[L12] Rapid Computation of Thermodynamic Quantities for Molecular Recognition Processes

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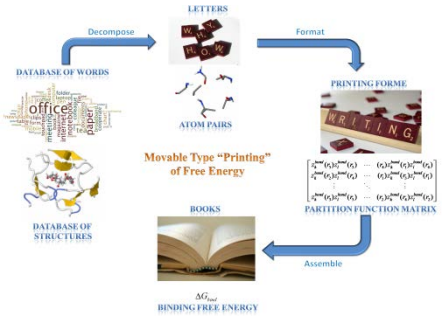

Scheme 1. Visual Summary of the movable type algorithm

Docking ("posing" ligands in a binding pocket) 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. To address this we developed the Movable Type sampling (MTS) method that rapidly creates molecular ensembles that can be used to estimate free energies, entropies and enthalpies using statistical mechanics. The MTS method employs an elegant approach to generate the necessary statistical mechanical ensembles by using a grid-based pair-wise representation of a physics-based potential like the AMBER or CHARMM force field combined with atom pair probabilities extracted from structural databases like the Protein Databank (PDB) or the Cambridge Structural Database (CSD). In the realm of structure-based drug design MTS 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, enthalpies and entropies. This approach improves the quality of the potential (scoring) function by reducing computational uncertainty, rapid ensemble generation and accurately incorporating entropy effects. In this presentation will be give a number of examples where we compute thermodynamic and structural quantities associated with a myriad of biological processes rapidly, accurately and at a minimal computational cost relative to currently available methods.