

VIRTUAL SCREENING

Gliding
to success

When high-resolution structural data for a protein target are available, computationally 'docking' molecules from large databases into the protein structure and scoring their calculated binding affinities can be a valuable aid for enriching the libraries used in screening assays with molecules that are likely to be active. The accuracy of the docking and scoring is crucial to the success of such approaches, and two recent papers in the *Journal of Medicinal Chemistry* describe a new docking methodology — named Glide — that can outperform methods that are generally viewed as representing the current state-of-the-art in docking, such as GOLD and FlexX.

A key problem in docking is that assessing the interaction of all possible conformations, orientations and positions of a given ligand with even one rigid model of the protein receptor is expensive in terms of computational time, and so becomes impractical in database screening unless the library is small. But if all such interaction possibilities are not assessed, important possibilities could be missed.

As described in the first paper, Glide aims to address this issue by approximating a complete systematic search of the conformations, orientations and positions of the docked ligand, allowing large libraries to be screened in a reasonable period of time. This is achieved by using a series of hierarchical filters so that the most



computationally expensive calculations are performed only on a very small fraction of the possible docking solutions for each of the compounds in a large database screen. To boost accuracy while restraining computational costs, the authors also used a strategy in which only a small fraction of the hits identified by Glide were redocked using a more computationally expensive 'extra-precision' version of the program.

Assessment of the docking accuracy of Glide by redocking the ligands from 282 protein–ligand complexes in the Protein Data Bank into the corresponding proteins showed that Glide was nearly twice as accurate as GOLD, and more than twice as accurate as FlexX for ligands having up to 20 rotatable bonds. So, how would this translate into an ability to enrich screening collections with active compounds?

To provide some insight into this question, and as reported in the second paper, the authors tested the ability of Glide to identify known active compounds in a database of druglike 'decoy' ligands selected to be representative of a typical corporate compound collection. Nine

widely differing protein targets were assessed, including thymidine kinase, the oestrogen receptor and HIV protease. Glide was successful in yielding 'enrichment factors' of at least 10 — which corresponds to all the active compounds being in the top 10% of the binding scoring list — for five of the nine targets, and more than five for all but one. Furthermore, comparison with previously published data on thymidine kinase and the oestrogen receptor found that Glide performed better than GOLD 1.1, FlexX 1.8 or DOCK 4.01. It will be interesting to see how successful Glide is in real-life screening situations, and in dealing with the particularly challenging issue of protein flexibility.

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References and links

ORIGINAL RESEARCH PAPERS

Friesner, R. A. *et al.* Glide: a new approach for rapid, accurate docking and scoring. 1. Method and assessment of docking accuracy. *J. Med. Chem.* **47**, 1739–1749 (2004) | Halgren, T. A. *et al.* Glide: a new approach for rapid, accurate docking and scoring. 2. Enrichment factors in database screening. *J. Med. Chem.* **47**, 1750–1759 (2004)

FURTHER READING Bleicher, K. *et al.* Hit and lead generation: beyond high-throughput screening. *Nature Rev. Drug Disc.* **2**, 369–378 (2003)