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MDR SurFlexDock, a web-tool for enhanced protein surface structural sampling in docking experiments

João Luiz de Almeida Filho, Heitor Modenesi Fraga, Jorge Hernandez Fernandez

In current computational biology, one of the most popular experimentation technics is Docking, that can be summarized as the discovery of the best fit of ligand, or a set of ligands, in a specific part of the protein of interest. As proteins are flexible and dynamic macromolecules that continually alternate their surface conformations, nowadays the accurate representation of the protein surface facing ligands is one of the most important challenges on docking experiments. However, the receptor flexibility impact in the computational cost of the experiment. Currently, most docking tools undergo various conformations of a flexible ligand on a rigid receptor surface aiming at saving computational resources and experimental time. To overcome the problem of protein flexibility several strategies are used to better sample the conformational space of the receptor. In this context, we are developing MDR SurFlexDock, a web-tool that allows analyze the interaction of small protein-ligand complexes through enhanced structural sampling of receptor surface with low computational cost. The MDR SurFlexDock pipeline uses discrete molecular simulation to increase the conformational sampling on the receptor surface using gradual thermalization in explicit solvent and Na+ and Cl- ions. The receptor surface is submitted to clustering analysis over the simulation trajectories with 2.0 Á cut-off and the three most representative conformations are used in consecutive docking experiments. At the end, the results are sent to the user by email, presenting in a simple and graphical way the results obtained of each docking experiment and calculating the inhibition constant (Ki) for each ligand. We believe the use of discrete conformational search in solvated receptors increase the possibilities to better represent the physiological environment in protein-ligand docking experiments. As proof of concept, MDR SurFlexDock was able to improve ligand docking results (Ki) from µM magnitude to nM, allowing a better description of integrin-ligand interactions. The pipeline used by MDR SurFlexDock is highly scalable and was designed for low computational cost. MDR SurFlexDock is being developed in Django and will be available under GPL license for academic users.

Palavras-chave: Docking, Molecular Simulation, Surface Structural Sampling.

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