Physical Chemistry Seminar

Tuesday, September 17, 2013 | **11:00 am** | **Room 1315 Chemistry Building**

Free Energies from a Molecular Printing Press

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Host: Professor Qiang Cui

Docking (posing) calculations coupled with binding free energy estimates (scoring) are a mainstay of structure-based drug design. Docking and scoring methods have steadily improved over the years, but remain challenging because of the extensive sampling that is required, the need for accurate scoring functions and challenges encountered in accurately estimating entropy effects. This talk addresses the use of ensemble principles to directly address these issues and, thereby, accurately estimate protein-ligand binding free energies. In particular, we analytically demonstrate that sampling reduces computed binding free energy uncertainties and then highlight several methods that incorporate these concepts. For example, the moveable type method, employs an elegant approach to generate the necessary ensembles by using a “binned” pairwise knowledge-based potential combined with atom pair probabilities extracted from known protein-ligand complexes. This allows us to rapidly compute the ligand, protein and protein-ligand (inclusive of solvation effects) ensembles which then can be used to directly estimate protein-ligand binding free energies using basic statistical mechanical principles. This approach improves the quality of the potential (scoring) function by reducing computational uncertainty, sampling phase space in one shot and accurately incorporating entropy effects. This allows us to compute binding free energies rapidly, accurately and yields molecular poses at a minimal computational cost relative to currently available methods based on statistical mechanics.

Refreshments will be available prior to the seminar at 10:45 a.m. outside room 1315

Graduate Students may meet with the speaker at 1:00 p.m. in Room 8305F