The New Tale of Some Old Drugs

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Abstract

In-silico drug repositioning is a recent trend in drug discovery that aims at revealing new pharmacological properties for drugs that are already in medical practice. We present the results of a new approach in drug repositioning, which employs clustering and community detection in drug-drug interaction networks. As such, we built a drug-drug interaction complex network (*i.e.*, interactome), where nodes represent drugs and links represent the interactions between drugs according to DrugBank4.1. By applying a combination of two clustering methods, namely energy model layout and modularity algorithms, we generated 9 topological communities and 7 modularity classes respectively. The pharmacological properties for 85% of the analyzed drugs are confirmed by other drug databases, and specialized literature. However, 15% of the drugs do not exhibit the pharmacological properties indicated by their topological communities or modularity classes; therefore, these properties are considered repositioning hints. Some of these hints were tested by in vivo and in vitro experiments, as well as by clinical trials. Here, we present such examples of drug repositioning hints that were subsequently investigated and confirmed.

Keywords: drug-drug interactions, drug repositioning, complex network analysis

Introduction

The drug discovery process is laborious, time-consuming and susceptible to failure [1], [2]. Indeed, during the last couple of decades we did not witness an increasing number of newly discovered molecules. Therefore, drug repositioning becomes a feasible strategy for uncovering new pharmacological properties for drugs that are already used in medical practice [3]. Here, we discuss the results of a new approach for drug repositioning, which consists of analyzing drug-drug interactions networks. As such, we build a drug-drug interactome, namely a complex network containing 1141 drugs (nodes) for which interactions are reported in DrugBank4.1 [4] public database; in our network interactions are represented as links between drugs. By appling a dual clustering technique (*i.e.*, energy model layout and modularity algorithms [5], [6]) we obtain 9 topological communities and 7 modularity classes. Expert analysis reveals that each community is characterized by relevant pharmacological properties [5]. These properties are confirmed for 85% of the drugs, by scanning databases and relevant literature. The remaining 15% of drugs do not seem to exhibit the pharmacological properties that are indicated by the topological communities or modularity classes. We interpret such cases, as well as the cases of drugs that are placed in the overalpping zones between topological communities, as repositioning hints [5]. To test the predicted pharmacological properties, some hints are subjected to vivo and in vitro experiments, as well as to clinical trials. In this paper, we follow the story of such drug repositionings that were predicted by the technique presented in [5], then experimentally investigated and confirmed.

Methodology

To build the drug-drug interactome, we consider the information on drug-drug interactions from DrugBank4.1, then interpret drugs as *nodes*, while *links* represent drug interactions, using Gephi [7]; nodes are sized according to their degree (*i.e.*, number of incident links). The resulted complex network of drug interactions is clustered with two concurrent algorithms: modularity class and force directed layout (ForceAtlas 2 [7]). The topological clusters resulted from employing ForceAtlas 2 generally coincide with the modularity classes represented with distinct colours. This type of analysis is characteristic to the field of social networks [8], [9]. Using expert analysis, we associate a dominant pharmacologic property to each topological cluster and each modularity class, then validate the assigned labels by scanning e-literature. Our drug repositioning hints are rendered as either drugs which are apparently misplaced (*i.e.*, seem not to comply with the assigned label/property) or drugs which lie within the overlapping zone between topological communities (*i.e.*, drugs which may have all the properties which characterize communities which overlap). The entire methodology is summarized in Fig. 1.

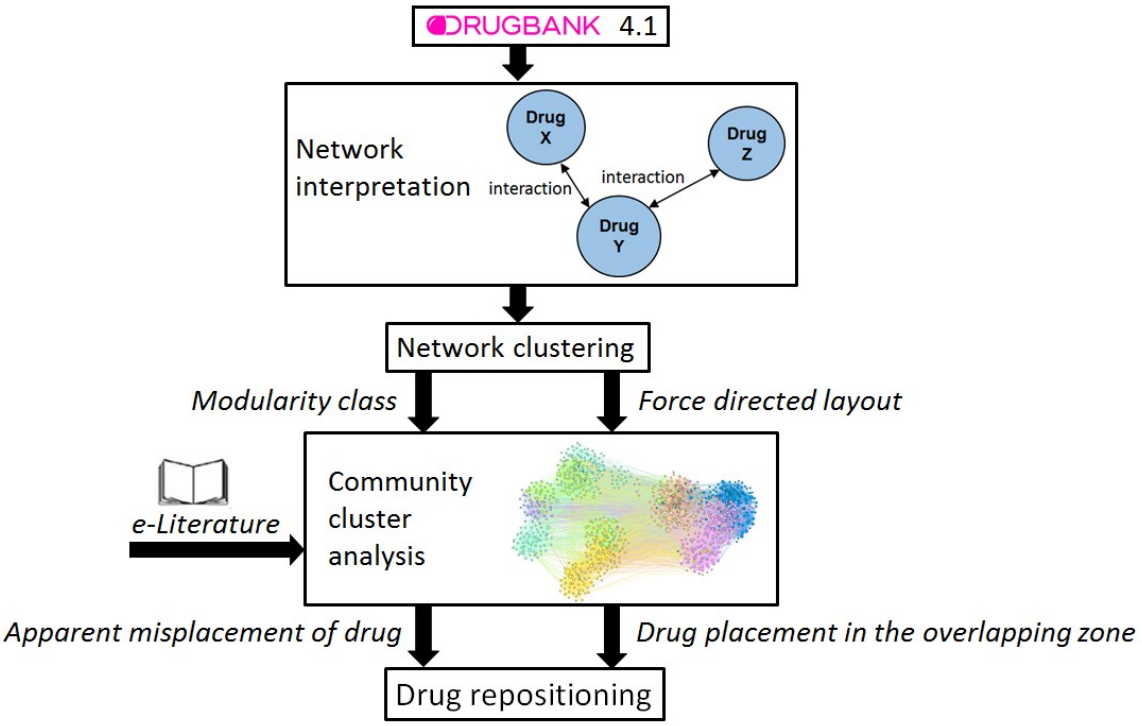

Fig. 2. Overview of the network-based in silico drug repositioning methodology [5], using drug-drug interaction information taken from specialized comprehensive databases

Results

Confirmations of Our Predicted Properties

According to each drug topology and modularity class, our dual clustering technique is able to reveal multiple properties of a drug molecule, namely pharmacokinetic, pharmacodynamic and pharmaco-toxicological, using only drug interaction data. At the same time, when a drug is placed in the overlapping zone of *k* topological clusters it may manifests the *k* pharmacological properties that characterize those clusters. In the following sub-sections, we present some interesting examples of how our methodology works.

Pharmacokinetic Properties Confirmations

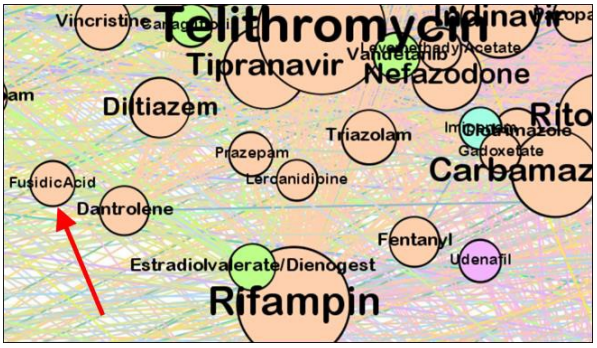

Fig. 3. Zoomed detail from our clustered drug-drug interaction network which indicates the placement of fusidic acid within topological cluster of drugs interfering with cytochrome P450 enzymes [5].

In our drug-drug interaction network, fusidic acid (see Fig. 2) is placed in the topological community of cytochromes P450 substrates, inhibitors and inducers [5]; the velvet maroon modularity class confirms this property. This pharmacokinetic property of fusidic acid is confirmed by reference [10], demonstrating that fusidic acid is eliminated primarily via CYP 3A4 pathway.

Pharmacodynamic Properties Confirmations

Fig. 3 presents two examples of drugs for which our methodology predicts new pharmacodynamic properties: acyclovir and nebivolol. Fig. 3a indicates that acyclovir is a light blue node which is placed within topological community of Immune system related drugs [5]. Light blue modularity class indicates drugs with anticancer properties, as well as drugs targeting autoimmune disorders and musculoskeletal system [5]. Acyclovir is an antiviral agent which induces apoptosis in tumor cells and inhibits tumor cell proliferation when it is encapsulated in lipid/calcium/phosphate nanoparticles [11]. Moreover, a recent research estimates, by applying an in-silico approach, that acyclovir exerts antitumor effect by inhibiting β-transducin repeat-containing protein (βTrcp1) [12]. As indicated, both topology and modularity of acyclovir are confirmed [5] by different research tools. Fig. 3b shows the topological position of nebivolol within community containing sympathetic system acting drugs.

Indeed, nebivolol is an adrenergic beta1 blocker [4]. Nebivolol belongs to the golden-brown modularity class, indicating that nebivolol may interfere with platelet activity and plasma potassium levels. Falciani *et al*., demonstrate that nebivolol inhibits platelet aggregation in human plasma by a mechanism that differs from other beta-blockers [13], confirming nebivolol's modularity class [5].

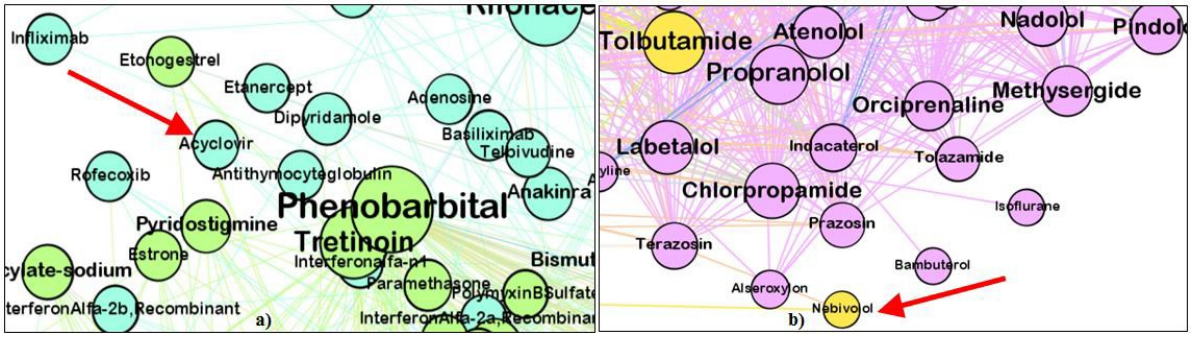

Fig. 4. Zoomed detail from our clustered drug-drug interaction network which indicates the placement of a) acyclovir within the topological community containing immune system related drugs, and b) nebivolol within topological community of sympathethic system acting drugs [5].

Pharmaco-toxicological Properties Confirmations

Ampicillin, amoxicillin, penicillin G and penicillin V are penicillin antibiotics used for treating infections caused by susceptible bacteria [4]. In our drug-drug interactome, these penicillin drugs, as presented in Fig. 4a, are clustered within the topological community of drugs interfering with

epilepsy, which are either anticonvulsant or epileptogenic drugs; they are also pertaining to green modularity class, indicating drugs that are related to hemostasis and epilepsy [5]. Their topological placement is explained by literature: a review paper presents the neurotoxic effects of penicillins, concluding that penicillin G is highlighted as the most dangerous penicillin agent in terms of seizure inducing potential [14]. Fig. 4b indicates with red arrows aminoglycoside antibiotics that are topologically clustered within the community of drugs acting on neuromuscular junction. All drugs clustered in this topological community pertain to the light blue modularity class, which contains drugs targeting cancer, rheumatoid arthritis and neuromuscular transmission [5]. The potential pharmaco-toxicological effect after systemic use of aminoglycosides is underlined in the drugs.com database [15], thus recovering a specific side effect of aminoglycosides, while also emphasizing the predicting power of our methodology [5].

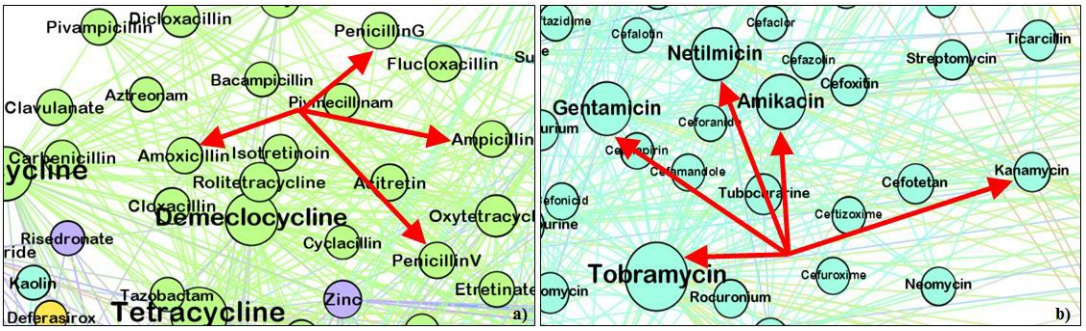

Fig. 5. Zoomed detail from our clustered drug-drug interaction network which indicates the placement of: a) ampicillin, amoxicillin, penicillin G and penicillin V within the topological community of epilepsy related drugs, and b) amikacin, gentamicin, kanamycin, netilmicin, and tobramycin within the topological community containing neuromuscular transmission acting drugs [5].

Confirmations of Multiple Pharmacological Properties in the Overlapping Zones

Ofloxacin and pefloxacin are two fluoroquinolones that are placed in the topological community of metal cation complexes, also in the overlapping area with the topological community of drugs acting on neuromuscular transmission (see Fig. 5) [5]. Pefloxacin stands out by its light blue color (*i.e.*, modularity class), which is associated with drugs related to cancer, autoimmune disorders and neuromuscular transmission [5]. Ofloxacin pertains to the purple modularity class which indicates both metal cations and drugs having chelating properties. Indeed, ofloxacin complies with the tag of the corresponding modularity class [5]. Both the topology and the modularity class are confirmed by their ability to form complexes with metal cations, thus having consequences on the pharmacokinetic profile (decreased gastro-intestinal absorption) and on the pharmacodynamic activity (improved antibacterial effect, anticancer, antifungal or antiparasitic activity) [16]. Also, ofloxacin and pefloxacin have a neuromuscular blocking effect [15].

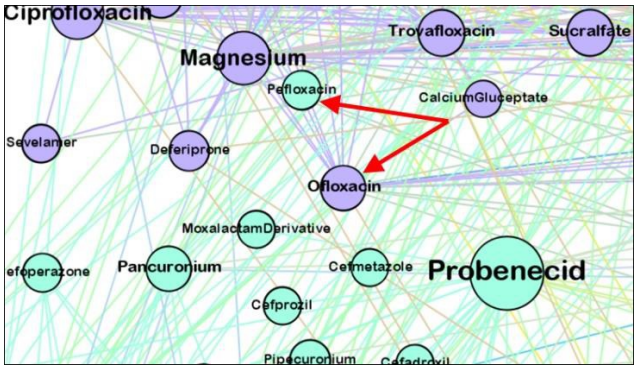

Fig. 6. Zoomed detail from our clustered drug-drug interaction network, which indicates the placement of pefloxacin and ofloxacin in the overlapping zone between topological community containing neuromuscular transmission acting drugs (which is characterized by a light blue modularity class) and topological community of metal cations complexes (which is characterized by purple and green modularity classes) [5].

Recent Confirmations of Our Repositionings Hints

Repositionings Confirmed by Animal Studies

Fig. 6 presents two drugs for which recent animal experiments proove the pharmacological properties predicted by [5]. In Fig. 6a we show the placement of montelukast, an anti-inflammatory for airway diseases, as a golden-brown node – corresponding to the modularity class that characteriezes drugs interfering with platelet activity and kalemia level. Montelukast lies within the topological community of drugs which act on the Sympathetic Nervous System. Our dual clustering methodology recovers the platelet inhibitory activity and brings out the potential interference with adrenergic system for montelukast [5]. Recent research authored by Dobrek *et al*., demonstrates, using rats' experiments, that montelukast acts on the Autonomic Nervous System – independently on its leukotriene receptors antagonism –, and that it can restore the sympathetic disfunction, thus improving the sympthoms in bladder overactivity [17]. Melatonin, as presented in Fig. 6b, is a green node within the topological community of epilepsy related drugs. Melatonine is a biogenic amine used in cyrcadian rythm sleep disorders and for its antioxidant properties [4]. A review paper [18] concludes that the relationship between melatonin and seizures is not sufficiently supported by relevant data in previous literature. However, Rocha *et al*., [19] start their study on rats from the ascertainment of a circadian component on seizure manifestation, responsible for modifications in melatonin production. The authors determine that the expression levels of melatonin receptors MT1 and MT2, as well as the mRNA expression level, are altered in pilocarpine-induced status epilepticus in rats, in both silent and chronic phases [19].

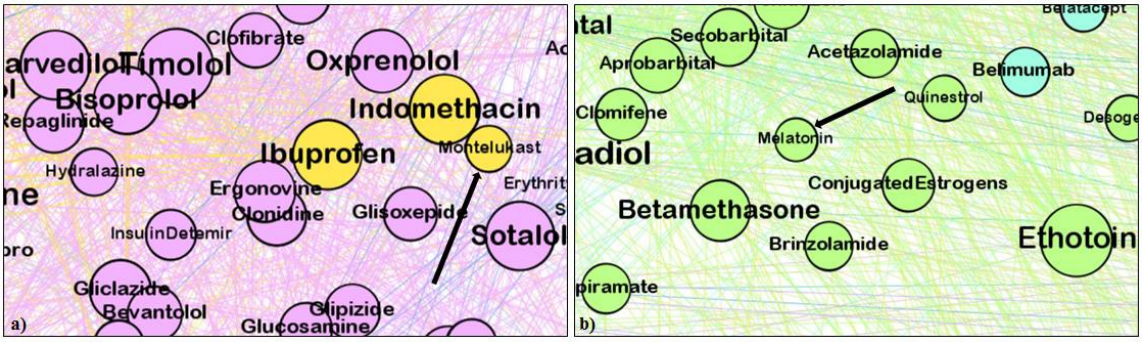

Fig. 7. Zoomed detail from our clustered drug-drug interaction network which indicates the placement of a) montelukast within the topological community of Sympathetic Nervous System acting drugs; b) melatonin within the topological community of Epilepsy relatd drugs [5].

Repositioning Hint Evaluated in Clinical Trials

Lamivudine, as presented in Fig. 7, pertains to the light blue modularity class that lays within topological community of immune system related drugs. The light blue modularity class includes drugs with anticancer and immunomodulatory properties, as well as drugs used for the treatment of rheumatoid arthritis and other autoimmune musculoskeletal diseases. In our previous work [5], we indicate that lamivudine – as a direct acting antiviral drug used to treat hepatitis B and HIV infections [4] – has an apparent inopportune and unexplained placement according to other databases and literature; consequently, such a situation indicates that lamivudine can be repositioned. As confirmation, a recent clinical trial examines the effectiveness of lamivudine in p53 mutant metastatic colorectal cancer [20].

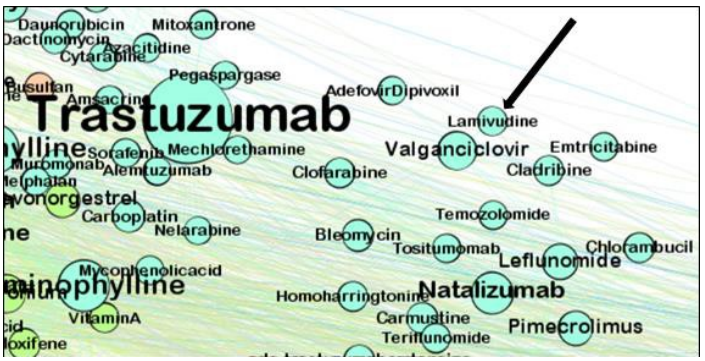

Fig. 8. Zoomed detail from our clustered drug-drug interaction network which indicates the placement of lamivudine within the topological community of immune system related drugs [5].

Conclusion

Underpinned by its ability to represent complex systems and big data, network science offers effective strategies for drug repurposing. As shown, the dual clustering of the drug-drug interaction network is able to predict many repositionings which were subsequently confirmed by in vivo and in vitro experiments.

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