Robotics Inspired Proteomics

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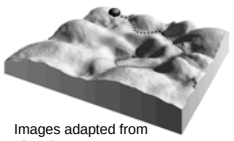
Protein Amino Acid Sequence | 3-Dimensional Folded Protein | Protein Motion and Docking | Facilitate Cures and Understanding of the Cell

Protein Structure Prediction

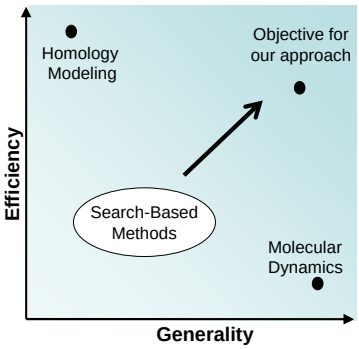
Protein Folding in Nature



Images adapted from Theodore .L. Brown

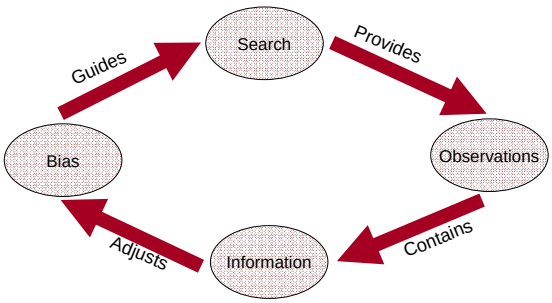
The biologically occurring state of a protein is called the native state. As a protein transforms from the amino acid sequence into its 3-D confirmation, it is constrained by chemical and physical properties of the individual atoms, and this interplay of forces is often depicted as traversal over an energy landscape.

Our Approach



We define **generality** as the ability to make template-free predictions, and **efficiency** as the computation time required to make predictions with maximum accuracy. Homology modeling considers similar proteins with known structures, molecular dynamics folds a protein from first principles, and search-based methods use short homologous fragments to find the minimum energy in solution space.

We exploit the information that is obtained **during** the search itself. Every step of search uncovers information about the prediction target, and this information can be used to further guide the search.



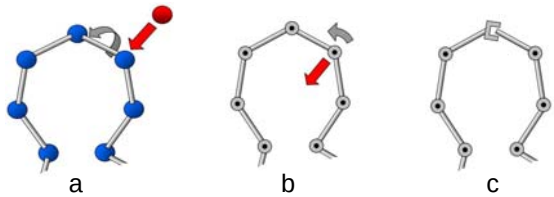
Results

Rosetta is a leading computational approach which uses a Monte Carlo simulated annealing search strategy which has performed very well in CASP competitions. **Our Approach** Uses the Rosetta score function but uses our improved search strategy. A lower RMSD designates a better match with the "true", native structure.

Rosetta 8.5 RMSD | Native | Our Approach 4.2 RMSD

Protein Motion and Docking

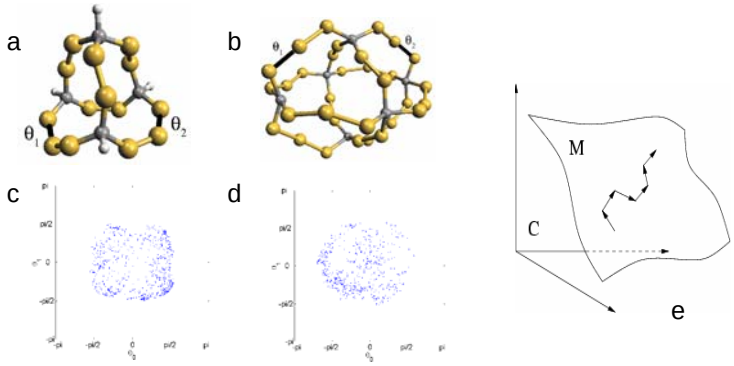
Viewing a Protein as a Robot



a b c

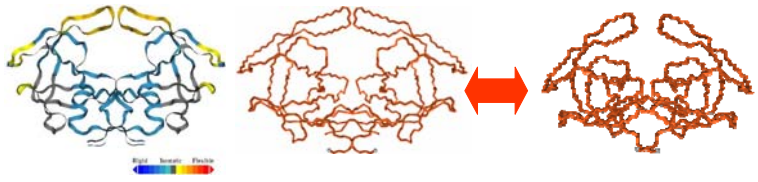
We model proteins as robotic chains, and by applying kinematic projections, forces acting in Euclidean space are projected into the conformational space, as shown in (a) and (b). The projection respects the kinematic constraints of the mechanism. We consider closed loops to consist of two open loops with enforced end-point constraints (c).

Motion Planning Under Constraints



Motion inside a protein occurs in a low degree of freedom space which is a subset of the entire configuration space (C), which we call the protein's self-motion manifold (M), (e). Molecules a and b have self motion manifolds as show in c and d. The two molecules have 3 and 7 loop closure constraints, and after considering covalent bonds and loop constraints and by utilizing the self-motion manifold, we are able to maintain loop closure. (Work done in collaboration with Audrey Lee and Ileana Streinu)

Protein Motion



k m n

We merge the concepts of protein robot simulation with motional planning using the self-motion manifold to model the self-motion of HIV-1 protease, PDB 1HHV, (m, n). The real-time motion is caused by a spherical ligand interacting with the flexible flap of the active site, and our model fits well with experimental flexibility and rigidity results (k) by D. J. Jacobs, A. Rader, M. F. Thorpe, and L. A. Kuhn.