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Prediction of synergistic drug combinations

Zohar B. Weinstein[1], Andreas Bender[2] and Murat Cokol[3,4]

Abstract

Given the large number of possible drug combinations, computational methods to prioritize the most effective treatments are critical. Here, we present four methodologies for predicting synergistic drug interactions. Mechanism based synergy prediction utilizes well-characterized biological data to predict drug interactions based on drug target interactions. Guilt by association methods predict novel interactions based on similarity to compounds with known interactions. A frequentist approach uses a drug's known tendency to exhibit drug interactions. Compound descriptor array based methods use machine learning approaches to relate compound interactions with arrays of observations regarding a compound. The increasing success of drug synergy prediction methods offer a means toward designing rational drug combinations.

Addresses

[1] Department of Pharmacology and Experimental Therapeutics, Boston University School of Medicine, Boston, MA, USA
[2] Centre for Molecular Informatics, Department of Chemistry, University of Cambridge, Cambridge, UK
[3] Department of Molecular Biology and Microbiology, Tufts University School of Medicine, Boston, MA, USA
[4] Laboratory of Systems Pharmacology, Harvard Medical School, Boston, MA, USA

Corresponding author: Cokol, Murat (murat_cokol@hms.harvard.edu)

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Combination therapies are the *de facto* treatment for many diseases including tuberculosis, HIV and cancer [1–3]. With the emergence of microbial pathogens resistant to virtually all antibiotics, and drying antimicrobial drug discovery pipeline, drug combinations offer treatment optimization against infectious diseases [4,5]. However, drugs may "interact" and the combination may have greater or lesser efficacy than expected, resulting in synergistic or antagonistic interactions, respectively [6,7]. Utilizing synergistic combinations while avoiding antagonistic combinations may be of paramount importance for the success of a treatment.

Predicting drug interactions

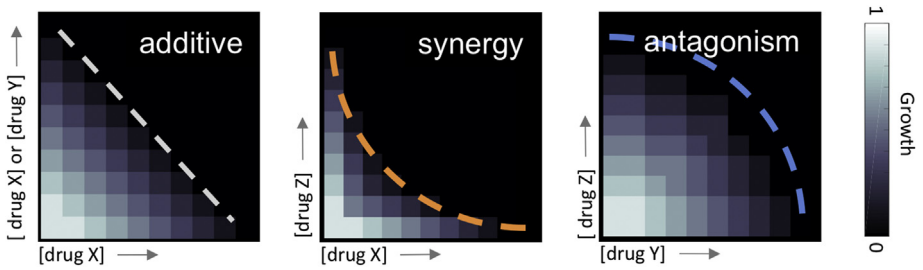
Experimental *in vitro* measurement of drug interactions is costly and labor intensive, involving the preparations of drug combinations and the recording of phenotypes (Figure 1) [6,7]. For a set of 100 drugs, there are 4950 unique combinations of drug pairs, each with the possibility of exhibiting synergy. The current experimental cost of drug interaction testing, however, prohibits the screening of such large drug interaction matrices. Computational tools to predict combinations can prioritize compound pairs for further synergy tests, overcoming the costs of brute force screening approaches [8–10]. By integrating currently available drug interaction data with increasing knowledge of drug properties and their cellular effects, we can better understand the biological basis of drug interactions. The prediction of drug synergy has inspired DREAM challenges, where predictions for large sets of pairwise drug interactions are solicited from the scientific community [11].

The results of a pairwise drug interaction screen can be represented as a network, where nodes are drugs, and edges are synergistic, antagonistic or additive interactions [12]. The challenge of predicting novel pairwise drug interactions is analogous to defining a new edge in the network.

Mechanistic predictions are based on specific knowledge of drug mechanism of action of each compound [13]. Two compounds may exhibit synergy if they target parallel pathways or if one increases the bioavailability of the other [14]. Accordingly, the understanding of the pathways affected by a compound can be used by experts to generate hypotheses on the interaction of compounds. The hypothesis that *drugs whose targets are encoded by two genes with synthetic lethality are expected to show synergy* has attracted attention [15]. Another study modeled the flux in metabolic pathways affected by each drug to predict synergy [16]. Importantly, these studies required the compound structure or metabolic pathways, respectively, and the genetic interactions alone were not sufficient for synergy prediction, emphasizing data integration for the prediction of complex biological phenomenon. One difficulty concerning mechanistic predictions is that drug target or mechanism of action data is not available for most compounds.

In *guilt by association methods*, an interaction is transferred from one drug to another based on mechanism of action or

Figure 1



Drug interaction types. Sensitive assessment of drug interaction types using a traditional checkerboard assay is shown. In a checkerboard assay, cells are exposed to two drugs, linearly increasing from no drug to minimal inhibitory concentration on each axis. A heatmap for growth demonstrates the growth response to the drugs. For non-interacting drugs (shown here is the null model of a drug combined with itself), isophenotypic contours for levels of growth inhibition are parallel lines (left). Synergistic combinations require less drug to achieve the same level of inhibition as individual drugs, as seen by a concave isophenotypic contour (middle), while antagonistic combinations are represented by convex isophenotypic contours (right).

chemical structure similarity, analogous to predicting protein function based on gene conservation [17]. For example, erythromycin and clarithromycin vary structurally only by one carbon and two hydrogen atoms (2% difference in molecular weight), and both target the 50S ribosomal subunit. As expected, interactions with other drugs are highly correlated between these two antibiotics [18]. Therefore, knowledge of erythromycin's interaction with drug X is a good predictive tool for clarithromycin's interaction with drug X, based on their similar chemical structures. Another example is compounds haloperidol, fenpropimorph and dyclonine, which target ergosterol biosynthesis in the yeast. The interactions of these three drugs are also very similar, allowing prediction of new interactions with guilt by association [19]. This prediction method is dependent on a large set of interaction tests among related compounds. While drugs with similar targets cluster together in drug interaction networks, individual interactions may still vary.

Frequency based methods predict a drug interaction by considering the previously reported interaction frequencies. For example, if drug A has shown synergy in 50% of tested cases in a large set of experiments, then it is expected to show synergy with a novel compound with 0.5 probability. Consider the pyruvate analog bromopyruvate, which may kill glycolysis dependent tumor cells. A recent screen found that bromopyruvate is antagonistic with almost all compounds it was tested with in yeast [20]. A frequency based method would predict that bromopyruvate will show more antagonisms with new compounds. While it can yield reliable predictions for some drug pairs, this prediction method requires a previous screen to establish the interaction frequency of each drug.

Compound descriptor array (CDA) based methods

This class of methods uses compound descriptor arrays (CDAs), which are arrays of numbers that correspond to any type of quantitative information related to a drug. This information may be either related to its chemical structure, or derived from biological experiments (e.g. protein affinity fingerprints) [21]. CDA-based methods then use statistical or machine learning models to relate such quantitative data on drugs, which are meant to capture their ability to modulate a biological system, to the drug interactions they exhibit.

CDAs can be obtained experimentally or computationally. Experimental CDAs may include chemogenomic profiles, which report the sensitivity of genome wide gene deletion sets to a drug [22,23], or bioactivity measurements against a large panel of isolated proteins, similar to those conducted in safety pharmacology [24]. An alternative means of assessing genes associated with drug sensitivity is transcriptomic profiles after drug exposure [25]. Using these data sets, the CDA has a length equivalent to the number of genes that are evaluated. Each value in this array may correspond to the drug sensitivity change in response to a gene deletion or a transcription change in response to a drug. Other experimental CDAs include metabolomics data and compound physicochemical properties [26,27].

CDAs may also be obtained computationally. The chemical structure of a drug can be transformed into a binary CDA depending on the presence or absence compound substructures [28]. Compound physicochemical properties may also be derived computationally [29]. The advantage of these computational CDAs is that they are cheap to obtain and often readily available. The disadvantage is that they lack the biological context of experimental CDAs.

Prediction of drug interactions using CDAs requires a training set of compound CDAs and observed interactions among these compounds (Figure 2 left). In a network representation, the CDA is a node property, whereas a drug interaction is an edge property associated