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Review of *In Silico* Methods for Multi-drug Combination Discovery

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Abstract: *Combination therapy has emerged as a highly effective strategy for medicating complex diseases. With the proliferation of diverse biological data, computational methodologies have been extensively employed to pinpoint candidate drug combinations. Over the recent years, numerous models for predicting drug combinations have come to the fore, and several systematic reviews have been published on this topic. However, these reviews primarily focus on two-drug models, with limited attention given to multi-drug or high-order drug combinations. Therefore, the objective of this review is to provide a comprehensive overview of existing multi-drug prediction models. The review begins by itemizing potential data sources that may aid in the prediction of multi-drug combinations. It then summarizes the various computational models utilized for exploring multi-drug combinations. Finally, the review concludes by highlighting the key challenges and future directions for predictive multi-drug models.*

Keywords: *Multi-drug Combination, High-order Drug Combination, Predictive Methods, Computational Model, Machine Learning*

1. Introduction

Combination therapy is defined as the union of two or more curative substances. A growing number of studies have revealed that multi-drug therapies are effective in a broad spectrum of diseases, including cancer[1-3], virus infections such as human immunodeficiency virus (HIV)[4], cardiovascular disease[5], diabetes[6], and malaria[7], significantly propelling the development of modern medical. In cancer, for example, utilizing combination therapies that involve targeted anti-cancer agents can potentially address drug resistance, improve the efficacy of existing medications, lessen the toxicity of single agents at limiting doses, and expand the range of available treatments[8]. Kopetz and his colleagues demonstrated that compared to standard therapy, the combination of encorafenib, cetuximab, and binimetinib lead to considerably longer overall survival and a greater response in patients with metastatic colorectal cancer with the *BRAF* V600E mutation[9]. As for diabetes, Xie et al. evaluated the effectiveness of the combination treatment with gamma-aminobutyric acid (GABA), dipeptidyl peptidase 4 (DPP-4) inhibitors, proton pump inhibitors and insulin in type 1 diabetes (T1D) patients and indicated that this combination could notably decrease fasting blood glucose, HbA1c level, daily insulin dosage, and fasting plasma C-peptide etc.[6].

Computational approaches, which are efficient in both time and cost, have been widely used to speed up the evaluating and prioritizing process of candidate drug combinations, which includes systems biology techniques, mathematical methods, stochastic search algorithms and machine learning (ML) approaches[10,11]. NEXGB[12] introduced extreme gradient boost (XGBoost) to forecast the synergistic relationships between drug combinations and cancer cell lines, which involves the extraction of topological features associated with the target protein within a protein-protein interaction (PPI) network. DeepSynergy[13], regarded as the initial deep learning approach developed for predicting synergistic relationship between drug combinations and cancer cell lines, applied a feed-forward neural network (FNN) to compute the synergy scores of drug combinations. GraphSynergy[14] informed the PPI network by a spatial-based graph convolutional network (GCN) to guide drug combination predictions. DeepTraSynergy[15] made synergistic anticancer drug combination predictions by employing transformers to understand the features of multimodal input. KGANSynergy[16] developed a comprehensive knowledge graph attention network to effectively leverage neighbor information of known drugs and cell lines and anticipate drug synergy.

In the past few years, many researchers have already conducted comprehensive reviews in these drug combination prediction models. Wang et al. delved into the drug synergy quantitation models and the drug synergy prediction models applying deep learning (DL) methods, and gave an insight into the current major

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obstacle and potential future challenges faced by deep learning approaches[17]. Besharatifard et al. systematically analyzed various GNN based drug combination prediction models, where the predictive performance of different models was compared and the advantages and limitations of distinct methods were discussed[18]. Chen et al. devoted attention to the data used for exploring combinatorial drug effects and provide a comprehensive overview of diverse multi-omics data integration-based approaches, concluding that multi-omics data holds great potential for guiding novel synergistic therapy development[19]. Wang et al. summarized classic drug-drug interaction (DDI) databases and popular DDI prediction approaches based on ML, and outlines the key challenges and future directions of DDI prediction[20]. Zhao et al. summarized ML-based score function-based models developed to detect DDI interactions and discussed their strengths as well as limitations[21].

However, these reviews predominantly concentrate on two-drug scenarios while devote scant attention on multi-drug or high-order drug combinations which are also significant in the treatment of intricate diseases. Consequently, this review centers on predictive methodologies for multi-drug combination tasks, including drug synergy, DDI, and adverse drug events. First, we list and classify related data sources that have the potential to enhance the capability of multi-drug combination prediction. Then, we summarize recent computational methods for predicting multi-drug combinations applying machine learning, stochastic searching or data mining techniques. Finally, we examine the current challenges and future directions concerning multi-drug combination predictions.

2. Potential Data Sources for Multi-drug Combination Prediction

The procedure of drug discovery encompasses four fundamental steps: (1) target identification and validation, (2) lead compound discovery and optimization, (3) pre-clinical studies, (4) clinical development. Each step yields different types of data including chemical information, pharmacogenomic data, clinical records, multi-omic data such as genomic, proteomic and metabolomic data, among other aspects. Cheerfully, all these data can be used to investigate the effects of the agents in amalgamation, since every type of data offers distinct biological insights. These varied data types could be broadly classified on three hierarchical levels: molecular level, cellular level and individual level. Table 1 outlines a number of freely accessible and popular datasets which are conducive to investigating multi-drug combinations.

Table 1: Summary of potential data sources for multi-drug combination prediction.

Data Type		Database	URL	Description
Molecular level	Drug centric data:	ChEMBL[22]	https://www.ebi.ac.uk/chembl	Chemical, physical and biological properties of drugs
		PubChem[23]	https://pubchem.ncbi.nlm.nih.gov	
		DrugBank[24]	https://www.drugbank.com	
		DDinter[25]	https://ddinter.scbdd.com	DDIs
	Target centric data	PDB[26]	https://www.rcsb.org	Proteins, genes, or biological pathways
		STRING[27]	https://string-db.org	
		BingdingDB[28]	http://www.bindingdb.org	
		STITCH[29]	http://stitch.embl.de	
		TTD[30]	https://db.idrblab.net/ttd	
		KEGG[31]	https://www.kegg.jp	
Cellular level		GDSC[32]	https://www.cancerrxgene.org	Dose-response data of single drug or drug combinations
		DrugComb[33]	https://drugcomb.fimm.fi	
		DrugCombDB[34]	http://drugcombdb.denglab.org	
		CCLE[35]	https://sites.broadinstitute.org/ccle	Profiling data of cells
		DepMap[36]	https://depmap.org/portal/home	
Individual level		FAERS	https://www.fda.gov/drugs/drug-approvals-and-databases/fda-adverse-event-reporting-system-faers-database	Clinical ADEs records

2.1 Molecular Level

2.1.1 Drug Centric Data

In drug prediction tasks, various drug features are utilized to guild predictions. These features are typically derived from the chemical or physical properties of the drug and offer valuable insights into the characteristics and possible interactions of the drugs[37]. ChEMBL[22], an exceptionally extensive database, holds a wide range of information regarding bioactive molecules with drug-like properties, merging chemical, bioactivity and

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genomic data. In the same way, PubChem[23] serves as the most extensive global repository of publicly available chemical information, encompassing a wide array of data such as chemical and physical properties, biological activities, safety profiles, toxicity information, and so on. Drugbank[24] integrates detailed drug information with thorough details about drug targets and drug actions.

2.1.2 Target Centric Data

Drug targets might take of a form of a protein (such as an enzyme, receptor, or transporter), a gene, or a biological pathway. Typically, gene-/protein- focused databases usually collects the information about amino acid sequences, gene terms and PPIs, which serve as the foundation for rational drug design[38]. Protein Data Bank[26] (PDB), recognized as the inaugural open-access digital data resource in the biological science, is a data center for the worldwide archive of three-dimensional structural data for large biological macromolecules like proteins, DNA, and RNA. STRING[27] is a database that comprises both established and predicted protein-protein interactions, which include direct (physical) and indirect (functional) associations, currently covering 59,309,604 proteins from 12,535 organisms.

2.2 Cellular Level

The response of cancer cells to the pharmacological agents, whether administered as monotherapy or in combination therapy, can elucidate potential targets the exhibit similarly responses to the same drug or to drugs with similar action mechanisms[39]. This idea can be instrumental in predicting effective multi-drug combinations. The Genomics of Drug Sensitivity in Cancer[32] (GDSC) database represents the largest free source of data regarding drug sensitivity in cancer cells and molecular markers of drug response. It has characterized 1,000 human cancer cell lines and evaluated their responses to hundreds of compounds. DrugComb[33] and DrugCombDB[34] are specialized databases focus on the curation of synergistic drug combinations across a diverse array of cancer cell lines. Both of them computed multiple synergy scores to ascertain the overall synergistic or antagonistic effects of drug combinations.

2.3 Individual Level

It is worth mentioning that clinical records are rarely used in drug-pair predictive methods, compared to they are frequently used in multi-drug models. Advancing the mining of high-order DDI events induced by adverse drug effects from large-scale electronic health record (EHR) databases has garnered significant attention as an innovative research domain[40]. FEARS, also referred as the FDA Adverse Event Reporting System, is a comprehensive database containing adverse drug events (ADEs) reports received from manufacturers under regulatory requirements, as well as direct reports from consumers and healthcare professionals.

3. Multi-drug Combination Prediction Methods

Since there is no consensus on the computational methods for estimating and predicting multi-drug combinations, a number of approaches, techniques and theories have been developed to tackle different multi-drug combination challenges covering multi-drug synergy, multi-drug interactions and multi-drug adverse response. We categorize these multi-drug prediction approaches in four groups: classic ML methods and DL methods, stochastic searching methods and data mining methods (Table 2).

Table 2: Summary of computational methods for multi-drug combination prediction.

Type of method	Model	Algorithms	Year	Characteristic	Number of Drugs
Classic machine learning	Larkins-Ford et al.[41]	RF, BART, KNN, LR, XGBoost, Naïve Bayes, neural network	2022	Using in vitro data of pairwise drug combinations to prediction in vivo high-order drug combinations	3 or 4
	PINet1.0[42]	RWR	2022	Using biological pathway interaction networks to predict optimal drug combinations	2 ~ 5
Deep learning	DeepMDS[43]	FNN	2022	Integrating multi-omics data to forecast multi-drug synergy	≥2
	D3I[44]	Attention mechanism	2019	To Predict cardinality-invariant and order-invariant	≥2

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				high-order DDIs	
	SMC-HNCL[45]	Attention mechanism	2024	To predict synergistic multi-drug combination based on heterogeneous network representation learning with contrastive Learning	≥2
	DeepDrug[46]	GNN	2025	To identify lead combinations of approved drugs for treating AD	2~6
	BAITSAO[47]	LLM	2024	A Foundation Model for tasks related to drug synergy prediction	≥2
Stochastic searching	SD2ID2S[48]	SD2ID2S	2018	To quantify and discover the patterns of high-order DDIs	≥2
Data mining	Yao et al.[49]	Apriori algorithm	2020	To evaluate the directional effects of high-order DDIs	2~7
	BMC3PM[50]	BMC3PM	2023	A personalized drug combination protocol applying individual pattern of perturbed gene expression	1~5
	Shi et al.[51]	Mixture drug-count response model, class-based mining	2024	To discover high-risk hig-horder drug combinations and their low-risk althernative drug combinations	3~4

3.1 Classic Machine Learning Methods

Machine learning algorithms, which belong to the realm of artificial intelligence (AI), can learn relationships among input data, such as interactions of drug-drug or drug-target, by seamlessly integrating various feature types, and formulate ideal strategies for analyzing these data without pre-defined parameters. Historically, classic ML techniques have been employed to enhance and streamline drug discovery processes, frequently in conjunction with other *in silico* approaches [52].

Larkins-Ford et al. hypothesized that in vivo high-order drug combinations can be forecasted using in vitro data of pairwise drug combinations[41]. To analyze the data, which comprising two- and three-drug combinations among 10 commonly used anti-tuberculosis drugs, both unsupervised and supervised ML algorithms were utilized. Initially, principal component analysis (PCA), an unsupervised ML method, was employed for preliminary data analysis, revealing a robust predictive signal. Subsequently, in order to enhance classification accuracy, seven ML methods including random forest (RF), bayesian additive regression tree (BART), XGBoost, k-nearest neighbor (K-NN), logistic regression (LR), Naïve Bayes and neural networks were assessed respectively using repeated random partitioning. PINet1.0[42] introduced a biological model grounded in the pathway interaction network to identify optimal drug combinations for different diseases. PINet, the pathway interaction network, is composed of four categories of entities: drugs, genes, diseases and pathways, along with eight types of interactions among these entities: drug-gene, drug-disease, drug-pathway, gene-gene, gene-disease, gene-pathway, disease-pathway and pathway-pathway. The restart random walks (RWR) algorithm was employed to capture the “disease state” and the “drug state”, thereby generating a probability distribution that reflect the influence of a disease or drug on human. The PINet was then utilized to predict both optimal pair-wise and high-order drug combinations.

3.2 Deep Learning Methods

3.2.1 Feedforward Neural Network

DeepMDS[43] aims at using a deep learning method that integrated multi-omics data to forecast multi-drug synergy for personalized anti-cancer therapies. First, a dataset was curated, which included gene expression profiles from cancer cell lines, information regarding the targets of anti-cancer drugs, and the drug response across a diverse array of cancer cell lines. Then a fully connected deep neural network was developed to estimate half maximum inhibitory concentration (IC50) values in a regression context and to generate classification labels in a classification context. The performance of DeepMDS was notable, achieving a mean square error (MSE) of 2.50 in the regression task and attaining a peak classification accuracy of 0.94.

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3.2.2 Attention Mechanism

For the first time, D^3I[44] applied deep learning to predict high-order DDI prediction. This model was designed to predict cardinality-invariant and order-invariant DDIs. D^3I leverages four distinct types of information pertaining to the drugs: side-effect data, target data, therapeutic indication data, and chemical substructure fingerprints. The architecture of the model comprises three key components: an encoder that transformers drugs into latent representations, an aggregator that synthesizes a single embedding for the input drug combination using strategies such as max pooling, mean pooling, and self-attention mechanisms, and a predictor that assesses the probability of adverse drug reactions (ADRs) for a drug combination. Furthermore, D^3I is capable of accurately predicting ADRs for combinations of drugs that, when considered individually, do not elicit ADRs.

SMC-HNCL[45] is an innovative methodology for forecasting synergistic multi-drug combinations by thoroughly examining the extensive information available in drug heterogeneous networks. Two different methods were used to capture the drug features. One uses a contrastive learning-based approach within the drug-target heterogeneous network to gather more comprehensive information. The other calculates the unique drug anatomical therapeutic chemical (ATC) codes using Jaccard coefficient. These drug features are then fused by attention mechanism, and a multi-head self-attention based group representation method is employed to learn representations of drug combinations, innovatively realizing synergistic multi-drug combination prediction.

3.2.3 Graph Neural Network

DeepDrug[46] is aiming at identifying the lead combinations for treating Alzheimer's disease (AD), with following innovations. Firstly, it incorporates long genes, immune and aging pathways, as well as somatic mutation markers linked to AD, while also integrating expert knowledge to expand the range of candidate targets. Secondly, DeepDrug captures crucial pathways linked with AD by constructing a signed directed heterogeneous biomedical graph with a large number of nodes and edges, and node/edge weighting. Thirdly, it utilizes GNN to encode the weighted biomedical graph into a new embedding space, enabling the capture of granular relationships across different nodes. Lastly, it systematically selects high-order drug combinations based on a threshold that accounts for diminishing returns.

3.2.4 Large Language Model

BAITSAO[47] represents a newly developed foundation model (FM) specifically engineered for drug synergy prediction. In recent times, foundation models have brought about significant enhancements in the performance of deep learning across diverse domains. In the realm of natural language processing (NLP), these models, commonly referred to as large language models (LLMs), have attracted widespread attention. The authors constructed the training datasets for BAITSAO utilizing context-enriched embeddings derived from LLMs to serve as the initial representation of drugs and cell lines. Following the validation of the relevance of these embeddings, BAITSAO was pre-trained using a comprehensive drug synergy database within a multi-task learning framework, characterized by meticulous task selections. The outcomes of extensive experiments underscored the advantages of the model architecture and the impact of pre-training. BAITSAO is readily adaptable for the execution of novel downstream tasks pertinent to drug synergy analysis.

3.3 Stochastic Search Algorithms

The initial computational approaches employed to address the prediction of drug combinations involved a class of stochastic search algorithms that do not necessitate the presence of positive and negative samples (training data) for the resolution of optimization problems[39]. The study SD^2ID^2S[48] marks a pioneering effort in examining the quantification and identification of patterns among high-order DDIs. The authors hypothesized that when two drugs are co-administered alongside a group of other analogous drugs, it is plausible that these two drugs may possess similar therapeutic objectives and target comparable therapeutic pathways. They structured their investigation around the concepts of nondirectional DDI relations (DDI-nd's) and directional DDI relations (DDI-d's), subsequently developing weighted complete graphs and weighted hyper-graphlets for their respective representation to access the similarities among sets of co-administered drugs. A notable feature of this research concerning drug-drug similarities in DDI-nd's and DDI-d's is its convolutional nature, specifically, the similarity between two drugs is utilized to derive the similarity of another pair of drugs. Following this, the authors crafted a stochastic algorithm aimed at learning drug-drug similarities based on DDI data.

3.4 Data Mining Methods

Data mining, the procedure of unearthing potentially valuable information and knowledge from a large

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amount of random data. Due to its outstanding capabilities in evaluating patient risks, offering support for clinical treatment and developing predictive disease models, data mining has emerged as a cutting-edge topic in the study of clinical data, especially in large-scale medical public databases[53].

Yao et al. applied a frequent itemset mining method to predict the directional effects of high-order DDIs using myopathy-related ADE data collected from FEARS database[49]. The authors applied Apriori algorithm to discover frequent drug combinations that involved up to seven drugs. By tallying the occurrences of each candidate drug combinations in both cases and control groups, they created a contingency table for directional DDI effect estimation. Their analysis not only confirmed previously reported DDIs but also uncovered a number of novel DDIs. Additionally, the authors further developed a scalable tool to visualize high-order DDI effects.

BMC3PM[50] seeks to establish a protocol for treating effectively through personalized drug combination therapy. To achieve this, Mokhtari et al. developed the concept of the individual pattern of perturbed gene expression (IPPGE), which is derived from a comparative analysis of a patient's differentially expressed genes (DEGs) in breast cancer relative to normal gene expression levels. By employing a network-based algorithm, the researchers identified one or more drug combinations tailored to each patient by concurrently analyzing the IPPGE and the corresponding drug signatures. Additionally, a directed differential network (DDN), which incorporates biological pathway data, was used to forecast the impact of the identified drug combinations on gene expression. The study revealed that each patient's IPPGE was unique.

Shi et al. apply an innovative data mining approach to discover high-risk and alternative low-risk high-order drug combinations[51]. They selected data of older adults who had visited emergency departments from Medicare fee-for-service and MarketScan Medicare supplemental information. In a case-control setting, they explored the associations between the drug combinations exposure and ADEs. The high-risk high-order drug combinations were pinpointed using a mixture drug-count response model, while the low-risk alternative drug combinations were identified through therapeutic class-based mining. The study found that high-risk, high-order drug combinations could be substituted with low-risk alternative drug combinations within similar therapeutic classes.

4. Challenges and Future Directions

Although published multi-drug prediction studies have made excellent achievements with reliable prediction results, there is still a long way to go. Firstly, labeled multi-drug data is in desperately limited availability. The number of verified data of drug pairs is much more than that of high-order drug combinations. In order to facilitate equitable comparison and evaluation of drug combination prediction models, a "gold standard" dataset should also be established. Secondly, it is essential to integrate more different types of informative data derived from all kinds of biomedical entities, which might improve the accuracy of prediction. Finally, the full potential of AI techniques in multi-drug predictive tasks has yet to be realized. It is recommended that researchers adopt more sophisticated AI models to advance multi-drug prediction efforts.

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