

FITTED 2.2: A Docking Software Program that Docks Small Molecules into Flexible and Partially Solvated Proteins

Information Summary

Reference Code:	ROI 08034
Technology overview:	FITTED 2.2 is a suite of programs to dock flexible ligands into flexible proteins. This software relies on a genetic algorithm to account for mutual flexibility and location of water molecules, and on a novel application of a switching function to retain or displace water molecules and to form potential covalent bonds with the protein side-chains.
Applications:	Virtual screening of compounds for their affinity towards a protein target.
Validation:	Successful and accurate docking of various enzyme inhibitors (i.e., HIV-1 protease, trypsin, MMPs, mannosidase), receptor agonists and antagonists (glutamate receptor) and virtual screening of enzyme inhibitors (i.e., CDK2, thymidine kinase, HCV polymerase) receptor agonists and antagonists (estrogen receptor).
Inventors:	Moitessier Nicolas et al et. al
Opportunity:	Efficient implementation of a new molecule docking methodology with improved accuracy.
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Technology Description

Several comparative studies of docking programs show the poor accuracy of some of the commercially available packages. This failure results in part from the use of an inaccurate protein model. Although inhibitors are in general accurately docked back to their corresponding protein structure (self-docking), docking

to other structures (cross-docking) usually performs poorly. Several docking programs treat the proteins as rigid object and do not account for conformational changes upon binding which results in poor performance in cross docking studies. The use of the rigid protein model usually causes an inaccurate prediction of ligand/affinities activities and low enrichment factors in virtual screening studies. FITTED 2.2 improves the accuracy of existing molecule docking software program. It uses a more accurate protein models and is based on a pharmacophore-oriented docking method combined with a genetic algorithm based docking approach. The later takes advantage of more than one structure to dock compounds in virtually flexible proteins. A library of experimentally observed protein conformations is used and composite structures are created in order to model the protein flexibility and to explore a wide region of conformational space. The proteins, ligands and potential bridging water molecules are described as genes and a mixed Lamarckian/Darwinian evolution optimizes the whole complex.

Advantages

- Accuracy – a significant increase in the accuracy of the virtual docking process is observed.
- Speed – aspects of the program that are common to all runs are performed only once.

Market need:

An integral part of the drug discovery process is to in silico screen libraries (virtual screening) of compounds in order to prioritize compounds for biochemical assays and, most importantly, to introduce rationale in the selection process. Presently, almost all the docking protocols used are based on a rigid receptor model and do not take into account the mobility of the ensemble of amino acids that constitute the binding site of the ligand.



Dr. Nicolas Moitessier is Assistant Professor at McGill University, Montreal, Canada and is also a member of CERMM (Center for Research in Molecular Modeling). He received his undergraduate training and his Ph.D from Université Henri Poincaré-Nancy I(France) under the guidance of Dr. Yves Chapleur (Directeur de Recherche au CNRS) within the Groupe SUCRES (UMR CNRS 7565). He carried out thesis research on computer-aided design and synthesis of carbohydrate-based biologically relevant molecules. He was first involved in the design and preparation of IP 3 and Adenophostin A mimics using Sharpless asymmetric dihydroxylation. In collaboration with the theoretical chemistry group, he then focused on the computer-aided design and synthesis of carbohydrate-based antagonists of

integrins.

In 1998, he joined the group of Prof. Stephen Hanessian. His interests centered on the docking study and the asymmetric synthesis of conformationally constrained MMP inhibitors. He was also involved in a project related to the preparation of aminoglycoside antibiotics and in the design and preparation of BACE-1 inhibitors. In 2001, he moved back to Nancy to start an academic career (Chargé de Recherche, CNRS) then returned to Montréal in 2003 as Assistant Professor in the Department of Chemistry of McGill University. His current interests integrate computational chemistry and organic/medicinal chemistry, spanning software development to sugar chemistry. Nicolas Moitessier is co-author of 33 publications and co-inventor of 2 patents.