StructRank: A New Approach for Ligand-Based Virtual Screening

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Abstract

Screening large libraries of chemical compounds against a biological target, typically a receptor or an enzyme, is a crucial step in the process of drug discovery. Virtual screening (VS) can be seen as a ranking problem which prefers as many actives as possible at the top of the ranking. As a standard current Quantitative Structure Activity Relation (QSAR) models apply regression methods to predict the level of activity for each molecule, and then sort them to establish the ranking. In this paper we propose a top-*k* ranking algorithm (StructRank) based on Support Vector Machines to solve the early recognition problem *directly*. Empirically, we show that our ranking approach not only outperforms regression methods but another ranking approach recently proposed for QSAR ranking, RankSVM, in terms of actives found.

Introduction

High-Throughput Screening, the physical screening of large libraries of chemicals, is the dominant technique for the identification of lead compounds in drug discovery.[1] In recent years computa-

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tional methods, known as Virtual Screening (VS),[2] have gained much attention as an alternative and complementary approach since they can be performed comparatively cheap and fast;[3] the usefulness of *in silico* screenings has been demonstrated in several studies.[4,5]

Virtual Screening can be divided into structured-based and ligand-based[6] approaches. Given the drug targets 3D-structure and 3D-structures of ligands, structure-based VS predicts and scores confirmation and orientation of the ligands within the active site of the receptor.[7] Ligand-based VS on the other hand uses knowledge about a set of ligands that are known to be active for the given drug target. This information is used to identify structurally similar molecules in a database.[7] Different approaches are available depending on the number of known actives, however, all approaches share the common assumption that, with respect to the descriptors, structurally similar molecules are likely to have similar properties.[8] In other words, neighboring molecules are likely to exhibit the same levels of activity.

Given a sufficient number of known actives one can build a Quantitative Structure Activity Relation (QSAR) model. QSAR models correlate numerical molecular descriptors[9] as physiochemical and topological properties with a biological property such as binding affinity. For each molecule, the former is usually assembled in a *vector of features:* $\mathbf{x} \in \mathbb{R}^d$ while the latter is summarized as label $y \in \mathbb{R}$. Describing molecules and their properties by pairs $(\mathbf{x}, y)$ paves the way for machine learned QSAR models. Prominent techniques include *Multiple Linear Regression* (MLR)[10] and *Partial Least Squares* (PLS)[11] and more recently Support Vector Machines for Regression (SVRs), Random Forests, Neural Networks and Gaussian Processes.[12–15] Various reviews[16–18] offer a detailed overview over these approaches and their application to ligand-based Virtual Screening.

The task in VS, also known as "early recognition problem",[19,20] can be characterized as follows: Given a library of molecules, the task is to output a ranking of these molecules in terms of their binding coefficient for the investigated drug target, such that the top-k molecules can be selected for further investigations. All of the above mentioned methods solve this task by performing a regression analysis: They learn a function $f : x \mapsto y,\ f :\ \mathbb{R}^d \to \mathbb{R}$ that predicts a label for

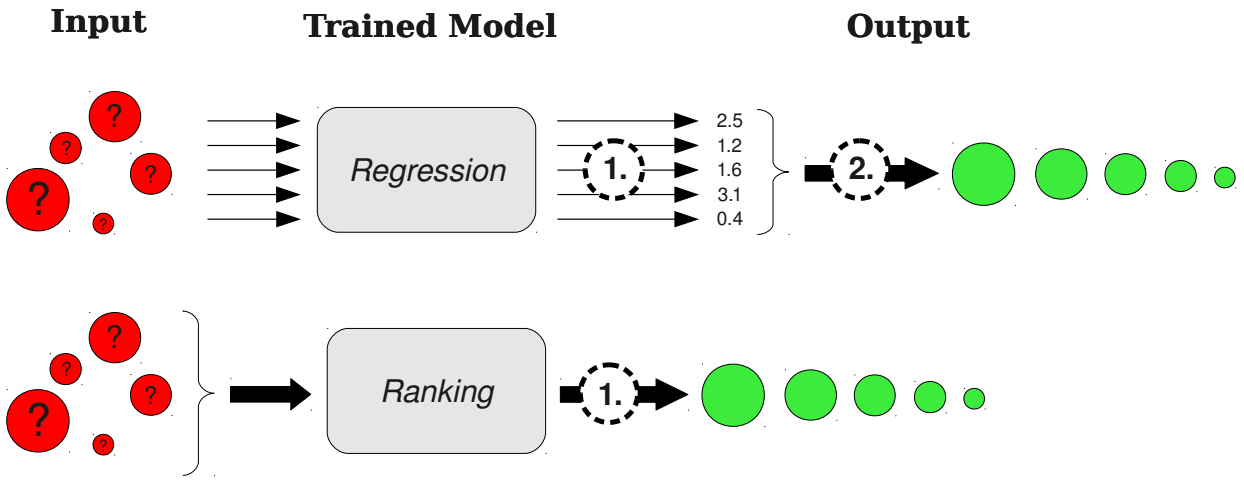


Figure 1: Two different ways to solve the ranking task of Virtual Screening: a) State-of-the-art approaches use a 2-step approach. In the first step a regression model is used to predict binding coefficients for all molecules in the library. In a second step the molecules are sorted according to their predictions. b) Our ranking approach directly predicts the ranking within a single step.

any molecule given its features. To establish the subset of candidate molecules, predictions are made for all molecules in the database. In a second step an ordered list is generated based on this predictions. This two step approach is shown in Figure Figure 1 (top). Finally the top n ranked compounds are selected to be investigated in more detail.

However, Virtual Screening approaches primarily aim to find molecules exhibiting high binding affinities with the target while the predictive accuracy with respect to the labels y is only of secondary interest. Although a perfect regression model would also imply a perfect ranking of the molecules of interest, the impact of suboptimal regressors on the ranking is not easily captured as equal models in terms of their mean squared error could give rise to completely different rankings. Thus, the question rises whether the detour via regression is necessary and whether the task can be addressed in a more natural way. In this article, we propose a top-k ranking algorithm, **StructRank**, that *directly solves the ranking problem* and that *focuses on the most promising molecules* (cf. Figure 1, bottom).

The driving force for the research of new ranking approaches so far has been the Information Retrieval community.[21,22] Aiming to improve the results of search engines, documents need to be ranked within the first hits, according to their relevance for a given search query. In the

Virtual Screening Community the use of ranking approaches has been rare. An approach that directly minimizes a ranking loss was applied recently by Wasserman et al.[23] and Agarwal et al.[24] RankSVM[25,26] maximizes the number of correctly ordered pairs of molecules for all ranks. Wassermann et al. report superior performance for RankSVM on classification datasets; Agarwal et al. state that RankSVM performs similar as baselines tested for QSAR as well as classification datasets.

Whereas RankSVM attempts to optimize the complete ranking, StructRank focuses on the topmost ranks by optimizing the rank loss NDCG.[27] As previously stated by Agarwal et al.[24] approaches that lay special focus to this aspect should be able to outperform RankSVM. Our experiments can confirm this assumption: StructRank outperforms RankSVM as well as Support Vector Regression in terms of actives ranked within the top-k. We report results for NDCG as well as two established Virtual Screening performance measures: Enrichment Factor (EF)[28] and Robust Initial Enhancement (RIE).[29]

The remainder of the article is structured as follows: The next section describes our top-k ranking approach, StructRank, and then briefly reviews the baseline methods RankSVM and SVR. We then introduce the Virtual Screening datasets in Section 3 and the toy example that where used for performance evaluation. We report on empirical results in Section 4 and conclude with a discussion in Section 5.

Methods

The formal problem setting of ranking for Virtual Screening is as follows: Given a set $\mathscr{T}$ consisting of n molecules $(\mathbf{x}_i, y_i)_{i=1}^n$, where $\mathbf{x}_i \in \mathbb{R}^d$ denotes the feature vector of the i-th molecule containing the molecular descriptors, and $y_i \in \mathbb{R}$ is a scalar representing the biological/chemical property of that molecule, e.g. binding affinity. We aim at learning a function $f(x)$ which learns to rank the molecules according to their targets y_i. That is, if $y_i > y_j$ for molecule i and j, we want that $f(\mathbf{x}_i) > f(\mathbf{x}_j)$. Moreover, as the purpose of virtual screening methods is to rank actives *early* in an

ordered list (recall the "early recognition problem"[19,20]), we want the learning machine to focus on the top-k molecules in the ranking.

Our top-k ranking SVM for QSAR utilizes work by Chapelle et al.[30] They build on Structured Support Vector Machines (Structured SVMs),[31] a very flexible learning machine that has been applied to many different learning tasks in Information Retrieval,[30,32] natural language parsing,[33] protein sequence alignment.[34]

In the following paragraphs we describe Structured Support Vector Machines and adjust them to the task of ranking molecules. Additionally we propose a new method to evaluate QSAR rankings: Normalized Discounted Cumulitive Gain (NDCG).

Evaluating Rankings

To assess the quality of rankings for QSAR, we propose to use a popular ranking measure that originates from the Information Retrieval community: Normalized Discounted Cumulative Gain (NDCG, see appendix for precise definition). Originally, NDCG[27] was introduced to evaluate the results of web searches. It measures how similar a predicted ranking is compared to the true ranking. NDCG has several important properties:

- NDCG_k only evaluates the first k positions a predicted rankings, thus an error on positions below rank k is not punished.
- Furthermore the first k positions are weighted, which means that errors have different influence on the final score depending on which position of the ranking they occur. Naturally position one is the most important, with lower positions discounted by the log of their rank r: $\log_2(1+r)$.
- Finally, **NDCG!** is normalized, thus if the predicted ranking equals the true ranking the score is 1. Thus, to tranlate it into loss function we could simply use $\Delta(\mathbf{y},\hat{\mathbf{y}}) = 1 - NDCG(\mathbf{y},\hat{\mathbf{y}})$.

In summary, NDCG aims at pushing the molecules with the biggest binding affinity on top of the ranking.

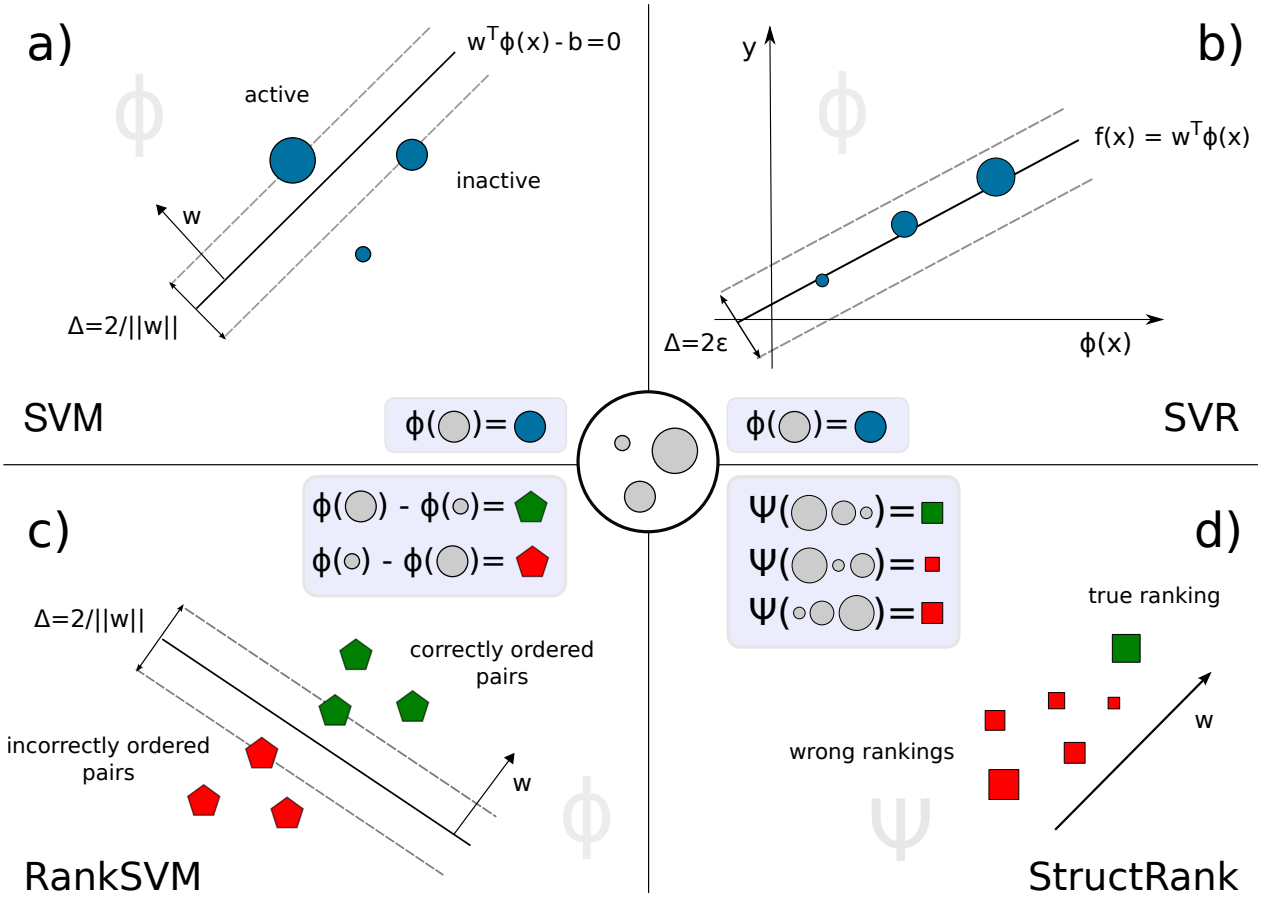


Figure 2: Comparison of different Support Vector Machines: **a)** Support Vector Machines for classification learn a linear hyperplane $\mathbf{w}^T \phi(\mathbf{x}) = b$ with maximum margin Δ that optimally separates active from inactive molecules. **b)** Support Vector Regression learns a function $\mathbf{w}^T \phi(x)$ that predict binding affinities for each molecule as correct as possible. **c)** Ranking SVM generates difference vectors of all possible pairs of molecules. Afterwards similar to a) a linear hyperplane is learned that separates correctly and incorrectly ordered pairs. **d)** Ψ takes a set of molecules $\tilde{\mathbf{x}}$ and a ranking $\mathbf{y}$ of this set and maps it onto a point in the joint feature space. StructRank learns a function $\mathbf{w}^T \Psi(\tilde{\mathbf{x}}, \mathbf{y})$ which assigns the highest score to the point representing the true ranking.

Structured Support Vector Machines for QSAR

We will now briefly describe the framework of Structured SVMs and focus on only the basic concept. For a more detailed coverage we refer to the paper of Tsochantaridis et al.[31]

Our ultimate target is to learn a function $f : \mathscr{X} \to \mathscr{Y}$: Given a set of molecules $\tilde{\mathbf{x}} = (\mathbf{x}_1, \ldots, \mathbf{x}_n) \in \mathscr{X}$, f returns a ranking $\mathbf{y} \in \mathscr{Y}$ of this set. In order to establish f, Structured SVMs learn a discriminant function $F : \mathscr{X} \times \mathscr{Y} \to \mathbb{R}$. F can be thought of as a *compatibility* function, that measures how well a certain ranking $\mathbf{y}$ fits the given set of molecules $\tilde{\mathbf{x}}$. The final prediction is given by the ranking $\mathbf{y}$ that achieves the maximal score $F(\tilde{\mathbf{x}}, \mathbf{y})$. Thus we have

$$f(\tilde{\mathbf{x}}) \quad = \quad \underset{\mathbf{y} \in \mathscr{Y}}{\operatorname{argmax}} F(\tilde{\mathbf{x}}, \mathbf{y}).$$

F is defined over a combined space of sets of molecules and corresponding rankings, a so called "joint feature space". To be able to learn F directly in that combined space, we define a function Ψ that maps each pair of a set of molecules $\tilde{\mathbf{x}}$ together with a ranking $\mathbf{y}$ (of $\tilde{\mathbf{x}}$) onto one corresponding data point in the joint feature space. Details on the joint feature map used in our approach may be found in the appendix. Given the joint feature map Ψ, F is defined as a linear function in the joint feature space:

$$F(\tilde{\mathbf{x}}, \mathbf{y}) \quad = \quad \mathbf{w}^T \Psi(\tilde{\mathbf{x}}, \mathbf{y}),$$

this way F is the scalar product of the corresponding joint feature map of $\tilde{\mathbf{x}}$ given a particular ranking $\mathbf{y}$ and the learned parameter vector $\mathbf{w}$.

Modeling F can be cast as follows: Given a set of molecules $\tilde{\mathbf{x}}$ we want the true ranking $\bar{\mathbf{y}}$ to score highest among all possible rankings $\mathbf{y} \in \mathscr{Y}$ transforming into constraints

$$\mathbf{w}^T (\Psi(\tilde{\mathbf{x}}, \bar{\mathbf{y}}) - \Psi(\tilde{\mathbf{x}}, \mathbf{y})) \geq 0 \quad \forall \mathbf{y} \in \mathscr{Y} \setminus \bar{\mathbf{y}}.$$

Alike classic Support Vector Machines for Classification[35] this can be turned into a maximum-

margin problem, where we want the difference between the true ranking $\bar{\mathbf{y}}$ and the closest runner-up $\text{argmax}_{\mathbf{y}\neq\bar{\mathbf{y}}}\, \mathbf{w}^T\Psi(\tilde{\mathbf{x}},\mathbf{y})$ to be maximal (see eq. eq:primal$_{s}truct_{s}impleintheappendix$).$Alsowewantdifferenty'sgetsc$
$Apredictedrankingwithonlytworanksinterchangedcomparedtothetrueranking is much better than a predicted ranki$
$dependentmargin(margin\ scaling^{31,36})$: $\mathbf{w}^T(\Psi(\tilde{\mathbf{x}},\bar{\mathbf{y}})-\Psi(\tilde{\mathbf{x}},\mathbf{y}))\geq\Delta(\mathbf{y},\bar{\mathbf{y}}) \quad \forall\mathbf{y}\in\mathscr{Y}\setminus\bar{\mathbf{y}}$(1)where 1-NDCG$_k$ is used for $\Delta(\mathbf{y},\bar{\mathbf{y}})$. Furthermore a *slack variable* ξ is introduced that reflects the maximal error made for the set of constraints in (eq:margin$_{r}escaling$).$Finally,toimproveperformance,weemployaboo$
$werandomlydrawmdifferentsubsets^{j}$ of molecules from the training set. Applying the methodology described so far to each subset j we obtain the final optimization problem

$$\begin{aligned} \min_{w,\xi} \quad & \frac{1}{2}\mathbf{w}^T\mathbf{w}+C\sum_{j=1}^{m}\xi^j \\ \text{subject to} \quad & \mathbf{w}^T(\Psi(\tilde{\mathbf{x}}^j,\bar{\mathbf{y}}^j)-\Psi(\tilde{\mathbf{x}}^j,\mathbf{y}))\geq\Delta(\bar{\mathbf{y}}^j,\mathbf{y})-\xi^j \quad \forall j,\forall\mathbf{y}\neq\bar{\mathbf{y}}^j \\ & \xi^j\geq 0 \end{aligned} \tag{2}$$

Note that there is a very high formal similarity to the original SVM formalization (see eq. eq:SVM in the appendix) with the differences: (a) margin rescaling, (b) joint feature map and (c) very large quantity of constraints. A visualization of the function learned is given in Figure 2d). The corresponding dual form of (eq:primal$_{s}truct$)$isgiveninthe appendix(eq.eq:dual_{s}truct)$.

For an set $\tilde{\mathbf{x}}$ with n molecules, there exist $n!$ possible ways of ranking these molecules. Imposing a constraint for each possible ranking would lead to problems becoming too big of being solved. Therefore, Tsochantaridis et al.[31] proposed a cutting plane approach that iteratively adds new constraints which violate the current solution. They show that there exists a polynomially sized subset of constraints whose solution fulfills all constraints of the full optimization problem. Astonishingly, the optimization problem can be solved efficiently, an example is the cutting-plane approach (algorithm alg:struct$_{s}vmintheappendix$).

Baselines

We compare the novel ranking approach to two algorithms both belonging to the family of Support Vector Machines: Support Vector Regression (SVR), a state-of-the-art regression method, often used for Virtual Screening and Ranking SVM (RankSVM), another ranking approach.

Support Vector Regression (SVR)

Support Vector Regression[37] is an adaption of classic Support Vector Classifiers for regression. Like their classification counterpart they follow the Structural Risk Minimization principle introduced by Vapnik,[35] finding a trade-off between model complexity and training error. SVRs learn a linear function f in some chosen kernel feature space.[38] The final predictor is given by

$$f(\mathbf{x}) = \sum_{i=1}^{N} \alpha_i k(\mathbf{x}_i, \mathbf{x}) + b. \tag{3}$$

The α's weight the influence of training points $\mathbf{x}_i$ on the prediction $f(\mathbf{x})$. A ε-sensitive loss function is minimized, penalizing only predictions $\hat{y} = f(\mathbf{x})$ that differ more than ε from the true label y.

$$\ell(y, \hat{y}) = |(y - \hat{y})|_\varepsilon = \begin{cases} |(y - \hat{y})| & \text{for} \quad |(y - \hat{y})| > \varepsilon \\ 0 & \text{else} \end{cases} \tag{4}$$

See Figure 2b) for a visualization of SVR. Different studies[13,39–41] showed that SVRs can outperform Multiple Linear Regression and Partial Least Squares and perform on par with Neuronal Networks. As implementation we used LIBSVM together with an Matlab interface available from `http://www.csie.ntu.edu.tw/~cjlin/libsvm/`.

Ranking SVM

As a second baseline we tested a second ranking approach: Ranking SVM.[25,26] Falling into the category of *pairwise* ranking approaches, it maximizes the performance measure *Kendall's* τ. It mea-

sures the number of correctly ordered pairs within a ranking of length n, taking into account all possible $\frac{n(n-1)}{2}$ pairs. *Kendall's* τ has two crucial differences compared to NDCG: All positions of the ranking have an influence on the final performance unlike for NDCG, where only the top k positions matter. Additionally all positions have the same weight, unlike for NDCG, where higher positions are more important. The principle of Ranking SVM is visualized in Figure 2c). We used the implementation of Chapelle (`http://olivier.chapelle.cc/primal/ranksvm.m`), which we extended for the use of kernels, according to.[42]

Data

We use Virtual Screening datasets from the supporting information of the paper of Sutherland et al.[43] where spline-fitting together with a genetic algorithm was tested to establish a good classifier on five datasets. We selected a subset of three datasets most suitable for regression: The benzodiazepine receptor (BZR), the enzymes cyclooxygenase-2 (COX-2) and dihydrofolate reductase (DHFR). We will now briefly describe the biological function of each target and give some information about the corresponding dataset.

BZR

Being an ion channel located in the membrane of various neurons, BZR inhibits the neuron when bound by its endogenous ligand GABA. Drugs like Benzodiazepine can have their own allosteric binding site. They increase the frequency of channel opening thereby amplifying the inhibitory effect of GABA.[44]

The dataset contains 405 molecules that were derived mostly from the work of two research groups (Haefely et al. and Cook et al.). We removed 73 compounds with inexact measurements ($a < x$) which are not suitable for regression approaches. The remaining **340 molecules** had labels ranging from 4.27 to 9.47 pIC_{50}.

COX-2

The enzyme Cyclooxygenase 2 (COX-2) together with it's isoform COX-1[45] takes part in the synthesis of prostanoids. While COX-2 is an adaptive enzyme which is only produced in response to injury or inflammation, COX-1 is a constitutive enzyme which is produced constantly and provides for a physiological level of prostaglandins.[46] Drugs that inhibit COX-2 were shown to reduce gastrointestinal side-effects but at the price of increased cardiovascular risk.[47]

The dataset consists of 467 COX-2 inhibitors. They were assembled on the basis of the published work of a single research group (Khanna et al.). We again deleted 53 molecules with inexact measurements. The remaining **414 molecules** had labels ranging from 4 to 9 pIC_{50}.

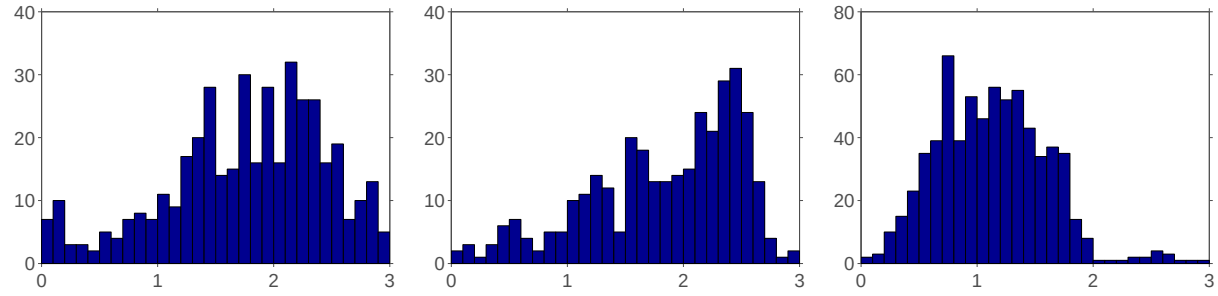
DHFR

The enzyme Dihydrofolate Reductase (DHFR) is involved in the syntheses of purins (adenine and guanine), pyrimidins (thymine) and some amino acids like glycine. As rapidly dividing cells like cancer cells needs high amounts of thymine for DNA synthesis they are particularly vulnerable to the inhibition of DHFR. Methotrexat, for example, is a DHFR-inhibitor which is used in treatment amongst others of childhood leukemia and breast cancer.[48]

The dataset contains a set of 756 inhibitors of Dihydrofolate Reductase assembled on the basis of the work of one research group (Queener et al.) and we removed 74 compounds with inexact measurement. The remaining **682 molecules** had labels ranging from 3.03 to 10.45 pIC_{50}.

Descriptor Generation and Data Preparation

For descriptor generation we used Dragon in version 5.5. Like done in previous studies[49,50] we used the following subset of Dragon blocks: 1, 2, 6, 9, 12, 15, 16, 17, 18, and 20. This yielded 728–772 descriptors, depending on the dataset. We then *normalized* the feature vectors to zero mean and unit variance on the training set. In order to keep the results between datasets in terms of NDCG comparable we *scaled* binding coefficients for each dataset into the range $[0, 3]$ as this is



(a) COX-2 ("dense") (b) BZR ("medium") (c) DHFR ("sparse")

Figure 3: The distribution of binding coefficients for the Virtual Screening datasets. The x-axis shows the binding coefficients (scaled into the range [0,3] for each dataset). The y-axis shows the number of molecules having that certain binding coefficient. Depending on the number of molecules with very high binding coefficients we can refer to them as "dense" (COX-2), "medium" (BZR) and "sparse" (DHFR).

a typical range when NDCG is used as scoring function for information retrieval datasets.[27]

If we examine the distribution of binding coefficients for each dataset (see Figure 3), we can distinguish different types of distributions: For COX-2 we see a high number of molecules with high binding coefficients, thus we call this dataset "dense". DHFR on the other hand has only a low number number of molecules with high binding coefficients, thus we call this dataset "sparse". BZR is in between with few molecules possessing very high binding coefficients. We will make use of this distinction later in the result section.

Test Framework

We used k-fold cross-validation to access performance for the Virtual Screening datasets. In order to have constant training set sizes (about 225 molecules), we varied the number of folds for each data set: we splitted BZR into three and COX-2 into two folds. Each fold was used as test set, whereas the other two folds (one fold) were used for training and parameter optimization. This was done by an inner cross-validation with 5 folds. For DHFR we also employed three folds but used the single folds for training and the other two as test set, thus also getting about 225 molecules in the training set. These cross-validations were performed 7 times for DHFR and BZR, and 10 times for COX-2.

As all three approaches share the same underlying SVM framework, they need to determine the same parameters within the cross-validation loop; for the RBF-kernel

$$k(\mathbf{x}_i, \mathbf{x}_j) = \exp\left(-\frac{(\mathbf{x}_i - \mathbf{x}_j)^T(\mathbf{x}_i - \mathbf{x}_j)}{2d\sigma^2}\right). \tag{5}$$

the parameters are $\sigma^2 \in \{0.1, 1, 10\}$ and d given by the number of descriptors. The SVM-parameter C controlling the model complexity was chosen from the set $\{0.01, 0.1, 1, 10, 100\}$. For the SVR we varied the tube width between $\{0.01, 0.1, 1\}$. For our StructRank approach we also selected the number of ranks over which we optimized using 10, 20 and 30 as parameters.

Alternative Performance Measures

We add two performance measures well known in the Virtual Screening community: Enrichment Factor (EF)[28] and Robust Initial Enhancement (RIE).[29] As shown by Truchon et. al,[19] area under the ROC Curve is not suitable for the "early recognition problem" of Virtual Screening.

RIE and ER only distinguish between active and inactive molecules, contrary to NDCG, which takes precise binding affinities into account. Therefor we have to impose thresholds in order to separate molecules into actives and inactives. To provide for challenging ranking problems (i.e. a low ratio of actives/inactives) we chose 8.5 pIC_{50} (BZR), 8.0 pIC_{50} (COX-2) and 7.5 pIC_{50} (DHFR) resp. According to these thresholds the datasets contain 60, 70 and 38 actives (BZR, COX-2 and DHFR).

The *Enrichment Factor* measures how many more actives are found in an defined fraction ζ of the ordered list, relative to a random distribution. Thus like NDCG it only looks at the top k positions of the ranking, but weights each position equally. It is given by

$$EF = \frac{\sum_{i=1}^{n} \delta_i}{\zeta \cdot n} \tag{6}$$

where n is the number of actives. δ_i is 1 if the active is ranked within the defined fraction of the list, otherwise it is 0. *Robust Initial Enhancement* measures how much better a given ranking of actives

is compared to their random distribution within the ranking. It considers the complete ranking, but like NDCG weights positions descending (depending on the parameter α, see 7). It is given by

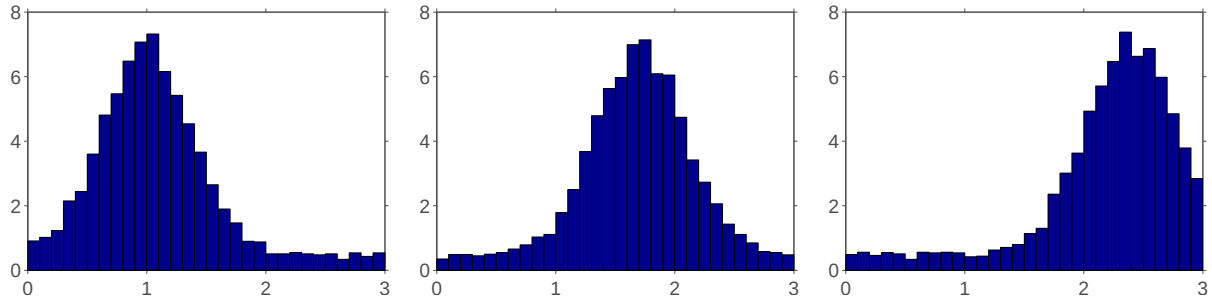
$$RIE = \frac{\sum_{i=1}^{n} \mathrm{e}^{-\alpha r_i}}{\left\langle \sum_{i=1}^{n} \mathrm{e}^{-\alpha r_i} \right\rangle_r} \tag{7}$$

where r_i is the relative rank (i.e. the rank divided by the length of the ranking), and $1/\alpha$ is the fraction of the list that is most important for the final score, which has a similar meaning as the cutoff k of *NDCG*. The denominator is the mean score when the actives are distributed randomly across the ordered list.

Toy Example

Before analyzing real-world VS data we designed a toy example to reproduce a set of different label distributions typically found in Virtual Screening data sets: Datasets which possess only a low number of molecules with high binding affinities. And those which contain a medium or high number of those molecules. Therefore we applied the following approach: We selected 300 training sets (100 of each type) with distribution of labels as outlined above. Each training set consisted of 75 examples. Figure 4 shows the histograms, each averaged over all 100 sets.

The aim is to compare the influence of the different label distributions on ranking performance. We thus draw validation and test sets with uniform label distributions for all three types of training sets: We train models for different parameter combinations and select the optimal parameter combination on a validation set. Using the resulting model, ranking performance was measured out of sample on a left out test set. The function we used to generate these datasets was: $f(\mathbf{x}) = x_1^4 - x_2^3 - x_3^2 - x_4^4$., randomly drawn from the space of 4-dimensional polynomials. We sampled 100.000 times from the 4-dimensional unit cube $x \in \{[-1,1]^4\}$. Labels again were scaled into the range [0,3] and the feature vector $\mathbf{x}$ was normalized.



(a) "sparse" (b) "medium" (c) "dense"

Figure 4: The histograms show the average label distribution for all three types of training sets (cf. text). The y-axis shows the number of elements having label given by the x-axis.

Results

We will now report on results obtained for the three Virtual Screening datasets, published by Sutherland et al.[43] Performance is measured for Support Vector Regression (SVR), Ranking SVM and our proposed StructRank approach. Furthermore a toy example will shed some light on the results obtained for the Virtual Screening datasets.

Virtual Screening Datasets

We measure ranking performance in terms of NDCG, ER and RIE for both our baselines and our ranking approach StructRank. Performance is measured for the first 10 ranks, which means cutoffs of 10 for $NDCG_{10}$ and ER_{10}, as well as a parameter α for RIE, which puts the most weight on the top 10 ranks. We performed k-fold cross-validation as described before, were all three approaches were optimized for NDCG. Figure 5 shows the results in terms of NDCG. Error Bars indicate standard error. Table 1 includes results for NDCG as well as ER and RIE. Significant improvements (level of significance 0.05) are indicated by bold numbers over approaches given as superscript. Additionally our approach is highlighted in gray. For all three performance measures, higher numbers indicate better rankings.

Starting with the dense dataset **COX-2** we observe that all three approaches perform nearly equally well in terms of NDCG, with no approach gaining a significant advantage over the others.

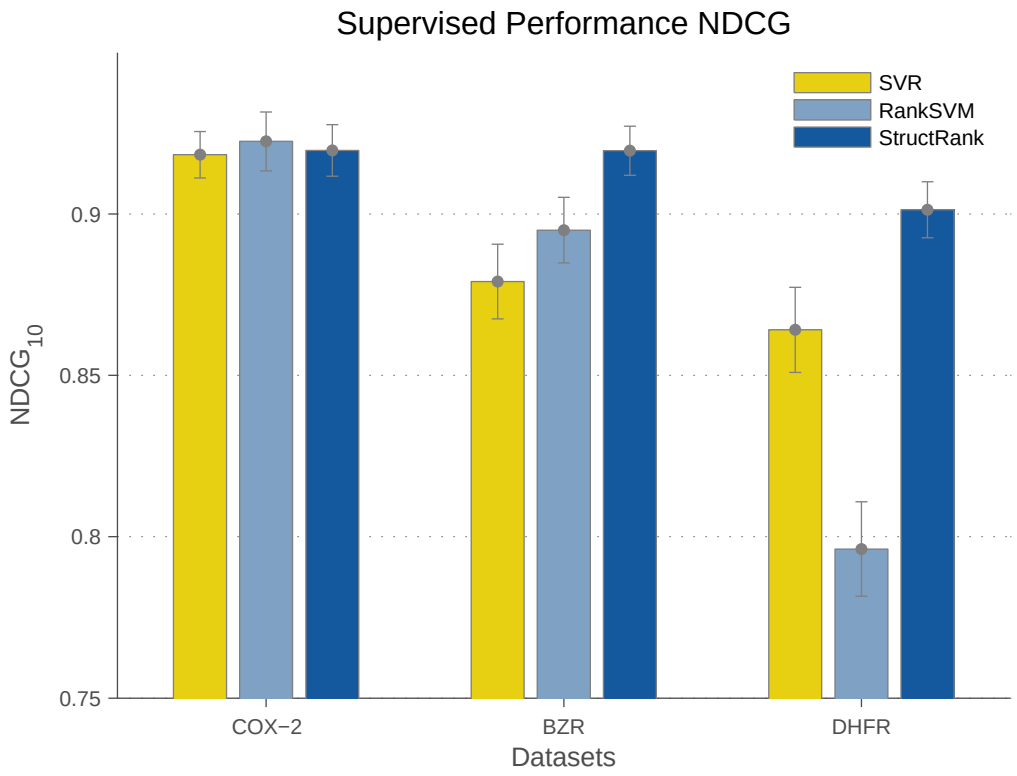


Figure 5: Averaged ranking performance measured in NDCG for the Virtual Screening datasets. Error bars indicate standard error.

These results are confirmed by the two "Virtual Screening" performance measures ER and RIE. For **BZR**, which could be classified as "medium" in terms of the high labeled molecules, our approach performs better than both baseline algorithms in terms of NDCG, improving significantly over SVR. RankSVM also can outperform SVR. These results are confirmed by ER but not by RIE. Finally, for the "sparse" dataset **DHFR**, our approach can significantly outperform both baseline methods in terms of ranking performance. This results holds for NDCG as well as ER and RIE. RankSVM is outperformed with a p-value below 0.001. Furthermore SVR can outperform RankSVM in terms of both Virtual Screening ranking measures.

Subsuming our observations, we state that our ranking approaches can outperform both baselines for the BZR and the DHFR set while for the "dense" dataset COX-2, all approaches perform equally. This dataset contains many molecules with high labels, thus the event that one of these molecules is ranked high by chance is very likely. For BZR we see (Figure 3) that the topmost

Table 1: Results for the virtual screening datasets for all baselines and our Structural Ranking approach (highlighted in gray). Bold numbers mark significant improvements with p-value ≤ 0.05 over approaches given as superscript: $^1 \hat{=}$ SVR and $^2 \hat{=}$ RankSVM. For all performance measures higher numbers indicate better results.

	Method	COX-2	BZR	DHFR
$NDCG_{10}$	SVR	0.920	0.877	**0.872**^{2}
	RankSVM	0.928	**0.901**^{1}	0.798
	StructRank	0.921	**0.919**^{1}	**0.905**^{1,2}
ER_{10}	SVR	5.452	3.955	**16.061**^{2}
	RankSVM	5.583	**4.310**^{1}	13.966
	StructRank	5.326	**4.527**^{1}	**17.168**^{1,2}
RIE	SVR	4.692	3.481	**11.939**^{1}
	RankSVM	4.736	3.575	11.010
	StructRank	4.595	3.698	**12.604**^{1,2}

bins, representing molecules with the highest labels, are sparsely populated. But subsequent bins, representing molecules with slightly lower labels, show a dense population like for COX-2. But these "sparse" bins seem to make it harder to obtain the perfect ranking, as performance drops in terms of NDCG for SVR and RankSVM. For the "sparse" dataset DHFR we can observe another decline in terms of ranking performance. Containing only very few molecules with high labels, this dataset seems to be the hardest but also the most realistic VS scenario. Thus we observed a continuous decline of performance of the baseline methods with decreasing number of high labeled molecules.

Toy Example

Three different label distributions are generated as described in the data section. Performance is again measured for SVR, RankSVM and StructRank. The results, which are shown in Figure 6, reveal nearly the same behavior as for the real world Virtual Screening datasets. The "dense"-type dataset has a big number of data points with large label and is therefor comparable to COX-2. Like for COX-2 all approaches perform nearly the same. The "medium"-type dataset has less data points with large labels and is comparable to BZR. Performance drops for both baselines, whereas

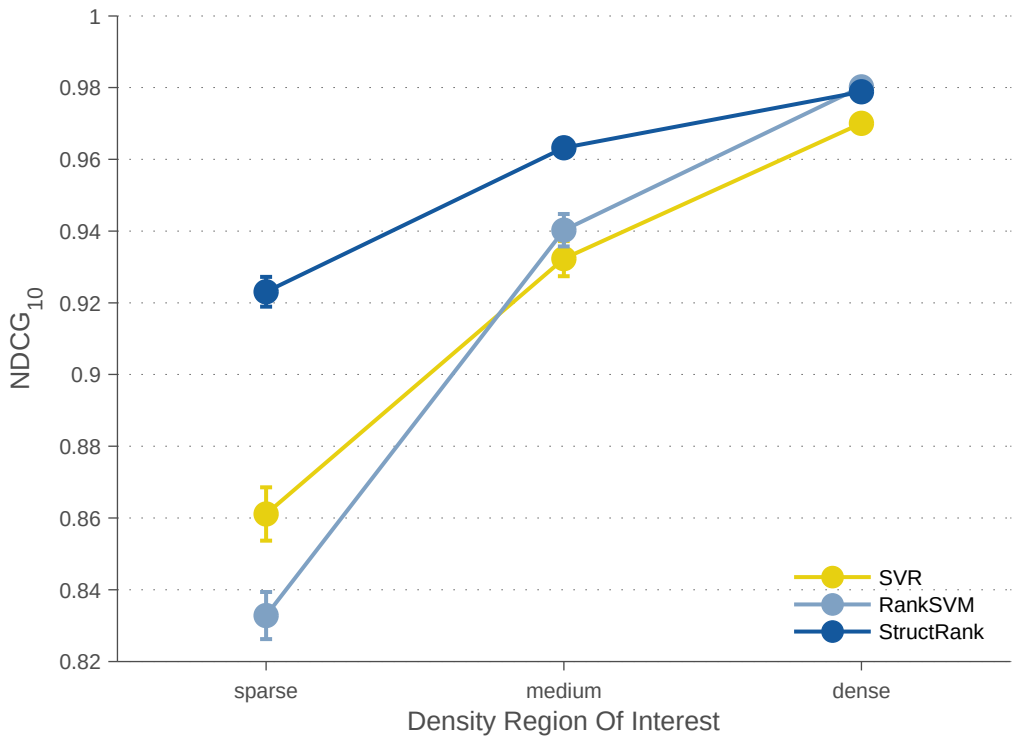


Figure 6: Ranking performance of Support Vector Regression (SVR), Ranking SVM (RankSVM) and Structural Ranking (StructRank) for three different types of training sets. The region with high labeled examples was covered either sparsely, medium or densely. Error bars indicate standard error.

StructRank's performance stays nearly the same. Also like for BZR RankSVM performs slightly better than SVR.

Finally the "sparse"-type dataset is comparable to DHFR, having the lowest number of data points with large labels. Being the most difficult dataset all approaches display a drop in ranking performance. Nevertheless for StructRank the drop is small compared to the baselines, which are both clearly outperformed. Interestingly, SVR and RankSVM display the same behavior as for the Virtual Screening datasets: While RankSVM has the lead over SVR for the "medium" dataset, SVR has over RankSVM for the "sparse" dataset.

Run Time Comparison

This section gives an overview of the CPU time needed by each approach for training and prediction. Given values present average values for the Virtual Screening datasets, i.e. training a model with about 225 molecules and obtain a prediction for the test set. SVR requires the least CPU time to train a model since it needs to solve only one optimization problem. RankSVM has to solve a much more complex optimization problem which is reflected in the increased time needed. For StructRank the optimization problems become too big to be solved within one step. Thus an iterative cut-and-bound technique[31] is applied, where for each iteration a convex quadratic subproblem has to be solved. This repeated convex optimization step is the reason for the increase of CPU time by the factor of 25 compared to the SVR. For prediction time we have inverse results with the ranking approach perform fastest.

Discussion and Outlook

This work investigated the use of ranking approaches when building QSAR-models for ligand-based Virtual Screening. Two ranking approaches, optimizing NDCG (StructRank) and Kendall's τ (RankSVM), were compared to one state-of-the-art approach for Virtual Screening: Support Vector Regression. The performance was measured using NDCG as well as two established VS metrics: Enrichment Factor and Robust Initial Enhancement.

This was the first time a ranking approach similar to StructRank was used within the field of QSAR modeling. Regarding the mathematical concept using a ranking approach like StructRank offers two advantages for Virtual Screening:

Table 2: Average CPU time for training/prediction for the Virtual Screening datasets.

	SVR	RankSVM	StructRank
Training	0.18 s	1.71 s	2.32 s
Prediction	0.31 s	0.05 s	0.05 s

1. **direct optimization of rankings**: StructRank directly optimizes a ranking measure, compared to the indirect optimization of regression approaches, which in the first place optimize a regression performance measure.

2. **focus on highly binding compounds**: Because of its composition, NDCG focuses on molecules with high binding coefficients, whereas regression approaches like SVR or ranking approaches like RankSVM pay equal attention to each molecule owing to the structure of their loss functions. Thus necessary complexity for solving the problem may be wasted uniformly over the data instead of focusing the algorithms complexity on high rank entries.

One potential drawback of our approach might be the comparatively large runtime. For datasets of similar size to those used in this work this poses no real obstacle, for very large datasets further approximative algorithmic contributions will have to be used similarly to Information Retrieval.

The evaluation results demonstrate that for datasets which posses only a small or medium number of molecules with high binding coefficients (e.g. BZR and especially DHFR) our approach performs significantly better than the baselines. For datasets which show a high density for these molecules, ranking approaches deliver no real advantage (e.g. for COX-2). These findings are underlined by the toy example: Whereas our ranking approach outperforms SVR and RankSVM clearly for the "sparse" type dataset, the advantage is lost for the "dense" type dataset.

Concluding we note that Structural Ranking represents a promising new approach that is very natural for Virtual Screening. To facilitate the further use of ranking approaches for Virtual Screening, we published our source code together with a documentation on the webpage: `http://doc.ml.tu-berlin.de/structrank/`.

Acknowledgement

This work was supported in part by the DFG Grant MU 987/4-1 and the FP7-ICT Programme of the European Community, under the PASCAL2 Network of Excellence, ICT-216886. We would like to thank talete srl for supporting a public DRAGON test descriptor set.

Appendix

Classic Support Vector Classification

Originally Support Vector Machines where formulated by Vapnik[35] to solve classification tasks: Given a set of data points, belonging to either class +1 or -1, how can one separate these classes and additionally maximize the margin around the hyperplane such that $y_i(\mathbf{w}^T\phi(\mathbf{x}_i)+b) \geq 1$ for all $\mathbf{x}_i$. The optimization problem is given by

$$\begin{aligned} \min_{\mathbf{w},b,\xi} \quad & \frac{1}{2}\mathbf{w}^T\mathbf{w} + C\sum_{i=1}^{n}\xi_i \\ \text{subject to} \quad & y_i(\mathbf{w}^T\phi(\mathbf{x}_i)+b) \geq 1-\xi_i, \\ & \xi_i \geq 0,\ i=1,\ldots,n. \end{aligned} \tag{8}$$

ξ_i are called slack variables and are nonzero for points that violate $y_i(\mathbf{w}^T\phi(\mathbf{x}_i)+b) \geq 1$, i.e. for those that are either misclassified or within the margin ± 1 around the hyperplane $w^T x - b = 0$.

NDCG

Given the true ranking $\bar{\mathbf{y}}$, a predicted ranking $\hat{\mathbf{y}}$ and a cut-off k, NDCG is given by the DCG (Discounted Cumulative Gain) for the predicted ranking normalized by the DCG of the true ranking.

$$NDCG_k(\bar{\mathbf{y}},\hat{\mathbf{y}}) = \frac{DCG_k(\hat{\mathbf{y}})}{DCG_k(\bar{\mathbf{y}})} \qquad DCG_k(\mathbf{y}) = \sum_{r=1}^{k}\frac{2^{\mathbf{y}(r)}-1}{log_2(1+r)} \tag{9}$$

where $\hat{y}(r)$ is the binding coefficient y_i of the molecule $\mathbf{x}_i$ ranked at position r.

Joint Feature Space

For a set of molecules $\tilde{\mathbf{x}} = (\mathbf{x}_1,\ldots,\mathbf{x}_n)$ and a ranking $\mathbf{y}$ of this set the joint feature map Ψ is given by

$$\Psi(\tilde{\mathbf{x}},\mathbf{y}) = \sum_{i=1}^{n}\phi(\tilde{\mathbf{x}}_i)A(\mathbf{y}_i) \tag{10}$$

as proposed by Chapelle.[30] ϕ is a mapping into a Hilbert space corresponding to a kernel function $k(\mathbf{x_i}, \mathbf{x_j})$, e.g. the RBF-kernel. The new vector in Ψ is a sum of vectors $\phi(\tilde{\mathbf{x}}_i)$ weighted by their ranks according to $A(r) = \max(0, k+1-r)$. Only molecules corresponding to the first k ranks are incorporated.

Structured Support Vector Machines

Here we present a more technical description of Structured Support Vector Machines supplementing the description given in the paper before. The "naive" maximum-margin problem is given by

$$\begin{aligned} \min_{w,\xi} \quad & \frac{1}{2}\mathbf{w}^T\mathbf{w} \\ \text{subject to} \quad & \mathbf{w}^T(\Psi(\tilde{\mathbf{x}}^j, \bar{\mathbf{y}}^j) - \Psi(\tilde{\mathbf{x}}^j, \mathbf{y})) \geq 1 \quad \forall j, \forall \mathbf{y} \neq \bar{\mathbf{y}}^j \end{aligned} \tag{11}$$

Keep in mind that each $\tilde{\mathbf{x}}^j$ consists of a set of k molecules $\mathbf{x}_i$ and the corresponding $\bar{\mathbf{y}}^j$ holds the corresponding true ranking of all molecules within the set. All $k! - 1$ other possible rankings of $\tilde{\mathbf{x}}^j$ are represented by $\mathbf{y}$. After replacing the constant margin 1 with a loss-dependent margin Δ and introducing slack variables ξ^j for each set $\tilde{\mathbf{x}}^j$ we get the final optimization problem

$$\begin{aligned} \min_{w,\xi} \quad & \frac{1}{2}\mathbf{w}^T\mathbf{w} + C\sum_{j=1}^{m}\xi^j \\ \text{subject to} \quad & \mathbf{w}^T(\Psi(\tilde{\mathbf{x}}^j, \bar{\mathbf{y}}^j) - \Psi(\tilde{\mathbf{x}}^j, \mathbf{y})) \geq \Delta(\bar{\mathbf{y}}^j, \mathbf{y}) - \xi^j \quad \forall j, \forall \mathbf{y} \neq \bar{\mathbf{y}}^j \\ & \xi^j \geq 0 \end{aligned} \tag{12}$$

The corresponding dual is given by

$$\max_{\alpha} \quad -\frac{1}{2}\alpha^T L \alpha + \mathbf{b}^T\alpha \tag{13}$$

$$\text{subject to} \quad \sum_{y \in \mathscr{Y}} \alpha_{\mathbf{y}}^j \leq C, \quad \alpha_{\mathbf{y}}^j \geq 0 \quad \forall j, \forall \mathbf{y} \neq \bar{\mathbf{y}}^j \tag{14}$$

where we have an α for each possible ranking $\mathbf{y}$ of subset $\tilde{\mathbf{x}}^j$. The matrix L consists of entries $(L)_{i\mathbf{y},j\mathbf{y}'} = (\Psi(\tilde{\mathbf{x}}^i,\bar{\mathbf{y}}^i) - \Psi(\tilde{\mathbf{x}}^i,\mathbf{y}))^T(\Psi(\tilde{\mathbf{x}}^j,\bar{\mathbf{y}}^j) - \Psi(\tilde{\mathbf{x}}^j,\mathbf{y}'))$ and $b_{i\mathbf{y}} = \Delta(\bar{\mathbf{y}}^i,\mathbf{y})$.

Abbreviations

BZR	Benzodiazepine Receptor
COX-2	Cyclooxygenase 2
DHFR	Dihydrofolate Reductase
NDCG	Normalized Discounted Cumulitive Gain
QSAR	Quantitive Structure-Activity Relationship
RankSVM	Ranking SVM
StructRank	Structural Ranking
SVM	Support Vector Machine
SVR	Support Vector Regression

Supporting Information Available

The algorithm as well as the toy example data may be found at `http://doc.ml.tu-berlin.de/structrank/`. This material is available free of charge via the Internet at `http://pubs.acs.org`.

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