

Thesis Abstract

Molecular mechanical simulations of biomolecules require an accurate potential energy function (forcefield) in order to produce meaningful results. Most current forcefields are highly parameterized in order to correctly reproduce high level theory and experiment. Increasingly, new biomolecules are designed and studied that have atypical configurations such as metal centers and nonstandard amino acids. To avoid a lengthy process to develop new parameters for each new system encountered, a generic forcefield is desired. A hierarchical approach is undertaken herein to achieve this flexibility and accuracy.

Building upon the rule based generic forcefields UFF and Dreiding, a new biological universal forcefield, BUFF, is presented for the simulation of proteins and other biological molecules. In addition to its UFF and Dreiding based terms, the BUFF has additional hydrogen bond terms, specialized protein backbone torsions, and a process for deriving charges for amino acids that is independent of other parameterization. These additional parameters have been fit to *ab initio* quantum mechanical calculations carried out on model systems.

Validation studies of peptide trimers demonstrate that the BUFF accurately reproduces the quantum mechanical torsional energies. Several other common, highly parameterized forcefields are also applied to the same tripeptide systems, as well as short α -helical chains and other model systems in order to make a comparison to the BUFF. These studies show that while the BUFF is universal and can be quickly deployed on new

systems, such as unnatural amino acids or metal containing systems, it is also at least as accurate as other commonly employed, but highly parameterized, forcefields. The biological universal forcefield described herein is presented as complementary to the MSC forcefield derived for simulations of DNA and other nucleic acids.