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Quo Vadis, Virtual Screening? A Comprehensive Survey of Prospective Applications

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Introduction

Virtual screening (VS[a]) of compound databases has become a popular hit identification technique and a major playground for computational method development.[1] Relevant methods are typically classified as structure-based virtual screening (SBVS), predominantly docking, or ligand-based virtual screening (LBVS) methods, which are based on concepts of ligand similarity. Currently popular similarity-based and docking methods had their scientific origins in the 1970s and 1980s, respectively,[2−6] but the first time the term "virtual screening" appeared in a peer-reviewed publication was in 1997.[7] Since then the VS field has experienced ever increasing popularity and rapid growth. In fact, new and conceptually diverse VS methods are introduced on a regular basis and benchmark investigations to evaluate various VS approaches dominate the VS literature.[1] Here, the lack of commonly accepted community standards for method evaluation and comparison currently presents a major bottleneck for the further development of this field.[8,9] Hence, in the case of "retrospective" VS studies that employ benchmark calculations on preselected compound activity classes, it is difficult to judge the performance of newly introduced methodologies, reproduce benchmark calculations, compare different methods on the basis of literature data, and put VS performance into scientific context.

In addition to retrospective analyses, VS studies are often carried out "prospectively", i.e., by computational selection and experimental evaluation of candidate compounds in order to identify novel hits. The primary goal of prospective VS typically is to find structurally diverse compounds (previously unknown chemotypes) having a desired biological activity.[10−13] Because of the intrinsic link to experimental evaluation, prospective VS applications are often considered the "ultimate proof" of the value of SBVS and LBVS methods. However, as with retrospective VS analysis, prospective applications are also not free of caveats.[14] For example, the identification of active compounds does not per se "validate" a particular VS recipe as long as it is not proven that much simpler approaches would not have produced similar results. Furthermore, VS hits are often insufficiently experimentally characterized to confirm specific target binding and inhibition. In addition to these methodological caveats, there are also "strategic" issues to consider that complicate the assessment of applied VS. For example, only "positive" results (i.e., successfully identified hits) are reported in the scientific literature. Currently, there is little, if any, opportunity or incentive to communicate "negative" results, which would certainly help to evaluate the failures and successes of prospective VS campaigns and compare the performance of alternative approaches. Last but not least, many VS applications carried out in industrial environments are kept confidential, and compounds of interest are not disclosed. Hence, whether or not VS publications from industry provide a representative view of applied VS in pharmaceutical research is not certain.

We have been interested in obtaining a detailed picture of the applied VS field to better understand the state-of-the-art in prospective VS. A number of questions have been asked: Where are prospective VS studies published? What are the utilized methods? How successful are they? What are preferred targets? How potent are newly identified compounds? Obtaining answers to these and other questions ultimately meant that we needed to carry out a comprehensive survey of the currently available scientific literature. Although certainly not all successful applications are documented in peer-reviewed publications, these publications do present the most reliable source for relevant information. The systematic analysis of original research publications has been a labor-intensive, yet highly educational effort. Because we individually extracted applied VS information from original reports, our analysis has a high degree of confidence. Herein we present the results of this analysis. On the basis of our findings, we comment on the performance of different prospective VS approaches and provide a perspective of the field.

Literature Survey

We have systematically queried chemical, computational, and life science journals using the keyword "virtual screening". Journals containing "virtual screening" papers were only considered if they still exist and if they obtained an impact factor of at least 2 in 2009. We focused on journals where VS studies frequently appear (e.g., *Journal of Chemical Information and Modeling*, *Journal of Medicinal Chemistry*, and *Bioorganic Medicinal Chemistry*) and, in addition, journals with particularly high impact factors where studies involving VS are occasionally published (e.g., *Nature Chemical Biology* and *Angewandte Chemie, International Edition*).

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[a] Abbreviations: VS, virtual screening; LBVS, ligand-based virtual screening; SBVS, structure-based virtual screening; SAR, structure−activity relationship; 2D, two-dimensional; 3D, three-dimensional; GPCR, G-protein-coupled receptor.

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Table 1. Prospective Structure- and Ligand-Based Virtual Screening Studies[a]

journal	no. SBVS	no. LBVS
Journal of Medicinal Chemistry	129	33
Bioorganic Medicinal Chemistry Letters	74	26
Bioorganic Medicinal Chemistry	43	10
Journal of Chemical Information and Modeling	24	9
ChemMedChem	19	12
European Journal of Medicinal Chemistry	8	4
Chemical Biology & Drug Design	7	2
Journal of Computer-Aided Molecular Design	6	2
ACS Chemical Biology	3	2
ChemBioChem	3	2
Nature Chemical Biology	2	3
Angewandte Chemie (*International Edition*)	2	2

[a] For each journal, the number (no.) of prospective SBVS and LBVS studies is reported. Journals are ranked by the total number of VS publications.

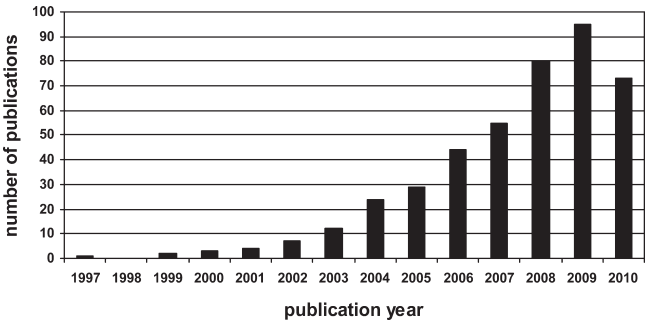

Figure 1. Prospective virtual screening applications. The total number of prospective VS publications that have appeared between 1997 and 2010 (through July 15th) in the 12 surveyed journals is reported.

This ultimately led to the selection of 12 journals as a source for our analysis, listed in Table 1. From these journals, we extracted a total of 2995 "virtual screening" papers that were then inspected for prospective VS applications. A publication only qualified for further analysis if candidate compounds were selected on the basis of VS calculations and experimentally tested in a clearly specified assay. If computational selection and/or experimental testing were unclear, the paper was no longer considered. Our initial survey identified 429 publications that met our criteria and qualified for further analysis (Table 1). This was a relatively large number of source publications, but it was still possible to study all of these papers in detail. Of the VS calculations we analyzed, ~16% originated from the pharmaceutical industry, ~68% originated from academia, and ~16% were collaborations between industry and academia.

We first monitored the history of prospective VS applications. As shown in Figure 1, the first prospective VS study was published in 1997[7] and beginning in 1999, there has been a steady and significant increase in the annual number of such investigations. In 2010, a total of far more than 100 relevant publications are expected to appear. As reported in Table 1, essentially five journals were found to dominate the prospective VS field, *Journal of Medicinal Chemistry* (where relevant publications occur most frequently), followed by *Bioorganic Medicinal Chemistry Letters* and *Bioorganic Medicinal Chemistry* and, with lower frequency of occurrence, *Journal of Chemical Information and Modeling* and *ChemMedChem*. In the remaining seven journals, prospective VS papers appear only occasionally.

Preferred Virtual Screening Methods

We then divided the publications into SBVS and LBVS studies, as also reported in Table 1. Many docking studies utilized ligand-based similarity methods to prescreen a compound database and reduce it in size. These studies clearly fall into the structure-based category because the hits were ultimately identified via docking. In addition, a limited number of studies used X-ray structural data of target proteins (active sites) to derive different types of queries for LBVS; e.g., active ligand conformations for 3D similarity searching were taken from X-ray structures. Accordingly, these investigations were also categorized as structure-based. By contrast, if docking was exclusively used to determine binding modes of hits identified via similarity searching, these studies were naturally classified as ligand-based virtual screens.

We found that prospective SBVS applications were much more frequent than LBVS applications, with a total of 322 compared to only 107 publications. As reported in Table 1, this distribution is determined by publications in the most popular journals. For example, in *Journal of Medicinal Chemistry*, the ratio of SBVS to LBVS applications is 4:1, in *Bioorganic Medicinal Chemistry Letters* it is ~3:1, and in *Bioorganic Medicinal Chemistry* it is ~4:1.

SBVS and LBVS studies were then further classified on the basis of specific scientific approaches, as reported in Figure 2. SBVS categories include docking into X-ray or NMR structures, docking into homology models, and "implicit use" of 3D structural information including, for example, the development of target structure (active site) based pharmacophore models for database searching. With 215 published studies, docking into X-ray structures clearly dominates the SBVS field, but 73 publications also report the successful use of homology models as docking templates. By contrast, NMR structures have thus far only been rarely utilized. LBVS studies are further divided into 2D approaches (e.g., 2D fingerprint similarity searching), 3D approaches (e.g., 3D pharmacophore searching), and combinations of 2D and 3D methods. With 55 reports, LBVS studies utilizing 3D methods are more frequent than 2D methods (37) and 2D/3D combinations (15).

Target Distribution

Next we analyzed which proteins were targeted by VS and which protein families were targeted by either SBVS or LBVS. For this purpose, we followed the target classification scheme of the ChEMBL[15] database of bioactive compounds. As shown in Figure 3, enzymes present by far the largest target class (273 studies), followed by membrane receptors (59). This distribution can be rationalized by taking into account the overall dominance of SBVS approaches where active sites of enzymes represent the prime targets. An abundance of structural data on enzymes is available, in contrast, to membrane receptors where structural data is still sparse. However, as shown in Table 2, a number of studies also report docking into molecular models of G-protein-coupled receptors (GPCRs), which have traditionally been mostly investigated by LBVS methods. Among enzymes, protein kinases are most frequently targeted, followed by proteases (Figure 3). For kinases and proteases, many highly resolved structures of enzyme−inhibitor complexes are available in addition to SAR data, which provides a knowledge base that substantially supports SBVS approaches because predicted ligand poses can be related to experimentally observed ones and key interactions can be

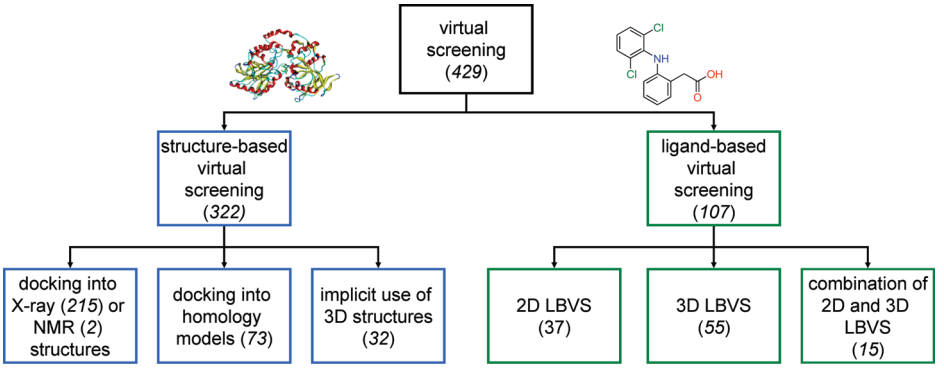

Figure 2. Classification of virtual screening applications. Reported VS applications were classified according to the computational methods that were utilized. The total number of VS applications falling into each category is reported in parentheses.

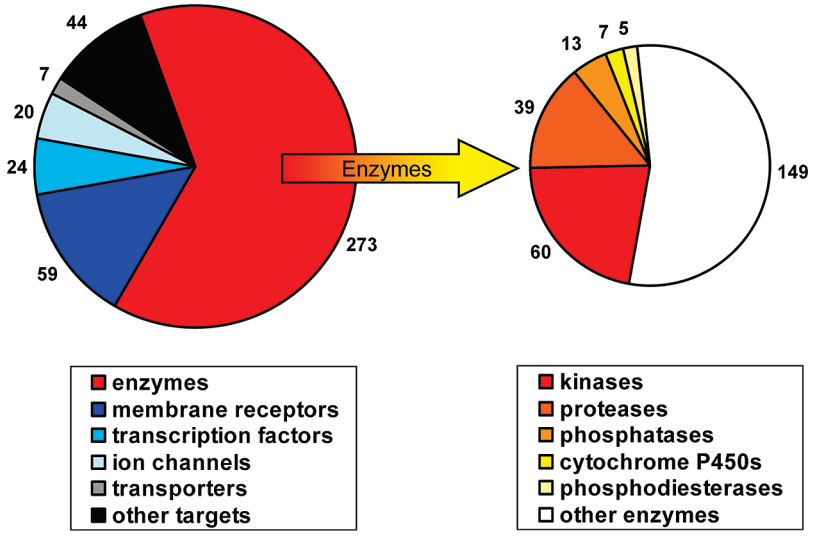

Figure 3. Protein families targeted by virtual screening. Target families are categorized following the ChEMBL classification scheme (left pie chart), and enzymes are further divided into families (right).

analyzed. However, despite the strong focus on kinases and proteases, more than half of the targeted enzymes do not belong to the five major families, illustrating that there is considerable diversity among enzymes selected for VS investigations.

Potency Distribution of Hits

In general, hits with low nanomolar potency are only rarely identified by VS[12] that, similar to biological screening, predominantly provides hits for further chemical exploration (but not optimized leads). We have studied the potency distribution of VS hits by dividing the spectrum of reported potencies into four value ranges, i.e., <1, $1-10$, $10-100$, and >100 μM. For potency analysis, only hits with defined potency end points (IC_{50}, EC_{50}, K_i, or K_d) were considered and from each publication, the most potent hit was selected. Hits for which measures such as "percent relative inhibition" were reported were not taken into account. On the basis of these criteria, 286 SBVS and 93 LBVS publications qualified for potency analysis. When we monitored the potency of reported hits over time for LBVS and SBVS methods, no obvious trends were observed. Figure 4 shows a global comparison of SBVS and LBVS methods. Only 11 publications reported hits with >100 μM potency, which would be considered borderline active, but a total of 85 studies reported weakly active compounds falling into the $10-100$ μM range.

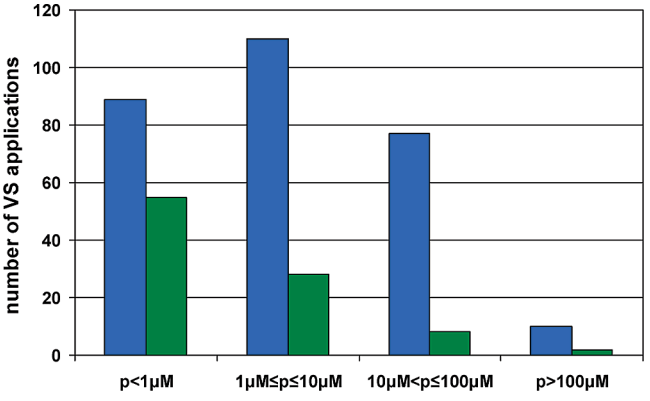

Figure 4. Potency distribution of virtual screening hits. Reported VS hits discovered by SBVS (blue) or LBVS (green) approaches were assigned to four potency (p) ranges.

Interestingly, although many more successful SBVS than LBVS applications are reported to date, the potency of hits identified by LBVS is on average considerably higher than for SBVS. Most of the LBVS hits fall into the <1 μM potency range, whereas the majority of SBVS hits populate the $1-10$ and $10-100$ μM ranges. Table 3 reports the hit distribution for different LBVS and SBVS methods (according to Figure 2). Here, these trends are also evident. Moreover,

Table 2. Virtual Screening Targets[a]

	enzyme	membrane receptor	transcription factor	ion channel	transporter	other targets
SBVS	238	24	20	9	1	27
LBVS	35	35	4	11	6	17

[a] The number of successful SBVS and LBVS applications directed against different target classes is reported. Targets were classified according to the ChEMBL scheme.

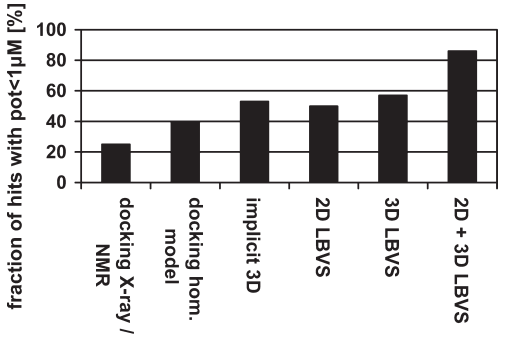

Figure 5. Distribution of potent hits for different virtual screening methods. The fraction of hits with potency of $< 1\ \mu$M among all hits is reported for different VS approaches.

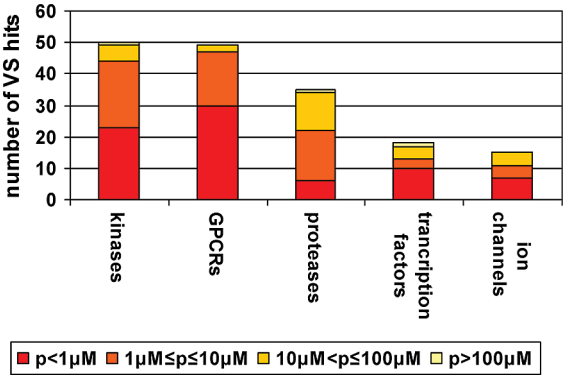

Figure 6. Potency distribution of hits for major target families. The number and potency (p) ranges of VS hits are reported for the five major target families according to Figure 5.

perhaps also surprisingly, the distribution of hits identified by ligand docking into homology models is shifted toward higher potency values than the distribution of hits identified by docking into experimental structures. In addition, the distributions of hits identified by 2D and 3D LBVS methods are similar, but combinations of 2D and 3D approaches predominantly identify hits with $< 1\ \mu$M potency. These combinations typically apply machine learning methods in combination with 2D and 3D molecular descriptors (i.e., molecular representations derived from 2D molecular graphs and 3D conformations) and also sequential combinations of 2D ligand similarity and 3D pharmacophore searching. Figure 5 reports the fraction of hits with $< 1\ \mu$M potency identified with different approaches, which reveals that docking methods yield the lowest fraction of potent hits, although they represent by far the largest number of prospective VS applications.

We also calculated average hit potency values for all VS studies from the pharmaceutical industry, academia, and collaborations between industry and academia. The average potency of a hit from an industrial and academic laboratory was ~4 and ~19 μM, respectively. The average potency of a hit resulting from collaboration was ~16 μM. The significant difference in average hit potency between industry and academia might have several reasons. For example, industrial laboratories are primarily focused on drug discovery, whereas academic institutions are usually much more focused on method development and application. Also, it can be expected that researchers in the pharmaceutical industry often have more target and compound information available than investigators in academia. Another possible reason might be that internal compound collections of the pharmaceutical industry grow over time with a particular focus on therapeutic areas of interest and usually contain more advanced compounds than publicly available screening collections.

The potency distribution of hits for the major target families was also studied. The results are shown in Figure 6. Among the three most frequent target families (kinases, GPCRs, and proteases), the largest fraction of potent hits ($< 1\ \mu$M) is obtained for GPCRs (~61%) that are mostly targeted by LBVS approaches, followed by kinases (~46%). Interestingly, for proteases, a comparably small fraction of potent hits is reported (only ~17%). For the less frequent transcription factor and ion channel targets, approximately half of the hits fall into the $< 1\ \mu$M potency range.

Finally, we analyzed the potency distribution of hits reported in different journals (Table 4). Among the three journals with most reported validated hits, *Journal of Medicinal Chemistry* contains the largest fraction of hits with potency falling into the $< 1\ \mu$M and $1-10\ \mu$M ranges (~82%), followed by *Bioorganic Medicinal Chemistry Letters* (~76%). Only ~59% of the hits reported in *Bioorganic Medicinal Chemistry* fall into the < 1 and $1-10\ \mu$M ranges (Table 1). In *ChemMedChem* and *Journal of Chemical Information and Modeling* where considerably fewer practical VS applications have thus far been reported, the corresponding hit fractions are ~64% and ~75%, respectively. Thus, there are some notable differences in the potency of VS hits that are reported in different journals.

Summary

Our analysis has revealed that the majority of prospective VS studies have thus far been reported in only a small number of journals. In addition, we have found that docking investigations clearly dominate the prospective VS field at present. We see an increasing number of successful VS studies that are based on docking into homology models, and the potency of such identified hits is on average higher than for hits identified by docking into X-ray structures, although model-based docking calculations are more approximate in nature. In this context, it is interesting to note that NMR structures have thus far only rarely been used in practical VS applications. Currently there are three times more SBVS than LBVS applications available, but LBVS methods identify hits that are on average more potent. In particular, nearly all of the still limited number of LBVS investigations that combine 2D and 3D components yield potent hits. Furthermore, kinases, GPCRs, and proteases are the most popular VS targets. For kinases and GPCRs, potent submicromolar VS hits are

Table 3. Potencies of Hits Identified Using Different Virtual Screening Approaches[a]

VS approach	$< 1\ \mu M$	$1\ \mu M \leq$ pot $\leq 10\ \mu M$	$10\ \mu M <$ pot $\leq 100\ \mu M$	$> 100\ \mu M$
		SBVS		
docking into X-ray/NMR structures	48	77	57	9
docking into homology models	25	22	15	1
implicit use of 3D structures	16	9	5	0
		LBVS		
2D LBVS	16	11	4	1
3D LBVS	27	15	4	1
combination of 2D and 3D LBVS	12	2	0	0

[a] The number of published VS hits per potency (pot) range is reported for different SBVS and LBVS approaches. Only VS hits with defined potency end points were considered, and the most potent hit per publication was selected.

Table 4. Potencies of Virtual Screening Hits Reported in Different Journals[a]

journal	$< 1\ \mu M$	$1\ \mu M \leq$ pot $\leq 10\ \mu M$	$10\ \mu M <$ pot $\leq 100\ \mu M$	$> 100\ \mu M$
Journal of Medicinal Chemistry	60	55	24	2
Bioorganic Medicinal Chemistry Letters	38	33	19	3
Bioorganic Medicinal Chemistry	14	15	16	4
ChemMedChem	11	7	9	2
Journal of Chemical Information and Modeling	10	11	7	0
European Journal of Medicinal Chemistry	5	4	2	0
Chemical Biology & Drug Design	2	1	2	0
Journal of Computer-Aided Molecular Design	1	4	1	1
ACS Chemical Biology	1	2	2	0
ChemBioChem	1	0	3	0
Nature Chemical Biology	3	1	0	0
Angewandte Chemie (*International Edition*)	2	2	0	0

[a] The number of published VS hits per potency (pot) range is reported. Journals are ranked by the total number of VS hits with defined potency end points (the most potent hit per publication is considered).

frequently obtained, in contrast to proteases, where the majority of reported hits are only weakly potent. However, protein kinases and proteases only represent ~36% of all enzymes targeted by VS, and more than 50% of these enzymes do not belong to the five major families. Taken together, the results of our analysis have provided us with a rather detailed view of the prospective VS landscape and there have certainly been a few surprises.

Virtual Screening Perspective

The steadily growing number of successful VS applications that are reported mirrors general progress made in this field. Whether this apparent progress is mostly due to methodological advances and a deeper understanding of potential problems with VS, technical, and computational infrastructure progress or merely due to wider availability of VS technology is a different question. Regardless, there is a clear trend that successful applications are increasingly published.

During our survey, we have observed additional trends that are more difficult to highlight on the basis of simple statistics. For example, most of the VS studies we analyzed involved more or less subjective compound selection steps. Without doubt, assigning priorities to compounds on the basis of intuition, experience, or knowledge plays an important role in VS. This is good news from the point of view that investigators who successfully apply VS methods do not ultimately rely on approximate and in part questionable scoring and compound ranking schemes but is bad news from the point of view that our computational methods are still limited in their ability to reliably predict biological activity from chemical structure. However, the role of expert knowledge in VS is not only crucially important at the level of compound selection but already much earlier. Simply put, required expertise scales with increasing complexity of VS approaches.

Methodological Complexity and Expert Knowledge. The complexity of VS methods generally increases from 2D to 3D approaches. By use of a state-of-the-art molecular modeling package, a 2D fingerprint search is as straightforward to carry out as a docking calculation, even for a nonexpert user, although the complexity of docking is much higher than of fingerprint searching and involves many more critical parameters. How to prepare a docking template, define the binding site, and prioritize intermolecular interactions is at least as challenging as the interpretation of the actual screening results on the basis of ligand posing and approximate scoring (and goes much beyond the magic of "default" parameter settings). Essentially at each stage of the process, expert knowledge and experience are highly beneficial.

Taking this into account, what about the rather puzzling observation, at least at first glance, that docking into homology models produces on average hits with higher potency than docking into X-ray structures? In our survey, we have certainly seen a number of docking studies producing highly potent hits but many others where hits were only weakly active. Preparing a homology model for LBVS adds yet another layer of complexity to the process, and even more expertise is required to utilize the model in a careful and appropriate manner. So we should assume that investigators who are able to successfully dock into homology models (again, only successful applications are published) must know quite well what they are doing at each level of the process. This might perhaps explain why more potent hits are often identified in such cases than in "average" X-ray structure-based docking exercises (the emphasis being "average" because a meaningful use of X-ray data for SBVS is far from being simple).

Weakly Active Compounds. Many prospective VS studies identify only weakly active compounds, at least by medicinal chemistry standards. However, a weak hit is not just like another. We have found that several studies published in leading journals report weakly or borderline active VS hits against novel targets, for which only little ligand information is available. By contrast, there are other cases where reporting weakly active compounds might indeed be questionable. Protein kinase inhibitors are a good example. State-of-the-art kinase inhibitors are active in the low nanomolar range, and the kinase field is already (one would be tempted to say) "littered" with weakly potent compounds. How difficult is it really to find yet another one? Are elaborate virtual screens required to identify weak hits if so much is already known? Probably not. It is therefore not surprising that computational and medicinal chemists might often have different views about the value of computational hit identification, at least in cases such as kinases. However, if a "first-in-class" hit is identified against a novel target, even if only weakly potent, the situation is different.

Method Validation. This also points at the problematic issue of how to prospectively "validate" VS methods and protocols. It should be easy to understand that a complex multicomponent VS effort is not rigorously validated if it ultimately yields, for example, one or a few weakly active kinase inhibitors. However, problematic issues associated with VS method validation go much deeper. For example, we have observed that many studies that employ fully flexible ligand docking utilize 2D filters and other LBVS methods to, in some instances, dramatically reduce the number of candidate compounds. In such cases, it often remains unclear what the (enrichment) contribution of the docking step has been and to what extent the final results were dependent on the ligand-based preselection. This is especially the case because compounds are usually hand-selected to provide a final candidate list, as mentioned above. The "sequential" nature of such applications is also related to another question that is often raised: What is better, and what is worse? For example, there continues to be much debate in the VS field whether 2D or 3D approaches would generally be superior, and different investigations promote different views, depending on methodological preferences. However, on the basis of currently available literature data, this question simply cannot be answered. In our analysis, we have been able to highlight statistical trends concerning the distributions of successful LBVS and SBVS applications or potency values of hits. However, these statistical trends do not provide ultimate answers. There are currently no studies available that report "parallel" prospective applications of different ligand- and/or structure-based methods with consistent experimental hit evaluation. Such studies might be suitable for a more rigorous comparison of prospective method performance. It is one of the future challenges for the VS field to establish a framework for such comparisons.

Needles in Haystacks? The capacity of VS calculations to enrich active compounds can also be discussed in the context of another obvious trend. Essentially all of the studies we surveyed focus on small or very small compound selection sets, often tens to on the order of a hundred candidates. Given the accuracy limitations of current computational screening methods, this type of search for "needles in haystacks" does not necessarily play into the strength of VS methods (of course, making successful applications even more interesting). Rather, for a fair assessment of VS potential, it should also be important for the field to increasingly focus on the enrichment ability of VS methods. For example, selecting by VS ~1% of a sizable compound database for a limited biological screening campaign might often lead to significant increase in hit rates compared to random screening.[16,17] The integration of computational and experimental screening is still an underdeveloped application area of prospective screening, albeit with probably significant potential, provided a number of technical (e.g., compound handling) and cultural hurdles (e.g., rational selection versus high-throughput mentality) can be overcome.

Assay Conundrum. We have also observed that the biological activity of VS hits is often evaluated in very different assay formats (even for related targets) that do not necessarily prove specific binding or inhibition. Considering the fact that many only weakly active VS hits are reported, it is conceivable that there might be a significant number of false positives involved. Clearly, as much as VS method development would benefit from the availability of well-defined and generally applicable benchmark community standards, prospective VS applications would very much benefit from establishing general minimal requirements for hit validation including, for example, proof of specific inhibition and dose-response behavior. Here, Chief Editors of the leading publication venues for prospective VS studies are called upon to synchronize their efforts and establish consistent hit validation criteria. Currently, only a few journals have considered these issues and formulated appropriate guidelines.

Compound Novelty. In addition to in part inconsistent experimental evaluations that are reported, claims are made in many publications concerning the structural novelty of newly identified hits (in accord with the popular scaffold hopping paradigm). However, SciFinder[18] or similar search calculations reveal that this is not always the case. We are aware of a number of instances where previously known active compounds have essentially been "rediscovered" by computational means. Why do the authors not know? This is a critical issue for the credibility of VS efforts. Hence, we would propose that retrospective substructure and/or similarity search results of the scientific and patent literature should be required as an additional hit validation criterion such that the most similar known active compounds can be directly compared with new VS hits. This would be expected to further strengthen the scientific rigor of prospective VS applications and help to balance claims if appropriate, another potentially important step for the future development of the VS field. Again, it would be best if leading journals would take the lead and implement additional requirements for VS applications in their guidelines.

Outlook. In conclusion, we have presented a thorough analysis of currently available prospective VS applications on the basis of literature data to better understand the state-of-the-art in this field. On the basis of our findings, we have highlighted a number of trends, put them into perspective, and pointed out a few critical issues. However, the global outlook is fairly positive. Within the past ~15 years, the VS field as we see it today has become established in pharmaceutical settings. As in any scientific field, there are unsolved problems here, concerning both the development and retrospective evaluation of VS methods and their prospective applications. But these problems can be readily addressed, as discussed for exemplary cases herein, and it is hoped that further progress will be made in these and other areas as the VS field continues to grow.

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Biographies

Peter Ripphausen studied Pharmaceutics at the University of Düsseldorf, Germany. Since 2008, he is a Ph.D. student in the Department of Life Science Informatics headed by Prof. Jürgen Bajorath. At present, his work focuses on applied virtual screening. His Ph.D. work is supported by a post graduate program of the *Deutsche Forschungsgemeinschaft* (Graduiertenkolleg 804).

Britta Nisius received a Bachelor's degree and a Master's degree in Computational Life Science from the University of Lübeck, Germany. In 2008, she joined the Department of Life Science Informatics at the University of Bonn, Germany, headed by Prof. Jürgen Bajorath for her Ph.D. studies. Currently, she works on method development for ligand-based virtual screening. Her Ph.D. work is supported by the Computational Chemistry Department of Bayer HealthCare, Wuppertal, Germany.

Lisa Peltason received her degree in Bioinformatics from Tübingen University (Germany) in 2006. Subsequently, she joined the Department of Life Science Informatics at Bonn University (Germany) headed by Prof. Jürgen Bajorath, where she worked on the development of numerical and graphical methods for the systematic computational analysis of structure−activity relationships. Her Ph.D. work also involved a collaboration with the Lead Discovery Department of Boehringer Ingelheim Pharma, Biberach (Germany). Lisa obtained her Ph.D. in Computational Life Sciences in 2010.

Jürgen Bajorath is Professor and Chair of Life Science Informatics at the University of Bonn, Germany. He is also an Affiliate Professor in the Department of Biological Structure at the University of Washington, Seattle, WA. His research interests include early phase drug discovery and the development of computational methods for molecular similarity analysis and the systematic exploration of structure−activity relationships. For more details, see https://www.lifescienceinformatics.uni-bonn.de.

References

(1) Geppert, H.; Vogt, M.; Bajorath, J. Current trends in ligand-based virtual screening: molecular representations, data mining methods, new application areas, and performance evaluation. *J. Chem. Inf. Model.* **2010**, *50*, 205–216.
(2) Adamson, G. W.; Bush, J. A. A method for the automatic classification of chemical structures. *Inf. Storage Retr.* **1973**, *9*, 561–568.
(3) Gund, P. Three-dimensional pharmacophoric pattern searching. *Prog. Mol. Subcell. Biol.* **1977**, *5*, 117–143.
(4) Willett, P. Searching techniques for databases of two- and three-dimensional structures. *J. Med. Chem.* **2005**, *48*, 1–17.
(5) Kuntz, I. D.; Blaney, J. M.; Oatley, S. J.; Langridge, R.; Ferrin, T. E. A geometric approach to macromolecule−ligand interactions. *J. Mol. Biol.* **1982**, *161*, 269–288.
(6) Brooijmans, N.; Kuntz, I. D. Molecular recognition and docking algorithms. *Annu. Rev. Biophys. Biomol. Struct.* **2003**, *32*, 335–373.
(7) Horvath, D. A virtual screening approach applied to the search for trypanothione reductase inhibitors. *J. Med. Chem.* **1997**, *40*, 2412–2423.
(8) Jain, A.; Nicholls, A. Recommendations for evaluation of computational methods. *J. Comput.-Aided Mol. Des.* **2008**, *22*, 133–139.
(9) Nicholls, A. What do we know and when do we know it? *J. Comput.-Aided Mol. Des.* **2008**, *22*, 239–255.
(10) Schneider, G.; Neidhart, W.; Giller, T.; Schmid, G. "Scaffold hopping" by topological pharmacophore search: a contribution to virtual screening. *Angew. Chem., Int. Ed.* **1999**, *38*, 2894–2896.
(11) Renner, S.; Schneider, G. Scaffold-hopping potential of ligand-based similarity concepts. *ChemMedChem* **2006**, *1*, 181–185.
(12) Eckert, H.; Bajorath, J. Molecular similarity analysis in virtual screening: foundations, limitations and novel approaches. *Drug Discovery Today* **2007**, *12*, 225–233.
(13) Stumpfe, D.; Bajorath, J. Applied Virtual Screening: Strategies, Recommendations, and Caveats. In *Methods and Principles in Medicinal Chemistry. Virtual Screening. Principles, Challenges, and Practical Guidelines*; Sotriffer, C., Ed.; Wiley-VCH: Weinheim, Germany, in press.
(14) Bajorath, J. Computational studies, virtual screening, and theoretical molecular models. *J. Med. Chem.* **2010**, *53*, 1–2.
(15) ChEMBL target classification. http://www.ebi.ac.uk/chembldb/index.php/target/family.
(16) Engels, M. F.; Venkatarangan, P. Smart screening: approaches to efficient HTS. *Curr. Opin. Drug Discovery Dev.* **2001**, *4*, 275–283.
(17) Parker, C. N.; Shamu, C. E.; Kraybill, B.; Austin, C. P.; Bajorath, J. Measure, mine, model, and manipulate: the future for HTS and chemoinformatics? *Drug Discovery Today* **2006**, *11*, 863–865.
(18) *SciFinder*; Chemical Abstracts Service, Inc.: Columbus, OH; https://scifinder.cas.org.