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Relating Anatomical Therapeutic Indications by the Ensemble Similarity of Drug Sets

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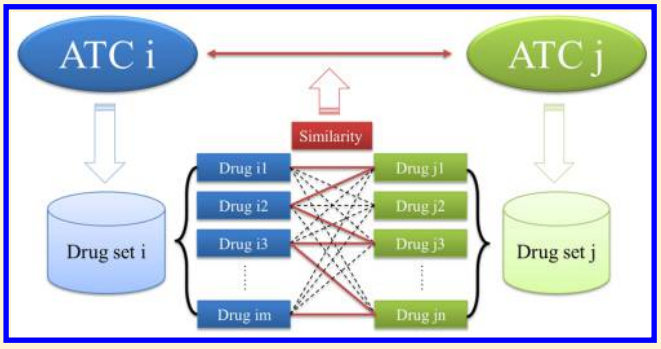
Supporting Information

ABSTRACT: The anatomical therapeutic chemical (ATC) system is a world standard to define drug indications. Despite its broad applications in pharmaceutical and biomedical research, only a few studies that examine the relationships among ATC classes have been published. Here we present a similarity-based approach, named the indication similarity ensemble approach (iSEA), that innovatively correlates ATC classes by their drug set similarity. Our study demonstrated that iSEA was capable of relating ATC classes, and these relationships could accurately assign the right indications for approved drugs and make reasonable predictions about possible clinical indications for unclassified drugs, which would provide valuable information for drug repositioning. Additionally, on the basis of iSEA, we constructed the first ATC relationship network to reflect correlations among ATCs from a network view, which would further render novel insight to understand the intrinsic relationships in the ATC system.



INTRODUCTION

For drug discovery and development, it is essential and important to associate experimental drugs with corresponding therapeutic indications or discover novel indications for approved drugs. An international standard to define the indication is the anatomical therapeutic chemical (ATC) classification system, which is controlled by the WHO Collaborating Centre for Drug Statistics Methodology (WHOCC) and is widely used for drug classification. In ATC, a drug is categorized by its anatomical, therapeutic, pharmacological, and chemical properties that are determined experimentally. Because of the enormous time and financial burdens involved in testing new indications for individual drugs, computational approaches have been widely applied to expedite the research process and eventually reduce the cost.[1]

Currently, similarity-based algorithms have been widely used to study the relationships between drugs and indications. Among them, several studies have been undertaken on the ATC system. Gurulingappa et al. predicted potential ATC classes for unclassified drugs using information extracted from the literature.[2] Recently, Chen et al.[3] developed a method to predict the ATC classification of drugs by their chemical similarities and interactions with other drugs. Unlike plenty of research conducted to study the relationships among diseases,[4,5] only a few studies have focused on the relationships among ATC classes. This may be partially due to the fact that an ATC class is initially defined by the anatomical locations and pharmacological properties of drugs, which is difficult to correlate quantitatively with a drug, a target protein, or a specific disease. A previous study indicated that drug−drug interactions have been successfully inferred by information about ATC classes of drugs, which suggests it is possible to relate ATC classes based on their involved drug sets.[6]

The ATC system presents a hierarchical treelike structure with nodes in different branches that could not be associated, whereas drug repositioning would likely link indications from different anatomical and therapeutic groups. For instance, Viagra (sildenafil citrate), currently a primary drug in the treatment of erectile dysfunction, was originally designed as a PDE-5 inhibitor for pulmonary arterial hypertension (PAH). Another example is Thalidomide, which is currently used for severe erythema nodosum leprosum. It was first developed as a sleeping pill for pregnant women, and severe side effects consisting of birth defects blocked its use for this indication. For drugs with multiple indications, such as acetylcysteine, they were labeled with multiple ATC codes in the current ATC system. Acetylcysteine is a drug used as a mucolytic agent to reduce the viscosity of mucous secretions and shows antiviral effects in patients with HIV, which results in three different ATC codes (R05CB01, S01XA08, and V03AB23) with totally different anatomical and therapeutic properties.

A question to be answered would be whether those ATC classes involving similar drugs are related to each other. A logical hypothesis is that two indications would be correlated to each other if they share the same or similar drugs. This similarity-based theory has been adopted for the study of relationships between proteins, where proteins are related on

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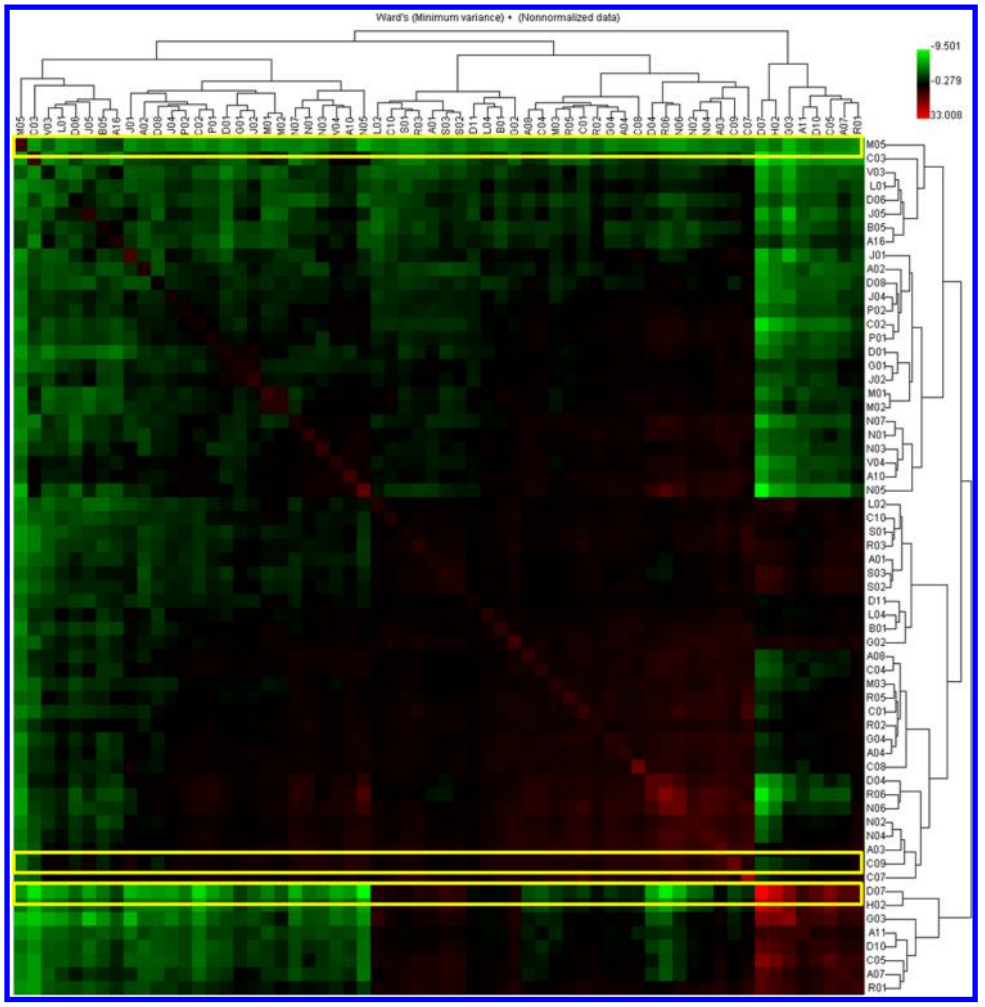

Figure 1. Heat map of Z scores for 62 ATCs. For each ATC, the Z scores between it and all other ATCs (including self-comparison) were calculated and clustered.

the basis of their ligand set similarity.[7] Because it was difficult to study indications directly as a result of the lack of quantitative features to describe them, a drug set similarity-based approach would be a suitable method for an indication study.

Here we introduced a novel approach to studying indication relationships, namely, the indication similarity ensemble approach (iSEA). Similar to the similarity ensemble approach (SEA),[8] the iSEA approach studies the relationships among anatomical therapeutic indications by their drug chemistry. The relationships among a single drug and indications were also investigated and employed to find potential indications for drug repositioning. Additionally, we also constructed a connective network to reflect ATC relationships systemically, which would provide novel insight in better understanding the ATC system.

MATERIALS AND METHODS

Data Collection. A total number of 1574 drug−ATC pairs are collected from DrugBank 3.0[9] after removing antibodies, mineral compounds, inorganic compounds, metal complex, and peptides, which include 1205 drugs and their corresponding ATC codes. For the drugs, we removed the counterions and maintained the protonation stage of drugs under the physiological condition of pH 7.4. The ATC classes of drugs are labeled to the secondary category level (such as A01), which leads to 62 ATCs in this study. To study the correlations among ATCs, we used the 1509 drug−ATC relationships involving 1151 FDA-approved drugs. In other words, the drug set of ATCs is constructed using only these known drug−ATC relationships with approved drugs. The remaining 54 drugs, mostly experimental or withdrawn drugs involved with 65 drug−ATC relationships, are thus used as an external data set in drug-repositioning studies. The detailed drug−ATC relationships used in our study are listed in Supporting Information Table S1

Drug−Drug Similarity Calculation. The drug similarity is measured on the basis of its chemical fingerprints, as calculated by the PaDel-Descriptor.[10] Three common fingerprints—CDK, MACCS, and PubChem fingerprint—are applied in this study and contain 1024, 166, and 881 fingerprints, respectively. For each drug pair, Tanimoto scores (Ts) are calculated by three fingerprint methods separately, and the average Ts value of three fingerprints is taken as the final Ts to evaluate the drug−drug similarity.

Evaluating Score and Z Score of ATC Pairs. The overall similarity between ATCs is evaluated by the similarity between corresponding drug sets. In details, the evaluating score (Es) of two ATCs is measured as the sum of the Tanimoto score of all drug pairs, as shown in eq 1 .

$$\mathrm{Es} = \sum_{i=1}^{m}\sum_{j=1}^{n} \mathrm{Ts}_{ij} \quad (1)$$

A permutation test is then applied to measure the Z score of each ATC pairs for two purposes: (1) to eliminate the influence of the drug set size on Es and (2) to evaluate whether the correlation between ATCs is significant. In detail, permutated drug sets with the same number of drugs are generated for each ATC through random selection from 1151 drugs. During each of the 1000 repetitions, the permutated Es is also measured as the sum of Tanimoto scores between permutated drug sets. We then measure the distribution of the permutated Es for each ATC pair and indicate its corresponding normal distribution because about 90% of permutated Es values of ATC pairs have shown a significant p value of >0.05 in a χ^2 test. Finally, the μ and σ of the normal distribution of the permutated Es values are used to calculate the final Z score of ATC pairs. Because the permutated Es follows a normal distribution, it is considered that if the Z score of one ATC pair is >1.96 then these two ATCs would have a statistically significant correlation.

Drug-Repositioning Prediction. To discover potential relationships between drugs and ATCs, the Es and Z score of drug−ATC relationship is calculated in the same manner for the ATC−ATC relationships. The performance of iSEA with respect to drug repositioning is first internally evaluated by calculating the ranking orders of known ATCs for FDA-approved drugs. In detail, 1509 drug−ATC pairs are used as an internal validating data set, and another 65 drug−ATC pairs from DrugBank are then taken as an external validating data set. For each individual drug, its Z scores with all 62 ATCs are calculated and sorted. The ranking orders of ATC classes are used to judge whether our algorithm would enrich known ATC relationships at the top of the ATC sorting list. In particular, the average Z score and ranking orders of known ATCs and the number of known ATCs ranked in the top 10 are measured in order to evaluate the drug-repositioning performance.

Network Construction and Visualization. The ATC relationship network is constructed on the basis of significant ATC correlations and visualized with Cytoscape (version 2.8.2).[11] Nodes in the ATC network are ATCs, and edges in the network represent the correlation between ATCs. Over the whole network, two nodes will be connected if their Z score is statistically significant (>1.96).

Topological properties, such as the degree and betweenness for nodes in the ATC network, are calculated. Betweenness is the number of shortest paths from all nodes to others through this node, and in this study, it would represent the connectivity relationships among ATC classes. Degree measures the number of edges with a single node, and it would indicate how closely the current ATC class is related to other classes in the network. All topologies are calculated with a Cytoscape embedded network analysis plugin.[11]

RESULT

Similarity Scores between Drug Sets. Overall, 62 versus 62 drug set comparisons were made, involving 1151 FDA-approved drugs and 662 976 (1151 × 1152/2, including self-comparison) drug pairs. Our results indicated that the Tanimoto scores of most drug pairs were quite low (Supporting Information Figure S1) and only 12 637 (1.91%) drug pairs had a Ts of >0.6, including 1151 self-comparisons. In other words, 98.09% of drug pairs had a Ts of <0.6, which is typically considered to indicate dissimilarity.

The overall evaluating score (Es), an estimation of the similarity between two ATCs, is measured as the sum of all of the Ts values of drug pairs. Because Es values of ATC pairs are strongly dependent on the size of the drug sets (R^2 = 0.9758, Supporting Information Figure S2), the Es values are not comparable between ATC pairs if the sizes of their drug sets are different. The Z score is therefore introduced to eliminate the influence of the drug size and determine whether two ATCs are significantly correlated. With the permutation test repeated in 1000 repetitions, the Z scores of each ATC were calculated and shown as a clustering heat map in Figure 1. There were a total of 370 ATC pairs with a Z score of >1.96, including 58 ATC self-comparisons (such as A01 vs A01). Interestingly, there were still four ATC classes with a Z score of <1.96 even with a negative score, such as L01 (−2.4010) and V03 (−0.8839). This result was not surprising because L01 was labeled for antineoplastic agents, including various types of drugs such as alkylating agents, antimetabolites, alkaloids, and cytotoxic antibiotics, which would be totally structural distinct from each other even if they were categorized in the same ATC. However, V03 was labeled for all other therapeutic products that also contained various types of drugs.

From Figure 1, we found that ATCs could be categorized into subgroups according to their Z scores with each other. Specifically, D07, C09, and M05 were selected as three representative Z-score distribution examples because they were located in the different subclusters as with different Z-score traits (highlighted in yellow). D07, labeled for corticosteroids (dermatological preparations), showed a significant correlation with 15 indications (including self-comparison) with a Z score of >1.96. Not surprisingly, the self-correlation of D07 showed the highest Z score as 33.01. The following ATC class with the second-highest Z score was another expected ATC class, H02 (Z score = 24.97), labeled for corticosteroids for systemic use. C09, labeled for agents acting on the renin-angiotensin system, has shown significant correlations with 29 ATCs with a Z score of >1.96. The broad correlations between C09 and other ATCs might indicate that the renin-angiotensin system would be critical in many biological processes and diseases. However, M05, labeled for drugs to treat bone diseases, showed no significant correlations with other ATCs, which demonstrated that drugs for bone diseases possessed unique chemical features in comparison with drugs used for other ATCs.

Predicting ATC Classes for FDA-Approved Drugs. To evaluate the predictive performance of iSEA, the Z scores of 1151 approved drugs with 62 ATCs were calculated and ranked. For each approved drug, its known ATC class was evaluated by its ranking order within the whole Z-score list. As shown by the results summarized in Table 1, there were a total

Table 1. Result of Ranking Order of Approved Drugs and the External Data Set

	approved drugs	external data set
number of drugs	1151	54
number of drug−ATC pairs	1509	65
average predicted Z score	4.95	3.44
averaged ranking order	9.43/62	13.24/62
ATCs in top 10 ranking	1128/1509 (74.75%)	38/65 (58.46%)

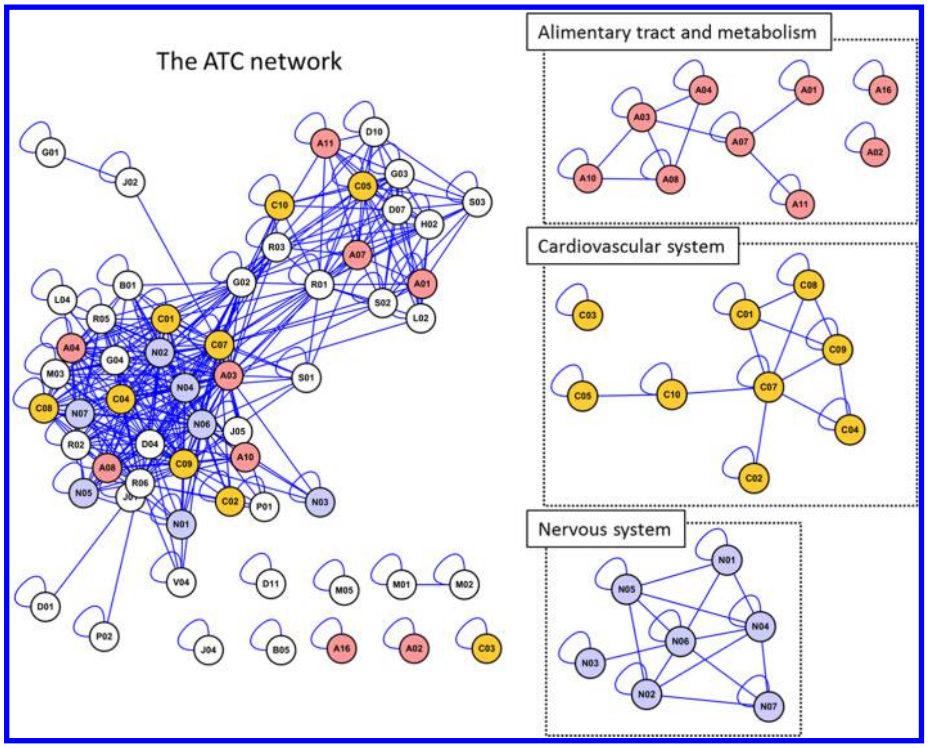

Figure 2. ATC network includes 58 ATCs and 370 significant correlations, as visualized by Cytoscape 2.8.2. A Z score of >1.96 was used to define connections. ATC classes in different anatomical locations were colored differently, and the edge color reflects the Z score between two ATCs. Subclusters of the ATC class in stomatological preparations (A), a cardiovascular system (C), and a nervous system (N) are also extracted and shown.

of 1509 known, approved drug−ATC relationships, and the average Z score of 1509 known relationships was 4.95, which is significantly larger than 1.96. The average rank order for all relationships was 9.43, which was significantly lower than the results of random prediction (expected to be 31 on average). Almost three-quarters (1128/1509) of known ATC class relationships were on the top 10 ranking list.

Several potential drug−ATC correlations were predicted by iSEA with even higher Z scores than previously known relationships between drugs and ATCs. For instance, the ATC codes of Flunisolide (DB00180) are R01AD04 and R03BA03 in the DrugBank, where R01 was predicted to be sixth in rank and R03 was in ninth in rank with Z scores of 7.20 and 4.44, respectively (Supporting Information Table S2). There were a total of 15 ATCs have a Z score of >1.96 with Flunisolide, such as D07, which had the highest Z score (17.91), which was also expected because Flunisolide was a corticosteroid receptor agonist that was close to the description of the D07 class, corticosteroids for dermatological preparations.

Predicting ATC Classes for Drugs in the External Drug Set. The good prediction performance on approved drug−ATCs may be attributed to the fact that these approved drug−ATC relationships have already been used in ATC drug set construction. Therefore, to evaluate the predicting performance of iSEA more rigorously, 65 drug−ATC pairs with 54 experimental or withdrawn drugs were used in this study as an external data set to test the predictive performance of drug repositioning by iSEA. Not all 65 external drug−ATC pairs were used to construct the ATC drug set. The ranking order of ATCs for drugs in the external data set was measured in the same manner for drug−ATC pairs of approved drugs. As shown in Table 1, the average Z score of 65 external drug−ATC pairs was 3.44, also significantly larger than 1.96, and the average rank order of ATC was 13.24, significantly lower than 31. In particular, there were 38 drug−ATC pairs with their known ATC classes ranked in the top 10. For instance, J01 was predicted to be the highest ATC (first) for Virginiamycin M1 (DB01669) and showed a high rank order with Temafloxacin (DB01405, ninth) and Ribostamycin (DB03615, fourth). Temafloxacin was a drug that was withdrawn from the market because of its lethal adverse reactions, and it was primarily applied as an antibacterial agent that was consistent with the J01 class. Virginiamycin M1 and Ribostamycin were two experimental drugs that were designed for the treatment of bacterial infections. All of them were primarily designed for J01 and this indication was successfully predicted by iSEA for these three drugs. This result indicated that iSEA was a promising approach to predicting drug−ATC relationships.

ATC Network Construction. An ATC network was constructed by connecting significantly correlated ATC pairs, which had a Z score of >1.96. As a result, the whole network contained a total of 58 nodes of ATCs with 370 connections. There were seven discrete nodes with self-linkage only and two nodes (M01 and M02) forming a small cluster by connecting only to each other. The giant component of the ATC network contained 49 ATCs and 360 connections, as shown in Figure 2.

We then focused on the connected relationships between ATCs in the same anatomical location, such as a cardiovascular system (C) and nervous system (N). The subcluster of these ATCs might reflect their internal correlation and closeness in a particular anatomical location. As a result, most ATCs in subclusters were connected, which suggested there would be some intrinsic relationships between those ATCs within the same anatomical category.

Topologies of nodes in the ATC network wereQ measured. Since betweenness among different clusters were not comparable, only nodes in the giant component of the ATC network were considered. As a result, nodes with the highest betweenness are listed in Table 2. In general, the high betweenness is also associated with a high degree. The ATC class with high betweenness and degree would indicated that it might be more similar to other ATC classes. For instance, C07, labeled for beta-blocker agents, showed the highest betweenness and degree in the ATC network. Additionally, it has been predicted to be highly correlated (Z score >1.96) with most of the ATCs in cardiovascular system, and it is presented as the hub in the cardiovascular system subclusters (Figure 2). C07 was also predicted to be highly correlated with ATC classes such as the alimentary tract and metabolism (A, 6 ATCs), cardiovascular system (C, 7 ATCs), nervous system (N, 5 ATCs), and respiratory system (R, 5 ATCs). This result indicated that beta-blocking agents might have nonselective effects on other indications. For instance, beta receptors, the target of beta blockers, were found on cells of the sympathetic nervous system and would lead to a stress response, which might be a reason that C07 also showed a close relationship with the nervous system.

Table 2. Node Topologies in the ATC Network

	ATC	betweenness	degree
1	C07	0.185	33
2	G02	0.123	25
3	A03	0.121	33
4	C09	0.121	30
5	R06	0.107	28

Drug Repositioning of Approved Drugs. In this work, we were also interested in discovering unrecognized indications of drugs in order to reposition them for novel clinical applications. In iSEA, a high Z score for one unknown drug−ATC pair may suggest a potential novel indication for this therapeutic agent.

To demonstrate the utility of iSEA in drug repositioning, two ATC classes were taken in this drug-repositioning study to represent two different conditions in term of internal drug diversity inside one ATC class. The first example was the C01 class, which is labeled for cardiac therapy. Among 1151 approved drugs, 50 drugs possessed known relationships with C01 that involves diverse drugs for distinct therapeutic indications, such as antiarrhythmics, cardiac stimulants, and vasodilators. Drugs in C01 encompassed several chemical classes, including glycosides, organic nitrates, and quinolone-like compounds. C01 would be a challenge for iSEA to relate drugs to this class because the chemical similarity was the foundation to relating them by our method. The Z score for the self-comparison of C01 was 6.21. Another example is C07 with a Z score of 20.86 for self-comparison, indicating a high degree of chemical similarity among drugs in this ATC. And iSEA was expected to show good performance in this class.

We calculated Z scores for 1151 approved drugs with C01 and ranked them to find potential C01 agents. Among the 297 approved drugs with Z scores >1.96 with C01, 33 drugs were known C01 agents. For instance, amyl nitrite (DB01612), labeled as an antidote (V03), had a significantly high Z score (3.15) with C01. Although it was not categorized in C01, amyl nitrite is employed medically to treat heart disease such as angina and cyanide poisoning. Research proved that it could induce a nonspecific relaxation of vascular smooth muscle that could lead to coronary vasodilation and the relief of myocardial ischemia according to DailyMed.[12] In addition to beneficial outcomes, our results also found that drugs with a high Z score for C01 might also show adverse reactions in the cardiac system. For instance, Orciprenaline (DB00816), also known as metaproterenol, was a beta-adrenergic agonist used in the treatment of asthma and bronchospasms. In our study, it showed a high correlation (Z score = 6.29, fifth rank in all approved drugs) with C01. It has been reported to cause cardiac arrhythmias and sudden death in laboratory animal experiments[13] and has been labeled in contraindications with patients with cardiac arrhythmias and other cardiac diseases. Similarly, Isoetharine (DB00221), also a selective beta 2-adrenergic receptor agonist, showed a high correlation with C01 (Z score = 6.20, sixth rank in all approved drugs). It was generally replaced by Alupent/metaproterenol in the late 1980s in part because of its high cardiac risk. Another example was Terbutaline (DB00871, Z score = 5.67 with C01), which also presented an elevated cardiovascular risk through an increased heart rate, cardiac arrhythmias, and myocardial ischemia in pregnant women (reported by DailyMed).

Results on C07 showed that the Z scores of all 22 known C07 drugs were >1.96 and 18 of them were located in the top 20 list based on their Z score ranking (data shown in Supporting Information Table S3). We inspected the potential of the remaining two drugs as beta-blocking agents. Metipranolol (DB01214) was labeled as S01ED04; however, it was actually a nonselective beta blocker[10] and could be used in the treatment of diseases such as glaucoma and central serous chorioretinopathy.[14] The other drug was Levobunolol (DB01210), which has also been demonstrated to be a beta-blocker agent.[15] Our results from drug repositioning for C01 and C07 indicated that iSEA could be used to find potential novel ATCs for approved drugs.

DISCUSSION

Fingerprint Criteria. The correlations among five fingerprint conditions were investigated, including three individual fingerprint methods and the average/maximum scores of these three methods. The Tanimoto score between two drugs was calculated from five conditions of chemical fingerprints. The Pearson correlation for Tanimoto scores was calculated for each drug pair, and the overall correlation between two fingerprints was then measured by the average Pearson correlation of all 1151 approved drugs.

The results of this study are summarized in Table 3. The average and maximum scores of three fingerprint methods were

Table 3. Pearson Correlation among Five Conditions of Fingerprint Selection

	average	maximum	CDK fingerprint	MACCS fingerprint	PubChem fingerprint
average	1.000	0.922	0.809	0.852	0.898
maximum	0.922	1.000	0.671	0.703	0.964
CDK fingerprint	0.809	0.671	1.000	0.520	0.677
MACCS fingerprint	0.852	0.703	0.520	1.000	0.613
PubChem fingerprint	0.898	0.964	0.677	0.613	1.000

highly correlated; however, three fingerprints were relatively different among each other. And the average score from three fingerprint methods was more closely correlated to three methods than the maximum value.

Predicting Novel ATC with iSEA. One of the most important aims of this work is to support the drug-repositioning study, in other words, to find novel indications of approved drugs or predict potential indications of unclassified drugs. Most current drug-repositioning approaches are based on the hypothesis that similar drugs are indicated for similar diseases,[16] thus the drug−drug similarity and the disease−disease similarity have been widely used to find new applications of existing drugs, such as side effects,[17] transcriptional responses following treatment,[18,19] and so forth. However, it was hard to describe the ATC indication quantitatively; therefore, it is difficult to study the similarities between indications and the similarities between drugs and indications. To the author's knowledge, iSEA was the first attempt to describe an ATC indication with chemical information about its drug ensemble, which was then used to measure the relationship between ATC classes and drugs.

In this study, iSEA predicted the new indications of drugs by the quantitative Z scores between drugs and ATCs, which represented the overall similarity between the test drugs and current drugs with known indications. In this study, we calculated Z scores of 1151 approved drugs and 54 experimental or withdrawn drugs with 62 ATC classes. As a result, we showed that iSEA was successful not only in discovering novel indications for approved drugs but also in predicting ATC classes for an external drug set. We demonstrated that some of our predictions were in accordance with the available drug descriptions, which suggested that further study could be undertaken for these potential indications for validation.

ATC Correlations in Network Pharmacology. Our work also indicated that there were still many significant correlations between ATCs although the chemical similarity between most drug−drug pairs was low. In fact, there were a total of 370 relationships between 58 ATC classes, and on average each ATC would be correlated with 6.38 other ATCs. However, the strength of correlation between ATC classes was not the same. As the Z score increases, the correlation between two ATCs is also strengthened. Therefore, ATC pairs with high Z scores would be more valuable in understanding the underlying relationships among ATC classes.

Network pharmacology[20] has become a critical concept in studying complicated relationships between biological entities such as genes,[21] diseases,[22] proteins, and metabolites; therefore, it might also be suitable to study relationships between ATCs. The classic ATC system offers valuable information about drugs, and our attempt to construct an ATC network provides new insight into the correlations across ATCs in order to understand better the connections between different therapeutic indications.

The major aim of this study was to associate ATCs according to their indirect relationships between drug sets, and our study has already revealed promising results of iSEA for this application. Although the chemical fingerprint was successfully applied in a previous study to measure ligand similarity, similarity based on chemical fingerprints also encountered limitations in molecular complexity and size effects.[23] A possible improvement of iSEA could be the incorporation of multiple similarity strategies to evaluate drug similarity such as shared targets, side effects, and pharmacophores in order to represent the relationships between ATCs better.

CONCLUSIONS

In this study, we presented a novel approach, iSEA, to study the relationships between ATCs. We have shown that ATC classes could be related to each other by their drug set similarities. Our results revealed both expected and unexpected relationships between ATC classes, which might be used to understand the ATC system better and provide an opportunity for a drug-repositioning study. Our method was validated by successfully predicting indications of approved and unclassified drugs, and the results suggested that at least some of the predicted relationships merit further investigation. Additionally, we constructed an ATC network to present complicated relationships among ATC classes, which was the first attempt to study ATC relationships from a network point of view.

ASSOCIATED CONTENT

Supporting Information

Distribution of the Tanimoto score (Ts) for whole drug pairs. Linear relationship between drug pair size and evaluating score (Es). All 1574 drug−ATC pairs used in this study. Result of Z scores of Flunisolide. Z score for C07 with 1151 approved drugs in a drug-repositioning study. This material is available free of charge via the Internet at http://pubs.acs.org.

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Notes

The authors declare no competing financial interest.

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