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Special Topic: AI for Biology

AI in drug development: advances in response, combination therapy, repositioning, and molecular design

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Abstract Artificial intelligence (AI) is revolutionizing the field of drug development, particularly in addressing key challenges such as drug response prediction, drug combination design, drug repositioning, and drug molecule generation. Traditional drug discovery is hindered by long timelines, high costs, and low success rates, necessitating innovative technologies to accelerate the process. AI technologies, such as deep learning, graph neural networks, and generative models, have demonstrated significant potential in enhancing the accuracy of drug response predictions, optimizing drug combination strategies, identifying opportunities for drug repositioning, and generating drug molecules with specific biological activities. These advancements not only accelerate the drug development process but also open up new possibilities for precision medicine. This review discusses the latest applications and developments of AI in drug discovery, highlighting the breakthroughs and challenges AI addresses in drug development. By summarizing the current research progress, this study provides theoretical support and practical guidance for further applications of AI in drug development.

Keywords artificial intelligence, deep learning, drug research, drug repositioning, genomic data

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1 Introduction

Drug response prediction, drug combination design, drug repositioning, and drug molecule generation are pivotal tasks in drug development, directly influencing the efficacy and safety of disease treatments. Drug response prediction aims to reveal the interactions between specific drugs and the biological system, providing a theoretical foundation for personalized medicine and therapeutic efficacy assessment [1–3]. Drug combination research explores the synergistic effects of combined therapies, with the goal of enhancing efficacy, reducing drug resistance, and minimizing side effects [4, 5]. Drug repositioning discovers new indications for existing drugs, thereby accelerating the development process and reducing costs [6–8]. Meanwhile, drug molecule generation designs novel compounds with specific biological activities and physicochemical properties, thereby expanding the chemical space of potential therapeutic agents [6, 9] Research in these areas not only addresses major public health challenges but also tackles industry issues such as long drug development timelines and low success rates, thereby providing both theoretical support and technological tools to accelerate the development of new drugs.

Current drug development primarily involves four key stages: target discovery, drug screening, clinical trials, and post-marketing surveillance [10]. In the target discovery phase, researchers identify potential therapeutic targets through omics technologies and biomarker exploration; during the drug screening phase, high-throughput screening or computational simulations are used to identify candidate compounds; the clinical trial phase focuses on validating the safety and efficacy of the drug; and post-marketing

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surveillance monitors the long-term efficacy and potential adverse reactions of the drug [11]. However, these traditional processes are not only time-consuming and labor-intensive but also face challenges such as high failure rates and substantial costs. Therefore, there is an urgent need for more efficient technologies to optimize and complement these processes [12], enhancing the success rate of drug development and accelerating the time to market.

Although significant progress has been made in drug development, several key issues remain to be addressed [13]. Firstly, there is still considerable uncertainty in drug response and toxicity prediction, especially in cancers with high heterogeneity, which presents challenges for personalized treatment and efficacy evaluation [14]. Secondly, the mechanisms underlying the synergistic effects of drug combinations remain unclear, and existing combination design methods lack systematization and efficiency, limiting their clinical applicability [15]. Thirdly, drug repositioning approaches largely depend on expert knowledge, which, although valuable for identifying new indications for existing drugs, is unable to fully explore all potential application scenarios and necessitates further refinement [16]. Finally, drug molecule generation is constrained by limitations in chemical space exploration, the prediction accuracy of drug efficacy, and the evaluation of synthetic feasibility, challenges that remain unresolved in the context of novel drug design and assessment [17]. To overcome these challenges, there is an urgent need to develop innovative technologies and methods to improve the efficiency and quality of drug development, accelerating its clinical application.

In recent years, artificial intelligence (AI) has found increasingly extensive applications in the field of biopharmaceuticals, offering novel solutions for drug development and fostering significant advancements in personalized treatment strategies [18–22]. Deep learning models, owing to their distinctive abilities in high-dimensional data processing, feature extraction, and pattern recognition, facilitate accurate drug response prediction, thus providing robust support for personalized therapeutic decision-making [9, 23, 24]. Models based on graph neural networks (GNNs) and multimodal learning have achieved remarkable progress in drug combination design, significantly enhancing the accuracy of synergy effect prediction [25]. Simultaneously, AI-driven approaches leveraging data mining and knowledge graph construction have greatly improved the discovery capabilities for drug repositioning, allowing the identification of potential new indications from vast amounts of existing data [26]. Moreover, generative models such as generative adversarial networks (GANs) and variational autoencoders (VAEs) have demonstrated exceptional capabilities in exploring chemical space, facilitating the design of tailored molecular structures to address the complexities of modern therapies [27]. These innovative advancements not only drive transformative changes in drug development, shortening development timelines and reducing costs, but also provide robust technological support for personalized medicine and novel drug discovery.

This paper aims to review the latest advancements in AI for drug response prediction, drug combination optimization, drug repositioning, and drug molecule generation, while exploring the potential and challenges of these technologies in addressing key issues in drug development. By systematically summarizing and analyzing existing research, we aim to provide a comprehensive knowledge framework for this field, stimulate further academic interest, and promote interdisciplinary collaboration, ultimately advancing the application and development of AI in drug discovery. The contributions of this study are as follows: (1) systematically organizing AI applications in drug development, creating a knowledge map and classification framework, (2) analyzing AI's technical advantages and application scenarios, offering practical insights, (3) highlighting the importance of interdisciplinary collaboration, exploring integration with biology and pharmacology, (4) identifying bottlenecks like data quality and model interpretability, proposing solutions and future directions, (5) constructing a comprehensive knowledge framework to support AI application and industrialization in drug development.

2 Core AI technologies in drug development

Drug development is typically divided into preclinical and clinical stages, with AI making a significant impact mainly in the preclinical phase [28]. This stage involves critical steps like disease mechanism research, target identification, and compound screening, where AI enhances efficiency through data-driven insights and advanced computational algorithms [29]. AI-driven pharmaceutical technologies reduce development time and costs by optimizing multiple processes [30]. Deep learning methods, in particular, are noteworthy for their theoretical strength and practical breakthroughs. Below, we analyze the characteristics of key deep learning methods and their applications at various stages of drug development.

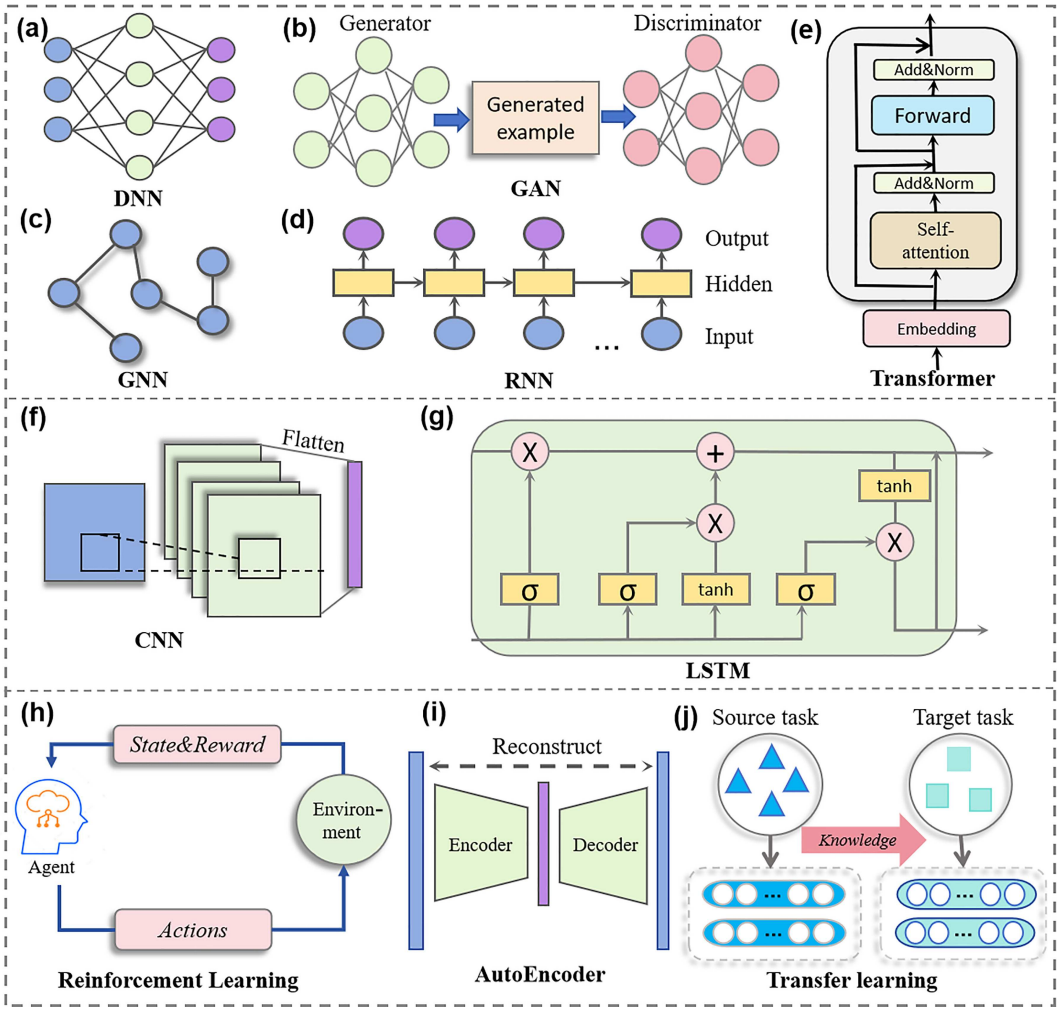

Figure 1 (Color online) Core AI methods in drug development. (a) DNN architecture; (b) GAN architecture; (c) GNN architecture; (d) RNN architecture; (e) Tansformer architecture; (f) CNN architecture; (g) LSTM architecture; (h) reinforcement learning architecture; (i) autoencoder architecture; (j) transfer learning architecture.

Deep neural networks (DNNs) excel at capturing complex nonlinear relationships through multi-layer architectures (Figure 1(a)), which adjusts the weights through backpropagation and automatically extracts features for large-scale and complex data to aid in drug discovery, such as drug-target interaction (DTI) prediction and drug compound activity prediction [31,32]. Convolutional neural networks (CNNs) specialize in spatially structured data (Figure 1(f)) and extract spatial features through convolutional layers, which are extensively applied in molecular crystal structure analysis and compound image recognition [33, 34]. In drug development, CNNs optimize virtual screening by analyzing 2D images and 3D molecular structures, enhancing candidate identification and predicting spatial compatibility between molecules and targets to improve binding precision [35]. Recurrent neural networks (RNNs) (Figure 1(d)) and long short-term memory networks (LSTMs) (Figure 1(g)) are focused on sequential data, applied in molecular sequence generation, protein folding prediction, and genomic analysis [36–40], and LSTMs solve the problem of disappearing gradients in RNNs to better model long-term dependencies. GNNs specialize in analyzing graph-structured data (Figure 1(c)), widely used for molecular property prediction, drug interaction network analysis, and protein structure simulations [41,42]. By propagating information between nodes (atoms) and edges (bonds), GNNs capture complex non-Euclidean relationships between molecules. GANs use adversarial training to generate samples that resemble real data distributions (Figure 1(b)), excelling in chemical space exploration and novel molecule design [43–45]. The Transformer model (Figure 1(e)), with its attention-based architecture, improves sequence modeling efficiency, widely applied in natural language processing (NLP), molecular sequence generation, and protein structure prediction [46, 47]. The self-attention mechanism enables the model to efficiently capture long-distance

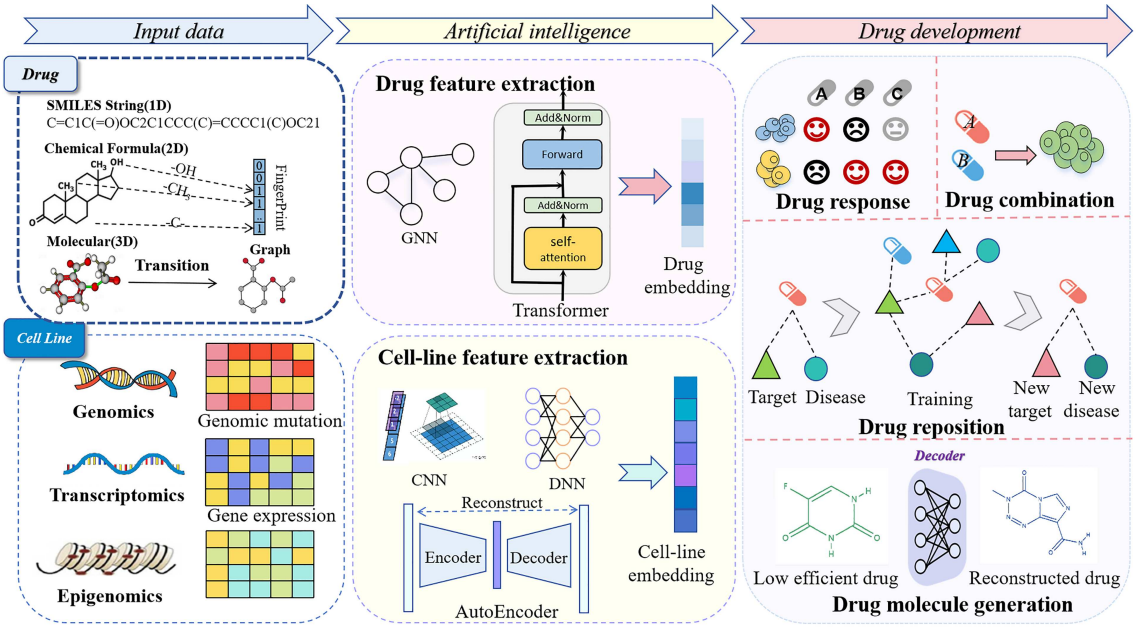

Figure 2 (Color online) AI-driven workflow for drug development.

dependencies. Transfer learning applies domain knowledge to solve problems in other areas (Figure 1(j)), particularly useful in data-scarce scenarios, widely applied in cross-disease and cross-target predictions in drug development, such as drug repositioning [48,49]. Deep autoencoders learn efficient data representation through encoding and decoding processes (Figure 1(i)), applied in compound representation, protein structure prediction, and novel drug design [50,51]. Reinforcement learning (RL) (Figure 1(h)), using the "exploration and exploitation" strategy, solves complex decision-making problems, widely applied in molecule optimization, drug design, and personalized drug dosage optimization [9,52].

3 Specific methods and applications of AI in drug development

3.1 Data foundations and workflow overview

In drug response prediction, drug molecule representation is crucial and falls into sequence-based, graph-based, and image-based methods. Simplified molecular input line entry system (SMILES) [53], a widely used sequence-based method, encodes molecular structures into strings and uses Transformer models to extract features, offering a compact and standardized format with simplicity and efficiency. As drug databases expand, many now include 2D and 3D molecular descriptions for hundreds of drugs, providing richer structural information. These multi-dimensional data have enriched representation methods and accelerated the development of deep learning models, enhancing AI's potential in drug response prediction.

Figure 2 illustrates the interrelationship and workflow among input data, AI methods, and drug research, emphasizing synergistic interactions and information flow. The AI-integrated drug development process is summarized as follows. First, data such as drug properties, genomic information, and labels are prepared. Next, AI methods extract feature representations of drugs or biological cells, forming a foundation for modeling. These feature vectors and task-specific labels are input into machine learning or deep learning models, where parameters are optimized to improve predictive performance. After training, the model is evaluated using performance metrics to identify the best version and tested on an external set to assess generalization. Finally, predictive results are validated through biological experiments or literature, and interpretability analyses uncover underlying biological mechanisms.

AI models leverage extensive molecular and biological data from sources like GDSC [54], CCLE [55], and DrugBank [56] to identify patterns that guide drug selection and enhance early-stage screening efficiency. Modern drug research integrates genomic, pharmacological, and clinical datasets to support therapeutic development. High-throughput genomics techniques identify mutations, gene expression profiles, and regulatory pathways [57], while whole-genome and whole-exome sequencing reveal cancer genome variations

to uncover drug targets and resistance mechanisms [58]. Single-cell technologies capture tumor heterogeneity, aiding in designing targeted drug combinations. Epigenomic data reveal chromatin accessibility and regulatory elements [59]. Drug databases like DrugBank and CMap offer pharmacological insights, which, combined with clinical data, enable predictive models of drug efficacy and safety [60]. Together, these datasets underpin precision medicine and personalized treatment strategies [61].

AI plays a transformative role in drug development by accelerating stages from drug screening to molecular design. In data processing, AI structures and analyzes complex datasets to identify high-quality data and potential drug candidates from vast libraries, reducing trial-and-error processes. A 2019 Cell cover story reported AI's success in discovering novel antibiotics from over 100 million molecules, validated in mice experiments [62]. In data analysis, AI efficiently identifies disease-related targets using machine learning and deep learning, expediting the transition from biological mechanisms to therapeutic discovery while aiding in drug resistance and patient response prediction [63]. By analyzing genomic and single-cell data, AI identifies resistance biomarkers and stratifies patients, enabling precision medicine [64]. For molecule generation, AI models like GANs and VAEs design novel compounds with optimized properties, while RL refines structures to enhance efficacy and safety [65, 66]. AI's capacity to manage large-scale, high-dimensional data has established it as an indispensable tool, driving efficient, data-driven drug discovery [67].

3.2 Deep learning models efficiently predict 3D structures of molecules and complexes

Target-based drug design dominates drug development, with proteins being the primary targets. Understanding molecular and complex three-dimensional structures is fundamental to life sciences and drug development, offering insights into interactions, binding mechanisms, and functional properties essential for effective therapeutic strategies [68]. Traditional methods for structural determination are time-intensive and constrained by experimental limitations. Deep learning models address these challenges by enabling efficient and accurate molecular structure prediction, demonstrating exceptional applicability even in complex scenarios and significantly advancing molecular biology and drug discovery. AlphaFold [69], developed by DeepMind under Google, has predicted structures for approximately 200 million proteins, covering nearly all known organisms.

Drug discovery depends on molecular structures like proteins, drugs, and ligands to analyze binding mechanisms and interactions. Determining a single protein's 3D structure can take months or years, especially without similar known structures, making structural coverage a challenge. AlphaFold 2 addresses this by leveraging deep learning for end-to-end 3D structure prediction directly from amino acid sequences, bypassing manual feature engineering and complex simulations [69]. It uses templates for known structures and constructs multiple sequence alignments for unknown ones to extract evolutionary information and predict conserved and variable regions. AlphaFold 2 achieves a high prediction accuracy (average GDT score of 92.4), comparable to experimental techniques like cryo-electron microscopy. AlphaFold 3 further advances this capability by incorporating diverse input types and introducing enhanced feature representations and diffusion modules with SwiGLU activation, improving performance [70]. It achieves at least 50% better accuracy in predicting interactions between proteins and other molecules, doubling accuracy for critical interactions like protein-ligand and antibody-target protein binding. Additionally, AlphaFold 3 models large biomolecules and small molecules, making it a highly promising tool for drug design.

Deep learning models excel in predicting the 3D structures of molecules and complexes, offering significant efficiency and speed advantages, and have become pivotal in life sciences and drug development [71]. By employing end-to-end sequence-to-structure learning, these models drastically reduce the time needed for traditional structural analysis, accurately predicting protein and molecular structures even without known similar templates. The AlphaFold series enhances precision and expands applicability through advanced feature representations and innovative architectures, supporting predictions across diverse molecular types and complexes [72]. Additionally, integrating self-supervised and contrastive learning significantly improves the models' ability to capture molecular properties and interactions. These advancements underpin the understanding of molecular mechanisms, optimization of drug design, and development of new therapies, thereby accelerating progress in life sciences.

3.3 Artificial intelligence improves efficiency and predictive accuracy of drug-target interactions

Successful drug development involves critical factors such as target selection, drug interactions, pharmacokinetics, and safety evaluation. Investigating how molecular structures affect DTIs is crucial, as it provides key insights into drug action mechanisms [73]. After achieving precise structural characterization, exploring its functional implications becomes essential in drug discovery. Deep learning, with its ability to analyze complex datasets, has become a transformative tool for predicting DTIs [74]. It bridges the gap between structure and function, offering insights into how structural features translate into functional outcomes, thereby advancing efficient drug development strategies [75]. For example, in amyotrophic lateral sclerosis (ALS), motor neurons in the brain and spinal cord degenerate, leading to loss of muscle control. Existing ALS drugs cannot reverse neurodegeneration. However, using the AI-based target discovery platform PandaOmics [76], scientists at Insilico Medicine have identified previously unreported potential therapeutic targets, offering new hope for ALS treatment.

AI predicts compound-target binding affinity, aiding drug design to enhance efficacy. The vast mutation diversity in antibody complementarity-determining regions makes traditional in vitro affinity maturation time-consuming and costly [77]. Although molecular dynamics simulations are accurate, their computational inefficiency limits large-scale mutation screening. Deep learning models significantly improve affinity prediction accuracy and reliability. The GearBind method [78] uses a pretrainable deep neural network to model protein-protein interactions via hierarchical geometric information propagation. Pretrained on large-scale unlabeled protein structures, it contrasts native structures with randomly mutated counterparts sampled from a rotamer library, focusing on side-chain torsion angles. This approach captures native structural features and distinguishes between wild-type and mutant proteins.

Conventional methods for predicting DTIs typically rely on the known three-dimensional structures of drugs and targets. However, the structural data for certain drug targets remain limited. MIDTI [79] overcomes this limitation by constructing various graphs that incorporate not only chemical and genetic information but also semantic relationships between biological entities, such as targets, drugs, diseases, and side effects. By leveraging a multi-view similarity network fusion strategy and a deep interaction attention mechanism, MIDTI effectively predicts DTIs, providing a more comprehensive and robust approach to DTI prediction. However, when the input consists solely of molecular descriptions of drugs and amino acid sequences of protein targets, structure-based approaches often struggle to achieve high prediction accuracy. ConPlex [80] addresses this issue by utilizing a pretrained protein model and categorizing datasets into two types based on data coverage: high-coverage and low-coverage datasets. High-coverage datasets encompass a wide range of proteins to evaluate diversity, while low-coverage datasets focus on specific protein families to assess specificity.

In conclusion, AI significantly enhances the efficiency of DTI research. By integrating molecular docking, virtual screening techniques, and deep learning models, AI predicts ligand-protein interactions and employs molecular dynamics simulations to improve prediction accuracy [80]. Deep learning models complement existing ligand-protein binding screening strategies by analyzing 3D structures to determine binding energies between candidate drugs and proteins, thereby selecting the most suitable ligands and improving DTI prediction accuracy. Leveraging target-drug molecular interactions, AI can calculate the binding affinities between drugs and their targets, enabling the virtual screening of lead compounds from chemical databases. This approach greatly enhances the specificity of drug research, increases the hit rate of bioactivity assays, and effectively reduces development costs.

3.4 Deep learning advances predictive models for drug sensitivity

Drug response refers to the physiological, pharmacological, and biochemical reactions when a drug interacts with cells, tissues, or organs, encompassing its efficacy, toxicity, metabolism, and excretion, and reflecting individual variability in drug responses [81]. The study of drug response includes therapeutic outcomes, as well as absorption, distribution, metabolism, excretion (ADME), and the influence of genetics, disease, and environmental factors on the drug's effect [82]. Drug response is crucial for assessing drug efficacy and identifying areas for improvement, guiding new drug design and optimization. Research primarily focuses on predicting drug responses in cancer treatments. Rapid advancements in AI have significantly enhanced the accuracy, efficiency, and scalability of drug response predictions, fostering innovation in this field [83].

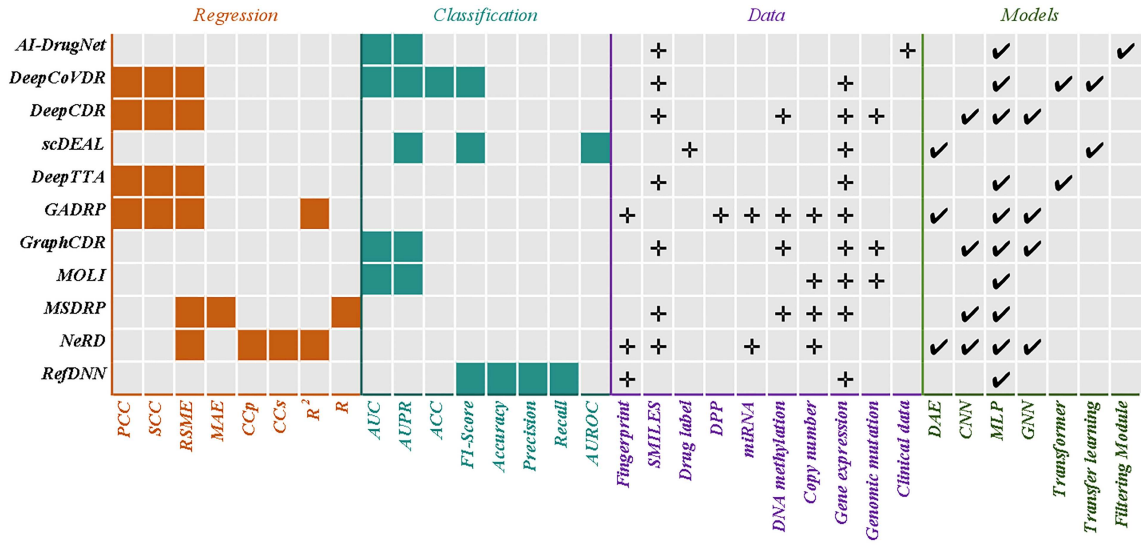

Figure 3 (Color online) Representative methods for drug sensitivity prediction. DPP: drug physicochemical properties.

AI models for drug response prediction typically combine drug data with omics data, producing output values such as half-maximal inhibitory concentration (IC50), 50% growth inhibitory concentration (GI50), or area under the dose-response curve (AUC) to describe the dose-response relationship [1]. While earlier studies used either drug or omics data, recent research focuses on integrating both to improve predictive accuracy. Drug response prediction tasks are divided into regression and binary classification. Regression predicts specific values, while binary classification assesses drug-disease sensitivity or resistance. Evaluation metrics differ: regression tasks use Pearson correlation coefficient (PCC), Spearman correlation coefficient (SCC), and root mean square error (RMSE), while classification tasks use AUC, the area under the precision-recall curve (AUPR), and F1 score. Figure 3 illustrates key AI methods for drug sensitivity prediction, along with their associated data, models, and evaluation metrics.

DNNs have become indispensable tools in drug response prediction due to their exceptional ability to extract features and make predictions from high-dimensional omics data. MOLI [84] is the first end-to-end integrated method to use DNNs, taking somatic mutations, copy number alterations (CNAs), and gene expression data as input, and using a DNN to extract features and ultimately predict drug response. Similarly, RefDNN [85] consists of multiple ElasticNet models to compute representations of high-dimensional gene expression data, and uses a DNN classifier to predict drug responses based on these representations.

Sequence-based representation methods typically use SMILES as input data for drug molecules and employ Transformer models for feature extraction. DeepChem [86] provides a function to derive molecular graphs from SMILES strings, which is widely applied in graph-based representation methods. Graph structures effectively capture the atoms and their relationships in drug molecules and use GNNs for feature extraction. In contrast, drug molecule images can also be used as input, with CNNs employed for feature extraction. Among current research, sequence-based SMILES representations and graph-based representations are the two dominant approaches, each offering unique advantages [87].

For instance, in DeepCDR [88], a graph convolutional network (GCN) [89] is constructed to extract feature vector representations from drug molecular graphs. Similarly, the Nerd model also employs multi-layer GCN networks to extract drug. Both methods share the common feature of using graph structures to represent drug molecules, enabling precise capture of atomic relationships and complex molecular features. Moreover, DeepCDR integrates multiple subnetworks to extract multi-omics features from genomic, transcriptomic, and epigenomic data, enhancing the prediction performance. This integration of multi-omics data highlights the potential of combining drug features with cellular and genetic information [90].

In addition, some studies attempt to model the interaction between drugs and cancer cell lines (CCLs) as a graph structure. In GraphCDR [91], cancer cell line representations learned through DNNs and drug representations learned via GNNs are used as node attributes in a cancer drug response (CDR) graph, with CCLs and drugs as nodes and sensitive responses as edges. The GNN encoder is employed to learn

the latent embeddings of CCLs and drugs from the CDR graph for prediction. This graph-based modeling approach not only captures the relationships between drugs and cell lines efficiently but also optimizes predictions through GNNs. Similarly, in GADRP [92], a sparse drug cell line pairs (DCP) network is constructed, combining similarity information between drugs, cell lines, and DCPs, with drug features represented as DCP node attributes, and similarities between DCP nodes represented by edges. This approach also emphasizes the importance of drug-cell line interactions and enhances prediction accuracy through the network structure.

Since the introduction of the Transformer model in 2017, it has become a revolutionary architecture in deep learning [93], particularly in the field of NLP. SMILES strings, as a sequence representation, can be treated as textual data, enabling the use of Transformer models for feature extraction. The self-attention mechanism in Transformer models allows for the efficient capture of complex relationships between atoms and bonds in SMILES sequences, thus generating more accurate drug representations. In DeepTTA [94], SMILES of drugs are treated as a sequence, decomposed into substructures, and input into a Transformer encoder-based neural network to obtain the drug's representation vector. In this approach, the self-attention mechanism in Transformer models improves prediction accuracy by capturing dependencies between different parts of the drug molecule. DeepCoVDR [95] is an improved version of DeepTTA, employing a graph Transformer and feedforward neural network to mine information from both drugs and cell lines. Additionally, the cross-attention module in the Transformer is used to compute the interaction between drugs and cell lines. Unlike traditional Transformer methods, DeepCoVDR enhances the model's capability to handle drug-cell line interaction data by integrating the graph Transformer, thereby improving prediction performance.

Other methods have also made significant progress in this field. For example, scDEAL [96] is a deep transfer learning framework that predicts cancer drug responses at the single-cell level by integrating large-scale cell line data. The innovation of scDEAL lies in coordinating large RNA-seq data related to drugs with single-cell RNA-seq data and applying models trained on RNA-seq data to predict drug responses in single-cell data. This approach emphasizes the synergistic effect between different data sources and uses deep transfer learning to improve prediction accuracy. Similarly, MSDRP [97] constructs drug-drug, drug-cell line, and cell line-cell line similarity matrices and uses inner and outer products to extract and fuse features, providing new insights for drug response prediction.

Deep learning has demonstrated significant advantages in drug sensitivity prediction, offering powerful tools for analyzing and modeling complex biological data. However, the progression and pathogenesis of many diseases often involve multiple biological pathways, making it challenging for single drugs to target all relevant mechanisms effectively. As the complexity of treating such diseases continues to grow, the limitations of single-drug therapies have become increasingly apparent, positioning combination therapy [98] as an indispensable strategy in addressing these challenges.

3.5 Deep learning-enabled innovations in modeling drug combinations and synergistic effects

Developing drug combinations that target multiple pathways simultaneously has become a key strategy for enhancing therapeutic efficacy and reducing side effects [24, 99]. Drug combinations allow for the simultaneous targeting of multiple cellular pathways, maximizing the cytotoxic effects on diseased cells while potentially reducing the likelihood of resistance development [100]. By selecting drugs with synergistic effects [101], combination therapies can be tailored to address the heterogeneity within tumors, as each drug in the combination may target distinct cellular subpopulations, thereby increasing the probability of complete disease eradication [102].

Early research on drug synergism typically relied on wet-laboratory experiments, which are time-consuming, expensive, and carry inherent risks [103]. However, advancements in high-throughput sequencing technologies have greatly expanded the scope of genomics and transcriptomics, providing rich datasets for disease-related research. These datasets encompass genetic variations, gene expression, and protein functions across diseases, healthy tissues, animal models, and cell lines [104]. As the volume of data increases dramatically, traditional analytical methods and individual expert knowledge are no longer sufficient to meet the needs of precision medicine. In this context, the application of AI is progressively reshaping drug combination research, offering new approaches to drug synergy prediction. Table 1 [105–112] summarizes the application of representative AI methods in drug combination research.

Table 1 Representative AI methods for drug combination prediction.

Method	Model	Input	Evaluation	Code
DeepTraSynergy [105]	PPI network, Transformer	SMILES, protein-protein interactions, drug-protein interactions, cell line-protein interactions	AUC-ROC, AUC-PR, ACC, recall, F1 score	https://github.com/fatemeh-rafiei/DeepTraSynergy
TranSynergy [106]	Transformer, MLP	Drug-target interaction, gene expression, gene dependency	MSE, SCC, PCC, PR-AUC, ROC-AUC	https://github.com/qiaoliuhub/drug_combination
DeepDDS [107]	GNN, Attention mechanism	SMILES, gene expression	ROC-AUC, PR-AUC, ACC, BACC, PREC, TPR, KAPPA	https://github.com/Sinwang404/DeepDDS/tree/master
MTLSynergy [108]	Multi-task learning, Autoencoder, MLP	SMILES, gene expression	MSE, RMSE, PCC, ROC-AUC, PR-AUC, ACC	https://github.com/TOJSSE-iData/MTLSynergy
DFFNDDS [109]	BERT, Attention mechanism	SMILES, fingerprint, gene expression	ACC, ROC-AUC, BACC, MCC, F1 score, recall, average precision, precision, KAPPA	https://github.com/sorachel/DFFNDDS
GAECDS [110]	GAE, GCN, CNN, MLP	Fingerprint, gene expression	ACC, AUC, AUPR, recall, precision, F1 score	https://github.com/junelyemm/GAECDS
Muthene [111]	Multi-task learning, GCN, GAT	Drug-drug interaction, drug-drug adverse effect, drug target interaction, gene expression	MSE, MAE, PCC	https://github.com/arantir123/HNEMA
DTSyn [112]	GCN, Transformer	SMILES, gene expression	ROC-AUC, PR-AUC, ACC, BACC, PREC, TPR, KAPPA	https://github.com/PaddlePaddle/PaddleHelix/tree/dev/apps/drug_drug_synergy/DTSyn

Drug combination prediction often relies on similarity metrics, assuming that drugs with similar structures or targets may exhibit similar effects or interact with one another [113]. Furthermore, mathematical models are widely employed to interpret pharmacokinetic and pharmacodynamic data to optimize dosing regimens. AI technologies, such as machine learning, deep learning, and data analysis, can rapidly process and analyze large-scale genomic, clinical, and drug-related data to extract similarity information, predict interactions between drugs and targets, and optimize the effects of drug combinations. AI-based models have already been applied to predict drug combinations for various diseases, including cancer, infectious diseases, HIV, and hypertension [114]. For instance, the AI algorithm ComboFM [115] accurately predicts whether combinations of anticancer drugs exhibit synergistic effects, thereby enhancing their combined cytotoxicity against cancer cells. By leveraging higher-order tensor modeling, ComboFM effectively captures the interactions within drug combinations. Validation using pharmacogenomic screening data from tumor cell lines demonstrated that ComboFM achieves outstanding predictive performance across diverse scenarios.

In machine learning, drug combination prediction is framed as either a multi-class classification or regression task. Most studies on classification classify combinations into synergistic or non-synergistic categories, whereas regression tasks are focused on predicting synergy scores [116, 117]. For example, Zhou et al. [118] developed a model using CatBoost, XGBoost, and RF, confirming the strong therapeutic effect of Lapatinib and Pazopanib in breast cancer. With the rapid development of deep learning, an increasing number of deep learning models are being applied to drug combination prediction. Deep learning uses DNNs for feature extraction and prediction. Models based on Transformer and GNNs are widely used in recent studies. For instance, TranSynergy [106] employs a self-attention mechanism to model gene-gene interactions, using DNNs for prediction. The DTSyn [112] model integrates fine-grained and coarse-grained Transformer encoders to capture associations between chemical substructures and genes, and between chemicals and cell lines. DTSyn has demonstrated superior performance in multiple cross-validation tasks. DeepTraSynergy [105] predicts drug synergism using multi-modal inputs, including drug-target, protein-protein, and cell-target interactions, and has achieved high accuracy on drugs.

3.6 Artificial intelligence accelerates drug repositioning with enhanced precision

Drug repositioning repurposes existing drugs for new therapeutic uses, offering significant cost and time advantages compared to traditional drug discovery, as the safety and pharmacokinetics of these drugs are already established [12]. This strategy is particularly effective in tackling resistance or addressing

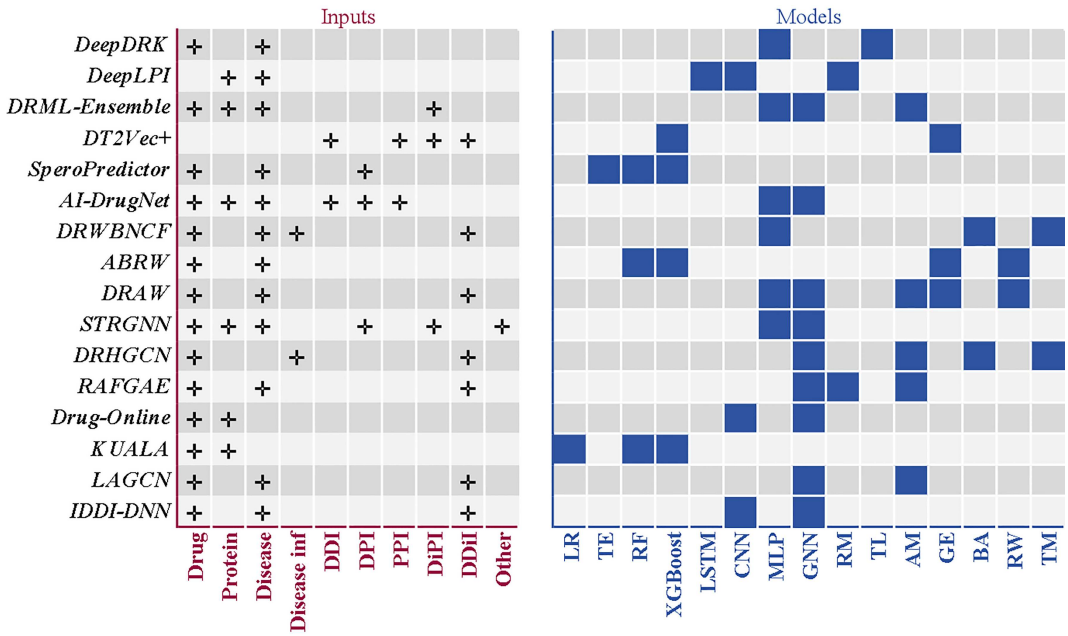

Figure 4 (Color online) Representative methods for drug reposition. Disease inf: disease description information; DDI: drug-drug interactions; DPI: drug-protein interactions; PPI: protein-protein interactions; DiPI: disease-protein interactions; DDiI: drug-disease interactions; LR: linear regression; TE: tree ensemble; RF: random forest; RM: residual mechanism; TL: transfer learning; AM: attention mechanism; GE: graph embedding; BA: bilinear aggregator; RW: random walk; TM: text mining.

emerging diseases. By leveraging AI to analyze large-scale data, drug repositioning identifies therapeutic potential in approved drugs, expediting discovery and reducing costs [119].

The rapid advancement of AI and computational technologies has integrated these tools into drug development stages, from molecular structure analysis to biological interaction predictions, enabling efficient repositioning. This paradigm shift transforms traditional drug discovery, advancing precision medicine. Drug response prediction underpins drug repositioning, providing essential support for its success. For instance, DeepDRK [120] utilizes DNNs to process integrated multi-omics data, including drug structural similarity, DTIs, and drug efficacy on CCLs, providing a foundation for drug repositioning. Similarly, scDEAL [96] applies transfer learning to harmonize bulk gene expression data with single-cell data, successfully addressing the scarcity of single-cell drug response datasets and offering innovative solutions for drug repositioning tasks.

Understanding a drug's mechanism of action (MOA) is crucial for uncovering novel therapeutic patterns and enabling drug repositioning. MitoReID [121] employs mitochondrial morphology and membrane potential as proxies for MOA by using metric learning to optimize extracted temporal features for sample matching. This approach facilitates MOA inference for unknown drugs, aiding repositioning efforts. For Alzheimer's disease, DRIAD [122] leverages gene expression profiles at different pathological stages and drug-induced gene perturbations in neurons to train a predictor for evaluating drug-induced cellular disruptions, thus providing insights into repositioning candidates.

Biomedical knowledge graphs (KGs), encompassing entities such as diseases, genes, and drugs, enable the discovery of latent associations between entities, offering valuable insights for drug repositioning. For example, deepDR [123] uses positive pointwise mutual information (PPMI) and collective variational autoencoders (cVAE) to predict drug-disease associations. LAGCN [124] enhances GCNs with attention mechanisms to optimize heterogeneous network integration, improving predictive accuracy. Similarly, STRGNN [125] incorporates topological regularization in GNNs to analyze multimodal networks for repositioning.

Addressing complex network integration, approaches like DRWBNCF [126] and DRHGCN [127] combine bilinear aggregation and GCNs to enhance predictions in heterogeneous networks. AdaDR [128] employs consistency constraints and attention mechanisms to fuse network embeddings, achieving multidimensional modeling of drug-disease relationships. Moreover, TxGNN [129] extracts latent rules from knowledge graphs, supplementing the treatment gap for certain diseases while providing interpretable predictions through multi-hop knowledge paths. Figure 4 illustrates representative methods for drug

repositioning.

In conclusion, AI in drug repositioning offers promising prospects for precision medicine and drug development. Future research may focus on (1) building larger, high-quality multimodal biomedical knowledge bases for robust model training, (2) improving model interpretability for better clinical applicability, and (3) advancing the integration of heterogeneous networks and cross-domain knowledge to address data sparsity and noise in complex biological systems. These advancements will further expand AI's impact on drug discovery and effectively address unmet clinical needs.

3.7 Generative models revolutionize drug molecule design and optimization

AI utilizes deep learning generative models to analyze features of known molecules and generate novel structures. Techniques such as VAEs and GANs optimize drug structures, enhance efficacy, and identify novel candidates. Drug molecule generation focuses on designing compounds with specific biological activities and physicochemical properties. By learning from existing molecules and their interactions, AI expands the chemical space of drug discovery, enabling innovative molecular designs through deep learning frameworks that integrate generative models and neural networks.

AI-driven advancements in molecular modeling and drug generation facilitate the design of innovative compounds targeting specific disease-associated molecules. These approaches improve binding affinity, reduce off-target effects, and enhance bioavailability, optimizing therapeutic potential. Moreover, integrating large language models, such as ProteinGPT [130], enables the generation of protein-based drug candidates that meet predefined criteria, highlighting AI's transformative potential in drug discovery and biomaterial design. Chemical language models (CLMs), which are designed to process string-based drug data, learn the syntactic and semantic features of drug molecules. This capability allows CLMs to generate drug-like molecules with specific desired properties, contributing significantly to molecular design and optimization. Building on this foundation, HybridCLMs [131] implement two distinct pretraining strategies tailored for different objectives. The first strategy employs an autoregressive training approach to create generative models capable of designing novel drug-like molecules. In contrast, the second strategy leverages the ELECTRA pretraining method to develop classification models that assess the accuracy and plausibility of generated tokens, ensuring the reliability of the outputs.

Further advancing the field, the s4dd model demonstrates the advantages of structured state space sequence (S4) models in CLMs [132]. By learning global patterns from molecular sequences and generating molecules character by character, s4dd succeeds in creating bioactive and structurally complex drug-like molecules. These advancements illustrate the growing sophistication of CLMs in capturing both the structural and functional nuances of drug molecules, paving the way for more precise and efficient drug discovery methodologies. Knowledge graphs composed of proteins, drugs, and diseases encapsulate interactions among various entities, enabling the discovery of latent biomedical knowledge through network topology analysis. Among these methods, DRAGONFLY [133] integrates graph transformation neural networks and CLMs to uncover hidden information in drug-target interaction networks. By leveraging multi-node information from interaction networks, DRAGONFLY circumvents the need for target-specific fine-tuning, focusing instead on ligand- and structure-based drug design. This approach significantly reduces dependency on experimental data. In addition, DeepBlock [6] employs a block generation network to capture relationships between protein sequences and compound molecules. Not only does it generate molecular blocks, but it also uses assembly algorithms to reconstruct these blocks into complete drug molecules. Consequently, DeepBlock facilitates protein sequence-based drug molecule generation while providing a robust foundation for optimizing molecular properties by integrating block attributes and their chemical interactions. Moreover, the three-dimensional structure of molecules provides critical latent information for drug generation. For example, GEOM-CVAE [134] leverages molecular images and geometric protein graphs to independently learn 3D structural features of drugs and proteins, generating target-specific drugs via protein constraints. Similarly, TamGen [16] integrates protein sequence and 3D structure information from a protein encoder with latent features from a context encoder, embedding these into a compound decoder for target-specific drug generation and molecular optimization. At the same time, PMDM [135] uses a dual-diffusion model to construct local covalent edges for chemical bonds and global edges for van der Waals forces, enabling drug-like molecule generation based on protein pocket structures. Additionally, pharmacophore information is crucial for uncovering drug-target binding features. For instance, PGMG [136] generates drug-like molecules linked to specific pharmacophores by learning their relationships with molecules. These methods significantly reduce reliance on task-specific

Table 2 Summary of methods in drug molecular generation. 1D: SMILES string; 2D: molecule graph; 3D: 3D graph; RL: reinforcement learning; TL: transfer learning; TF: transformer; DM: diffusion model.

	Drug			Method												
	1D	2D	3D	LLM	VAE	TF	RL	GCN	LSTM	RNN	GNN	GTNN	BGNet	GAN	TL	DM
DrugLLM	★			✓												
GMG-NCDVAE	★			✓	✓											
LA-CycleGAN	★					✓	✓									
MomdTDSRL	★					✓	✓									
Taiga	★					✓	✓									
TransGEM	★					✓										
TransAntivirus	★					✓										
Sc2Mol	★				✓	✓										
PGMG	★					✓		✓								
POLYGON	★				✓		✓									
TamGen	★				✓	✓										
Multitarget-ligands	★								✓						✓	
CRAG		★		✓						✓						
MG2 N2		★									✓					
SEED		★					✓				✓					
DRAGONFLY		★							✓			✓				
DeepBlock		★											✓			
DNMG			★				✓							✓	✓	
GEOM-CVAE			★		✓			✓			✓					
PMDM			★													✓

transfer or RL, especially when fine-tuning datasets are limited. Table 2 summarizes the methods for drug molecule generation.

Multi-target drugs excel in treating multifactorial diseases by modulating multiple pathways. However, traditional methods struggle to design such drugs systematically. AI-driven drug generation has thus emerged as a key focus. For instance, POLYGON [137] employs a VAE to embed drug molecules and RL to prioritize subspaces for dual-target inhibition, synthetic accessibility, and drug-likeness, iteratively generating high-quality dual-target drugs. Similarly, multitarget ligands use transfer learning on a fine-tuned chemical language model to design molecules targeting two specific proteins. While promising, these methods are limited to dual-target drugs, highlighting the need for advancements in generating molecules targeting more than two targets.

4 Summary and outlook

AI in drug development is rapidly advancing, particularly with deep learning (DL) methods applied to drug discovery, response prediction, and personalized medicine. The limited availability of annotated data presents opportunities for active learning, allowing model training with fewer samples. The adoption of end-to-end DL frameworks is expected to increase, enabling more comprehensive use of diverse data types. Incorporating biological knowledge into models will enhance accuracy and interpretability. AI tools are becoming more accessible through cloud platforms, enabling users without coding skills to utilize them. Looking ahead, AI is set to drive actionable insights for personalized treatment strategies, drug repurposing, and optimized drug combinations, transforming drug development into a more efficient and personalized process.

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