

## Reduced point charge models of proteins - Influence of protein-solvent interactions

Laurence Leherte, Daniel P. Vercauteren

*Laboratoire de Physico-Chimie Informatique, Unité de Chimie Physique Théorique et Structurale, Department of Chemistry, Namur MEDicine & Drug Innovation Center (NAMEDIC), University of Namur, Rue de Bruxelles 61, B-5000 Namur, Belgium*

We investigate the influence of various solvent models on the structural stability and the protein-water interface of three Ubiquitin complexes (PDB access codes: 1Q0W, 2MBB, 2G3Q) modelled using Amber99sb with two different point charge distributions. A previously developed reduced point charge model (RPCM) [1], where each amino acid residue is described by a limited number of point charges, is tested and compared to its all-atom (AA) version. The complexes are solvated in TIP4P-Ew or TIP3P water molecules, involving either a correction of the Lennard-Jones protein- $O_{\text{water}}$  interaction parameters [2] or the coarse-grain SIRAH water description [3]. Molecular Dynamics (MD) simulation conditions are first refined for complex 1Q0W, whose ligand is a single helix structure that has the ability to bend due to a low  $\alpha$ -propensity region occurring in its amino acid sequence. Results are further confirmed by MD simulations carried out on complexes 2MBB and 2G3Q.

MD results show that the best agreements between the RPCM and AA models are obtained when using (i) the TIP4P-Ew water force field (FF) with a correction factor  $\gamma = 0.7$  or (ii) the hybrid TIP3P/SIRAH FF with a sufficiently large box size and a molecule/bead ratio of 1.2 to 1.4. At the RPCM level, a decrease in  $\gamma$  or the inclusion of SIRAH particles allows to weaken the protein-solvent interactions. It results in a slight collapse of the protein structure and a less dense hydration shell, thus involving a decrease in the protein-water and water-water H-bonds. The dynamics of the surface protein atoms and of the water shell molecules is also slightly refrained, thus allowing to generate stable RPCM trajectories, at a reduced computational cost. Conversely, solvation conditions such as the uncorrected TIP4P-Ew FF and the TIP3P FF at  $\gamma = 1.1$  proposed by Best *et al.* [2] favor the unfolding of protein RPCMs.

- [1] L. Leherte, *Mol. Simul.* **42**, 289 (2016).
- [2] R.B. Best, W. Zheng, J. Mittal, *J. Chem. Theory Comput.* **10**, 5113 (2014).
- [3] L. Darré, A. Tek, M. Baaden, S. Pantano, *J. Chem. Theory Comput.* **8**, 3880 (2012).