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Research Paper

Supervised Probabilistic Approach for Drug Target Prediction

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Bayesian ranking based drug-target relationship prediction has achieved good results, but it ignores the relationship between drugs of the same target, which affects the accuracy. Aiming at this problem, a new method is proposed—drug-target relationship prediction based on grouped Bayesian ranking. According to the reality that the drugs interacting with a specific target have similarities, a grouping strategy is introduced to make these similar drugs interact. A theoretical model based on the grouping strategy is derived. The method is compared with five typical methods on five publicly available datasets and produces results superior to the compared methods.

Keywords: *Supervised Learning, Probabilistic Classification, Bayesian Classifier, Drug Prediction, Grouping Strategy*

1. Introduction

Computer-aided drug design is an interdisciplinary field of study that includes studies in biology, chemistry, physics, and informatics, to accelerate the drug discovery process. The key to drug development is to determine whether there is an interactive relationship (Drug-Target Interaction, DTI) between the drug and the target. Although it is possible to determine the presence of drug-target interactions in vitro and in vivo [1], these methods are time-consuming and expensive [2]. Therefore, computer technology can predict possible DTIs, and drugs can be screened through experiments [3], which may effectively lower the price of

releasing new drugs to the market [4]. Currently, docking simulation and machine learning are the two primary categories of computer prediction DTI approaches. The docking simulation method [5] uses the 3D structure of the target to identify whether there is a potential binding site for the drug. Still, it is very time-consuming and requires the 3D design of the target, and not all marks have 3D structures. Recent study [6] reveals that the machine learning-based scoring algorithms may be replaced by traditional molecular docking scoring methods with better prediction outcomes. Machine learning approaches typically exploit the features of the drug and target structure [7], the side effects of the drug [8], and knowledge of the confirmed DTIs [9]. The quick advancement of machine learning technology in recent years has made it possible to predict DTI with high accuracy. The machine learning-based techniques may be loosely categorized as classification, matrix factorization, kernel methods, and network inference techniques. Support Vector Machine (SVM) is a classification method that has been used by Literature [10] and Literature [11] to predict DTI. Dual Kernelized Bayesian Matrix Factorization (KBMF2K) [12] and Multiple Similarity Collaborative Matrix Factorization (MSCMF) [13] are classical methods of matrix factorization. Kernel methods mainly include the drug-target kernel method (PKM) [14], network Laplacian regularized least squares method (NetLapRLS) [15], and regularized Least Squares with Kromecker Product Kernel (RLS-Kron) [16]. Literature [17] established a bipartite local model & learned the drug-target interaction network, a typical network inference method. However, none of these basic methods can predict new drugs or targets. Literature [18] and Literature [19] address this problem by interacting with neighbour information to expect new medicines or marks. The above-mentioned methods focus on predicting the probability of the presence or absence of interactions for all unknown drug-target pairs, resulting in high time complexity. To reduce the time complexity, literature [20] proposed a new idea to focus on drug-centered research and rank the interacting targets of specific drugs, respectively. Targets ranked higher are most likely to interact with that drug, and unknown targets are individually identified for each drug based on the predicted interaction probability. They used Bayesian Personalized Ranking Matrix Factorization (BPR-MF) to predict DTI, called Bayesian Ranking (BR). Although BR shows promising results, its major limitation is that all drugs are independent and cannot cause some similar medicines to interacting. According to the fact that there is a similarity between drugs that interact with a specific target, to make these similar drugs interact, this paper groups these similar drugs and derives a theoretical model of grouping Bayesian ranking. Finally, it is verified by experiments that its performance is improved.

2. Principles and Related Work

2.1 Principle

Five published drug-target interaction datasets, namely, nuclear receptors (NRs), G protein-coupled receptors (GPCRs), ion channels (ICs), enzymes (E), and kinases (Kinase), are used in this paper. Table 1 presents the statistics for each dataset. Each dataset contains three matrices: (1) drug-target interaction matrix; (2) drug similarity matrix; (3) target similarity matrix. There are several approaches to compute drug & target similarity. In this study, the target and drug similarity, respectively, are determined using the

same technique as mentioned in the comparison method, with the target similarity being estimated using a sequence alignment approach, namely Smith-Waterman algorithm. The drug similarity is calculated by the 2D Tanimoto coefficient in the Kinase dataset, and the SIMCOMP [21] method is used for the rest datasets.

Table 1. Dataset Statistics

Data set	No. of drugs	No. of targets	Total No. of known interactions	Total No. of recently validated interactions
Enzyme	444	665	2927	503
ion channel	211	205	1477	1368
GPCRs	224	96	636	619
Nuclear receptor	55	27	91	28
Kinase	1422	157	2799	—

2.2 Basic Symbols and Problem Description

This paper assumes that there are m drugs and n targets, D denotes the set of medicines, and T denotes the set of marks. A binary matrix $y \in R^{m \times n}$ is used to show the relationship of interaction between the therapy and the target, each element $y_{ij} \in \{0,1\}$. If the drug is validated experimentally against the target and there is an interaction, then set to 1; otherwise, set to 0. Define a new drug set $D^N = \{d_i | \sum_{j=1}^{n} y_{ij} = 0, \forall 1 \leq i \leq m\}$ and a new target set $T^N = \{t_j | \sum_{i=1}^{m} y_{ij} = 0, \forall 1 \leq j \leq n\}$. The drug similarity matrix is denoted by $S^D \in R^{m \times m}$, and the target similarity matrix is denoted by $S^T \in R^{n \times n}$. The purpose of matrix factorization is to map the drug and target into a common latent space. Here, $u_i \in R^f$ denotes the drug id latent factor, and $v_j \in R^f$ denotes the potential factor of target t_j, f denotes the number of latent factors. Consider $U \in R^{m \times f}$ and $V \in R^{n \times f}$ as the matrix of all latent drug factors and all target latent factors, respectively. The predicted probability $\hat{r}_{ij}$ of the interaction between d_i and t_j is computed as $\hat{r}_{ij} = u_i \times v_j^T$, so $\hat{Y} = UV^T$ can represent the final predicted drug-target interaction matrix $\hat{Y}$. The training set for each drug is further defined as a triple training set $D_s \subset D \times T \times T$, where $D_s = \{(d_i, t_j, t_k) | r_{ij} = 1 \wedge r_{ik} = 0\}$. In this paper, a drug-centric re-localization approach predicts DTI. The main goal is to rank all targets for any drug $d \in D$, with the top-ranked target having the highest likelihood of interacting with drug d.

2.3 Bayesian Ranking Method

The Bayesian ranking method is based on the three major assumptions of the BPR-MF algorithm [20]. The following are three significant assumptions on which the BPR-MF algorithm is based:

(1) The interaction behaviour between drug & target is independent.

(2) The drug's & the target's feature matrices both adhere to a Gaussian distribution with a mean value of 0 and a constant variance.

(3) The error between the predicted & actual value, respectively, of the drug-target interaction relationship matrix must satisfy a Gaussian distribution with a mean of 0 and a constant variance.

This paper adopts the combined method of Bayesian sorting and matrix factorization, denoted as BPR-MF, based on three basic assumptions. Firstly, a corresponding probability model is established based on these assumptions, and then the Bayesian formula is used to maximize the posterior probability, and the related optimization criterion is established. Finally, it is solved to obtain the corresponding drug & target feature matrix, and then the drug target is reconstructed—relational networks for prediction of unknown drug-target relationships.

For each drug, to find all of its correct target rankings as much as possible, the posterior probability must be maximized by the Bayesian formula as follows:

$$p(\Theta|\succ_d) \propto p(\succ_d|\Theta)\, p(\Theta) \quad (1)$$

Among them, Θ is a parameter for matrix factorization. Based on assumption (1), the probability function $p(\succ_d|\Theta)$ of a specific drug can be obtained by the following:

$$\prod_{d \in D} p(\succ_d |\Theta) = \prod_{(d,t_j,t_k) \in D_s} p(t_j \succ_j t_k|\Theta) \quad (2)$$

The following formula determines if a drug's likelihood of interacting with the target t_j is higher than its likelihood of interacting with the target t_k:

$$p(t_j \succ_d t_k|\Theta) = \sigma(\hat{r}_{djk}(\Theta)) \quad (3)$$

Among them, $\sigma(x) = 1/(1+e^{-x})$ and $\hat{r}_{djk}(\Theta)$ is the evaluation function that represents the relationship among drug d, target tj, and target t_k. For matrix factorization, $\hat{r}_{djk}$ is defined as $\hat{r}_{djk} = \hat{r}_{dj} - \hat{r}_{dk}$; the model parameter Θ is a latent factor for the drug and target: Θ = (U,V). Based on assumption (2), the prior probability density of the model parameter Θ is obtained as a normal distribution: $p(\Theta) \sim N(0,\lambda_\theta I)$, where λ_θ refers to model-specific regularization parameter. Therefore, the objective function f can be deduced by the Bayesian ranking method as follows:

$$f = \ln p(\Theta|\succ_d) = \ln p(\succ_d|\Theta)\, p(\Theta) = \ln \prod_{(d,t_j,t_k) \in D_s} p(t_j \succ_d t_k|\Theta) p(\Theta)$$

$$= \sum_{(d,t_j,t_k) \in D_s} \ln \sigma(\hat{r}_{djk}(\Theta)) + \ln p(\Theta)$$

$$= \sum_{(d,t_j,t_k) \in D_s} \ln \sigma\left(\hat{r}_{djk}(\Theta)\right) - \lambda_\theta ||\Theta||^2$$

$$= \sum_{(d_i,t_j,t_k) \in D_s} \ln \sigma\left(\hat{r}_{ij} - \hat{r}_{ik}\right) - \lambda_R(||U||^2 + ||V||^2) \quad (4)$$

2.4 Advantages of Bayesian Ranking Method

A core step of the Bayesian ranking method is constructing a new training set. The difference is that the training sample here is not a drug-target pair but a triple consisting of a drug and a target, denoted here as (d,ti ,tj), where the drug d interacts

with the target ti, but the interaction with the target tj is unknown. The Bayesian ranking method uses triples as a new training set. Compared with traditional methods, it is no longer necessary to predict whether there is an interactive relationship between all unknown drug-target pairs, but only for the targets that interact with specific drugs. The higher the target ranking, the more likely it is to interact with the medicine. The unknown target is determined for each drug as per the predicted interaction probability, which can significantly reduce the time complexity.

3. Grouping Bayesian Sorting Method

In this part, two new definitions are described first, and then new assumptions and the basis for their establishment are proposed. Finally, a theoretical model of Group Bayesian Ranking (GBR) is derived based on the new assumptions to smooth new drugs and targets.

3.1 Grouping Idea

Definition 1 (Individual interaction): An individual exchange is the probability of interaction between drug id& target t_j. For example, the probability of interaction between drug id& target t_j is denoted as $\hat{r}_{ij}$.

Definition 2 (Group interactions): A group interaction is the set of drugs that interact with a specific target and the probability of that target interacting. For example, the probability of interaction among a drug set G and a target t_j is referred to as $\hat{r}_{Gj} = \frac{1}{|G|}\sum_{d_i \in G} \hat{r}_{ij}$. Where $G \subseteq D_{t_j}^{tr}, D_{t_j}^{tr}$ represents the ensemble set of drugs known to interact with the target Tj.

New hypothesis: If the drug-target pair (d_i, t_j) is known to have an interactive relationship, and whether the drug-target pair (d_i, t_k) interacts is unknown, the new hypothesis proposed in this paper is expressed by the following formula express:

$$(G,t_j) \succ (d_i,t_k) \quad (5)$$

Where $G \subseteq D_{t_j}^{tr}$ and $d_i \in G$. New hypotheses can be introduced more intuitively through Figure 1. Drugs d_1, d_2, d_3 are known to interact with target t_1, but it is unknown whether drug d_1 interacts with target t_2. According to definition 1, $\hat{r}_{11}$, $\hat{r}_{21}$, and $\hat{r}_{31}$ are all greater than $\hat{r}_{12}$, so $\frac{\hat{r}_{12}+\hat{r}_{21}+\hat{r}_{31}}{3} \succ \hat{r}_{12}$ also holds, that is, $\hat{r}_{G1} \succ \hat{r}_{12}$, and a new hypothesis is obtained: $(G,t_1) \succ (d_1,t_2)$, where $G = \{d_1,d_2,d_3\}$.

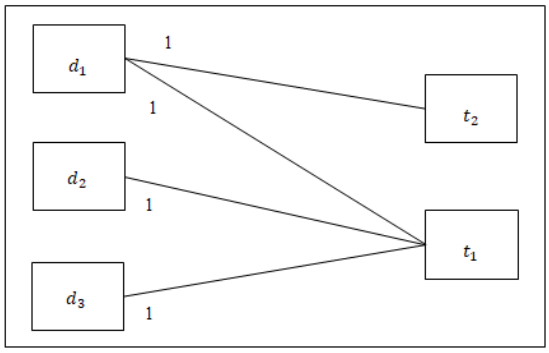

Figure 1. Drug-target Interaction Diagram

The implementation steps of the grouped Bayesian sorting method are shown in Algorithm 1.

Algorithm 1: Grouping Bayesian Sorting Method

Inputs: Interaction matrix Y; Similarity matrix S^D,S^T; Size of the drug (or target) neighbour k

Output: Updated interaction matrix $\hat{Y}$

Step 1: Initialize U,V,b

Step 2: Change S^D,S^T to include only the top k nearest neighbours of each item

Step 3: Make each drug-target pair (d_i,t_j) such that $r_{ij} = 1$

Step 4: Randomly select the target t_k so that $r_{ik} = 0$

Step 5: Randomize the drugs that interact with the specific target t_j so that the group size |G|=1,2,3,4,5

Step 6: Update b_j ,b_k , u_i , v_j , v_k

Step 7: Go back to step 3 until a predetermined or max number of iterations has been attained

3.2 Establishment of the New Hypothesis

This paper makes reasonable assumptions based on the following two aspects of information:

1) For the target: if the drug interacts with the target Tj, other drugs can also interact with the target t_j. The probability of interaction between drug id& target t_j is greater than the probability of interaction with the target t_k. So (G,t_j) $\succ d_i$ can be used instead of (d_i,t_j)$\succ$(d_i,t_k).
2) For drugs: It is natural to introduce interactions among all medicines that interact with a specific target Tj, because these drugs are in a similar relationship. The drug groups G $\subseteq D_{t_j}^{tr}$ share a common similarity and they all interact with the target t_j.

3.3 Theoretical Model

To study the different degrees of influence of individual interactions and group interaction on the prediction results more precisely, they are combined linearly:

(G,t_j) + (d_i,t_j) $\succ$ (d_i,t_k) or $\hat{r}_{Gij} \succ \hat{r}_{ik}$ (6)

where$\hat{r}_{Gij} = \rho\hat{r}_{Gj} + (1 - \rho)\hat{r}_{ij}$. $0 \le \rho \le 1$ is the trade-off parameter for fusing two different interactions, which can be determined by testing the validation set. Based on BR, the above assumptions, replacing $\hat{r}_{ij}$ with $\hat{r}_{Gij}$, each drug has a new target ordering, called grouped Bayesian arrangement. Therefore, the final grouped Bayesian ranking method objective function is as follows:

$$f = \sum_{(d_i,t_j,t_k)\in D_s} ln\sigma\left(b_j + \hat{r}_{Gij} - (b_k + \hat{r}_{ik})\right) - \lambda_R(||U||^2 + ||V||^2 + ||b||^2 + CA) \quad (7)$$

Where b_j and b_k are the biases of targets t_j and t_k, b is the bias of all marks, and CA is the regularization term for the latent factor distance. Assuming a triple (d_i, t_j, t_k) $\in D_s$ in the training set, CA can be expressed by the following formula:

$$CA = \lambda_c \left(\sum_{i=1}^{m} S_{i,\bar{i}}^{D} \left| u_i - u_{\bar{i}} \right|^2 + \sum_{j=1}^{n} S_{j,\bar{j}}^{T} \left| v_j - v_{\bar{j}} \right|^2 + S_{k,\bar{j}}^{T} \left| v_k - v_{\bar{j}} \right|^2 \right) \quad (8)$$

This paper optimizes the objective function f using extended stochastic gradient descent (SGD) with model parameters Θ including u_i, v_j, v_k, bj, and b_k. First, the gradient of the parameters in the objective function needs to be calculated, and then according to the respective gradient, the model parameters are updated as in Equation 9:

$$\Theta = \Theta + \eta \frac{\partial f}{\partial \Theta} \quad (9)$$

3.4 Smooth New Drugs and New Targets

This section utilizes neighbour information to anticipate interactions between new drugs and new targets. Bayesian ranking technique cannot predict new drugs & targets and can learn their underlying factors only via negative examples (unknown DTI), which may damage the whole model. In order to identify possible variables of unknown medications or unknown targets, this research uses neighbourhood information based on the concept of collaborative filtering [22].

$$\begin{cases} u_i = \frac{1}{\sum_{\bar{i} \in N^+(d_i)} S_{i,\bar{i}}^{D}} \sum_{\bar{i}=1} S_{i,\bar{i}}^{D} u_{\bar{i}} \\ v_j = \frac{1}{\sum_{\bar{j} \in N^+(t_j)} S_{j,\bar{j}}^{D}} \sum_{\bar{j}=1} S_{j,\bar{j}}^{T} v_{\bar{j}} \\ b_j = \frac{1}{\sum_{\bar{j} \in N^+(t_j)} S_{j,\bar{j}}^{D}} \sum_{\bar{j}=1} S_{j,\bar{j}}^{T} b_{\bar{j}} \end{cases} \quad (10)$$

Among them, $N^+(d_i)$ and $N^+(t_j)$ are the set of k nearest neighbors of known drug & targets, respectively. During the experiments, k = 5 so that the model is simplified.

4. Experiment and Result Analysis

This paper uses the area under the ROC curve (AUC), the normalized discounted cumulative gain [8] (nDCG), and the Mean average precision (MAP) as evaluation indicators. AUC and MAP values are used as evaluation indicators in almost all drug-target relationship predictions. In contrast, the nDCG value is an evaluation indicator only proposed in the recent literature [8], which has a great reference value, so it is included in the evaluation in this paper. Using hierarchical correlation features, nDCG can distinguish DTI predictions with higher potential impact. nDCG only considers the impact of the top k objects on DTI prediction by natural truncation, ignoring the small impact of unimportant things and reducing the time complexity.

4.1 Experimental Setup and Comparison Methods

To be comparable with previous research methods [15, 18, 20], this paper adopts five 10-fold cross-validations (CV) experiments to analyze the performance of the GBR prediction method. And compare the technique with 5 typical DTI prediction

methods, such as Gaussian kernel-based Weighted Nearest Neighbor [11] (WNN-GIP), Cooperative Matrix Factorization [13](CMF), Network Laplacian Regularization Least Squares [15](NetLapRLS), Bipartite Local Model with Nearest Neighbor Information [18](BLM-NII) and Bayesian Ranking Method [20](BR). During experimentation, the average of each cross-validation were calculated and ran it 5 times repeatedly, randomly dividing the known DTI into 10 parts to get a final AUC value. And use the same method to calculate the nDCG value and MAP values.

4.2 Parameter Setting

Theoretically, finding that the more neighbour's and k are selected, the better the performance is not complex. Still, when the number of neighbours increases to a specific value, the performance improvement is not apparent. The time complexity will continue to grow, resulting in the algorithm's low efficiency. For example, in drug-target relationship prediction, as the group size |G| value increases, the performance improves, but the time complexity increases exponentially. When |G| = 1, the improved method is the BR method, so selecting the appropriate k value and |G| value is essential. To deeply understand the impact of selecting the number of neighbours and group size on the GBR method, the parameter adjustment range is set to k∈{3,5,8,15,20,30} and |G|∈{1,2,3,4,5} select the appropriate k value and |G| value through experiments. As observed from Table 2 and Figure 2, when the number of neighbours k >8, the performance improvement is not much apparent. As observed from Table 3 and Figure 3, when the packet size |G| is greater than 3, the nDCG improvement is significantly reduced, and some even decrease.

Table 2. Data w.r.t. influence of the number of neighbours

Algorithm	k=3	k=5	k=8	k=15	k=20	k=30
NR	0.935	0.942	0.945	0.944	0.946	0.947
GPCR	0.926	0.928	0.936	0.934	0.935	0.937
IC	0.949	0.957	0.959	0.96	0.96	0.961
E	0.89	0.896	0.899	0.902	0.9	0.899
K	0.924	0.926	0.927	0.927	0.928	0.928

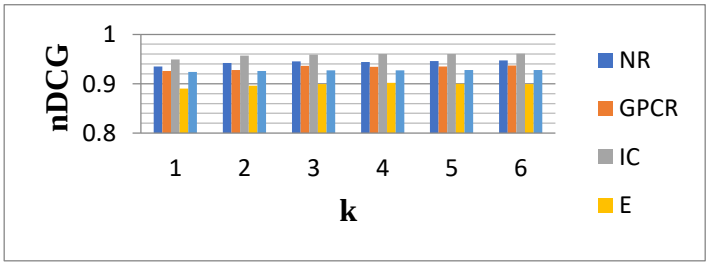

Figure 2. Influence of the number of neighbours

Table 3. Data w.r.t. effect of group size

Algorithm	|G|=1	|G|=2	|G|=3	|G|=4	|G|=5
NR	0.922	0.926	0.933	0.934	0.935
GPCR	0.928	0.931	0.937	0.938	0.942
IC	0.945	0.954	0.962	0.965	0.967
E	0.896	0.9	0.908	0.905	0.91
K	0.92	0.921	0.926	0.927	0.925

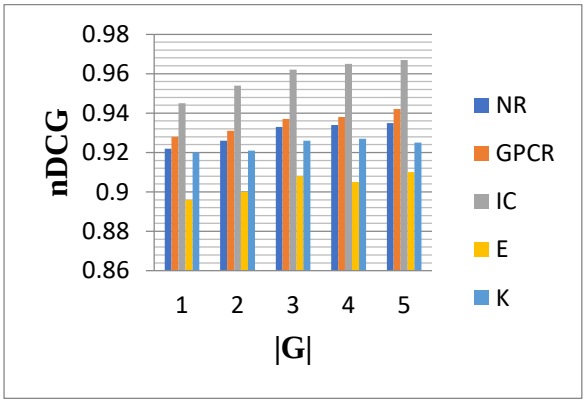

Figure 3. Effect of group size

5. Conclusion

This paper considers the effect of grouping interactions on the Bayesian ranking method. First, according to the reality that drugs interacting with a specific target have similarities, these similar drugs are grouped to obtain a grouped drug set. Then new hypotheses are proposed according to the grouped drug set, and the theoretical model of grouped Bayesian ranking is deduced based on the new ideas. Finally, the paper also incorporates neighbour information to smooth the prediction of new drugs and targets. The corresponding experiments prove that this paper's method outperforms the typical performance techniques. Future work plans to develop a new way for similar grouping targets to improve performance further.

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