DATE: 04/10/22

WEBLEM 7: CombiGlide

Aim: CombiGlide: A building molecular database along with special emphasis on retriebal using structure input.

Introduction:

The number of drug-discovery initiatives that have a high-resolution crystal structure of the receptor available in recent years has increased, and this trend is projected to continue, as a result of the human genome project and high-throughput crystallography studies. A common computational strategy in this case is to dock molecules into the receptor from a physical or virtual database and then apply an appropriate scoring function to calculate the binding affinity. Numerous dockings programmes are widely used by the pharmaceutical and biotechnology sectors; the most common ones seem to be GOLD, FlexX, and DOCK. Over the past few years, these programmes have shown significant success with virtual screening applications.

Grid-based ligand docking with energetics is the new docking technique used by the Glide software suite from FirstDiscovery. Glide was created to screen large libraries quickly enough while doing the most thorough possible search of the positional, orientational, and structural space. This was accomplished by using several hierarchical filters, as will be described in more detail below. The current performance characteristics of Glide are as follows.

1) On an AMD Athelon MP 1800+ CPU running Linux, docking times for data sets with 0–10 rotatable bonds typically take less than one minute.
2) In comparison to what is published in the present literature for widely used docking algorithms, robustness in binding mode prediction is qualitatively greater. For instance, a comparison with the results obtained by the creators of GOLD shows that for the 72 noncovalently bound cocrystallized ligands of the GOLD test set15 that have 10 or fewer rotatable bonds, Glide's average rmsd is 1.46 A while GOLD's is 2.56. Even more favourably, FlexX is compared. Similar conclusions can be drawn from comparisons for ligands with up to 20 rotatable bonds.
3) The predicted binding affinities for cocrystallized complexes are reasonable (2.3 kcal/mol rmsd), although they could certainly be better.
4) The results of the library screening, which are given in the paper that follows, 16 are quite positive. Additionally, compared to earlier Glide versions, Glide 2.5 yields database enrichment factors that are noticeably greater.

Overview: Docking Methodology

Glide employs a system of filters to search for probable ligand locations in the receptor's active-site region. The shape and properties of the receptor are described by different sets of fields on a grid that enable progressively more accurate scoring of the ligand posture. These fields are generated during the preprocessing steps of the calculation, thus they only need to be computed once for each receptor.

The following procedure results in a number of initial ligand conformations. These conformations are given in a compact combinatorial form and are chosen from an extensive list of the minima in the ligand torsion-angle space. Given these ligand conformations, preliminary searches are made across the ligand's full phase space to identify viable ligand poses.

While avoiding the use of stochastic methods, which can miss important phase-space regions occasionally and prevent the development of a truly robust algorithm, his prescreening significantly reduces the region of phase space over which computationally expensive energy and gradient evaluations will later be carried out. While Glide is unique in that it relies on comprehensive systematic search techniques, reasonable computational speed necessitates approximations and truncations.

Using a typical molecular mechanics energy function along with a distance-dependent dielectric model, the ligand is minimised in the field of the receptor starting from the poses chosen by the initial screening.

Finally, on the three to six lowest-energy sites discovered in this manner, a Monte Carlo method is employed to search for close torsional minima. Such a method may occasionally be required to accurately orient peripheral groups and potentially alter internal torsion angles. The standard molecular mechanics energy function offers a trustworthy model for predicting binding modes even in the absence of a solvent.

However, it is sufficient for ranking different ligands, such as ligands with different net charges. A modified and improved version of the ChemScore! scoring tool, GlideScore, is created to forecast binding affinity and rank-order ligands in database screens. Combining the GlideScore, the ligand-receptor molecular mechanics interaction energy, and the ligand may determine the optimal docked configuration.

It is necessary to modify the scoring method, particularly the molecular mechanics component, to take into account the fact that the protein structure utilised for docking is frequently not optimised to fit a particular ligand. This is the key last issue. Most actives cannot fit because the protein cavity is too small when docking a library of ligands into a single stiff receptor shape. Van der Waals radii of often chosen (e.g., nonpolar) protein and/or ligand atoms are scaled down to expand the binding pocket in order to prevent this. According to studies, this tactic is effective here. The default values are sufficient, even if altering the scale parameters for a specific receptor typically leads to superior enrichment.

Scoring Function:

The starting point for Glide scoring is the empirically based ChemScore function of Eldridge et al., which can be written as:

$$\Delta G_{\text{bind}} = C_0 + C_{\text{lipo}}\sum f(\text{r}_{\text{lr}}) + C_{\text{hbond}}\sum g(\Delta \text{r})\, h(\Delta\alpha) + C_{\text{metal}}\sum f(r_{\text{lm}}) + C_{\text{rotb}}H_{\text{rotb}}$$

The summation include all ligand-atom/receptor-atom pairs classified as lipophilic by ChemScore, whereas the third term encompasses interactions involving ligand-receptor hydrogen bonds. For lengths or angles that are within nominal bounds and fall inside greater threshold values, f, g, and h are functions that provide a complete score (1.00) and a half score (1.00-0.00), respectively. For instance, g(r) is 1.00 if the H—-X hydrogen bond distance is less than or equal to 0.25 of the nominal value of 1.85, but it linearly decreases to zero if it is between 2.10 and 2.50. In a similar manner, h(R) equals 1.00 if the Z-H—- X angle is between 150° and 120° and zero between 180° and 30°.

GlideScore 2.5 modifies and extend the CHemScore function as follows:

$$\Delta G_{\text{bind}} = C_{\text{lipo-lipo}}\sum f(\text{r}_{\text{lr}}) + C_{\text{hbond-neut-neut}}\sum g(\Delta r)\, h(\Delta\alpha) + C_{\text{hbond-neut-charged}}\sum g(\Delta r)\, h(\Delta\alpha) + C_{\text{hbond-charged-charged}}\sum g(\Delta r)\, h(\Delta\alpha) + C_{\text{max-metal-ion}}\sum f(r_{\text{lm}}) + C_{\text{rotb}}H_{\text{rotb}} + C_{\text{polar-phob}}V_{\text{polar-phob}} + C_{\text{coul}}E_{\text{coul}} + C_{\text{vdW}}EvdW + \text{solvation terms}$$

According to ChemScore, the phrase "lipophilic-lipophilic" means. The ChemScore form is used for the hydrogen-bonding term as well, but it is divided into variously weighted components depending on whether the donor and acceptor are both neutral, one is neutral and the other is charged, or both are charged. The first of these contributions is discovered to be the most stabilising and the final, the charged-charged term, to be the least significant in the optimised scoring system. While using the same functional form as ChemScore, the metal-ligand interaction term differs in three key aspects.

First, only interactions with anionic acceptor atoms are taken into account (such as either of the two oxygens of a carboxylate group). With this adjustment, Glide is now able to distinguish metalloproteases' significant propensity for coordinating the functionality of anionic ligands to metal centres. In addition, when two or more metal ligations are discovered, Glide 2.5 only counts the best interaction. We chose a decent value for the coefficient—-2.0 kcal/mol—even though the parameter refinement would have favoured a value that was even more drastically negative. Third, we evaluate the metal ion's net charge in the unligated apo protein (generally straightforward via examination of the directly coordinated protein side chains). An anionic ligand is preferred if the net charge is positive.

Docking Accuracy:

The capacity of Glide to mimic the cocrystallized ligand geometries of a sizable group of 282 publicly accessible PDB24 complexes is assessed in this section. This set contains the majority of the well-known GOLD and FlexX test set members, 50 PDB complexes that were used to evaluate Glide for potential customers, and an additional 50 complexes whose experimental binding affinities were used to create one or more of the empirical scoring functions mentioned in the literature (e.g., ChemScore). These complexes were used to calibrate the GlideScore algorithm along with others discovered in the FlexX and GOLD test sets. Our coverage of the GOLD and FlexX sets is incomplete since Glide cannot handle ligands with more than 35 rotatable bonds or ligands that are covalently linked (seven cases: 1aec, 1ase, 1blh, 1tpp, and 1lmp) (one case: 2er6). Furthermore, one complex (6rsa) was ignored since it has a vanadium atomic species, which is missing parameters from Glide's OPLS-AA force field.

CombiGlide includes the following capabilities and features:

Library enumeration:
1. Enumerate complete combinatorial libraries.
2. Untangles and minimizes structures.

Interactive enumeration:
1. Define and manage collections of fragments (R groups).
2. Enumerate complete combinatorial libraries.

Virtual Combinatorial screening:

1. Performs rapid screening of large virtual combinatorial libraries against 3D targets
2. Are orders of magnitude faster than docking the entire library
3. Performs flexible docking using the standard and extra precision (XP) modes of Glide
4. Provides multiple post-docking library selection strategies and options
5. Allows for incorporation of predicted ADME properties into selection process
6. Analyzes selected libraries for enrichment of actives and chemical features

All workflows:

Provides automated reagent file prearation: 2D to 3D conversion, generation of reasonable ionization and tautomeric states, stereoexpansion, assignment of attachment points

↓

Uses a “core plus side chains” approach

↓

Offers extensive flexibility in initial core placement

↓

Uses an intuitive, user-friendly wizard-based GUI for setting up and monitoring jobs and for visualization of docked poses

References:

1. Friesner, R. A., Banks, J. L., Murphy, R. B., Halgren, T. A., Klicic, J. J., Mainz, D. T., Repasky, M. P., Knoll, E. H., Shelley, M., Perry, J. K., Shaw, D. E., Francis, P., & Shenkin, P. S. (2004). Glide: a new approach for rapid, accurate docking and scoring. 1. Method and assessment of docking accuracy. Journal of medicinal chemistry, 47(7), 1739–1749. https://doi.org/10.1021/jm0306430
2. CombiGlide 2.8: User Manual. (n.d.). Retrieved October 3, 2022, from http://gohom.win/ManualHom/Schrodinger/Schrodinger_2012_docs/combiglide/combiglide_user_manual.pdf