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An overview of the state-of-the-art in predictive modelling of compound combination activity and the value and significance of systems informatics in identifying combinations for therapeutic purposes.

Modelling of compound combination effects and applications to efficacy and toxicity: state-of-the-art, challenges and perspectives

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The development of treatments involving combinations of drugs is a promising approach towards combating complex or multifactorial disorders. However, the large number of compound combinations that can be generated, even from small compound collections, means that exhaustive experimental testing is infeasible. The ability to predict the behaviour of compound combinations in biological systems, whittling down the number of combinations to be tested, is therefore crucial. Here, we review the current state-of-the-art in the field of compound combination modelling, with the aim to support the development of approaches that, as we hope, will finally lead to an integration of chemical with systems-level biological information for predicting the effect of chemical mixtures.

Introduction and background

In the 1989 movie directed by Tim Burton, Batman describes the Joker's strategy to bring doom to Gotham's people: ''Each product only contains one component. The poison only works when they're mixed. Hair spray won't do it alone. But... hair spray and perfume and lipstick will be toxic''. The possibility that compounds modulate each other's effect(s) is a well known and frequent phenomenon, be it a desired positive effect in the case of drug combinations or an undesirable toxic effect, as in the case of Joker's devious plot. Compound combinations have been a popular approach in interfering with erroneous and undesirable activity in biological systems,

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Dr Krishna C. Bulusu is a Postdoctoral Research Associate in the Bender group with the Centre for Molecular Informatics at the Department of Chemistry, University of Cambridge, where he leads the subgroup: Compound Combination Modelling, comprising two postdocs and four PhD students. The aim of this group is to exploit the wealth of biological and chemical knowledge available in the public domain to generate biologically meaningful mode-of-action hypotheses for combinations of chemicals, which will facilitate efficient modelling and prediction of the additive, synergistic or antagonistic behaviour of compound combinations. Krishna received his PhD from the Institute of Cancer Research, University of London, in 2014 and holds a Masters degree in bioinformatics from the University of Edinburgh.

Dr Andreas Bender is a lecturer for molecular informatics with the Centre for Molecular Informatics at the Department of Chemistry of the University of Cambridge, leading a group of about 20 postdocs, PhD and graduate students and academic visitors. In his work, Andreas is involved with the integration and analysis of chemical and biological data, aimed at understanding phenotypic compound action (such as cellular readouts and also organism-level effects) on a mechanistic level, ranging from compound efficacy to toxicity. He received his PhD from the University of Cambridge as a Cambridge Gates Scholar in 2005 and worked in the Lead Discovery Informatics group at Novartis in Cambridge, MA, as well as at Leiden University in The Netherlands before his current post.

Dr Rajarshi Guha is a research scientist at NIH NCATS where he has developed storage, analytic and visualisation infrastructures for RNAi and small molecule combination screening. His research interests include network analysis and machine learning applied to chemical and biological systems. Over the past 10 years he has worked in a variety of areas related to computational drug discovery including the development of novel algorithms to characterise various aspects of SAR, building predictive models of bioactivity for a variety of targets and implementing software tools and platforms that make these methods and models available to fellow chemists and biologists. Before joining the NIH he was a visiting Assistant Professor in the School of Informatics, Indiana University (where he currently holds an Adjunct Professorship). He is an active member of the open source cheminformatics and computational chemistry community and was the Chair of the ACS Division of Chemical Information (2012).

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be it drug combination therapy for treating complex network-driven diseases such as cancer [1,2] or antifungals and antibiotic combinations targeting infectious diseases [3,4].

This popularity can be attributed to multiple factors, which include overcoming drug resistance [5,6] and multitargeted therapies for perturbing multiple nodes of pathway(s) of interest for better efficacy [7]. Synergistic drug combinations aside, there is also a crucial need to study compound combinations towards understanding the toxic effects of chemical mixtures, either in a drug–drug combination, for example carbamazepine toxicity in combination with several drugs and inhibitors [8,9], or a drug–natural-product combination, for example the well-studied impact of grapefruit juice on the bioavailability of certain drugs [10,11]. Combination therapy has also been extensively studied in traditional Indian [12] and Chinese medicine [13], as has the impact of these traditional medicines when administered in combination with Western medicine [14,15].

Compound combination behaviour can be broadly classified as synergistic, antagonistic or additive. Synergy, in this context, is the result of combining two or more chemical compounds to produce an effect that is greater than additive effects (where additive effects are computed from the individual effects based on specific mathematical models) [16]. The use of compound combinations can be either beneficial to the biological system these are intended towards, as in the case of combination therapy [1], or produce an intended harmful effect, as found for antifungals [17], or an unintended harmful effect, such as for synergistic toxicity [18]. By contrast, antagonism is the phenomenon when a compound combination produces an overall effect that is less than the additive effects of the individual compounds.

Despite the significance of compound combinations in therapeutic and toxicity studies, the ability mechanistically to explain and model compound combinations in a systematic fashion is currently limited. Published reviews discuss the urgent need for multitarget therapeutics and systematic approaches to identify communication hubs between pathways that can be targeted by drugs [6,19]. However, the approach taken to map and understand the systems level view of the organism or disease comprehensively is expensive, time consuming and not necessarily feasible. Although there have been several reports that elucidate the mechanism of action (MOA) of a compound combination [20–22], most reports focus on observational studies of a limited number of combination effects in specific organisms and diseases. Table 1 provides a list of studies that have followed gene-expression-, pathway-annotations/network- and modelling-based approaches towards assessing compound combinations across different disease areas, as well as generalised studies. A similar table listing complementary studies can be accessed in a recent publication by Ryall and Tan [23]. The dynamics of networks of pathways can be investigated through the use of mathematical network models, and the outcome of potential target inhibition within the model can be compared to assay readouts to allow MOA hypothesis generation of a combination [24,25]. These models could make use of large-scale datasets of compound combination responses. Even though limited in terms of availability, opportunities to train and test predictive models can be provided. Table 2 provides a list of publicly available combination data resources or datasets. This information, along with available large-scale chemical and biological resources in the public domain (Table 3), could be used to construct an integrated pipeline to assess compound combination behaviour. Combining the chemical and biological fingerprints mentioned above, along with gene expression profiles in disease cell lines, wherever available, could add further weight to such analysis. However, there are still certain aspects of data missing that are crucial to assessing combinations. For example, many datasets only consider single doses, and thus could prevent appropriate quantification of synergistic (or antagonistic) behaviour using classical methods. In addition, if the dosage is not therapeutically relevant, it might not be suitable for translational development.

Following such an integrated approach, as described in this section, Fig. 1 suggests a modelling pipeline towards predicting the synergistic and/or antagonistic behaviour of compound combinations. The aim of this pipeline is to integrate and explain the observations from combination assays. For a suggested compound combination, the model will be able to search bioactivity space and integrate available chemical and biological information that includes network and pathway annotations, gene expression profiles and chemical fingerprint similarities. This could help identify patterns that contribute towards synergy predictions for the compound pair, as well as develop a MOA hypothesis for the combination. These predictions could then be further validated by *in vitro* and/or *in vivo* experiments. This review explores the challenges, limitations and, more importantly, the value and perspectives of predictive modelling of compound combination effects in therapeutic development and toxicological studies.

Applications and impact of drug combinations

The applications of studying and analysing the synergistic, additive or antagonistic behaviour of compound combinations can be manifold. These range from therapeutic applications, such as drug combinations, to counter selectivity and resistance, to assessing safety of household chemical combinations through toxicity studies. Drug–target selectivity has long been a high priority, yet not always achievable, part of the drug discovery pipeline [26]. However, many kinase inhibitors and central nervous system (CNS)-active drugs exhibit promiscuity that is often crucial to achieve better efficacy [27,28]. In a study by Lehár *et al.*, the authors performed large-scale simulations of bacterial metabolism and ~94,000 multidose experiments across multiple diseases to show that synergistic drug combinations display higher specificity to certain cellular contexts than single agent activities [29]. Furthermore, results validated in a rat model showed that the anti-inflammatory drug prednisolone and the antidepressant nortriptyline display therapeutic synergy, but not toxicity. Selectivity in this case was achieved through the differential expression of the proteins targeted by these drugs in stimulated peripheral blood mononuclear cells (PBMCs). This evidence could have broad implications in identifying and studying therapeutically relevant selectivity for drug combinations.

Combination therapeutics have also been utilised as an approach to overcome drug resistance of pathogens [21]. This strategy has been popular in antimalarial and antituberculosis drug discovery and usually involves the first drug acting on mutants resistant to the second drug when administered together [30,31]. Drug combinations are a standard-of-care in many cancers, by