Intramolecular Polarisable Multipolar Electrostatics from a Machine Learning Method

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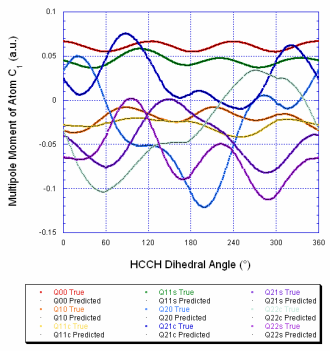

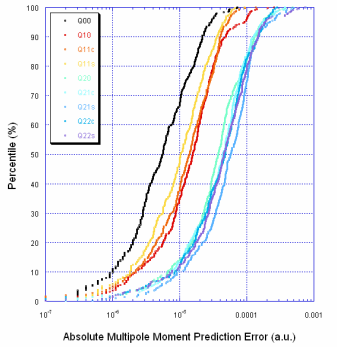

Molecular mechanics methods are ubiquitous in the computational study of chemical problems. Evaluation of the energy of a system with these methods is often many orders of magnitude less computationally expensive than *ab initio* calculation of the same property. However, application to biological systems highlights several shortcomings [1]. In particular, such systems tend to be highly polar leading to difficulty in modeling electrostatic interactions with typical simple expressions. The replacement of inherently limited point charges by a multipolar energy expression relieves this problem by providing a more realistic description of the charge density. In addition, we have applied a machine learning method called Kriging [2] in conjunction with the atomic partitioning at the heart of Quantum Chemical Topology [3,4] to capture the changes in multipole moments with nuclear configuration, that is, the intra-atomic polarisation. The proposed method retains the speed advantage of force field methods over *ab initio* calculations but provides a far more accurate electrostatic picture. Applied to the molecule ethanol as a pilot system, the method produces very accurate results for both the multipole moments and the total molecular 1-4 and higher electrostatic interaction energy over a full range of conformations, with a maximum absolute energy error for any conformation below 0.01 kJmol^{-1}. Extension of the method to other classes of molecules is straightforward. An important advantage of Kriging is that the method remains accurate for systems with a large number of atomic coordinates describing the nuclear configuration. Work towards a general force field for proteins that employs the described methodology is underway.

[1] J.W. Ponder, D.A. Case, *Adv. Protein Chem.,* **2003**, *66*, 27-85.
[2] M.G. Darley, C.M. Handley, P.L.A. Popelier, *J. Chem. Theory Comput.*, **2009**,*5*,1474-1489.
[3] R.F.W. Bader, Atoms in Molecules: A Quantum Theory, **1990**, *Clarendon Press, Oxford, UK*.
[4] P.L.A. Popelier, Atoms in Molecules: An Introduction, **2000**, *Pearson Education, London, UK*.