One Concept, Three Implementations of 3D Pharmacophore-Based Virtual Screening: Distinct Coverage of Chemical Search Space

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Received April 9, 2010

Feature-based pharmacophore modeling is a well-established concept to support early stage drug discovery, where large virtual databases are filtered for potential drug candidates. The concept is implemented in popular molecular modeling software, including Catalyst, Phase, and MOE. With these software tools we performed a comparative virtual screening campaign on HSP90 and FXIa, taken from the 'maximum unbiased validation' data set. Despite the straightforward concept that pharmacophores are based on, we observed an unexpectedly high degree of variation among the hit lists obtained. By harmonizing the pharmacophore feature definitions of the investigated approaches, the exclusion volume sphere settings, and the screening parameters, we have derived a rationale for the observed differences, providing insight on the strengths and weaknesses of these algorithms. Application of more than one of these software tools in parallel will result in a widened coverage of chemical space. This is not only rooted in the dissimilarity of feature definitions but also in different algorithmic search strategies.

INTRODUCTION

Pharmacophore modeling is a well-established method for screening of large databases during the early phases of drug development. Several reviews cover the method as well as examples of its successful application.[1−5] The advantages are obvious: Chemical groups of a ligand that are decisive for interaction with a protein are represented by a small number of different pharmacophore features. The feature set contains at least positively or negatively charged groups, hydrogen-bond donors or acceptors, and hydrophobic regions.[6,7] This representation of the ligand structure as chemical functionality allows for a fast comparison with other molecules. The level of abstraction is helpful for the discovery of compounds that are structurally different from the template ligands and, thus, is useful for rationalized scaffold hopping. Still, pharmacophore features are not too abstract to allow for an easy and intuitive interpretation of a structure−activity relationship. The restriction to exclusively describe ligand groups that take part in ligand binding avoids combinatorial problems encountered by screening approaches that consider the macromolecular target structure (or parts of it) at an atomic level of detail. This is typically a disadvantage of scoring functions that have to distinguish between several plausible docking poses in structure-based drug design.

The pharmacophore concept is implemented in numerous software tools. The programs compared in this study primarily reflect the popularity of the software and do not essentially indicate superior performance. Catalyst[8] has become part of Accelrys' Discovery Studio,[9] Phase[10,11] is accessible by Schrödinger's graphical interface Maestro,[12] and Chemical Computing Group's MOE[13] has a pharmacophore module. For a comprehensive survey on pharmacophore modeling software, the interested reader is referred to Leach et al.[2] We have analyzed the differences of these tools earlier in a qualitative manner.[7] In the current study, we were interested in quantification of the differences between virtual screening results when working on a particular target employing the same approach but different implementations of the pharmacophore modeling concept. We expected to find subtle differences in pharmacophore interpretation or screening speed but found surprisingly different virtual screening results.

For a comparative assessment of the resulting hit lists, we avoided ligand-based pharmacophore elucidation procedures that require the alignment of ligands and certainly would introduce important discrepancies to the screening results. Instead, the locations of chemical features were directly derived from protein−ligand complexes for two targets (HSP90 and FXIa) taken from the 'maximum unbiased validation' (MUV) data set.[14] This data set has been selected for testing, as it contains both known active and experimentally confirmed inactive compounds and is larger than other validation sets, like the directory of useful decoys (DUD).[15] On the other hand, the MUV set with 30 actives and 15 000 inactives per target is considerably smaller and more manageable than, for example, the ZINC database[16] as a decoy set. Moreover the design of the MUV set tries to prevent artificial enrichment by providing inactives that are

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10.1021/ci100136b
Published on Web 06/28/2010

structurally close to the active compounds. Structural diversity of active compounds unfortunately leads to a low retrieval rate but does not prevent the investigation of differences between the pharmacophore screening implementations. HSP90 (heat shock protein 90) and FXIa (factor XIa) were selected because of the availability of comprehensive X-ray data, including drug-like ligands bound to the targets. Another reason for choosing these targets was the set of interactions between ligand and protein that allowed for keeping the number of hydrophobic features at a low level. Hydrophobic features are already known to be interpreted differently,[7] so we focused on the investigation of more comparable features like hydrogen-bond (H-bond) donors and acceptors.

HSP90. Heat shock protein 90 is a molecular chaperone involved in folding, activation, and stabilization of several proteins. Especially in cancer cells it shows an increased level of activity that is linked to the regulation of oncogenic proteins. Inhibiting HSP90 results in the interruption of signaling pathways and the degradation of receptors and transcriptional factors responsible for carcinogenesis.[17−19] A large number of recent reviews exhaustively cover HSP90. At present, there are 13 Hsp90 inhibitors in clinical trials.[20,21]

FXIa. Factor XIa is the activated form of Factor XI. The trypsin-like serine protease is a member of the blood coagulation cascade, involved in the amplification phase and in maintaining clot integrity. Conventional antithrombotic drugs bear the risk of severe bleeding by targeting several coagulation proteases. Inhibitors of FXIa promise to affect only the amplification phase of the cascade without interrupting the function of normal hemostasis.[22] For FXIa inhibitors there is much less data accessible than for HSP90. However, there is still a large amount of high-throughput screening data and six crystal structures available.[23]

In the following, we will first give an impression of the differences in hit retrieval with geometrically identical models using each program's default settings. We define models to be 'geometrically identical' if the same coordinates are used for feature placement and if they match the same active compounds in each software tool. In the next step, we harmonize feature definitions, screening parameters, and exclusion volume sphere settings, taking into account all documented and analyzed peculiarities of each program, in order to make the results as consistent as possible (i.e., to maximize the overlap of the retrieved virtual hit lists). These results will be discussed in detail to elaborate a rationale for the differences in pharmacophore implementation and to allow for a better understanding and interpretation the results from these programs. The extent of differences between pharmacophore programs suggests that a specific pharmacophore model is restricted to the corresponding software tool in its validity to discriminate active from inactive ligands.

METHODS

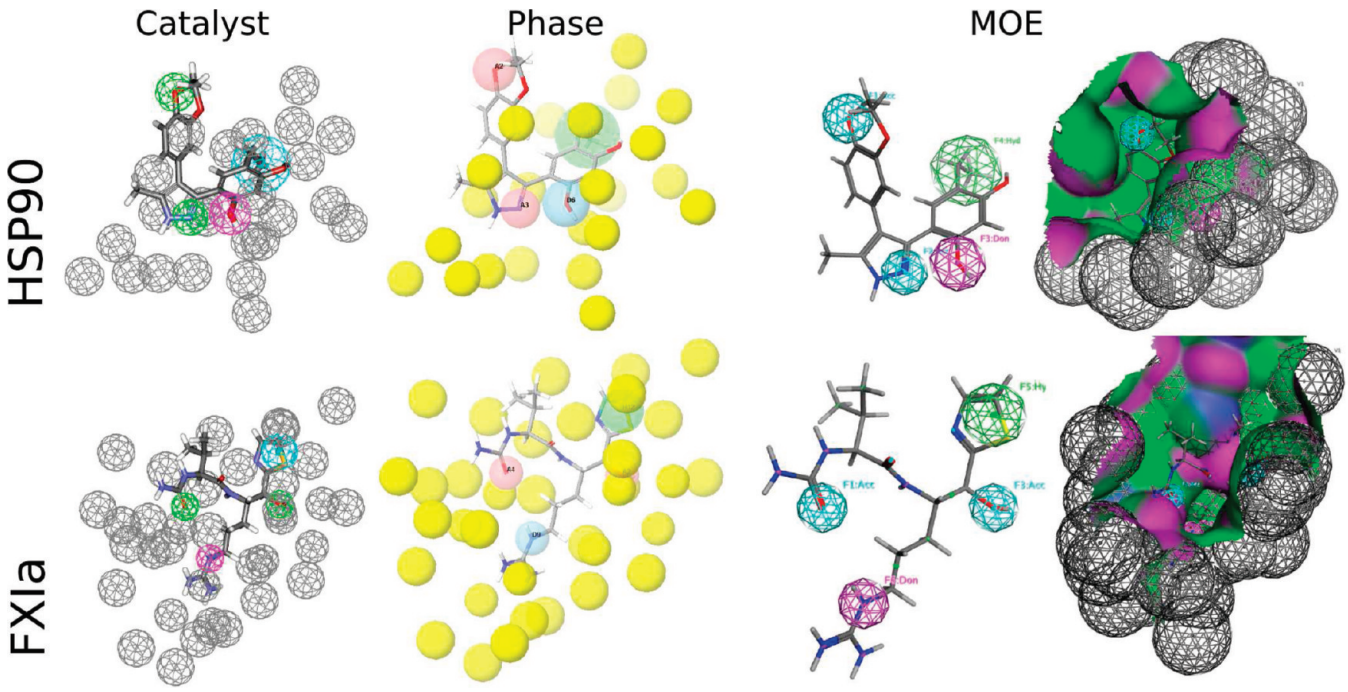
MUV Data Sets[14] for the targets HSP90 and FXIa were downloaded from http://www.pharmchem.tu-bs.de/lehre/baumann/MUV.html (access date: March 17, 2009). A multiconformer data set was created from the active as well as from the inactive compounds using Omega,[24] version 2.0 (default settings allowing up to 400 conformers per molecule). The resulting multiconformational database was imported into Catalyst[8] (version 4.11) without any modification, further named the 'unmodified' database. The function 'wash' in MOE (version 2008.10)[13] was used to deprotonate strong acids and protonate strong bases and to add explicit hydrogens as necessary for pharmacophore screening in MOE. A copy of this database was imported to Phase[11] (version 3.0) and as a 'modified' database to Catalyst.

Initial 'Unmodified' Hypotheses and Settings. Starting with X-ray structures 2CDD (HSP90) and 2FDA (FXIa), hypotheses were generated by inspecting the ligand and its interaction pattern with the aid of LigandScout.[25,26] The bioactive conformation of the ligand was subsequently transferred to each program where it was decorated with pharmacophore features by using the respective built-in feature mapping routines. In MOE the 'unified' feature scheme was used. In Phase, the parameter 'distance matching tolerance' was increased from 2 Å (default) to twice the largest tolerance sphere radius to make the distance-matching step sensitive to tolerance sphere radii. In an iterative process feature selection and tolerance spheres were refined to maximize the enrichment and the number of commonly retrieved actives. In the end, both targets were described by two H-bond acceptors, one H-bond donor, and one hydrophobic feature (see Scheme 1). The coordinates and tolerance spheres were identical in all programs except for a minor variation of the hydrophobic feature placement. In Catalyst and MOE ('unified' feature scheme), we omitted direction vectors and projection points of H-bond features to rule out the observed differences in direction assignments. In Phase, it is not possible to avoid feature directionality without modifying feature definitions. However, we did not alter the definitions for the initial pharmacophore models.

Twenty-four exclusion volume spheres (EVSs) for HSP90 and 35 for FXIa were created by adding exclusion volumes with a radius of 1.5 Å on all heavy atoms of the protein within a distance of 7 Å from any ligand atom. Subsequently, overlapping volumes were geometrically clustered to reduce the number of restricting volumes for more efficient virtual screening. On each α carbon on the protein side within a distance threshold of 7 Å, an additional EVS was placed. For HSP90 the optimal radii were found to be the same for all EVS: 1.0, 1.35, and 2.75 Å in Phase, Catalyst, and MOE, respectively. In the case of FXIa, exclusion volume radii ranged from 1.0 to 1.2 Å in Phase, 1.2 to 1.4 Å in Catalyst, and 2.9 Å in MOE. MOE does not assign van der Waals radii to ligand atoms, resulting in the peculiar sizes of MOE's exclusion volume spheres. In MOE the optimal radius was found by generating an interaction surface for the binding pocket. Exclusion volume sphere radii were required to be large enough to touch the interaction surface thereby compensating for the missing ligand's van der Waals radii.

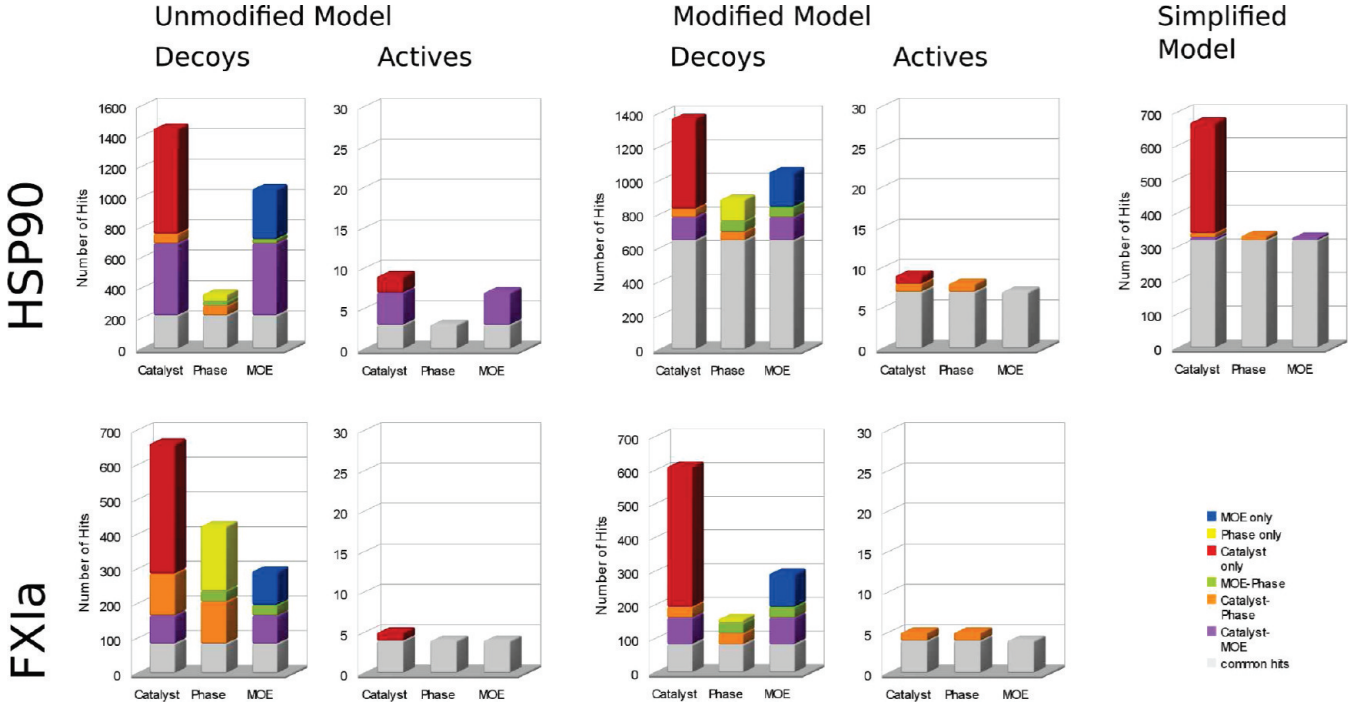
Modified Hypotheses. Only feature definitions were changed for converting the 'unmodified' model into the 'modified' one, in order to test for screening discrepancies beyond feature definitions. First, a pharmacologically not meaningful 'simplified' model was created to evaluate feature harmonization. It consists of two H-bond donor and two H-bond acceptor features without directionalities created on the basis of the ligand in PDB structure 2CDD (HSP90). It is geometrically identical for all software packages. Indeed, MOE retrieves 327 compounds in the HSP90 decoys set and Phase 332. There is an overlap of 319 compounds between

Scheme 1. A Set of Geometrically Identical Features Was Used for Pharmacophore Model Generation in Catalyst, Phase, and MOE[a]



[a] Exclusion volume spheres have the same coordinates in all programs but differ in their tolerance spheres due to differences in the consideration of ligand volume. In MOE, they require to be larger because the ligand is not considered to be voluminous.

Scheme 2. Hit Lists for Unmodified, Modified, and Simplified Models[a]



[a] Although very similar in retrieving active compounds, there is only a small overlap between the hit lists resulting from screening the decoy compounds. After harmonizing the feature definitions, the 'modified model' still leads to different results for the decoys set. Differences arise from alignment, scoring, and EVSs. The 'simplified' model consists of only two H-bond donors and two H-bond acceptors and demonstrates the differences exclusively arising from alignment and scoring.

Phase and MOE. They even report the same root-mean-square deviation (rmsd) between ligand and pharmacophore models in several test cases. Catalyst retrieves 669 hits without missing any obtained by the other tools (see Scheme 2 for a graphical representation). The larger number of hits turned out to emerge from differences in retrieval as well as from scoring of the molecules. The modifications elaborated for maximum hit list overlap of the 'simplified' model were applied to the 'unmodified' model to yield the geometrically identical 'modified' model.

The high agreement between the feature definitions could be reached by using the precharged version of the conformer database also for Catalyst, which does not expect the compounds to be charged by default. In Catalyst the definition of the H-bond donor feature was extended by four groups: secondary and tertiary amines, amidines, and 4-ami-

nopyridines. Sulfur atoms were excluded from H-bond acceptor functionality. The ExcludedVolumeXFactor in the pharmacophore model file was changed from 0.85 to 1 in order to stop the hidden downsizing of chosen EVS radii.

The chemical feature definitions from all three programs were analyzed and subsequently used to replace Phase's original ones to come closer to that of Catalyst and MOE. The change most relevant for this study is the replacement of the original set of H-bond vectors by H-bond point features without direction preference.

In MOE, the original feature definitions were kept. The feature scheme 'unified' was used, since MOE does not allow customization of features out-of-the-box. However, this scheme is largely consistent with the feature sets of the other tools.

RESULTS AND DISCUSSION

Pharmacophore Model Generation. The primary objective of this study was to identify differences in pharmacophore interpretation, virtual screening, and three-dimensional (3D) alignment, not to find the chemically most relevant model covering all interactions observed in different X-ray structures. We followed the set of criteria below to reach maximum comparability of the hypotheses (priorities high to low):

(1) Identical feature coordinates should be applicable in all software tools. This restricts the selection of feature types other than hydrophobic features, as they are placed on different locations in all programs.

(2) The same active compounds should be found by a model regarded as geometrically identical in all software tools. This was not only important to test the selection of features but also for adapting exclusion volume sphere settings that were otherwise not comparable among the programs.

(3) A good enrichment of actives among inactives is usually considered very important for virtual screening and pharmacophore modeling. For comparability reasons, this criterion was ranked third during this study.

The X-ray structures with PDB-code 2CDD (HSP90) and 2FDA (FXIa) served as basis for structure-based design. For initial model generation, default settings were kept in each software tool. A detailed description is given in the Methods Section. EVSs were necessary to improve model restrictivity that suffered from the low number of pharmacophore features resulting from the comparability criterion. After all, the hypotheses presented are at the optimum with respect to retrieval of the same set of active molecules, while largely preserving the programs' default settings. Since no activity values are reported for active compounds, it was not possible to prefer particularly active molecules during hypothesis generation.

For enhancing comparability, feature definitions, but neither initial coordinates nor tolerances, were altered to yield the 'modified' model; a detailed description of changes is given in the Methods Section. MOE's original feature definitions were kept. This does not reflect any preferences for MOE's feature definitions but was the most practical way to reach feature definition equality in order to elucidate further discrepancies between the tools. In the beginning of our study, we expected the feature definitions to be the decisive reason for a small overlap of the results. Despite equal feature definitions, there was no way to reach hit list equality. Several reasons will be discussed in the following sections.

Table 1. Combination of Hit Lists[a]

	HSP90	FXIa
Catalyst	3.1	3.8
Phase	4.2	4.7
MOE	3.3	6.8
combined	6.8	23.5

[a] By only accepting molecules found by all software tools increases enrichment. The 'unmodified' hypotheses were used.

Differences in Numbers. The most important criterion during model generation was comparability. It was reached by preferably using H-bond features without directionality, keeping the number of hydrophobic features low and using the same coordinates and tolerance spheres. The set of active compounds was used as a benchmark; high overlap between the actives reported by each program was considered a confirmation of model equivalency in terms of feature selection and exclusion volume radii. As can be seen in Scheme 2, we largely reached comparability between the compounds retrieved from the actives set, albeit at the expense of good retrieval rates. Despite our focus on comparability, the results from screening the decoys set impressively demonstrate significant differences between the software packages. They do not just differ in number of retrieved hits, as it would be the case when a smaller hit list is a subset of the larger one, they rather identify complementary chemical spaces.

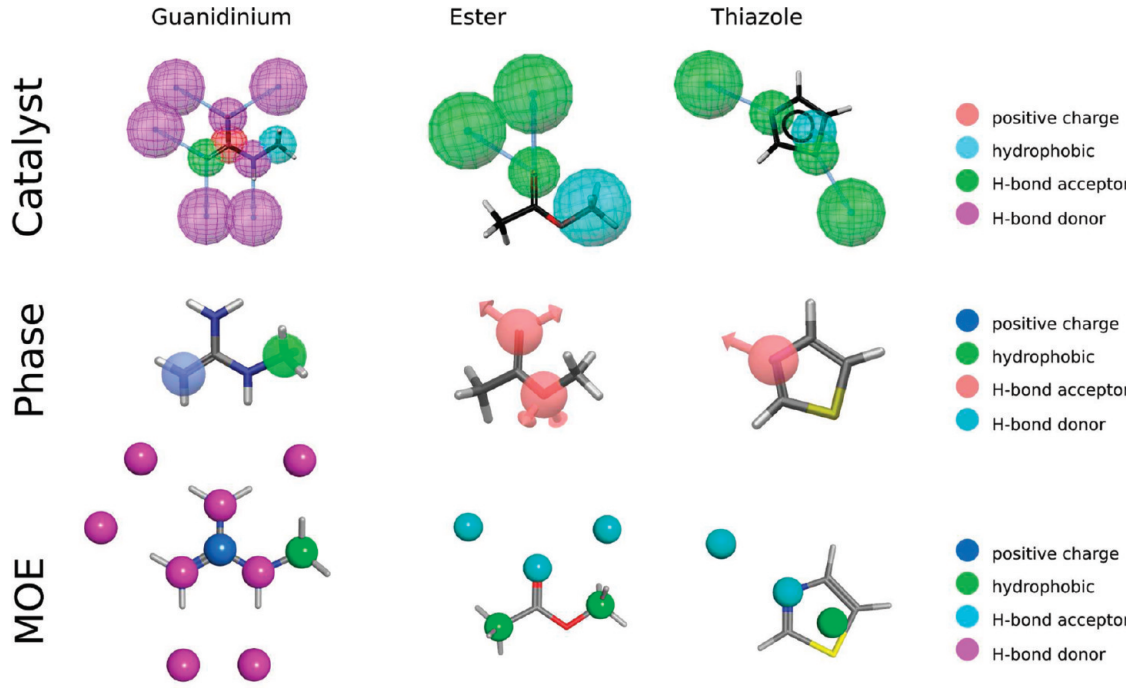
Search space complementarity is pronounced enough to lead to better enrichment values when combining the hit lists. Taking into account only molecules that were found by all software packages increases the enrichment (see Table 1).

Pharmacophore model modification, i.e., feature definition harmonization, leads to very good hit list agreement for the 'simplified' model (see Scheme 2) that consists of two H-bond donors and two H-bond acceptors without vectors, indicating a preferred direction. The reason for the larger hit list of Catalyst can be exclusively ascribed to the alignment and scoring process. The more pharmacologically relevant 'modified' model is geometrically identical with the 'unmodified' model but includes modified feature definitions. It represents the maximum overlap we were able to achieve between the different pharmacophore screening implementations. Skipping the EVSs would reduce the differences but would result in a pharmacophore model useless for virtual screening, as it retrieves up to one-third of the decoy molecules as screening hits.

Reasons for Low Overlap Between Hit Lists. *Features and Feature Definitions.* Electrostatic and van der Waals interactions contribute to the enthalpic part of noncovalent ligand binding. Correspondingly, typical pharmacophore features describe at least positively and negatively charged groups on the ligand, H-bond donors and acceptors, aromatic rings, and hydrophobic regions.[6,27] To some extent the latter ones also represent entropic contributions, as the burial of hydrophobic surfaces is usually associated with a gain of entropy.[28,29] A survey on feature definitions and placements is given by Wolber et al.[7]

Whereas it is trivial for a chemist to identify, for example, a guanidinium group as positively charged, feature assign-

Scheme 3. MOE, Phase, and Catalyst Differ in the Way They Assign Pharmacophore Features to Functional Groups[a]



[a] The positive-charge feature representing the guanidinium group is centered in Catalyst and MOE but located on the sp^2 nitrogen in Phase. Catalyst and MOE additionally assign H-bond donor features. Catalyst even assigns H-bond acceptors to the sp^2 nitrogen atom (green sphere). The feature decoration of the ester differs in the directions and the presence or absence of the H-bonds as well as hydrophobic features. All programs find an H-bond acceptor on thiazole's nitrogen atom. Catalyst and MOE assign an additional hydrophobic feature. Catalyst additionally decorates the sulfur atom with an H-bond donor feature.

ments differ among the programs (see Scheme 3). Though these rules agree on the placement of a positively charged feature on this chemical group, the accurate feature placement differs as well as the assignment of H-bonding features. Only Phase does not assign any H-bond features at all, MOE proposes numerous H-bond donor features, and Catalyst even assigns a H-bond acceptor feature on the sp^2 nitrogen atom, leading to discrepancies in virtual hit retrieval.

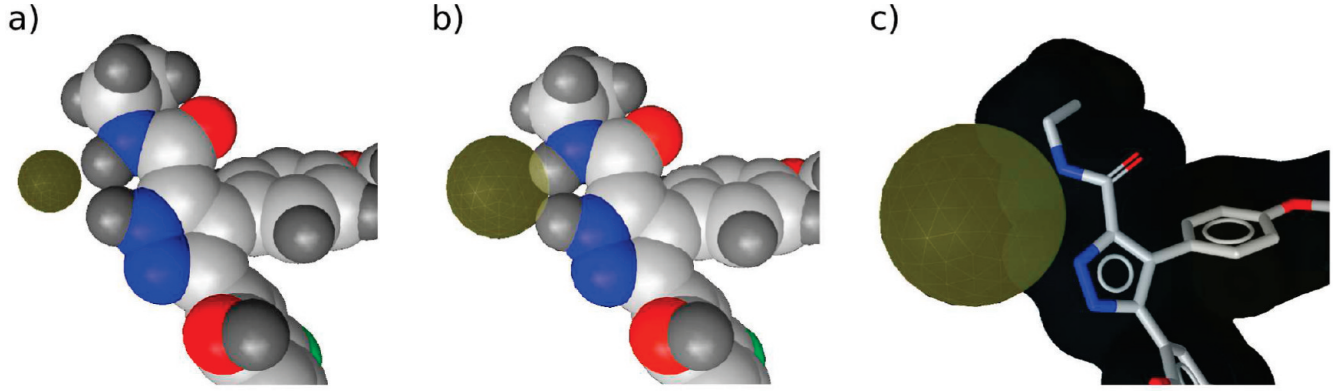
Similarly, the assignment of H-bond donors and acceptors considerably differs between the programs. Phase by default places H-bond donor features on hydrogen atoms of H-bond donors.[27] The other tools assign all H-bond features to the respective heavy atoms. By default, the H-bond features of Phase are vectors. Their directions are determined by the underlying ligand groups and are not changeable. Taking the carbonyl-oxygen in an ester group as an example, Phase will place an H-bond acceptor with two arrows in the lone-pair direction (Scheme 3). Catalyst would also use a vector but proposes the elongation of the double bond as additional direction. MOE will again propose the two lone-pair directions for placing projected points. Instead of being part of vector features, MOE's projected points are independent entities. Our comparability criterion forced us to reduce the H-bond features to points instead of vectors.

The examples given were unambiguous in their classification as charged or H-bond acceptor groups. Complications in H-bond assignment arise from the chemical environment, especially in aromatic or conjugated systems, and from tautomerism.[30] H-bond donating or accepting groups differ considerably in their propensity to form strong or weak H-bonds.[31,32] Although H-bond strength can be assessed and ranked, there is no universally valid way to classify them as they are susceptible to the environment when bound to a protein and to solvation/desolvation effects. Complexity of the assignment problem is reflected by ambiguities in H-bond feature mappings. An example of assignment differences is the sp^2 oxygen of an ester (Scheme 3). Phase finds a H-bond acceptor with two directions, Catalyst proposes one direction, and MOE does not place a feature at all, corresponding to findings by Boehm et al.[33]

Hydrophobic features are the most important sources of feature assignment differences. Only consisting of a point and a tolerance sphere, they have to represent ligand regions which might be extended and of complex shape. Shape complementarity to the binding pocket importantly contributes to the overall binding affinity and, thus, leads to decisive questions. What is the best location for a hydrophobic feature representing several ligand atoms? How many feature points are optimal to describe a hydrophobic region? Which constellation of atoms is hydrophobic at all? Catalyst's algorithm to identify hydrophobic regions is described by Greene et al.[6] Although it is similarly implemented in Phase,[10] it does not lead to identical feature placement (see Wolber et al.[7] for examples). For comparability reasons, the number of hydrophobic features in our hypotheses was kept small.

Exclusion Volume Spheres. EVSs represent regions in space not allowed to be penetrated by the ligand. In structure-based pharmacophore model design, they represent protein side chains. By reducing the space accessible to the ligand, they significantly increase the restrictivity of the model. When using identical coordinates and tolerance spheres, differences arise from hidden parameters like Catalyst's 'ExcludedVolumeXFactor' that reduces the tolerances when not set to 1. The idea of this parameter is to soften EVSs to account for binding pocket flexibility. To decide whether a

Scheme 4. Different Ways to Consider the Overlap between an EVS (Yellow) and a Ligand[a]



[a] (a) van der Waals radius is assigned to every ligand atom (optional in Phase). (b) Hydrogen atoms are not considered for ligand volume (in Catalyst and default in Phase). (c) The ligand is not considered to be voluminous, only atom centers are not allowed to be located within an exclusion volume sphere (MOE).

ligand atom penetrates an EVS or not, Catalyst and Phase assign van der Waals radii to every heavy atom in the ligand (Scheme 4). Phase provides the option to consider hydrogen atoms too, but it does not do so by default. In contrast, MOE classifies an EVS as penetrated when a ligand atom center lies within the tolerance sphere. Even bonds are allowed to run through an EVS. Consequently the EVS needs to be larger. Twice the atom's van der Waals radius is a good starting point for further optimization.

3D Alignment and Screening. Superposition of a database compound and a query pharmacophore can be formally divided into two steps. First, potential hit compounds are selected if they match the features and interfeature distances of the query pharmacophore. This rough filter step can reach high screen-out rates of 80−100%.[2] The actual alignment with a rmsd minimization takes place in a second step. In Phase, the first 'find' step collects compounds that fulfill numbers and types of features as well as intersite distances and stores them in a 'match file'. In the 'fetch' step, the relevant compounds are aligned to the query pharmacophore. Thereby they are additionally filtered and ordered by using EVSs, a scoring function, and numerical limits.[34] In MOE, the SVL-scripts 'dmatch' and 'Superpose2' perform equivalent tasks but are not intended to be executed separately.[35] In contrast, hit lists reported by Catalyst result from the first step only and are therefore rather estimated. Actual alignment of compound and model is a separate procedure only performed if the fit value calculation is requested. Consequently, screening with our 'simplified' model (see Method Section) that avoids differences from feature definitions or EVSs results in equal hit lists for Phase and MOE but a double-sized hit list for Catalyst. Some of the additional hits have features not located within the feature tolerances spheres, some have slightly negative fit values, but for some others, there is no reason why the other tools miss them.

Fitting and Scoring. While it could be expected that feature tolerances indicate the radius around feature coordinates where the corresponding feature on the ligand is allowed to be positioned after the alignment, we found these tolerances not completely exploited by Phase and protruded by Catalyst. In Phase, the parameter 'distance matching tolerance' is responsible. By default it is set to 2 Å. When comparing the distance between two features on the ligand with the corresponding distance in the pharmacophore model, we obtain the tolerance that is allowed for a successful mapping. For feature tolerances larger than 1 Å, the parameter has to be set to twice the value of the feature tolerances.

Catalyst does not require each ligand feature to be located within the hypothesis tolerance sphere. It calculates an overall fit value instead. Each feature contributes $1 - (\text{distance}/\text{tolerance})^2$. A feature weight factor is omitted for simplification. Ligand features outside the tolerance sphere will result in a negative contribution but can be outweighed by others.

General Experiences. This study demonstrates the differences between pharmacophore screening results with two thoroughly elaborated examples. Human rhinovirus coat protein was used as a target during preparatory stages. The respective binding pocket was a hydrophobic tube with usually only one H-bond formed at the entrance.[36] Virtual screening carried out with Catalyst, Phase, and MOE on assemblies of drug-like molecules lead to even more drastic differences in screening results than presented herein. The effect of an increased enrichment after hit list combination was more pronounced too. We credit the discrepancies in screening results to the high proportion of hydrophobic features in the pharmacophore models. However, previous experiences as well as the results of the present study suggest the differences between the pharmacophore tools to be a general phenomenon. It may be even more pronounced when not focusing on model comparability as we did by, for example, skipping the feature directionality.

Starting the pharmacophore generation process with default settings in every software tool, we found Catalyst to achieve good retrieval rates of active compounds easily. Although Catalyst usually finds many inactives too, the overall enrichment was satisfying. Phase in its default mode is the most restrictive tool, favoring it for projects where small virtual screening hit lists are desired. Loss of actives is compensated by good enrichtment values. Default settings in MOE lead to pharmacophore models with low restrictivity that can be improved by reducing feature tolerance radii.

CONCLUSIONS

Despite the convincing clarity of the pharmacophore concept, we found surprisingly different results when applying three different software implementations (MOE, Catalyst, and Phase) to two targets. Some of them are caused not only by different chemical feature definitions but also by different hit retrieval algorithms, which are obviously

unable to cover search space in a comprehensive way. Several suggestions for the practical application of 3D pharmacophore modeling using these three program applications result from our study.

A gain in diversity of hit lists can be expected by using more than one pharmacophore modeling tool. Our study shows an increased enrichment when combining hit lists of all software packages tested. Feature definitions—in particular hydrophobic features—are the main reason for differences in hit lists. Other important reasons are exclusion volume sphere placing, hit ranking, and alignment algorithms. There is no easy clue for an optimal set of feature definitions. The best choice will depend on the target that should be described. An adaption of feature definitions to a target can be expected to improve predictive quality of a pharmacophore model.

Significant differences between virtual screening results indicate that a specific pharmacophore model does not provide a universally valid representation of a protein−ligand interaction, but a representation that is valid in the context of the software used for model generation. A three-dimensional (3D) pharmacophore model optimized for one pharmacophore approach is not easily transferable to another one. The results will not only differ in size of the hit lists (with Phase hit lists usually being the most restrictive and MOE being the opposite unless using large exclusion volumes) but also in scaffolds retrieved during screening. We found Catalyst to be least restrictive as well as most successful in aligning compounds to a simplified hypothesis consisting of only two H-bond donors and two H-bond acceptors. However, we rather recommend gaining profound knowledge of parameters, settings, and concepts of one of the discussed pharmacophore screening implementations than using a specific one.

ACKNOWLEDGMENT

This work was supported by the Austrian Science Fund (Projects P19756 and S10702−B03). We thank Christian Laggner and Thierry Langer for helpful discussions. We thank Christian Laggner, Theodora Steindl, and Thierry Langer for helpful discussions.

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CI100136B