

EROS-DOCK and EROS-DOCK MULTI-BODY Approach

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Protein-protein docking aims to predict the 3D structure of a binary complex using the structures of the individual proteins. This typically involves searching and scoring in a six-dimensional space. Many docking algorithms use FFT techniques to exhaustively cover the search space and to accelerate the scoring calculation. However, the results often depend on the initial protein orientations with respect to the Fourier sampling grid. Furthermore, Fourier-transforming a physics-base force field can involve a serious loss of precision.

Here, we present a novel docking algorithm, EROS-DOCK (Exhaustive Rotational Search based Docking) to rigidly dock two proteins using a series of exhaustive 3D rotational searches, in which non-clashing orientations are scored using ATTRACT coarse-grained force field. Eros-DOCK retains the exhaustive nature of FFT-based search algorithms while using a sensitive physics-based scoring function. Rather than calculating an $O(N*M)$ interaction energy explicitly at every grid point, we use a quaternion “ π -ball” to represent the space of all possible 3D Euler angle rotations, and we recursively sub-divide the π -ball in order to cover the rotational space in a systematic way. We apply a “branch-and-bound” approach for the efficient pruning of rotations that will give steric clashes.

The algorithm was tested on a benchmark of 173 complexes, and results were compared with those of a ATTRACT. Eros was able to find local minima that were not explored by the ATTRACT gradient-driven atom-based search. After refinement by a short coarse-grained minimization, EROS-DOCK results were significantly superior to ATTRACT's results according to the standard CAPRI criteria.

This is the first time that a branch-and-bound based rotational search is applied to the 6D rigid-body protein docking problem. Given the first success of EROS-DOCK, we are now applying it to multi-body combinatorial docking.

This multi-body approach takes advantage of tools as the fast RMSD proposed in [], to compute in an efficient way the RMSD between two transformation matrices and we use 3D rotational maps to find possible good solutions.

Since a multi-body complex can be seen as a graph, we build possible multi-body solutions from pairwise solutions, where a pairwise solution is an edge that connects a node pair to obtain a connected graph. However, It is necessary to know all the edges that remain unknown. It is possible to expect that if the one unknown edge corresponds to a good solution, such solution can be found in the corresponding pairwise solutions list. Our idea is to perform an efficient search applying the “branch-and-bound” approach of the 3D rotational map to detect rotations that lead to pairwise solutions, and using the fast RMSD we can know how similar is the unknown edge to some pairwise solution.

For a first stage, we have implemented this approach for three multi-body complexes, and it was tested using several complexes. From the results, we can determine this approach can be used to perform and efficient multi-body docking. For consequent work, we will extend it to deal with more than 3 molecules.