Mini-review

What *in silico* molecular docking can do for the 'bench-working biologists'

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Required by an increasing amount of scientists, the *in silico* docking field is in full expansion, new algorithms and methods appearing at an exponential rate. The sheer range of available programs is overwhelming for the bench-working biologist, which is often discouraging by the lack of a graphical user interface, good user manual or literature to validate a given program. This mini-review attempts to present the docking problem and available solutions from a non-bioinformatician point of view and makes a selection of the available servers and programs. These tools are evaluated from several points of view, as numbers of citations, ease of usage and computer requirements. Finally, the capabilities and limitations as well as specific applications of *in silico* docking techniques are presented.

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1. Introduction

Most of the proteins perform their functions by interacting with either small (substrates or effectors) or large (other proteins, DNA or RNA) molecules. Understanding how these intermolecular complexes are formed is essential for tasks such as selecting protein targets for therapeutic intervention, drug design or enzyme engineering. Today, the available information on biological activity and proteins structure has increased to a level that makes the computational prediction of protein complexes, or molecular docking, possible.

Used mostly by pharmaceutical R&D scientists (Rao *et al.* 2009), molecular docking experiments are increasingly needed by 'common' biologists for performing various tasks such as screening for enzymatic substrates or validation of experimental data. A bench-working biologist with no bioinformatics background might find difficult to answer frequent questions such as: Which program to use? Should I use rigid body or soft docking? Should I use RMSD or the grid score for ranking the output? How much time will take it to get my results? This review will address these questions with particular emphasis on the evaluation of the currently available programs and web-servers from a more practical point of view, dealing with problems such as ease of use, required computer power or evaluation of the results.

2. Molecular docking problem

Docking is a term used for computational schemes that attempt to predict the structure of the intermolecular complex formed between two or more constituent molecules: a receptor and a ligand (Sousa *et al.* 2006). The receptor is most of the time a protein, while the ligand can be another protein, a nucleic acid or a small molecule (a potential drug, substrate, inhibitor, etc.) (figure 1). The problem that molecular docking must solve can be defined as follows: given the atomic coordinates of two molecules, predict their 'correct' bound association.

3. Rigid body, flexible, blind and local docking

The first docking program was developed by the Kuntz group and named DOCK (Kuntz *et al.* 1982). It worked very similar to the 'lock and key' model: finding complexes with a high

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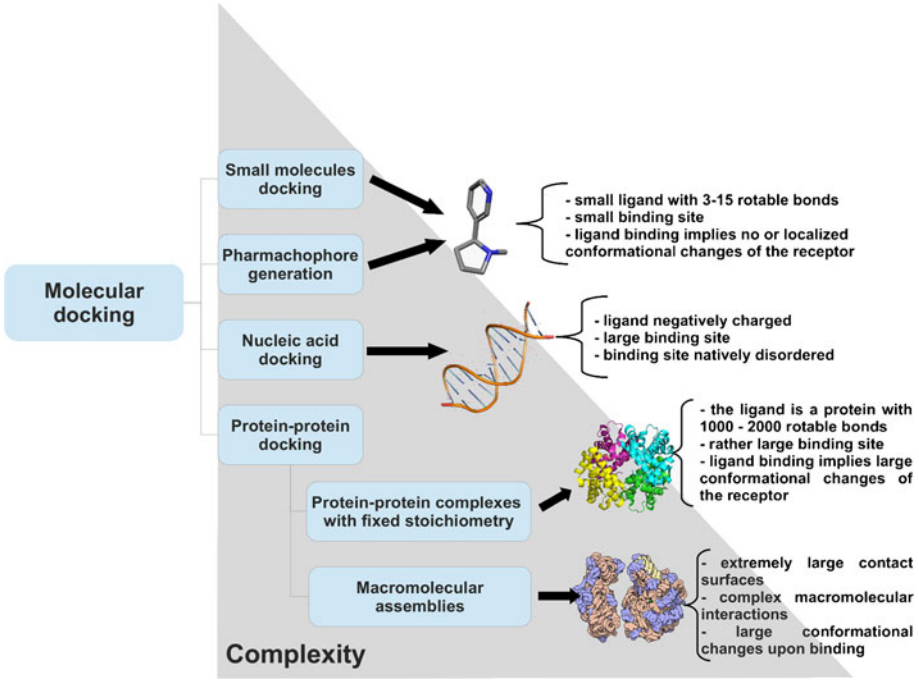

Figure 1. The diversity and complexity of the molecular docking problem related to the ligand.

degree of shape complementarity between the ligand and the receptor. In this approach, both the ligand and the receptor have very stiff structures, thereby the name *rigid body docking*. Although simplistic, the method was successfully used for the analysis of the serine proteases specificity (Ribeiro *et al.* 2010) or for estimating the protein mutational effects on DNA binding (Fanelli and Ferrari 2006).

The formation of molecular complexes in biology is nevertheless better described by the induced fit theory (Teague 2003; Wang and Pang 2007), and so most of the current docking programs (table 1 and supplementary material) take into account the flexibility and movements of side chains and backbone of both the receptor and the ligand, performing the so-called *flexible docking*. Docking a flexible ligand to the surface of a rigid protein is a standard feature nowadays, taking ~100 seconds per ligand–receptor pair (Lamb *et al.* 2001). Adding protein flexibility is a different story as it makes the task much slower (Carlson 2002). Several implementations of flexible protein docking do exist. *Soft docking* is the simplest method, allowing small degree of overlap between the ligand and the protein; the method it is very fast, but cannot account for large conformational changes (i.e. movement of an aminoacid in the catalytic site) (Ferrari *et al.* 2004). *Side chain flexibility* is another method in which the backbones are kept fixed and the aminoacids side chains are flexible (Desmet *et al.* 1997; Meiler and Baker 2006). *Molecular relaxation* method is a combination of rigid body docking for placing the ligand in the putative binding site fallowed by energy minimization of the complex. This method can include side chain flexibility and some degree of backbone flexibility with the down side of being slow (Davis and Baker 2009). The real cutting edge in flexible protein docking is modelling backbone flexibility, due to enormous complexity in size and degrees of freedom (Moreira *et al.* 2010). *Protein ensemble docking* uses an ensemble of protein structures to represent different possible conformational changes, thereby reducing the complexity of backbone flexibility (Huang and Zou 2010). The available approaches to docking with full receptor flexibility have been reviewed by Cozzini and colleagues (Cozzini *et al.* 2008).

Additional biochemical information can be used to increase the computation time and the reliability of the results (Halperin *et al.* 2002). By indicating a precise place in the receptor molecule where the ligand is supposed to bind (as, for example, inside a known binding pocked), a *guided docking* (Fitzjohn and Bates, 2003) is performed. When no information regarding the ligand is available, a so-called *blind docking* approach is used. This method has been successfully used to identify putative binding site of allosteric modulators in acetylcholine nicotinic receptors (Iorga *et al.* 2006) or potential selective aromatase expression regulators (SAERs) (Gueto *et al.* 2009).

The real state of the art in docking is represented by the the prediction of the three-dimensional structure of protein–protein complexes. In this case, the ligand is also represented by a protein. This is generaly refered as eather *protein–protein docking* or, more simply, *protein docking* (Chen *et al.* 2003).

Table 1. Top-three most-cited programs and servers used for *in silico* docking

Program/Server	Docking capabilities*	Website	Observations
Programs			
AutoDock 4 (Morris *et al.* 1998)	RB, FL, FR *(limited side chain flexibility),* LD, BD	*http://autodock.scripps.edu/*	Free, command line program available for Linux, OSX, Windows, Solaris. A very god graphical user interface is also available from the program developers: AutoDockTools (ADT); it allows the user to select which atoms of the ligand and the protein are able to be joined by a covalent bound
Glide (Friesner *et al.* 2004, 2006; Halgren *et al.* 2004)	RB, FL, BD	*https://www.schrodinger.com/products/14/5/*	Commercial application available for Linux and Windows
FlexX (Rarey *et al.* 1996; Kramer *et al.* 1999)	RB, FL	*http://www.biosolveit.de/FlexX/*	Commercial program available for Linux and Windows, part of the LeadIT software solution
			Good user interface
			Takes account of the metal coordination
Servers			
ZDOCK Server (Chen *et al.* 2003)	RB, LD, PP	*http://zdock.bu.edu/*	Mainly developed for protein-protein docking, can use .pdb as input files
ClusPro Server (Comeau *et al.* 2004a, b)	RB performed with DOT or ZDOCK, PP	*http://cluspro.bu.edu*	Input can be either the coordinate files of two structures (DNA or RNA) or directly the PDB codes
			One of the best ranked servers in the CAPRI 2009 and 2010 experiments Janin 2010 Lensink/ Wodak 2010
			Based on PIPER (Kozakov *et al.* 2006)
PatchDock (Schneidman-Duhovny *et al.* 2005)	RB, BD, LB, PP	*http://bioinfo3d.cs.tau.ac.il/PatchDock*	The input consists of two molecules: proteins, DNA, peptides, drugs.
			The output is a list of potential complexes sorted by shape complementarity
			Tusing the same method, the SymmDock server is also available for prediction of complexes with C_n symmetry

For a complete list of available software, see the supplementary material available on the Journal of Biosciences Website at *http://www.ias.ac.in/jbiosci/dec2012/supp/Mihasan.pdf*.

*RB, rigid body; FL, flexible ligand; FR, flexible receptor; BD, blind docking; LD, local docking; PP, protein–protein docking.

4. Programs and servers

The tools available for predicting the binding mode of two known structures can be classified from a computational point of view as either a standalone program or a server.

In the past, *in silico* protein docking was invariably performed by a handful of scientists using 'in the house' developed software. Today, docking experiments are required by an increasingly diverse group of scientists, most of them needing rapid solutions and not being prepared to spend months learning complicated programming or scripting languages. This largely explains why Autodock is currently the most successful docking program, with over 3300 citation since its launch in 1998 (figure 2A). The program is open source, which means that no cumbersome licensing, acquisition and deployment processes are needed, the time elapsed from downloading the program to actual hands-on usage being around 5–10 min (Geldenhuys *et al.* 2006). Also, the authors offer a free set of tools that can be readily used to set up, run and analyse dockings from an intuitive graphic user interface (GUI).

Appeared much later in the field of molecular docking, the web-servers are receiving lately an increasing number of citations (figure 2B). By using a web-browser window to submit the structure of the ligand and receptor, the bench-working biologist is freed from the troubles of implementing and maintaining complicated software (Fischer 2006). All the computations are done elsewhere and the user waits for the results most of the time by email.

Ease of use is reflected in the number of citations received by a given program, but it is not by far the most important aspect. The quality of binding poses as well as the correct

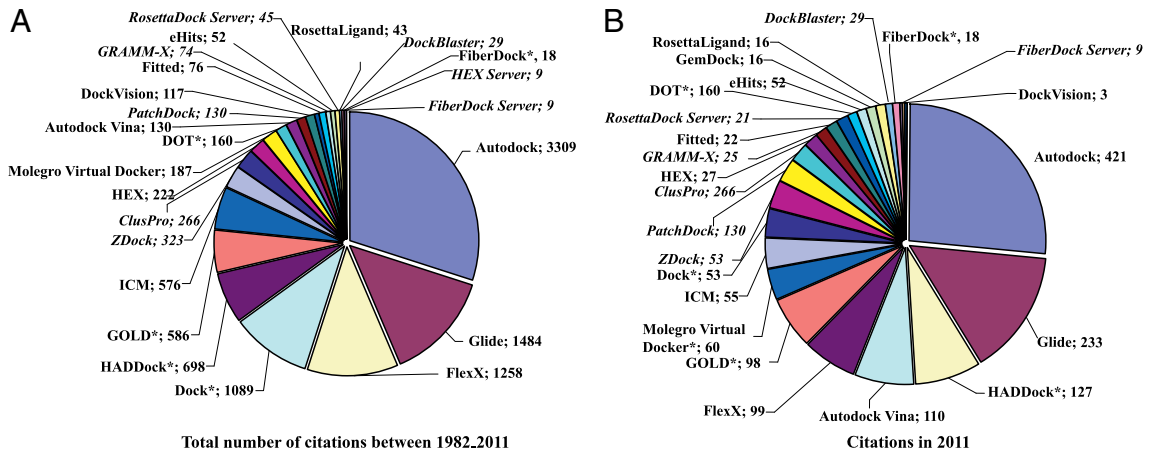

Figure 2. Some of the most common docking programs (bolt type) and servers (italics) ranked according to (**A**) number of citations and (**B**) trends in the number of citations per year analysed from the ISI Web of Science (2010), considering any of the original references as indicated in table 1 and the supplementary material. With asterisk (*) are marked the command-line-only programs.

evaluation of binding energies must be the key elements when deciding which program or server to use. As this cannot be easily inferred by the average biologist, there are several projects that focus on benchmarking docking programs and servers (Janin *et al.* 2003; Huang *et al.* 2006; Vogel *et al.* 2011). CAPRI is the most famous, with the *Proteins* journal having a special issue dedicated to this event every two years.

5. Evaluation of the docking poses

The finality of a docking experiment is not a single structure but a collection of possible poses of the ligand bound to the receptor. Usually, the success of a program is measured by the root-mean-square deviation (RMSD) between the experimentally observed heavy-atom positions of the ligand and those predicted by the program. Poses with an RMSD <2 Å are considered a success, and dockings whose RMSDs lie between 2 and 3 Å are considered a partial successes (Cole *et al.* 2005). RMSD is usable only when the experimentally structure of the complex exists. In the real-world scenario of drug discovery, enzyme substrate identification or protein–protein interaction, such information does not exists (Pedotti *et al.* 2011), making RMSD obsolete.

For the bench-working biologist, the evaluation of the docking results relies mainly on a *scoring function* that ranks the binding poses according to specific properties (binding energy, ligand efficiency, etc.). The scoring functions are usually implemented in the program itself, only a few programs (GOLD or DockIt) allowing the user to choose between two or more different scoring functions. So, which one is the best and produces the most reliable results? This is a difficult question that several authors have dealt with but have failed in providing a clear answer (Halperin *et al.* 2002; Moitessier *et al.* 2008, Huang and Zou 2010; Huang *et al.* 2010). The evaluation and validation of a docking result or pose must be primarily based upon existing experimental data, such as mutational analysis, binding constants, incomplete structures, etc. A fully automated method for correct and reliable docking without any human intervention still does not exist.

6. Capabilities and limitations

Molecular docking has a very wide array of applications, each having its own detailed set of algorithms, specifically tailored to improve speed and reliability. Accordingly, each application has its strengths and limitations. Based on to the type of ligand docked, there are several distinctive applications of molecular docking.

6.1 *Small molecules docking*

The goal of protein–small molecule docking is to predict the binding site and/or the binding orientation of a ligand in the receptor. The ligand is a whole molecule, usually obtained from a database such as ZINC (Irwin and Shoichet 2005) or PubChem (Wang *et al.* 2009). It has been successfully employed for identification of mechanistics behind the inhibition of human monoamine oxidase (Cerqueira *et al.* 2011) for validation of experimental data on a new ω-amidase (Cobzaru *et al.* 2011) or for identification of targets for site-directed mutagenesis (Hamza *et al.* 2011).

One limitation of protein–small molecule docking resides in the receptor structure itself. Sufficient resolution for reliable small molecule docking is only achieved below 1.2 Å (Gohlke and Klebe 2002), while most crystallographic structures have resolution values between 1.5 and 2.5 Å. The

homology models, used more and more in the field, have an even poorer resolution (Ferrara and Jacoby 2007; Mihasan 2010). It is generally accepted that a resolution below 2.2 Å is sufficient for yielding good results for most common application, and so extreme care must be taken when selecting the receptor molecule (Sousa *et al.* 2006).

Another limitation of protein–small molecule docking resides in the scoring function used, as most of them disregard the role played by covalently bound inhibitors, cofactors or metal ions. Nevertheless, several programs do manage to overcome these limitations (see supplementary material for details).

6.2 *Pharmachophore generation*

This is mostly used for drug design. In this approach, one starts from a collection of small ligands that were experimentally observed to interact with the given receptor. These ligands are treated as fragments and docked into the binding site. By combinatorially selecting and step-by-step ligating groups of atoms, the binding molecule is grown. This method has been successfully used for the discovery of novel non-peptide inhibitor of caspase-3 (Lakshmi *et al.* 2009), new antimalarial compounds (Rodrigues *et al.* 2011) or novel dopamine D(3) receptor inhibitors (Xin-Xian *et al.* 2011). The main drawback of pharmacophore generation is the fact that it reduces the available drug diversity as pointed out by Su *et al.* (2001).

6.3 *Nucleic acid docking*

Although several DNA-binding proteins families have been described (Luscombe *et al.* 2000), a simple 'code' describing the side-chain/base interactions between proteins and DNA/RNA was not yet found (Pabo and Nekludova, 2000). Very few algorithms and applications of protein–DNA/RNA docking are available in the literature, but due to its potential in drug design, the RNA docking field is expected to grow in magnitude (Halperin *et al.* 2002). One of the few specialized programs for DNA–protein docking is MONTY (Knegtel *et al.* 1994), but AutoDock has also been used to dock small molecules into a DNA receptor (Sun *et al.* 2012).

6.4 *Protein–protein docking*

This attempts to simulate molecular recognition (Halperin *et al.* 2002). The size of the molecules alone makes it a most challenging task, not to mention that the laws governing molecular interactions at this level are far from being established.

In order to simplify the process, most of the programs begin by treating the subject molecules as rigid or semi-rigid bodies (Moreira *et al.* 2010), then add further degrees of flexibility by using 'soft' scoring functions, by including side chain flexibility or domain hinging movements (Smith *et al.* 2005). This approach has been successfully used for performing tasks such as modelling the *Escherichia coli* FtsB/FtsL/FtsQ cell division complex (Villanelo *et al.* 2011) or studying binding interactions between Bcl-2 L10 and BH3 domain of BAX (Bhargavi *et al.* 2010).

Albeit important successes, the protein docking procedures are still in a mainly theoretical stage, hampered by the prediction of false-positives and false-negatives (Moreira *et al.* 2010). The large number of reviews on protein–protein docking available (Smith *et al.* 2005; Andrusier *et al.* 2008; Ritchie 2008; Rao *et al.* 2009; Moreira *et al.* 2010; Chaudhury *et al.* 2011) do indicate that the scientific community is making an considerable effort to further develop the methodology, and so improvements are expected in the near future.

7. Conclusion

The *in silico* docking methods has undergone significant changes and improvements over the past decades. From the command-line-only programs developed for specific tasks to the freely available web-servers, the docking tools available for the bench-working biologists have evolved towards an increased ease of use. Today, docking a small molecule to a protein is a simple task that can be performed by the average user on any computer in a reasonable time. More specialized tasks such as screening large libraries or protein–protein docking involve a more in-depth knowledge on search algorithms and more feedback from the user. One of the future challenges of *in silico* docking field is making the whole process completely automated and truly available for the masses. The emerging servers are the right step in this direction and we envision that the so-called *meta-servers*, able to select and perform all kinds of different types of dockings under one unitary interface, will appear in the near future.

Of course, one major challenge of the docking field is the fact that the so-called *computational molecular docking problem* (Kuntz 1992) is not completely solved yet. Receptor flexibility, especially backbone flexibility and movement of several key secondary elements of the receptor involving ligand binding and the catalyst, as well as modelling cofactors, effectors and solvation effects are still the major hurdle in docking studies The docking algorithms need to be further improved in these directions for an increased reliability of the results. Indisputable, the 'star' of the docking field, the protein–protein docking, will have the most benefits from all these advances.

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