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FireDock: a web server for fast interaction refinement in molecular docking†

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ABSTRACT

Structural details of protein–protein interactions are invaluable for understanding and deciphering biological mechanisms. Computational docking methods aim to predict the structure of a protein–protein complex given the structures of its single components. Protein flexibility and the absence of robust scoring functions pose a great challenge in the docking field. Due to these difficulties most of the docking methods involve a two-tier approach: coarse *global search* for feasible orientations that treats proteins as rigid bodies, followed by an accurate *refinement* stage that aims to introduce flexibility into the process. The FireDock web server, presented here, is the first web server for flexible refinement and scoring of protein–protein docking solutions. It includes optimization of side-chain conformations and rigid-body orientation and allows a high-throughput refinement. The server provides a user-friendly interface and a 3D visualization of the results. A docking protocol consisting of a global search by PatchDock and a refinement by FireDock was extensively tested. The protocol was successful in refining and scoring docking solution candidates for cases taken from docking benchmarks. We provide an option for using this protocol by automatic redirection of PatchDock candidate solutions to the FireDock web server for refinement. The FireDock web server is available at http://bioinfo3d.cs.tau.ac.il/FireDock/.

INTRODUCTION

Protein–protein interactions are essential for many biological processes in the cell. In recent years, there has been a major progress in high-throughput identifications of interacting proteins (1). Despite recent advances in the Structural Genomics project (2), the number of experimentally solved structures of protein–protein complexes remains very low (3). Therefore, computational methods are essential for 3D characterization of protein–protein interactions.

Protein–protein docking aims to predict the 3D structure of a protein complex given the structures of the individual proteins that assemble it. Protein flexibility (4) and the absence of robust scoring functions present a major challenge in the docking field. The flexibility of proteins includes both backbone and side-chain movements, and dealing with it significantly extends the search space for the optimal complex structure (5,6). In addition, state of the art scoring functions are not tolerant enough to the inaccuracies in the predicted structures (7). Therefore, near-native solutions may not be highly ranked. Due to these difficulties, many docking methods apply a two-stage approach. First, *soft rigid docking* is performed (8–11), allowing a certain amount of steric clashes. Then, thousands of solution candidates are refined and re-scored in a *refinement stage* (5,6). In this stage, each solution candidate is improved by modeling the protein flexibility and optimizing the rigid-body orientation.

Most of the refinement methods use an optimization of the side-chain conformations and/or rigid-body orientation in order to minimize a certain scoring function. Only a few of them incorporate backbone flexibility.

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One of the main differences between the refinement methods is in the approach used for side-chain optimization: Monte-Carlo (MC) (12,13), graph theory-based methods (14,15), linear programming (LP) (16), etc. The optimization of the rigid-body orientation usually involves a randomized perturbation followed by energy minimization. The minimization is performed using methods such as Steepest Descent (17), Newton–Raphson (18,19), Quasi-Newton (12,16) and more.

There are several web servers that deal with different aspects of the docking challenge: ZDock (20) and PatchDock (21) perform rigid-body docking. ClusPro (22,23) can filter, cluster and rank docking solution candidates. SmoothDock (24) is a newer version of ClusPro that also refines the representatives of the largest clusters . RosettaDock (12,25) web server allows local search in the vicinity of a single given input solution candidate. The GRAMM-X (26) and Hex (27) web servers perform rigid-body docking followed by an optimization of the rigid-body orientation.

FireDock method for flexible refinement and scoring of protein–protein docking solutions was developed by Andrusier *et al*. (16) and was previously available only for downloading. Here we present the FireDock web server that provides a user-friendly interface for running this protocol online. It is the first web server for refinement of protein–protein docking solutions that includes a side-chain optimization component. It allows a high-throughput refinement of up to 1000 solution candidates. The method simultaneously targets the problem of flexibility and scoring of solutions produced by fast rigid-body docking algorithms. The output provides a list of refined complexes, sorted by a binding energy function, and a 3D visualization for observing and comparing between the refined complexes.

Additionally, we suggest a platform for performing full docking protocol: rigid-body docking by the PatchDock web server (21) and a redirection of the results for refinement and scoring by FireDock web server. This protocol was thoroughly tested (16) on protein–protein docking benchmarks (28,29).

THE FIREDOCK METHOD

The input to the FireDock algorithm is a set of candidate complexes. Each complex consists of two proteins: *receptor* and *ligand*. The method refines each candidate and ranks all the candidates according to the binding energy.

The FireDock (16) method includes three main steps:

(1) Side-chain optimization: The side-chain flexibility of the receptor and the ligand is modeled by a rotamer library. The optimal combination of rotamers for the interface residues is found by solving an integer LP problem (30–32). This LP minimizes a partial energy function consisting repulsive van der Waals and rotamer probabilities terms.
(2) Rigid-body minimization: This minimization stage is performed by a MC technique that attempts to optimize an approximate binding energy by refining the orientation of the ligand structure. The binding energy consists of softened repulsive and attractive van der Waals terms. In each cycle of the MC method, a local minimization is performed by the quasi-Newton algorithm (33,34). By default, 50 MC cycles are performed.
(3) Scoring and ranking: This final ranking stage attempts to identify the near-native refined solutions. The ranking is performed according to a binding energy function that includes a variety of energy terms: desolvation energy (atomic contact energy, ACE), van der Waals interactions, partial electrostatics, hydrogen and disulfide bonds, π-stacking and aliphatic interactions, rotamer's probabilities and more.

The FireDock method was extensively tested (16) on docking candidates generated by the PatchDock method (10,21) for cases from benchmark 1.0 and 2.0 (28,29). FireDock succeeded in ranking a near-native solution in the top 15 predictions for 83% of the 30 enzyme–inhibitor test cases and for 78% of the 18 semi-unbound antibody–antigen test cases.

FIREDOCK WEB SERVER

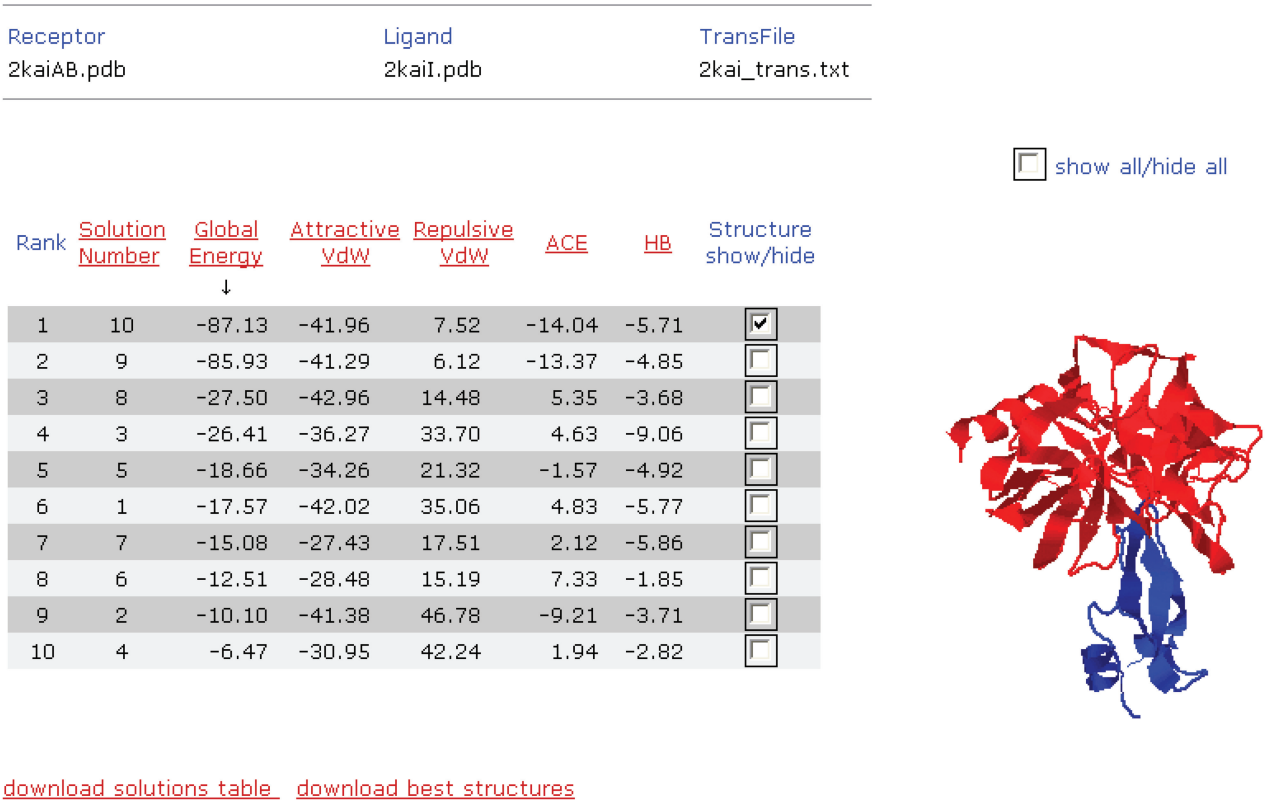
The FireDock web server is available at http://bioinfo3d.cs.tau.ac.il/FireDock/.

Input

There are two input options for the FireDock web server. In the first option, the user uploads or specifies codes of two Protein Data Bank (PDB) (35) files (*receptor* and *ligand*) and provides a list of up to 1000 transformations (the required format is detailed in the *Help* page of the web server). Each transformation, when applied on the ligand, produces a candidate docking solution. In the second option, the user can upload an input PDB file, with each docking solution represented by a MODEL. The candidate solutions for FireDock can be generated by rigid-body docking methods, such as PatchDock (10,21), methods that use Fast Fourier Transform (FFT) such as ZDOCK (20,36), GRAMM-X (26), Hex (27), etc. The PatchDock server (http://bioinfo3d.cs.tau.ac.il/PatchDock/) includes an option for automatic redirection of the solution candidates to FireDock.

In addition, the user may modify the 'Number of output structures' parameter. This parameter determines the number of best scoring candidates for which a PDB file with the refined structure will be generated. The server allows generating up to 100 PDB files. A link to the output web-page is sent to the email of the user as soon as the refinement process is finished.

The server includes optional advanced parameters for adjusting the refinement and scoring for a specific biological system. The user can specify the type of the complex (Default, Antibody–Antigen or Enzyme–Inhibitor), which is used for adjusting the weights of the scoring function. Furthermore, the user can specify if the proteins are in their bound or unbound conformation and if certain side-chains are known to be flexible or fixed.



Receptor	Ligand	TransFile
2kaiAB.pdb	2kaiI.pdb	2kai_trans.txt

show all/hide all

Rank	Solution Number	Global Energy ↓	Attractive VdW	Repulsive VdW	ACE	HB	Structure show/hide
1	10	-87.13	-41.96	7.52	-14.04	-5.71	☑
2	9	-85.93	-41.29	6.12	-13.37	-4.85	☐
3	8	-27.50	-42.96	14.48	5.35	-3.68	☐
4	3	-26.41	-36.27	33.70	4.63	-9.06	☐
5	5	-18.66	-34.26	21.32	-1.57	-4.92	☐
6	1	-17.57	-42.02	35.06	4.83	-5.77	☐
7	7	-15.08	-27.43	17.51	2.12	-5.86	☐
8	6	-12.51	-28.48	15.19	7.33	-1.85	☐
9	2	-10.10	-41.38	46.78	-9.21	-3.71	☐
10	4	-6.47	-30.95	42.24	1.94	-2.82	☐

download solutions table download best structures

Figure 1. The output table of FireDock server.

Other advanced parameters determine the level of refinement. The 'Restricted' refinement mode allows only the clashing residues to be flexible. The 'Full' refinement mode allows all the interface residues to be flexible and uses an extended rotamer library. We recommend using the restricted mode at first, for coarse refinement, and to use the full mode on the final best candidates. The user can also set the number of rigid-body optimization cycles. This parameter influences the range of rigid-body movements around each original solution candidate. Finally, the user can scale the atomic radii used in energy calculations. This parameter influences the extent of acceptable steric clashes in the final refined solutions. We recommend using 0.8 for coarse refinement ('Restricted' mode) and 0.85 for a final refinement ('Full' mode) of the best candidates.

Output

The output of the server is a table of all the input solutions, where each row corresponds to a single input complex (Figure 1). The table is sorted by global energy values. Refined complex structures are generated for up to 100 lowest energy candidates. The user can view the complexes in a Jmol applet window (37). Different complexes can be viewed simultaneously for comparison and the 3D structures can be downloaded as PDB files. The table can be sorted by different energy terms, such as the attractive and repulsive van der Walls forces, the ACE and the contribution of the hydrogen bonds (HB) to the global binding energy. An extended table with full specifications of the values of each energy term can be downloaded.

CONCLUSIONS

The FireDock web server presented here is the first web server for addressing the problem of protein flexibility in docking and allows a high-throughput refinement of docking candidates. Due to the high efficiency of the algorithm, we are able to present a web server that allows online refinement of large number of candidates within reasonable running times. The web server interface is easy to understand and simple, requiring no previous knowledge in docking algorithms. In addition, we provide an option for redirection of the solution candidates from the PatchDock web server to the refinement process of FireDock. This allows the users to perform a full docking protocol of global search (PatchDock) and local refinement (FireDock) in a fully automated manner. The algorithm of FireDock was proven to be successful in the task of refinement and selection of near-native solution out of thousand candidates (16). We believe that the server will enable biologists to use this state-of-the-art docking algorithm in order to predict the structure of new protein–protein complexes.

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Conflict of interest staetement. None declared.

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