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RESEARCH ARTICLE

# Study of drug function based on similarity of pathway fingerprint

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## ABSTRACT

**Drugs sharing similar therapeutic function may not bind to the same group of targets. However, their targets may be involved in similar pathway profiles which are associated with certain pathological process. In this study, pathway fingerprint was introduced to indicate the profile of significant pathways being influenced by the targets of drugs. Then drug–drug network was further constructed based on significant similarity of pathway fingerprints. In this way, the functions of a drug may be hinted by the enriched therapeutic functions of its neighboring drugs. In the test of 911 FDA approved drugs with more than one known target, 471 drugs could be connected into networks. 760 significant associations of drug–therapeutic function were generated, among which around 60% of them were supported by scientific literatures or ATC codes of drug functional classification. Therefore, pathway fingerprints may be useful to further study on the potential function of known drugs, or the unknown function of new drugs.**

**KEYWORDS** pathway fingerprint, drug–drug network, therapeutic target, function prediction

## INTRODUCTION

Drug discovery is known as time-consuming and laborious. To bring a single *de novo* compound to drug market, more than $800 million will be spent on average with a time period of ~15 years (Adams and Brantner, 2006). Moreover, about 90% of drugs fail during the testing process in phase I clinical trials (Krantz, 1998). The high expenditure but low productivity has aroused widely concern on the traditional drug discovery strategy. One of the suggestions has been proposed to mine drugs from those existing or failure compounds (Chong and Sullivan, 2007; Tobinick, 2009). Thus it becomes increasingly important to explore the potential functions of those known drugs or experimental compounds.

Although experiments may provide precise information, the time-consuming and costly process would heavily hinder the application. Many studies have indicated that computational approaches can timely provide very useful insights for both basic research and drug development, such as predicting drug–target interaction networks (He et al., 2010), predicting HIV cleavage sites in proteins (Chou, 1996), prediction of body fluids (Hu et al., 2011a), predicting protein metabolic stability (Huang et al. 2010), predicting signal peptides (Chou and Shen, 2007), predicting the network of substrate–enzyme–product triads (Chen et al., 2010), predicting protein subcellular locations (Chou et al., 2011), predicting biological functions of compounds based on chemical–chemical interactions (Hu et al., 2011b). Actually, several novel mathematical approaches and physical concepts have been introduced into molecular biology, such as Mahalanobis distance (Chou, 1995), pseudo amino acid composition (Chou, 2001), graph and diagram analysis (Zhou and Deng, 1984; Andraos, 2008; Chou, 2010), cellular automaton (Xiao et al., 2009), grey theory (Xiao et al., 2008), low-frequency (or Terahertz frequency) phonons (Chou, 1989), which can significantly stimulate the development of biological and medical science. Especially, drug-related network based on graph theory has provided a useful platform for systematically investigating the existing drugs. For instance, Yildirim et al. (Yildirim et al., 2007) firstly constructed drug–target network, according to the relations of drug, target and therapeutic functions that were collected in DrugBank (Knox et al., 2011).

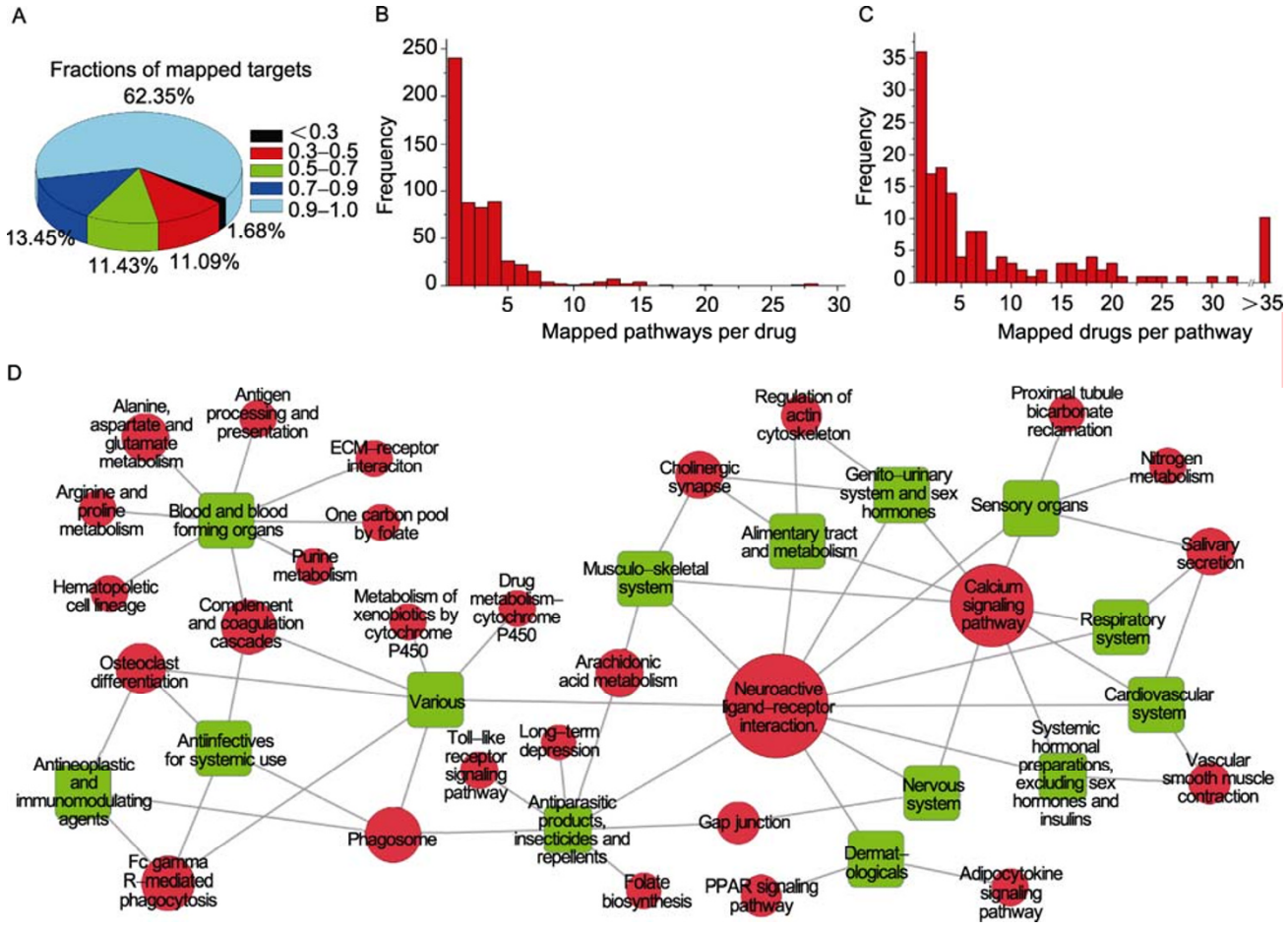


**Figure 1. Relationships between drugs and pathways.** (A) Numeric distribution of drugs according to the ratio of their targets covered by feature pathways. (B) Numerical distribution of the pathways per drug. (C) Numerical distribution of drugs per pathway. (D) Bipartite graph of 14 anatomical main groups and corresponding top 3 frequently targeted feature pathways. Pathways are represented by red roundness, while green box means an anatomical main group (first level of ATC group).

In addition to the therapeutic function indicated in ATC (Anatomical Therapeutic Chemical) system, they investigated the topological features of existing drugs between different therapeutic function groups. Later on, a drug–therapy network was built by Nacher (Nacher and Schwartz, 2008), to study the relations between drugs and their corresponding therapeutic functions.

These methods have mainly focused on individual target, where the drug–drug relations were identified by targeting the same target. However, from a system aspect, proteins do not always perform their functions isolated but interact with other cellular components to form complexes or pathways (Barabási and Oltvai, 2004). Drugs without common targets could also exert the similar therapeutic effect to the same disease, owing to the phenomenon that different targets participate in the same pathway which is closely associated with the pathological process. Obviously, such important information could be utilized to infer drug's therapeutic functions. Here, we introduce a novel computational approach, the so-called "Pathway Fingerprint Similarity," for studying drug functions. According to the drug–drug network built by the similarity of pathway fingerprint, the function of a drug could be suggested by the enrichment of therapeutic function of its neighboring drugs.

## RESULTS

### The relationships between drug/function and feature pathway

Firstly, we define pathway fingerprint as a binary vector that represents the significantly enriched pathways of drug targets. In this paper, each significantly influenced pathway is called feature pathway. In order to investigate whether the pathway fingerprint could represent the effects of a drug, we calculated the proportion of drug targets that included in the feature pathways for each drug. As it shows in Fig. 1A, 75.80% of drugs were discovered, of which, more than 70% of targets

 

were included in the corresponding feature pathways. Moreover, 62.35% of drugs with more than 90% of targets were detected in feature pathways. All of these indicate that the pathway fingerprint could well represent the potential function of most drugs.

Figure 1B shows the distribution of feature pathways for drugs. 354 (59.50%) drugs could significantly influence more than one pathway. Nadide, a nutritive drug approved by FDA, which binds to 144 protein targets, may regulate 28 feature pathways. Under the "one target, one disease" paradigm of previous drug design (Wermuth, 2004), the multiple feature pathways may not only contain the molecular basis of the main therapy, but also indicate several other new functions. For example, Trastuzumab is an antibody drug used for breast cancer, which is designed to inhibit ErbB-2 in ErbB signaling pathway. Several lines of clinical evidence showed that Trastuzumab could treat other cancers that closely related with ErbB signaling pathway, such as ovarian cancer (Delord et al., 2010), glioblastoma (Mineo et al., 2004), head and neck cancer (Kondo et al., 2008), lung cancer (Azzoli et al., 2002). Moreover, Osteoclast differentiation pathway (another feature pathway of Trastuzumab) may regulate the balance between bone formation and resorption which is the molecular basis of osteopetrosis/osteoporosis (Lazner et al., 1999; Anandarajah et al., 2008). Figure 1C shows the distribution of drugs of feature pathways. Averagely, each feature pathway could be targeted by 12 (median 4) drugs. Neuroactive ligand–receptor interaction pathway was the most targeted pathway which could be significantly influenced by 241 (40.50%) drugs. Receptors, such as G protein-coupled receptors (GPCRs), iron channel receptors in the pathway, were frequently designed as drug targets may be the reason.

In order to get a global view of the relations between 14 anatomical main groups and their frequently (top 3) targeted feature pathways, we built a bipartite graph in Fig. 1D. It is obvious that neuroactive ligand–receptor interaction and calcium signaling pathway were targeted by drugs in several anatomical main groups, such as cardiovascular system, nervous system, alimentary tract and metabolism. It may indicate that drugs in these anatomical main groups could result in several other effects because of such interactions. In fact, antipsychotic drugs were always found to induce side effects on metabolic or cardiovascular system (e.g. obesity, diabetes, hypertension) (Fodor, 2011; Liao et al., 2011). In addition, antineoplastic and immunomodulating agents, anti-infective agents and hematological therapy agents may show a different therapy model from other anatomical main groups, owing to sharing few feature pathways. While, Fc-gamma R-mediated phagocytosis, phagosome, were frequently targeted by immune-related drugs, namely, antineoplastic and immunomodulating agents, and anti-infective agents.

**Drug–drug network**

From the results discussed above, the therapeutic functions of most drugs could be well represented by the corresponding pathway fingerprint. Feature pathways could indicate the therapeutic interactions between drugs in different anatomical main groups. Herein, we built a drug–drug network aiming to study the therapeutic functions of the drugs with similar pathway fingerprint. After the selecting process described in MATERIALS AND METHODS, 6680 drug–drug pairs involving 471 individual drugs were generated (Fig. 2A). Moreover, 411 drugs labeled with ATC code, correspond to 5167 drug–drug pairs. All of the anatomical main groups and 61 therapeutic main groups that were indicated in ATC codes were covered by these drugs. In the drug–drug network, drugs were clustered together with the similar pathway fingerprint. It could be inferred that the clustered drugs tend to exert similar therapeutic functions on the basis of regulating similar biological processes. Combined with ATC classification system, the proportions of drug–drug pairs in the same anatomical main groups (first level of ATC) and therapeutic main groups (second level of ATC) were 52.20%, 22.08%, respectively. If a drug seems to connect with the drugs from the same therapeutic main group, that may indicate its potential therapeutic function.

Cinnarizine is an anti-histaminic drug mainly used for the control of vomiting due to motion sickness. As it shows in Fig. 2B, it connected with seven anti-cardiovascular system drugs. Six of them (Amlodipine, Nitrendipine, Nimodipine, Nilvadipine, Nisoldipine, and Isradipine) are labeled with "C08," which represents calcium channel blockers. Those drugs are always used to treat hypertension through regulating the vascular contraction and expansion. While, Cinnarizine was found to block calcium channel and induce vascular expansion (Deitchman et al., 1980). Moreover, the combination of Clofibrate and Cinnarizine for hypertension therapy has already been applied as a US patent by Metz et al. (patent Id: 4156003)

Ethopropazine is primarily used as an antidyskinetic to treat Parkinsonism. And Carbachol is a cholinergic agonist which was approved for the treatment of glaucoma. In Fig. 2C, their other neighbors belong to the therapeutic main group of muscle relaxants, which was obviously distinguished from themselves. Actually, Ethopropazine was always used as an antispasmodic agent in clinic therapy (Timberlake and Schwab, 1952). Kamikawa et al. proved that Carbachol could regulate the contraction of smooth muscle on the guinea-pig esophageal muscularis mucosae (Kamikawa and Shimo, 1987).

Mecasermin is a recombinant of human insulin-like growth factor 1 (IGF-1) which is used for the long-term treatment of growth failure in children with severe primary IGF-1 deficiency (Fintini, Brufani and Cappa, 2009). In Fig. 2D, it connected with 3 anti-diabetes drugs (insulin lispro, insulin

 

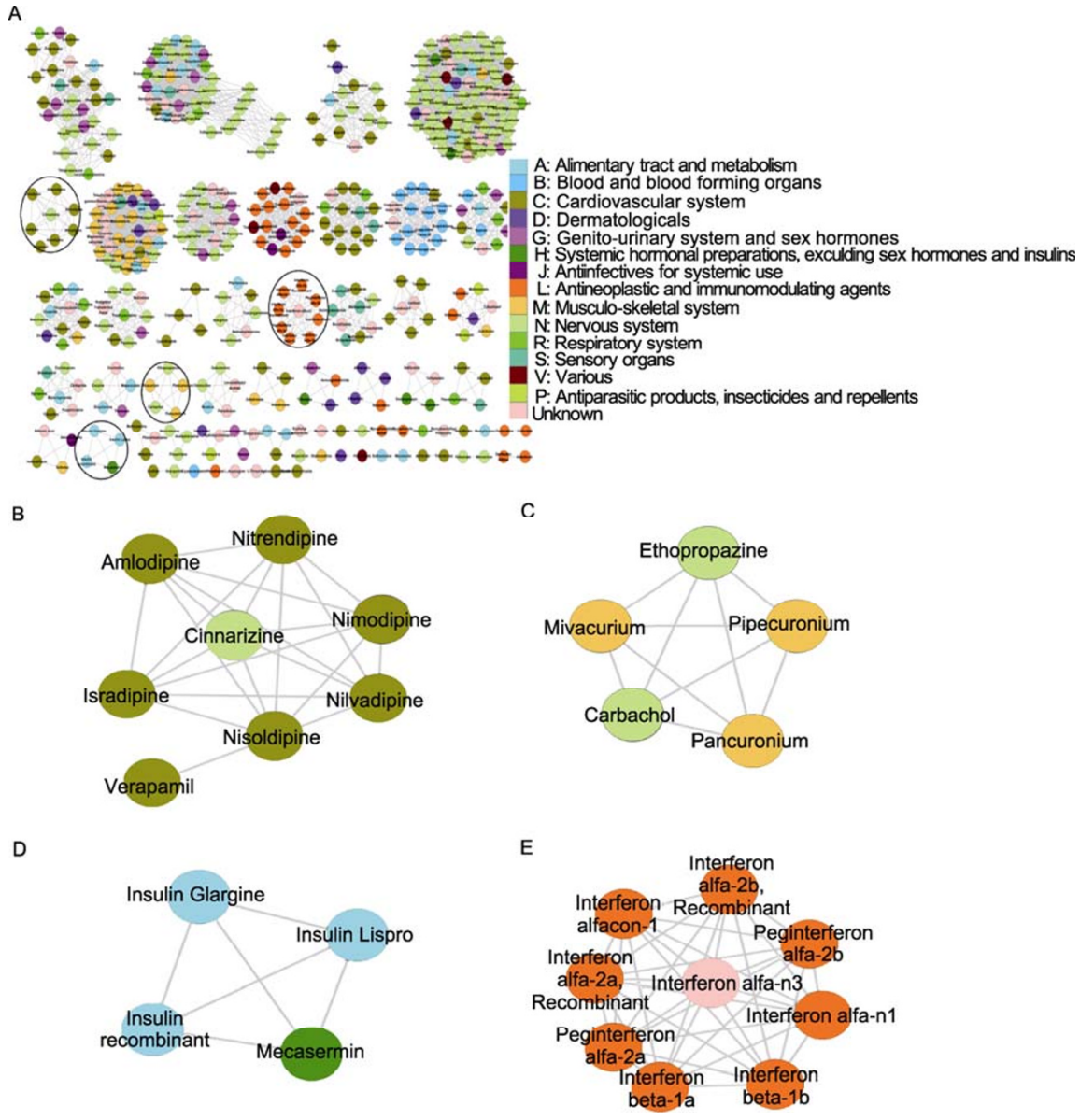


**Figure 2. Drug–drug network and four extracted subnetworks.** (A) Drug–drug network. Each node in the network represents a drug. Different colors are mapped according to the 1st-level ATC sub-group. Drugs with specifically and significantly similar pathway fingerprint are linked by edges. (B–E) are 4 examples extracted from the network.

glargine and insulin recombinant). This may indicate that Mecasermin could regulate similar biological process with the neighbors. In fact, Mecasermin was proved to perform beneficial effects in diabetes (Keating, 2008).

In addition, although interferon alpha-3 was assigned with no ATC code, it was closely linked to 8 other interferons in Fig. 2E. That well matched the fact of similar therapeutic function of interferons.

Besides those, we predicted the new functions of the 418 drugs with no less than 3 neighbors. In this condition, 760 drug–therapeutic function pairs were generated (see supplementary data), covering 21 therapeutic main groups indicated in second level of ATC system, corresponding to 339 drugs (298 of them with known ATC codes). In the predicted results, 175 drugs (58.72%) were well matched with their known therapeutic functions. 458 drug–therapeutic function pairs (60.26%) could be supported by scientific literatures. Others may indicate potential therapeutic functions of drugs.

## DISCUSSION

Molecular fingerprint was initially proposed to study the chemical structure of small molecules. It makes it easier to compare the structures and investigate the association be-

 

tween the function and chemical structure. However, there may be some gaps between biological effect and chemical structure. Actually, compounds always exert their functions through binding protein targets. Proteins generally carry out their functions by the form of pathway. In this paper, pathway fingerprint which was used to represent the significantly regulated pathways of drug targets was first proposed to investigate the therapeutic functions of drugs.

Although drugs were designed under the paradigm of "one target, one disease," a lot of them were found to target additional targets. This may lead to new functions owing to regulating several other biological processes. In the drug–drug network, drugs with the similar pathway fingerprint would cluster together. We designed the drug function prediction method according to the functional distribution of their neighbors in the network. 60.26% of the predicted results were supported by scientific literatures. This method could also be used to infer functions of active compounds, as long as we build a compound–drug network based on the similarity of pathway fingerprint.

In all, pathway may offer a new perspective to understand the drug–therapeutic function relations. Especially, the drug–drug network based on the similarity of pathway fingerprint may give some insights into the discovery of new indication or sides effects for existing drugs. Since user-friendly and publicly accessible web-servers represent the future direction for developing practically more useful models, simulated methods, or predictors, we shall make efforts in our future work to provide a web-server for the method presented in this paper.

## MATERIALS AND METHODS

#### Drug–drug network construction (see workflow in Fig. 3)

#### Pathway selection

A 'pathway' is defined as a manually annotated basic biological functional unit. KEGG (Kanehisa et al., 2010) serves as a comprehensive resource for pathway information. As a result, 185 basic pathways were collected, including 5703 genes (all of the disease pathways in KEGG are excluded).

#### Drug target and the corresponding pathway fingerprint

911 FDA approved multi-target drugs are collected in DrugBank v3.0, which occupies 60.37% of approved drugs in the database. Then the Fisher's exact test that was utilized in DAVID (Huang et al., 2009) was chosen to evaluate the pathway enrichment of targets for each drug. A pathway with an enriched *p* value of no more than 0.01 is identified as a feature pathway and it would be tagged "1" in the pathway profile vector; otherwise, it would be tagged "0." The binary vector defined as pathway fingerprint was finally obtained. In this study, each drug could get a 185 dimension vector according to the influence on collected pathways. Finally, 595 of the drugs contained at least one feature pathway.

#### Calculating the similarity of pathway fingerprint between drugs

Herein, Tanimoto coefficient (Willett, Barnard and Downs, 1998) was used to evaluate the similarity of pathway fingerprint. Given a drug pair A and B, the Tanimoto coefficient for binary vectors was defined as formula (I)

$$T(A,B) = \frac{c}{a+b-c} \quad \text{(I)}$$

In this formula, *a* is the number of feature pathways for drug A, *b* is the number of feature pathways for drug B, and *c* is the number of feature pathways shared by drugs A and B.

#### Specificity test on the similarity of pathway fingerprint for each drug pair

In order to test whether the similarity of drugs A and B was specifically related to the special feature pathways of drugs, a control group is constructed. Retaining the pathway fingerprint sequence of the drug A, random pathway fingerprints of the drug were generated by randomly sorting the pathway 100,000 times. For each random pathway fingerprint of drug A, the tanimoto coefficient was calculated with pathway fingerprint of drug B. Then the random tanimoto coefficient set S (A,B) between drugs A and drug B was obtained. Z-score calculated by formula (II) was used to evaluate the specificity of the similarity (3 was set as the threshold)

$$Z = \frac{T(A,B) - mean(S(A,B))}{std(S(A,B))} \quad \text{(II)}$$

#### Significance test on the similarity of pathway fingerprint for each drug pair

A set M which contains the entire tanimoto coefficient between all drug pairs was generated. Whether tanimoto coefficient of each drug pair was significantly larger than the average of *M* was tested (3 was set as the threshold).

#### Drug ATC classification system and drug function prediction

The ATC system is used for the classification of drugs' functions (http://www.whocc.no/atc/structure_and_principles/). In this system, drugs are assigned with a seven characters code that could classify drugs at 5 different levels. The first level of the ATC code indicates 14 anatomical main groups and consists of one letter (e.g. 'C' means cardiovascular system). The second level of the code indicates the therapeutic main group and consists of two digits (e.g. 'C02' means anti-hypertensive). In this study, the potential functions of a drug were inferred, according to the distribution of its neighbors in the therapeutic main groups. Specifically, a hypergeom test described in formula (III) was taken to evaluate the functional enrichment of the drugs' neighbors in the drug–drug network.

$$p_{(drug\ A, function\ i)} = 1 - \sum_{x=0}^{k} \frac{C_M^x \cdot C_{N-M}^{n-x}}{C_N^n} \quad \text{(III)}$$

 

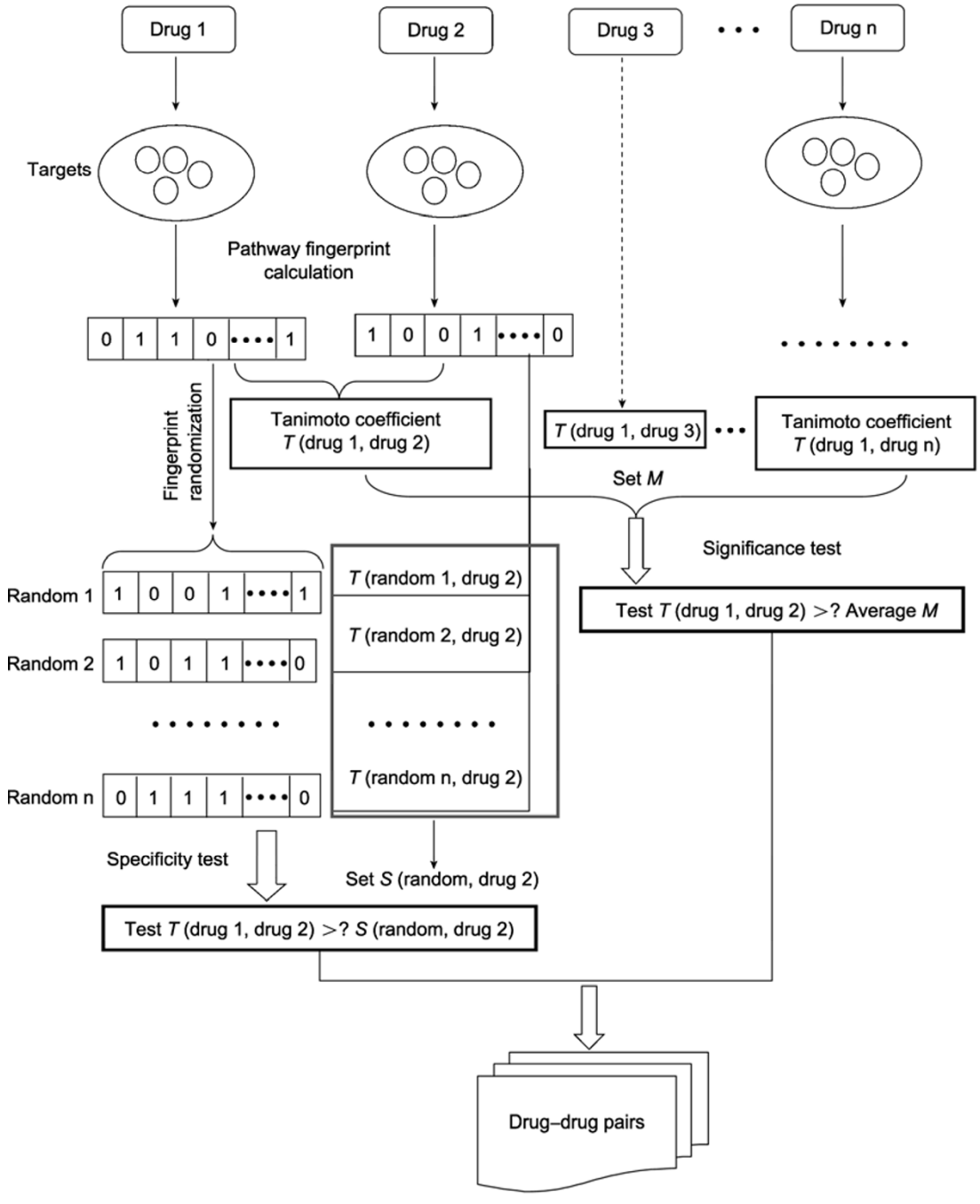


**Figure 3. Workflow of constructing the drug–drug pairs.**

*N*: number of nodes in the network minus 1; *n*: degree of drug A; *M*: if drug A belongs to the therapeutic main group i, *M* is the number of drugs in the network minus 1. Otherwise, *M* is the number of drugs in the network. *k*: number of drug A's neighbors that belong to therapeutic main group i. Two additional requirements need to be satisfied. (1) Drug A must be directly linked with no less than 3 drugs in the network; (2) No less than 3 of drug A's neighbors were included in the therapeutic main group i.

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## REFERENCES

Adams, C.P., and Brantner, V.V. (2006). Estimating the cost of new drug development: is it really 802 million dollars? Health Aff (Millwood) 25, 420–428.

Anandarajah, A.P., Schwarz, E.M., Totterman, S., Monu, J., Feng, C.Y., Shao, T., Haas-Smith, S.A., and Ritchlin, C.T. (2008). The effect of etanercept on osteoclast precursor frequency and enhancing bone marrow oedema in patients with psoriatic arthritis. Ann Rheum Dis 67, 296–301.

Andraos, J. (2008). Kinetic plasticity and the determination of product ratios for kinetic schemes leading to multiple products without rate laws: new methods based on directed graphs. Can J Chem 86, 342–357.

Azzoli, C.G., Krug, L.M., Miller, V.A., Kris, M.G., and Mass, R. (2002). Trastuzumab in the treatment of non-small cell lung cancer. Semin Oncol 29, 59–65.

Barabási, A.L., and Oltvai, Z.N. (2004). Network biology: understanding the cell's functional organization. Nat Rev Genet 5, 101–113.

Chen, L., Feng, K.Y., Cai, Y.D., Chou, K.C., and Li, H.P. (2010). Predicting the network of substrate-enzyme-product triads by combining compound similarity and functional domain composition. BMC Bioinformatics 11, 293.

Chong, C.R., and Sullivan, D.J. Jr. (2007). New uses for old drugs. Nature 448, 645–646.

Chou, K.C. (1989). Low-frequency resonance and cooperativity of hemoglobin. Trends Biochem Sci 14, 212–213.

Chou, K.C. (1995). A novel approach to predicting protein structural classes in a (20-1)-D amino acid composition space. Proteins 21, 319–344.

Chou, K.C. (1996). Review: Prediction of HIV protease cleavage sites in proteins. Anal Biochem 233, 1–14.

Chou, K. C. (2001). Prediction of protein cellular attributes using pseudo amino acid composition. PROTEINS: Structure, Function, and Genetics (Erratum: ibid, 2001, 44, 60) 43, 246–255.

Chou, K.C. (2010). Graphic rule for drug metabolism systems. Curr Drug Metab 11, 369–378.

Chou, K.C., and Shen, H.B. (2007). Signal-CF: a subsite-coupled and window-fusing approach for predicting signal peptides. Biochem Biophys Res Commun 357, 633–640.

Chou, K.C., Wu, Z.C., and Xiao, X. (2011). iLoc-Euk: a multi-label classifier for predicting the subcellular localization of singleplex and multiplex eukaryotic proteins. PLoS One 6, e18258.

Deitchman, D., Braselton, J.P., Hayes, D.C., and Stratman, R.L. (1980). The ganglion-blocked, angiotensin II-supported rat: a model for demonstrating antihypertensive vasodilator activity. J Pharmacol Methods 3, 311–321.

Delord, J.P., Quideau, S., Rochaix, P., Caselles, O., Couderc, B., Hennebelle, I., Courbon, F., Canal, P., and Allal, B.C. (2010). Trastuzumab induced in vivo tissue remodelling associated in vitro with inhibition of the active forms of AKT and PTEN and RhoB induction in an ovarian carcinoma model. Br J Cancer 103, 61–72.

Fintini, D., Brufani, C., and Cappa, M. (2009). Profile of mecasermin for the long-term treatment of growth failure in children and adolescents with severe primary IGF-1 deficiency. Ther Clin Risk Manag 5, 553–559.

Fodor, M. (2011). [Current views on the metabolic syndrome and the effects of antipsychotic drugs]. Psychiatr Hung 26, 196–200.

He, Z., Zhang, J., Shi, X.H., Hu, L.L., Kong, X., Cai, Y.D., and Chou, K.C. (2010). Predicting drug-target interaction networks based on functional groups and biological features. PLoS One 5, e9603.

Hu, L.L., Chen, C., Huang, T., Cai, Y.D., and Chou, K.C. (2011a). Predicting biological functions of compounds based on chemical-chemical interactions. PLoS One 6, e29491.

Hu, L.L., Huang, T., Cai, Y.D., and Chou, K.C. (2011b). Prediction of body fluids where proteins are secreted into based on protein interaction network. PLoS One 6, e22989.

Huang, T., Shi, X.H., Wang, P., He, Z., Feng, K.Y., Hu, L., Kong, X., Li, Y.X., Cai, Y.D., and Chou, K.C. (2010). Analysis and prediction of the metabolic stability of proteins based on their sequential features, subcellular locations and interaction networks. PLoS One 5, e10972.

Huang, W., Sherman, B.T., and Lempicki, R.A. (2009). Systematic and integrative analysis of large gene lists using DAVID bioinformatics resources. Nat Protoc 4, 44–57.

Kamikawa, Y., and Shimo, Y. (1987). Different spasmolytic effects of smooth muscle relaxants on the guinea-pig esophageal muscularis mucosae contracted by carbachol or high potassium in vitro. Eur J Pharmacol 136, 39–48.

Kanehisa, M., Goto, S., Furumichi, M., Tanabe, M., and Hirakawa, M. (2010). KEGG for representation and analysis of molecular networks involving diseases and drugs. Nucleic Acids Res 38, D355–D360.

Keating, G.M. (2008). Mecasermin. BioDrugs 22, 177–188.

Knox, C., Law, V., Jewison, T., Liu, P., Ly, S., Frolkis, A., Pon, A., Banco, K., Mak, C., Neveu, V., et al. (2011). DrugBank 3.0: a comprehensive resource for 'omics' research on drugs. Nucleic Acids Res 39, D1035–D1041.

Kondo, N., Ishiguro, Y., Kimura, M., Sano, D., Fujita, K., Sakakibara, A., Taguchi, T., Toth, G., Matsuda, H., and Tsukuda, M. (2008). Antitumor effect of gefitinib on head and neck squamous cell carcinoma enhanced by trastuzumab. Oncol Rep 20, 373–378.

Krantz, A. (1998). Protein-site targeting. Diversification of the drug discovery process. Nat Biotechnol 16, 1294.

Lazner, F., Gowen, M., Pavasovic, D., and Kola, I. (1999). Osteopetrosis and osteoporosis: two sides of the same coin. Hum Mol Genet 8, 1839–1846.

Liao, C.H., Chang, C.S., Wei, W.C., Chang, S.N., Liao, C.C., Lane, H.Y., and Sung, F.C. (2011). Schizophrenia patients at higher risk of diabetes, hypertension and hyperlipidemia: a population-based study. Schizophr Res 126, 110–116.

Mineo, J.F., Bordron, A., Quintin-Roué, I., Loisel, S., Ster, K.L., Buhé, V., Lagarde, N., and Berthou, C. (2004). Recombinant humanised

 

anti-HER2/neu antibody (Herceptin) induces cellular death of glioblastomas. Br J Cancer 91, 1195–1199.

Nacher, J.C., and Schwartz, J.M. (2008). A global view of drug-therapy interactions. BMC Pharmacol 8, 5.

Timberlake, W.H., and Schwab, R.S. (1952). Experimental preparation W-483 in the treatment of Parkinson's disease. N Engl J Med 247, 98–100.

Tobinick, E.L. (2009). The value of drug repositioning in the current pharmaceutical market. Drug News Perspect 22, 119–125.

Wermuth, C.G. (2004). Multitargeted drugs: the end of the "one-target-one-disease" philosophy? Drug Discov Today 9, 826–827.

Willett, P., Barnard, J.M., and Downs, G.M. (1998). Chemical similarity searching. J Chem Inf Comput Sci 38, 983–996.

Xiao, X., Lin, W.Z., and Chou, K.C. (2008). Using grey dynamic modeling and pseudo amino acid composition to predict protein structural classes. J Comput Chem 29, 2018–2024.

Xiao, X., Wang, P., and Chou, K.C. (2009). GPCR-CA: A cellular automaton image approach for predicting G-protein-coupled receptor functional classes. J Comput Chem 30, 1414–1423.

Yildirim, M.A., Goh, K.I., Cusick, M.E., Barabási, A.L., and Vidal, M. (2007). Drug-target network. Nat Biotechnol 25, 1119–1126.

Zhou, G.P., and Deng, M.H. (1984). An extension of Chou's graphic rules for deriving enzyme kinetic equations to systems involving parallel reaction pathways. Biochem J 222, 169–176.

 