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Correction to Classical Electrostatics for Biomolecular Simulations

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Popelier and co-workers have developed the Quantum Chemical Topology Force Field (QCTFF), based on the Quantum Chemical Topology (QCT) method. The QCT method is a generalisation of the Quantum Theory of Atoms in Molecules, which generates topological atoms of finite size and particular shapes, using only the gradient of the electron density. QCTFF embraces multipolar electrostatics as a way to overcome the inherent limitations of point charge electrostatics. QCTFF captures polarisation effects (beyond dipole moments) through a machine learning method called kriging. Kriging establishes a *direct* mapping between a given atom's multipole moment and the coordinates of the atoms surrounding it. This procedure handles both inter[1]- and intramolecular[2] polarisation. QCTFF handles the remaining non-electrostatic energy contributions by kriging, thereby offering a seamless treatment of all energy contributions. All training information is sampled from supermolecular clusters, thereby abandoning the framework of long-range perturbation theory that underpins some multipolar force fields. This decision makes the modelling of an ion in aqueous solution[3] conceptually smooth[4-10] . In principle, the method is independent of the basis used, and the QCT partitioning naturally treats charge penetration effects and charge transfer[6]. QCT multipolar electrostatic models have also been used in molecular dynamics simulation, albeit still in the rigid body context. The fully flexible case is feasible and currently being implemented in the program DL_POLY_4. The simulation work shows *both quantitative and qualitative* differences in spatial distribution functions calculated for liquid water[11], aqueous imidazole[12] and hydrated serine[13], again demonstrating the need for multipole moments[14].

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The authors provide the following addition to include references that were inadvertently left out in the original review.

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