the CHARMM force field
- Parameter modification causes changes in the solvation structure and other observables
- Models could be validated by neutron scattering data

Acknowledgements

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