

Introduction

Automated docking is a key component of computer-aided drug design. Glide performs efficient docking of compounds, reliably identifying binding modes and predicting binding affinities of candidates.

Results

Accuracy

Predicting the correct binding mode for a ligand is of crucial importance for obtaining reliable docking results in high-throughput docking. In testing Glide on 239 co-crystallized structures from the PDB, the RMS deviations are smaller than 1 Å for more than half of the test cases, and smaller than 1.5 Å for two-thirds of them.

Comparisons have also been done with published results from the well-known docking codes, Gold [1] and FlexX [2]. Only common PDB structures from the datasets were considered in the comparison. As can be seen from the tables below, Glide performs very well.

Average RMS Deviation	
Gold	Glide
3.03 Å	1.62 Å

Table 1. Comparison of 93 co-crystallized structures from the PDB

Average RMS Deviation	
FlexX	Glide
3.67 Å	1.67 Å

Table 2. Comparison of 191 co-crystallized structures from the PDB

Enrichment Factors

Enrichment factor (EF) studies have been performed using Glide on systems that have a number of well-known active binders. The systems' active sites are of very different nature, ensuring that Glide is

proven efficient over a wide range of active sites. Overall, the GlideComp scoring performed well for 6 out of 7 systems. GlideComp is a combination of GlideScore and the Coulomb-van der Waal energy score. For the last system, Thermolysin, a metalloprotease, Glide's Emodel score performed best.

In all instances, the studies were based on recovering 80% of the known binders, and the decoy ligands were taken from the CMC (877) and the PDB (229). Table 3 summarizes the enrichment factors obtained from GlideComp for the different systems.

System	Enrichment Factor
Thymidine Kinase	19
Estrogen Receptor	53
CDK-2 Kinase	5
Sugar-Binding Prot.	66
HIV Protease	28
Thrombin	24
Thermolysin	14*

* Emodel scoring

Table 3. Enrichment Factors for recovering ~80% of known binders

Thymidine Kinase (TK) and the Estrogen Receptor (ER)

This study was initiated in order to compare Glide to published results using other popular docking codes [3]. TK is considered to be a 'hard' test due to the nature of the binding site (Gln side-chain conformation dependent on the nature of the binding ligand, unknown influence of water upon binding) and because only two of the known ligands are submicromolar binders. ER, on the other hand, is a relatively easy target, with mostly nanomolar binders, and less active site conformational dependency on the binding ligand. The results for docking eight out of the ten actives for the different docking codes and scoring functions are listed in Table 4.

Docking Method	Scoring Function	--- EF ---	
		TK	ER
Glide	GlideComp	19	53
Dock	DockEnergy	3.2	5
Dock	PMF	4	1.5
FlexX	FlexX	9	1.4
FlexX	PMF	9	2.8
FlexX	DockEnergy	2.5	17
Gold	Gold	9	14
Gold	DockEnergy	0.9	42

Table 4. Enrichment Factors for docking 8 actives to the TK and ER receptors.

Figure 1 shows the position of the best Glide docking pose of the dT ligand for TK, compared to the co-crystallized dT ligand taken from the PDB. dT is the co-crystallized ligand in the 1kim PDB complex. The RMS deviation between the ligands is 0.35Å.

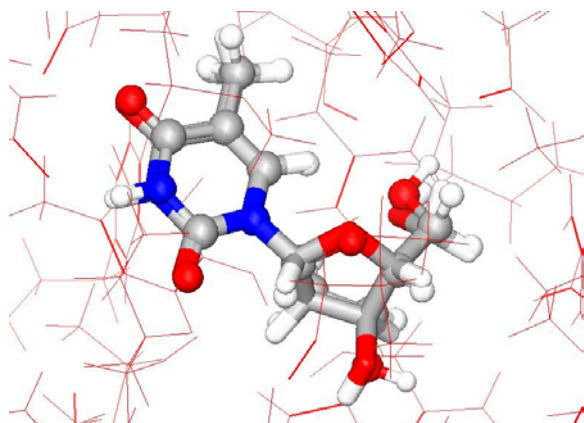


Figure 1. The best Glide solution for dT compared to the original PDB complex (1kim). The Glide solution is represented as ball & stick, while the co-crystallized ligand is represented as tube.

Conclusion

Glide is a highly efficient solution for screening virtual libraries. Using the internal conformer generator, Glide performs a thorough search of the receptor active site and identifies drug candidates having correct binding modes. Using a highly sophisticated scoring function, Glide also successfully rank-orders the ligand-receptor binding affinities.

References

- [1] <http://www.ccdc.cam.ac.uk/prods/gold/value.html>
- [2] <http://cartan.gmd.de/flexx/html/flexx-eval.html>
- [3] Bissantz et al., *J. Med. Chem.* **2000**, *43*, 4759-4767