Reliably and repeatably predicting free energies by combining MM-PBSA with LES

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Calculating free energies of binding for protein-protein interactions accurately and reliably remains a challenging goal for biomolecular simulations. The MM-PB/GBSA approaches are widely used to predict and rank relative binding free energies ($\Delta\Delta G$) for complexes and their mutants. However, the accuracy and repeatability of their predictions is plagued by inherent difficulties with molecular dynamics (MD) – how can we be sure of generating converged free energy estimates and sampling experimentally relevant dynamics on the MD timescale?

Previous work in our group [1] and by others [2] has highlighted the use of multiple independent trajectories in improving precision of $\Delta\Delta G$ estimates, as well as the potential advantages of using post-process alanine scanning for cancellation of errors between native and mutant trajectories. However, post-process alanine scanning is not suitable in cases where mutation may induce local structural changes in the protein. Therefore, we propose an alternative approach to generating mutant dynamics using a heterogeneous form of Locally Enhanced Sampling (LES).

We perform LES simulations combining copies of native and mutant structures simultaneously, then extract the trajectories of native and mutant structures separately and calculate $\Delta\Delta G$. This combines the cancellation of errors present in post-process alanine scanning with allowances for small local rearrangements on residue mutation, potentially far better replicating the experimental dynamics. In addition, the size of the LES region (in which we allow local differences between native and mutant) is entirely flexible, and likewise the protocol also allows for mutations to residues other than alanine.

Preliminary results have shown good agreement with experimental data for a variety of mutations, hence we are currently extending the protocol to situations where traditional MM-PB/GBSA or post-process alanine scanning has failed to predict $\Delta\Delta G$s correctly.

1. R. T. Bradshaw, et al., *Prot. Eng. Des. Sel.*, **2011**, *24*, 197-207.
2. S. Genheden and U. Ryde, *J. Comp. Chem.*, **2009**, *31*, 837-846.