Web TIES: A Portal for Relative Binding Free Energies with a Flexible Superimposition Algorithm based on Dual Topology with support for NAMD 2/3 and OpenMM

The alchemical approach to Relative Binding Free Energy calculations requires a high-quality mapping of atoms across compared ligands. Our new software TIES 20 uses a flexible recursive joint-traversal algorithm for the generation of the Maximum Common Substructure. On average, by enabling partial ring morphing, smaller alchemical regions were computed. Initially, we evaluated the software with NAMD 2 using the dual topology approach, although support for NAMD3 and OpenMM is being released now. We show a clear relationship between the size of the alchemical region and the uncertainty in the predicted binding energies. We further show that AM1-BCC modifies the charges closer to the site of the mutation, decreasing the size of the alchemical region substantially, allowing for easier convergence. Our results demonstrate that having 5 replicas per lambda window significantly improves reproducibility of the binding energies in comparison to just one replica, but even so the reproducibility highly depends on the complexity of the system. Finally, we are releasing a web portal ccs-ties.org along with a python toolkit for analysis to facilitate the preparation, execution and analysis of Relative Binding Free Energies.