Drug-target interaction prediction using Doubly Graph Regularized Matrix Completion

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Abstract

Motivation: The identification of interactions between drugs and target proteins is crucial in pharmaceutical sciences. The experimental validation of interactions in genomic drug discovery is laborious and expensive; hence, there is a need of efficient and accurate in silico techniques which can predict potential drug-target interactions to narrow down the search space for experimental verification.

Results: In this work, we propose a new framework, namely, Doubly Graph Regularized Matrix Completion, which predicts the interactions between drugs and proteins from three inputs: known drug-target network, similarities over drugs and those over targets. The proposed method focuses on finding a low rank interaction matrix that is structured by the proximities of drugs and targets encoded by graphs.

Extensive cross validation experiments on four benchmark datasets using standard evaluation metrics (AUPR and AUC)‘ show that the proposed algorithm improves the predictive performance and outperforms recent state-of-the-art computational methods.

Availability and Implementation:
https://github.com/aanchalMongia/DGRMCforDTI

Author summary

This work introduces a computational approach, namely Doubly Graph Regularized Matrix Completion (DGRMC), to predict potential interactions between drugs and targets. The novelty of DGRMC lies in structuring drug-target interaction matrix by the proximities of rows (drugs) and columns (targets) by introducing graph regularization terms to standard low-rank matrix completion problem. In addition, we further improve the prediction accuracy by sparsifying the drug and target similarity matrices, respectively. For performance evaluation, we conducted extensive experiments on four benchmark datasets. The experimental results demonstrated that DGRMC outperforms recent state-of-the-art methods under three different cross-validation settings, in terms of the area under the ROC curve (AUC) and the area under the precision-recall curve (AUPR).

Introduction

The field of drug discovery in Pharmaceutical sciences is plagued with the problem of high attrition rate. The task is to find effective interactions between chemical

compounds (drugs) and amino-acid sequences/ proteins (targets). This is traditionally done through wet-lab experiments which are known to be costly and laborious. An effective and appropriate alternative to avoid costly failures is to computationally predict the interaction probability. A lot of algorithms have been proposed for DTI (Drug-target interaction) prediction in recent years [1, 2], which use small number of experimentally validated interactions in existing databases such as ChEMBL [3], DrugBank [4], KEGG DRUG [5], STITCH [6] and SuperTarget [7]. Identification of drug-target pairs leads to improvements in different research areas such as drug discovery, drug repositioning, polypharmacology, drug resistance and side-effect prediction [8]. For instance, Drug repositioning [9, 10] (reuse of existing drugs for new indications) may contribute to its polypharmacology (i.e. having multiple therapeutic effects). One of the many successfully repositioned drugs is Gleevec (imatinib mesylate). It was originally thought to interact only with the Bcr-Abl fusion gene associated with leukemia but later, it was found to also interact with PDGF and KIT, eventually leading it to be repositioned to treat gastrointestinal stromal tumors as well [11, 12].

There are three major classes of computational methods for predicting DTI: Ligand based approaches, Docking based approaches and Chemogenomic approaches. Ligand based approaches leverage the similarity between target proteins' ligands to predict interactions [13]. These approaches use the fact that similar molecules tend to share similar properties and usually bind similar proteins [14]. However, lack of known ligands per protein in some cases might compromise the reliability of results. Docking based approaches are well-accepted and utilize the 3D structure information of a target protein and a drug; and then run a simulation to estimate the likelihood that they will interact or not [15–17]. But docking is heavily time consuming and cannot be applied to protein families for which the 3D structure is difficult to predict or is unavailable [18] for example the G-protein coupled receptors (GPCRs).

Chemogenomic approaches overcome the challenges of traditional methods and thus, have recently gained much attention. The approaches under this category work with widely abundant biological data, publicly available in existing online databases and process information (chemical structure graphs and genomic sequences for the drugs and targets) from both the drug and target sides simultaneously for the prediction task. These approaches can further sub-classified based on the representation of the input data: Feature based methods and Similarity based methods. Feature based techniques are machine learning methods, which take their inputs in the form of feature vectors, representing a set of instances (i.e. drug-target pairs) along with their corresponding class labels (i.e. binary values indicating whether or not an interaction exists). Examples of typical feature based methods include Decision Tree (DT), Random Forest (RF) [25] and Support Vector Machines (SVM) to build classification models based on the labeled feature vectors [19]. Positive instances are the known interactions and negative instances, the non-interactions. It should be noted that negative instances here include both non-interactions and unknown drug-target interactions (false negatives). The other category of chemogenomic techniques, Similarity based methods, use two similarity matrices corresponding to drug and target similarity, respectively, along with an interaction matrix which indicates which pairs of drugs and targets interact.

Let us discuss the similarity between the said DTI problem and the problem of collaborative filtering (CF). CF is a standard problem in information retrieval. It is used in recommendations systems (e.g. in Netflix movie recommendations and Amazon product recommendations). There is a database of user's and their ratings on items (movies, products, etc.). Obviously, not all the ratings are available; users typically rate only a small subset of items. The objective is to estimate the ratings of all the users on all the items. If that can be done accurately, recommendation accuracy increases. The similarity between DTI and CF should be straightforward now; the drugs play the role

of users and the targets play the role of items. The interactions are similar to the ratings. Over the years, many approaches originally developed for CF have been leveraged to solve the DTI problems. In both CF [20] and DTI [21–23], the initial techniques were based on simple neighborhood based models. In order to predict the interaction of a (active) drug on a target, the first step is to find out similar (neighbor) drugs by computing some kind of a similarity score. Once the neighborhood is obtained, the interaction value from the drugs in the neighborhood are weighted (by the normalized similarity score) to interpolate the interaction of the active drug on the target. The second approach was based on bipartite local models. In such models, a local model is built for every drug and target. For example in [24] an SVM was trained for each to predict interaction of each drug on all targets and each target on all drugs. Finally, the decision from the two were fused. This is just an example, there are other techniques falling under this generic approach like [25, 26]. The third category is based on network diffusion models. One technique for DTI prediction based on such models is based on random walk on the network with a predefined transition matrix [27]. Another work falling under this category, predicts interactions by finding simple (without loops) between nodes of the network. The fourth approach is based on matrix factorization. These techniques were originally developed for collaborative filtering [28]. It is assumed that the drugs and targets are characterized by latent factors. The probability of interaction is high when the latent factors match; i.e. when the inner product has a high value. Therefore, it is logical to express the interaction matrix as a (inner) product of drug and target latent factors. This allows matrix factorization (and its variants) to be applied [29, 30]. The fifth and final approach is based on classification. The chemical / biological information is used to generate features for drugs and targets individually. The two features are then concatenated and the corresponding interaction is assumed to the class corresponding to this feature. Any standard classifier can be used for the final classification. In such class of techniques the emphasis is on different feature selection mechanisms [31, 32].

In a very recent review paper [2] it was empirically shown that matrix factorization based techniques yields by far the best results. The fundamental assumption behind matrix factorization to work is that there are very few (latent) factors that are responsible for drug target interactions. This is reason, one can factor the DTI matrix into a tall (drug) latent factor matrix and a fat (target) latent factor matrix. Mathematically speaking, the assumption is that the DTI matrix is of low-rank. Matrix factorization is being used to model low-rank matrices for the past two decades since the publication of Lee and Seung's seminal paper [33]. However, matrix factorization is a bi-linear non-convex problem; there are no convergence guarantees. In order to ameliorate this problem, mathematicians proposed an alternate approach based on nuclear norm minimization [34–36]. The nuclear norm is the closest convex surrogate to the rank minimization (known to be NP hard) problem and there are provable mathematical guarantees on its equivalence to rank minimization. To the best of our knowledge, studies in DTI have been based on matrix factorization techniques; there have been no work on nuclear norm based matrix completion. This would be the first work to model DTI on these lines. However the standard matrix factorization technique, is unable to incorporate similarity information of the drugs and the targets. In a recent study [GRMF] it was shown that the best results are obtained when matrix factorization incorporates graph regularization. Also, graph regularization [37] has been shown to prevent overfitting while learning the data manifold and hence improve the accuracies in various frameworks, like content based filtering, dimensionality reduction [38, 39], clustering [40, 41], semi-supervised learning [42], etc

Following the same lines, we propose to regularize the standard nuclear norm minimization by graph regularization for both drugs and targets. To the best of our

Table 1. Drugs, Targets and Interactions in each dataset used for validation.

Datasets	NR	GPCR	IC	E
Drugs	54	223	210	445
Targets	26	95	204	664
Interactions	90	635	1476	2926

knowledge this is the first work on doubly (for both drugs and targets) graph regularized nuclear norm minimization.

Materials and methods

Dataset Description

We use the four benchmark datasets introduced in [21] concerning four different classes of target proteins, namely, enzymes (Es), ion channels (ICs), G protein- coupled receptors (GPCRs) and nuclear receptors (NRs). The data was simulated from public databases KEGG BRITE [43], BRENDA [44] SuperTarget [7] and DrugBank [4].

The data gathered from these databases is formatted as an adjacency matrix, called interaction matrix between drugs and targets, encoding the interaction between n drugs and m targets as 1 if the drug d_i and target t_j are known to interact and 0, otherwise.

Along with the interaction matrix, drug similarity matrix S_d and a target similarity matrix St are also provided. In S_d, each entry represents the pairwise similarity between the drugs and is measured using SIMCOMP [45]. In S_t, the similarity score between two proteins is based on the amino acid sequences of target protein and is computed using normalized Smith–Waterman [46].

Table 1 summarizes the statistics of all four datasets.

Low rank Matrix Completion

Let us assume that X is the adjacency matrix where each entry denotes interaction between a drug and target (1 if they interact, 0 otherwise). Unfortunately, we only observe this matrix partially because all interactions are not known. If Y denotes the partially observed adjacency matrix, the mathematical relation between X and Y is expressed as:

$$Y = A(X) \tag{1}$$

Here A is the sub-sampling operator. It is a binary mask that has 0's where the interaction X has not been observed or is unknown and 1's where they have been. Our problem is to recover X, given the observations Y, and the sub-sampling mask A. It is known that X is of low-rank. Ideally, X should be recovered by (2). Unfortunately, rank minimization is an NP hard problem with doubly exponential complexity, therefore solving it directly is not feasible.

$$\min_X rank(X) \text{ such that } Y{=}A(X) \tag{2}$$

Traditionally a low rank matrix has been modelled as a product of a thin and a fat matrix and recovered using Matrix Factorization techniques [33]. But, Matrix Factorization is a bi-linear non-convex problem, therefore there is no guarantee for global convergence. In the past decade, mathematicians showed that the rank minimization problem can be relaxed by its convex surrogate (nuclear norm minimization) with provable guarantees [34, 35] This turns out to be a convex problem

that can be solved by Semi Definite Programming. More efficient solvers have also been proposed. Problem (1) is expressed as (4)

Here the nuclear norm is defined as the sum of singular values of data matrix X. It is the l1 norm of the vector of singular values of X and is the tightest convex relaxation of the rank of matrix, and therefore its ideal replacement.

$$\min_X ||Y - A(X)||_F^2 + \lambda ||X||_* \tag{3}$$

The problem (3) does not have a closed form solution and needs to be solved via Iterated soft thresholding (refer Algorithm 1) [47].

$$\min_X ||X||_* \text{ such that } Y{=}A(X) \tag{4}$$

Here, (3) is a constrained formulation for the noiseless scenario, usually its relaxed version, (4) is solved. One of the efficient solvers is Singular value shrinkage (SVS) algorithm.

Algorithm 1 Singular value shrinkage

procedure MATRIX-SVS(Y, A, λ)
  Initialize: $X = rand$, a
    For loop , iterate (k)
      $B_k = X_{k-1} + \frac{1}{a} A^T (Y - A \circ X_{k-1})$
      Compute SVD of $B : B_k = USV^T$
      Soft threshold the singular values: $\Sigma = soft(S, \lambda/2)$ ▷ refer equation 15
      $X_k = U \Sigma V^T$
      $X_k \leftarrow X_k^+$
  End loop 1

Doubly Graph regularized Matrix Completion

Low rank Matrix Completion is not our contribution, it has been around since the past decade. However, it has not been used for Drug target interaction. The problem with Nuclear norm minimization (NNM) is that it cannot accommodate associated information such as Similarity matrices for Drugs and targets (S_d and S_t). But it has been seen in prior Matrix factorization based approaches, that incorporating the similarity information is crucial for improving the DTI prediction results. Therefore, its imperative that NNM should also be capable of accommodating such similarity information. To achieve this, we propose DGRMC.

Graph regularization assumes that points close to each other in the original space should also be close to each other in the learned manifold (**Local Invariance assumption**). Regularized version allows the algorithm to learn manifolds for the drug and target spaces in which the data is assumed to lie.

The doubly graph regularized version of matrix completion, aims to prevent over fitting and enhance generalizing capabilities. It is incorporated into that formulation as Laplacian weights corresponding to drugs and targets:

$$\min_X ||Y - A(X)||_F^2 + \lambda ||X||_* + \mu_1 Tr(X^T L_d X) + \mu_2 Tr(X L_t X^T) \tag{5}$$

where $\lambda \geq 0$, $\mu_1 \geq 0$ and $\mu_2 \geq 0$ are parameters balancing the reconstruction error of NNM in the first two terms and graph regularization in the last two terms, $Tr(.)$ is the trace of a matrix, $L_d = D_d - S_d$ and $L_t = D_t - S_t$ are the graph Laplacians [48] for S_d

(drug similarity matrix) and S_t (target similarity matrix), respectively, and $D_d^{ii} = \Sigma_j S_d^{ij}$ and $D_t^{ii} = \Sigma_j S_t^{ij}$ are degree matrices.

Poblem (5) is solved using a variable splitting approach [49]. The augmented Lagrangian is expressed as (6). We introduce two new proxy variables Z and Y such that $Z^T = X$ and $Y = X$.

$$\min_{X,Y,Z} ||Y - A(X)||_F^2 + \lambda ||X||_* + \mu_1 Tr(ZL_dZ^T) + \mu_2 Tr(YL_tY^T) + \nu_1 ||Z^T - X||_F^2 + \nu_2 ||Y - X||_F^2 \tag{6}$$

The variables are updated using ADMM [50, 51]. This leads to the following sub problems (7), (8) and (9)

$$X \leftarrow \min_X ||Y - A(X)||_F^2 + \nu_1 ||Z^T - X||_F^2 + \nu_2 ||Y - X||_F^2 + \lambda ||X||_* \tag{7}$$

$$Y \leftarrow \min_Y \mu_2 Tr(YL_tY^T) + \nu_2 ||Y - X||_F^2 \tag{8}$$

$$Z \leftarrow \min_Z \mu_1 Tr(ZL_dZ^T) + \nu_1 ||Z^T - X||_F^2 \tag{9}$$

Problem (7) can be expressed as a standard NNM probelm (by column stacking the variables).

$$\left\| \begin{pmatrix} Y \\ \sqrt{\nu_1} Z^T \\ \sqrt{\nu_2} Y \end{pmatrix} - \begin{pmatrix} A \\ \sqrt{\nu_1} I \\ \sqrt{\nu_2} I \end{pmatrix} X \right\|_F^2 + \lambda ||X||_* \tag{10}$$

To solve for Y and Z, we differentiate (8) and (9) wrt Y and Z, respectiveley.

$$Y = \arg\min_Y (F_1) \text{ where } F_1 = \mu_2 Tr(YL_tY^T) + \nu_2 ||Y - X||_F^2 \tag{11}$$

$$Z = \arg\min_Z (F_2) \text{ where } F_2 = \mu_1 Tr(ZL_dZ^T) + \nu_1 ||Z^T - X||_F^2 \tag{12}$$

$$\frac{\partial F_1}{\partial Y} = \mu_2 (YL_t^T + YL_t) + 2\nu_2 (Y - X) \tag{13}$$

$$\frac{\partial F_1}{\partial Y} = \mu_2 Y (L_t^T + L_t) + 2\nu_2 (Y - X) \tag{14}$$

Since L_t is a symmetric matrix, $L_t = L_t$. So,

$$\frac{\partial F_1}{\partial Y} = 2\mu_2 YL_t + 2\nu_2 (Y - X)$$

Equating the derivative to zero, we get:

$$\nu_2 Y + \mu_2 YL_t = \nu_2 X \tag{15}$$

The matrix equation of this form (AX+XB=C) is Sylvester equation. Such an equation has a unique solution when the eigenvalues of A and -B are distinct. A similar sylvester equation and update step for Z can be obtained by differentiating F_2 and equating to 0.

$$\nu_1 Z + \mu_1 ZL_d = \nu_1 X^T \tag{16}$$

The pseudo-code for DGRMC has been given in algorithm 2. The standard NNM is a convex problem and graph regularization penalties are also convex, so entire formulation (5) is convex, therefore it is bound to converge to a global minima.

Algorithm 2 Doubly Graph regularized Matrix completion

procedure DGRMC(X, S_d, S_t)
  Sparsify: S_d, S_t
  Initialize: $\lambda, \mu_1, \mu_2, \nu_1, \nu_2, Z = X^T, Y = X, L_d = D_d^{-1/2} L_d D_d^{-1/2}, L_t = D_t^{-1/2} L_t D_t^{-1/2}$,
    $AA \leftarrow \begin{pmatrix} A \\ \sqrt{\nu_1} I \\ \sqrt{\nu_2} I \end{pmatrix}$
  For loop , iterate (k)
    $YY_k \leftarrow \begin{pmatrix} Y \\ \sqrt{\nu_1} Z^T \\ \sqrt{\nu_2} Y \end{pmatrix}$
    $X_k \leftarrow MATRIX - IST(YY_k, AA, \lambda)$
    $Y_k \leftarrow$ solve-sylvester$(\nu_1 I, \mu_1 L_d, \nu_1 X')$
    $Z_k \leftarrow$ solve-sylvester$(\nu_2 I, \mu_2 L_t, \nu_2 X)$
  End loop 1

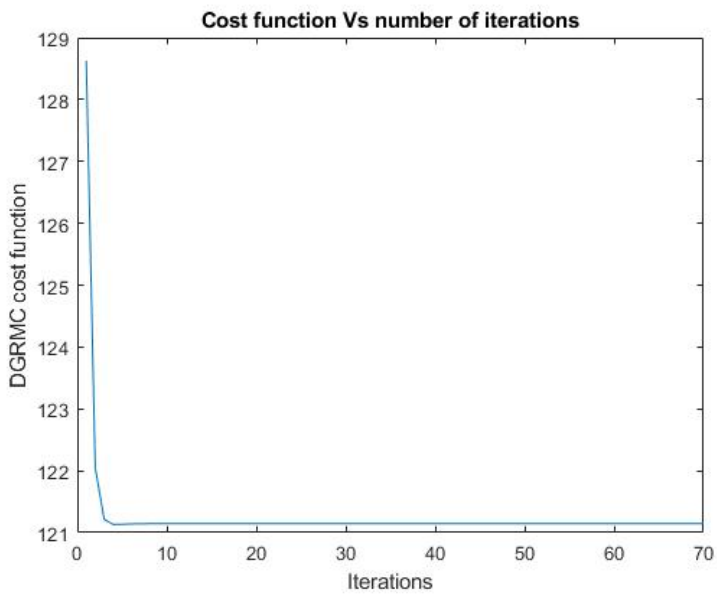

Fig 1. Converge plot for NR dataset with validation setting CVS1.

Time Complexity of DGRMC

The algorithm is iterative, so we only discuss the time complexity per iteration. In each iteration, we solve two sylvester equations and one NNM. NNM itself is an iterative algorithm that requires solving Singular value decomposition in each iteration, the order of complexity is $O(n^3)$. The complexity of solving sylvester equationis $O(n^b.log(n))$ [52] where b is between 2 and 3.

Results and Discussion

Experimental Setup

We validated our proposed method by comparing it with recent and well-performing prediction methods proposed in the literature. Out of the 5 approaches with which we compare,

- Three are specifically designed for DTI task (WGRMF: Weighted Graph Regularized Matrix Factorization, CMF: Collaborative Matrix Factorization, RLS_WNN: Regularized Least square Nearest neighbour profile) [30, 53, 54];
- One being traditional matrix completion (MC: matrix completion) [47] and
- Last one being a naive solution to our problem, available as an unpublished work (MCG: matrix completion on graphs). Of note, Space complexity of MCG is $O(n^4)$ while that of DGRMC is $O(n^2)$. [55])

All baselines designed for DTI problem are recent and are already compared against older methods.

We performed 5 repetitions of 10-fold cross validation (CV) for each of the methods under three cross validation setting (CVS) [2]:

- CVS1: random drug–target pairs are left out as the test set. It is the conventional setting for validation adn evaluation.
- CVS2: entire drug profiles are left out to be used as test set. It tests the algorithm's ability to predict interactions for novel drugs i.e. drugs for which no interaction information is available.
- CVS3: entire target profiles are left out to be used as test set. It tests the algorithm's ability to predict interactions for novel targets.

In 10-fold CV, data was divided into 10 folds and out of those 10 folds, one was left out as the test set while the remaining 9 folds were treated as the training set. As the evaluation metrics, We used:

- AUC: AUC stands for "Area under the ROC Curve." That is, AUC measures the entire two-dimensional area underneath the entire ROC curve (a plot showing the true positive rate for a method as a function of the false positive rate). AUC provides an aggregate measure of performance across all possible classification thresholds. One way of interpreting AUC is as the probability that the model ranks a random positive example more highly than a random negative example. The higher it is, the better the model is.
- AUPR: We also evaluated the performance by AUPR (Area Under the Precision-Recall curve), because AUPR punishes highly ranked false positives much more than AUC, this point being important practically since only highly ranked drug-target pairs in prediction will be biologically or chemically tested later in an usual drug discovery process, meaning that highly ranked false positives should be avoided. The precision-recall curve shows the tradeoff between precision and recall for different threshold. A high area under the curve represents both high recall and high precision, where high precision relates to a low false positive rate, and high recall relates to a low false negative rate. High scores for both show that the classifier is returning accurate results (high precision), as well as returning a majority of all positive results (high recall).

Preprocessing:

Each of the drug an target similarty matrices S_d and S_t have been sparsified by using p-nearest neighbour graph approach as introduced in [30].

$$\forall i, j$$
$$N_{ij} = \begin{cases} 1, j \in N_p(i) \& i \in N_p(j) \\ 0, j \notin N_p(i) \& i \notin N_p(j) \\ 0.5, else \end{cases}$$

where $Np(i)$ is the set of p nearest neighbors to drug d_i. Similarity matrix is then sparsified by element-wise multiplying it with N_{ij}. Also, instead of graph laplacians (L_d and L_t), we have used normalized graph laplacians ($D_d^{-1/2} L_d D_d^{-1/2}$ and $D_t^{-1/2} L_t D_t^{-1/2}$) as normalized graph Laplacians are known to perform better in many cases [42].

Parameter settings

For setting the parameters of our algorithm, we performed cross validation on the training set on the parameters $p, \lambda, \mu_1, \mu_2, \nu_1, \nu_2$ to find the best parameter combination for each dataset, under each cross-validation setting. For the other methods, we to set the parameters to their optimal (which were found to be already optimal) in [1].

Interaction Prediction

Tables 2, 4 and 6 show the AUPR results and tables 3, 5 and 7 show the AUC results from the above-mentioned cross validation settings. DGRMC performs competitively and in most cases outperforms the state-of-the art prediction methods. It should be noted that the results on the NR data set are comparatively unstable because of its excessively small size [56].

Conclusion

Drug-target interaction prediction is a crucial task in in genomic drug discovery. Many computational techniques have been proposed in literature. In this work, we presented a novel chemogenomic approach for predicting the drug-target interactions, DGRMC (Doubly Graph regularized Matrix Completion). It is a graph regularized version of the tradition Matrix completion algorithm. The algorithm is generic and can be used for prediction in protein-protein interaction [57], RNA-RNA interaction [58], etc.

Evaluation was performed using three different cross validation settings, namely CVS1 (random drug-target pairs left out), CVS2 (entire drug profile left out) and CVS3 (entire target profile left out) to compare our method with 5 other state-of-the-art methods (three specifically designed for DTI prediction). In most of the cases, our algorithm shows the best performance, outperforming the baselines, while in rest of the cases, the results are competetive and favourable for its practical usage.

Table 2. AUPR results for interaction prediction under validation setting CVS1.

AUPR	DGRMC	MC	MCG	WGRMF	RLS_WNN	CMF
E	0.9014(0.0018)	0.7882(0.0022)	0.7621(0.0025)	0.8768(0.0020)	0.8093(0.0045)	0.8837(0.0026)
IC	0.9298(0.0026)	0.8868(0.0028)	0.8346(0.0025)	0.9225(0.0022)	0.8459(0.0106)	0.9373(0.0019)
GPCR	0.7483(0.0039)	0.6481(0.0116)	0.5956(0.0102)	0.7370(0.0024)	0.6933(0.0226)	0.7543(0.0017)
NR	0.6408(0.0234)	0.3950(0.0298)	0.4558(0.0202)	0.6016(0.0378)	0.7072(0.0290)	0.6383(0.0149)

Table 3. AUC results for interaction prediction under validation setting CVS1.

AUPR	DGRMC	MC	MCG	WGRMF	RLS_WNN	CMF
E	0.9798(0.0004)	0.8753(0.0023)	0.9596(0.0015)	0.9647(0.0013)	0.9635(0.0014)	0.9705(0.0013)
IC	0.9829(0.0012)	0.9415(0.0015)	0.9539(0.0010)	0.9747(0.0022)	0.9786(0.0026)	0.9832(0.0008)
GPCR	0.9531(0.0028)	0.8110(0.0055)	0.8977(0.0047)	0.9432(0.0010)	0.9458(0.0044)	0.9493(0.0031)
NR	0.9083(0.0058)	0.5882(0.0253)	0.8315(0.0165)	0.8892(0.0153)	0.9329(0.0114)	0.8679(0.0124)

Table 4. AUPR results for interaction prediction under validation setting CVS2.

AUPR	DGRMC	MC	MCG	WGRMF	RLS_WNN	CMF
E	0.4089(0.0104)	0.0114(0.0005)	0.0457(0.0008)	0.4019(0.0128)	0.2409(00272)	0.3848(0.0094)
IC	0.3650(0.0178)	0.0473(0.0035)	0.0925(0.0013)	0.3666(0.0169)	0.3090(0.0200)	0.3538(0.0137)
GPCR	0.4175(0.0076)	0.0404(0.0017)	0.1091(0.0044)	0.4247(0.0113)	0.3463(0.0106)	0.4059(0.0104)
NR	0.5620(0.0262)	0.1120(0.0206)	0.2404(0.0337)	0.5695(0.0136)	0.5373(0.0216)	0.5203(0.0250)

Table 5. AUC results for interaction prediction under validation setting CVS2.

AUPR	DGRMC	MC	MCG	WGRMF	RLS_WNN	CMF
E	0.8260(0.0108)	0.5060(0.0090)	0.7413(0.0118)	0.7982(0.0144)	0.7755(0.0093)	0.7952(0.0110)
IC	0.7913(0.0090)	0.5512(0.0034)	0.7196(0.0071)	0.7902(0.0149)	0.7669(0.0140)	0.7576(0.0125)
GPCR	0.8805(0.0024)	0.5855(0.0039)	0.7745(0.0027)	0.8800(0.0025)	0.8524(0.0072)	0.8067(0.0067)
NR	0.8452(0.0215)	0.5294(0.0200)	0.6992(0.0244)	0.8615(0.0244)	0.8390(0.0261)	0.8124(0.0228)

Table 6. AUPR results for interaction prediction under validation setting CVS3.

AUPR	DGRMC	MC	MCG	WGRMF	RLS_WNN	CMF
E	0.8087(0.0156)	0.0124(0.0005)	0.0691(0.0009)	0.8070(0.0185)	0.5465(0.0144)	0.7808(0.0131)
IC	0.8079(0.0096)	0.0421(0.0043)	0.2256(0.0038)	0.8128(0.0069)	0.7437(0.0088)	0.7786(0.0108)
GPCR	0.5963(0.0336)	0.0549(0.0105)	0.1061(0.0027)	0.6093(0.0314)	0.5397(0.0193)	0.5989(0.0323)
NR	0.4356(0.0177)	0.0850(0.0227)	0.2669(0.0288)	0.4643(0.0183)	0.4907(0.0326)	0.4774(0.0173)

Table 7. AUC results for interaction prediction under validation setting CVS3.

AUPR	DGRMC	MC	MCG	WGRMF	RLS_WNN	CMF
E	0.9246(0.0091)	0.5234(0.0057)	0.8065(0.0012)	0.9338(0.0071)	0.9067(0.0105)	0.9272(0.0050)
IC	0.9346(0.0041)	0.4724(0.0065)	0.7871(0.0069)	0.9460(0.0034)	0.9286(0.0046)	0.9368(0.0032)
GPCR	0.8798(0.0134)	0.5683(0.0310)	0.6289(0.0151)	0.8892(0.0110)	0.8694(0.0146)	0.8966(0.0073)
NR	0.7263(0.0211)	0.3767(0.0204)	0.6522(0.0297)	0.7967(0.0132)	0.8124(0.0202)	0.8373(0.0083)

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