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Using robotics to fold proteins and dock ligands

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ABSTRACT

The problems of protein folding and ligand docking have been explored largely using molecular dynamics or Monte Carlo methods. These methods are very compute intensive because they often explore a much wider range of energies, conformations and time than necessary. In addition, Monte Carlo methods often get trapped in local minima. We initially showed that robotic motion planning permitted one to determine the energy of binding and dissociation of ligands from protein binding sites (Singh *et al.*, 1999). The robotic motion planning method maps complicated three-dimensional conformational states into a much simpler, but higher dimensional space in which conformational rearrangements can be represented as linear paths. The dimensionality of the conformation space is of the same order as the number of degrees of conformational freedom in three-dimensional space. We were able to determine the relative energy of association and dissociation of a ligand to a protein by calculating the energetics of interaction for a few thousand conformational states in the vicinity of the protein and choosing the best path from the roadmap.

More recently, we have applied roadmap planning to the problem of protein folding (Apaydin *et al.*, 2002a). We represented multiple conformations of a protein as nodes in a compact graph with the edges representing the probability of moving between neighboring states. Instead of using Monte Carlo simulation to simulate thousands of possible paths through various conformational states, we were able to use Markov methods to calculate the steady state occupancy of each conformation, needing to calculate the energy of each conformation only once. We referred to this Markov method of representing multiple conformations and transitions as stochastic roadmap simulation or SRS. We demonstrated that the distribution of conformational states calculated with exhaustive Monte Carlo simulations asymptotically approached the Markov steady state if the same Boltzman energy distribution was used in both methods. SRS permits one to calculate contributions from all possible paths simultaneously with far fewer energy calculations than Monte Carlo or molecular dynamics methods. The SRS method also permits one to represent multiple unfolded starting states and multiple, near-native, folded states and all possible paths between them simultaneously. The SRS method is also independent of the function used to calculate the energy of the various conformational states.

In a paper to be presented at this conference (Apaydin *et al.*, 2002b) we have also applied SRS to ligand docking in which we calculate the dynamics of ligand-protein association and dissociation in the region of various binding sites on a number of proteins. SRS permits us to determine the relative times of association to and dissociation from various catalytic and non-catalytic binding sites on protein surfaces. Instead of just following the best path in a roadmap, we can calculate the contribution of all the possible binding or dissociation paths and their relative probabilities and energies simultaneously.

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