Predicting Strategies for Lead Optimization via Learning to Rank

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Received: August 21, 2018, Accepted: September 18, 2018

Abstract: Lead optimization is an essential step in drug discovery in which the chemical structures of compounds are modified to improve characteristics such as binding affinity, target selectivity, physicochemical properties, and toxicity. We present a concept for a computational compound optimization system that outputs optimized compounds from hit compounds by using previous lead optimization data from a pharmaceutical company. In this study, to predict the drug-likeness of compounds in the evaluation function of this system, we evaluated and compared the ability to correctly predict lead optimization strategies through learning to rank methods.

Keywords: lead optimization, learning to rank, computer-aided drug design, machine learning

1. Introduction

During drug discovery, enormous attempts are being made to identify better drug candidates. Since the cost of drug discovery has been drastically increased, recently the process of drug discovery typically takes 12–14 years [1] and costs approximately 2.6 billion USD [2]. The process of drug discovery is sometimes likened to looking for a needle in a haystack; it is the process of finding out suitable compounds from vast “chemical space.” First, compounds are screened on the basis of their binding affinity to a target protein to obtain hit compounds. Then, in hit-to-lead and lead optimization steps, these hits are optimized to obtain drug candidates. Subsequently, the optimized compounds are designated for preclinical and clinical testing. Compounds that pass these tests are finally approved as drugs. Lead optimization, in which the chemical structures of lead compounds are modified to obtain with improved properties, is an essential step in drug discovery [3], [4]. Properties such as binding affinity, selectivity, physicochemical and ADMET (absorption, distribution, metabolism, excretion, toxicity) properties are optimized in the hit-to-lead and lead optimization steps [5], [6] (Fig. 1).

In order to reduce the cost of these processes, diverse approaches have been developed. Combinatorial chemistry and high-throughput screening are the key technologies to accelerate the drug discovery from experimental biology [7], [8], while computer-aided drug discovery (CADD), which has been utilized since the 1960s, are also leading current drug discovery. The methods of CADD can be combined with various biological data including genomic sequence, protein tertiary structure, and chemical structure, and can be utilized in various steps in drug discovery: target identification, compound screening, and ADME (absorption, distribution, metabolism, excretion, toxicity) properties prediction [9], [10], [11]. To this end, methods in CADD such as virtual screening, have been widely applied in drug discovery to reduce experimental costs [12], [13]. It is expected that CADD reduces the cost of drug development by 50% [14].

Nearly all of the cost of lead optimization originates from the synthesis of many compounds in an effort to explore the entire chemical space, but this exploration typically results in only a few, or if any, potential candidates. A discovery strategy that minimizes the number of compounds synthesized would greatly improve the efficiency of candidate development, since 17% of total drug discovery cost were invested for lead optimization [1]. However, researches on lead optimization are limited since practical data of lead optimization have not been published from pharmaceutical companies.

The ultimate research objective in this study was to develop an in silico compound optimization system to produce optimized compounds from hit compounds (Fig. 2). In this system, two modules are iteratively applied. The first module focuses on the exploration of candidate compounds, and the second evaluates the identified candidates. The exploration module is based on virtual modification of compounds by using matched molecular pairs (MMPs) or chemical reaction-based method. An MMP is a pair of compounds that differing in only in one part of their chemical structure [16], and MMPs have previously been used for ADME prediction [17] and compound optimization [18]. Chemical reaction-based method simulates virtual chemical re-
Fig. 1 Scheme of lead optimization. The hit compound is optimized through step-wise exploration. In each step, new compounds are synthesized and evaluated. Compounds with unfavorable properties are pruned and will not be explored in further steps. In this figure, binding affinity towards the target protein is used as an example of the evaluation function.

Fig. 2 Concept of an in silico compound optimization system. The system learns optimization strategies from previous lead optimization projects. When new hit compounds are input, the two modules are iteratively applied: exploration module and evaluation module. In the exploration module, modified compounds are virtually explored from input compounds using a virtual compound optimization system [15]. In the evaluation module, input compounds are evaluated by learned strategy.

actions to generate new compounds, and have previously been used for compound optimization [15]. As this method uses practical chemical reactions for exploration, generated compounds are more synthesizable than MMP-based systems.

In contrast, quantitative structure-activity relationships (QSARs) [19], [20] and quantitative structure-property relationships (QSPRs) [21], [22] have been widely used to evaluate compounds. However, such methods permit the simultaneous comparison of only a limited number of properties. Various physicochemical-property-based metrics or substructure-based drug-likeness indices, such as solubility [23], Lipinski’s rule of five [24], and quantitative estimate of drug-likeness (QED) [25], have been developed to assess the drug-likeness of compounds. Machine-learning-based approaches such as support vector machine (SVM) and neural network (NN) have also been applied to distinguish drug-like from non-drug-like compounds [26], [27], [28]. However, these methods remain inadequate because they were originally developed only to distinguish drugs from non-drugs. Consequently, there is a high demand for new methods that can predict drug-likeness of compounds that have been gradually optimized during lead optimization.

Learning to rank is a machine learning method that is well suited for addressing this issue. Figure 3 shows the idea of learning to rank method. This method, which has been developed in the field of information retrieval, predicts the order of a set
of data [29] rather than the class or specific value of each data. Learning to rank methods have previously been applied to virtual screening, where the accuracies outperformed simple SVM and support vector regression (SVR) [30], [31]. Learning to rank methods can be categorized as pointwise, pairwise, and listwise methods. In pointwise methods, a value is assigned to each data point, and those value are sorted to determine the order. In pairwise methods, the ordering is first determined for pairs of data points, and the ordered pairs are then sorted to determine the final order as in Fig. 3. In listwise methods, the order of a dataset is directly predicted. Among these methods, listwise method is not suited for this task since large datasets are required to train listwise method.

In this study, we propose a strategy for lead optimization based on compounds that have previously been synthesized at Takeda Pharmaceutical Company Limited. In this strategy, we predicted the order of synthesis of compounds, because compounds synthesized later during optimization are more likely to be drug-like. All factors that are implicitly involved in the order of optimization are considered in this method. We compared six different learning to rank methods, including both pointwise and pairwise methods.

2. Materials and Methods

2.1 Dataset

The dataset used in this study consisted of in-house data from 31 projects corresponding to previous lead optimization studies at Takeda Pharmaceutical Company Limited. The data from each project contained information on compounds synthesized in a previous study. The total number of compounds are 15,097, and the number of compounds consisted in each project ranged from 291 to 583, with a mean of 486. 14 out of 31 projects are used for parameter tuning, and other 17 projects are used for testing by cross validation.

The labels used for the machine learning represented the order of synthesis, because compounds that synthesized later are more likely to be drug-like than compounds that synthesized earlier. All compounds were numbered in time order, and the assigned numbers were normalized before use. For the pairwise methods, only pairs from the same project were used for training.

2.2 Features

All compounds in the dataset were encoded as feature vectors. In this study, the feature vector consisted of Extended-connectivity fingerprint (ECFP) [32], which is topological fingerprint for molecular characterization. The algorithm of ECFP fingerprint is described in Fig. 4, using 4-methyloxazole as an example. Substructures starting from each atom are iteratively combined to the neighbor atoms until the diameters of substructures reach specified number. Each of the constructed substructures corresponds to one bit of the fixed-length feature vector by using a hash function. Hash collisions are allowed when assigning more than one structure to one bit.

In this study, the maximum diameter of substructures and the length of bits was 6 and 512, respectively. None of the feature bits had the same value for every compound, and there were no highly correlated feature pairs with correlation coefficients of > 0.95.

2.3 Machine Learning Methods

In this study, several pointwise and pairwise methods of learning to rank, namely support vector machine (SVM) with a linear kernel, SVM with a radial basis function (RBF) kernel, random forest, rankSVM [33], [34], logistic classification and lasso, were compared in terms of their prediction accuracy. The methods and their corresponding method types, descriptions are summarized in Table 1. The detail of hyperparameter tuning, namely the ranges of tuned hyperparameters and final values is summarized in Table 2. The hyperparameters of these methods were optimized by using 14 out of 31 projects of the dataset, which contain different proteins and compounds to avoid train-test overlap. For Python 3.5.2 with scikit-learn version 0.18.1 [35] was used for implementation.
Table 1 Details of the methods used in this study. The methods, their corresponding method types (pointwise or pairwise), and descriptions are described.

| Method       | Type      | Description                           |
|--------------|-----------|---------------------------------------|
| SVM (linear) | pointwise | Support vector machine, linear kernel, regression |
| SVM (rbf)    | pointwise | Support vector machine, RBF kernel, regression |
| random forest| pointwise | Random forest, regression              |
| rankSVM      | pairwise  | SVM linear kernel, classification      |
| logistic     | pairwise  | Logistic regression for classification |
| lasso        | pairwise  | Least square regression for classification with L1 regularization |

Table 2 Details of the hyperparameter tuning. The methods, their corresponding hyperparameters, the ranges of tuned hyperparameters, and the final hyperparameter values are described.

| Method       | Hyperparameter names | Range                  | Final values |
|--------------|----------------------|------------------------|--------------|
| SVM (linear) | C                    | $10^{-5}, 10^{-4}, \ldots, 10^{10}$ | $10^{-5}$    |
| SVM (rbf)    | $C, \gamma$          | $C : 10^{-3}10^{-2}, \ldots, 10^{5}$, $\gamma : 10^{-4}10^{-5}, \ldots, 10^{6}$ | $C : 1.0$, $\gamma : 0.1$ |
| random forest| Number of features   | 5, 10, \ldots, 85     | 25           |
| rankSVM      | $C$                  | $10^{-3}, 10^{-2}, \ldots, 10^{1}$ | 1.0          |
| logistic     | $\alpha$             | $10^{-3}, 10^{-2}, \ldots, 10^{1}$ | 10           |
| lasso        | $\alpha$             | $10^{-3}, 10^{-2}, \ldots, 10^{1}$ | $10^{-3}$    |

We used a linear classifier for the pairwise methods for the following reason. In pairwise methods, the ranking task of two data points $(x_i, y_i)$ and $(x_j, y_j)$ can be transformed into the binary classification task of $(x', y') = (x_i - x_j, \text{sign}(y_i - y_j))$ if the classifier is linear, where $x_i \in \mathbb{R}^k$ denotes the feature vector of $i$-th data and $y_i \in \mathbb{R}$ denotes the label of $i$-th data [33]. Here $k$ denotes the number of features. For the pairwise methods, the minibatch training was used due to the number of training data. The training data are randomly split into minibatches, and subsequently the weight of each feature in these methods are iteratively updated using the gradient of loss function by means of the stochastic gradient descent method [36] through each minibatch. It is needed because the order of training data is the square of the data, as the pairs of data are used in pairwise method. The minibatch training was conducted for 10 epochs until the training loss is not decreased. The minibatch size was 500, which roughly corresponds to the number of compounds in each project.

2.4 Evaluation

The evaluation was conducted by using project-wise leave-one-out cross validation. It means that each project was independently evaluated using other 16 projects as training data to reduce over-
fitting. As an evaluation metric, Spearman’s correlation coefficient $\rho$ was used to evaluate the prediction accuracy. The definition is:

$$\rho = 1 - \frac{6 \times \sum d_i^2}{n(n^2 - 1)}$$  \hspace{1cm} (1)

where $d_i$ denotes the difference of rank of $i$-th data, and $n$ denotes the number of data. The range of values is $-1 \leq \rho \leq 1$ and the expected $\rho$ value for the random prediction is 0.

3. Results and Discussions

Table 3 shows the mean rank correlation coefficients among 17 projects. All methods except the lasso had statistically significant positive correlations, thus indicating that their predictions showed a significant positive correlation with the true order compared with random prediction.

One possible reason for the relatively poor performance of the lasso method may be the characteristics of the feature vectors. The solutions predicted by the lasso method tends to be more sparse than logistic regressions or ridge regression. In this dataset, the feature vectors may have been too dense to obtain sparse solutions. Moreover, the accuracy of the pointwise methods was higher than that of the pairwise methods in general. This finding indicated that comparing compounds between different projects contributed to more successful prediction, because such comparison were performed in the pointwise methods but not in the pairwise methods.

Table 3 Prediction accuracies of all methods. The mean Spearman’s rank coefficient $\rho$ among 17 projects was used for evaluation. The $*$: $p < 0.05$.

| Method       | Type  | Mean rank correlation coefficient $\rho$ |
|--------------|-------|----------------------------------------|
| SVM (linear) | pointwise | 0.321*                                 |
| SVM (rbf)    | pointwise | 0.344*                                 |
| random forest| pointwise | 0.301*                                 |
| rankSVM      | pairwise | 0.238*                                 |
| logistic     | pairwise | 0.262*                                 |
| lasso        | pairwise | -0.041                                 |

Figure 5 shows the correlation coefficients for all projects for the SVM (rbf), logistic classification, and lasso methods. SVM (rbf) and logistic classification were the best methods among the pointwise and pairwise methods, respectively. Because the lasso did not achieve effective prediction, it is also included for comparison. SVM (rbf) and logistic classification achieved high correlation for projects 1, 6, 9, 12, and 17 though all methods failed to predict projects 4, 11, and 13. Succeeded projects seemed to have similar pattern of optimization strategy and the pattern was recognized by machine learning methods and other projects might have dissimilar pattern to other projects.

And Fig. 6 shows similarity of compounds in all project using Tanimoto coefficient of ECFP6. Dissimilar and similar compounds are described as dark and bright color of cell, respectively. Projects 1–17 are used for cross validation and projects 18–31 are used for hyperparameter tuning. As shown in this figure, almost all pair of compounds from different projects are dissimilar except project 1 and 6, though compounds from the same project tend to be similar. Prediction accuracy for project 1 and 6 were relatively higher than others, but the order of optimization for other projects can be predicted with certain accuracy. Furthermore, the weight of linear models were examined for the understand of the optimization strategy. More than the half of the features were positive weight in all models. This implies that compounds which have more “on” bits were predicted to be synthesized latter. The number of “on” bits in ECFP6 corresponds to the variation of substructures of the compound. Thus, the prediction models reflect the tendency that compounds become complex as the optimization proceeds.

4. Conclusion

In this study, we have shown the optimization strategy using six learning to rank models in order to predict the drug-likeness of compounds as an evaluation function of the in silico compound optimization system. All results indicated that the order of syn-
thesis can be predicted with significant correlation using dataset which contains 17 optimization projects from an established pharmaceutical company. The results also suggested that compounds dissimilar to the test compounds contribute to the prediction and the optimization trend are reflected in the trained model. Although lead optimization is a complex, challenging process, we strongly believe our system will create a smooth and efficient optimization process in drug discovery.

5. Competing interests

The authors declare the following competing financial interest(s): Hideto Hara and Kentaro Rikimaru are employed by Takeda Pharmaceutical Co. Ltd.

6. Acknowledgement

The authors would like to thank N. Arai for useful discussions. This work was partially supported by the Research Complex Program “Well-being Research Campus: Creating new values through technological and social innovation” from Japan Science and Technology Agency (JST), the Japanese Society for the Promotion of Science (JSPS) KAKENHI Grant Numbers 15H02776 (To M.S.) and 16J09021 (To N.Y.), and the Platform Project for Supporting Drug Discovery and Life Science Research (Basis for Supporting Innovative Drug Discovery and Life Science Research (BINDS)) from AMED under Grant Number JP18am0101112.

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