Optimizing Gō-like coarse-grained models for protein-protein interactions

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Acknowledgements

Financial support for this research was provided by the National Science Foundation.

Protein-protein interactions in the cell

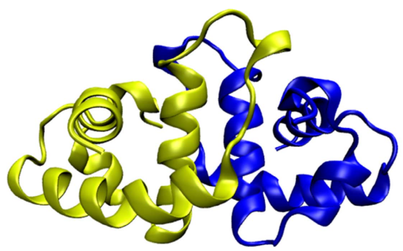
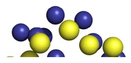


Figure 1: Crystal structure of the HdeA homodimer (PDB: 1BG8), which regulates the proper folding of aggregates at low pH in enteropathogenic bacteria.



Proteins are rarely isolated in their natural cellular environments. Accepted estimates of average (mammalian) cellular protein concentration range from 1-5 million proteins/μm^3 (1 protein/20 Å^3). This concentration suggests proteins interact frequently. Previous work indicates the regulatory role of protein-protein interactions (PPIs) in a variety of biological processes, including chaperone-assisted folding[1] of intermediates (see HdeA, Figure 1).

Here we discuss efforts to optimize a PPI potential (V^{inter}) for C_α-based molecular modeling (Figure 2) of HdeA dimeri-

"Decoy" ensembles to improve specificity

Cellular protein concentrations also suggest that specificity, or preference for a specific binding partner/interface, may play a role in the regulatory mechanisms of protein-protein interactions. We "train" specificity into our model by optimizing ε with respect to the Z-score[5], calculated from ensemble average interaction energies (V^{inter}) of correctly bound and "decoy" poses. 100 initial decoy poses were identified with Z-dock[6], and compose the nonnative ensemble. 10 bound poses were chosen by clustering CHARMM[7] Gō model simulation output (<1 Å RMSD to native) beginning from the native structure, and selecting conformations with low V^{inter}.

Optimizing residue-residue interaction strengths (ε) using a genetic algorithm

Define 10 population members (sets of 20 ε)

Preliminary Results

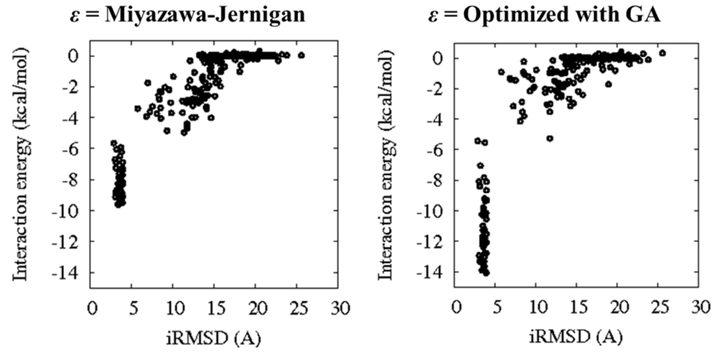


Figure 3: *Inter*-molecular residue-residue interaction energies (V_{ij}^{inter}) are plotted relative to the RMSD to native (bound pose) residue-residue distances. V_{ij}^{inter} are plotted for native and nonnative ensemble members. Miyazawa-Jernigan self-