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Computational Models of Neurological Disorder

Computational Drug Networks: a computational approach to elucidate drug mode of action and to facilitate drug repositioning for neurodegenerative diseases

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While computational approaches based on chemical structures have been extensively used in drug discovery, drug induced transcriptional responses provide a complementary view of their effects. Network visualizations facilitate the exploration of the chemical space in a comprehensive, integrated view. Systematic approaches can be particularly useful for repositioning drugs acting on the CNS, where polypharmacology, targets promiscuity and pharmacokinetic properties must be finely tuned. Here we present a review of the most recently developed methodologies for comparative structure-based and transcriptomics analyses together with applications to the field of Drug Repositioning. We also show an application example in which we searched for drugs and perturbagens inducing cellular autophagy, a suitable strategy to improve phenotype of neurological diseases.

Introduction

Drug repositioning represents a convenient alternative to the classical drug discovery pipeline by identifying new therapeutic applications for existing marketed drugs [1]. During past decades, the main strategy for drug development has been high-throughput screening to identify compounds showing activity against single therapeutic targets or pathways. However, the ratio of successfully identified drugs to screened molecules has decreased dramatically [2]. The ''one drug, one disease, one target'' paradigm has been overcome by the more comprehensive polypharmacology and Systems Biology approaches, especially for CNS diseases. Moreover, integrated approaches can rely on multiple layers of biological information extracted from genes, pathways, targets and

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drugs as interaction networks [3,4], providing new alternatives for drug discovery and repositioning for neurological and CNS disorders from a systemic perspective.

Chemical networks

The classical computational medicinal chemistry approach investigates Structure Activity Relationships (SAR) between drugs, by structurally comparing them and searching for New Chemical Entities (NCEs) or repositioning. The concept is based on the chemical similarity principle milestone assessing that structurally similar drugs are likely to have similar biological activity and MoA [5]. Usually, in computational medicinal chemistry, a drug is represented as a set of physicochemical or molecular features (e.g., molecular substructures, chemical groups, atomic pathways that are responsible for biological activity) encoded by molecular fingerprints.

Drug chemical structure similarities can provide interesting opportunities for repositioning and target identification. The increasing amount of publicly databases of chemical structures and high-throughput screening data ([6–9]; see Table 1 of [10]) will be crucial sources of information for drug development methodologies in the next future. For instance, the PubChem database (ref.), one of the most famous source of drug biological and chemical information, contains over 100,000,000 compound and substance records linked to biological property information and bioassays for target identification collected from several scientific studies and analysis wolrdwide.

In order to manage the huge amount of data coming from the different annotation sources, network visualizations have been exploited in which nodes represent drugs and edges between nodes highlight relations such as significant similarity of the corresponding chemical structures or transcriptional effects. Network-based drug discovery aim to systematically investigate the space of small molecules in order to disclose their modes of action and/or identify innovative therapeutic treatments [2,11].

Chemical similarity networks (representing structurally similar small molecules as connected nodes in a network) have been applied to identify off-targets and metabolic effects and thus predict polypharmacology, side effects and novel therapeutic effects for several different compound sources and annotation databases [12–21].

One of the most recent uses of chemical similarity networks for drug repositioning regards CSNAP3D [22], a 3D upgrade of the CSNAP framework for large-scale network-based drug target prediction based on ligand superposition. A CSNAP3D analysis incorporating 2D and 3D similarity metrics led to the identification of peculiar pharmacophore features of HIVRT inhibitors Efavirenz, Nevirapine and Tivirapine, which are rather different in their molecular shape. The algorithm has been experimentally validated by analysing novel antimitotic compounds and identifying several low molecular weight microtubule-stabilizing agents that mimic the Taxol binding mode and exhibit anticancer activity.

However, drug-target interaction networks cannot be used to predict potential targets for new chemical entities, such as newly synthesized chemical structures or drugs failed in clinical trials. To this end, Wu *et al*. [23] proposed an integrated network and chemoinformatics tool, named Substructure Drug Target Network Based Inference (SDTNBI), for large-scale DTI (Drug-Target Identification) prediction and drug repositioning. SDTNBI uses chemical substructures, which are a set of features that can be shared by chemical structures, to bridge the gap between known drugs and new chemical entities. They were able to identify nonsteroidal anti-inflammatory drugs (NSAIDs) as novel anticancer drugs, targeting AKR1C3, CA9, CA12 or CDK2.

An important aspect in medicinal chemistry for brain disease regards drug optimization for brain penetrance (Brain–Blood–Barrier permeability). Drug bio-availability is a critical step in the development of CNS drugs for neurological and neurodegenerative disorders such as Alzheimer disease (AD), Parkinson disease (PD), Huntington disease (HD), multiple sclerosis (MS), amyotrophic lateral sclerosis (ALS) and encephalitis [4,24]. In this particular context, drug repositioning represents a particularly convenient strategy because compound profiles have already been pharmacokinetically optimized and approved in Phase I clinical trial [25].

Table 1. Top-10 drug neighbours of Sirolimus.

Rank	Drug/perturbagens neighbours	Mantra distance	Target	MoA
1	Wortmannin	0.547	PI3K	Anticancer
2	PI3K_Ex20dmso/inh_F	0.588	PI3K	
3	Quinostatin	0.614	PI3K	Anticancer
4	ERK CI1040 Panc2.13	0.659	ERK	Anticancer
5	Trifluoperazine	0.662	DRD2	Antipsychotic
6	Insulin reverse signature	0.67	IGF-1	
7	Latamoxef	0.678	pbpC	Antibiotic
8	Methylergometrine	0.689	DRD1	Antipsychotic
9	Emetine	0.716	40S ribosomal sub-unit	Antihelmintic
10	Co-dergocrine mesilate	0.717	ADRA2A-1A, 5HTRs, DRD1-2	AD/dementia