MATCH
Communications in Mathematical and in Computer Chemistry

MATCH Commun. Math. Comput. Chem. **55** (2006) 271-278

ISSN 0340 - 6253

CURRENT MOLECULAR DOCKING TOOLS AND COMPARISONS THEREOF

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(Received November 17, 2005)

Abstract: Current software applied to dock a highly flexible small molecule to a macromolecular target is discussed. In addition, several recent comparisons of protein-ligand docking tools are presented.

Introduction

Molecular docking is a computational method to study the formation of intermolecular complexes of one smaller molecule with a larger molecule, which usually is a protein of known three-dimensional structure. Different types of interactions between the molecules can be distinguished: protein-protein, protein-DNA, DNA-ligand, protein-ligand.

In this report a summary of current computer software for molecular docking of a small molecule (ligand) to the active site of a protein target is discussed. Some extensive reviews on docking have been published recently [1-4]. Many computer programs have been developed in this field during the last two decades [5-16]. The first methods assumed that both the ligand and the protein were rigid structures. Current methods of choice use flexible ligands, whereas protein conformation is restricted. Some programs allow for partial protein flexibility.

Molecular docking tools

Docking describes a process, where a ligand molecule is placed into the active site of a protein target in three-dimensional space. Two aspects are important: prediction of affinity between the ligand and the protein and prediction of correct pose of the ligand in the active site of the protein. Affinity prediction is connected with different ligands from collection. Some fit better than others did. Pose prediction is connected with the same ligand molecule but in different orientations. The point is to predict relevant, top-score ligand from the set and to predict its accurate pose in a reasonable timeframe and without errors. The binding of a ligand to a receptor is evaluated by its good complementarity in terms of shape and

physicochemical interaction to the given protein target. Molecular docking consists of two steps: searching and scoring. Searching relies on a certain search algorithm to explore potential binding poses. Scoring involves evaluating tightness for molecules from collection and ranking them accordingly. Scoring functions are especially important since minimization algorithms rely on these functions. Several reviews on scoring and assessing of scoring functions have been published recently [18-21].

A number of docking programs have been developed during the last two decades and made available to academic institutions at little or no charge. Table 1 summarizes current protein-ligand docking tools. Basic characteristics such as supported platforms, license terms, as well as applied docking algorithms and scoring functions are presented.

Table 1. Basic characteristics for current protein-ligand docking tools*.

Entry	Program Ref**	Designer / Company	Licence terms	Supported platforms	Docking approach	Scoring function
1	2	3	4	5	6	7
1	AutoDock [5]	D. S. Goodsell and A. J. Olson The Scripps Research Institute	Free for academic use	Unix, Mac OSX, Linux, SGI	Genetic algorithm Lamarckian genetic algorithm Simulated annealing	AutoDock (force-field methods)
2	DOCK [6]	I. Kuntz University of California, San Francisco	Free for academic use	Unix, Linux, Sun, IBM AIX, Mac OSX, Windows	Shape fitting (sphere sets)	ChemScore, GB/SA solvation scoring, other
3	FlexX [7]	T. Lengauer and M. Rarey BioSolveIT	Commercial Free evaluation (6 weeks)	Unix, Linux, SGI, Sun Windows,	Incremental construction	FlexXScore, PLP, ScreenScore, DrugScore
4	FRED [8]	OpenEye Scientific Software	Free for academic use	Unix, Linux, SGI, Mac OSX, IBM AIX, Windows	Shape fitting (Gaussian)	ScreenScore, PLP, Gaussian shape score, user defined
5	Glide [9]	Schrödinger Inc.	Commercial	Unix, Linux, SGI, IBM AIX	Monte Carlo sampling	GlideScore, GlideComp
6	GOLD [10]	Cambridge Crystallographic Data Centre	Commercial Free evaluation (2 months)	Linux, SGI, Sun, IBM, Windows	Genetic algorithm	GoldScore, ChemScore user defined
7	LigandFit [11]	Accelrys Inc.	Commercial	Linux, SGI, IBM AIX	Monte Carlo sampling	LigScore, PLP, PMF

*Other current docking tools are: ICM [12], ProDock [13] ,QXP [14], Slide [15], Surflex [16].
**Internet addresses of selected home pages are given [17].

DOCK 1.0 [6] was the first automated receptor-ligand docking program. It was design in 1982 by Irwin Kuntz in The Department of Pharmacology at The University of California at San Francisco. At present there are at least a dozen docking tools on the market, the most commonly used being: AutoDock [5], DOCK [6], FlexX [7], GOLD [10], LigandFit [11] and the relatively new tools: Glide [9], FRED [8] and the youngest Surflex [16].

As a consequence of the growing number of available three-dimensional protein structures, molecular docking has become a useful tool in medicinal chemistry [22]. Structure-based design and discovery of novel drugs relies on premise that 3D structures of protein can be used to derive new protein ligands with improved binding properties [23-25].

Traditional *in vitro* high throughput screening is the dominant, although expensive method to discover novel leads for drug development. Therefore virtual screening by protein-ligand docking can be attractive alternative when a structure of the target is available [26-30]. The screening of large databases for possible lead compounds has recently become a routine procedure. This way a large number of compounds can be evaluated against a target in rapid and automated manner. In this process smaller sets of pre-filtered, top-scored molecules are selected as candidates for biological assays. Among many applications published recently there are several examples of novel enzyme inhibitors discovery by virtual screening. The most frequently applied docking programs in these studies reported in the last three years are: DOCK [31-33], FlexX [34-37], GOLD [37-38] and Glide [39].

Recent comparative studies

As there are a number of programs available on the market, the question arises: which program to use? The choice of a docking tool should be based on the objective of the project. For virtual screening of corporate libraries consisting of millions of compounds the key criterion is reasonable timeframe. The user should start with a fast tool followed by more accurate ones. Similarly simple ligand docking aiming at *de novo* design of drugs and their optimisation requires the use of the more accurate tool.

During the last two decades many protein-ligand docking tools have been developed and as a consequence several comparisons among them were made and published [41-51]. Comparison of protein-ligand docking programs is not straightforward [40]. Each program has advantages and disadvantages in terms of docking accuracy, ranking accuracy and computational time consumption. It is difficult to draw general conclusion since those

programs are based upon different docking approaches (Table 1, column 6) and use different scoring functions (Table 1, column 7). Besides, the users do not have access to all docking codes and they do not always use test sets of sufficient diversity, which may lead to some programs providing better results than other. However some general strengths and weaknesses of current docking tools can be found in recent comparisons.

Comparative studies on several current docking tools developed during the last three years are listed in Table 2. In column 2 the programs compared are listed, while in columns 3 and 4 comparative approaches A or B are presented and the number of explored protein targets is indicated. Generally speaking, two approaches in comparative studies can be applied:

A. Docking experiments on a data set of protein-ligand complexes, which rely on the ability to reproduce accurate X-ray ligand pose in relation to macromolecular target within certain rms deviation, usually 1.0-3.0 Å. In this manner, comparisons can be made in terms of docking accuracy.
B. Virtual screening of a library containing small molecules against different protein targets. In this study, known active compounds are added to a large set of molecules. Docking program should be able to select the active compounds out of a large set of inactive ones. This separation is expressed as enrichment factor. Reproducibility and ranking accuracy are additional features compared. Reproducibility means how many times each program finds the experimental binding pose as its top-ranking choice.

As far as docking accuracy is concerned, GOLD [41] and Glide [41, 42, 46] are usually compare well with other programs. Docking accuracy depends on type of protein target and properties of the ligand. Molecular properties of ligands, such as molecular weight, number of rotatable bonds, number of polar atoms on docking performance are often studied. It is commonly believed that docking accuracy significantly decreases for ligands with large number of rotatable bonds. GOLD [41] and CDOCKER [49], being less sensitive in this respect are recommended programs. In comparisons made in terms of enrichment factor, Glide [43, 46] and Surflex [47] turned out to be the most effective programs.

In both approaches A and B, computational time consumption can be compared. Single docking requires a time range of several seconds up to minutes. Depending on the purpose of docking performance, the user can choose a very fast tool in order to carry out virtual high- or ultra high-throughput screening. For example LigandFit [41], FlexX [45] and FRED [44] are

considered very fast programs, while Glide [41] and AutoDock [45] are the slowest and not recommended for docking of large collections of ligands without pre-filtering.

Table 2. Comparative study on common protein-ligand docking programs.

Entry	Programs compared	Number of explored protein targets		Ref
		Approach A	Approach B	
1	2	3	4	5
1	FlexX, DOCK, GOLD, LigandFit, Glide	69	-	[41]
2	GOLD, FlexX, Glide, Surflex	282	-	[42]
3	Glide, GOLD, FlexX, DOCK	-	9	[43]
4	Glide, FRED, FlexX	-	7	[44]
5	AutoDock, DOCK, FlexX, GOLD, ICM	37	11	[45]
6	Glide, GOLD, ICM	200	3	[46]
7	DOCK, FlexX, FRED, Glide, GOLD, Slide, Surflex, QXP	100	1	[47]
8	FlexX, GOLD, ICM, LigandFit, DOCK, QXP	11	-	[48]
9	DOCK, FlexX, GOLD, CDOCKER	41	-	[49]
10	DOCK, DockVision, Glide, GOLD	-	5	[50]
11	GOLD, QXP	-	1	[51]

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AutoDock: http://www.scripps.edu/pub/olson-web/doc/autodock/
DOCK: http://dock.compbio.ucsf.edu/
FlexX: http://www.biosolveit.de/flexx
FRED: http://www.eyesopen.com/products/applications/fred.html
Glide: http://www.schrodinger.com/products/glide.html
GOLD: http://www.ccdc.cam.ac.uk/products/life_sciences/gold/
ICM: http://abagyan.scripps.edu/flpldock.html
LigandFit: http://www.accelrys.com/products/cerius2/cerius2products/c2ligandfit.html

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