

Towards scalable and accurate molecular dynamics using the SIBFA polarizable force field

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Abstract. We present a short overview of the recent developments and applications of the SIBFA (Sum of Interactions Between Fragments Ab initio computed) polarizable force field.

Molecular dynamics (MD) simulations are now an important tool in the chemistry laboratories as they enable the evaluation of macroscopic properties through the use of statistical physics or serve as theoretical microscope to help experimentalists to understand structural properties of biological systems or materials. For a long time, simulations were mainly performed using first generation (i.e. non polarizable) force field models that have the key advantage to enable a fast evaluation of both energies and forces allowing sufficient efficiency to perform million (if not billions) of MD steps. This condition is mandatory to allow sufficient sampling to approach the ergodic hypothesis. For these reasons, community codes such as AMBER [1], CHARMM [2], GROMACS [3] or NAMD [4] appeared and provided large scale capabilities for ~~the~~ modelers in link with massively parallel simulations on supercomputers and/or on Graphics Processing Unit (GPUs) cards. Until recently, simulation possibilities with more advanced polarizable force fields such as SIBFA (Sum of Interactions Between Fragments Ab initio computed) [5] or AMOEBA [6] were still limited by their inherent speed and scalability. This has very recently changed with the advent of GPU codes such as Tinker-OpenMM [7] and thanks to the availability of a massively parallel interface (MPI) version of Tinker denoted Tinker-HP.[8] These modernization/parallelization efforts combined with new algorithmics have changed the status of polarizable force fields which are not slow anymore. They can now perform long simulations providing enough sampling for free energy computations. In this context, the AMOEBA force field is becoming a popular tool. However, other polarizable force fields will soon become available on the Tinker-HP platform which offers various new algorithmic advances dedicated to polarizable force fields. For example, Tinker-HP includes an fast and accurate non-iterative Truncated Conjugated Gradient (TCG) polarization solver [9] offering analytical forces (no MD drifts anymore!) which is available together with more standard iterative methods such as JI/DIIS or Preconditioned Conjugate Gradient (PCG).[10] It also includes an efficient domain decomposition (dd)-Cosmo polarizable continuum method [11] and various polarizable QM/MM possibilities.[12]

In this context, the SIBFA force field is now available thanks to a final derivation of all its gradients and it will benefit from all these advances. SIBFA is a polarizable force field formulated and calibrated on the basis of ab initio Quantum Chemistry energy decomposition analyses such as SAPT [13] or CSOV. [14] Using distributed multipoles, its purpose is to enable the simultaneous and reliable computations of both intermolecular and conformational energies governing the binding selectivities of biologically and pharmacologically-relevant molecules.

In SIBFA, the intermolecular interaction energy is computed as a sum of five separate contributions [5]:

$$\Delta E_{\text{tot}} = E_{\text{MTP}^*} + E_{\text{rep}} + E_{\text{pol}} + E_{\text{ct}} + E_{\text{disp}}$$

E_{MTP^*} is the electrostatic (multipolar) contribution, computed with distributed multipoles derived from the ab initio wave function of the constitutive fragments. It includes a short-range penetration correction. [15] The multipoles (up to quadrupoles) are located on the atoms and bond barycenters. E_{rep} is the short-range repulsion energy, computed as a sum of bond-bond, bond-lone pair, and lone pair-lone pair interactions. [16] E_{pol} is the polarization energy contribution, computed with distributed, anisotropic polarizabilities. These are located on the centroids of the localized orbitals, heteroatoms and bond barycenters, and are also derived from ab initio QC computations. E_{ct} is the charge-transfer energy, in which a coupling with the polarization is introduced, and E_{disp} is the dispersion energy contribution.

In recent years, SIBFA has been shown to be a reliable and accurate method enabling a very rich diversity of applications owing to its capability of dealing with charged systems including metal cations. Of course, biological systems are the main target offering complex studies on metalloprotein systems, nucleic acids, or systems interacting with metals.[17] It also enables to tackle systems usually mostly devoted to quantum chemistry studies [18] such as lead compounds [19] or lanthanides and actinides.[20] The availability of SIBFA in a periodic boundary condition context using Smooth Particle Ewald [21] is the key step in the new possibilities offered to the Tinker-HP user. Tinker-HP now allows to perform hundreds of nanosecond simulations on difficult systems including free energy computations such as those presently done by AMOEBA. [22] The work presently undertaken also offers novel perspectives for the Tinker-HP implementation of the third generation Gaussian Electrostatic Model GEM force field which is based on electron density [23]

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