Digging deep for GOLD: How buriedness may be used to discriminate between actives and inactives in docking

Noel M. O'Boyle, Suzanne R. Brewerton and Robin Taylor
Cambridge Crystallographic Data Centre, Cambridge, UK. E-mail: oboyle@ccdc.cam.ac.uk; Web: http://www.ccdc.cam.ac.uk

Introduction

When protein-ligand docking software is used for virtual screening, the goal is to identify true ligands (actives) in a dataset consisting mainly of non-binders (inactives). Actives tend to bind deep in the binding site. This suggests that scaling the score assigned to particular interactions based on the burial depth may allow better discrimination between actives and inactives. This should lead to improved results (increased enrichments) in virtual screens. We describe the incorporation of burial depth scaling (BDS) into the ChemScore scoring function in the docking software, GOLD.

Figure 1 – The goal is to make it easy to pick out active molecules from a large database.

Experimental Method

A burial depth scaling function, ***f(ρ)***, (**Figure 2**) was introduced into the ChemScore scoring function that scaled individual hydrogen bonds based on the depth at which they occurred. A constant scaling, S_{lipo}, was introduced for lipophilic interactions (burial depth scaling for lipophilic interactions was not found to perform better). The optimal parameter values were determined using positive and negative data generated using the Astex Diverse Set [**1**], 85 high-quality protein-ligand complexes. The positive data were correctly docked poses of the known ligands (or in 6 cases, the locally-optimised crystal structure). For each active, negative data were generated by docking 99 inactives which were selected to be topologically distinct from the active yet physicochemically similar.

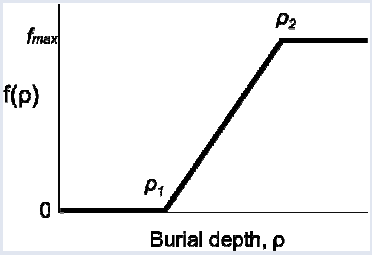

Figure 2 - Burial depth scaling function *f(ρ)*

By varying the parameters ρ_1, ρ_2, f_{max}, and S_{lipo}, a brute-force optimisation procedure was used to optimise the mean rank of the score of each active with respect to its 99 inactives. The final results were tested with a test set of new inactives.

Results

The optimisation procedure improved the mean rank of the active molecules from 18.6 to 12.5 (top rank is 1), with only a few actives decreasing in rank (**Figures 3, 4**). The overall effect was to reward hydrogen bonds deep in the active site, and to reduce the contribution of lipophilic interactions. For the test set, the ranks improved from 18.8 to 12.6.

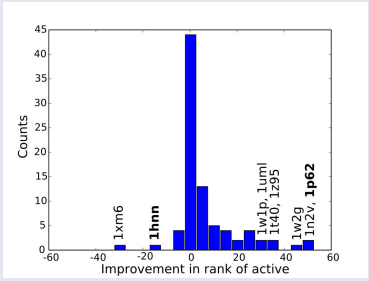

Figure 3 – Histogram showing the effect of BDS on the ranks of the actives.

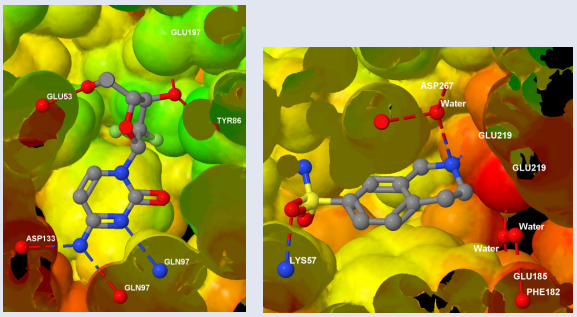

Figure 4 - Protein-ligand complexes (i) 1p62 and (ii) 1hnn. Surface coloured by burial depth (red is deep, blue is shallow).

Conclusions

Incorporating burial depth into the ChemScore scoring function in GOLD leads to improved enrichments across a wide range of pharmaceutically relevant proteins. Negative data may successfully be used to identify and address deficiencies in empirical scoring functions (see also [**2**]).

Burial depth scaling is available as an option in GOLD 4.0.

Future Work

Can burial depth scaling also be used during the docking process itself, rather than simply in rescoring docked poses? Preliminary work shows that the clash term needs to be retrained to avoid rewarding deep hydrogen bonds at the expense of good poses.

1 Hartshorn, M. J.; Verdonk, M. L.; Chessari, G.; Brewerton, S. C.; Mooij, W. T. M.; Mortenson, P. N.; Murray, C. W. *J. Med. Chem.* **2007**, *50*, 726-741.
2 Pham, T. A.; Jain, A. N. *J. Med. Chem.* **2006**, *49*, 5856-5868.