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Drug-target interaction prediction: A Bayesian ranking approach

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ABSTRACT

Background and objective: *In silico* prediction of drug-target interactions (DTI) could provide valuable information and speed-up the process of drug repositioning – finding novel usage for existing drugs. In our work, we focus on machine learning algorithms supporting drug-centric repositioning approach, which aims to find novel usage for existing or abandoned drugs. We aim at proposing a per-drug ranking-based method, which reflects the needs of drug-centric repositioning research better than conventional drug-target prediction approaches.

Methods: We propose *Bayesian Ranking Prediction of Drug-Target Interactions* (BRDTI). The method is based on *Bayesian Personalized Ranking* matrix factorization (BPR) which has been shown to be an excellent approach for various preference learning tasks, however, it has not been used for DTI prediction previously. In order to successfully deal with DTI challenges, we extended BPR by proposing: (i) the incorporation of target bias, (ii) a technique to handle new drugs and (iii) content alignment to take structural similarities of drugs and targets into account.

Results: Evaluation on five benchmark datasets shows that BRDTI outperforms several state-of-the-art approaches in terms of per-drug nDCG and AUC. BRDTI results w.r.t. nDCG are 0.929, 0.953, 0.948, 0.897 and 0.690 for G-Protein Coupled Receptors (GPCR), Ion Channels (IC), Nuclear Receptors (NR), Enzymes (E) and Kinase (K) datasets respectively. Additionally, BRDTI significantly outperformed other methods (BLM-NII, WNN-GIP, NetLapRLS and CMF) w.r.t. nDCG in 17 out of 20 cases. Furthermore, BRDTI was also shown to be able to predict novel drug-target interactions not contained in the original datasets. The average recall at top-10 predicted targets for each drug was 0.762, 0.560, 1.000 and 0.404 for GPCR, IC, NR, and E datasets respectively.

Conclusions: Based on the evaluation, we can conclude that BRDTI is an appropriate choice for researchers looking for an *in silico* DTI prediction technique to be used in drug-centric repositioning scenarios. BRDTI Software and supplementary materials are available online at www.ksi.mff.cuni.cz/~peska/BRDTI.

1. Introduction

Pharmaceutical science is an interdisciplinary research area comprising the findings from biology, chemistry, physics and informatics, with drug discovery being its main objective. One of the key steps in the process of drug discovery is to identify interactions between drugs and targets. Although the existence of interactions can be reliably confirmed by in vitro binding assays (e.g., [1–4]), such methods are still expensive in terms of both time and monetary value [5]. Therefore, *in silico* methods (i.e., virtual screening) can be applied to predict possible DTIs and the most promising candidates can be verified experimentally [6–10] instead of performing an exhaustive in vitro search of novel interactions. Such approach is highly valuable in various scenarios such as developing drugs for rare diseases [11], repurposing off-patent drugs [12] or drugs failed in clinical trials [13] and can significantly reduce the cost of introducing novel drugs to the market [14].

There are two major classes of *in silico* prediction methods: docking simulations and machine learning methods. Docking simulations (e.g., [6–8,10,15,16]) leverage the 3D structure of targets in order to identify potential binding sites of the compounds. Docking simulations are biologically well-accepted but time consuming and require 3D structures of targets. Furthermore, some researchers report that standard molecular docking scoring functions may be replaced by machine learning based scoring functions with improved prediction results [17,18].

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Machine learning methods in general leverage features based on the structure of drugs and targets (e.g., [9,19–21]), drugs' side-effects [22], and the knowledge of already confirmed DTIs [23–32]. In particular, in case of Bipartite Local Models (BLM) [23] and its extensions (e.g. [25,32]), prediction of each DTI is based on the neighborhood of involved drug and target. Xia et al. [26] proposed a semi-supervised approach based on Laplacian regularized least square method (RLS) with kernels derived from known DTIs (NetLapRLS). Van Laarhoven et al. [27] proposed to use regularized least squares with Gaussian interaction profile kernel (GIP). The method was later improved by incorporating weighted nearest neighbors to be able to predict interactions also for new drugs and targets (WNN-GIP) [28].

Another line of research focused on developing matrix factorization techniques for DTI prediction. The core idea is to map both drugs and targets into a shared low-dimensional latent feature space and to use this representation to calculate the probability of drug-target interactions. Matrix factorization techniques differ from one another especially in the optimization criteria, the choice of iterative optimization method and the exact inference of DTI probability. In particular, Gönen [29] proposed a kernelized Bayesian matrix factorization (KBMF) method. KBMF utilizes drugs' and targets' similarity kernels $\mathbf{K}_d$, $\mathbf{K}_t$, decomposes original DTI matrix as $\mathbf{R} \approx \mathbf{K}_d^T \mathbf{A}_d \mathbf{A}_t^T \mathbf{K}_t$ and thus considers drugs' and targets' similarity in DTI prediction. Zheng et al. [30] proposed the multiple similarities one-class matrix factorization (MSCMF) model with additive regularization based on multiple drug and target similarity matrices. Liu et al. [31] proposed neighborhood regularized logistic matrix factorization (NRLMF), with similar regularization terms as in MSCMF, however the similarity matrices were reduced via the nearest neighbor approach.

Previously mentioned approaches focused on predicting the probability of interactions between *all* unknown drug-target pairs. Another alternative is to order unknown targets for *each* drug separately according to the expected interaction probability. We will further denote it as *per-drug ranking*. Although, for the first sight, the difference might appear to be minor, it affects both the evaluation protocol as well as the internal model of prediction methods, such as the optimization criteria of matrix factorization. *Per-drug ranking* approach is in accordance with drug-centric repurposing approach as described e.g. by Liu et al. [33]. Drug-centric repurposing approach is based on discovering new interactions for an existing drug d (especially for drugs demonstrated to be safe in Phase I clinical trials, but failed in subsequent Phase II and III trials). In such cases, only the ranking of interactions with d are relevant. For similar tasks, several methods were proposed in the *personalized ranking* domain, such as BPR [34] or RankALS [35].

In this paper, we develop a DTI prediction model based on the Bayesian Personalized Ranking matrix factorization (BPR) [34]. BPR was designed to solve a ranking problem with positive-only information, which is a key challenge in the DTI prediction problem. However, other relevant circumstances of DTI prediction are not taken into account by BPR. Therefore, we extended BPR to comply with the DTI prediction setting. In particular, the proposed BRDTI is able to handle the case of new drugs and takes chemical and genetic similarities of drugs and targets and target bias into account. Note that, although we focus on the drug-centric approach, after appropriate modifications BRDTI can be utilized for disease-centric repurposing scenarios as well. To the best of our knowledge, this is the first approach to utilize a matrix factorization technique from the *personalized ranking* domain for DTI prediction and to evaluate the predicted DTIs with respect to the drug-centric repurposing scenario.

Table 1
Basic statistics of the DTI datasets used in evaluation.

Dataset:	GPCR	Ion Channel	NR	Enzymes	Kinase
Drugs	223	210	54	445	1421
Targets	95	204	26	664	156
Positive interactions	635	1476	90	2926	2798
Sparsity	97.0%	96.6%	93.6%	99.0%	98.7%
Recently confirmed interactions	618	1367	27	502	–

The main contributions of this paper are:

- BRDTI method for prediction of DTIs.
- We evaluate predictions both in terms of AUC and per-drug normalized discounted cumulative gain (nDCG). As we will discuss, the per-drug nDCG reflects the requirements of drug-centric approach for drug repositioning better than the widely-used AUC.
- Comparative evaluation of BRDTI and four state-of-the-art methods with respect to this scenario.
- Datasets of recently confirmed DTIs, extending the ones published by Yamanishi et al. [24].

2. Materials and methods

2.1. Materials

To evaluate the proposed methods, we use five benchmark datasets: G-Protein Coupled Receptors (GPCR), Ion Channels (IC), Nuclear Receptors (NR) and Enzymes (E) datasets originally published by Yamanishi et al. [24] and the Kinase (K) dataset [36]. Each of the first four datasets contains a binary interaction matrix between drugs and targets, in which each entry indicates whether the interaction between the corresponding drug and target is known or not. In contrast, Kinase contains continuous values of binding affinity for drug–target pairs. In order to produce a binary interaction matrix, we used the same cutoff threshold as Pahikkala et al. [37]. Drug-to-drug similarities were computed based on the chemical structure of the compound via the SIMCOMP algorithm (GPCR, IC, NR and E datasets) or via the 2D Tanimoto coefficients (Kinase dataset). Target-to-target similarities were computed as the normalized Smith-Waterman score of amino acid sequences of target proteins.

To verify the proposed novel DTIs predicted by the proposed methods, we also constructed the dataset of recently confirmed DTIs on the same sets of drugs and targets as in the original four dataset by Yamanishi et al. [24]. The dataset was constructed by collecting the drugs' and targets' profiles from up-to-date versions of KEGG [38], DrugBank [39] and Matador [40] databases and parsing the verified DTIs. This dataset is available in supplementary materials. Table 1 contains some basic statistics of both original and extended datasets.

2.2. Basic notation and problem formalization

In this paper, we denote the set of drugs as $D = \{d_1, \ldots, d_n\}$ and the set of targets as $T = \{t_1, \ldots, t_m\}$, where n and m are the number of drugs and targets respectively. The $n \times m$ matrix $\mathbf{R}$ represents known drug-target interactions. $\mathbf{R}$ is a binary matrix with entries $r_{i,j} = 1$ denoting that a drug d_i has been experimentally verified to interact with a target t_j, otherwise: $r_{i,j} = 0$. The matrix $\mathbf{S}^D \in \mathbb{R}^{n \times n}$ represents drug similarity. Each element $s^D_{i,k}$ contains the similarity between drugs d_i and d_k. Analogically, the matrix $\mathbf{S}^T \in \mathbb{R}^{m \times m}$ represents target similarity.

We further define sets of novel drugs D^N and targets T^N as the drugs (targets) without any known interaction: $D^N = \{d_i \in D;\ \sum_{j=1}^{m} r_{i,j} = 0\}$, $T^N = \{t_j \in T;\ \sum_{i=1}^{n} r_{i,j} = 0\}$.

Matrix factorization methods aim to map both drugs and targets into a shared latent space, where f denotes its dimension (number of latent factors), $\mu_i \in \mathbb{R}^f$ denotes the latent factors of drug d_i and $\nu_j \in \mathbb{R}^f$ denotes the latent factors of target t_j. We further define $\mathbf{U} \in \mathbb{R}^{n \times f}$ as the matrix of all drugs' latent factors and $\mathbf{V} \in \mathbb{R}^{m \times f}$ as the matrix of all targets' latent factors. The predicted probability of interaction $\hat{r}_{i,j}$ between drug d_i and target t_j is defined as the dot product of its latent factors $\hat{r}_{i,j} := \mu_i \times \nu_j^T$, thus the matrix of predicted DTIs $\hat{\mathbf{R}}$ can be inferred as $\hat{\mathbf{R}} = \mathbf{U}\mathbf{V}^T$. We further define the *per-drug* training set as the set of triples $D_s \subset D \times T \times T$, $D_s := \{(d_i, t_j, t_k): r_{i,j} = 1 \wedge r_{i,k} = 0\}$.

We consider the problem of DTI prediction from the perspective of drug-centric repositioning scenario. Thus, the objective for the DTI prediction method is as follows:

- For arbitrary fixed drug $d \in D$, provide total ordering of all considered targets $<_d$ such that top-ranked targets should interact with the drug d with the highest probability.

2.3. Bayesian personalized ranking matrix factorization

In this section we describe the BPR method [34] in the context of DTI prediction. BPR aims to optimize *per-drug ranking* by reducing it to pairwise classification of interacting and non-interacting targets. Optimization criterion is based on correctness of the pairwise classification and maximized via stochastic gradient descend with bootstrap sampling of training points.

More specifically, the Bayesian formulation of finding correct per-drug ranking of all targets $t \in T$ is to maximize posterior probability:

$$p(\Theta \mid >_d) \propto p(>_d|\Theta)\ p(\Theta)$$

where Θ represents parameters of matrix factorization. The $>_d$ is desired, but latent ordering, specific for the drug d. BPR method further assumes independency of drugs on each other, independency of ordering pairs of targets on any other pairs, totality and antisymmetry of the ordering. Hence, the drug-specific likelihood function $p(\Theta \mid >_d)$ can be combined for all drugs as follows:

$$\prod_{d \in D} p(>_d|\Theta) = \prod_{(d,t_j,t_k) \in D_s} p(t_j >_d t_k|\Theta)$$

The individual probability that drug d interacts with target t_j rather than with t_k is defined as follows:

$$p\left(t_j >_d t_k|\Theta\right) := \sigma\left(\hat{r}_{d,j,k}(\Theta)\right)$$

where σ is the logistic sigmoid function $\sigma(x) := 1/(1+e^{-x})$ and $\hat{r}_{d,j,k}(\Theta)$ is a real-valued evaluation function of the underlying model, capturing the relationship between drug d, target t_j and target t_k. For matrix factorization, the natural definition of $\hat{r}_{d,j,k}$ is to substract predicted ratings of known and unknown interaction: $\hat{r}_{d,j,k} := \hat{r}_{d,j} - \hat{r}_{d,k}$ and model parameters Θ are the latent factors of drugs and targets: $\Theta = (\mathbf{U}, \mathbf{V})$. BPR method further assumes the prior density of model parameters to be of normal distribution with zero mean $p(\Theta) \sim N(0, \lambda_\theta I)$, where λ_θ is a model specific regularization parameter. Thus the optimization criterion BPR-OPT can be derived as follows:

$$\begin{aligned}
\text{BPR} - \text{OPT} :&= \ln p(\Theta \mid >_d) \\
&= \ln p(>_d|\Theta)\ p(\Theta) \\
&= \ln \prod_{(d,t_j,t_k) \in D_s} p(t_j >_d t_k|\Theta) p(\Theta) \\
&= \sum_{(d,t_j,t_k) \in D_s} \ln\ \sigma\left(\hat{r}_{d,j,k}(\Theta)\right) + \ln\ p(\Theta) \\
&= \sum_{(d,t_j,t_k) \in D_s} \ln\ \sigma\left(\hat{r}_{d,j,k}(\Theta)\right) - \lambda_\theta \|\Theta\|^2 \\
&= \sum_{(d_i,t_j,t_k) \in D_s} \ln\ \sigma\left(\hat{r}_{i,j} - \hat{r}_{i,k}\right) - \lambda_R\left(\|\mathbf{U}\|^2 + \|\mathbf{V}\|^2\right)
\end{aligned}$$

2.4. Modifying BPR for DTI prediction

Although there is a certain level of similarity between DTI prediction problem and the personalized ranking in preference learning, these problems differ in several important aspects. First, some well-founded metrics of drugs' and targets' similarity were proposed (e.g., [24,36]) and the underlined latent space model should reflect those similarities. Furthermore, DTI prediction methods should be able to provide predictions also for drugs and targets without any known interactions. The rest of this section provides insight on how we extended BPR in order to comply with these requirements.

2.4.1. Content alignment for BPR

We note that drugs and targets are not independent and we can define similarity matrices $\mathbf{S}^D$,$\mathbf{S}^T$ describing relations between drugs and targets respectively. The aim of content alignment is to reflect the aforementioned similarities during the matrix decomposition process. Therefore, we extend the BPR optimization criterion by an additive regularization based on the similarity of objects (drugs and targets) and its latent factors. Using the work of Nguyen and Zhu [41], we implemented a regularization based on the squared norm of the latent factors distance. The regularization was applied on both the drug, the interacting target and the non-interacting target of training set entries $(d_i,t_j,t_k) \in D_s$. The optimization term CA for the training set entry $(d_i,t_j,t_k) \in D_s$ is as follows:

$$\text{CA} = \lambda_C \left(\sum_{\bar{i}=1}^{n} \mathbf{S}^D_{i,\bar{i}} \left\| \mu_i - \mu_{\bar{i}} \right\|^2 + \sum_{\bar{j}=1}^{m} \mathbf{S}^T_{j,\bar{j}} \left\| \nu_j - \nu_{\bar{j}} \right\|^2 + \mathbf{S}^T_{k,\bar{j}} \left\| \nu_k - \nu_{\bar{j}} \right\|^2 \right)$$

However, our intention is to impose the latent factors' similarity only on highly similar drugs or targets as the large volume of objects with low similarity could significantly bias the results. In order to achieve this, the similarity matrices $\mathbf{S}^D$ and $\mathbf{S}^T$ were reduced to contain only the top-k most similar neighbors to each drug and target. In order to keep the model simple, we empirically define $k = 5$. This approach is in line with the one used by Liu et al. [31] and in addition to the performance improvements, it also increases computational efficiency.

2.4.2. Adding target bias to BPR

In preference learning, much of the observed variation can be attributed to the latent effects associated solely with the objects, independent of their interactions [42]. Such effects may be captured by bias terms in the prediction model. In DTI datasets some targets have higher number of interactions than others, thus their probability to interact with a drug is higher in general. To cope with this effect, we incorporated target bias into the optimization criteria and DTI prediction. Denoting the bias of target t_j as b_j and the vector of all biases as $\boldsymbol{b}$, the biased optimization criteria BPR-OPT$_{\text{bias}}$ and biased DTI prediction $\hat{r}_{i,j,\boldsymbol{b}}$ can be defined as follows.

$$\begin{aligned}
\hat{r}_{i,j,\boldsymbol{b}} &= b_j + \mu_i \times \nu_j^T \\
\text{BPR} - \text{OPT}_{\text{bias}} &= \sum_{(d_i,t_j,t_k) \in D_s} \ln\ \sigma\left(\hat{r}_{i,j,\boldsymbol{b}} - \hat{r}_{i,k,\boldsymbol{b}}\right) \\
&\quad -\lambda_R\left(\|\mathbf{U}\|^2 + \|\mathbf{V}\|^2 + \|\boldsymbol{b}\|^2\right)
\end{aligned}$$

Algorithm 1 Optimization of BRDTI method.

Function Optimize_BRDTI
Input: f, η, λ_R, λ_C, max_*iterations*, k, $\mathbf{R}$, $\mathbf{S}^D$, $\mathbf{S}^T$
Output: $\hat{\mathbf{R}}$
1:**Initialize U, V, *b***
2:**Alter** $\mathbf{S}^D$, $\mathbf{S}^T$ to contain only top-k closest neighbors for each item
3:**Repeat:**
4: **Foreach** (d_i, t_j): $r_{i,j} = 1$:
5: **Draw** random t_k: $r_{i,k} = 0$
6: **Update** $b_j, b_k, \boldsymbol{\mu}_i, \boldsymbol{\nu}_j, \boldsymbol{\nu}_k$
7: **end foreach**
8:**Until** max_*iterations* is reached

$$= \sum_{(d_i,t_j,t_k)\in D_s} \ln\ \sigma\left(b_j + \hat{r}_{i,j} - \left(b_k + \hat{r}_{i,k}\right)\right) - \lambda_R\left(\|\mathbf{U}\|^2 + \|\mathbf{V}\|^2 + \|\boldsymbol{b}\|^2\right)$$

2.4.3. DTI prediction for novel drugs and targets

In case of the novel drugs $d \in D^N$ and targets $t \in T^N$ with no known interaction, BPR method can only learn their latent factors through negative examples (unknown DTIs). However, as those DTIs are not confirmed to be negative (in fact, some of them are actually confirmed DTIs, hidden during the training phase), learning from negative-only information inevitably corrupts the model. In order to overcome this problem, we use neighborhood-based approach for novel drugs and targets. After the training phase, latent factors and biases of each novel drug $d_i \in D^N$ and novel target $t_j \in T^N$ are approximated by the linear combination of its neighbors' latent factors:

$$\mu_i = \frac{\sum_{\tilde{i}\neq i} \mathbf{S}^D_{i,\tilde{i}}\mu_{\tilde{i}}}{\sum_{\tilde{i}\neq i} \mathbf{S}^D_{i,\tilde{i}}}; \quad \nu_j = \frac{\sum_{\tilde{j}\neq j} \mathbf{S}^T_{j,\tilde{j}}\nu_{\tilde{j}}}{\sum_{\tilde{j}\neq j} \mathbf{S}^T_{j,\tilde{j}}}; \quad b_j = \frac{\sum_{\tilde{j}\neq j} \mathbf{S}^T_{j,\tilde{j}} b_{\tilde{j}}}{\sum_{\tilde{j}\neq j} \mathbf{S}^T_{j,\tilde{j}}}$$

2.4.4. BRDTI method

To sum up, we propose *Bayesian Personalized Ranking Prediction of Drug-Target Interactions* (BRDTI) method, which is assembled as follows. The original BPR method's regularization is extended with content alignment CA, biased DTI prediction formula $\hat{r}_{i,j,\boldsymbol{b}}$ is used and in case of novel drug or target, neighborhood-based approximation is applied. The final BRDTI optimization criterion is:

$$\text{BRDTI} - \text{OPT} = \sum_{(d_i,t_j,t_k)\in D_s} \ln\ \sigma\left(b_j + \hat{r}_{i,j} - \left(b_k + \hat{r}_{i,k}\right)\right) - \lambda_R\left(\|\mathbf{U}\|^2 + \|\mathbf{V}\|^2 + \|\boldsymbol{b}\|^2 + \text{CA}\right)$$

Bootstrapped stochastic gradient ascend is used to maximize the BRDTI-OPT criterion. Update rules for each parameter are as follows:

$$b_j = b_j + \eta\left(x - \lambda_R b_j\right)$$

$$b_j = b_j + \eta\left(x - \lambda_R b_j\right)$$

$$\mu_i = \mu_i + \eta\left(x \cdot \left(\nu_j - \nu_k\right) - \lambda_R\mu_i - \lambda_R\lambda_C\left(\mathbf{S}^D_i\mu_i - \sum_{\tilde{i}=1}^{n} \mathbf{S}^D_{i,\tilde{i}}\mu_{\tilde{i}}\right)\right)$$

$$\nu_j = \nu_j + \eta\left(x \cdot \mu_i - \lambda_R\nu_j - \lambda_R\lambda_C\left(\mathbf{S}^T_j\nu_j - \sum_{\tilde{j}=1}^{m} \mathbf{S}^T_{j,\tilde{j}}\nu_{\tilde{j}}\right)\right)$$

$$\nu_k = \nu_k + \eta\left(x \cdot (-\mu_i) - \lambda_R\nu_k - \lambda_R\lambda_C\left(\mathbf{S}^T_k\nu_k - \sum_{\tilde{j}=1}^{m} \mathbf{S}^T_{k,\tilde{j}}\nu_{\tilde{j}}\right)\right)$$

where $x = \sigma\left(b_j + \hat{r}_{i,j} - (b_k + \hat{r}_{i,k})\right)$ and hyperparameters η, λ_R and λ_C are learning rate, general regularization and content alignment regularization respectively. Algorithm 1 contains pseudocode of the proposed method.

Table 2
Per-drug nDCG for unknown DTIs prediction. The best results and the results without a significant difference to it ($p < 0.05$ according to paired t-test) are in bold.

Per-drug nDCG	BLM-NII	WNN-GIP	NetLapRLS	CMF	BRDTI
GPCR	0.887	0.890	0.917	0.910	**0.929**
Ion Channels	0.928	0.895	0.930	**0.954**	**0.953**
Nuclear Receptors	0.919	0.920	**0.941**	0.910	**0.948**
Enzymes	0.872	0.860	0.871	0.873	**0.897**
Kinase	0.470	0.289	0.670	**0.694**	**0.690**

2.5. Normalized discounted cumulative gain

As we consider DTI prediction to be a *per-drug ranking* problem, we evaluate ranked lists for each drug separately and use normalized discounted cumulative gain (*nDCG*) as evaluation metric, which was shown to be the best graded relevance ranking metric with respect to the stability and sensitivity [43]. For the ranked list p DCG is calculated as follows:

$$DCG(p) = \sum_{i=1}^{|p|} \frac{r_i}{\log_2(i+1)}$$

where r_i denotes the relevance of its ith element. In our case $r_i = 1$ or $r_i = 0$ depending on whether the interaction corresponding to this element of the list is contained in the test set. The normalization is done by dividing the DCG by the DCG of the ideal ordering of the same size. Thus $nDCG \in [0, 1]$; higher values indicate better performance.

There are several advantages of using nDCG as evaluation metric for DTI.

1) Each position in the ranked list is associated with a gradually decreasing weight, reflecting the potential impact of relevant object placed on the respective position. This reflects well the drug repositioning scenario, where confirmation of each further candidate DTI is both temporally and monetarily expensive.
2) nDCG may use graded relevance characteristics, allowing to distinguish DTIs with higher potential impact from the others.
3) nDCG can be naturally truncated to consider only top-k objects and thus reflect the scenario, where exhaustive validation of all proposed DTIs is not possible and we can only verify several predicted DTIs.

3. Evaluation and results

Similarly as in previous studies (e.g., [30]), the performance of BRDTI method was evaluated via five times repeated 10-fold cross-validation (5×10-fold CV). In each of the five repetitions, we randomly assign known DTIs to one out of ten splits. Then, we run 10-fold CV. In each of the ten iterations of 10-fold CV, a different split is used as test set, while the remaining splits are used as training set (matrix R). We adopted normalized discounted cumulative gain (nDCG) as an evaluation metric and evaluate the results in a per-drug fashion. We report the average nDCG values over all drugs and CV runs and denote it as *per-drug nDCG*. In order to remain comparable with previous studies, we also provide results in terms of AUC.

The proposed BRDTI method was compared with four state of the art approaches: BLM-NII [25], WNN-GIP [28], NetLapRLS [26] and CMF [30]. Grid-search was used to tune methods' hyperparameters, details can be found in supplementary materials.

3.1. Results

Table 2 shows results in terms of nDCG. BRDTI method achieved the best results on GPCR, Nuclear Receptors and Enzymes datasets

Table 3
AUC for unknown DTIs prediction. The best results and the results without a significant difference to it ($p < 0.05$ according to paired *t*-test) are in bold.

AUC	BLM-NII	WNN-GIP	NetLapRLS	CMF	BRDTI
GPCR	0.943	0.931	0.799	0.938	**0.955**
Ion Channels	0.980	0.955	0.864	**0.981**	**0.982**
Nuclear Receptors	0.902	0.894	0.847	0.846	**0.923**
Enzymes	0.971	0.960	0.960	0.960	**0.981**
Kinase	0.850	0.657	0.764	**0.937**	0.914

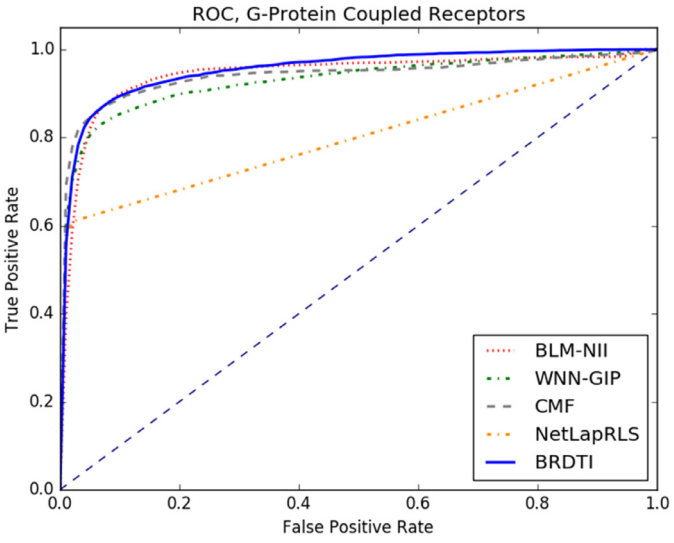

Fig. 1. ROC curves of the evaluated DTI prediction methods on GPCR dataset.

Table 4
Per-drug nDCG for unknown DTIs prediction – comparing variants of BPR with BRDTI. The best results and the results without a significant difference to it ($p < 0.05$ according to paired *t*-test) are in bold.

Per-drug nDCG	BPR	BPR-NA	BPR-CA	BPR-NA-CA-F	BRDTI
GPCR	0.865	0.909	0.887	0.866	**0.929**
Ion Channels	0.915	0.942	0.934	0.929	**0.953**
Nuclear Receptors	0.906	**0.944**	0.920	0.928	**0.948**
Enzymes	0.824	0.887	0.838	0.816	**0.897**

and second best (without significant difference) on Ion Channel and Kinase datasets. In pairwise comparison (paired *t*-test, $p < 0.05$), BRDTI significantly outperformed its competitors in 17 out of 20 cases w.r.t. nDCG. Table 3 shows the results in terms of AUC. BRDTI achieved the best results w.r.t. AUC except on Kinase dataset, where it ended second. BRDTI significantly outperformed its competitors in 18 out of 20 cases w.r.t. AUC. The performance of the methods is further illustrated in Fig. 1 by ROC curves on the GPCR dataset. Other datasets exhibited similar ROC curves and thus we omit them. We can conclude that BRDTI can be successfully applied to predict DTIs for existing drugs.

Table 4 shows the results of nDCG for several variants of the BPR algorithm. The evaluated variants are:

- Original BPR algorithm without further modifications (BPR)
- BPR with neighborhood approximation for new drugs and targets (BPR-NA)
- BPR with content alignment (BPR-CA)
- BPR with neighborhood approximation and content alignment performed on full $\mathbf{S}^D$and $\mathbf{S}^T$ matrices (BPR-NA-CA-F)
- Final BRDTI method

Described variants represent design choices made during BRDTI assembling and the results support our decisions as BRDTI significantly outperformed the other approaches.

3.2. Predicting recently confirmed DTI

In this section, we illustrate that BRDTI not only achieves high accuracy in terms of nDCG and AUC, but its predictions are biologically feasible as well. Note that the drug–target interactions contained in the Enzyme, Ion Channel, GPCR and NR datasets were extracted several years ago and they have been kept unchanged to allow comparison between DTI prediction methods. Further interactions between the same drugs and targets have been confirmed recently (i.e., after the publication of the original datasets). Our intention is to demonstrate that BRDTI is a viable method for disclosing unknown interactions as it is capable of predicting the aforementioned recently confirmed interactions by learning from those interactions that were known previously (i.e., from interactions contained in the original datasets). Therefore, we trained BRDTI and its competitors using all the interactions of the original datasets, predict per-drug ranking of all unknown drug-target pairs and compare the predictions with the list of recently confirmed DTIs. Fig. 2 illustrates the approach.

We validated predicted interactions in up-to-date versions of KEGG, DrugBank and Matador databases. Overall, 2514 recently confirmed DTI were found. However, for a substantial portion of drugs (61%), there were no recently confirmed interactions and thus they were excluded. Table 5 depicts the results w.r.t. top-10 considered targets for each drug. BRDTI performs the best, closely followed by NetLapRLS. Performance of CMF is considerably lower compared to the results in the original datasets.

3.3. Drug repurposing based on the DTI predictions

Next, we will illustrate that the predictions of BRDTI may contribute to promising therapeutic hypotheses. As an example, we point out that we predicted the validated interaction between Pentazocine (D00498) and Opioid receptor kappa1 (hsa4986). The receptor is distributed in various parts of the brain, and Pentazocine is indeed used as an analgetic. For Parkinson disease, recent studies proposed the examination of glutamate metabotropic receptor 4 (GRM4, hsa2914) positive allosteric modulators as supplementary treatment [44–47]. While Eglumetad (D03966) is known to have antianxiety activity and to be a glutamate metabotropic receptor 2 (GRM2, hsa2912) agonist, we predicted Eglumetad to interact with GRM4 as well. As Parkinson patients often have anxiety, it would be interesting to examine Eglumetad as a supplementary therapy in Parkinson patients with anxiety.

Finally, we point out that Lipoyltransferase 1 gene (LIPT1) defects cause Leigh disease [48] and, in case of severe defects, fatal lactic acidosis [49,50]. We hypothesize that in some cases of LIPT mutations, an agonist could help to increase enzymatic activity. We predicted Biotin (D00029) to interact with LIPT1 (hsa51601). Biotin is transported across the blood-brain barrier and it was proposed as a treatment of multiple sclerosis previously [51]. Based on our aforementioned prediction, it would be interesting to examine Biotin as a potential therapy for LIPT1 mutations as well.

4. Discussion

This paper considers the problem of DTI predictions for drug-centric repositioning approach. We pointed out that such an approach may benefit from carefully optimized ranking of possible targets for a specific drug and presented a novel DTI prediction method, BRDTI. The novelty of the method comes from applying *per-drug* ranking optimization criteria, while projecting drugs and targets to the shared latent space. Furthermore, content alignment of latent vectors is applied for similar drugs and targets, unknown drugs and targets are blended via its neighbors and target bias is applied. BRDTI method was extensively evaluated over five datasets

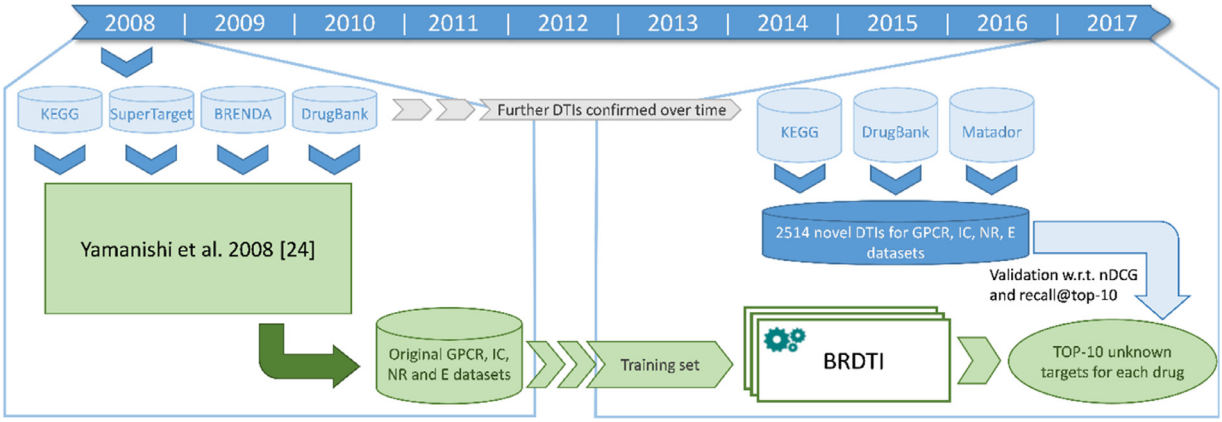

Fig. 2. Evaluation workflow using recently confirmed DTIs.

Table 5
Prediction of novel DTIs – top-10 predictions for each drug. In each column, the values represent *nDCG* and *recall@top-10* respectively. The best results and the results without a significant difference to it ($p < 0.05$ according to paired t-test) are in bold.

nDCG / recall@top-10	BLM-NII	WNN-GIP	NetLapRLS	CMF	BRDTI
GPCR	0.704 / **0.740**	0.640 / 0.635	**0.738** / **0.730**	0.635 / 0.677	**0.765** / **0.762**
Ion Channels	0.479 / 0.486	0.408 / 0.361	**0.552** / 0.512	0.356 / 0.366	**0.566** / **0.560**
Nuclear Receptors	**0.744** / **0.962**	0.613 / 0.808	**0.807** / **1.000**	**0.796** / **0.992**	**0.826** / **1.000**
Enzymes	**0.328** / 0.351	0.250 / 0.259	**0.354** / **0.382**	0.030 / 0.066	**0.356** / **0.404**

together with four state-of-the-art approaches. Overall, BRDTI performed the best with respect to *per-drug* nDCG as well as AUC. We also evaluated BRDTI predictions on recently confirmed interactions. Also in this case, BRDTI method achieved very good results and confirmed to be suitable for future predictions. Note that substantial decrease in performance of all methods in Enzymes dataset can be explained by the ratio between recently confirmed DTIs and all unknown interactions in the original dataset. Whereas for Enzymes dataset, there were only 502 recently confirmed DTIs (0.17% of all unknown DTIs), the ratio was an order of magnitude higher for the other three datasets (3.0% for GPCR, 3.3% for IC and 2.1% for NR). Generally, there is relatively large overlap in the method's ranked lists. However, in several occasions, BRDTI was the only method able to predict any confirmed DTIs for a specific drug, e.g., connection of *Trimethoprim* (D00145) - *Thymidylate synthetase* (hsa:7298) and *Chlorothiazide* (D00519) - *Renin* (hsa:5972).

However, results of recently confirmed DTI prediction also illustrate that there is still room for improvement as some of the new interactions were neglected by all evaluated methods. This can be illustrated on the example of *Haldol* (D00136), for which 10 new interactions are known, however none of the evaluated method listed any of these interactions into the top-10 predictions. As there were neither strong similarities between original and new targets, nor substantial collaborative information through similar drugs, it is important to define and incorporate further concepts of similarity into the prediction models (e.g., [52,53]).

The full list of DTIs predicted by BRDTI method can be found in supplementary materials. Also, note that BRDTI source codes can be easily modified to run BRDTI on further datasets, see also the instructions in the supplementary materials.

Success of BRDTI method encourages us to test further ranking methods, e.g., RankALS [35] for DTI prediction task. Furthermore, it would be interesting to develop DTI prediction techniques that are able to take specific conditions (temperature, cell type or subtype, presence or absence of a disease, etc.) into account and make DTI predictions for those conditions. For example, Wenzel et al. [54] reported that their bimetallic cytotoxic complexes were shown to be easily taken up by cancer cells at 37 °C, whereas experiments at 4 °C showed no uptake. Incorporation of the aforementioned conditions into DTI prediction methods, in order to allow for more specific predictions, is left for future work.

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Supplementary materials

Supplementary material associated with this article can be found, in the online version, at doi:10.1016/j.cmpb.2017.09.003.

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