# Research in Pharmacy and Health Sciences

**Review Article**

# Molecular Docking an Enchanted Way in The Discovery of Novel Molecule in Designing Drug: A Focused Review

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**ABSTRACT**

Current review paper revolves around the method of molecular docking. It involves regarding the basics of the docking studies. It also focused on the biological and pharmaceutical significance of the molecular docking, considerable efforts have been directed towards improving the methods used to predict docking. There is general concept about molecular docking is lock and key in which the finding is correct relative orientation of the key which can best fitted into the lock and then the lock can be open easily. How the accurate structure can be designed and what are the correct activities are predicted are the main two aims of the docking studies are preferred in the given studies and some examples are also added within the review for the evidence which supports the importance of docking studies.

**Keywords:** Molecular docking, Affinity, Scoring function, Protein binding, Ligand.

## INTRODUCTION

The docking process includes the forecast of ligand conformation and orientation (or posing) within a targeted binding site. Docking is a method which predicts the preferred orientation of one molecule to a second when bound to each other to form a steady complex. Knowledge of the preferred orientation in turn may be used to predict the strength of association or binding affinity between two molecules [1]. The associations between biologically relevant molecules such as proteins, nucleic acids, carbohydrates, and lipids play a central role in signal transduction. Furthermore, the comparative orientation of the two interacting partners may affect the type of signal produced (e.g., agonism v/s antagonism). Therefore docking is useful for predicting both the strength and type of signal produced. Docking is frequently used to predict the binding orientation of trivial molecule drug candidates to their protein targets in order to in turn predict the affinity and activity of the small molecule. Hence docking plays an important role in the rational design of drugs. Given the biological and pharmaceutical significance of molecular docking, considerable efforts have been directed towards improving the methods used to predict docking.

Regarding these challenges, docking is generally devised as a multi-step process in which each step introduces one or more additional degrees of complexity. The process begins with the application of docking algorithms that pose small molecules in the active site. This in itself is challenging, as even relatively simple organic molecules can contain many conformational degrees of freedom. Sampling these degrees of freedom must be performed with sufficient accuracy to identify the conformation that best matches the receptor structure run [2]. Algorithms are complemented by scoring functions that are designed to predict the biological activity through the evaluation of interactions between compounds and potential targets. Early scoring functions evaluated compound fits on the basis of calculations of approximate shape and electrostatic complementarities. Relatively simple scoring functions continue to be heavily used, at least during the early stages of docking simulations. Pre-selected conformers are often further evaluated using more complex scoring schemes with more detailed treatment of electrostatic and van der Waals interactions, and inclusion of at least some solvation or entropic effects [3]. It should also be noted that ligand-binding events are driven by a combination of enthalpic and entropic effects, and that either entropy or enthalpy can dominate specific interactions. This often presents a conceptual problem for contemporary scoring five functions, because most of them are much more focused on capturing energetic than entropic effects [4].

Molecular docking can be thought of as a problem of *"lock-and-key"*, where one is interested in finding the correct relative orientation of the *"key"* which will open up the *"lock"* (where on the surface of the lock is the key

hole, which direction to turn the key after it is inserted, etc.). Here, the protein can be thought of as the "*lock*" and the ligand can be thought of as a "*key*". Molecular docking may be defined as an optimization problem, which would describe the "best-fit" orientation of a ligand that binds to a particular protein of interest. However, since both the ligand and the protein are flexible, a *"hand-in-glove"* analogy is more appropriate than *"lock-and-key"*. During the course of the process, the ligand and the protein adjust their conformation to achieve an overall "best-fit" and this kind of conformational adjustments resulting in the overall binding is referred to as **"induced-fit"** [5].

**2**. **Objective of Docking Studies**
2.1 Accurate structural modeling.
2.2 Correct prediction of activity.

In addition to problems associated with scoring of compound conformations, other complications exist that make it challenging to accurately predict binding conformations and compound activity. These include, among others, limited resolution of crystallographic targets, inherent flexibility, induced fit or other conformational changes that occur on binding, and the participation of water molecules in protein–ligand interactions. Without doubt, the docking process is scientifically complex [6-12].

Docking gives an idea about how the ligand is going to bind to the active site of the receptors and also about the extent to which conformational changes can be brought in the receptor structure when the ligand binds to it and hence the response elicited by the drug can be measured [13]. The emphasis on molecular docking is to computationally simulate the molecular recognition process [14]. The aim of molecular docking is to accomplish an optimized conformation for both the protein and ligand and relative orientation between **Formula regarding prediction**
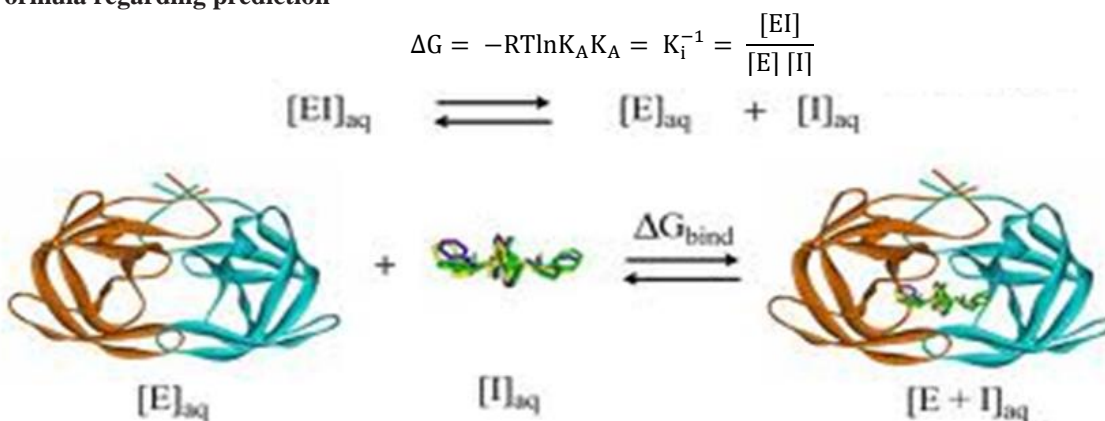
protein and ligand such that the free energy of the overall system is minimized [15-21]. Docking has been a proficient choice for the modeling of 3-dimensional structure of the receptor-ligand complex and evaluating the stability of the complex that determines the specific biological recognition. The docking problem can be subdivided into two steps [22-23].

- Exploring the conformational space of ligands that bind to target molecules.
- Scoring this set, i.e. ranking it in accordance to the estimated binding affinity.

That is a conformation of ligand is typically generated, and with the help of scoring function compared to the earlier conformations [24]. The current conformation is then accepted or rejected on the basis of the score for that respective conformation [25]. Then again a new conformation is generated, and the search process iterates to an endpoint. Thus, searching and scoring can be tightly coupled in docking [21].

**3. Theory Predicting Docking Strategies**
For an enzyme and inhibitor, docking aims at correct prediction of the structure of the complex [E+I] = [EI] under equilibrium conditions. The figure illustrates the binding of inhibitor (I) to enzyme (E) [26-27]. The free energy of binding ($\Delta G$) is related to binding affinity by equations as shown. Prediction of the correct structure (posing) of the [E+I] complex does not require information about $K_A$. However, prediction of biological activity (ranking) requires this information; scoring terms can therefore be divided in the following fashion [28-32]. When considering the term [EI], the following factors are important: steric, electrostatic, hydrogen bonding, inhibitor strain (if flexible) and enzyme strain (Fig.1). When considering the equilibrium shown in equation, the following factors are also important: desolvation, rotational entropy and translational entropy [33-34].

$$\Delta G = -RT\ln K_A K_A = K_i^{-1} = \frac{[EI]}{[E]\,[I]}$$

$$[EI]_{aq} \rightleftharpoons [E]_{aq} + [I]_{aq}$$



**Fig.1 Theoretical view of docking strategies**

## 4. Molecular illustration of docking and involve methodology

To evaluate various docking methods, it is significant to deliberate how the protein and ligand are represented [33-34]. There are three basic representations of the receptor: atomic, surface and grid. Among these, atomic representation is normally only used in aggregation with a potential energy function and often only during final ranking dealings (because of the computational complexity of evaluating pair-wise atomic interactions) [35-36].

Surface-based docking programs are typically, but not exclusively, used in protein–protein docking. Connolly's methods attempt to align points on surfaces by minimizing the angle between the surfaces of opposing molecules. Therefore, a rigid body approximation is still the standard for many protein–protein docking techniques [37-41].

The use of potential energy grids was established by Good ford, and various docking programs use such grid representations for energy calculations [42]. The basic idea is to store information about the receptor's energetic contributions on grid points so that it only needs to be read during ligand scoring [43]. In the most basic form, grid points store two types of potentials: electrostatic and van der Waals [44]. Shows a representative grid for capturing electrostatic potentials, and illustrates the electrostatic potential of a bound inhibitor plotted on its molecular surface [45].



**Fig 2. Grid representations: A)** plot of a grid capturing the electrostatic potential around its active site with bound inhibitor. **B)** Shows a 'cut-away' electrostatic potential grid of the enzyme around the bound inhibitor

### 4.1 Methods involved in docking

The protocol encompasses standard protocols provided by Schrodinger for virtual screening of large databases which includes HTVS, SP &XP. (Fig.03)

### 4.1.1 Protein preparation and docking

The crystal structure was retrieved from protein data bank website with PDB Id and prepared in Schrodinger protein preparation wizard. Crystal structure was subjected to protein preparation wizard for filling missing loops and side chains (using Prime), ionization, H-bond optimization, heterogeneous state generation, protonation and overall minimization. All other ligands, water and ions were removed except ATP molecule [46-49]. Grid file for docking was constructed considering ATP molecule as centroid of grid box of 10°A size [50-51]. The ATP binding site was selected for grid generation and all ligands were docked as described in (figure: screening protocol) with default parameters in virtual screening workflows in Schrodinger, Maestro v10.4.

### 4.1.2 HTVS-High throughput virtual screening

HTVS is the technique intended for the rapid screening of very large numbers of ligands. This has much more restricted conformational sampling than SP docking and so cannot be used with score in place [52].

### 4.1.3 SP-Standard precision

The standard precision screening is indented for the docking of ligands of unknown quality in large numbers. Usually SP screening carried out after HTVS using 5% or 10% molecules of the ligand library (Table. 1).

### 4.1.3 XP-Extra precision

Extra precision is a tool that is designed for docking precisely on good ligand poses. XP docking and scoring

is the more powerful and discriminating procedure in the identification and scoring of ligands [53].

**Table. 1: New docking programs—novel features**

| Program name | Novel features |
|---|---|
| AutoDockVina | Automation of input and output [19]<br>No limit on variables (number of atoms, rotatable bonds, grid map size, etc.)<br>Parallelism and multithreading on multicore machines |
| GENIUS | Binding constraints via Essential Interaction Pairs (EIP) |
| H-DOCK | Docking by hydrogen bond matching and shape complementarity |
| NeuroDock | Generation of docked poses by self-organization of atom coordinates without the need for input/seed conformation |
| VoteDock | Consensus scoring |
| PD-DOCK | Parameter optimization for docking scores [<br>Simplified theoretical model of docking scores |
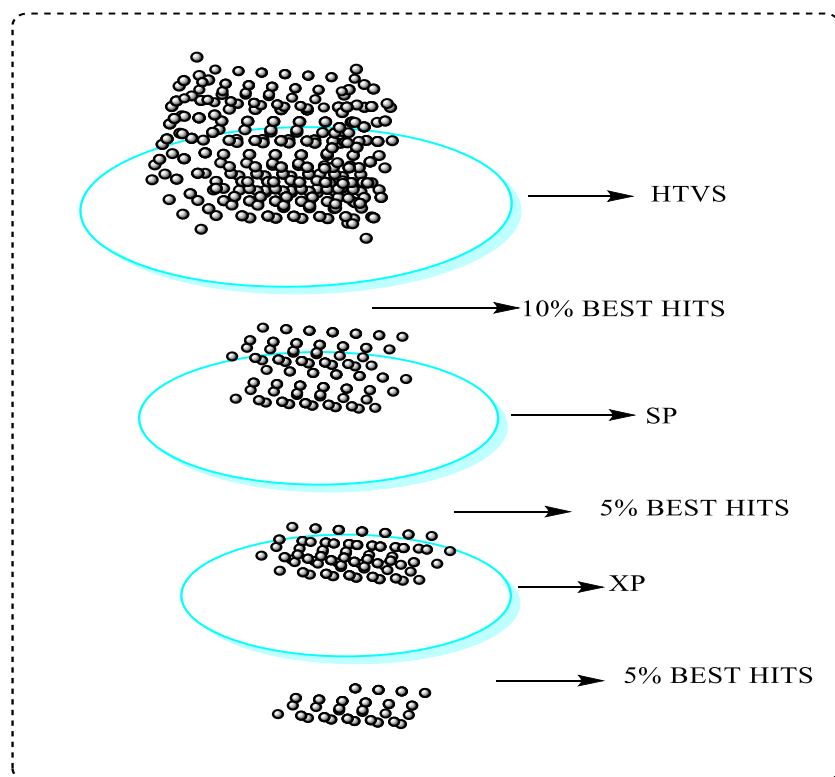


**Fig.3 Protocol followed for the screening process**

## 5. Example including docking studies

Some of the examples concluding in this article regarding the docking studies here the score and many more things are included.

### 5.1 Anticancer studies

The complexation of a possible anticancer agent 2-methoxyestradiol (2-ME) with fifth generation (G5) PAMAM dendrimers have different surface purposeful groups for therapeutic application. The complexation trial shows that approximately 6-8 drug molecules can be complexes with one dendrimer molecule nevertheless the type of the dendrimer terminal groups. The bioactivity of 2-ME complexed with dendrimers was originated to be considerably reliant on the surface charge of G5 dendrimers. The surface alteration of dendrimers with unlike charges is critical for the expansion of formulations of different anticancer drugs for therapeutic applications. Dendrimer-based nanotechnology considerably advances the area of under fire cancer imaging and therapy. The difference of outside acetylated fluoresce in isocyanate (FI) and folic acid (FA) modified G5 PAMAM dendrimers, and dendrimer-entrapped gold nanoparticles through parallel modifications in terms of their precise internalization to FA receptor which express cancer cells. Molecular

dynamics limitation of the two dissimilar nanostructures reveals that the exterior area and the FA moiety allocation from the centre of the geometry are somewhat dissimilar. Biogenic polyamines are important for cell growth and discrimination, while polyamine analogues exert antitumor activity in numerous experimental model systems, counting breast and lung cancer. Dendrimers are extensively used for drug delivery in vitro and in vivo. the bindings of biogenic polyamines, spermine (spm), and spermidine (spmd), and their artificial analogues, 3,7,11,15-tetrazaheptadecane.4HCl (BE-333) and 3,7,11,15,19-pentazahenicosane.5HCl (BE-3333) to dendrimers of dissimilar composition, PEGylated poly(amidoamine) dendrimer (mPEG-PAMAM) G3, mPEG-PAMAM G4 and PAMAM G4. Biogenic polyamines show stronger similarity toward dendrimers than those of artificial polyamines, while weaker interface was experiential as polyamine cationic charges improved and suggested that dendrimers can act as transporter vehicle for deliver antitumor polyamine analogues to goal tissues [54].

**Several biomedical applications are**-
- Impact of Solvent and Dendrimer Topology.
- Impact and Versatility of the End Groups.
- Dendrimers Interaction with Lipid Membranes.
- Modeling Dendrimers for Drug Delivery Applications.
- Modeling Dendrimers as Therapeutic Agent.

Evolution to high-density stuffing occurs between generations 4 and 5. Volume difference between neutral and low pH calculated from R show a theatrical enhance commencement at generation 5.

## 6. Expression of Ligand Activity in Docking
The most of docking algorithmic programs are nonintegrated in nature. So, many publication clear that the ligand representation and their conformation and speciation, have important consequences on docking outcomes.

### 6.1 Action of input ligand conformation
Feher and Williams obtained the variability of docking consequences as a function of input ligand conformations [55] by using GOLD, Glide, and FlexX, [56] they destabilized this variability into two nondependent effects: the insufficiency of the conformational search during docking (major) and random chaotic effects due to sensitivity to (small) input disruptions. To assess the effects of such upsets, they used the $0.1^0$, $1^0$, and $10^0$ torsional grid ensembles for ligand input. The authors further explained their formerly endorsement about the use of multiple conformation as input by developing specific guidelines for a range of program (Table.2).

## 6.2 Technique for conformational behaviour of ligands
*Precomputed conformations*
The main issue of precomputed conformation is the computational cost, mainly for highly flexible ligands. However, the reducing the size of the input conformational ensemble may result in the loss of the biologically related conformation within that input. To challenge this dilemma, Yongye et al. developed a novel collecting scheme (NMRCLUST), which does not require user-defined cutoffs [57]. They tested this objective ensemble clustering against 65 complexes and showed that it executed nearly as well as OMEGA and that a smaller number of conformers were sufficient to capture the biologically relevant conformation.

*Genetic processes*
Fuhrmann et al. started an LGA, which allows handling a large number of degrees of freedom [58], their amalgam method, linking a multi-deme LGA and a gradient –based local optimizer was used in conjunction with the Gehlhaar scoring function. The amalgam method was verified on the Astex diverse set for flexible ligand–receptor docking and was found to be quicker and clearly superior to other LGAs, which employ stochastic optimization techniques.

## 6.3 Special effects of ligand protonation, tautomerism, and stereomerism
The discussion of the significance of ligand tautomeric forms has continued in 2010–2011, with conflicting findings reported.
Milletti and Vulpetti [59] explored the impact of several options of tautomer enumeration in VS. Testing against seven targets from the DUD set, they found that, similar to earlier studies described in, three protocols ((i) all possible tautomeric forms; (ii) all forms with predicted abundance of ≥5% in water; and (iii) only the most stable form) produced comparable results, indicating that including the most stable tautomer may be an optimal strategy because it is most computationally efficient. The authors have included the caveat that the effect may be system dependent. Thus, as a test set of only seven targets was used, it would be interesting to extend such analysis to a larger test set.

In a more wide investigation (176 complexes of 15 receptors), Park et al. used a variety of tautomer enumeration protocols: ensemble, a most stable form, and the protonation state that gives the best docking score.[60] The docking was carried out with Glide, and the estimated binding affinities were correlated with the experimental values. Differing to Milletti and Vulpetti,[61] Park et al. found that using the collective approach leads to developments in correlation in 9 cases out of 15. However, in accord with Milletti and Vulpetti, Park et al. also noted that the effectiveness of each protocol was system dependent.

Exner and ten Brink presented their revised method to generate ligand protonation states with the structure protonation and recognition system.[61] They have validated the effectiveness of this method, in conjunction with docking by the Protein–Ligand ANT System (PLANTS), and its advantages: superiority via the previously used combinatorial approaches, time saving due to decreased number of required protomers, alleviation of issues with highly charged protomers, and increased success rate via penalties for microspecies with lower possibility.

The work by Brooijmans and Humblet [62] produced some conflicting results, which depended on the amalgamation of ligand enumeration technique and a scoring approach. However, they have regularly shown that pH range for generation of tautomer and ionization states should be more conservative (i.e., closer to 7.0) than the 5.0–9.0 range tested. In our opinion, the best approaches for ligand representation and guidelines for ligand enumeration remain to be further developed and refined.

### 6.4 Other aspects of ligand-related developments
A multiple-ligand concurrent-docking approach [63] was developed to deal with cases where binding involves more than one "ligand" molecule, for example, substrate and cofactor, ligand and water(s), or multiple fragments. Multiple-ligand simultaneous-docking was applied within AutoDock4 and was successful for two systems, where conventional single-ligand docking failed.

**Table. 2 Measure of program performance**

| Programs compared | Test set (number of complexes) | Performance measure |
|---|---|---|
| **AutoDock4.0**; DOCK6.0; | Kinase complexes (711 for cognate tests, 421 for cross-docking | Pose prediction: RMSD |
| **Glide4.5; GOLD3.2**; LigandFit2.3; Surflex2.0 Flap; **Glide**; GOLD Affinity prediction: ROC AUC and EF10% [59] **Q-Dock**LHM; **FINDSITE**LHM; | PDBbind (195) DUD (7) Docking accuracy: 278 unique kinase ligand structures; ligand ranking: ZINC (10000); virtual screening: DUD | Pose prediction: RMSD; affinity prediction: score vs. Kd and Ki Affinity prediction: ROC AUC and EF10% Pose prediction: fraction of correctly predicted binding residues; affinity prediction: ligand ranking; EF10%; BEDROC20; AUAC; ACT-50% |
| **Ligand Fit**, GOLD, Surflex, Glide, AutoDock, FlexX, eHiTS Glide XP, Glide SP, Glide HTVS, ICM, FRED-HR CG, Surflex, Surflex-Ring, DOCK, FRED CG, PhDock, FlexX | DUD (40); Cross 2009 set (68) | Pose prediction: RMSD affinity prediction: ROC AUC; ROC at 0.5% – 10% |

### Conclusion
The extensive series of examples illustrated and discussed above - taken from peer review of published data emphasize the role and potentiality of molecular modeling in the pre and post development of its dendrimer complex. Accurate and reliable molecular modeling can be performed more easily than experiments. In silico evaluation can take into account the molecular specificity of the problem and dramatically reduce the time and cost required to formulate a new device and therapeutic intervention, and eventually translate it into the clinical setting. Much functional information regarding the construction and dynamics of dendrimers has been gain. The successful simulation of the dendrimer arrangement has provide a foundation for extend the simulation to the connections of dendrimers with additional molecules. Because of their possible use in various disease studies as mentioned above, Molecular Modelling with Dendrimer complex configuration are chiefly expensive in conniving better drug carrier and address issues that are tricky to be explore by laboratory experiment.

### Abbreviation:
HTVS-High throughput virtual screening
SP-Standard Precision
XP-Extra precision
VS-Virtual Screening

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