Chem Biol Drug Des 2015; **85:** 137–144

Research Article

Drug Repurposing Based on Drug–Drug Interaction

Bin Zhou[1,2], Rong Wang[1,2], Ping Wu[3] and De-Xin Kong[1,2,*]

[1]*State Key Laboratory of Agricultural Microbiology, Huazhong Agricultural University, Wuhan 430070, China*
[2]*Center for Bioinformatics, College of Life Science and Technology, Huazhong Agricultural University, Wuhan 430070, China*
[3]*College of Science, Huazhong Agricultural University, Wuhan 430070, China*
**Corresponding author: De-Xin Kong, dxkong@mail.hzau.edu.cn*

Given the high risk and lengthy procedure of traditional drug development, drug repurposing is gaining more and more attention. Although many types of drug information have been used to repurpose drugs, drug–drug interaction data, which imply possible physiological effects or targets of drugs, remain unexploited. In this work, similarity of drug interaction was employed to infer similarity of the physiological effects or targets for the drugs. We collected 10 835 drug–drug interactions concerning 1074 drugs, and for 700 of them, drug similarity scores based on drug interaction profiles were computed and rendered using a drug association network with 589 nodes (drugs) and 2375 edges (drug similarity scores). The 589 drugs were clustered into 98 groups with Markov Clustering Algorithm, most of which were significantly correlated with certain drug functions. This indicates that the network can be used to infer the physiological effects of drugs. Furthermore, we evaluated the ability of this drug association network to predict drug targets. The results show that the method is effective for 317 of 561 drugs that have known targets. Comparison of this method with the structure-based approach shows that they are complementary. In summary, this study demonstrates the feasibility of drug repurposing based on drug–drug interaction data.

Key words: drug development, drug repurposing, drug-drug interaction, target prediction

Abbreviations: ATC, anatomical therapeutic chemical; DDI, drug–drug interaction; DIP, drug interaction profile.

Received 3 April 2014, revised 6 June 2014 and accepted for publication 10 June 2014

Drug development is a grueling process, which costs large amounts of money and time. During the process, numerous candidate drugs cannot successfully reach the market due to their side-effects. To solve this problem, researchers have put forward many approaches for predicting the toxicity of a candidate drug (1). Provided that a candidate drug is predicted to be harmful to humans, it will be removed from drug development pipeline before clinical trials. Nevertheless, there are still many problems unsolved concerning drug toxicity prediction (2). As a consequence, alternatively many scientists propose repurposing existing drugs toward new indications for the reason that launched drugs are generally safe (3). Drug repurposing not only reduces the risk of drug adverse reactions, but also greatly shortens drug development pipeline and saves costs (3). Of those methods for drug repurposing, using drug similarity to establish the relationships among drugs and thus to repurpose drugs has caught much attention (4). The underlying assumption is that if two drugs are in some way similar enough, then they are likely to share targets and physiological effects, thus having the potential to treat the same diseases. Drug similarity can be evaluated from many aspects and by many measures (4). For instance, chemical structural similarity has been widely applied to drug target prediction (5). On the other hand, phenotypic similarity [similarity between the effects of drugs on organisms at various levels, e.g., at gene expression level (6) or at whole organism level (7)] has also emerged as a relatively new approach for inferring drug targets. Additionally, Cheng *et al.* (8) combined structural similarity with phenotypic similarity to predict polypharmacological profiles for existing drugs. Although a great deal of drug information has been used for drug repurposing, there are still many resources unexploited.

Among the hitherto unexploited resources, drug–drug interaction (DDI) information can help us repurpose drugs toward new indications. When a drug influences the effects of another drug, interaction between them occurs, which is referred to as DDI. DDI data may contain the information on drug targets or physiological effects.

In this study, we utilized drug interaction profiles (DIPs) of drugs to compute drug similarity scores and built a drug association network. DIP for a particular drug refers to the set composed of all drugs that interact with this drug. Based on the network, some interesting phenomena could be observed. For example, drugs with similar physiological effects tend to cluster together. The ability of this network to predict targets for drugs was preliminarily validated. Therefore, this network has many applications, including identifying drug targets and drug effects. These provide new insights into drug repurposing.

© 2014 John Wiley & Sons A/S. doi: 10.1111/cbdd.12378

17470285, 2015, 2, Downloaded from https://onlinelibrary.wiley.com/doi/10.1111/cbdd.12378 by Tu Muenchen Bibliothek, Wiley Online Library on [01/12/2022]. See the Terms and Conditions (https://onlinelibrary.wiley.com/terms-and-conditions) on Wiley Online Library for rules of use; OA articles are governed by the applicable Creative Commons License

Methods and Materials

Data collection

Drug–drug interaction, drug structure, drug Anatomical Therapeutic Chemical (ATC) code (9), and drug target data were collected from DrugBank (10). There were a total of 6711 drugs in the database. After removing drugs without DDI information, 1074 drugs were left, with 10 835 DDIs. To guarantee the reliability of the data for drug similarity computation, only 700 drugs that interact with at least six other drugs were retained for further analysis.

Similarity computation based on DDI

Drug similarity was calculated based on their DIPs using weighted Tanimoto similarity coefficient (11), which formed a symmetric similarity matrix. Provided that A and B are two drugs of interest, then their similarity score S(A,B) = SI (A,B)/SU(A,B). Here, SI(A,B) refers to score of I(A,B) (intersection of DIPs of A and B, namely the set consisting of all drugs that interact with both A and B). SU(A,B) refers to score of U(A,B) (union of DIPs of A and B, that is, the set consisting of all drugs that interact with at least one of A and B). Figure 1 illustrates the process of similarity score calculation.

When comparing two DIPs, some cautions must be noticed, especially the contribution of every individual element in DIP (which refers to a particular drug) to drug similarity judgment. Specifically, some drugs have many interacting partners, while others may interact with just a few drugs. For example, if drug X can strongly inhibit a particular cytochrome P450 enzyme, it may interact with the drugs that are metabolized by this enzyme. This is because the interference of these drugs' metabolism elongates the duration of their action and potentiates their effects. Drug X could have multiple interacting drugs, so even if two drugs both interact with X, the two drugs are not necessarily similar. On the other hand, if a drug interacts with mere two drugs, then these two drugs are more likely to be similar. Therefore, different elements in DIP (i.e., different drugs) may contribute differently to drug similarity judgment. Based on this, a corresponding weight was assigned to every element in DIP when computing drug similarity scores. The weight of a particular element was set to the reciprocal value of the number of the drugs, which interact with this drug (this element).

Here, we did not discriminate between synergistic and antagonistic DDIs. In our opinion, both types of DDIs contain the information on drug target. Moreover, currently DDI information is limited. Distinguishing between the two kinds of DDIs will further reduce usable data for the construction of drug association network. Therefore, it is appropriate to integrate these two types of DDIs and not discriminate between them when calculating drug similarity.

Drug association network

After calculating all similarity scores, only the drug–drug pairs with a similarity score above a threshold were retained, which formed a drug association network with nodes representing drugs and edges representing drug–drug similarity scores between the two connected drugs. The threshold was set to 0.3, which retained approximately 1% of the total similarity scores (edges). The network was rendered with Cytoscape v2.8.2 by Force-Directed BioLayout, with the edges being weighted by 1—similarity scores (12). Subsequently, the drugs were clustered using Markov Clustering Algorithm (performed with clusterMaker-1.9 plugin for Cytoscape) with edge weights

	Interaction profile
A	C, D, G
B	C, D, M
I(A,B)	C, D
U(A,B)	C, D, G, M

	No. of interacting drugs	Weight
C	3	1/3
D	3	1/3
G	6	1/6
M	6	1/6

	Score	Formula
SI(A,B)	1/3 + 1/3	Weight(C) + Weight(D)
SU(A,B)	1/3 + 1/3 + 1/6 + 1/6	Weight(C) + Weight(D) + Weight(G) + Weight(M)
S(A,B)	2/3	SI(A,B) / SU(A,B)

Figure 1: An instance for computing the similarity score between drugs A and B using their drug interaction profiles. Imagine that two drugs (A and B) possess the given two drug interaction profiles, respectively. Then, their intersection I(A,B) is the set of C and D, while their union U(A,B) is the set of C, D, G, and M. Combining this with the weights of C, D, G, and M (1/3, 1/3, 1/6, 1/6, respectively), it can be known that SI(A,B) and SU(A,B) are 2 of 3 (1/3 + 1/3) and 1 (1/3 + 1/3 + 1/6 + 1/6), respectively. Finally, it is concluded that S(A,B), namely similarity score between A and B, is 2 of 3.

17470285, 2015, 2, Downloaded from https://onlinelibrary.wiley.com/doi/10.1111/cbdd.12378 by Tu Muenchen Bibliothek, Wiley Online Library on [01/12/2022]. See the Terms and Conditions (https://onlinelibrary.wiley.com/terms-and-conditions) on Wiley Online Library for rules of use; OA articles are governed by the applicable Creative Commons License

being set to similarity scores (13). Nodes were colored according to ATC codes of drugs (conducted by nodeCharts-0.94 plugin for Cytoscape). ATC Classification System is proposed by World Health Organization (WHO) for the classification of drugs. ATC code shows the function, pharmacology, and chemical structure of a particular drug.

Target prediction based on DDI

In the drug association network, each drug is associated with one or more drugs, which may suggest that they share targets. In addition, as recorded in DrugBank, nearly all drugs in the network (561 in 589) have one or more targets. Thus, known targets of a drug can be assigned to its associated drugs, which can reveal new drug–target relationships. Here, we proposed an approach for scoring and prioritizing the degree of match between each drug and its possible targets. The approach is illustrated in Figure 2.

To evaluate the capability of this approach for drug target prediction, for the 561 drugs that have known protein targets, we examined the rankings of every drug's all known targets in its predicted target list. Rank value (R) of a drug was defined as the highest ranking of its known targets. Obviously, a lower R means a better prediction. Of note, a right prediction occurs when $R = 1$. If no known targets of a particular drug exist in its predicted target list, R of this drug was set to 1000.

	Similarity	Drug	Targets
A	0.4	B	f, g
A	0.5	C	k, e
A	0.6	D	f

	Protein	Match score	Formula
A	f	1.0	S(A,B) + S(A,D)
A	k	0.5	S(A,C)
A	e	0.5	S(A,C)
A	g	0.4	S(A,B)

Figure 2: An instance of the method for predicting targets for drug A. In the upper table, A is connected to three drugs (B, C, and D) with similarity scores being 0.4, 0.5, and 0.6, respectively. Targets for B, C, and D are also given in the last column. The prioritized predicted target list for drug A can be obtained, in which A is associated with protein f, k, e, and g in order of match score. Detailed computation procedures are as follows: (i) all protein targets of the drugs that are connected to A in the network are collected; (ii) for A and each protein collected, the upper table is searched for the rows where A and the protein both exist; (iii) similarity scores of the retrieved rows are summed up, giving the match score of A and this protein; (iv) the possible targets for A are ranked in order of match score.

Target prediction based on chemical structure

Of the 700 drugs that interact with at least six other drugs, 676 are suitable to perform structural similarity computation. We calculated the similarity scores between the 676 drugs based on chemical structure using ECFP_4 fingerprint (14) and Tanimoto coefficient as similarity measure. To compare the two methods (namely based on structure or DDI) for target prediction, we retained merely the similarity scores that were above a threshold so that the ratio of remaining scores is similar to that of DDI-based method (2375/244 650). These similarity scores could also form a network similar to the drug association network based on DDI. Then, this network based on structure was employed to predict drug targets in the same manner as drug association network (refer to section 'Target prediction based on DDI'). The predicted targets could also be compared with the known targets in DrugBank (see section 'Target prediction based on DDI'), which could assist in assessing the performance of the target prediction method based on chemical structure.

Results

Distribution of drug interacting partner number

Number of interacting drugs may differ considerably among different drugs. Therefore, the distribution of drug interacting partner number was analyzed to get a systematic knowledge of DDIs. Figure 3 demonstrates that drug interacting partner number follows power law distribution with $r^2 = 0.8345$. As can be seen, most drugs interact with few other drugs, while only a small number of drugs interact with many other drugs. This result illustrates why a weight should be separately assigned to every drug in DIP.

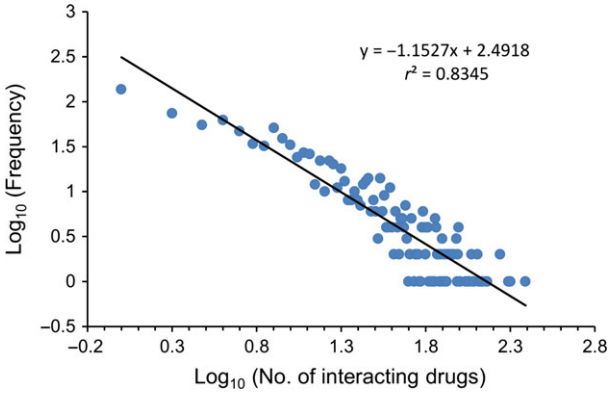

Figure 3: Distribution of drug interacting partner number. The number is fit to power law distribution, as indicated by the straight line.

17470285, 2015, 2, Downloaded from https://onlinelibrary.wiley.com/doi/10.1111/cbdd.12378 by Tu Muenchen Bibliothek, Wiley Online Library on [01/12/2022]. See the Terms and Conditions (https://onlinelibrary.wiley.com/terms-and-conditions) on Wiley Online Library for rules of use; OA articles are governed by the applicable Creative Commons License

Drug association network

By comparing DIPs of 700 drugs that interact with at least six other drugs, we obtained 244 650 similarity scores. There were 2375 scores ≥0.3, approximately accounting for top 1% of the total similarity scores. Therefore, 0.3 was chosen as the threshold and the scores above this threshold formed a drug association network (Figure 4) with 589 nodes and 2375 edges.

The drugs are clustered into 98 groups. Edge widths are proportional to corresponding similarity scores. Nodes are colored according to the first letters of ATC codes of drugs, which indicate their anatomical main groups. For the drugs that have several ATC codes starting with different first letters, a pie chart is painted on each node that shows the several first letters of this drug. The area of every individual first letter is proportional to the frequency of this letter in all first letters of ATC codes of this drug. Drugs without ATC codes are colored light purple. As shown in Figure 4, drugs with similar ATC codes tend to cluster together.

On the basis of this drug association network, we are able to predict the physiological effects of some drugs. In cluster 6 (enclosed with the red polygon), most drugs have ATC codes starting with N06A (antidepressants), but linezolid (ATC: J01XX08, an antibacterial agent) is one of the exceptions. Therefore, it can be inferred that linezolid may also have the antidepressive effects. After searching for relevant information, we found that linezolid is also a nonselective, reversible inhibitor of monoamine oxidase (10), which can lead to its antidepressive effects. This confirms our prediction and shows that the association between drugs in the network suggests relevant targets or physiological effects.

Target prediction performance based on DDI

Of the 589 drugs in the network, 561 have protein target data in DrugBank, with a total of 2310 drug–target interactions. We tried predicting targets for the 561 drugs and subsequently for each drug compared the predicted targets with known targets (see Tables S1 and S2 for predicted and actual targets). By inspecting the highest ranking of known targets of each drug in its prioritized predicted target list (i.e., rank value of this drug, *R*), we can assess the target prediction performance of this drug association network (see Table S3 for rank value of every drug based on DDI). From Figure 5, we can notice that of the 561 drugs that have known targets, 317 drugs have

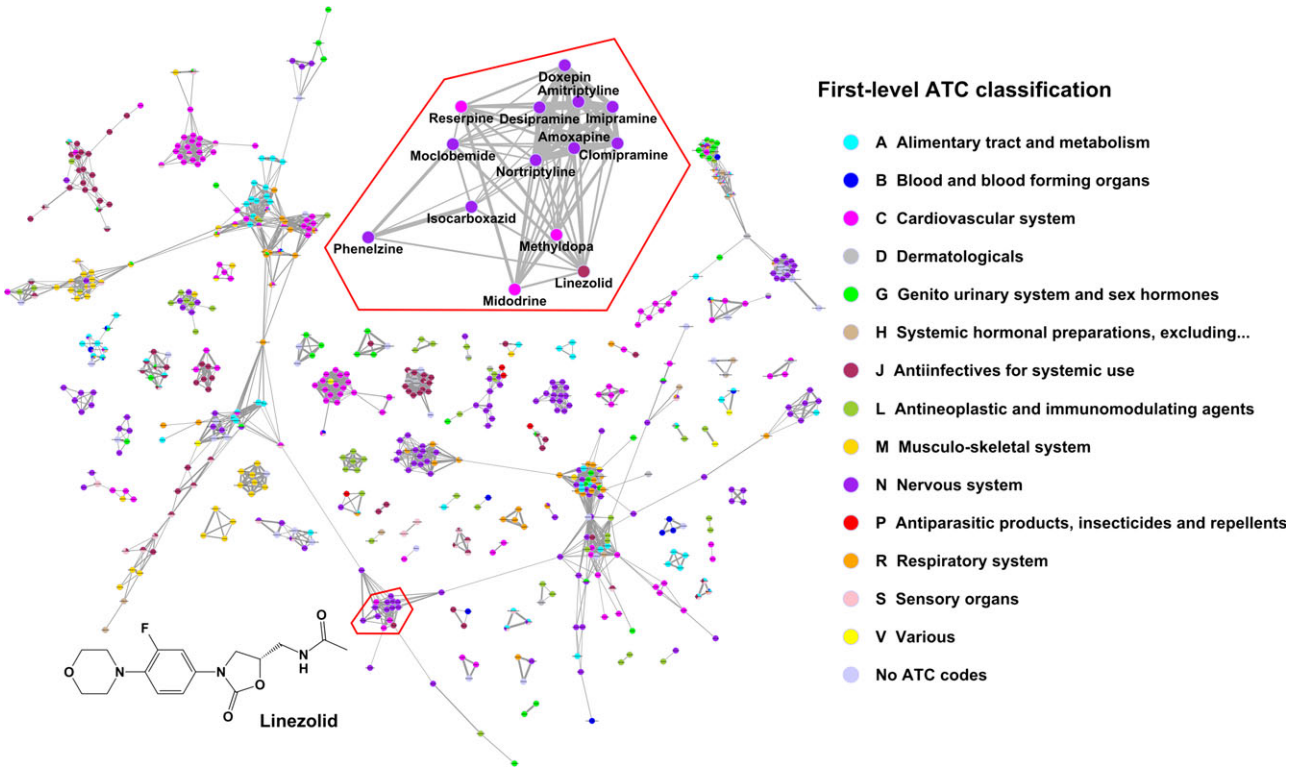

Figure 4: Drug association network. This network was deduced from drug–drug interaction data. In this network, each node represents a drug and is colored by its first-level anatomical therapeutic chemical (ATC) classification. The classification is shown on the right. Each edge represents a similarity score between the two connected drugs, and its width is proportional to the score. Only similarity scores that are ≥0.3 were retained and rendered with this network. The subnetwork of linezolid is highlighted, enclosed by a red polygon. Chemical structure of linezolid is shown in the lower left.

17470285, 2015, 2, Downloaded from https://onlinelibrary.wiley.com/doi/10.1111/cbdd.12378 by Tu Muenchen Bibliothek, Wiley Online Library on [01/12/2022]. See the Terms and Conditions (https://onlinelibrary.wiley.com/terms-and-conditions) on Wiley Online Library for rules of use; OA articles are governed by the applicable Creative Commons License

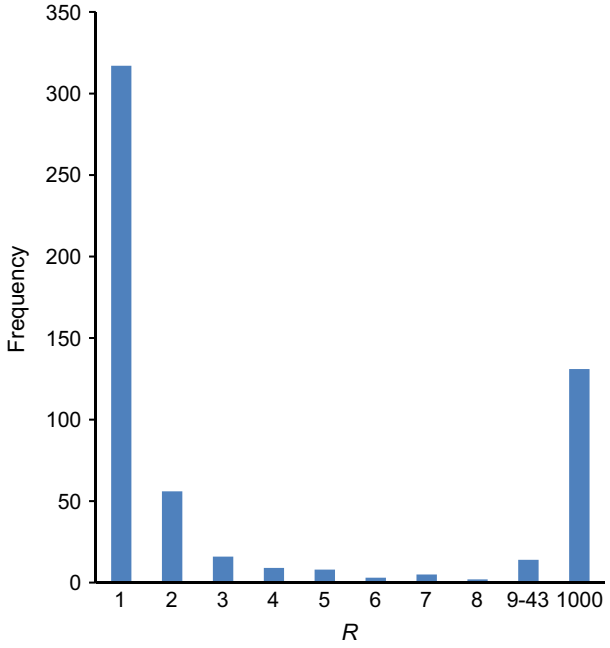

Figure 5: Distribution of drug rank value (*R*) based on drug–drug interaction (DDI). For concision and clarity, *R*s in the range 9–43 are merged into the group 9–43.

an *R* of 1, which means that in most cases, protein of the highest probability in our prediction is indeed a true target of the drug. This result shows that the target prediction method is effective for the most drugs investigated here. Moreover, for some drugs, although the first-ranking protein is not its known target, the protein bears evolutionary relationship to some known targets of the drug. For example, first-ranking protein of dihydroergotamine is 5-hydroxytryptamine 2A receptor. According to target data in DrugBank, it is not a known target of dihydroergotamine, but this drug targets 5-hydroxytryptamine 2B receptor. This provides support for the target prediction method from the perspective of target similarity. Actually, dihydroergotamine is a known 5-HT2A antagonist (15) although this activity was not recorded in DrugBank. This further proves our prediction about dihydroergotamine.

The search in other bioactivity databases and reports showed that loxapine and maprotiline merited our notice. Table 1 shows the match scores and actual activities of loxapine and maprotiline against high-ranking predicted targets.

The predicted target list of loxapine contains 65 proteins. Of them, the first three are muscarinic acetylcholine receptor M1 (M1), histamine H1 receptor (H1), and D(2) dopamine receptor. The third-ranking protein is a known target of loxapine in DrugBank, while the first and the second are unrecorded. The search in ChEMBL database and relevant reports found that loxapine is active on M1 and H1. Besides D(2) dopamine receptor, other known targets of loxapine in DrugBank are 5-hydroxytryptamine 2A receptor (ranking 6th), D(1A) dopamine receptor (ranking 8th), and 5-hydroxytryptamine 2C receptor (ranking 13th).

The predicted target list of maprotiline contains 50 proteins. In DrugBank, for maprotiline, known target of the highest ranking is alpha-1A adrenergic receptor (ranking 5th), following another four proteins in the list. However, the search in ChEMBL database found that maprotiline is active on all these four proteins. In addition to alpha-1A adrenergic receptor, other known targets of maprotiline in DrugBank are histamine H1 receptor (ranking 6th), muscarinic acetylcholine receptor M1 (ranking 8th), muscarinic acetylcholine receptor M3 (ranking 20th), muscarinic acetylcholine receptor M5 (ranking 21st), muscarinic acetylcholine receptor M4 (ranking 22nd), muscarinic acetylcholine receptor M2 (ranking 23rd), and sodium-dependent noradrenaline transporter (ranking 39th).

Target prediction performance based on chemical structure

The similarity scores between the 676 drugs were computed based on their chemical structures. We only retained the scores above 0.24, resulting in the largest 2221 of a total of 228 150 (similar to the proportion 2375/244 650). These similarity scores could also form a network with 592 nodes (drugs) and 2221 edges (similarity

Table 1: Match score and actual activity of loxapine and maprotiline on respective targets

Drug	Ranking	Score	Target	Actual activity (nM)
Loxapine	1	5.83	Muscarinic acetylcholine receptor M1	EC_{50} = 287 (16), IC_{50} = 5500[a]
	2	4.95	Histamine H1 receptor	EC_{50} = 5 (17)
	3	3.44	D(2) dopamine receptor	Known target[b]
Maprotiline	1	2.09	5-hydroxytryptamine 2A receptor	IC_{50} = 64[a], K_i = 18[a]
	2	1.79	D(1A) dopamine receptor	IC_{50} = 373[a], K_i = 187(402)[a,c]
	3	1.79	D(2) dopamine receptor	IC_{50} = 3463[a], K_i = 665(1154)[a,c]
	4	1.58	5-hydroxytryptamine 2C receptor	IC_{50} = 78[a], K_i = 41[a]
	5	1.27	Alpha-1A adrenergic receptor	Known target[b]

[a]ChEMBL bioactivity data (18).
[b]DrugBank target data.
[c]Results of two assays.

17470285, 2015, 2, Downloaded from https://onlinelibrary.wiley.com/doi/10.1111/cbdd.12378 by Tu Muenchen Bibliothek, Wiley Online Library on [01/12/2022]. See the Terms and Conditions (https://onlinelibrary.wiley.com/terms-and-conditions) on Wiley Online Library for rules of use; OA articles are governed by the applicable Creative Commons License

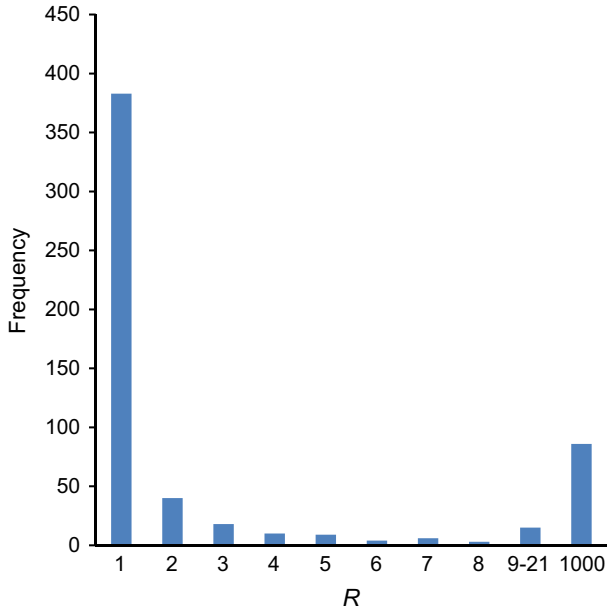

Figure 6: Distribution of drug rank value (*R*) based on chemical structure. For concision and clarity, *R*s in the range 9–21 are merged into the group 9–21.

scores). Of the 592 drugs, 574 have protein target data in DrugBank, with a total of 2351 drug–target interactions. According to the same method for predicting targets and evaluating performance as drug association network based on DDI, we acquired the distribution of drug rank value (*R*), which is illustrated in Figure 6 (see Tables S4–S6 for predicted targets, actual targets, and rank value of every drug, respectively).

Comparison between DDI-based and structure-based methods

Using structural similarity approach, we successfully predicted targets for 383 of a total of 574 drugs, but 86 drugs were completely beyond the ability of this method. In comparison, the success rate of the method based on DDI was 317 of 561, and there were 131 drugs for which no known targets existed in predicted target list. Superficially, it appears that chemical structure is better than DDI in target prediction. Nevertheless, me-too drug design strategy dominates traditional drug development, leading to the fact that among the approved drugs, those that share a target are often very similar in structure. Therefore, structure-based target prediction method may be startlingly productive for these drugs. However, currently the focus of drug development is shifting to scaffold hopping, that is, finding structurally novel drugs for an old target. Obviously, the structure-based approach will lose its power when it comes to this. In contrast, the approach based on DDI is phenotypic, thus providing additional information. This can be demonstrated by Table 2.

Table 2 lists the drugs for which *R* is 1000 by structure-based method while whose known targets exist in the predicted target list by the approach using DDI data. No. denotes the number of predicted targets for a particular drug. Of the 86 drugs that have an *R* of 1000 by the method based on structure, 27 exist in Table 2, of which 15 have an *R* of 1. This means that DDI-based method is applicable to some drugs that are entirely beyond the ability of structure-based method, which demonstrates that these two methods are complementary.

Discussion

Many factors contribute to DDI. DDI maybe occurs by pharmacokinetic factors. In other words, if a drug can impinge on adsorption, distribution, metabolism, or excretion of another drug, then these two drugs will interact with each other. A notable instance is about the inhibitors of some drug transporters, which influence the distribution of corresponding drugs. DDI can also be the consequence of pharmacodynamic factors and takes place when a drug impacts on the mode of action of another drug. For example, the for-

Table 2: Twenty-seven drugs that have an *R* of 1000 by structure-based method but whose *R* is not 1000 by DDI-based method

DrugBank ID	Name	*R*/No.	DrugBank ID	Name	*R*/No.
DB00238	Nevirapine	3/3	DB00968	Methyldopa	12/36
DB00268	Ropinirole	1/22	DB01033	Mercaptopurine	1/1
DB00307	Bexarotene	4/19	DB01104	Sertraline	1/11
DB00370	Mirtazapine	1/16	DB01122	Ambenonium	1/4
DB00384	Triamterene	3/18	DB01148	Flavoxate	2/36
DB00425	Zolpidem	1/56	DB01158	Bretylium	7/9
DB00579	Mazindol	1/35	DB01170	Guanethidine	2/25
DB00674	Galantamine	1/4	DB01171	Moclobemide	16/44
DB00714	Apomorphine	1/40	DB01195	Flecainide	4/40
DB00819	Acetazolamide	1/4	DB01241	Gemfibrozil	1/4
DB00843	Donepezil	1/19	DB01244	Bepridil	1/1
DB00883	Isosorbide Dinitrate	2/2	DB01247	Isocarboxazid	5/36
DB00903	Ethacrynic acid	1/23	DB01382	Glycodiazine	1/19
DB00912	Repaglinide	2/40			

17470285, 2015, 2, Downloaded from https://onlinelibrary.wiley.com/doi/10.1111/cbdd.12378 by Tu Muenchen Bibliothek, Wiley Online Library on [01/12/2022]. See the Terms and Conditions (https://onlinelibrary.wiley.com/terms-and-conditions) on Wiley Online Library for rules of use; OA articles are governed by the applicable Creative Commons License

mer may hinder the latter from binding to targets or stop the signaling cascade activated by the latter. In summary, DDI reflects a drug's pharmacokinetic or pharmacodynamic properties. On the other hand, the therapeutic effects of a drug are also decided by its pharmacokinetic and pharmacodynamic properties. Thereby, a close correlation may exist between therapeutic effects of drugs and their DIPs. The drug association network constructed in this study supports this point, in which drugs with similar ATC codes gather together. Accordingly, this network can be applied to the inference of the physiological effects of drugs.

Considering drug target prediction is currently a focus of attention for not only the pharmaceutical industry but also the scientific community, we tried using this drug association network based on DDI to predict drug targets. For most of the drugs investigated here, this DDI-based approach successfully placed their known targets in the predicted target lists.

Nevertheless, some shortcomings of this DDI-based approach should not be ignored. For example, DDI data are relatively scarce compared with drug chemical information, even with some other phenotypic information (e.g., gene expression profiles). The reason is that in most cases, only when a drug has already been used in practice can its DDI data be acquired.

However, this DDI-based approach for building the correlation between drugs still has some advantages. This method is based on phenotypic similarity (which contains the information on how drugs actually act in human bodies), instead of the assumption that chemically similar drugs exert similar effects on human bodies, which sometimes does not hold true. For instance, two structurally similar drugs may be metabolized separately via two remarkably distinct pathways, producing two groups of metabolites that differ much in chemical structure, targets, and physiological effects. In contrast, when using phenotypic similarity, we need not take into account the influence of drug metabolism. Moreover, for drug repurposing, it is more important to discover structurally novel chemicals for a given target than to find some structurally similar ones. DDI data may be better than structural information in scaffold hopping when we want some novel compounds of a certain activity. In short, under particular circumstances, using DDI data for target prediction is more appropriate than using chemical structural information. In summary, DDI information is somewhat unexploited and complementary to other drug information. This DDI-based method for predicting the targets and physiological effects of drugs can provide some new ideas for drug repurposing.

Acknowledgments

We thank John H. Morris for discussions of nodeCharts plugin. This work was supported by grants from National High-tech R&D Program of China (2011AA10A204), the National Natural Science Foundation of China (21075046, 21172124, 21275061), and the Fundamental Research Funds for the Central Universities (2013QC023). The funders had no role in study design, data collection and analysis, decision to publish, or preparation of the manuscript.

Conflict of Interest

No conflict of interest is declared.

References

1. Gleeson M.P., Modi S., Bender A., Marchese Robinson R.L., Kirchmair J., Promkatkaew M., Hannongbua S., Glen R.C. (2012) The challenges involved in modeling toxicity data in silico: a review. Curr Pharm Des;18:1266–1291.
2. Combes R.D. (2011) Challenges for computational structure–activity modelling for predicting chemical toxicity: future improvements? Expert Opin Drug Metab Toxicol;7:1129–1140.
3. Cavalla D. (2013) Predictive methods in drug repurposing: gold mine or just a bigger haystack? Drug Discov Today;18:523–532.
4. Kuhn M., Campillos M., González P., Jensen L.J., Bork P. (2008) Large-scale prediction of drug–target relationships. FEBS Lett;582:1283–1290.
5. Keiser M.J., Setola V., Irwin J.J., Laggner C., Abbas A.I., Hufeisen S.J., Jensen N.H. *et al.* (2009) Predicting new molecular targets for known drugs. Nature;462:175–181.
6. Iorio F., Bosotti R., Scacheri E., Belcastro V., Mithbaokar P., Ferriero R., Murino L., Tagliaferri R., Brunetti-Pierri N., Isacchi A., Bernardo D.D. (2010) Discovery of drug mode of action and drug repositioning from transcriptional responses. Proc Natl Acad Sci;107:14621–14626.
7. Campillos M., Kuhn M., Gavin A.-C., Jensen L.J., Bork P. (2008) Drug target identification using side-effect similarity. Science;321:263–266.
8. Cheng F., Li W., Wu Z., Wang X., Zhang C., Li J., Liu G., Tang Y. (2013) Prediction of polypharmacological profiles of drugs by the integration of chemical, side effect, and therapeutic space. J Chem Inf Model;53:753–762.
9. WHO Collaborating Centre for Drug Statistics Methodology (2012) Guidelines for ATC Classification and DDD Assignment 2013. Norway: Oslo.
10. Knox C., Law V., Jewison T., Liu P., Ly S., Frolkis A., Pon A., Banco K., Mak C., Neveu V., Djoumbou Y., Eisner R., Guo A.C., Wishart D.S. (2011) DrugBank 3.0: a comprehensive resource for 'Omics' research on drugs. Nucleic Acids Res;39:D1035–D1041.
11. Willett P., Barnard J.M., Downs G.M. (1998) Chemical similarity searching. J Chem Inf Comput Sci;38:983–996.

17470285, 2015, 2, Downloaded from https://onlinelibrary.wiley.com/doi/10.1111/cbdd.12378 by Tu Muenchen Bibliothek, Wiley Online Library on [01/12/2022]. See the Terms and Conditions (https://onlinelibrary.wiley.com/terms-and-conditions) on Wiley Online Library for rules of use; OA articles are governed by the applicable Creative Commons License

12. Smoot M.E., Ono K., Ruscheinski J., Wang P.-L., Ideker T. (2011) Cytoscape 2.8: new features for data integration and network visualization. Bioinformatics;27:431–432.
13. Morris J.H., Apeltsin L., Newman A.M., Baumbach J., Wittkop T., Su G., Bader G.D., Ferrin T.E. (2011) clusterMaker: a multi-algorithm clustering plugin for Cytoscape. BMC Bioinformatics;12:436.
14. Rogers D., Hahn M. (2010) Extended-connectivity fingerprints. J Chem Inf Model;50:742–754.
15. Kalkman H.O., Schneider F. (1996) Effects of ergotamine and dihydroergotamine on 5-hydroxytryptamine-2A receptors in the isolated rat aorta. Pharmacology;53:351–355.
16. Davies M.A., Compton-Toth B.A., Hufeisen S.J., Meltzer H.Y., Roth B.L. (2005) The highly efficacious actions of N-desmethylclozapine at muscarinic receptors are unique and not a common property of either typical or atypical antipsychotic drugs: is M1 agonism a pre-requisite for mimicking clozapine's actions? Psychopharmacology;178:451–460.
17. Weiner D.M., Burstein E.S., Nash N., Croston G.E., Currier E.A., Vanover K.E., Harvey S.C. *et al.* (2001) 5-Hydroxytryptamine2A receptor inverse agonists as antipsychotics. J Pharmacol Exp Ther; 299:268–276.
18. Gaulton A., Bellis L.J., Bento A.P., Chambers J., Davies M., Hersey A., Light Y., McGlinchey S., Michalovich D., Al-Lazikani B., Overington J.P. (2011) ChEMBL: a large-scale bioactivity database for drug discovery. Nucleic Acids Res;40:D1100–D1107.

Supporting Information

Additional Supporting Information may be found in the online version of this article:

Table S1. Predicted targets for 579 drugs based on DDI.

Table S2. Actual targets of 579 drugs for comparison with the DDI-based result.

Table S3. Rank value of every drug based on DDI.

Table S4. Predicted targets for 586 drugs based on chemical structure.

Table S5. Actual targets of 586 drugs for comparison with the structure-based result.

Table S6. Rank value of every drug based on chemical structure.

17470285, 2015, 2, Downloaded from https://onlinelibrary.wiley.com/doi/10.1111/cbdd.12378 by Tu Muenchen Bibliothek, Wiley Online Library on [01/12/2022]. See the Terms and Conditions (https://onlinelibrary.wiley.com/terms-and-conditions) on Wiley Online Library for rules of use; OA articles are governed by the applicable Creative Commons License