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Critical Assessment of the Automated AutoDock as a New Docking Tool for Virtual Screening

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ABSTRACT **A major problem in virtual screening concerns the accuracy of the binding free energy between a target protein and a putative ligand. Here we report an example supporting the outperformance of the AutoDock scoring function in virtual screening in comparison to the other popular docking programs. The original AutoDock program is in itself inefficient to be used in virtual screening because the grids of interaction energy have to be calculated for each putative ligand in chemical database. However, the automation of the AutoDock program with the potential grids defined in common for all putative ligands leads to more than twofold increase in the speed of virtual database screening. The utility of the automated AutoDock in virtual screening is further demonstrated by identifying the actual inhibitors of various target enzymes in chemical databases with accuracy higher than the other docking tools including DOCK and FlexX. These results exemplify the usefulness of the automated AutoDock as a new promising tool in structure-based virtual screening. Proteins 2006;65:549–554.** © 2006 Wiley-Liss, Inc.

Key words: virtual screening; drug discovery; docking; AutoDock; chemical database; automation

INTRODUCTION

The developments over the past two decades in molecular docking have provided a useful tool to identify lead compounds for a target protein through structure-based virtual screening of chemical databases. In practice, it can be considered as a valuable computational aid for enriching the chemical library used in screening assays with molecules that are likely to have biological activities.[1] But until recently drug discovery and chemical biology remain dominated by empirical screening, due to the inaccuracy in calculating the free energy of binding for protein–ligand association.[2] However, a large-scale empirical screening is becoming an increasingly difficult task because of the dramatic increase in pharmaceutical targets with the sequencing of human genome and also in the number of synthetic compounds. Therefore, there is an urgent need for a new virtual screening tool with a reliable scoring function that can be used to explore biologically relevant chemical spaces.

A number of docking programs for virtual screening have been reported including DOCK,[3] FlexX,[4] GOLD,[5] ICM,[6] GLIDE,[7] SLIDE,[8] LigandFit,[9] FRED,[10] and Surflex.[11] The main research interest in developing a new docking program has been focused on the scoring function in which a binding free energy contribution of individual protein–ligand interaction should be described. At least two types of scoring scheme are being used at present. One is the knowledge-based scoring function based on statistical analysis of particular atom–pair interactions and interaction distances in a large structural database of protein–ligand interactions. The other energy function is force-field based and similar to the nonbonded interaction energies of the potential functions in molecular mechanics. Recently, several popular docking programs with varying scoring functions have been evaluated in comparative manner to test the efficacies of their scoring functions in virtual screening.[12–16] Although the docking accuracies have had a dependence on the way programs are run, some docking packages such as ICM, Surflex, and LigandFit were shown to outperform the others in some test cases. It was also shown that a consensus scoring by combining several docking methods would improve the performance of virtual screening significantly.[17–19]

Since the development and improvement of the AutoDock program in 1990s,[20–22] it has been widely used in predicting a receptor–ligand binding configuration.[23] Suitable binding positions are found by combining a rapid energy evaluation through precalculated grids of affinity potentials with the Lamarckian genetic algorithm. Recent cross-docking experiments showed that AutoDock outperformed the DOCK, FlexX, and GOLD in predicting the correct binding modes that appear in the X-ray structures of protein–ligand complexes.[12] Despite such a good performance in docking simulation, it has not been used as a

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docking tool for virtual screening of chemical databases except for the case of AICAR transformylase.[24] The reasons for this might be the technical difficulty in automating the AutoDock to cope with a large number of compounds, as well as the low docking speed for a single ligand. The purpose of the present study is to provide independent benchmarks for the automated and accelerated AutoDock in virtual screening as compared to DOCK and FlexX. It will be shown that the automated AutoDock program can be one of the promising docking tools in virtual screening of chemical databases.

MATERIALS AND METHODS

Preparations of the Target Protein Coordinates

To assess the performance of the automated AutoDock in virtual screening as compared to the existing methods, we selected cyclin-dependent kinase 2 (CDK2), protein tyrosine phosphatase 1B (PTP1B), phosphodiesterase 4 (PDE4), and cyclooxygenase-2 (COX-2) as the target proteins with availability of known ligands and diversity of active sites kept in mind. The 3D coordinates were obtained from the PDB[25] entries corresponding to the crystal structures of CDK2, PTP1B, PDE4D, and COX-2 in their complexes with NU6102 (PDB code: 1H1S),[26] a peptidomimetic inhibitor (1G7F),[27] roflumilast (1XOQ),[28] and SC-558 (1CX2),[29] respectively. After removing the ligands and solvent molecules, hydrogen atoms were added to each protein structure. A special attention was paid to assign the protonation states of the ionizable Asp, Glu, His, and Lys residues. The side chains of Asp and Glu residues were assumed to be neutral if one of their side chain carboxylate oxygens were located within 3.5 Å from a hydrogen-bond accepting group including the backbone aminocarbonyl oxygen. Similarly, the lysine side chains were protonated unless the NZ atom was in proximity with a hydrogen-bond donating group.

Constructions of Compound Databases

The docking library for each target protein comprises its own 20 known inhibitors as well as 980 common compounds selected from the MDL Drug Data Report database. This selection was based on the drug-like filters that adopt only the compounds with physicochemical properties of potential drug candidates[30] and without reactive functional group(s). All of the compounds included in the docking libraries were then subjected to the Corina program to generate their 3D coordinates, followed by the assignment of Gasteiger–Marsilli atomic charges.[31] The structures of the known inhibitors of CDK2, PTP1B, PDE4, and COX-2 seeded in docking libraries are shown in the Supplementary Material.

Virtual Screening with Automated AutoDock

The AutoDock suite of program consists of three major parts: assignment of torsional motions and docking parameters of a ligand, precalculating 3D grids of interaction energy for the input ligand in the binding site, and the actual docking simulation. For a given ligand and a target protein, the second and the third steps consume most of computational time to a similar extent when 10–20 independent docking runs are performed. One of the characteristic features discriminating the original AutoDock from the other docking programs is that the atom types absent in the input ligand are excluded in the calculation of potential grids. This is because the original AutoDock was developed for the purpose of precise binding mode analysis of a single ligand instead of database screening. Therefore, the time-consuming grid calculation should be carried out for each ligand in database screening with the original AutoDock, which makes the program very inefficient in virtual screening. To make the AutoDock program a suitable docking tool for database screening by increasing the docking speed of individual ligands, we calculated the 3D grids of interaction energy for all possible atom types at one time. These uniquely defined potential grids for a receptor protein were then used for docking simulations of all compounds in chemical libraries. As the center of the common grids, we used the center of mass coordinates of the ligand that had been removed from the binding site of the target protein under consideration. These grid maps were of dimension 61 × 61 × 61 points with the spacing of 0.375 Å, yielding a receptor model that includes atoms within 22.9 Å of the grid center.

In the actual docking simulation of a compound in the docking library, we used the empirical scoring function of the original AutoDock program that has the following form:

$$\Delta G^{\mathrm{aq}}_{\mathrm{bind}} = W_{\mathrm{vdW}} \sum_{i=1} \sum_{j>i} \left(\frac{A_{ij}}{r_{ij}^{12}} - \frac{B_{ij}}{r_{ij}^{6}} \right) + W_{\mathrm{hbond}} \sum_{i=1} \sum_{j>i} E(t) \left(\frac{C_{ij}}{r_{ij}^{12}} - \frac{D_{ij}}{r_{ij}^{10}} \right) + W_{\mathrm{elec}} \sum_{i=1} \sum_{j>1} \frac{q_i q_j}{\varepsilon(r_{ij}) r_{ij}} + W_{\mathrm{tor}} N_{\mathrm{tor}} + W_{\mathrm{sol}} \sum_{i=1} \sum_{j>i} (S_i V_j + S_j V_i) e^{(-r_{ij}^2/2\sigma^2)}, \quad (1)$$

where W_{vdW}, W_{hbond}, W_{elec}, W_{tor}, and W_{sol} are weighting factors of van der Waals, hydrogen bond, electrostatic interactions, torsional term, and desolvation energy of inhibitors, respectively. r_{ij}, A_{ij}, and C_{ij}, and B_{ij} and D_{ij} represent the interatomic distance, the depths of energy well, and the equilibrium separations between the two atoms, respectively. The hydrogen bond term has an additional weighting factor, $E(t)$, representing the angle-dependent directionality. With respect to the distant-dependent dielectric constant, $\varepsilon(r_{ij})$, a sigmoidal function proposed by Mehler and Solmajer[32] was used in computing the interatomic electrostatic interactions between a receptor protein and its ligands. In the entropic term, N_{tor} is the number of sp^3 bonds in the ligand. In the desolvation term, S_i and V_i are the solvation parameter and the fragmental volume of atom i,[33] respectively. For each compound in the docking libraries, 10 docking runs were performed with the initial population of 50 individuals. Maximum number of generations and energy evalu-

ation were set to 27,000 and 2.5×10^5, respectively. All energy terms in Eq. (1) were calculated on the grid points with all-atom models of a protein receptor and a ligand.

Virtual Screening with FlexX

All default parameters, as implemented in Sybyl 6.9, were used for all target proteins and compounds in docking simulations. The active site and the interaction surface of the receptor were defined by using a reference ligand in the X-ray structure and cutoff distance of 6.5 Å. The conformational flexibility of the ligand was modeled by a discrete set of preferred torsional angles for acyclic single bonds. Base fragments were then selected automatically with the maximum number of four. A base fragment was placed into the active site based on the two algorithms. The first one superimposes triples of interaction centers of the base fragment with triples of compatible interaction sites. Second, the matching algorithm was used when the base fragment had fewer than three interaction centers. The empirical scoring function given in Eq. (2) was used for ranking the binding modes of each ligand in the prepared compound databases.[34]

$$\Delta G_{\text{bind}} = \Delta G_0 + W_{\text{hbond}} \sum_{\text{hbonds}} f(\Delta R, \Delta\alpha) + W_{\text{ionic}} \sum_{\text{ionic}} f(\Delta R, \Delta\alpha) + W_{\text{aro/aro}} \sum_{\text{aro/aro}} f(\Delta R, \Delta\alpha) + W_{\text{lipo}} \sum_{\text{lipo}} f^*(\Delta R) + W_{\text{tor}} N_{\text{tor}} \quad (2)$$

Here, $f(\Delta R, \Delta\alpha)$ is a scaling function penalizing deviations from the ideal distances and angles and $f^*(\Delta R)$ penalizes forbiddingly close contacts between lipophilic interactions involving nonaromatic groups. ΔG_0, W_{hbond}, W_{ionic}, $W_{\text{aro/aro}}$, W_{tor}, and W_{lipo} are adjustable parameters representing the weighting factors of a constant energy value, hydrogen bond, the interaction between charged atoms, aromatic–aromatic interactions, entropic term, and lipophilic interaction energy, respectively.

Virtual Screening with DOCK

First, a Connolly surface[35] of the binding site was generated by using a 1.4-Å probe radius, followed by the generation of a set of overlapping spheres that were then clustered according to their spatial distribution. The spheres located too distant from the binding site were eliminated in the final model cluster. To compute interaction energies, 3D grids of 0.3-Å resolution were centered on the binding site. These energy scoring grids were obtained by using an all-atom model and a distance-dependent dielectric function ($\varepsilon = 4r$) with a 10-Å cutoff. The size of the grid box was chosen to enclose all selected spheres using an extra margin of 6 Å. A flexible docking was then performed starting with a selection and matching of an anchor atom within a maximum of 500 orientations, followed by growth of the ligand with 25 configurations per cycle. The final step included energy minimizations with the following scoring function to generate a binding mode of the best energy score.

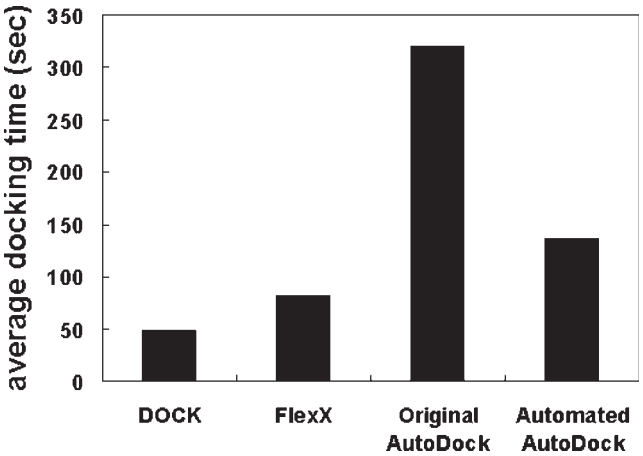

Fig. 1. Comparative view of the average docking time per molecule for various virtual screening tools. The average values are obtained with the 80 known inhibitors and the four target proteins (CDK2, PTP1B, PDE4D, and COX-2) under consideration.

$$\Delta G_{\text{bind}} = \sum_{i=1}^{\text{lig.}} \sum_{j>i}^{\text{rec.}} \left(\frac{A_{ij}}{r_{ij}^{12}} - \frac{B_{ij}}{r_{ij}^{6}} + \frac{q_i q_j}{\varepsilon(r_{ij}) r_{ij}} \right) \quad (3)$$

RESULTS AND DISCUSSION

A very low docking speed has prevented the AutoDock program from being considered as a useful tool in virtual screening of chemical databases, limiting its usage to calculating the binding modes of a single ligand. One of the reasons for such inefficiency is that the calculation of 3D potential grids for each putative ligand is a time-consuming task as comparable to its actual docking simulation with a target protein. Therefore, the total computing time for continued independent docking simulations of multiple ligands with AutoDock seems to be reduced to a substantial extent if the unique 3D potential grids would be used automatically for all ligands in common. Figure 1 shows the average speed of docking simulation in virtual screening with such an automated AutoDock in comparison to DOCK and FlexX as well as to the original AutoDock. We note that the use of uniquely defined potential grids for all compounds leads to more than twofold increase in overall docking speed, making the automated AutoDock a plausible tool in virtual screening. However, it is still two- to threefold slower than DOCK and FlexX. This indicates that for the automated AutoDock to be a useful tool for virtual screening, the scoring function in Eq. (1) should be accurate enough to make up for the relatively high computational cost.

To estimate the effects of the use of uniquely defined potential grids on the accuracy in virtual screening, we compare the binding free energies of the 80 known inhibitors for their respective target proteins calculated with the automated and the original AutoDock programs. As shown in Figure 2, the two results are well correlated irrespective of the target proteins, yielding a correlation coefficient $r^2 = 0.981$. This indicates that the

change of the potential grids based on individual ligand coordinates to the common ones built using the active site coordinates would have an insignificant effect on the docking results of AutoDock.

We have tested the performance of the automated AutoDock in virtual screening as compared to DOCK and FlexX. This comparative evaluation was done with the X-ray structures of CDK2, PTP1B, PDE4, and COX-2 as the target proteins and their respective docking libraries, each of which contains 980 randomly chosen drug-like molecules in common and 20 known inhibitors. Shown in Figure 3 is the percentage of true hits retrieved by the automated AutoDock in increasing fractions of the starting database in comparison to those retrieved by FlexX and DOCK. We note that the automated AutoDock always performs the best in providing the highest enrichment at every fraction cutoff except for 2% in COX-2. It consistently picks at least six actives seeded in top 5% of the database for each target under investigation, as compared to the ranges of 3–6 for FlexX and 0–3 for DOCK. The performance of the automated AutoDock becomes clearer when one compares their ability to pick out the most actives out of a cumulative total of 80 used in this study. When 5% of the database is considered, for example, the automated AutoDock retrieved a total of 45 actives out of the total 80 known inhibitors for all targets, contrary to 17 and 5 actives by FlexX and DOCK, respectively. For a smaller cutoff of 2%, the automated AutoDock retrieved 21 actives, while the numbers of actives are 10 and 3 for FlexX and DOCK, respectively. Thus, the outperformance of the automated AutoDock reveals a consistency in all targets and for all cutoffs, indicating that it can be a promising docking tool for virtual screening.

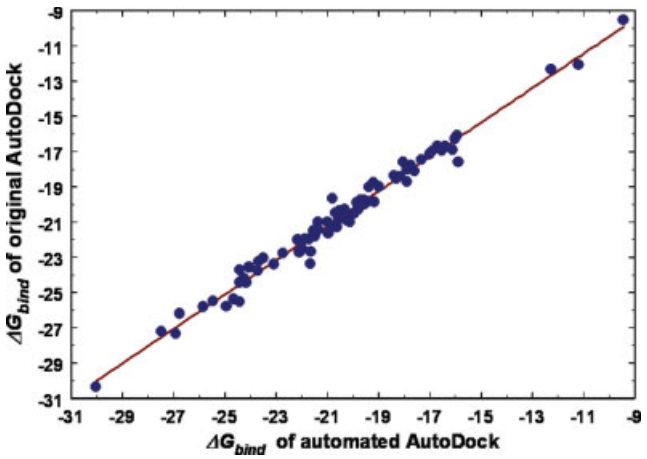

Fig. 2. Correlation between the calculated binding free energies with the automated and the original AutoDock programs.

The difference in accuracies of three docking programs in database screening can be understood by comparing their respective scoring functions. The worst performance of DOCK is not surprising because its scoring function lacks a few important binding free energy terms, including the angle-dependent directionality of a hydrogen bond and entropic penalty for the formation of a protein–ligand complex. On the other hand, there are two characteristic features that discriminate the scoring function of AutoDock from those of the other docking

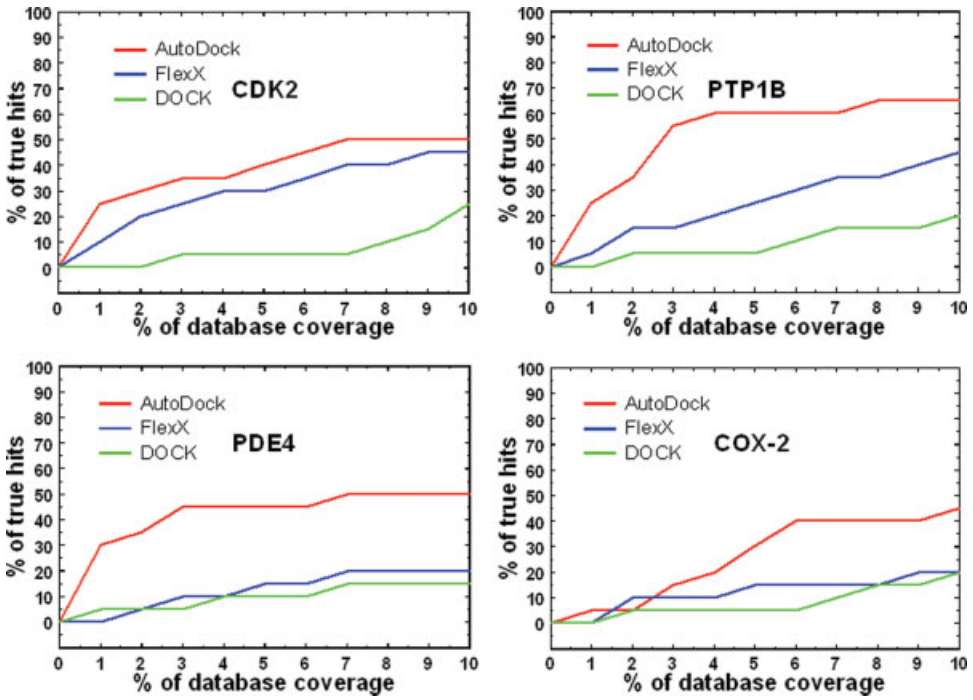

Fig. 3. The cumulative percentage of known inhibitors of CDK2, PTP1B, PDE4, and COX-2 recovered by virtual screening as a function of the top-scoring fraction of the database selected for generating a hit list.

programs: the uses of a sigmoidal distance-dependent dielectric function in the electrostatic term and desolvation cost for complexation of a ligand in the binding site. The former has an effect of modeling solvent screening in the electrostatic interactions between charged atoms.[31] This is important because the top-scored ligands obtained with a small value of dielectric constant tend to possess many atoms with high partial charges as a consequence of the overestimation of electrostatic interactions. The effect of ligand solvation is also important, particularly in comparing many putative ligands that differ in polarity and size. The hit compounds may have a severe charge separation on their molecular structures or be larger than expected unless the energy of the solvated state is considered in docking simulations.[36] Thus, a significant outperformance of AutoDock over the other two popular docking programs should be attributed to the inclusion of solvation term in the scoring function as well as a more proper description of electrostatic interactions between protein and ligand atoms.

We now turn to comparing the performance of the automated AutoDock revealed in this study with those of the other docking programs that have been reported previously in literature. Considering the top 1% of binders, the automated AutoDock places 5, 5, 6, and 1 inhibitor(s) of PTP1B, CDK2, PDE4, and COX-2, respectively, out of 20 seeded in their respective docking libraries. This corresponds to the overall hit rate of 21%, which is similar to that of the Surflex program and is much higher than those of Fred, GOLD, Slide, Glide, and QXP programs evaluated with tymidine kinase and its known inhibitors.[13] It is thus apparent that the automated AutoDock can be one of the best choices for docking tool in virtual screening of chemical databases.

It has been suggested that a low accuracy of currently available docking programs in virtual screening stems from the overestimation of the scores assigned to large molecules in comparison to small ones.[36] As mentioned above, such an overestimation is due in a large part to the neglect of desolvation cost in the scoring function. It should be noted in this regard that the desolvation free energy term in Eq. (1) is calculated for aliphatic and aromatic carbon atoms of a ligand in the current version of AutoDock, indicating an underestimation of ligand solvation effects in protein–ligand association. Therefore, the hit rate of the automated AutoDock would be enhanced by implementing properly developed solvation parameters for varying atom types in the scoring function. We will address this issue in the future study.

CONCLUSIONS

The present study reports the first example of assessing the performance of the AutoDock program in virtual database screening in comparison to the other popular docking programs. The automated AutoDock represents an advance in virtual screening of chemical databases with docking simulation. By using the unique 3D potential grids common to all ligands, we have been able to accelerate the overall virtual screening process by more than two times without a significant change in binding free energies of individual ligands. In comparison with the existing docking programs, it is significantly more accurate in terms of scoring putative ligands to the extent of two- to sevenfold enhancement of hit rate in database screening when 2% of database coverage is used as a cutoff. Despite such an outperformance, the scoring function needs to be improved in such a way to avoid the tendency to overestimate the scores of relatively large molecules. Efforts along these lines are currently underway.

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