

ARTICLES

Unconventional 2D Shape Similarity Method Affords Comparable Enrichment as a 3D Shape Method in Virtual Screening Experiments

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3D molecular shape similarity search has recently become an attractive method for virtual screening and scaffold hopping in drug discovery and chemical genomics research. Among these 3D similarity methods is ROCS (Rapid Overlay of Chemical Structures), a popular tool because of its efficiency and effectiveness. However, searching a large multiconformer molecular database remains a very challenging task because of the nature of such calculations. To simplify shape similarity calculations and potentially increase the efficiency for large scale virtual screening, we have explored an alternative shape similarity approach that does not depend on multiconformers of molecules. The hypothesis underlying this approach is that similar chemical structures tend to have similar 2D chemical depictions and that shape comparison techniques can be utilized to effectively compare the shapes between chemical depictions. We use a 2D depiction program to generate 2-D chemical drawings for both the query molecule and database molecules. We have built a 2D shape comparison program based on the OESHAPE Toolkit (OE Scientific, NM) that compares the molecular depictions and quantifies the shape similarity between the molecules. We demonstrate that this unconventional 2D shape similarity method performs fairly well in virtual screening experiments compared to the 3D Shape method ROCS, with an added advantage of its computational efficiency.

INTRODUCTION

2D (2-dimensional) and 3D (3-dimensional) similarity search in compound databases are popular tools in the pharmaceutical and biotech industry. They are widely used by both the medicinal chemist and the biological screening scientist in hit follow up and hit-to-lead projects. A wide variety of 2D similarity methods have been developed over the past two decades, and they can be broadly grouped into several categories. (1) Substructure-based similarity approaches calculate similarity values based on the Maximum Common Substructure (MCS) overlap between a query molecule and database molecules.^{1–3} This approach can provide substructure matching between the query and the computational hits from the database and thus offer chemical insights into why a molecule is a potential hit. Such insight is particularly liked by the medicinal chemist because it gives clues as to what modifications may be made to the computational hit, resulting in better compounds. (2) The fingerprint (FP) based similarity approach first determines what substructure fragments exist in the query molecule and the database molecules and calculates the binary fingerprint patterns for both the query and the database molecules. It then calculates the similarity values based on matches between the fingerprint patterns. Frequently used fingerprint methods include Daylight fingerprints and the MACCS key methods as they are readily available in commercial software packages (Daylight Chemical Information, NM, and MACCS key from MDL, now part of Symyx). (3) Topological

descriptors and atom-pair descriptors have also been used as the basis for molecular similarity calculations.⁴ Several groups have made significant contributions to the 2D similarity method in the past decades.^{5–7,4,8–12}

Although the efficiency of the aforementioned 2D similarity methods has been demonstrated in virtual screening experiments, the often cited limitations of these and other 2D approaches include their limited ability for scaffold hopping and the lack of structural insights provided by these methods. To address these issues, 3D similarity methods have been developed, which can provide molecular alignment in addition to calculating the similarity measures. The molecular alignment information is extremely useful for the medicinal chemist to conduct hypothesis generation in designing new molecules. Early development in this direction includes SQ¹³ and SEAL.¹⁴ More recently, ROCS has become the method of choice for 3D similarity calculations because of its efficiency to handle large multiconformer databases.^{15–17} However, it has been reported that at least 500 conformers are needed to efficiently cover the bioactive conformations of a ligand.¹⁸ This has a big impact on computational cost when searching large databases. Thus, there is a need for a more efficient method that can search large databases and provide the molecular alignment information between the query and the computational hits.

It is well-known that a seasoned medicinal chemist has the ability to perceive the similarity between 2D chemical structures simply by looking at their chemical drawings. They can then design analogues based on the visual inspection of the molecules. This observation implies that useful similarity

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relationship exists in the 2D chemical drawings for molecular discovery. Thus, we hypothesize that if one can systematically generate 2D chemical drawings of molecules, the similarity between the 2D molecular depictions may be useful for molecular virtual screening.

In this paper, we present a simple protocol (called EZSim) to implement and test this idea. In this protocol, we use a 2D depiction program to generate the chemical drawings for both the query and database molecules. We then employ a shape comparison program that takes the 2D chemical drawings as regular molecular objects, and performs shape similarity calculations. The similarity values are used to rank molecules in virtual screening experiments. To validate the efficiency of EZSim, forty sets of molecules, taken from the Directory of Useful Decoys (DUD)^{19,20} are used in the designed virtual screening experiments. We show that (1) EZSim affords similar enrichment as ROCS, a standard 3D Shape method, (2) it is less computationally expensive than ROCS, and (3) it provides alignment information between the structures, an added advantage useful for molecular design.

MATERIALS AND METHODS

In this section, we first describe the two similarity methods, namely, EZSim and ROCS. We then describe the details of the reference database used in the virtual screening experiments. Finally, we provide details on how the results of the virtual screening experiments were analyzed in the form of ROC (Receiver Operator Characteristic) curves and AUC (Area Under the Curve) values.

EZSim Similarity Method. This method treats 2D depictions of molecules as if they are regular 3D molecular objects with the Z coordinates of all the atoms set to 0. In theory, once such a representation of molecules is obtained, the ROCS program (OE Scientific) can be used for shape similarity calculations for any two structures. Because of some technical difficulties in using ROCS directly for this purpose, we have implemented the EZSim method based on the OEShape toolkit (OE Scientific, NM). This program can be used to effectively calculate the similarities between 2D depictions of molecules. The overall flow of the EZSim protocol is shown in Figure 1, which involves the following steps:

(1) Generation of 2D molecular drawings. The starting point for EZSim-based virtual screening is the input of the query and database molecules. These molecules originally are stored in SMILES format. A modified version of the Depict program (OE Scientific, NM) is used to generate the 2D coordinates of the atoms present in the SMILES strings for both the query and the database molecules. The modification involves adding an OE function designed to add explicit hydrogens to the input molecules. The computed 2D chemical drawings for both the query and the database molecules are stored in SDF file format.

(2) Shape similarity calculations with EZSim. The EZSim program reads in the query and each database molecule, represents them with Gaussian functions of the OEShape toolkit, and calculates the shape similarity value between the query and a database molecule. This program was built using the OEShape toolkit.²¹ It calculates the best overlay between the query and database molecules that gives the highest combo score. The combo

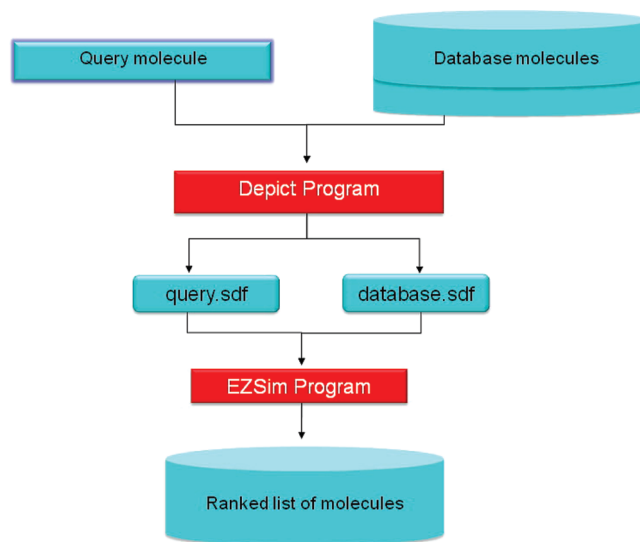


Figure 1. Flow diagram for the virtual screening process with EZSim.

Table 1. Comparison of the Computational Time Costs for Performing Virtual Screening Experiments Using EZSim and ROCS

target ^a	average time for ezsim (mins)	average time for rocs (mins)	speedup ^b
AR	0.6	2.3	4
ER	0.6	3.2	7
HSP90	0.2	51.2	259
MR	0.1	8.3	58
NA	0.4	57.4	160
PDE5	0.5	179.4	370
PR	0.2	3.9	18
RXR	0.2	18.7	95
SAHH	0.2	24.4	116
TK-SRC	1.4	105.0	73

^a Ten biological targets were taken for the DUD database. The targets include the following: androgen receptor (AR), estrogen receptor agonists (ER), human heat shock protein kinase (HSP90), mineralcorticoid receptor (MR), neuraminidase (NA), phosphodiesterase V (PDE5), progesterone receptor (PR), retinoic X receptor α (RXR), *S*-adenosyl-homocysteine hydrolase (SAHH), and tyrosine kinase SRC (TK-SRC). ^b The speedup is calculated as the ratio of time required by ROCS over that required by EZSim. The maximum speedup is about 370-fold.

score of a particular overlay between the query and a database molecule is the weighted sum of the shape Tanimoto score and the chemical score.²¹

After shape similarity scores are calculated, database molecules are then ranked based on these scores and output as a sorted list. This simple protocol implements an efficient, 2D shape matching method for virtual screening.

ROCS Similarity Method. ROCS (Rapid Overlay of Chemical Structures, OE Scientific, NM) was designed to perform shape-based overlays of conformers of a database molecule to a query molecule in one or more conformations. The overlays can be performed very quickly based on the description of molecules as atom-centered Gaussian functions.^{22–24} ROCS maximizes the rigid body overlap of the molecular Gaussian functions and therefore the shared volume between a query molecule and a conformation of a database molecule. The combo scoring option of the ROCS program was employed in the virtual screening experiments reported here. The method calculates the score of a database molecule based on the weighted sum of the Shape Tanimoto similarity score

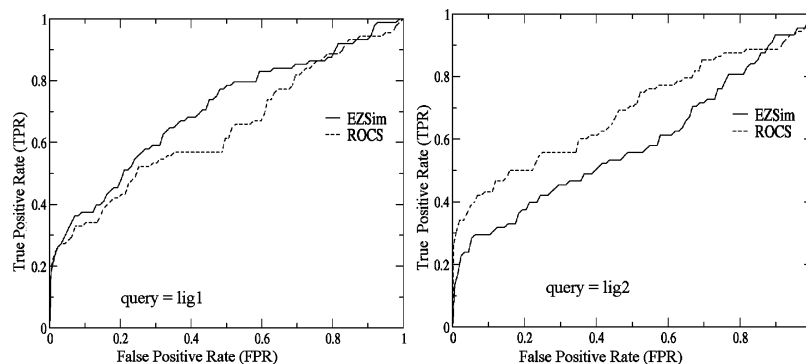


Figure 2. Two ROC plots comparing virtual screening results obtained with EZSim and ROCS. Target: Vascular endothelial growth factor receptor kinase from DUD. When two different ligands were used as the queries, the performance of EZSim and ROCS is reversed.

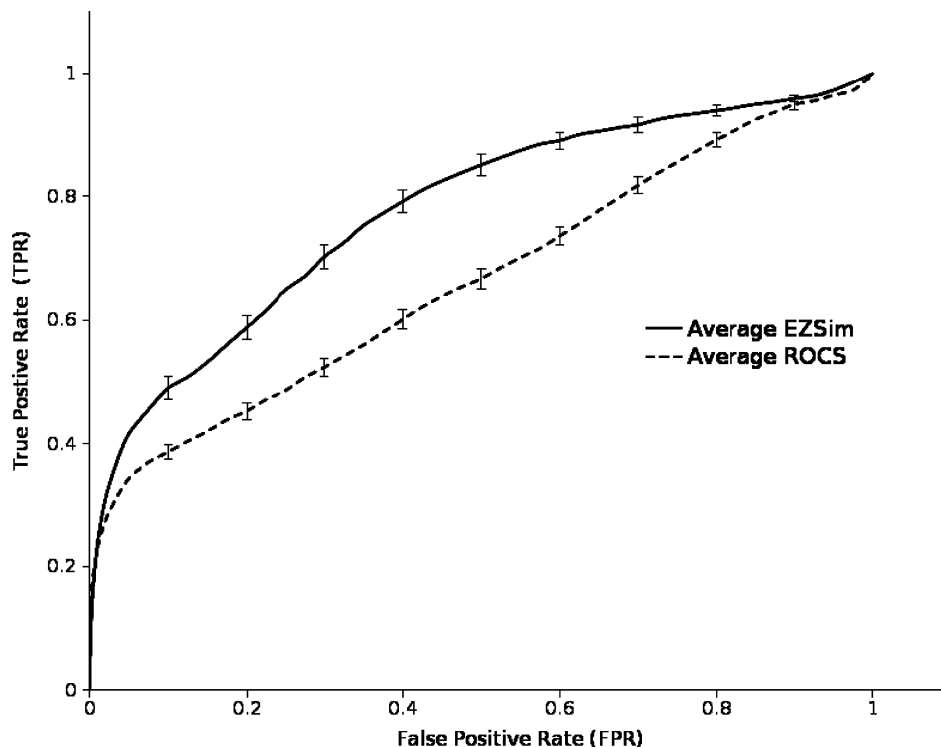


Figure 3. Average ROC curves for Androgen receptor (AR) data set using EZSim and ROCS. Error bars depicted are the standard error of the mean at those points.

and the chemical matching score between the query and the database molecule. The default chemical force field was employed. The multiconformers of the molecules were generated using the Omega program (Omega, version 2.1, OE Scientific, NM).

Database Preparation. To validate virtual screening methods, we chose to use the Directory of Useful Decoys (DUD) as the reference.¹⁹ The DUD database contains 2950 ligands for 40 different biological targets. To challenge a virtual screening strategy, each ligand in the DUD database has 36 decoys that are physically similar but topologically different. This approach prevents bias in virtual screening benchmarks because of similarities in physical properties. We used the second release of the DUD database, and it contained a total of 89 699 unique compounds. Forty sets of molecules include inhibitors/ligands for the following targets: PDE5, estrogen receptor (ER α), HIV-reverse transcriptase (HIV-RT), HIV-protease (HIV-PR), thymidine kinase (TK-SRC), etc. Each set included a mix of known ligands for a particular target and decoys (i.e., 36 decoys per known ligand).

The multiconformer database for use by ROCS was created using OMEGA, version 2.1, from the SMILES representation of the DUD database using the high-throughput settings (HTS) recommended by Kirchmair.¹⁸ This parameter setting was proved to identify more conformations similar to the known bioactive conformation. Also, this parameter setting is well suited for processing large molecular databases for use in various virtual screening campaigns, since it requires computing only a maximum of 50 conformations.

The 2D depiction database for use with EZSim was generated by employing the modified depict program described above to the DUD data sets. All hydrogen atoms were included. The input molecular format was SMILES for both the queries and the database molecules. The depicted molecules were stored in SD file format, which carries the 2D coordinate information for each depicted molecule.

Virtual Screening Experiments. Each of the known ligands for a target from the DUD database was used as the query to screen the database comprising of the known ligands and decoys for the corresponding target. In the case of ROCS,

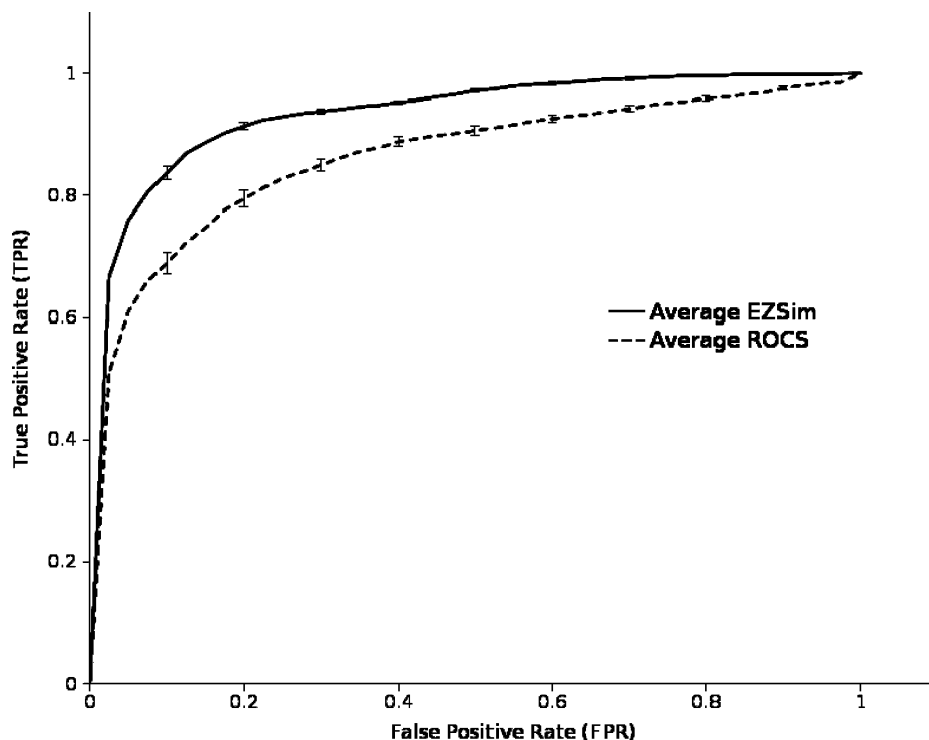


Figure 4. Average ROC curves for estrogen receptor (ER) agonists using EZSim and ROCS. Error bars depicted are the standard error of the mean at those points.

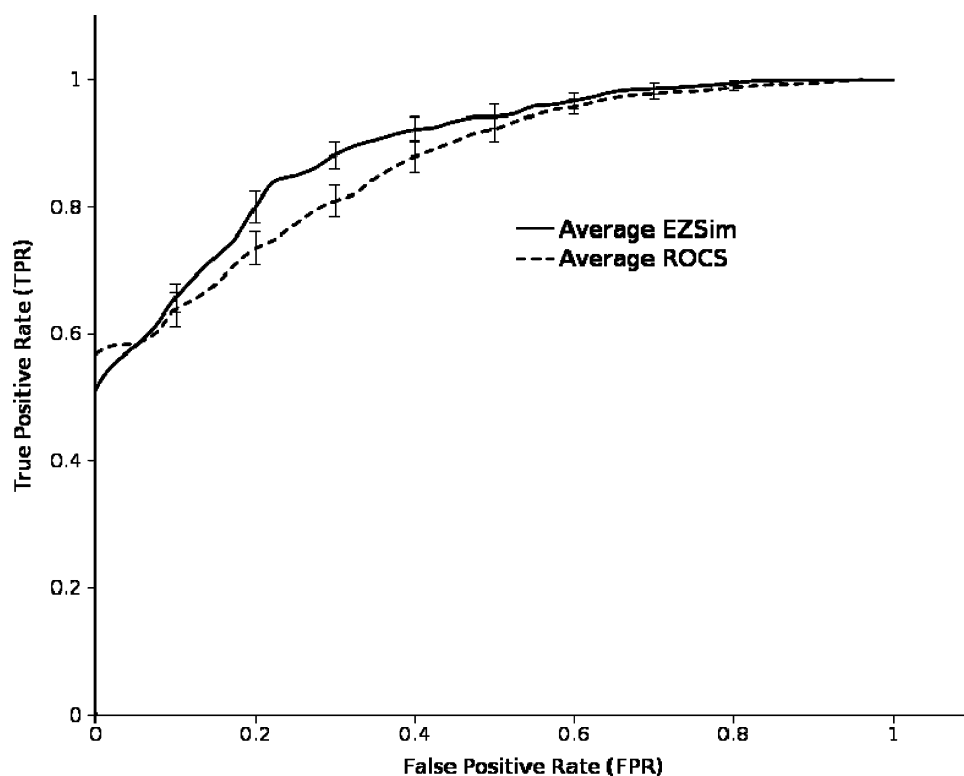


Figure 5. Average ROC curves for human heat shock protein (HSP90) kinase using EZSim and ROCS. Error bars depicted are the standard error of the mean at those points.

the multiconformer database for each target was used for virtual screening, while in the case of EZSim, the 2D depiction database of corresponding target was used. Every database molecule was scored by the corresponding scoring function of each method. Thus, the database molecules were scored and ranked according to the respective scores of each method. The sorted lists of molecules obtained with EZSim and ROCS were the results of the virtual screening experiments and were further

analyzed to obtain the enrichment data expressed as the ROC (Receiver Operator Characteristic) curves and the AUC (Area Under Curve) values. We note that the ROC curves are calculated based on results obtained from searching the database of known ligands and the corresponding decoy molecules for a particular target under study.

Calculation of the Enrichment Data. The virtual screening results obtained as described above were analyzed in terms

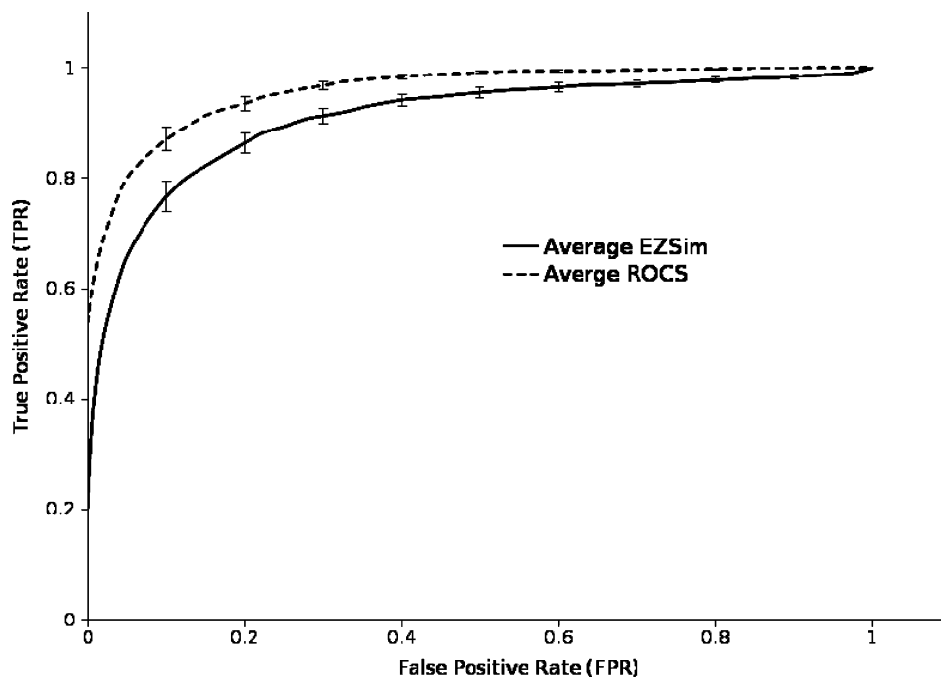


Figure 6. Average ROC curves for neuraminidase using EZSim and ROCS. Error bars depicted are the standard error of the mean at those points.

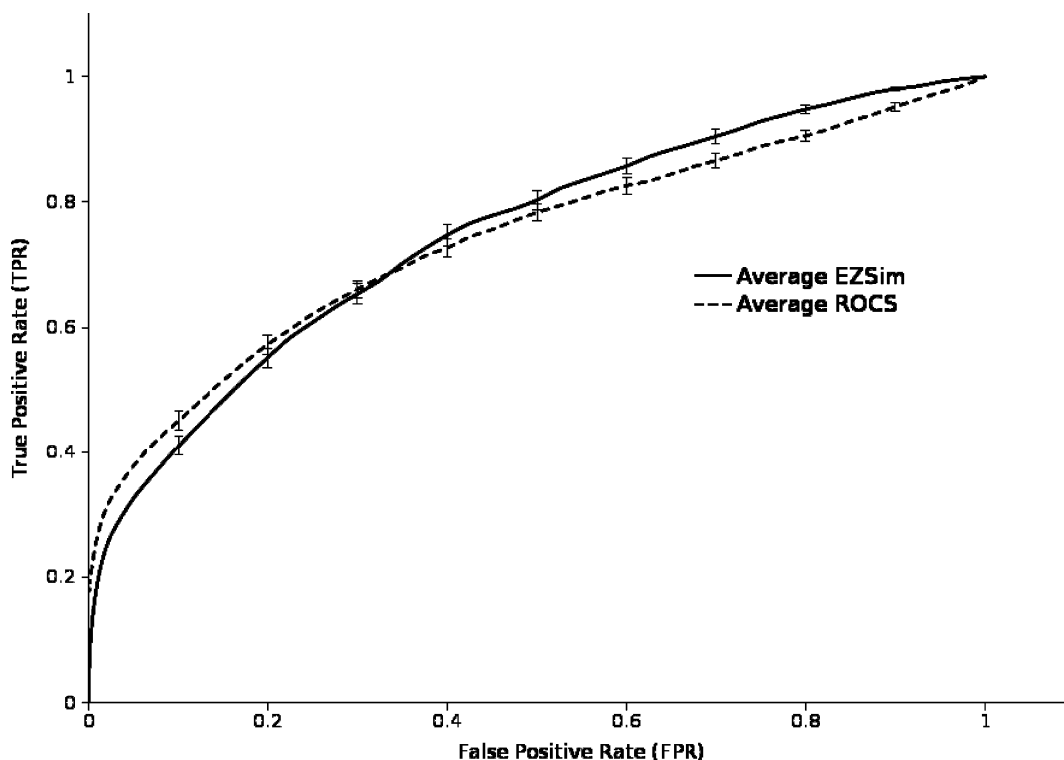


Figure 7. Average ROC curves for phosphodiesterase 5 (PDE5) using EZSim and ROCS. Error bars depicted are the standard error of the mean at those points.

of the ROC curves and the AUC values. Triballeau et al. provides a recent extensive review and application of ROC curve in drug discovery.²⁵ The ROC curve illustrates the evolution of the true positive rate versus the false positive rate for a given virtually screened data set from the DUD database. The true positive rate refers to the rate at which the screening method classifies true actives correctly among all known ligands, while the false positive rate refers to the rate at which the method identifies inactives as actives among all decoys

during the screening process. Figure 3–8 are typical ROC curves where X-axis is the false positive rate for molecules screened and the Y-axis represents the true positive rate. In theory, a random screening would give average classification rates along the diagonal of the ROC plot. The AUC of the ROC curve is widely accepted as means to compare multiple ROC curves. Theoretically, a perfect screening method should have an AUC of 1.0, while random screening method would have an AUC of 0.5.

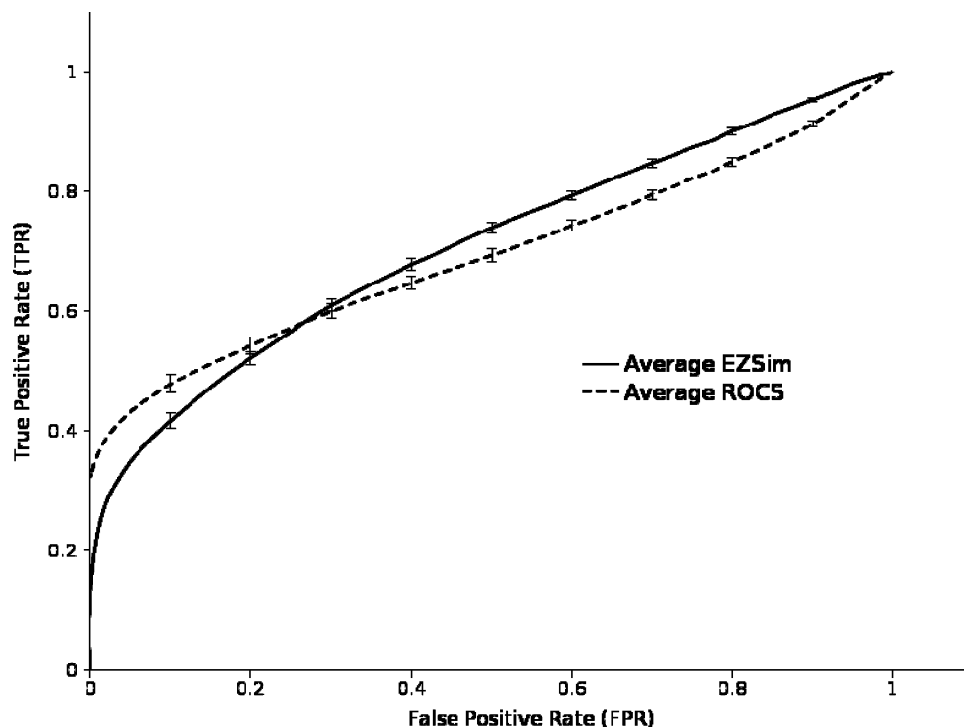


Figure 8. Average ROC curves for tyrosine kinase (TK) SRC using EZSim and ROCS. Error bars depicted are the standard error of the mean at those points.

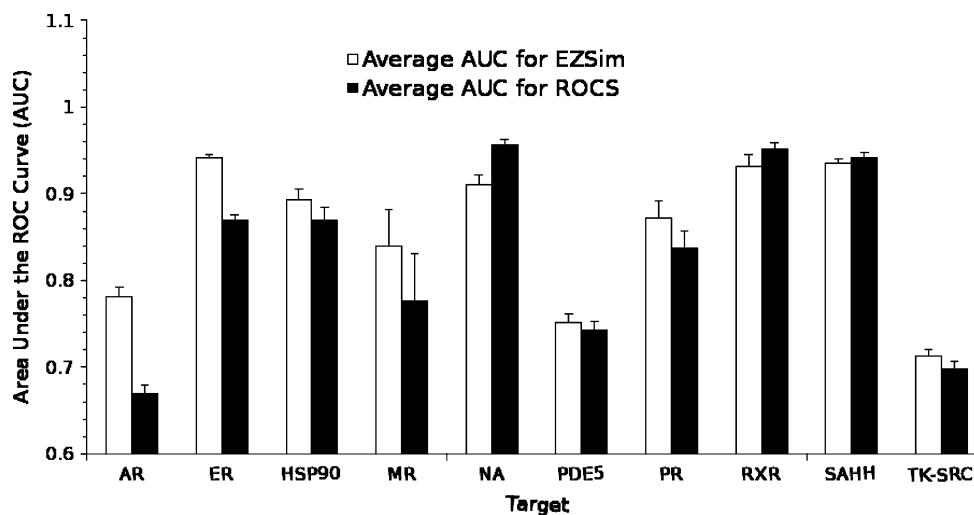


Figure 9. Average AUCs for 10 data sets using EZSim and ROCS as the virtual screening tools. Targets: androgen receptor (AR), estrogen receptor agonists (ER), human heat shock protein kinase (HSP90), mineralcorticoid receptor (MR), neuraminidase (NA), phosphodiesterase V (PDE5), progesterone receptor (PR), retinoic X receptor alpha (RXR), *S*-adenosyl-homocysteine hydrolase (SAHH), tyrosine kinase SRC (TK-SRC). Error bars depicted are the standard error of the mean at those points.

RESULTS AND DISCUSSION

Although the ultimate validation of a computational screening method would come from experimental testing of the virtual screening hits, we adopted a standard computational protocol for validating virtual screening methods. To this end, 40 sets of known actives and decoys were extracted from the DUD database. Virtual screening experiments were conducted, and the ROC curves and AUC values were obtained for each data set based on the virtual screening results obtained with EZSim and ROCS methods, respectively. (see Materials and Methods). For each validation data set, two averaged ROC curves were calculated that correspond to the two different virtual screening methods (EZSim and ROCS). The reason for using the averaged ROC curves is given in the following section and demonstrated

by example results shown in Figure 2. From Figures 3 to 8, the average ROC curves obtained with EZSim are labeled as solid lines while the average ROC curves obtained with ROCS are labeled as dotted lines. To summarize the performance of both computational methods across 10 representative targets, we show a bar graph of the average AUC values obtained for the 10 data sets (Figure 9). The computational costs of the virtual screening experiments using both EZSim and ROCS are shown in Table 1. Finally, the molecular alignments generated by both EZSim and ROCS methods are shown in Figure 10 for three different test cases. Detailed discussions of these results are as follows.

Average ROC Curves Are Statistically Better Indicators of Performance. In Figure 2, we show that when different

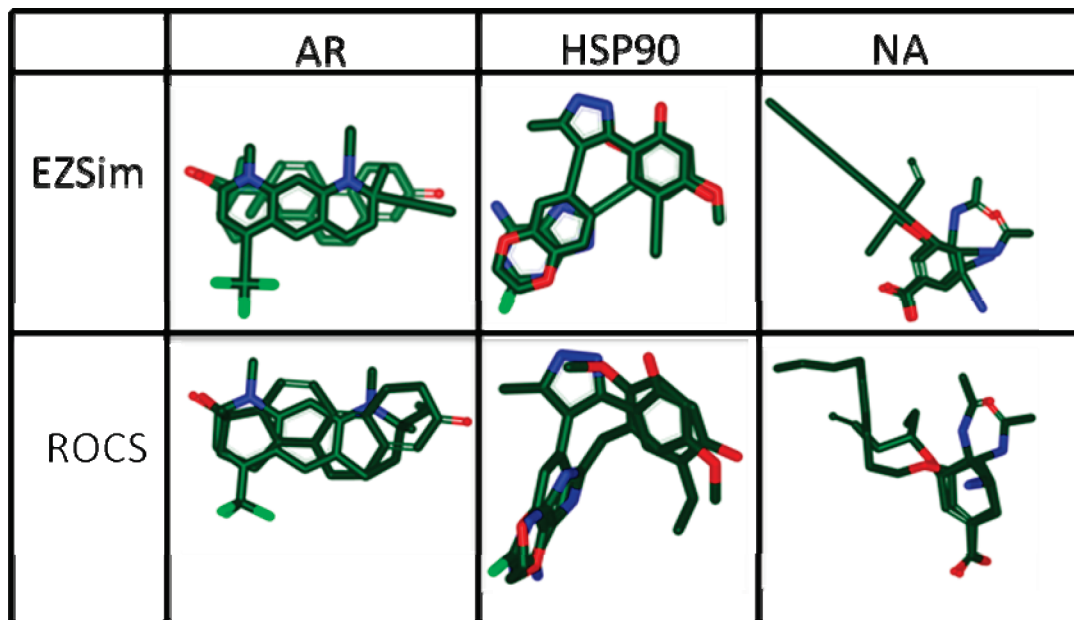


Figure 10. Overlays of retrieved ligands with their queries for 3 different targets from the DUD database, generated using EZSim and ROCS. Targets: androgen receptor (AR), human heat shock protein kinase (HSP90), and neuraminidase (NA).

known ligands were used as the queries, the ROC curves obtained with EZSim and ROCS look different, which led to opposite conclusions as to which method performs better. The ROC curves were plotted based on the results obtained using the VEGR2 data set from DUD. In the left ROC curve, the EZSim method performs better than the ROCS method. However, the reverse is true when a different ligand was used as the query, that is, ROCS performs better than EZSim. Thus, using only one selected molecule from a list of known ligands and using it as the query molecule to conduct virtual screening experiments is not a reliable way to evaluate the performance of a computational method. It is clear that the potential flaw of using one selected query is that the performances are different when different queries are used, especially when the set of known ligands for the target is diverse.

To conduct more objective comparisons and assess the strengths and weaknesses of ROCS and EZSim, we performed virtual screening with each of the known ligands for a target as the query and repeated the virtual screening experiments. Thus, for a given method (EZSim or ROCS), as many ROC curves and AUC values as the number of known ligands were obtained for each data set. For analysis of the performance of both methods, we used the average ROC curves (Figures 3–8) and the average AUC values (Figure 9). Error bars are put on each curve or the AUC bars to indicate the probable errors of the estimated averages. This approach provides a statistically more precise view of the performance of the methods, avoiding misleading conclusions resulting from the use of different queries.

EZSim Performs Similarly to ROCS. The ROC curves obtained for the androgen receptor set (Figure 3), estrogen receptor agonists (Figure 4), and human heat shock protein HSP90 (Figure 5) indicate that EZSim does a better job than ROCS in distinguishing the actives from the decoys. However, ROCS performs better than EZSim in the case of neuraminidase inhibitors (Figure 6). In other cases, such as phosphodiesterase 5 (Figure 7) and tyrosine kinase SRC (Figure 8), the ROC curves indicate similar performances by EZSim and ROCS.

Thus, we conclude that the EZSim method performs similarly to the ROCS method.

The bar chart of the AUC values (Figure 9) shows similar trend of performance by EZSim and ROCS. The accepted guideline for interpreting AUC values is that an AUC less than 0.5 indicates a poor performance, while an AUC of 1 is ideal. Thus, both methods performed well across the 10 representative targets. On the average, the data suggests that EZSim performs about the same as ROCS.

We also compared the results obtained by EZSim and ROCS-single conformer search, where only 1 conformer of each molecule is included in the database. This data is included in the Supporting Information (Figure S3). It turns out that EZSim performs better in 32 of the 40 tested cases in terms of the AUC, while both are equally efficient in terms of their computational costs.

Cost of Computation for EZSim is Much Lower than for ROCS. We compared the computational time requirements for both EZSim and ROCS. Though both methods used shape and chemical color matching, EZSim performs much better than ROCS with computational speedup ranging from 3- to 370-fold (Table 1). This advantage of EZSim over ROCS is because ROCS uses multiconformer representation for the molecules. Thus, each ROCS calculation scales with the product of the number of conformers for both the query and the database molecule. EZSim calculation requires only a single 2D depiction of the query and the database molecule. The computational speedup afforded by EZSim could be taken advantage of in screening larger databases. It is now tractable to use EZSim in screening the PubChem database using only an entry level distributed computing platform.

EZSim Generates Molecular Alignment Similar to ROCS. A few molecular alignments derived from the two virtual screening approaches are shown in Figure 10. The overlays generated by both EZSim and ROCS of a query and the retrieved known ligand are shown for androgen receptor set, HSP90 kinase set, and the neuraminidase data set. The overlay results suggest that EZSim-based molecular alignments (even though they are

based on 2D depictions) are quite consistent with the alignments generated by ROCS. Thus, EZSim generated alignments could be used as an easy framework for visually analyzing the similarity between drug molecules. This could prove useful for the medicinal chemist in deciphering SAR, guiding library design and improving the communication of results from cheminformaticians to medicinal chemists.

CONCLUSIONS AND PERSPECTIVES

We have developed an easy to implement, effective protocol that uses the 2D depictions of molecules as input for similarity search. The 2D depictions of the query and database molecules are then represented as Gaussian functions using the OEShape toolkit. Thus, fast shape overlays between the query and database molecules can be performed. This implementation seems to have captured the intricate details of 2D molecular depictions, the effect of which during virtual screening experiments has been demonstrated using the DUD data sets. Using EZSim, a variant of ROCS, we can yield comparable enrichment rates for known actives from the DUD data sets.

One of the many cited advantages of ROCS is the speed at which it screens multiconformer molecular databases (~600–800 conformers per second). EZSim inherits this advantage because it is built from the same OESHAPE library that was used in ROCS. However, EZSim has the added speed advantage over ROCS as it does not require the use of multiconformer database; rather it uses a single 2D depiction for the query and each database molecule. This gives EZSim up to 370-fold speedup in performance when compared to ROCS, with better or similar enrichment. This computational gain in performance could be harnessed to handle large databases (e.g., the PubChem database) on a modest distributed computing cluster. The time and disk space required for doing a similar task with ROCS would be prohibitively expensive. We have also analyzed the types of compounds found by each method. In general, less flexible compounds were found by EZSim more effectively than by ROCS, while ROCS performed better in cases of more flexible molecules.

We have also compared the performance of EZSim with that of ROCS-single conformer search (Table S1, Table S2, and Figure S3, Supporting Information). Although computational speed is comparable in most cases, EZSim performed better in most cases (32 out of 40 cases) than ROCS-single conformer search. Thus, the data supports the use of EZSim in cases of large scale virtual screening because of its speed and comparable performance to 3D ROCS.

EZSim can also generate reasonable molecular alignments of a set of molecules from their 2D depictions. Such an analysis could provide additional insights as to which regions of the molecules play an important role and which pharmacophoric elements may help discriminate active compounds against inactive ones. The 2D pharmacophores may prove effective in lead hopping and optimization.

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Supporting Information Available: Additional data and figures on the comparison of results obtained by EZSim and

ROCS single conformer search are included in this material. This information is available free of charge via the Internet at <http://pubs.acs.org/>.

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