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Research Progress in Network Medicine and Artificial Intelligence-Based Prediction of Drug Combination Synergy

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Abstract. Drug combination therapy can improve the treatment of complex diseases through multi-target intervention, but the number of candidate combinations expands rapidly with the size of the drug space, making purely high-throughput screening insufficient for research and clinical needs. Network medicine provides biological priors for assessing the rationale of combinations by integrating protein-protein interaction networks, disease modules and drug-target topology, whereas artificial intelligence can learn nonlinear features from heterogeneous data such as chemical structures, targets, omics profiles and cellular phenotypes. This review summarizes recent progress in drug combination synergy prediction based on network medicine and artificial intelligence. It compares network topology methods, conventional machine learning, graph neural networks and multimodal fusion models in terms of principles, applicable scenarios and limitations, and discusses their translational value in cancer, hypertension and other complex diseases. Current studies remain constrained by data sparsity, negative-sample bias, insufficient model interpretability and limited prospective validation. Future work should strengthen standardized data integration, mechanism-constrained modeling and joint dose-timing optimization to improve interpretability, generalizability and clinical usability.

Keywords: Drug combination synergy, Network medicine, Artificial intelligence, Multi-target intervention

1. Introduction

Malignant tumors, cardiovascular and cerebrovascular diseases, diabetes and infectious diseases are usually not caused by abnormalities in a single gene or protein. Instead, they arise from the coordinated dysregulation of multiple signaling pathways, molecular modules and regulatory networks. Although monotherapy is convenient for defining targets and doses, it is often limited in complex diseases by bypass pathway activation, acquired drug resistance and dose-limiting toxicity. Drug combination therapy can intervene in several functional modules at the same time, thereby improving efficacy, reducing the dose of each single agent and delaying resistance, and it has become an important strategy in antitumor, anti-infective and chronic disease treatment [1].

The main difficulty in drug combination development is the problem of combinatorial explosion. As the number of candidate drugs increases, the search space for two-drug and multi-drug combinations expands rapidly. Different doses, administration sequences and exposure durations

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further increase the cost of validation. Large-scale in vitro screening platforms and public data resources have provided basic data for drug combination research. For example, the O'Neil dataset, NCI-ALMANAC and DrugComb have accumulated extensive drug response data and synergy scores in cancer cell lines [2]. However, these data still suffer from uneven disease coverage, imbalanced positive and negative samples, substantial platform heterogeneity and reduced reliability when in vitro results are extrapolated to in vivo settings. Experimental screening alone is therefore insufficient for clinical translation.

The integration of network medicine and artificial intelligence provides a new route to address this problem. Network medicine places drug targets, disease genes and protein interactions within a unified biological network, enabling system-level assessment of whether a drug pair has complementary actions. Artificial intelligence can learn nonlinear relationships from high-dimensional heterogeneous data, including drug structures, targets, pathways, transcriptomes and cellular phenotypes. Focusing on drug combination synergy prediction, this review summarizes the development of network topology methods, conventional machine learning, graph neural networks and multimodal fusion models, compares their technical characteristics and discusses their value for clinical translation through representative application cases.

2. Theoretical basis of drug combination prediction

2.1. Concept of drug synergy

Drug synergy generally means that the actual effect of two or more drugs used in combination is greater than the expected effect inferred from the effects of the individual agents. The determination of synergy depends on the reference model. Common models include Bliss independence, Loewe additivity, the highest single agent model and the zero interaction potency model. Because these models make different assumptions about additivity, the same drug combination may lead to different conclusions under different scoring systems. For computational prediction, a clear definition of the synergy score source and threshold is a prerequisite for model training and cross-study comparison [3].

Mechanistically, drug synergy can be generated through pharmacokinetic, pharmacodynamic and immunomodulatory processes. One drug may alter the absorption, distribution, metabolism or excretion of another drug, thereby increasing its exposure in the target tissue. Two drugs may also act on upstream and downstream nodes of the same pathway, or on mutually compensatory parallel pathways, thereby suppressing escape mechanisms in the disease network. In cancer treatment, chemotherapy, targeted therapy and immunotherapy may also cooperate through antigen release, immunogenic cell death and relief of immune suppression.

2.2. Core concepts of network medicine

Network medicine represents a biological system as a complex network composed of nodes and edges. Nodes may correspond to genes, proteins, drugs, diseases or phenotypes, whereas edges may represent protein interactions, regulatory relationships, drug-target links or disease-gene associations. Protein-protein interaction networks form the basis of network medicine analysis. Disease-associated genes are often not randomly distributed in such networks; rather, they tend to form connected disease modules. The proximity between drug targets and disease modules can be used to evaluate whether a drug is likely to affect disease-relevant functional regions.

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In drug combination prediction, network separation s_AB is a representative topological indicator. This metric compares the average distance between two drug target sets with the internal distances within each target set, thereby measuring whether two drugs both reach the disease module while acting on topologically separated network neighborhoods. If two drugs both cover the disease module but their target regions do not overlap excessively, they are more likely to form a complementary exposure relationship. In contrast, if the target sets overlap substantially or both fail to cover the disease module, the therapeutic value of the combination is usually lower [4].

3. Evolution of research paradigms and method categories

3.1. Empirical screening and pathway analysis

Early drug combination studies mainly relied on clinical experience, pharmacological knowledge and single-pathway enrichment analysis. Researchers usually selected drugs acting on different nodes of known disease pathways and then performed experimental validation, such as combining DNA-damaging agents with DNA repair inhibitors, or combining cell-cycle inhibitors with signaling pathway inhibitors. These approaches have explicit mechanistic hypotheses, but their ability to identify unknown pathways, cross-module actions and nonlinear synergistic relationships is limited. As a result, they are not sufficient for systematic discovery of new combination patterns.

3.2. Network medicine-driven stage

With the accumulation of protein interactions, drug targets and disease gene data, network medicine has become an important framework for drug combination prediction. Cheng et al. [1] analyzed the topological relationships between drug targets and disease modules and found that effective combinations usually do not merely hit the same network region repeatedly [5]. Instead, they tend to cover the disease module while acting on separated neighborhoods. This finding shifted drug combination analysis from the static question of whether a target is hit to the systems-level question of how complementary coverage is formed within a disease network. As shown in Table 1, network medicine usually classifies drug-disease module relationships into several topological patterns, among which complementary exposure is considered most consistent with the biological logic of synergistic therapy.

Table 1. Major topological patterns of drug-disease module relationships in network medicine

Topological pattern	Relationship between targets and disease module	Predicted implication	Methodological value
Complementary exposure	Both drug target sets cover the disease module but act on topologically separated network neighborhoods	More likely to generate synergy through multi-module intervention	Suitable for prioritized recommendation and mechanistic validation
Overlapping exposure	Two drug target sets highly overlap within the disease module	May enhance inhibition of the same pathway but may also increase redundancy and toxicity	Requires joint assessment of dose and safety
Single-drug exposure	Only one drug target set is close to the disease module	Combination effect may be mainly driven by the active single agent	Can be used as a low-priority candidate or control

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Table 1. (continued)

Non-exposure	Neither drug target set is close to the disease module	Lacks clear disease-network rationale	Usually not prioritized as a candidate combination

3.3. Integration of network medicine and artificial intelligence

Since 2020, deep learning, graph neural networks, attention mechanisms and multimodal fusion models have gradually become mainstream approaches for drug combination synergy prediction. Unlike conventional machine learning, which depends heavily on manually designed features, deep learning models can directly learn representations from molecular graphs, drug targets, gene expression profiles and protein-protein interaction networks. Graph neural networks are particularly suitable for heterogeneous relationships formed by drugs, targets, diseases and cell lines. At the same time, researchers have begun to embed network propagation, pathway constraints and attention-based explanation mechanisms into models in order to alleviate the insufficient interpretability of purely data-driven methods [6].

3.4. Comprehensive comparison of mainstream methods

Different methods vary substantially in data requirements, explanatory ability, generalizability and computational cost. Network topology methods are centered on protein-protein interaction networks and disease modules, making them suitable for proposing interpretable candidate combinations when labeled data are limited. Conventional machine learning methods integrate handcrafted features such as drug structures, target functions and pathway enrichment. They have relatively low training cost, but depend strongly on feature engineering and sample quality. Graph neural networks can directly learn higher-order relationships in graph structures and are suitable for complex links among drugs, genes, proteins and cell lines. Multimodal fusion models further integrate chemical structures, omics, phenotypes and network information, showing greater potential for predictive performance, although model complexity and interpretability pressure increase simultaneously [7]. Table 2 summarizes the technical focus and application scenarios of these four categories.

Table 2. Comprehensive comparison of mainstream methods for drug combination synergy prediction

Method category	Feature sources	Suitable scenarios	Main advantages	Main limitations
Network topology methods	PPI networks, disease modules and drug-target distances	Early screening with limited labeled data and strong need for mechanistic explanation	Strong biological interpretability and convenient generation of mechanistic hypotheses	Depend on network and target annotation quality; difficult to model dose and nonlinear effects
Conventional machine learning	Drug fingerprints, target functions, pathway enrichment and cell-line features	Medium-scale datasets and controllable feature engineering settings	Simple implementation, low training cost and relatively reproducible results	Strong dependence on handcrafted features and limited cross-dataset generalization
Graph neural networks	Molecular graphs, PPI networks and drug-target-cell-line heterogeneous graphs	Scenarios requiring learning of higher-order network relations and molecular representations	Can automatically learn topological features and handle complex network data	Interpretation is difficult; vulnerable to data leakage and overfitting

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Table 2. (continued)

Multimodal fusion models	Structures, targets, omics, networks, phenotypes and text evidence	High-performance prediction and cell-state-specific modeling	More comprehensive information coverage and use of multi-layer biological evidence	Complex models; missing modalities and batch effects are difficult to handle

4. Representative models and key technologies

4.1. Common benchmark datasets

Drug combination synergy prediction depends on high-quality benchmark data. In vitro screening data usually provide drug pairs, cell lines, dose matrices and synergy scores, which serve as the main label source for supervised learning models. Drug structures, drug targets, protein-protein interaction networks, disease genes and cell-line omics data provide features and biological priors. As shown in Table 3, current studies commonly combine DrugComb, NCI-ALMANAC and the O'Neil dataset with DrugBank, HIPPIE, DisGeNET, CCLE or LINCS to construct multilayer representations of drugs, targets, diseases and cellular states [8].

Table 3. Common data resources for drug combination prediction and their modeling uses

Data resource	Data type	Main content	Modeling use	Representative references
DrugComb	Drug combination response database	Integrated drug combination and monotherapy response data across multiple diseases and cell lines	Training and evaluation of synergy prediction models and calculation of multiple synergy scores	[5]
O'Neil dataset	Cancer drug combination screening dataset	Dose-response matrices of two-drug combinations across multiple cancer cell lines	Common benchmark for early deep learning and mechanism-based models	[3]
NCI-ALMANAC	Anticancer drug combination screening resource	Systematic evaluation of FDA-approved anticancer drug pairs in the NCI-60 cell lines	Supports pan-cancer combination screening and external model validation	[4]
DrugBank, HIPPIE and DisGeNET	Drug-target, PPI and disease-gene resources	Drug-target links, protein interactions and disease module information	Construction of network topological features and heterogeneous graph structures	[1, 7]
CCLE, LINCS and related omics resources	Cell-line expression and perturbation data	Cellular states, gene expression and drug perturbation profiles	Cell-line-specific synergy prediction models	[7, 9, 10]

4.2. Network topology and conventional machine learning models

A representative network topology model is the prediction framework based on disease modules and target separation. This class of method does not necessarily require a large number of labeled samples. It can rank candidate combinations directly according to the positional relationships of drug targets in the protein-protein interaction network, and therefore has strong mechanistic

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interpretability. Its limitations are high dependence on network completeness and target annotation quality, and limited ability to capture dose, cellular state and nonlinear pharmacodynamic relationships.

Conventional machine learning methods usually extract drug fingerprints, target functions, pathway enrichment features, transcriptomic perturbation profiles and cell-line features manually, and then use random forests, support vector machines, gradient boosting trees or shallow neural networks for classification or regression. DeepSynergy inputs chemical information and cell-line genomic information into a deep neural network and demonstrated the advantages of deep learning over conventional models in early studies . These models are relatively stable to implement, but their performance depends heavily on the input features and training data distribution. Their generalization ability on external datasets or unknown drugs remains limited.

4.3. Graph neural networks and attention mechanisms

Graph neural networks learn relationships between nodes and their neighborhoods through message passing, and naturally handle molecular graphs, protein-protein interaction networks and drug-target heterogeneous graphs. GraphSynergy combines drug targets, cell-line-associated proteins and the PPI network, and uses graph convolution and attention mechanisms to identify key proteins that contribute to synergy [11]. DeepDDS uses drug molecular graphs and cell-line gene expression as inputs, learns drug structural representations through graph neural networks and attention mechanisms, and achieves favorable predictive ability in benchmark and independent test datasets [12].

The value of attention mechanisms lies not only in improving prediction performance, but also in providing an entry point for model interpretation. If attention weights consistently identify key substructures, proteins or pathways, they can provide candidate mechanisms for subsequent experimental validation. However, attention weights are not equivalent to causal explanations and still need to be validated by perturbation experiments, pathway enrichment and external evidence. Recent reviews also indicate that graph neural network models have both advantages and risks, especially in terms of generalization across cell lines, cancer types and unknown drugs [9].

4.4. Multimodal fusion and mechanism-constrained models

Multimodal fusion models attempt to integrate drug structures, target profiles, PPI networks, cell-line omics and drug response phenotypes in order to compensate for the insufficiency of any single modality. TranSynergy obtains drug target features through network propagation and combines them with gene expression or gene dependency data and a self-attention module, thereby improving synergy prediction and pathway deconvolution. MGAE-DC models synergistic, additive and antagonistic combinations as multiple graph channels, and learns shared cross-cell-line patterns and cell-line-specific patterns through graph autoencoders [13]. MD-Syn further fuses one-dimensional chemical language model features, two-dimensional molecular graph representations, PPI network node embeddings and multi-head attention mechanisms, showing strong stability in independent datasets [10].

The key issue for such models is how to handle scale differences, missing modalities and batch effects among heterogeneous data sources. An effective multimodal model should not simply concatenate features. Instead, it should build interpretable alignment among network structure, pathway constraints and cellular states. Future model design needs to answer three questions at the

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same time: whether a combination is synergistic, why it is synergistic and in which patient subgroup or cellular state it is likely to be synergistic.

5. Clinical application cases

In breast cancer, especially triple-negative breast cancer, computational models commonly use gene expression, drug targets and drug structures from cancer cell lines as inputs to predict treatment combinations that may have synergistic effects. Unlike a simple list of clinical drug combinations, network medicine and artificial intelligence analyses focus more on the technical logic behind a combination. For example, one drug may cover key modules such as DNA damage repair, cell cycle or PI3K/AKT/mTOR signaling, whereas the other drug may act on a compensatory network neighborhood. In this way, models can prioritize candidates for subsequent in vitro validation and help explain why certain combinations are effective in specific cell lines but limited in others.

In lung cancer, ovarian cancer and other solid tumor cell lines, NCI-ALMANAC and the O'Neil dataset have provided large-scale drug-pair response data for deep learning models. GraphSynergy, DeepDDS and MGAE-DC use these data to learn relationships among drug structures, cellular states and network topology, and then use attention weights or graph embeddings to suggest key proteins and pathways. The major application value of these studies lies in candidate combination screening and mechanistic hypothesis generation rather than direct replacement of clinical trials. Computational results can become executable clinical strategies only when model predictions, in vitro experiments, animal models and patient stratification evidence form a closed validation loop.

Hypertension research demonstrates the transferability of network medicine to non-cancer complex diseases. Using hypertension disease modules and approved antihypertensive drugs, Cheng et al. found that clinically effective combinations tended to form complementary exposure within the disease module rather than simply overlapping in targets [1]. This case indicates that network medicine is not limited to cancer cell-line data. It can also be used for mechanistic interpretation and prioritization of combination therapy in chronic diseases. For chronic diseases, future models need to incorporate pharmacokinetics, long-term safety, concomitant medication and real-world evidence in order to approach the clinical decision-making setting.

6. Current core challenges

First, data quality remains a fundamental limitation on model performance. Public synergy data mainly come from in vitro cell-line screening. Disease types, drug categories and cellular backgrounds are unevenly covered, and synergistic samples are usually fewer than non-synergistic samples, which easily biases models toward the majority class. Dose designs, synergy scoring methods and threshold standards also differ across databases, leading to substantial uncertainty in cross-dataset training and evaluation. Systematic evaluations have shown that model performance depends not only on algorithm architecture, but also strongly on drug representation, cell-line feature selection and data splitting strategies.

Second, model interpretation is still insufficient. Many deep learning models can output high AUC values or correlation coefficients, but they cannot fully explain the biological mechanisms behind their predictions. Attention weights, SHAP analysis and pathway enrichment can provide partial explanations, yet these explanations often remain correlative and cannot prove that a pathway has a causal role in synergy. For clinical translation, models need to provide testable mechanistic hypotheses, including key targets, alternative pathways, sensitive cellular states and actionable experimental validation plans.

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Third, generalization and clinical usability remain limited. Many models perform well under random data splits but decline markedly when applied to unknown drugs, unknown cell lines, cancer types not seen during training or patient-derived samples. Existing studies often simplify drug combination prediction into binary classification or synergy-score regression, while rarely considering dose, administration sequence, treatment duration and toxicity risk together. Regulatory and ethical issues also need to be addressed, including data privacy, model transparency, intellectual property ownership and the responsibility boundary of AI-assisted decision-making.

7. Future research directions and outlook

Future research should first improve data reusability and clinical relevance. It is necessary to establish unified procedures for synergy score conversion, sample metadata annotation and cross-platform batch correction, while explicitly retaining dose matrices, time points, cellular states and experimental conditions in datasets. To address insufficient negative samples and rare disease samples, active learning and uncertainty sampling can be introduced so that models preferentially recommend the most informative candidate combinations for experimental validation, thereby forming a closed loop of prediction, experiment and retraining.

At the model level, research should shift from solely pursuing prediction scores to mechanism constraints and causal interpretation. A more desirable direction is to embed network separation, pathway complementarity, drug-target propagation, protein structures and gene regulatory relationships as priors into models, so that learning from data is constrained by biological rules. For graph neural networks and multimodal models, external validation across drugs, cell lines and diseases should be reported, and sensitivity analyses after perturbing key pathways should be provided to distinguish stable mechanistic signals from data leakage or batch bias.

At the translational level, the prediction of whether a combination is synergistic should be extended to the prediction of which patients may benefit, at what dose and under which administration sequence. Patient-derived organoids, single-cell sequencing, spatial omics, electronic health records and drug adverse reaction data can be incorporated into a unified framework to construct dynamic network models for real clinical scenarios. This review argues that the core value of combining network medicine with artificial intelligence is not only to accelerate screening, but also to transform candidate combinations into interpretable, verifiable and stratifiable therapeutic hypotheses. Only after this is achieved can computational prediction truly enter the clinical research workflow.

8. Conclusions

Network medicine and artificial intelligence-based prediction of drug combination synergy is an important interdisciplinary direction in precision therapy for complex diseases. Network medicine provides systems-level interpretation of relationships between drug targets and disease modules, whereas artificial intelligence enhances feature learning from high-dimensional heterogeneous data. Current research has progressed from empirical screening and pathway analysis to a stage in which network topology methods, graph neural networks and multimodal fusion models advance in parallel. These methods have shown value for candidate combination screening and mechanistic hypothesis generation in tumors, hypertension and other diseases.

The field still faces challenges such as data sparsity, inconsistent scoring standards, insufficient model interpretability and lack of prospective validation. Future research should strengthen data standardization, mechanism-constrained modeling, joint dose-timing optimization and real-world

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validation, so that drug combination prediction can develop from a high-throughput ranking tool into an interpretable, verifiable and translatable decision-support platform for precision therapy.

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