Journal of
Cheminformatics

ORAL PRESENTATION   **Open Access**

The protein flexibility in receptor-ligand docking simulations

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From 5th German Conference on Cheminformatics: 23. CIC-Workshop
Goslar, Germany. 8-10 November 2009

Many small-molecule drugs work by binding specifically to a target protein in the cell. It is known for over a century that both the ligand and protein receptor change their conformation in the association process, which is called the induced-fit effect. Ligand conformational change is routinely treated in methods for in-silico drug discovery, because typical drug molecules have seldom more than 100 atoms. The flexibility of proteins, which often have more than 10000 atoms, is much harder to treat and was therefore neglected in most high-speed docking methods, limiting their accuracy and predictive value.

In this project we have developed an efficient numerical search procedure that succeeds to model the interaction between a flexible ligand and important flexible parts of the protein in a computationally affordable protocol. Our virtual screening software FlexScreen thus minimizes the total interaction energy of the emerging protein-ligand complex including flexible backbone regions. We have demonstrated the reliability and accuracy of this approach on several examples, for which at least two different receptor-conformations have been experimentally observed. We succeeded to predict the correct binding pose of a protein-ligand complex starting from the crystal structure of an unrelated protein conformation, where large conformational changes of the protein are necessary to bind the ligand. Correctly predicting such conformational changes makes our approach attractive for virtual screening of medium sized databases, in particular for kinases and other target receptors which have flexible binding pockets.

Published: 4 May 2010

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