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Computational prediction of drug-drug interactions based on drugs functional similarities

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ABSTRACT

Therapeutic activities of drugs are often influenced by co-administration of drugs that may cause inevitable drug-drug interactions (DDIs) and inadvertent side effects. Prediction and identification of DDIs are extremely vital for the patient safety and success of treatment modalities. A number of computational methods have been employed for the prediction of DDIs based on drugs structures and/or functions. Here, we report on a computational method for DDIs prediction based on functional similarity of drugs. The model was set based on key biological elements including carriers, transporters, enzymes and targets (CTET). The model was applied for 2189 approved drugs. For each drug, all the associated CTETs were collected, and the corresponding binary vectors were constructed to determine the DDIs. Various similarity measures were conducted to detect DDIs. Of the examined similarity methods, the inner product-based similarity measures (IPSMs) were found to provide improved prediction values. Altogether, 2,394,766 potential drug pairs interactions were studied. The model was able to predict over 250,000 unknown potential DDIs. Upon our findings, we propose the current method as a robust, yet simple and fast, universal *in silico* approach for identification of DDIs. We envision that this proposed method can be used as a practical technique for the detection of possible DDIs based on the functional similarities of drugs.

1. Introduction

During pharmacotherapy, drug interactions (DIs) can interfere with the treatment process and cause serious health complications as well as social and financial consequences. Therefore, prevention of pharmacotherapy errors is considered as a priority for health systems worldwide [1]. In most treatment procedures, therapy with multiple drugs or co-administration of drugs is common [2]. Drug-drug interaction (DDI) emerges when the pharmacological effect(s) of a drug influenced by another drug, which often results in some unexpected side effects [3]. The occurrence of DDIs may literally lead to various adverse drug reactions (ADRs) that cause inevitable detrimental consequences [4–6] and high costs for the health providers and hospitals [7,8]. ADRs can directly influence the patient health and the safety of pharmacotherapy modality, while 30% of which is related to DDIs [9]. Approximately 3% of all hospital admissions are related to DDIs [10] and considerable portion of all inpatient medication errors are related to DDIs [11]. The complex nature of DDIs makes them extremely difficult to predict, while ADRs are highly expensive to be diagnosed and practically hard to be treated.

New drugs are entering market every year (e.g., 45 novel drugs approved by FDA in 2015) and identification of DDIs is crucially indispensable. Methodologically, physicochemical (PC) properties of drugs and pharmacokinetic (PK) and pharmacodynamic (PD) features are involved in development of DDIs [12–14].

Identification of DDIs is possible through *in silico*, *in vitro* and *in vivo* experiments, while the two latter approaches appear to be very costly and in some cases impossible to be carried out. In addition, in most cases, DDIs elicit serious side effects that are hard to be measured through *in vitro* or *in vivo* experiments [15]. For example, ADRs that occur in chemotherapy of cancer or combination therapy during clinical trials are typical paradigms. Thus, considering the current advancement(s) in data-driven biology/pharmacology, there exist a high tendency and demands for the prediction of DDIs by means of *in silico* computational methods [16].

In drug development and identification of DDIs, several computational approaches have successfully been used [3,17–21]. Text mining methods [22] and prediction of DDIs based on protein-protein interactions network [3] are considered as powerful strategies for prediction of DDIs based on computational approaches.

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Prediction of DDIs with the aid of machine learning algorithms [23] and drugs molecular structures similarities [24] are another paradigms of *in silico* methods in DDIs prediction.

By reviewing the DDIs identification methods in the literature, in general, three types of methods have been distinguished, including: (i) *in vitro* and *in vivo* experimental methods, (ii) patient-oriented methods (e.g., patient's social networks [25], texts and medical records[15]), and (iii) *in silico* computational predictive methods. While the experimental and patient-oriented methods are laborious and costly, the computational approaches provide robust means for the DDIs prediction [26,27]. For instance, Tari et al. presented a text mining and reasoning approach based on drug metabolism. DDIs founded by this study displayed about 81.3% validity as compared to the DrugBank entries. However, the number drugs studied was low – they examined 256 drugs and found 494 DDIs [22]. Gottlieb et al. presented a computational framework for prediction of CYP-related DDIs and non-CYP-associated DDIs. In this study, 37,212 interactions were studied, through which about 11,445 CYP-related DDIs and 18,601 non-CYP-related DDIs were predicted [28]. Huang et al. reported on a systematic prediction method for PD-DDIs through protein-protein interaction network. They predicted 9626 potential PD-DDIs after studying on 1249 FDA approved drugs [3]. Vilar et al. presented a DDI identification method based on drug chemical and molecular structure fingerprint, and the similarity of drug pairs was calculated by Tanimoto coefficient based on their molecular fingerprints. After studying 9454 DDIs, they predicted 58,403 DDIs. However, in the human body, different chemical formulation may have similar behaviours that have not been yet covered [21]. Vilar et al., in another study, presented a similarity based model for the prediction of DDIs using 2D/3D molecular structure of drugs, interaction profile and side effects similarities. They studied 928 drugs and 9454 interactions, and predicted 430,128 possible DDIs [24]. As versatile high-throughput tools, these strategies have facilitated the drug discovery and development (DDD) processes [29]. Based on DrugBank [30], any given drug can associate with at least four biological elements, including: carriers, transporters, enzymes and targets (CTET). For example, estradiol is a hormonal drug that exemplifies such association with the biological elements in human body as shown in Fig. 1.

By definition, carriers are secreted proteins through which drug molecules are transferred within the biological fluids [31]. Transporters are membrane bound proteins that are involved in inward/outward transportation of drug molecules at cellular level [32]. Enzymes are proteins that are engaged with designated biochemical reactions (e.g., drug biotransformation by the cytochrome P450 enzymes). Targets are biological components that drugs interact with and alter their function to induce therapeutic effect(s) [33].

If a carrier, transporter, enzyme or target of a given drug is occupied or changed by another drug, then the pharmacological activity of the given drug is changed. Occurrence of such DDI may result in an increased or decreased/diminished therapeutic and or toxicological effects, and elicit ADRs and inevitable failure of the treatment modality. Thus, sharing common biological entity (i.e., carrier, transporter, enzyme or target) is likely to result in emergence of serious DDIs and ADRs, whose identification demand various *in vitro* sophisticated experimental techniques [34,35].

Computationally, similarity and dissimilarity measures have been exploited as the foundation of all modern pattern classification and clustering algorithms [36] in different scientific fields such as drug discovery and development (DDD). Based on the computational nature of similarity analysis, the binary vector similarity is common data format that has been used by most algorithms. However, recently some other similarity measures have been developed and used for non-binary vectors efficiently [37]. The three main categories of binary similarity measures are: (i) the Hamming/distance based methods, (ii) the inner product-based methods, and (iii) the correlation-based methods. Hamming based measures provide a number that simply denotes the difference between two binary strings (e.g., Euclidean and Hamming [38]). The inner product measures are basically calculated based on dot product of the binary vectors (e.g., Dice [39] and Russel-Rao [40]). In the literature, the Russell-Rao similarity measure has successfully been applied for different phenomena, including: hand writings [41], chemicals similarities [42] and fingerprints [43]. The correlation based measures utilize coefficients of correlation (e.g., Yule [44]). It should be noted that the binary feature vector similarity measures differ from each other in terms of inclusion/exclusion of negative matches. Also, to obtain optimized performance, there are

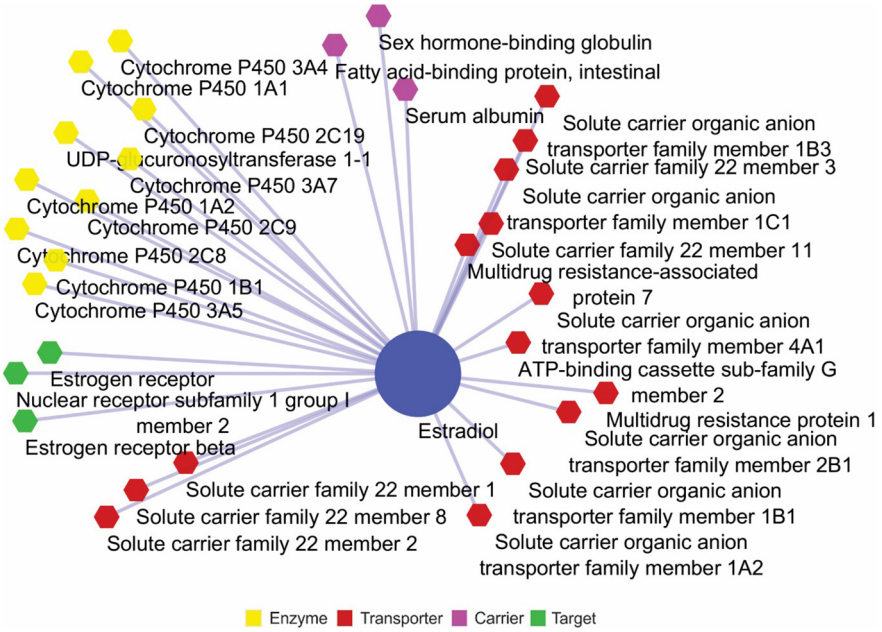

Fig. 1. Estradiol association with biological elements.