DockingShop: a Tool for Interactive Protein Docking

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Abstract

The molecular docking problem is to determine how molecules interact with other molecules and plays a key role in understanding how cells function. DockingShop is an integrated environment for interactively steering molecular docking by navigating a ligand or protein to the receptor's estimated binding site. This tool provides a graphical interface for molecular modeling featuring real-time visual guides, interactive manipulation, navigation, optimization, and dynamic visualization enabling users to apply their biological knowledge to steer the docking process.

1. Introduction

The simulation of unbound docking is significantly more difficult than bound docking because it requires computational schemes to reconstruct a complex using unbound structures. This additional complexity derives from conformational changes between the bound and unbound structures that take place during the binding process [1]. One of the challenges is the conformational change upon binding which involves significant backbone movement. Most docking algorithms have adopted a two-stage approach. In the *conformational space search* stage, both molecules are treated as rigid bodies and their relative position and orientation are fully explored based on Fourier transformations. However, such an approach does not allow users to inspect and assess possible solutions in real time and is computationally intensive due to the exhaustive conformational space search procedure inherent to the FFT process. The computational problem becomes even more difficult when the protein flexibility is taken into account and with the need to screen large databases of proteins and/or potential drugs [1]. In the *ranking of potential solutions* stage, potential conformational structures obtained in the previous stage are refined and re-ranked by using scoring functions to discriminate between native and non-native docked conformations and to find the lowest-energy binding mode of the ligand to the receptor. Several algorithms can rank correct solutions for certain predictive docking cases; however, for most complexes the highest ranked structures are still false positives [1]. Our goal is to develop a tool that provides support to different docking methods rather than a docking method itself. DockingShop provides an interactive molecular docking environment that includes real-time visual feedback to steer the docking process for rapid estimation of the conformational binding mode taking into account the flexibility of the side chains and backbone movement. Our tool integrates human intuition and biological knowledge to steer the prediction process.

2. Interactive Docking of Molecules

DockingShop allows users to bring two molecules close together and see them bind in real-time. Also, it provides an interface to use Pocket, an analytical-based method for detecting binding sites [2]. When a molecule is moved close to the binding site of another molecule, the orientation of either molecule can easily be changed to sample the conformational space. DockingShop also supports exploratory and interactive steering of molecular docking by leveraging user knowledge through integrating interactive visualization with real-time simulations. DockingShop visualizes computational parameters used in scoring functions as "live" guides to help users navigate a ligand or protein to the potential conformational binding mode, to understand the behavior of a protein structure during the molecular interaction, and to discriminate between native and non-native conformations.

DockingShop constantly monitors the position and orientation of hydrogen bonding sites along the backbone and between molecules, and renders a dashed line when hydrogen bonds are formed. Hydrogen bonds are represented in yellow or green for intra- or inter-molecular interactions and blue for interactions with water molecules. A transparent green sphere highlights the area surrounding a potential hydrogen

bond between molecules. These spheres help users identify the locations of hydrogen bonds among all rendered details. The length of a hydrogen bond is also shown along the dashed line and is continuously updated during the interaction.

DockingShop provides an interface layer for dynamically loading energy computation modules allowing users to couple different energy functions from commercial or internally developed packages. Our program has two schemes for the energy visualization, atom-based and volume-based. In the former, per-atom values are visualized by mapping colors to atoms' VDW spheres. This approach is useful to rapidly identify high-energy atoms inside the protein. Volume rendering of energy produces a cleaner and more appealing representation than per-atom rendering because it reduces occlusion and visual clutter caused by VDW spheres. Furthermore, DockingShop permits numerical analysis of the energy. This feature helps users to relate calculated quantities to molecular motions and to measure the effect of molecular interactions and structure alignments.

DockingShop calculates and visualizes atom collisions in real-time during interactive docking to assist users in evaluating the overlap, thus helping to achieve the desired molecular interactions when a protein or ligand is close to a binding pocket. Penetrations are penalized and scored. A grid-based algorithm detects all pairs of atoms inside a protein whose distance is less than 75% of the sum of their VDW radii and measures the spatial distance between different molecules. A ball of radius proportional to the penetration depth of the two intersecting atoms' VDW spheres is rendered in yellow or red to visualize the inter- or intra-molecular collision. The collision detection feature helps users reject a solution when the molecular penetrations exceed a tolerance threshold during visual assessments. These overlaps may be resolved by manipulations.

One of the advantages of our program is that it supports interactive real-time manipulation of protein structures without breaking the protein's chemical structure. It provides backbone flexibility for large and small backbone movements allowing conformational changes in the docking process. DockingShop's manipulations are based on those in ProteinShop [3]. ProteinShop uses an inverse kinematics (IK) algorithm to transforms parts of a protein with respect to other parts by rotating the backbone dihedral angles, without changing the bond lengths. Users can also finely adjust the protein structure by changing the dihedral angles of a selected residue within the range of the Ramachandran plot [4]. Another type of refinement allows the substitution of the side chain of a selected residue of a protein using a rotamer library [5]. This flexibility of side chains may resolve some overlaps between receptor and ligand. In addition, DockingShop permits to perform mutations, which allow users to change a residue for another while keeping the backbone fixed.

The ranking of these intermediate modes is based on an adjustable scoring function used as a comprehensive assessment to filter out many false positive solutions in early stages. This adjustable scoring function is based on a combination of individual parameters with different weights either positive or negative. Users can select which parameters they want to include in the scoring function and change the values of weights in the interactive user interface. The summation of all weighted parameters is the final score. Each parameter and ranking result is continuously updated to monitor the quality of a docking configuration and to aid in steering the prediction. A "hydrophobicity filter" in protein-protein docking cases [6] is included as part of the adjustable scoring function.

3. Conclusion

DockingShop helps users understand and simulate the molecular docking process through a steering mechanism with real-time visual and numerical feedback. It combines molecular structure modeling, interactive docking, and simulation of molecular interactions to create an application for exploration and experimentation in biology. DockingShop provides a graphical interface for integrating human intuition and biological knowledge.

References

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