GRIP DOCKING: A SIMPLE AND FAST DOCKING METHOD

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Introduction

The binding of small molecule ligands to protein targets is central to numerous biological processes. Protein binding sites exhibit highly selective recognition of small organic molecules, in that, evolution has equipped them with a complex three dimensional "lock" into which a specific "key" will fit. The accurate prediction of the binding mode between the ligand and protein, (the docking problem) is of fundamental importance in modern structure-based drug design. This has been exploited by medicinal chemists in the design of molecules selectively to augment or retard biochemical pathways and so exhibit a clinical effect. A primary challenge in lead discovery and optimization is to predict both ligand orientation and binding affinity; the former is often referred to as 'molecular docking'.

In general, there are two parts to the docking problem: a scoring or evaluation function that can discriminate correctly (i.e., experimentally observed) docking solutions (called poses) from incorrect ones; and a search algorithm that searches the configurational and conformational space for the candidate poses measured by the scoring function. A solution to the docking problem requires a powerful algorithm to search conformational space and an understanding of the processes of molecular recognition, so that reliable predictions of binding modes can be achieved. The algorithms that address this problem have received much attention [1], indicating the importance of docking to a drug design project.

The process of automated docking has been the subject of a major effort in the field of computer-aided molecular design [1] . Early approaches to ligand docking considred both protein and ligand to be rigid, as typified by the DOCK program [2]. Since the bioactive conformation of a bound ligand rarely corresponds to the isolated ligand X-ray structure [3], recent techniques have dealt with the issue of conformational flexibility. Deterministic approaches include the FLOG system of Miller et al. and FlexX of Rarey et al. [4,5]. The latter algorithm is very efficient and has been verified on 19 protein-ligand complexes. The principal techniques currently available are: molecular dynamics, Monte Carlo methods, genetic algorithms, fragment-based methods, point complementarity methods, distance geometry methods, tabu searches and systematic searches.

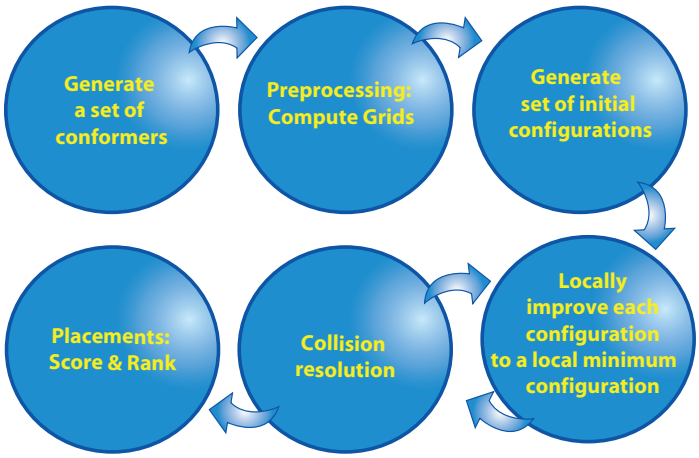
GRIP Methodology and Application

GRIP docking essentially requires a set of ligands with its conformers to be docked into a receptor cavity. In addition, it also allows use of the existing knowledge by providing ligand guided as well as cavity guided options. Using the information regarding receptor cavity and ligand Position (if known), it generates a grid around the reference ligand in the active site or the whole active site itself. GRIP docking consists of pre-computation of grids, sampling a set of initial poses and search of best possible poses by maximizing favorable interaction and minimizing the steric unfavorable and repulsive interaction. An outline of the GRIP docking procedure is delineated below:

1) Generation of conformations for all the molecules to be docked in the receptor.
2) Collection of information on active site of a given protein. If it is co-crystallized, the method uses the ligand position. Alternatively it uses information on the active side residues reported in literature. In absence of active site information, GRIP identfies the biggest cavity as the active site.
3) Defintion of a grid using available information as in point 2.
4) Computation of various energy grids using PLP atom types i.e. H-bond donor, H-bond acceptor, H-bond donor/acceptor, and non-polar groups.
5) Positioning of all the molecules on the centroid of the grid based on lowest interaction energy grid points.
6) Obtaining all the possible poses by exploring rotation of ligand at specific interval at the grid points and optimizing favorable/unfavorable grid point interactions.
7) Scoring the poses by using PLP method utilizing pre-calculated energy grids.

In the present study, performance assessment of GRIP docking was done considering efficiency (time taken) and accuracy (RMSD w.r.t. co-crystal ligand), calculated by its application on two different datasets .

For comparison of GRIP docking accuracy with existing methodologies such as Dock, FlexX, GOLD, GLIDE the following dataset was used. This consists of 65 co-crystallized proteins for which the docking results (using various methods above) have already been reported [6]. These methods have taken the co-crystallized ligand position as a reference. The pdb file of each of 65 proteins with its co-crystallized ligand was downloaded and cleaned. The co-crystallized ligand was then extracted and saved separately as reference ligand and the apo-protein was saved as target. The co-crystallized ligand for each receptor was perturbed for a sufficiently different pose which was fed in as the input ligand file to be docked by GRIP docking. Rotation axes were chosen in x,y,z directions around which the ligand was rotated systematically and exhaustively at the grid points. The comparative results are reported in table 1.
For estimation of GRIP docking efficiency, a dataset of 503 diverse drugs with 10 receptors have been considered for docking. At first a set of conformers were generated for each of the 503 drug molecules using Monte-Carlo method. The conformers within a rahge of 10 kcal/mol relative to global minimum energy, resulted in a total 3711 input conformers, which were considered for the study. Each receptor was prepared in the following way: the receptor structure was downloaded from the PDB site, cleaned, the co-crystallized ligand extracted as reference ligand, the apo-protein saved as receptor. The set of 503 drugs (3711 conformers) were then docked in each receptor using GRIP docking. Top 1000 ligand poses were reported for each receptor. Table 2 shows the time taken for the docking studies.



Results and Discussion

For each receptor the docked co-crystallized ligand was superimposed with the original co-crystallized ligand. The corresponding RMSD in Å as a measure of accuracy are reported below. Here, RMSD1 is the RMSD of superposition of the best aligned GRIP docked pose of the ligand with its original co-crystallized counterpart as in X-ray structure. RMSD2 is the RMSD of superposition of the docked ligand pose having minimum PLP score (best scored pose in the respective scoring function) with its original co-crystallized counterpart. The results in Table 1 clearly indicate the superior performance of GRIP docking compared to DOCK, FlexX, GOLD, Glide docking methods in terms of accuracy. In most of the 65 different receptors studied, there is a marked improvement of both RMSD1 and RMSD2 in GRIP compared to the others. In fact, a significant portion of the RMSD1 lies well below 1.0 for GRIP and Glide compared to the other methods. Following are some key improvements as observed in GRIP:

a) Out of 65 structures, the total number of docked structures with RMSD1 less than 0.5 (the most favored situation) is 43 (~66 %) in GRIP docking which is a little more than that for Glide docking (~55%), whereas it is less than equal to half that number for all other methods.
b) The total number of docked structures with RMSD1 more than 3.0 (the least favored situation) is the least in Glide (~3 %) followed by GRIP(~10%), GOLD (~10 %), FlexX (~26%) and DOCK (~26%).
c) The total number of docked structures with RMSD1 less than 1.0 or 2.0 (favored situation) is again maximum for GRIP and Glide compared to all the other methods which have much lower percentage of such structures.
d) Similarly, GRIP has the highest number of docked structures with RMSD2 <0.5 and 1.0 with a reasonably large margin than that for all other methods.
e) The total number of docked structures with RMSD2 more than 3.0 (the least favored situation) is the least for Glide (~ 20%), followed by GRIP(~ 29 %), GOLD (~32 %), FlexX (~42%) and DOCK (~25%).
f) The GRIP method is thus found to be better than all the other docking methods and comparable to Glide (cf. Table1, Figure1 and Figure 2).

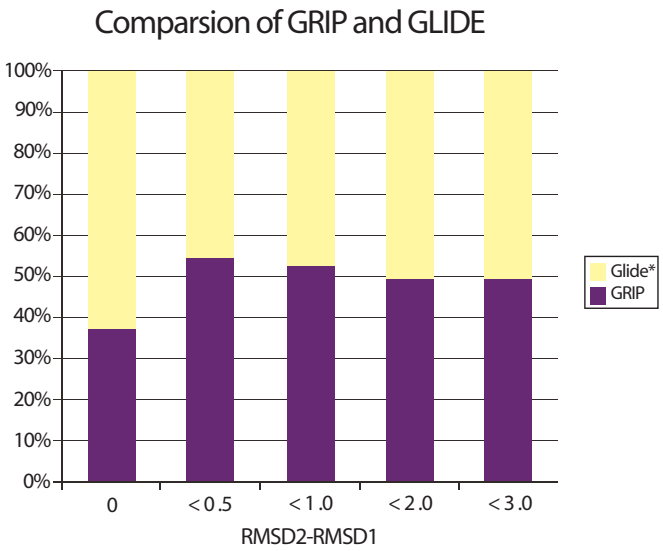
RMSD1 and RMSD2 are absolute parameters to assess the accuracy of the docking method and cannot be used directly to select the best pose. However the best pose is selected on the basis of minimum PLP score which in turn is related to RMSD2. Therefore the difference of RMSD1 and RMSD2 is a direct measure of how close the GRIP docked pose is to the experimental co-crystal pose. Since RMSD1 values of GRIP and Glide methods are comparable (cf. Table1), it is worthwhile exploring difference of RMSD1 and RMSD2 to understand the accuracy of these two methods in predicting the best docked pose with reference to the co-crystal pose. Table 2 indicates that although Glide is slightly better than GRIP for cases having RMSD1 equals to RMSD2, the overall performance of GRIP is better than Glide in terms of difference of RMSD1 and RMSD2 less than 0.5 and 1 Å, whereas they are comparable for this difference less than 2 and 3 Å as shown in figure 3.

Table 2: GRIP and Glide docking results with reference to MSD1 and RMSD2

Performance (RMSD2 -RMSD1)	DOCK*	FlexX	GOLD	Glide*	GRIP
Equals 0	4	10	14	7	4
< 0.5	32	32	39	39	46
< 1.0	40	40	45	46	50
< 2.0	46	52	55	55	54
< 3.0	51	54	56	59	56

* where 64 co-crystal structure were considered.

Figure 3: GRIP and Glide docking results with respect to RMSD1 and RMSD2



In the other experiment to check the efficiency of GRIP docking with the others, the docking time was estimated for 10 widely different receptors and 503 diverse drug set with 3711 conformers as discussed previously. Table 3 shows these results indicating that GRIP is a fairly robust and rapid docking method. It is observed that on an average it takes around 1.5 sec for each molecule to be docked using exhaustive GRIP procedure irrespective of the complexity of the receptor in terms of number of residues. If the method chosen is fast GRIP docking, then this docking speed increases dramatically.

Table 1: Comparative results for GRIP docking accuracy as compared to other methods with reference to RMSD1 and RMSD2

Performance	DOCK*	FlexX	GOLD	Glide*	GRIP
RMSD1 < 0.5	12	10	23	35	43
RMSD1 < 1.0	23	30	41	49	50
RMSD1 < 2.0	35	42	54	59	53
RMSD1 < 3.0	47	48	58	62	58
RMSD2 < 0.5	10	3	7	23	31
RMSD2 < 1.0	17	17	24	35	38
RMSD2 < 2.0	27	33	36	47	43
RMSD2 < 3.0	35	38	44	52	46

• Total 65 structures are studied for all methods except Dock and Glide methods for each of which results are available for 64 structures
RMSD1 in Å of the best pose (closest to the X-ray structure). RMSD2 in Å of the top-ranked pose from the X-ray structure.

Figure 1: Comparative performance of different docking methods with respect to RMSD1

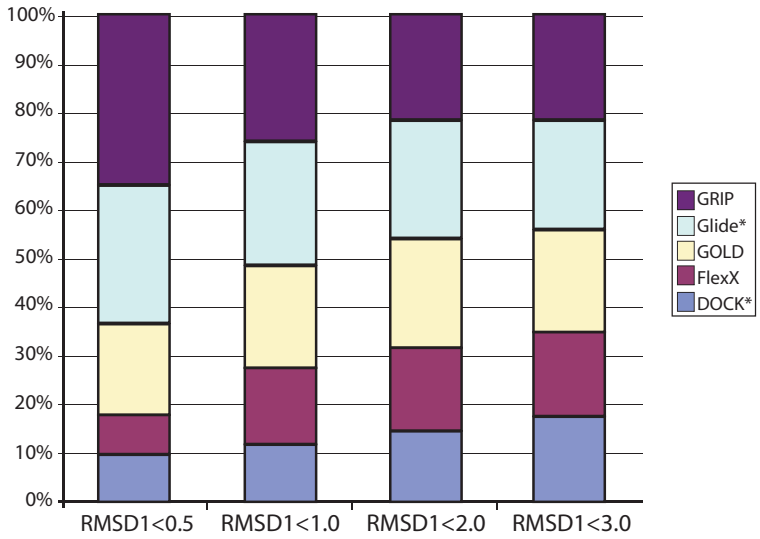


Figure 2: Comparative performance of different docking methods with respect to RMSD2

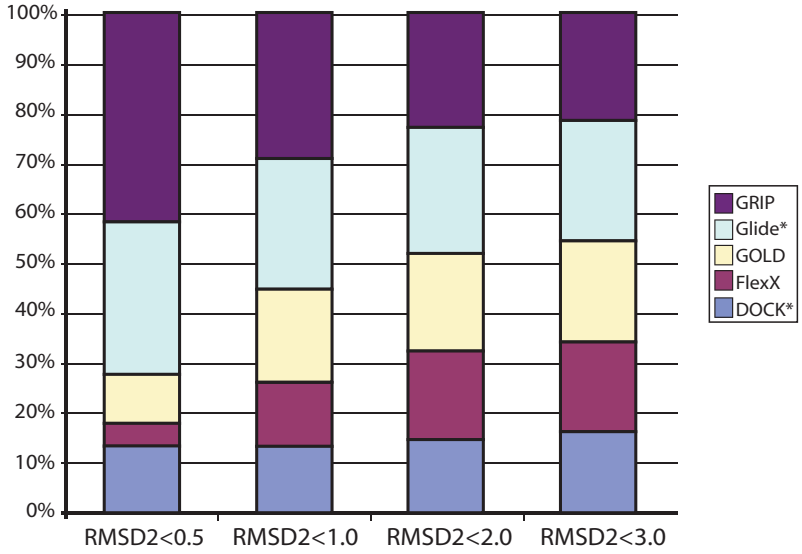


Table 3:Time taken for GRIP docking of 503 Legands with 10 receptors considered in the study

Receptor	No of residues	Time for GRIP docking (mins)
Monoamine Oxidase (2BK3)	496	96
Retinoic acid receptor beta (1XAP)	250	94
PPAR gamma (1I7I)	282	95
Glucocorticoid receptor (1M2Z)	257	92
IMPDH (1JR1)	514	93
Estrogen receptor alpha (1L2I)	254	108
Cholineesterase (2J4C)	523	89
ADP Ribose Polymerase (1UK0)	350	96
DNA Topoisomerase1 (1K4T)	580	96
Fibroblast Growth Factor receptor (1GJO)	312	108

Conclusions

In this work we have proposed a novel rigid docking method, innovatively employing the PLP scoring function for fast and accurate prediction of ligand-receptor interactions. The results in the study indicate the robustness of GRIP docking method together with its power in terms of efficiency and accuracy of the docking results. In addition it is also demonstrated that the proposed method could be used efficiently for virtual screening. The overall results illustrate the significant improvement in efficiency and accuracy of GRIP docking results compared to other docking methods like Glide, GOLD, FlexX and Dock. Thus GRIP provides a better alternative to existing docking methods.

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