**Developing and Testing Molecular Mechanics Force Fields for Biomedical Research**

Molecular simulations have been playing essential roles in biochemical and biophysical research. One of their major applications is to elucidate the molecular interactions between small molecule ligands and protein or nucleic acid targets so that rational design of high-potency agonists or antagonists can be conducted to enhance or eradicate the functions of their targets. A key to the success of such applications is the quality of molecular mechanics force fields (**MMFFs**). However, nowadays it is still very challenging to accurately predict the free energies of such interactions and processes. The major goal of this project is to significantly improve the quality and chemical space coverage of the existing as well as to develop a new generation of the general AMBER force fields (**GAFF**) for studying biomolecule-ligand interactions. The new general-purpose MMFF (referred to here and thereafter as **GAFF3**) will be based on a new charge model that is efficient, largely conformation-independent, and highly accurate for solvation free energy calculations. The developed GAFF force fields will be rigorously scrutinized and critically assessed through direct comparisons with experimental data of an extensive set of model systems. In the long run, a spectrum of high-quality GAFF3 compatible MMFFs will be developed for all types of biological macromolecules following a top-down force field parameterization strategy. The new set of MMFFs will be highly transferable and self-consistent for studying protein-ligand and nucleic acid-ligand interactions, and will enable more accurate calculations of the protein-ligand and nucleic acid-ligand binding free energies to facilitate computer-aided drug discovery. The large-scale FF assessment will be accelerated by utilizing GPUs in both MD simulations and alchemical free energy calculations. The successful pursuit of this project will result a set of GAFF2 force fields which are compatible with the current AMBER biomolecular force fields and released with the AMBER software package according to the roadmap. GAFF3, a new generation of general-purpose force field based on a high-quality charge model, will also be developed and released with AMBER software package. GAFF3 in combination with the GAFF3-compatiable biomolecular force fields will enable us to more accurately model biosystems and calculate the free energies of protein-ligand and nucleic acid-ligand binding, which will in turn greatly improve the success rate of computer-aided drug design.