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Beware of docking!

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Docking is now routine in virtual screening or lead optimization for drug screening and design. The number of papers related to docking has dramatically increased over the past decade. However, there are many issues to consider when undertaking a docking study. Frequent problems or issues arise, such as the wrong binding site of the target protein, screening using an unsuitable small-molecule database, the choice of docking pose, high dock score but failed in molecular dynamics (MD) simulation, and lack of clarity over whether the compound is an inhibitor or agonist. These problems should be cause for caution and concern before performing docking. Some papers show comprehensive biochemistry experiments but only a simple docking figure. This review presents some evidence to show that the docking might be questionable, despite a high score. In some cases, the accuracy of docking can even change from 0% to 92.66%. Thus, please beware of docking!

Docking for structure-based drug design

Since its beginnings in the 1960s, docking, along with the tremendous developments in physics, chemistry, informational technology, biochemistry, and computers, has become a powerful tool and an essential technique, not only in drug screening but also in protein–protein interactions and the behavior of nanomaterials. The current field of computer-aided drug design (CADD) is dominated by technologies used to dock small molecules into macromolecules, particularly protein targets, and its use is increasing year by year. In modern CADD, structure-based drug design is essential [1–4] and most big pharmaceutical companies have this department. Many commercial drugs are directly designed from CADD method [5]. Undoubtedly, docking techniques are very important scientific advances for understanding of chemical compounds, as noted particularly when three top computational scientists won the 2013 Nobel Prize in chemistry.

Protein–ligand or protein–protein docking is a computational technology to predict the orientation of a ligand when it is bound to a protein receptor or enzyme. In most cases, one can choose the best 'binding affinity' to be the potent ligand for further biochemistry experiments and development. Because docking is simple and the equipment requirement is low (it even works well on a personal computer), docking-related papers have sharply increased over the past decade (Figure 1). However, can we or should we trust the results of these docking studies? In this paper I provide a critical survey of the field, pointing out the strengths and weaknesses of the current family of docking protocols.

Careful evaluation shows that accuracy is a major problem with docking studies, because if the docking is not approached with precision then these papers will be of little value [6–8]. Questionable docking results can be found, even in high-profile journals. There are frequent problems such as an inaccurate binding site of the target protein, screening using an unsuitable small-molecule database, the choice of docking pose, high dock score (binding affinity) but failed in MD simulation, lack of clarity over whether the compound is an inhibitor or agonist, or the docking results are inconsistent with bioassays. The worst case is often found in some very high profile journals, which show an excellent bioassay but only with a simple docking figure. These problems in the interpretation of docking should be cause for caution and concern. Although some papers declare docking results with a high accuracy by comparing the ligand pose before and after docking, here I present some evidence that the docking might be still questionable. In some cases the accuracy of docking can even change from 0% to 92.66%.

Docking algorithms and programs

The original concept of docking comes from the concept of 'lock and key' of rational drug design, but the precise algorithms used to fit the 'key' (the ligand) into the 'lock' (the receptor protein) vary across programs. The latest developments in docking programs, the docking web server, screen software, and screen webserver are listed in Table 1, from which we can see that the number of new algorithms has been increasing in recent years. If we further analyze all the docking papers (Figure 2), we can see that the most commonly used docking programs are Autodock [9] and GOLD [10]. This does not mean that Autodock or GOLD are more accurate than other docking programs, they are merely more popular and well known. It is possible that their high citation rate is due to these programs being free and being created earlier than the other recent docking programs. Nowadays, a new algorithm to predict protein structure for docking, Rosetta (http://boinc.bakerlab.org/), has also been highly evaluated.

Although they vary, the different algorithms of each docking program must strike a balance between speed and accuracy. The algorithms for docking also vary by differences in scoring functions. Binding affinity is usually

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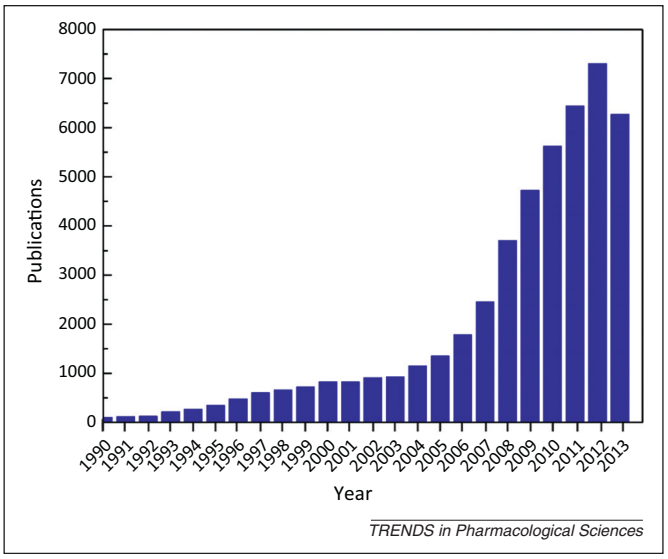

Figure 1. The increase in the number of papers, from 1990 to 2013, retrieved from the PubMed Central (PMC)-NCBI database (http://www.ncbi.nlm.nih.gov/pmc/). Keywords were 'docking' or 'dock' shown in the abstract or title.

considered to be a priority in the evaluation of the best candidate for virtual screening. There are several docking programs for a user to choose from based on his or her particular requirements. At present, docking algorithms emphasize different aspects of structure-based drug design (SBDD), such as fragment-based drug design [11–13], flexible docking [14], docking in water, solvation, and specific pH [15,16]. For example, if we need to screen more than 10 000 compounds from a database, then flexible docking maybe not a good choice unless we have a very powerful and high-speed computer. By contrast, if we need to dock only a few compounds in the specific protein binding site, at a specific pH, water, or solvation, then the flexible docking program might be a good choice. Choice of docking program therefore depends on what type of hardware you have and how large a database you are screening. For drug screening, the traditional Chinese medicine (TCM) database at Taiwan contains more than 61 000 compounds [17]; using the iScreen webserver for screening specific TCM and customized docking, multiple docking operations including standard, in-water, pH

Table 1. Recent software and webservers for docking and virtual screening as compiled and categorized by "http://www.Click2Drug.org" of the SIB Swiss Institute of Bioinformatics, which provides a comprehensive list of computer-aided drug design software and web services for structure-based and ligand-based calculations

Program name	Novel features	Refs
Docking Software		
Autodock	Free open-source EA-based docking software. Flexible ligand. Flexible protein side chains. Maintained by the Molecular Graphics Laboratory, Scripps Research Institute, La Jolla.	[82]
DOCK	Anchor-and-grow based docking program. Free for academic use. Flexible ligand. Flexible protein. Maintained by the Soichet group at the University of California San Francisco (UCSF).	[83]
GOLD	GA-based docking program. Flexible ligand. Partial flexibility for protein. Product of a collaboration between the University of Sheffield, GlaxoSmithKline, and the Cambridge Crystallographic Data Centre (CCDC).	[84]
Glide	Exhaustive search-based docking program. Exists in extra precision (XP), standard precision (SP) and virtual high-throughput screening modes. Ligand and protein flexible. Provided by Schrödinger.	[6]
SCIGRESS	Desktop/server molecular modeling software suite employing linear scaling semi-empirical quantum methods for protein optimization and ligand docking. Developed and distributed by Fujitsu.	[85]
GlamDock	Docking program based on a Monte-Carlo with minimization (basin-hopping) search in a hybrid interaction matching/internal coordinate search space. Part of the Chil^2 suite. Open for general research.	[185]
GEMDOCK (generic evolutionary method for molecular docking)	Program for computing a ligand conformation and orientation relative to the active site of target protein.	[87]
iGEMDOCK	Graphic environment for the docking, virtual screening, and post-screening analysis. Free for non-commercial researches. For Windows and Linux.	[87]
HomDock	Program for similarity-based docking, based on a combination of the ligand-based GMA molecular alignment tool and the docking tool GlamDock. Part of the Chil^2 suite. Open for general research.	[88]
ICM	Docking program based on pseudo-Brownian sampling and local minimization. Ligand and protein flexible. Provided by MolSoft.	[89]
FlexX, Flex-Ensemble (FlexE)	Incremental build-based docking program. Flexible ligand. Protein flexibility through ensemble of protein structure. Provided by BioSolveIT.	[86]
Fleksy	Program for flexible and induced fit docking using receptor ensemble (constructed using backbone-dependent rotamer library) to describe protein flexibility. Provided by the Centre for Molecular and Biomolecular Informatics, Radboud University Nijmegen.	[90]
FITTED (flexibility induced through targeted evolutionary description)	Suite of programs to dock flexible ligands into flexible proteins. This software relies on a genetic algorithm to account for flexibility of the two molecules 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 (covalent docking) with the protein side chains. Part of the Molecular FORECASTER package and FITTED Suite. Free for an academic site license (excluding cluster).	[91]
VLifeDock	Multiple approaches for protein–ligand docking. Provides three docking approaches: grid-based docking, GA docking, and VLife's own GRIP docking program. Several scoring functions can be used: PLP score, XCscore, and Steric + Electrostatic score. Available for Linux and Windows. Provided by VLife (http://www.vlifesciences.com/)	
ParaDockS (parallel docking suite)	Free open-source program for docking small, drug-like molecules to a rigid receptor employing either the knowledge-based potential PMF04 or the empirical energy function p-Score.	[92]