**Scope of Work (SOW)**

**Project Title:** Development and Test of Molecular Mechanics Force Fields for Biomedical Research

**Period of Performance:** 09/01/2019 to 08/31/2024.

**Document Date:** 1/24/2019

**Objective:** The major goal of the proposed project is to further develop the existing and 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) is based on a new charge model which is efficient, largely conformation-independent, and has high accuracy on solvation free energy calculations. In a long run, a spectrum of high-quality GAFF3 compatible MMFFs will be developed for all types of biological macromolecules for biomedical research. 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 and facilitate computer-aided drug discovery. The developed GAFF force fields will be rigorously scrutinized and critically assessed through direct comparisons with experiments in an extensive set of model systems.

**Scope:** Specific to the work to be done at Rutgers: large-scale assessment of the developed MMFF through GPU-accelerated free energy approaches recently developed by the PI.

**Tasks/Scientific Goals:**

Very recently a set of tools based on GPU-accelerated free energy methods have been developed by the PI, i.e., the 𝞴 -SAMS approaches, which speedup the convergence of alchemical transformations by roughly three to five folds. Given that the speedup of the AMBE GPU TI code over the CPU code is over two orders of magnitudes, now it is possible to assess the performance of new force-field in free energy calculations on GPU roughly three orders of magnitudes faster than on CPU. We will utilize the new GPU-accelerated free energy sampling (𝞴 -SAMS) to critically evaluate the proposed force fields:

* Establishing an extremely fast free energy simulation pipeline infrastructure;
* Performing simulations on a current golden-standard of protein-ligand free energy simulation data set;
* Producing meaningful error bars through multiple independent simulations.

**Personnel:**

* Taisung Lee (PI), Dr. Lee will be responsible for the whole project and will oversee and direct all aspects of the research project. He will plan the tasks necessary and design the software infrastructure for performing the assessment work.
* To be named, Postdoctoral researcher: will be advised by Dr. Lee will receive specialized multidisciplinary training within the LBSR, including free energy methods, and the applications of relevant biological systems. The postdoc researcher will be responsible for constructing and verifying proposed free energy pipeline based on various free energy methods, and he will perform testing/benchmarking proposed to-be-developed force fields.

**Deliverables and Timeline:**

* 1st Yr: A software infrastructure of fast free energy simulation pipeline for assessing the performance and errors of MMFF.
* 2 nd Yr: Perform the assessment of the current GAFF2. Deliver the assessment report by end of the project year.
* 3 rd Yr: Perform the assessment of the newly developed GAFF3. Deliver the assessment report by end of the project year.
* 4 th and 5th Yr: Perform the assessment of the newly developed MMFF based on new point charge models. Deliver the assessment report by end of the project year.