The Docking Mesh Evaluator

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1 Introduction

The Docking Mesh Evaluator (DoME) is a software for predicting a bound protein-ligand docking configuration by determining the global minimum of a potential energy function. Our present energy model is based on solvent effects defined implicitly using the Poisson-Boltzmann equation, as well as a pairwise Lennard-Jones term.

2 Software

Our approach consists of two phases. The first involves scanning the energy landscape for favorable configurations. This phase can be done once as a preprocessing step and need not be done again. The second phase involves the iterative underestimation of successive collections of local minima with convex quadratic functions, using the configurations from the first phase as initial seed points for optimization. The minima of the underestimators are then used as predicted values for the global minima. Both serial and parallel versions of this "coupled" optimization have been successfully implemented. Preliminary results are reported in [2].

Currently, our research is focused on optimizing parameters in the energy function, in order to obtain the best accuracy in predicting known docking configurations. In particular, we consider the benchmarking set of Chen et al. [1] for testing protein-protein docking algorithms. Of the 59 test cases it contains, 22 are enzyme-inhibitor complexes, 19 are antibody-antigen complexes, 11 are various diverse complexes, and 7 are difficult test cases whose solutions have significant conformational changes. These optimized parameters are expected to yield realistic results for biological problems whose solutions are unknown.

Flexibility in the protein-ligand model is being implemented using a hybrid of global optimization and rotamer search. Near the surface interface, subtle side-chain rearrangements are often necessary to model induced fit between the receptor and the ligand. These rearrangements can be modeled using candidate residue conformations, called rotamers. Using this approach, the protein backbone is held fixed while residues are allowed to take on various configurations. Such pseudo-flexibility is a more viable alternative to full backbone and side-chain flexibility, which requires inordinately many free variables, thus making the computational cost prohibitively expensive. Local shape complementarity analysis performed using the Fast Atomic Density Evaluator [3] will provide added efficiency by highlighting regions in which shape mismatches occur.

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