SDOCKER: A Method Utilizing Existing X-ray Structures To Improve Docking Accuracy

Guosheng Wu[†] and Michal Vieth*

Lilly Research Labs, Lilly Corporate Center, DC 1513, Eli Lilly and Company, Indianapolis, Indiana 46285

Received January 20, 2004

This paper introduces a new strategy for structure-based drug design that combines high-quality docking with data from existing ligand−protein cocrystal X-ray structures. The main goal of SDOCKER, a new algorithm that implements this strategy, is docking accuracy improvement. In this new paradigm, simulated annealing molecular dynamics is used for conformational sampling and optimization and an additional similarity force is applied on the basis of the positions of ligands from X-ray data that focus the sampling on relevant regions of the active site. Because the structural information from both the ligand and protein active site is included, this approach is more effective in finding the optimal conformation for a ligand−protein complex than the classical docking or similarity overlays. Interestingly, it was found that a 3D similarity-only approach gives comparable docking accuracy to the regular force field approach used in classical docking, given the final structures are minimized in the presence of the protein. The combination of both, as implemented in SDOCKER, is shown here to be more accurate. A significant improvement in docking accuracy has been observed for three different test systems. Specifically an improvement of 10%, 17.5%, and 10% is seen for 37 HIV-1 protease, 32 thrombin, and 23 CDK2 ligands, respectively, compared to docking using the force field alone. In addition, SDOCKER's accuracy performance dependence on the similarity template is discussed. The strategy of utilizing existing ligand X-ray information should prove effective in light of the multitude of structures available from structural genomics approaches.

Introduction

Early stages of inhibitor design are among the most fascinating experiences in drug discovery. They do remain, however, complex and time-consuming. Computational techniques provide opportunities to streamline and accelerate this stage.[1] When a high-quality three-dimensional structure of a receptor is available from X-ray crystallography or NMR spectroscopy, computational structure-based approaches[2] can be applied to aid inhibitor design efforts. Over the past decade, a large number of useful new methods for protein−ligand docking have been proposed, making docking a key tool in structure-based inhibitor design.[3] Molecular docking algorithms attempt to optimally place an existing or designed ligand in the active site of a receptor in order to estimate the binding mode of the ligand. Since knowledge of the binding mode can assist in the design of more potent ligands, docking accuracy is important for exploring new structure−activity relationship (SAR) directions.[4] In particular, the three-dimensional overlay of diverse ligands can lead to new ideas for modifying each of the scaffolds. Docking algorithms, however, suffer from limitations arising from approximations that include inadequate representation of a ligand's conformational space and the induced-fit effect of ligand to protein.[5−7]

An alternative method often used for generation of ligand overlays involves 3D similarity-based alignments.[4,8,9] These methods, used in ligand-based approaches to inhibitor discovery, do not require a protein structure. In principle, a strategy combining 3D similarity and docking should provide more accurate predictions of ligand binding modes.[10,11] Fradera and coworkers took advantage of this strategy and developed a similarity-driven docking approach[12] using a combination of DOCK[13] and MIMIC.[9] Their implementation used the DOCK docking function, composed of the protein−ligand interaction energy scaled by the MIMIC similarity index between a compound and a predefined template. Success of the method was gauged by the improvement of hit enrichment in database searching for the docking and similarity combination over the similarity search with MIMIC alone.[9]

This communication describes an implementation of similarity-assisted docking along with an examination of docking accuracy with and without the use of information present in multiple structures of protein−ligand complexes. Motivated by the work of Fradera and coworkers,[12] we extend the CDOCKER suite[14−16] to include a new algorithm, SDOCKER, which uses a hybrid docking function made up of force field energy and 3D similarity. Even though the general strategy employed in SDOCKER is similar to the one used by Fradera, it combines force field energies with 3D similarity in a novel and potentially more effective manner. The docking accuracy results of SDOCKER for three systems including 32 thrombin, 23 CDK2, and 37 HIV-1 protease ligands are discussed and contrasted to protein−ligand docking and ligand 3D similarity alignment.

* To whom correspondence should be addressed. E-mail: m.vieth@lilly.com. Phone: (317) 277-3959. Fax: (317) 276-6545.
[†] Current address: Concurrent Pharmaceuticals, Inc., 502 West Office Center Drive, Fort Washington, PA 19034

10.1021/jm040015y CCC: $27.50
Published on Web 05/07/2004

Materials and Methods

CDOCKER is a grid-based molecular dynamics (MD) docking algorithm that has demonstrated accuracy and efficiency in the reproduction of X-ray ligand binding modes.[14−16] SDOCKER combines the CDOCKER force field and search strategy with a new similarity-based component to the docking function. Instead of scaling the energy function,[12] the force field is supplemented by a 3D similarity term computed to a static, predefined template. The similarity template is defined from the structure of one or more ligands from the aligned protein−ligand X-ray complexes.

At each step of the MD simulated annealing docking protocol, the force field interaction of a ligand with the receptor, the ligand internal energy, and the similarity between the ligand and the predefined similarity template are considered. The similarity term focuses the conformational sampling into the relevant regions of the active site defined by the shape of the template. Focusing of the search space contributes to increased docking efficiency and accuracy and indirectly incorporates elements of protein flexibility. The final docking pose is the result of a balance between the protein−ligand interaction, ligand internal energy, and the "in site" shape similarity to known cocrystallized ligands.

Docking Function. The total docking energy for the ligand−protein system is the sum of the force field energy[17] and the similarity term, i.e.,

$$E_{\text{tot}}^{\text{New}} = E_{\text{tot}}^{\text{CHARMM}} + E_{\text{sim}} \tag{1}$$

where the force field energy comprises ligand receptor interaction energy and the ligand's internal energy, i.e.,

$$E_{\text{tot}}^{\text{CHARMM}} = \gamma E(\text{ligand\_receptor}) + E(\text{ligand}) \tag{2}$$

and the similarity penalty is described by

$$E_{\text{sim}} = - k_{\text{sim}} S_{\text{AB}} \tag{3}$$

where S_{AB} is the 3D similarity between a ligand's pose (A) and the fixed similarity template (B) and k_{sim} is the similarity force constant. The negative sign indicates that the system is driven to higher 3D similarity values. γ and k_{sim} are parameters allowing full switching between the flexible similarity overlays only ($\gamma = 0$) and the regular CDOCKER function[14] ($k_{\text{sim}} = 0$ and $\gamma = 1$).

In SDOCKER's similarity-assisted docking mode, the γ parameter is set to 1. The force constant k_{sim} can be adjusted on the basis of the properties and available information on the particular system. Our experience shows that k_{sim} values on the order of 10−100 kcal·mol^{-1} are optimal for most cases. For the systems considered in this study, 10 kcal·mol^{-1} is applied to thrombin and CDK2 sets while a value of 100 kcal·mol^{-1} is needed for more flexible HIV-1 protease ligands.

The similarity index S_{AB} between the ligand's pose and the similarity template depends on their relative orientation in three-dimensional space and can be defined in multiple ways.[8,18] Here, the similarity index is based on the shape overlap of the two molecules, taking the general concepts from the already published work:[19,20]

$$S_{\text{AB}} = \frac{P_{\text{AB}}}{\sqrt{P_{\text{AA}}}\sqrt{P_{\text{BB}}}} \tag{4}$$

where P_{AB} is defined as

$$P_{\text{AB}} = \sum_{i=1}^{N_{\text{A}}}\sum_{j=1}^{N_{\text{B}}} w_i w_j \, \mathrm{e}^{-\alpha R_{ij}^2} \tag{5}$$

and N_{A} and N_{B} indicate the number of atoms in the ligand A and the template B. R_{ij} is the distance between atom i in ligand A and atom j in template B. In this work, the weights w_i and w_j are set to 1, but they can also be adjusted according to atomic type or charge extending the similarity constraint beyond shape to, for example, electrostatics. The value of α is set to 0.5, resulting in an exponent close to 0 at a distance of about 3 Å.

The similarity template can be defined from the coordinates of the overlaid conformations of ligands from existing experimental structures of protein−ligand complexes. The template can be selected from the coordinates of one representative ligand or the averaged structure of a subset of several ligands.

Test Systems. Three well-characterized systems with the availability of multiple cocomplex structures were chosen to evaluate the performance of SDOCKER. As a result, our test set comprised 32 ligands complexed with thrombin, 23 ATP site CDK2 ligands, and 37 ligands complexed with HIV-1 protease.

Twenty-seven thrombin-ligand structures and five trypsin-ligand structures (1pph, 1tng, 1tnh, 1tnk, 1tnl) were extracted from the Protein Data Bank (PDB).[21] Because of the high sequence and structure similarity between trypsin and thrombin, it was assumed that the binding mode between trypsin and thrombin ligands (with respect to the structurally conserved binding site) would not differ significantly. The two-dimensional structures of 32 ligands are depicted in Figure 1. The alignment of all thrombin structures to 1ets as the template was performed with QUANTA 2000.[22] This alignment generated a superposition of 32 ligands in the active site as depicted in Figure 2. In addition to the thrombin active site structure from the 1ets complex, the thrombin structure from the 1dwc complex was also used. This second protein structure was used to test the dependence of docking results on the choice of the protein structure, similar to the work of Fradera.[12] The dependence of SDOCKER's docking accuracy on the selection of the similarity template, was performed with the thrombin structure from the 1ets complex and the systematic use of each of the 32 ligands as similarity templates. In another experiment, the 32 ligands were randomly assigned to one of two equal sized groups A and B and subsequently used to define similarity templates from the averaged structures. Docking experiments were then carried out on the A group using the B group similarity template followed by docking the B group ligands using the A group template.

For 23 aligned CDK2 (and 37 aligned HIV-1 protease) structures, the respective ligands were divided into two groups A and B in a manner similar to the thrombin case. The docking results for each group based on the similarity template defined from averaged ligands from the other group are reported. In this manner the results for each ligand are not biased by the inclusion of the shape information from its own X-ray structure. 1aq1 was selected as the protein structure for CDK2 system and 1hvi was selected for the HIV-1 protease. It should also be noted that the explicit water molecule important for some ligand binding to HIV-1 protease[23] was not included in our calculations.

Docking Protocols. All docking experiments we carried used a rigid protein and a fully flexible ligand. All nonbonded force field related terms for the protein−ligand interactions were precomputed and placed on a grid using a previously described protocol with a grid size of 0.5 Å.[14] In addition to the nonbonded force field terms, probes for similarity energy force were included in the grid.

Docking protocols for SDOCKER and CDOCKER[14] are briefly summarized here. For each ligand, an initial conformation is calculated using the Corina software,[24] followed by generation of 50 random orientations of the Corina conformer near the active site.[25] The docking process includes simulated annealing with grid-based interactions (including similarity terms where appropriate) for 40 ps, followed by the local minimization with full force field potential with the similarity interactions removed. Previously described experiments have shown that the final off-grid minimization step gives a statistically significant improvement of docking accuracy of on-grid docking results with a small increase (1%) in CPU time.[14]

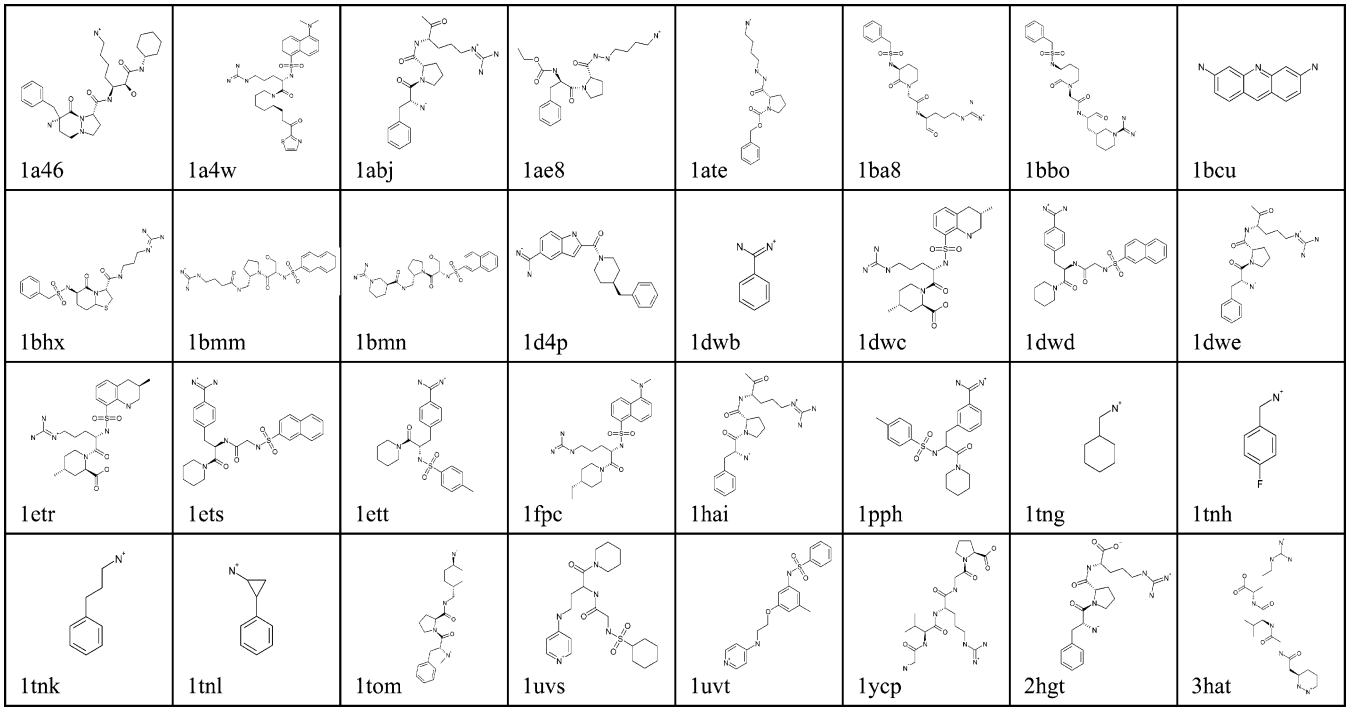

Figure 1. Two-dimensional ligand structures of thrombin test set. The PDB code is featured in the lower left-hand side of each box.

SDOCKER allows for control of the similarity and energy force field contributions with the k_{sim} and γ parameters. For benchmarking, the protocol with $k_{sim} = 0$ (eq 2) for docking and $\gamma = 0$ for 3D similarity alignment was employed. The results for SDOCKER's similarity alignments are indicated as "SHAPE" or "SHAPE_MIN" if the final minimization in the context of the receptor is applied. Thus, the four pose prediction schemes will be compared, with different levels of classical force field and similarity contribution as shown below:

CDOCKER, flexible ligand docking to rigid protein with classical force field

SDOCKER, flexible ligand docking to rigid protein with classical force field and 3D similarity template

SHAPE, flexible ligand alignment to similarity template

SHAPE_MIN, flexible ligand alignment to similarity template followed by classical force field minimization of the final pose in the context of the receptor

Comparison Statistics. Because of the random nature of the initial states used in the docking protocols, 10 independent docking runs for each ligand were carried out in order to generate an ensemble of results for statistical comparisons.[14] For each run, only the ligand's lowest energy pose is compared with the pose observed in the X-ray structure. A docking experiment of a ligand is defined as successful if the calculated heavy atom rmsd (root mean square deviation) between the docking and X-ray pose is less than 2.0 Å. A test case success rate is the number (or fraction) of successful runs for all ligands. Per ligand docking frequency is computed as the fraction of successful runs for each ligand in 10 independent trials.

Results and Discussion

Comparison of Different Protocols for the Thrombin Set. A test set of 32 thrombin ligands was used to evaluate the performance of the various docking strategies examined here. The protein and the similarity template from the 1ets PDB entry was employed unless indicated otherwise. The pose prediction strategies include classical force field docking by CDOCKER, 3D similarity alignment ($\gamma = 0$ from eq 2, denoted as SHAPE), 3D similarity alignment followed by minimization in the presence of protein (denoted by SHAPE_MIN), and a combination of docking with 3D similarity alignment by SDOCKER. Figure 3 shows a graphical representation of the results for the 32 ligands docked to thrombin with various docking strategies, and the numerical results are presented in Table 1.

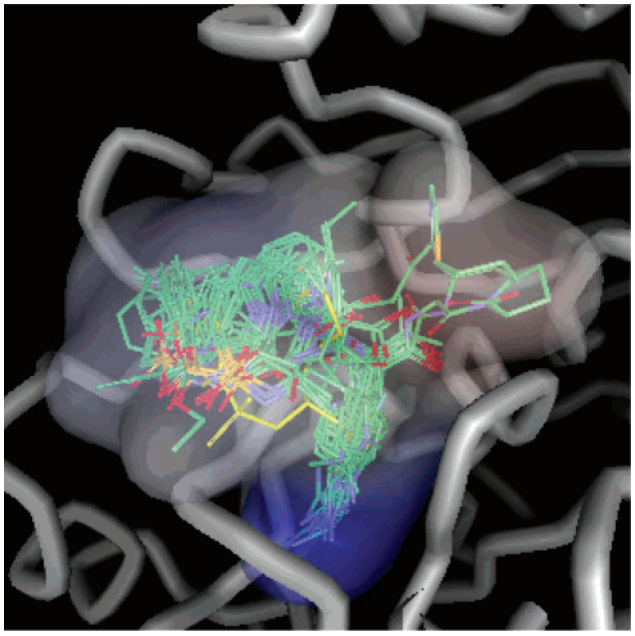

Figure 2. Superposition of 32 thrombin inhibitors based on the alignment of protein structures. For clarity, only heavy atoms of ligands and the active site (in tube) of the 1ets protein is shown only. Standard atom color coding is used (red for O, green for C, blue for N). A semitransparent van der Waals surface created from all ligands colored by electrostatic potential is also displayed.

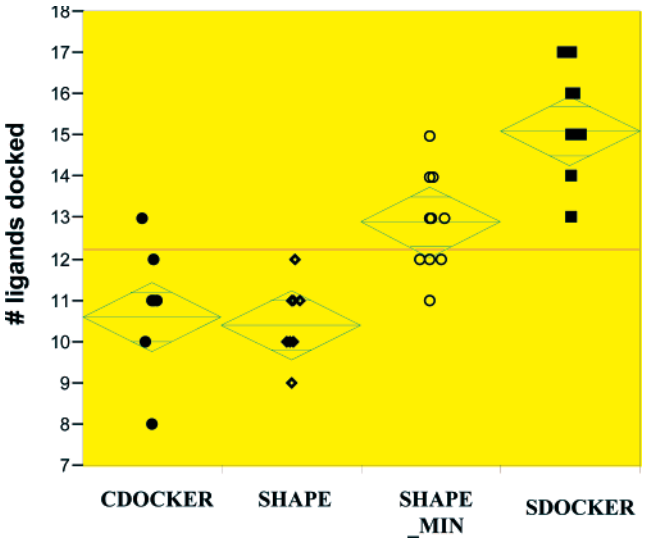

Figure 3. Distribution of the number of successfully docked structures with different docking strategies for 32 thrombin ligands. Each point represents one independent run of the protocol for 32 ligands in the protein from the 1ets structure (the results for 1dwc protein structure are not significantly different). The diamonds represent the mean values from 10 independent runs with 95% confidence intervals. SDOCKER's mean is significantly higher than those of the CDOCKER, SHAPE, and SHAPE_MIN approach.

Table 1. Thrombin Test Set Results[a]

	method			
	CDOCKER	SHAPE[b]	SHAPE_MIN[b]	SDOCKER[b]
Results for 1ets				
mean success[c]	10.6	10.4	12.9	15.1
N/32 (%)	33.1	32.5	40.3	47.2
standard deviation	1.6	1.0	1.2	1.4
Results for 1dwc				
mean success[c]	9.8	5.1	12.9	15.6
N/32 (%)	30.6	15.9	40.3	48.8
standard deviation	1.3	1.5	1.6	1.3

[a] The mean number of ligands that successfully docked is shown for different methods and protein structures. [b] The X-ray ligand conformation of 1ets or 1dwc was used as the similarity template for all methods except for CDOCKER. [c] Mean success is the number of successful docking runs for 32 ligands, averaged from 10 independent runs.

It was found that the CDOCKER results (a mean result of 10.6 ligands successfully docked) were not significantly higher than the mean SHAPE similarity result (10.4 successes), given that the pairwise *T* test for these two experiments showed a *P* value of 0.369.[26] Interestingly, a quantitatively significant and meaningful improvement to the similarity alignment based pose prediction is obtained with the final minimization of structures, i.e., the SHAPE_MIN protocol results yield 13 successes (the mean is 12.9). Finally, SDOCKER, which combines docking with 3D similarity, successfully places 15 of the 32 ligands (i.e., within 2.0 Å of the X-ray pose). The *T*-test analysis (a *P* value of 1.552×10^{-6}) reveals that SDOCKER's combination of 3D similarity with force field optimization significantly improves docking accuracy for this test system. Moreover, the choice of a different thrombin structure (from 1dwc) and similarity template (also from 1dwc) gives comparable results for SDOCKER but lower results for the SHAPE method (mean of 5.1). The difference is attributed to the effect of using a similarity template (detailed discussion in the similarity template section). The results suggest that a combination of docking and similarity is significantly more accurate than either docking or 3D similarity alignment in isolation.

A small variation exhibited by each strategy represented by standard deviations in Table 1 points to the limitation of the conformational sampling.

Fradera and co-workers[12] studied the thrombin system with 32 ligands with a similar docking strategy. They found 6 ligands within 2 Å rmsd of the ligands' X-ray structures with DOCK, 12 ligands with MIMIC for similarity overlay, and 9 (low sampling) or 11 (high sampling) with similarity-guided docking with DOCK and MIMIC. Although our results (Table 2) are not directly comparable because of the 14 proprietary structures used in Fradera's study,[12] SDOCKER appears to exhibit higher docking accuracy. The successful performance of MIMIC similarity in the previous work suggests the possibility for improvement of SDOCKER with more sophisticated similarity methods.

Dependence of Results on the Choice of Similarity Template. To test the dependence of docking accuracy on the similarity template, we performed an additional 32 SDOCKER simulations on the thrombin test set in which the similarity template was defined on the X-ray coordinates for each of the ligands while docking the remaining ligands. The number of successfully docked structures as a function of the template's heavy atom count is plotted in Figure 4. There is a trend showing that on average docking accuracy increases with the size of the ligand (expressed as the atom count) used to define a similarity template. SDOCKER's success rate with various similarity templates based on small ligands is also lower (with the exception of the 1tng template) than that of CDOCKER, i.e., without the use of similarity. On the other hand, most of the large templates yield a higher success rate than CDOCKER. The decrease of docking accuracy with small similarity templates may arise from the partial matching of "incorrect" fragments of the docked molecules. This could be related to the fact that only shape similarity is used. The strong dependence of SDOCKER's accuracy on the size of the similarity template, although suggestive, is probably a function of the thrombin test set because similar trends have not been observed for the CDK2 and HIV-1 protease systems. SDOCKER calculations using the two similarity templates defined on the averaged structure of 16 ligands from two groups (A and B) and all 32 ligands (all structures averaged as a similarity template) were also performed. The results from 10 runs averaged for the two ligand similarity templates give 16.2 successfully docked ligands. SDOCKER results from the similarity template defined from all 32 ligands averaged 16.9 successfully docked ligands. These results show that the incorporation of more ligands into the similarity template tends to give improved docking accuracy over a single ligand template. Similar improvement of docking accuracy with a multiple-ligand similarity template were observed for CDK2 and HIV-1 protease.

Docking Results: Thrombin. To emphasize this improvement of SDOCKER over CDOCKER, the final

Table 2. Detailed Results for Thrombin Ligands for CDOCKER and SDOCKER[a]

PDB	CDOCKER fraction	CDOCKER median rms	SDOCKER fraction	SDOCKER median rms	fraction (SDOCKER − CDOCKER)[b]	median rms (SDOCKER − CDOCKER)[c]
1ae8	0.4	3.3	1	1.2	0.6	−2.2
1bhx	0.1	2.6	0.7	1.6	0.6	−1
1ets	0.4	4.1	1	1.5	0.6	−2.6
1bmm	0.5	2	1	1.4	0.5	−0.6
1bmn	0	3.8	0.5	2	0.5	−1.8
1dwd	0.5	2.8	1	1.4	0.5	−1.4
1uvs	0	5	0.5	2	0.5	−3
1hai	0.6	1.1	1	1.1	0.4	0
1abj	0.7	1.2	0.9	1.1	0.2	−0.1
1afe	0	5.8	0.2	3	0.2	−2.8
1ett	0	3.7	0.2	3.8	0.2	0.1
1pph	0	3.7	0.2	3.6	0.2	−0.2
1a46	0	5.8	0.1	7.4	0.1	1.6
1dwe	0.8	1.1	0.9	1.1	0.1	0
1tom	0.9	1.1	1	1.1	0.1	0
1a4w	0	4.2	0	4.4	0	0.2
1bb0	0	3.8	0	3.6	0	−0.2
1bcu	0	4.4	0	4.4	0	0
1d4p	0	8.5	0	8.5	0	0
1dwb	1	0.4	1	0.5	0	0
1dwc	0	3.7	0	3.4	0	−0.3
1etr	0	3.6	0	3.4	0	−0.2
1fpc	0	5.6	0	5.7	0	0.1
1tng	1	0.4	1	0.4	0	0
1tnh	1	0.7	1	0.7	0	0
1uvt	0.6	1.9	0.6	1.9	0	0
1ycp	0	7.8	0	7.6	0	−0.2
2hgt	0	7.6	0	7.8	0	0.2
3hat	0	6.6	0	7.9	0	1.3
1ba8	0.1	4.1	0	3.2	−0.1	−0.9
1tnk	1	1.5	0.8	1.7	−0.2	0.2
1tnl	1	1.8	0.5	2.6	−0.5	0.8

[a] The fraction of successful prediction of the X-ray pose and the median rms in 10 independent runs is shown for each ligand. The results are based on the 10 independent runs for each ligand with the 1ets protein and the 1ets template (SDOCKER). [b] The difference between successful docking frequencies between SDOCKER and CDOCKER. The positive numbers indicate the fraction of runs of SDOCKER that led to improvement of pose predictions. The negative numbers indicate the fraction of runs of SDOCKER that led to the loss of pose prediction accuracy. [c] The difference between median rms from SDOCKER and CDOCKER. The negative numbers indicate the median rms improvement of SDOCKER, while the positive numbers indicate the median rms loss of docking accuracy.

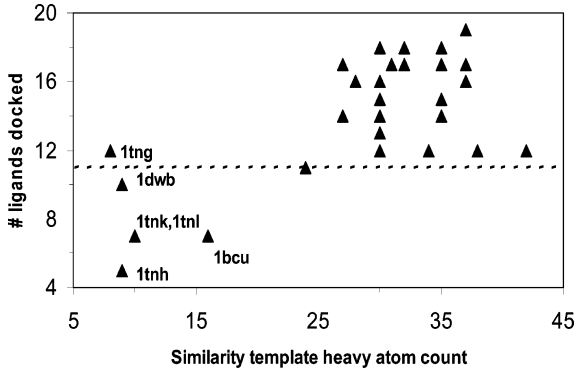

Figure 4. Number of successfully docked structures for SDOCKER for 32 thrombin ligands as a function of the number of heavy atom count in the similarity template. Each ligand was used to create the similarity template. The protein structure from the 1ets complex was used. The dotted line denotes the success rate from CDOCKER. The number of heavy atoms in the similarity template is a good predictor of successful docking. Despite the reasonably high value of the linear fit with R^2 of 0.52, the notion of correlation is not appropriate because the distribution of the number of heavy atoms is bimodal. Six templates with the number of heavy atoms less than 20 are labeled. Large templates, on average, lead to improvement in docking accuracy, while small templates can lead to a decrease in docking accuracy.

docked poses of 1ae8 is displayed in Figure 5 as an example. Figure 5a shows the X-ray overlay of the ligand conformations from the 1ae8 and the 1ets structures, Figure 5b shows the poses from 10 independent conformations using CDOCKER, and Figure 5c shows the 10 independent orientations from the SDOCKER experiments. All 10 independent runs lead to a successful docking with SDOCKER, while only 4 out of 10 are successful with CDOCKER.

Docking Accuracy Comparison for Thrombin, CDK2, and HIV-1 protease. In addition to the thrombin test case, SDOCKER and CDOCKER were compared on sets consisting of 23 CDK2 ligands and 37 inhibitors of HIV-1 protease. In all cases, the similarity template was defined on the basis of half the available ligands (group A) while the docking calculations were performed for the remaining ligands (group B). The docking procedure was repeated for the group A ligands with the similarity template defined from the ligands from the group B.

The mean results from 10 independent runs are summarized in Figure 6 and Table 3. The PDB codes of the complexes used in this study, the 2D ligand representations, and the detailed docking results for 10 independent runs are provided in the Supporting Information. In all cases SDOCKER shows statistically significant (as determined by pairwise T test showing P values less than 0.05; we also checked the adjusted multiple-test significance level) improvement of mean docking accuracy. The improvement is largest for thrombin (17.5%) with about 10% improvement for the HIV-1 protease and CDK2 ligands. It was also observed that if the X-ray conformation is used as an initial starting

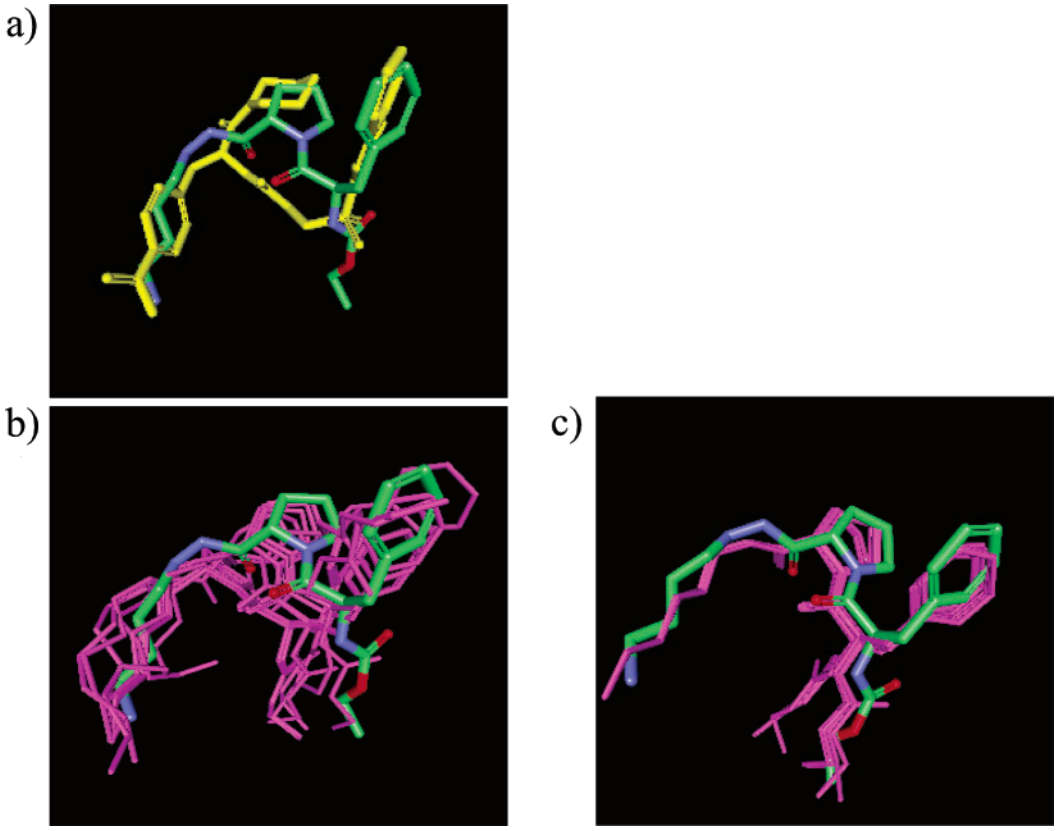

Figure 5. Graphical example of improvement of pose prediction results with the 1ae8 ligand in 10 independent runs. The protein and similarity template were both derived from the 1ets structure. The X-ray structure is colored by heavy atom types, and the docking structures are in magenta: (a) superposed ligand X-ray structures of 1ae8 (colored by atom types) and 1ets (in yellow); (b) superposed CDOCKER results for the 1ae8 ligand; (c) superposed SDOCKER results for the 1ae8 ligand.

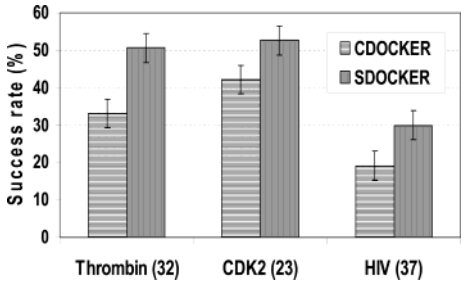

Figure 6. Averaged docking results for three test systems from 10 independent runs. For SDOCKER, two similarity templates were defined from the averaged structure of half of the available X-ray conformations while the results are reported for the other half. Both CDOCKER and SDOCKER use only a single rigid protein for the docking (1ets for thrombin, 1aq1 for CDK2, and 1hvi for HIV protease). The 95% confidence intervals for the mean values are shown. In all cases SDOCKER gives significantly higher success rates as defined by the *T*-test *P* values (<0.05).

structure, a similar improvement is observed for SDOCKER; however, the docking accuracy is consistently higher for all methods.[14,16]

As with any of the current docking methods, there are some ligands for which SDOCKER fails to predict the X-ray binding modes. Two limiting factors are ligand and protein flexibility.[16] SDOCKER indirectly addresses the issue of the ligand flexibility by reducing the ligand's search space to a bioactive-like region defined by the existing X-ray structure. This allows for the mean improvement of 10%, which is comparable to the results obtained by using the ligand's X-ray conformation to start the docking process. The protein flexibility limitation is not directly addressed by SDOCKER, but the comparison of self-docking (i.e., docking a ligand back to the X-ray structure from which it was extracted) results to results obtained by docking all ligands to one structure indicate that this limitation is small for thrombin and slightly larger for HIV-1 protease.[16]

Table 3. Comparison of Docking Success Rates with CDOCKER and SDOCKER for Three Test Systems[a]

	docking method	
	CDOCKER	SDOCKER
thrombin (*N*/32 (%))	10.6 (33.1)	16.2 (50.6)
CDK2 (*N*/23 (%))	9.7 (42.2)	12.1 (52.6)
HIV protease (*N*/37 (%))	7.1 (19.2)	11.1(30.0)

[a] The results from 10 independent runs are used to compute the mean number of docked ligands with rms less than 2 Å. For SDOCKER the similarity template is defined from half of the ligands, and the results are reported for the ligands not present in the template.

Conclusions

In this communication it was shown that docking accuracy can be improved by the effective utilization of the existing X-ray structures of ligands cocrystallized with the target protein. The strategy of combining docking with a 3D similarity function implemented in our new algorithm SDOCKER proved to be effective in three different systems, namely, thrombin, CDK2, and HIV-1 protease. It was also demonstrated that the choice of similarity template is an important determinant of the docking accuracy in this technique. By the

use of a similarity template, docking accuracy results were improved by at least 10% for three systems we have studied. Therefore, SDOCKER represents a very promising and important direction in the development of tools utilizing structural genomic information.[27] The ability to readily incorporate key information from many cocomplex structures into docking is critical in the design and iteration of structure-based inhibitor strategies.

Acknowledgment. The authors thank Dr. Jibo Wang for the initial implementation of the 3D similarity measure and Jim Wikel, Michael Lajiness, Drs. Jon Erickson, and Michael Shapiro for critical review and editing of the manuscript. Helpful discussions with Drs. Ian Watson and Daniel H. Robertson are acknowledged.

Supporting Information Available: PDB codes, 2D ligand information, and the detailed results of the dockings. This material is available free of charge via the Internet at http://pubs.acs.org.

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JM040015Y