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Application advances of deep learning methods for de novo drug design and molecular dynamics simulation

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Abstract

De novo drug design is a stationary way to build novel ligands in the confined pocket of receptor by assembling the atoms or fragments, while molecular dynamics (MD) simulation is a dynamical way to study the interaction mechanism between the ligands and receptors based on the molecular force field. De novo drug design and MD simulation are effective tools for novel drug discovery. With the development of technology, deep learning methods, and interpretable machine learning (IML) have emerged in the research area of drug design. Deep learning methods and IML can be used further to improve the efficiency and accuracy of de novo drug design and MD simulations. The application summary of deep learning methods for de novo drug design, MD simulations, and IML can further promote the technical development of drug discovery. In this article, two major workflow methods and the related components of classical algorithm and deep learning are described for de novo drug design from a new perspective. The application progress of deep learning is also summarized for MD simulations. Furthermore, IML is introduced for the deep learning model interpretability of de novo drug design and MD simulations. Our paper deals with an interesting topic about deep learning applications of de novo drug design and MD simulations for the scientific community.

This article is categorized under:

Data Science > Chemoinformatics

Data Science > Artificial Intelligence/Machine Learning

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KEYWORDS

de novo drug design, deep learning, explainable artificial intelligence, interpretable machine learning, MD simulation

1 | INTRODUCTION

De novo drug design is a traditional method used to design the novel ligands in the receptor pocket by assembling the fragments or atoms based on classical algorithms such as genetic algorithm and Monte Carlo method.^{1–3} Machine learning method which has a different style to the conventional drug design method, has positively impacted de novo drug design.³ Traditional machine learning methods extract data features by hand based on the related area of knowledge, meaning they are limited in their ability to process raw data.⁴ With the technological progress of machine learning and big data, more powerful machine learning methods, such as deep learning, can be used,^{5,6} which can learn hidden functional relationships from the original data and apply them to the new data. Deep learning uses multiple layers of nonlinear transformations that extract and combine information from data in order to distinguish more general trends and patterns from noise, and it also offers the opportunity to acquire features that have not yet been discovered by researchers and to break through the limits of existing knowledge.^{7–9} Since deep learning methods can leverage multiple processing layers to automatically extract task-related features, they have made rapid progress in the fields of image classification,¹⁰ speech recognition,¹¹ natural language processing, drug discovery, and MD simulations, among others.^{12–16} In particular, deep learning methods are highly suitable for de novo drug design.¹⁷ Indeed, some studies^{9,18,19} reveal that they have successfully improved drug development by finding more promising compound candidates and raising the success rate of candidate clinical trials. For example, a deep generative model named GENTRL¹⁹ has been reported for de novo inhibitors design of discoidin domain receptor 1 (DDR1) that involves fibrosis and other diseases. A total of 21 days is for the entire process of novel compound discovery, comprising molecular generation by GENTRL, biochemical assays of four compounds, cell-based assays of two ligands, and pharmacokinetics of one lead candidate in mice.

Molecular dynamics (MD) simulation is a type of computer simulation that analyzes the chemical and physical properties of atoms and molecules based on the classical force field that brings together the parameter sets and functional form for potential energy calculation of particles in the system.²⁰ MD simulations have become a common and successful method for drug discovery and research into the dynamical interaction mechanism between biomolecules and drugs.^{21–23} However, MD simulations face the problem of the accuracy-versus-efficiency dilemma.²⁴ It means their efficiency will be pulled down if accuracy is increased. In addition, although MD simulations display performance well on molecules and materials, the classical potential theory usually fails to reproduce the key quantum effects faithfully.²⁵ In recent years, deep learning methods have been introduced to the research area of MD simulations, to minimize the effort needed to obtain the accurate potential energy and force field as a result of training and testing the trajectory data of MD simulations. For example, the reported study shows that the transfer free energies can be predicted with a mean absolute error of ~4 kJ/mol by the spatial graph CNN (SG-CNN).²⁶ Both de novo drug design and MD simulation are promoted and evolved by deep learning methods. Drug design based on deep learning can generate candidate compounds that are significantly different structural wise from those already on the market and solve the problem regarding less diversity of drugs. MD simulations can also be further used to study the dynamical mechanism of new compound candidates that are designed by de novo methods. Although deep learning models have boosted the wide application of de novo drug design and MD simulation, it seems to be like a black box that needs to be explained. To make the deep learning models transparent, the research area called Interpretable Machine Learning (IML)^{27,28} or explainable artificial intelligence²⁹ has emerged for the interpretability of deep learning models. Here, our review aims to outline how the application advances of deep learning affect de novo drug design methods and MD simulations. The IML research reports are also introduced to better understand deep learning models of de novo drug design and MD simulation. This review is able to help computational biologists, medicinal chemists, and pharmacologists to understand the drug discovery progress through deep learning methods.

2 | DEEP LEARNING FOR DE NOVO DRUG DESIGN

De novo drug design is a way to build novel ligands within the appointed receptor pocket by assembling fragments or atoms.³⁰ Deep learning methods provide another new option for de novo drug design by training the chemical and

physical properties of drugs. Extracting the desired chemical and physical features is the key step in de novo drug design via deep learning methods.³¹ Searching the large space³² along with the discontinuous nature of the optimization domain of drugs,³³ represent a big challenge. Fortunately, deep learning methods provide an effective way to learn task-related feature extraction, automatically.⁴ In early studies, molecular generation task is expressed as a string generation, a notable example being the SMILES generation model.³⁴ However, SMILES generation model has two critical limitations: one being that the different SMILES strings can represent a single molecule,³⁵ the other being that it is not easy to express the essential chemical properties. With the development of graph neural network algorithms, the methods based on molecular graphs show better performance than SMILES string ways.³⁶ Also, traditional graph-based generation models generate molecular graphs in the form of nodes and edges.³⁷ Along these lines, Jin et al.³⁸ pointed out that the graph-based generation node by node was not an ideal approach for molecules because the molecules generated atom by atom would produce chemically invalid intermediaries. To solve these problems, the valid subgraphs were explored to generate molecular graphs via a junction tree and nodes in the tree. Common generative architectures include RNNs,³⁹ autoencoders (AEs), variational AE (VAE), adversarial AE (AAE),^{40–42} and generative adversarial networks (GANs),⁴³ among others. Of these, VAE and GANs are popularly used to train molecular generation models. The VAE-based generative models contain an encoder and decoder, the encoder is responsible for rendering molecules into the potential space in a continuous manner, while the decoder is able to map an optimized continuous representation from the potential space back to a molecule with improved performance. ChemVAE⁴⁴ is a VAE-based SMILES string generation model that can estimate the distribution of encoded molecules along each dimension of the latent space and generate the novel molecules with the required properties. SD-VAE⁴⁵ is an improved method to solve the syntactical and semantical problems of SMILES generation model. The GANs which consist of a generator and discriminator, are useful tools for de novo drug design. The generator produces new data to cheat the discriminator based on learned probability distribution, while the discriminator is responsible for distinguishing the real data from the fraudulent data of generator. The generator and discriminator evolve each other during the training process. For instance, objective-reinforced generative adversarial networks (ORGAN)⁴⁶ employs reinforcement learning and GAN methods to train the generative model for de novo drug design with the desired properties. In contrast, MolGAN⁴⁷ uses the annotation matrix and dense adjacency tensor to represent molecules, and trains the generative model to produce more novel drug-like molecules using GANs. Moreover, L-Net⁴⁸ is report to produce high-quality three-dimensional (3D) drug-like molecules based on molecular graphs deep generative models, directly.

2.1 | De novo drug design using classical methods

The number of drug-like molecules is reported as being from 10^{23} to 10^{180} depending on different estimated methods.³² Although computing power has been improved rapidly in modern times, such a large number of molecules still need to have a great deal of time and capital invested in them to discover potential candidate hit compounds. De novo drug design represents a fast and economical way to produce new novel structures with the desired chemical properties.¹⁵ Even though machine learning methods show good performance, they cannot substitute the classical way for de novo drug design completely. Some research results indicate the classical scoring functions show more stability for binding affinity prediction than the machine learning-based methods.⁴⁹ Over the past few decades, a great deal of de novo molecular design soft tools have emerged for drug discovery based on different classical algorithms such as the genetic algorithm⁵⁰ and Monte Carlo.⁵¹ However, most de novo soft tools are disappeared and unavailable for academic research purposes. Some excellent software such as LUDI⁵² and SPROUT⁵³ have commercial licenses that are not convenient for the studies based on the source code. Hence, the extant free and available soft tools are important for classical method studies of de novo drug design. Figure 1 shows two common classical methods for de novo drug design. In the first method, the initial seed is firstly placed in a suitable position in the pocket of the receptor. After that, the new molecular populations grow on the initial seed by genetic algorithm, Monte Carlo, and so on. The score function and properties prediction can be used to select the ligands meeting the criteria. Finally, the newly generated ligands can be ranked and clustered according to the values of binding affinity and structural similarity, among others (Figure 1a). MolAICal^{54,55} is a representative piece of software for de novo drug design that can grow the ligands fragment by fragment in the receptor pocket. In the second method, new ligands are firstly generated by classical algorithms such as Monte Carlo and genetic algorithms. Following this, the generated novel ligands are screened, based on the receptor pocket by molecular docking software. At last, the ligands are selected via the score function of molecular software (Figure 1b). The AutoGrow⁵⁶ is a typical soft tool that can use Autodock Vina⁵⁷ to design the newly generated ligands

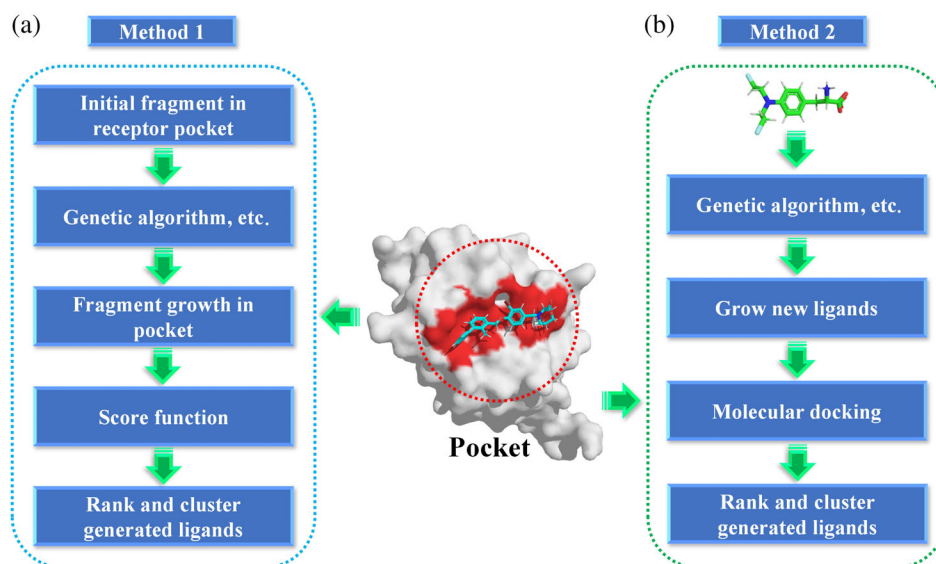


FIGURE 1 Two methods for de novo drug design using a classical algorithm. (a) In Method 1, de novo drugs are designed via the fragment growth based on the initial seed in the receptor pocket. (b) In Method 2, de novo ligands are generated without considering receptor structure by the classical algorithm. The molecular docking method is further used to evaluate the binding affinity of the generated ligands in the receptor pocket

TABLE 1 Free and available software and webserver for de novo drug design

Name	Description	Type	URL
MolAICal	A drug design software combined with artificial intelligence and classical programming	Software	https://molaical.github.io
OpenGrowth	An open source, flexible, and modular de novo drug design software using Monte Carlo approach	Software	http://opengrowth.sourceforge.net
LigBuilder	A multi-purpose and structure-based de novo drug design program using genetic algorithm	Software	http://www.pkumdl.cn:8080/ligbuilder3
AutoGrow	A computer-aided drug design software comprising fragment growth and docking algorithms	Software	https://durrantlab.pitt.edu/autogrow4
WADDAICA	A webserver tool for aiding drug design using artificial intelligence and classical algorithm	Webserver	https://bqflab.github.io
e-LEA3D	A webserver tool for de novo drug design, drug virtual screening, and combinatorial library design	Webserver	https://chemoinfo.ipmc.cnrs.fr/LEA3D/index.html

using a genetic algorithm. Table 1 lists some free and available software and webserver for de novo drug design using the classical algorithm. MolAICal⁵⁵ is a drug design tool using the deep learning model and classical algorithm, which can perform the fragment growth on the initial seed in the active pocket of receptors via genetic algorithm. The Vinardo score is employed by MolAICal to assess the binding affinity of growth ligands in the protein pocket. MolAICal can also filter out the growth ligands according to synthetic accessibility (SA), Lipinski's rule of five⁵⁸ and Pan-assay interference compounds (PAINS),⁵⁹ when the de novo drug design tasks are being carried out. OpenGrowth⁶⁰ grows de novo ligands based on a docked primary fragment and the Monte Carlo approach is used for OpenGrowth to select the suitable fragment on the active site of the protein. Furthermore, OpenGrowth can take into account protein flexibility with an appointed list of fragments, toxicity, synthesis, absorption, distribution, metabolism, and excretion (ADME). SMOG2001 and SMOG2015 scoring functions are employed for OpenGrowth to evaluate the binding affinities between protein and designed ligands.⁶¹ LigBuilder⁶² picks up growing or linking approaches for de novo drug design. The growth method chooses the genetic algorithm to select new fragments based on previous fragments that grow from the initial seed. The linking strategy constructs ligands from the pre-placed seeds that have been placed into the separate cavities of the receptor target. Empirical scoring function score and bioavailability score are used to select new ligand populations

when genetic algorithm proceeds with the fragment growth and link. In addition, virtual screening based on molecular docking can be used for de novo drug design. For instance, AutoGrow⁵⁶ designs de novo drugs by using evolutionary algorithms and molecular docking software such as AutoDock4⁶³ and AutoDock Vina.⁵⁷ AutoGrow firstly produces the new candidate populations through the genetic algorithm operators of selection, crossover, and mutation without considering the receptor pocket. All the binding affinities of generated ligands are then evaluated by AutoDock4 or AutoDock Vina program. Finally, new novel ligands are virtually screened based on the binding scores.

De novo drug design software needs a special running environment and computing resources. In contrast, webserver only needs the browser for de novo drug design without any special installation and libraries. Table 1 also lists the free and available webservers for de novo drug design. For example, WADDAICA⁶⁴ is a web server tool for de novo drug design using deep learning models and classical algorithms. It mainly contains two molecular design modules that contain the drug design deep learning model trained by the variational autoencoder (VAE) and de novo drug design by running classical programs in the background. WADDAICA assesses the binding affinity of ligands in the receptor pocket through Vinardo score that is trained on PDBbind database. The major module of de novo drug design in WADDAICA is built and based on MolAICal software. e-LEA3D⁶⁵ is a web server that can perform de novo drug design, virtual screening, and combinatorial library design, as well as being able to invent new ligands from scratch or user-defined scaffolds using a genetic algorithm that can optimize the combination of fragments with crossover and mutation operators. The binding scores between protein and generated ligands are evaluated by PLANTS program.⁶⁶ De novo drug design methods using classical algorithms still have merits and advantages for finding the potential novel compounds.

2.2 | De novo drug design using deep learning models

Deep learning methods for designing de novo drugs draw on similar ideas to those involved in traditional de novo drug design. Figure 2 summarizes two major methods based on the reported literature of deep learning for de novo drug design.⁶⁷ For the first method (Figure 2a), the ligands are independently encoded to the tensors, or the ligands and effective features of receptor are encoded to the tensors together. After that, suitable networks (GAN, VAE, etc.) are selected to train the deep learning model to match the experimental data (pIC₅₀, pK_i, 3D information, etc.) based on the input tensors. The trained deep learning models can discriminate the active and inactive compounds, and perform

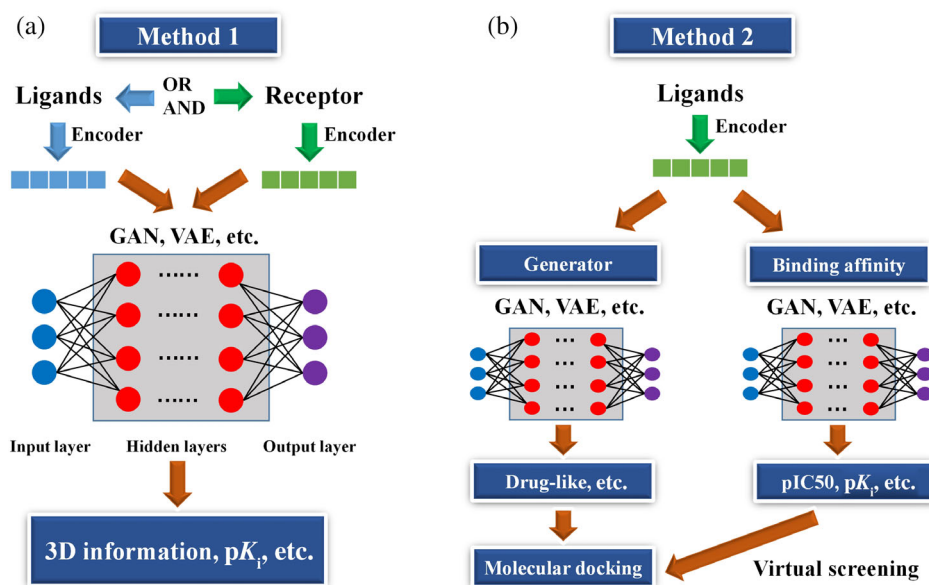


FIGURE 2 Two methods for de novo drug design using deep learning. (a) In Method 1, the trained deep learning model can be directly used to design and distinguish the novel active and inactive compounds based on pK_i, 3D information, and so forth. (b) In Method 2, the trained molecular generative model, deep learning model of binding affinity prediction, and molecular software are used together for de novo drug design

de novo drug design to find novel compounds, directly. Table 2 selects the representative deep learning frameworks for de novo drug design. For example, DeLinker⁶⁸ which utilizes 3D structural information can train the graph-based molecular generative model. Two fragments and their relative position and orientation in the receptor pocket are fed into the model to build the new linker in an iterative way “bond by bond” from the atoms pool. A generation model is trained under a variational autoencoder (VAE) framework by using a set of fragment-molecule pairs. The model can generate novel molecules based on the starting substructures and 3D structure information. Delinker shows good applicability and effectiveness on fragment linking,⁶⁹ scaffold hopping,⁷⁰ and proteolysis targeting chimera (PROTAC) design.⁷¹ MolAICal^{54,55} can generate the appropriate pieces using the deep learning model that is trained on the FDA-approved drug fragments. Then, it employs the classical algorithm to grow 3D ligands in the receptor pocket based on the trained deep learning model. There is also iDrug (<https://drug.ai.tencent.com/en>), which provides ligand-based drug design models that learn the relationship between biological activities and chemical structures of small molecules. This model can be used to screen available and small in-house molecular libraries in the absence of 3D protein structures. It is also worth mentioning how Khemchandani et al.⁷² proposed a multi-objective molecular generation method called DeepGraphMol which used reinforcement learning based on a graph convolution policy and consists of the molecular generation and property prediction. Under the guidance of expert pretraining and adversative loss, the validity of molecules is enhanced by reinforcement learning and graph convolution policy network. Additionally, DeepGraphMol can generate the molecules that have high binding affinities to the appointed receptor but much lower binding affinities to another receptor by modifying the weighted combination of pK_i values of two different targets. Furthermore, Masuda et al.⁷³ proposed a deep learning generative model without the given name that could produce 3D

TABLE 2 The free and available deep learning frameworks for de novo drug design and molecular docking software

Name	Description	URL
DeLinker	Graph-based deep generative model with structural knowledge	https://github.com/oxpig/DeLinker
MolAICal	A drug design software combined with AI and classical programming	https://molaical.github.io
iDrug	A drug discovery software platform	https://drug.ai.tencent.com/en
DeepGraphMol	A multi-objective, computational strategy for producing molecules with desirable properties	https://github.com/dbkgroup/prop_gen
SyntaLinker	Generative model based on a pair of fragments and additional restrictions	https://github.com/YuYaoYang2333/SyntaLinker
LigDream	Shape-based generative model for de novo drug design	https://github.com/compsciencelab/ligdream
GCPN	A graph convolution strategy network model for molecular generation	https://github.com/bowenliu16/rl_graph_generation
MolDQN	Molecular generative model combining domain knowledge of chemistry and reinforcement learning	https://github.com/google-research/google-research/tree/master/mol_dqn
MOSES	A benchmarking platform for molecular generation models	https://github.com/molecularsets/moses
DeepDTA	A 1D convolutional neural network for predicting binding affinity	https://github.com/hkmztrk/DeepDTA
Pafnucy	A 3D convolutional neural network for predicting binding affinity	http://gitlab.com/cheminfIBB/pafnucy
OnionNet	A deep convolutional neural network model for binding affinity prediction	https://github.com/zhenglz/onionnet
AttentionDTA	Drug-target binding affinity prediction using an attention mechanism	https://github.com/zhaoqichang/AttentionDTA_BIBM
GraphDTA	Drug-target binding affinity prediction with graph neural networks	https://github.com/thinng/GraphDTA
AutoDock	Molecular docking software	http://autodock.scripps.edu
AutoDock Vina	Molecular docking software	http://vina.scripps.edu
rDock	Molecular docking software	http://rdock.sourceforge.net
UCSF DOCK	Molecular docking software	http://dock.compbio.ucsf.edu
LeDock	Molecular docking software	http://lephar.com

ligands on the 3D active sites of the receptor. The libmolgrid tool is used to compute 3D grids with separate channels for every atom that is assigned to the state of element, aromaticity, H-bond donor, H-bond acceptor, or hydrophobicity. The iterative algorithms which involve gradient descent and beam search are selected for the conversion of a density grid to a discrete molecular structure.⁷⁴ The deep generative models are trained and based on CrossDocked2020 data set⁷⁵ by conditional variational autoencoders (CVAEs) and a GAN loss.⁷⁶ CVAEs input the density grid of a ligand and receptor together, and output a ligand density grid. The discriminator network is trained by three convolution layers, a leaky ReLU activation layer, an average pooling layer, and Adam optimization algorithm. This study demonstrates a promising way for de novo 3D drug design in the 3D receptor pocket directly using deep learning models.

2.3 | De novo drug design using deep learning models and molecular docking

There is another method for de novo drug design based on deep learning and molecular docking methods according to the research reports (Figure 2b).^{77–79} First of all, the deep learning generative model is trained for producing the new molecular SMILES library. Then, the 3D ligands which are converted from molecular SMILES strings are docked into the receptor targets. Finally, deep learning models of binding affinity prediction are used to virtually screen the de novo drugs. Of course, the drugs can also be ranked for virtual screening by score functions of molecular docking software (Figure 2b). Table 2 illustrates the selective free components for molecular generation, binding affinity prediction, and molecular docking software. Several of these will now be discussed. SyntaLinker⁸⁰ can be used to generate molecular structures from given fragments by deep conditional transformer neural networks that are trained and based on the data from ChEMBL⁸¹ database. It also uses the syntactic pattern recognition approach to filter out the difficult synthesis of compounds and highly complicated linkers among fragments. The case studies of fragment linking, lead optimization and scaffold hopping prove SyntaLinker to be a useful tool for fragment-based drug design. Ligdream⁸² provides source code to train the deep learning model for de novo drug design using long short-term memory (LSTM)⁸³ networks and convolutional neural networks (CNNs). The deep learning model trained by Ligdream can design novel functional groups and scaffolds based on the initial seed molecule. You et al.⁸⁴ proposed the Graph Convolutional Policy Network (GCPN) for generating goal-directed molecular graphs via reinforcement learning. GCPN combines graph representation, reinforcement learning, and adversarial training in a unified framework to guide molecular generation with specific properties. The trained model of GCPN can actively explore the molecular space to generate more novel molecules. It shows strong competitiveness in both molecule property optimization and conditional property optimization. For multi-objective molecular optimization tasks, Zhou et al.⁸⁵ proposed a Molecule Deep Q-Networks (MolDQN) that combined domain knowledge of chemistry and reinforcement learning techniques. In order to ensure the validations of all the generated molecules, the modifications of molecules are defined as the Markov decision process (MDP). Following this, the multi-objective reinforcement learning technique of Deep Q-Networks is used to solve the MDP with the rewards of desired properties. Unlike common policy gradient methods, MolDQN is based on efficient value function learning. The model learns from scratch without pretraining on any dataset, and its scope is not limited to molecules in a specific dataset. Elton et al.⁸⁶ summarized the pros and cons of recursive neural networks, generative adversarial networks, autoencoders, and reinforcement learning for drug design based on 45 related papers of generative modeling techniques, and so forth. In particular, reinforcement learning which is classified into value learning and policy learning can train the models targeted towards a specific object. For example, Chong et al.⁸⁷ employed the reversible upper confidence bound (rUCB) algorithm for reinforcement-learning drug design of intrinsically disordered proteins (IDPs) that played an important role in human diseases. Polykovskiy et al.⁸⁸ designed a benchmarking platform named Molecular Sets (MOSES), which was used to store several molecular generation models and to compare them using a set of metrics. The data which are used for training and testing on MOSES contain 1,936,962 molecules by filtering ZINC Clean Leads⁸⁹ collection. The platform contains several different models of molecular generation such as character-level recurrent neural networks (CharRNN),⁹⁰ Variational Autoencoders (VAE),⁴⁰ Junction Tree Variational Autoencoders (JTN-VAE),⁹¹ Adversarial Autoencoders (AAE),⁴² Latent Vector-Based Generative Adversarial Network (LatentGAN),⁹² and non-neural baselines. The authors evaluate the baseline models on the MOSES train set, and the results show that CharRNN currently has the best performance in terms of key metrics. The model not only shows the best results in the Fréchet ChemNet Distance⁹³ measure but also successfully discovers many novel scaffolds. It can be seen that MOSES provides a fair and comprehensive benchmark suite for molecular generation models.

The binding affinity between small molecules and targets predicted by the deep learning model is an important metric in the process of de novo drug design (Figure 2b). One of the most common deep learning methods involves the use

of deep convolutional neural networks (CNNs) that learn the three-dimensional structures of proteins and small molecules to evaluate potential binding compounds at specific targets.^{94,95} CNNs are designed to process data in the form of multi-dimensional arrays, which can effectively reduce the number of parameters for learning. Of these, DeepDTA⁹⁵ is reported to train the deep learning model of binding affinity prediction by CNNs based on the sequences of the proteins and SMILES strings of compounds. DeepDTA model shows significantly better results than both SimBoost and KronRLS algorithms on the KIBA dataset.⁹⁶ In addition, Stepniewska-Dziubinska et al.⁹⁷ proposed Pafnucy model to predict the binding affinity of protein–ligand complex based on CNNs. Notably, Pafnucy uses two general tricks that can be applied to other models for drug binding affinity prediction. The first trick is data augmentation by rotating the protein–ligand complex, which makes the model insensitive to the input orientation. The second one is the feature importance estimation by the distributions of weights and the impact of missing data. Pafnucy model can be used for structure-based ligand discovery and to guide ligand pose optimization during docking. Indeed, OnionNet,⁹⁸ which is proposed based on Pafnucy model, takes into account the element-pair-specific contacts between proteins and ligands, which are internal coordinates and invariant under rotational operations. The contacts are further divided into different distances that cover the local and nonlocal interaction information between ligands and proteins. The model trained by OnionNet shows a good scoring power by comparing with other scoring functions based on the v2016 core set of the PDBbind database and comparative assessment of scoring functions (CASF-2013) benchmark. Zhao et al.⁹⁹ introduced an end-to-end CNN-based model called AttentionDTA, which added attention mechanism to the process of drug–target affinity prediction. SMILES sequences of the drugs and the amino acid sequences of proteins are fed into the model and encoded. One-dimensional CNNs and attention mechanisms are used to effectively extract the representations between drugs and proteins, and then the binding affinities are obtained by fully connected neural networks. The attention mechanisms of AttentionDTA can identify the critical parts of the drug and protein sequences for drug–target affinity prediction, meaning it not only improves predictive power, but also makes the model interpretable. Nguyen et al.¹⁰⁰ proposed the GraphDTA model for predicting binding affinity between drugs and targets. In order to facilitate the capture of the structural information of the drug, the drug is inputted in the form of a graph, where the nodes represent atoms and the edges are the bonds of atoms. The target protein is inputted in the form of sequence, and the sequence features are learned by one-dimensional convolutional layer. GraphDTA uses molecular graphs and trials 4 graph neural network variants for drugs that contain Graph Isomorphism Network (GIN),¹⁰¹ Graph Convolutional Network (GCN),¹⁰² graph attention network (GAT),¹⁰³ and GAT-GCN combined graph neural network. The GraphDTA model outperforms the baseline on both the Davis and Kiba datasets. Here, we only select the representational part and available deep learning architectures for binding affinity prediction. In addition, there are many deep learning models such as LiGANN,¹⁰⁴ DeepDTAF,¹⁰⁵ DeepAtom,¹⁰⁶ and GANsDTA,¹⁰⁷ which are also good at binding affinity prediction.

The aforementioned deep learning frameworks can only produce molecular SMILES sequences or 2D conformations of ligands. However, rational drug design needs to obtain the 3D poses of generated ligands in the receptor pocket. The molecular docking method provides an effective way to search the rational 3D conformations of ligands that are generated by the deep learning models. Hence, it is very meaningful to summarize the free and available molecular docking tools. Table 2 also shows some molecular docking software that can be used to obtain the complex of receptors and ligands. The deep learning model of binding affinity prediction can be used to virtually screen *de novo* drugs based on molecular docking results (Figure 2b). AutoDock^{63,108} is one of the most widely used molecular docking programs based on a semi-empirical free energy force field. The comprehensive thermodynamic model is used for the force field to allow the incorporation of intramolecular energies into the predicted binding free energy via evaluating the energy changes of the bound and unbound states of molecules and receptors.¹⁰⁹ AutoDock performs the molecular docking via Monte Carlo Simulated Annealing (SA), Genetic Algorithm (GA), and Lamarckian Genetic Algorithm (LGA).¹¹⁰ AutoDock4 allows flexible processing of protein side chains similar to the conformational space exploration of the flexible ligand. AutoDock Vina⁵⁷ is another version of AutoDock for molecular docking and virtual screening. Compared with AutoDock 4, AutoDock Vina⁵⁷ can run multi-threading on multi-core processor, which significantly improves the running speed and prediction accuracy of ligand binding mode. Furthermore, AutoDock Vina uses the Broyden–Fletcher–Goldfarb–Shanno (BFGS) method for local optimization. Another example, rDock¹¹¹ which derives from program RiboDock¹¹² can be used for molecular docking of protein–ligand or RNA–ligand. The score function of rDock is the weighted sum of intermolecular, site intramolecular, ligand intramolecular, and external restraint terms, while the docking conformations are determined by genetic algorithm (GA)-based stochastic search engine, low-temperature Monte Carlo (MC), and minimization. The benchmark testing results show that rDock has a faster speed for virtual screening than AutoDock Vina. UCSF DOCK¹¹³ is a powerful and useful tool for rigid and flexible molecular docking. It uses the binding site spheres and graph-matching algorithm to place the fragments into the binding sites of receptor,

and then employs the anchor growth search algorithm for flexible molecular docking based on the rigid fragments connected by the rotatable bond (RB) of the prepared ligand. LeDock¹¹⁴ is free software that can explore the binding mode of ligands in the receptor pocket based on the shape complementarity and hydrogen bond anchors. The binding affinity of LeDock is determined by the terms of hydrogen bonding energy, van der Waals force, cutoff energy, ligand conformational strain, and electrostatic interaction energy. LeDock finds the ligand optimal conformation using the evolutionary algorithm with the simulated annealing search. It shows a good sampling power for finding the best pose of ligand in the receptor pocket. Here, we only select the freely representational and available molecular docking software. Some software such as GlamDock,¹¹⁵ MolAICAI,^{54,55} METADOCK 2,¹¹⁶ ArgusLab,¹¹⁷ and HomDock¹¹⁸ are also efficient and accurate tools for molecular docking.

3 | DEEP LEARNING FOR MD SIMULATIONS

Molecular dynamics (MD) simulations have been widely applied to biomolecules (DNA, RNA, proteins, etc.), materials, and drug design.¹¹⁹ Sometimes, de novo designed drugs do not have the precision binding pose in the receptor pocket. MD simulations can further optimize the binding pose of designed ligands in the receptor pocket based on the force fields. Based on MD simulations, molecular mechanics energies combined with Poisson–Boltzmann or generalized Born and surface area continuum solvation (MM/PBSA and MM/GBSA)^{120,121} can improve the accuracy of binding affinity between receptors and ligands. The traditional MD soft tools such as GROMACS,¹²² Amber,¹²³ NAMD,¹²⁴ and GROMOS¹²⁵ are the well-known MD simulation soft tools that have been used to discover novel drugs and study the binding mechanism between disease targets and drugs. In addition, LAMMPS¹²⁶ is a materials MD simulation software that provides accelerated performance on CPUs and GPUs regarding soft matter (biomolecules, polymers), solid-state materials (metals, semiconductors), coarse-grained MD simulations, and so on. Even though MD simulation is a powerful way to study biomolecule and ligands systems with an accompanying increase in computing power and high-performance software, it faces the problems of enormous amounts of data as well as having to deal with large complex simulated systems.¹²⁷ For example, ligand dissociated from the receptor pocket and receptor conformation change need millisecond-long MD simulations that will consume a great deal of time. Thus, if the entire computational cell model is built and run by MD simulations, it will take several months on the super computers with CPU and GPU clusters. Because a single computational cell model takes up more disk space than a protein or nucleic acid, huge amounts of data will be generated when MD simulations are performed for such a long-running time. These enormous amounts of MD simulated data take up further disk space making them difficult to analyze with a high dimensional structural space.¹²⁷ Deep learning methods represent a quick and effective way to deal with the big data of MD simulations. Deep learning can decrease the high-dimensional structure space to low-dimensional feature space that improves the efficiency and speed of MD simulated data analysis. In addition, deep learning applications for molecular simulations mainly include the prediction of quantum-mechanical energies and forces, force fields, the extraction of free energy surfaces and kinetics, coarse-grained molecular dynamics, thermodynamics, among others.¹²⁸ Figure 3 shows a common workflow of deep learning for MD simulations. First, the raw data for deep learning can contain the information of energy, force, virial, box, and so forth that are generated from simulated results of MD or AIMD simulations and so on. The representative descriptors are extracted from raw data. After that, deep learning networks (CNN, GAN, etc.) are employed to train and test the prediction model. Finally, deep learning models produce useful parameters and data for running MD simulations together with classical MD simulations software (Figure 3).

Plante et al.¹²⁹ employed the deep learning method to classify full agonist, partial agonist, and inverse agonist of GPCRs with high accuracy through dealing with the big MD trajectories. The coordinates X, Y, and Z of protein atoms in the MD trajectory are encoded to the red, green, and blue (RGB) of the pixels, while the neural network is trained to predict the class labels of GPCR ligand classifications by using confusion matrix. This study transforms the related information of MD trajectories into picture pixel representations for training deep learning models and represents an accurate and good way of discriminating the classes of ligands and the dynamical motif differences between two GPCRs targets. Bennett et al.²⁶ used atomic and molecular features to construct 3D-CNN and spatial graph CNN (SG-CNN) based on the atomistic molecular dynamics (MD) simulations that calculated transfer free energies of 15,000 small molecules from water to cyclohexane. The deep learning model was trained for predicting the transfer free energies based on MD simulated data. The 3D-CNN model shows lower accuracy than the SG-CNN model, which can achieve a mean absolute error of ~4 kJ/mol when compared with MD calculations. This study indicates that the deep learning model can replace expensive free energy calculations with a similar level accuracy of MD calculations. In 2017, Gastegger

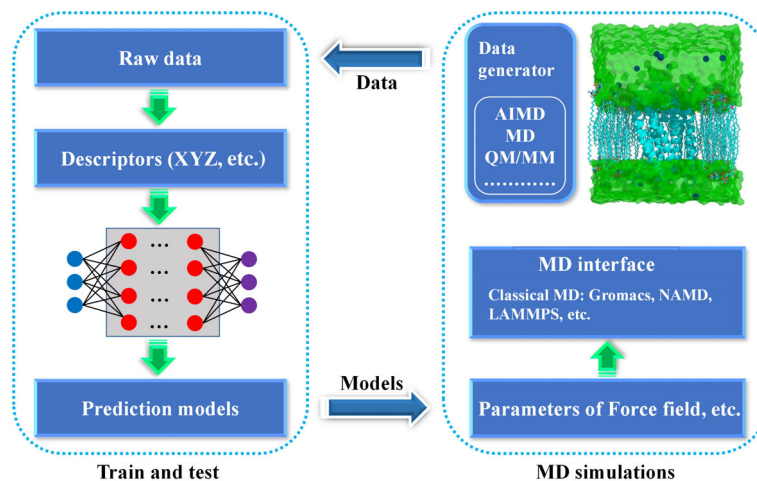


FIGURE 3 Deep learning for MD simulations

et al.¹³⁰ used the high-dimensional neural network potential (HDNNP) to yield reliable models of potential energy surface based on ab initio molecular dynamics simulations. The models which are trained on only a few hundreds of electronic structure reference points achieve a very accurate prediction of infrared spectra. Apart from that, the models show a good agreement with infrared spectra prediction of a methanol molecule, n-alkanes, and the protonated alanine tripeptide with the theoretical and experimental spectra. Another example involves Ferraro et al.,¹³¹ who employed machine learning to detect the dynamic patterns of allosteric inhibitor-bound and inhibitor-free TRAP1 based on the MD ensemble. It indicates that machine learning can maximize the information that is included in ns- μ s time scale MD simulations. Similarly, Marchetti et al.¹³² used the machine learning method to classify allosteric modulators as inhibitors and activators on basis of conformational ensembles that were extracted from MD simulated trajectories of molecular chaperon Hsp90. It shows the machine learning approach can be used to develop the potential allosteric drugs and extended to study other allosteric disease targets. In the last instance, Jamal et al.¹³³ extracted 2D descriptors, 3D descriptors, and MD descriptors from MD simulated trajectories that consisted of surface area (SASA), potential energy, total energy, radius of gyration (Rg), and solvent accessible. The models were trained by using artificial neural networks and random forest algorithms based on the 2D descriptors, 3D descriptors, and MD descriptors. This study indicates that MD descriptors are useful for the identification of bioactive compounds, chemical compound prioritization, and lead optimization. All these studies reveal the deep learning model trained on the simulated trajectories can achieve effective and accurate prediction at a low cost.

Deep learning ideas and techniques have been resoundingly applied to MD simulations for biomolecules and drugs. Some free and available deep learning source codes have been developed and shared for studying MD simulations (Table 3). TorchMD¹³⁴ which is written in Python programming language using PyTorch arrays, is a framework for MD simulations by mixing classical and machine learning potentials. It can perform the NVT ensemble simulations including a Langevin thermostat and start atomic velocities that are derived from Maxwell-Boltzmann distribution. Besides, TorchMD supports minimization, velocity Verlet algorithm, long-range electrostatics calculation, and simulations of periodic systems, as well as learning and simulating neural network potentials. The coarse-grained neural network potential is trained using the force matching approach for MD simulations of protein folding. The chignolin which is an artificial mini protein with 10 residues (GYDPETGTWG) is chosen for the case studies of TorchMD, whose results indicate that coarse-grained simulations by TorchMD can successfully capture the folding and unfolding conformations of chignolin. DeePMD-kit²⁴ is designed by Python/C++ programming languages that can interface with deep learning framework TensorFlow, high-performance classical MD software LAMMPS, and quantum MD package i-PI. DeePMD-kit uses TensorFlow to train and test models that can be used to evaluate the potential energy surface (PES) and forces. MD simulations can be performed efficiently as they are based on the trained potential energy and force field models. The example of DeePMD model is trained and based on the ab initio molecular dynamics (AIMD) of 64 water molecules. The example results indicate that the DeePMD model can reach the same level as DFT model in generating structure properties. There is also TensorMol,¹³⁵ which is a neural network model chemistry that is an efficient way to screen long-range electrostatic and van der Waals physics. It is an open-source Python package that can be

TABLE 3 Free and available deep learning codes for MD simulations

Name	Description	URL
TorchMD	A framework for molecular simulations mixing classical and machine learning potentials	https://github.com/torchmd
DeePMD-kit	A package for building deep learning-based model of interatomic potential energy and force field and performing molecular dynamics	https://github.com/deepmodeling/deepmd-kit
TensorMol	A package of neural network model chemistries	https://github.com/jparkhill/TensorMol
GAP-MD	Workflow of molecular dynamics simulations performed using this active learned Gaussian Approximation Potential (GAP) model	https://github.com/argonne-lcf/active-learning-md
CGnet	Coarse graining for molecular dynamics	https://github.com/coarse-graining/cgnet
sGDML	Reproducing accurate and data-efficient molecular force fields using machine learning	https://github.com/stefanch/sGDML
Coarse-Graining-Auto-encoders	A generative modeling framework of variational auto-encoders includes parameterizing coarse-grained force fields, learning discrete coarse-grained variables and decoding back to atomistic detail	https://github.com/learningmatter-mit/Coarse-Graining-Auto-encoders
mlmd	An open source python program that can compute the feature representation of molecules and perform MD simulations with machine learning empirical potentials	https://github.com/zeledon14/mlmd

used to study molecular dynamics, optimizations, Monte Carlo, open/periodic boundary conditions, meta-dynamics, infrared spectra by propagation, infrared spectra by harmonic approximation, nudged elastic band, and path integral simulations via the interface with I-PI MD engine. TensorMol methods show low cost and good accuracy for molecular simulation when compared with the density functional theory (DFT) method. The next example, Gaussian Approximation Potential (GAP) MD¹³⁶ is carried out by using an active learning GAP model that is fitted with an unsupervised machine learning (ML) scheme and Bayesian optimization technique. GAP MD simulations of 6144 atom systems of amorphous and liquid state reveal that the structural properties prediction of Hafnium dioxide (HfO₂) can reach AIMD precision. CGnet¹³⁷ is a machine learning framework that can generate coarse-grained force fields by leveraging continuous filter convolutions on graph neural networks. The generated coarse-grained force field by CGnet can be transferable and successfully reproduce the thermodynamics for biomolecular systems. sGDML^{138,139} is a symmetric gradient-domain machine learning model that can construct accurate molecular force fields based on a restricted number of samples of AIMD trajectories. It can faithfully reproduce global potential energy surfaces of molecules with accurate energies and atomic forces and has been triumphantly applied to classical and path integral molecular dynamics and structure optimization, among others. Coarse-Graining-Auto-encoders¹⁴⁰ is a generative modeling framework that can be used to parameterize coarse-grained force fields, learn discrete coarse-grained variables, and decode back to atomistic coordinates with high accuracy. It has been assayed on the computing model including gas-phase molecules with different resolutions, alanine dipeptide, bulk-phase periodic simulations, and so on. Finally, machine learning molecular dynamics (mlmd) is an open-source package that can calculate the feature representation of molecules based on structural information filter features (SIFF) and perform MD simulations with machine learning force fields. The mlmd program can train the machine learning force fields and is based on the data of Fireball, Abinit, and VASP to carry out NVT molecular dynamics on a molecular structure. All these deep learning source codes provide very good research ideas and templates for studying MD simulations.

4 | INTERPRETABILITY OF DEEP LEARNING MODELS

Even if most deep learning methods are able to make predictions with very high accuracy, they are not able to explain those predictions. The deep learning method is like a black box from which it is difficult to obtain detailed information and behaviors for de novo drug design and MD simulations. A new field in machine learning called Interpretable

Machine Learning (IML)^{27,28} or explainable artificial intelligence²⁹ is gaining popularity given the need to obtain additional information, be able to generalize rules from training data, and transfer those rules so that human experts from related or other fields can understand them.¹⁴¹ IML methods are classified into two major groups, the so-called model-specific and model-agnostic methods. Model-specific approaches use the knowledge of a certain interpretable model for understanding predictions. The main downside of this type of method is the lack of flexibility. Being tightly coupled to the model, it may be difficult to switch to another model. On the other hand, model-agnostic methods see the model as a black box and do not care how predictions are made. This feature gives them enough flexibility to be applicable to any type of model. Due to the flexibility that model-agnostic approaches show, the assessment of different models for the same task is possible.¹⁴²

IML methods can make deep learning models of de novo drug design and MD simulations more transparent. In addition, IML methods can obtain parts of deep learning models that make a better contribution to de novo drug design and MD simulations. Currently, IML in de novo drug design and MD simulation is still a very immature field. Nevertheless, a few examples using Shapley values, integrated gradients, and graph-convolution-based methods can be found in the literature. Shapley values are based on game theory to explain the contribution of an individual instance to the prediction.¹⁴³ In the context of Shapley values, players are represented by features and payouts by predictions. The overall idea of this method is to calculate how to distribute the payout among the players in a fair way. Back to the drug discovery world, we will be told how much each feature contributes to the docking or MD simulation.¹⁴¹ Based on the concept of Shapley values, the Shapley Additive Explanations (SHAP) method has been developed. The goal of SHAP is to find the optimal Shapley values for a collection of instances. For example, Jiménez-Rosés et al.¹⁴⁴ investigated the reasons behind the agonism or antagonism of ligands when binding to G protein-coupled receptors (GPCRs) targets. To do so, they created their own ligands database and performed molecular docking to generate several poses of each ligand. Once they had predicted all the atom interactions between the receptor and the ligand, they used ML to identify correlations between the interactions and activity of the agonist or antagonist. Based on this information, the next step was the development of two tree-based classifiers to predict whether a ligand would show agonist or antagonist activity against a target. The authors used the SHAP value method to check the feature importance of the models which were trained by random forest (RF) and boosting machine (XGBoost). Apart from that, machine learning docking scoring model can take advantage of SHAP explanations as well. Ye et al.¹⁴⁵ demonstrated a novel docking scoring function that was implemented through an XGBoost model. This new docking scoring function shows good enough performance to classify a set of ligands into actives and decoys in terms of area under curve (AUC). Consequently, SHAP has also proved useful at interpreting the ligand-binding mechanism of a given target. Moreover, the model lying within the scoring function has the capability of identifying binding patterns from protein–ligand complexes, which are explained by SHAP at a later stage. Furthermore, machine learning is a useful approach when predicting molecular dynamical material behavior. Lyngdoh et al.¹⁴⁶ integrated machine learning with MD to analyze the relationship of calcium-silicate-hydrate gel to create efficient cementitious binders. Since the best model they obtained was an artificial neural network, whose output consisted of a vector of probabilities, the interpretability was particularly necessary. The SHAP method was used to figure out the importance of each input feature in the final prediction.

Having a strong mathematical background, integrated gradients¹⁴⁷ is another model-agnostic approach that can be used to explain ML predictions. Integrated gradients assign an attribution value to each input feature by approximating the integral of the gradients along a straight path from a baseline to the instance that is being explained. As the calculation of the integral can be computationally challenging, the path is split into several steps instead. Accordingly, the sum of all the steps is considered as the attribution value for the feature. This approach was used by Chew et al.¹⁴⁸ for the interpretation of the predictions of SolventNet, which was a 3D CNN they developed. The model, which aimed to predict acid-catalyzed reaction rates for model biomass compounds, was trained on a dataset with data collected from MD simulations. Once the predictions were made, saliency maps created with the integrated gradient methods were generated to show the predictions graphically.

Moreover, the graph-convolution neural networks¹⁴⁹ is a powerful tool for de novo drug design and MD simulation. The interpretability of models trained by graph-convolution neural networks is an important active research field and these graph-convolution-based methods are grouped into subgraph identification and attention-based approaches.²⁷ The subgraph identification approach mainly identifies one or more crucial parts of a molecular graph for a given prediction. For example, GNNExplainer¹⁵⁰ is a model-agnostic approach to provide explanations for any Graph Neural Networks (GNN)-based traditional machine learning and deep learning model. GNNExplainer can discriminate a set of node features and a subgraph structure that play a key role in the GNN prediction. The test for mutagenic effect on *Salmonella typhimurium*¹⁵¹ showed GNNExplainer was able to find some known mutagenic functional groups. The attention-based approach borrows

from the attention mechanisms¹⁰³ that are together with message-passing algorithms to learn attention coefficients over a set of neighbors. These attention coefficients can show which neighbors are important to a node. Ryu et al.¹⁵² employed attention and gate mechanisms to extract structure features that related to polarity, solubility, photovoltaic efficiency, and synthetic accessibility of target molecules. The results showed that attention and gate mechanisms could capture the key structural features that closely corresponded to target properties from graph convolution.

As stated above, IML is still gaining importance in the context of drug design and MD simulation. However, there is still a long way to go, and many other interpretability methods might be applied for the deep learning models of de novo drug design and MD simulation in the future. A wide range of model-agnostic techniques, such as permutation importance, local interpretable model-agnostic explanations (LIME), or partial dependence plots (PDP), could potentially complement the aforementioned ones in the near future. In any case, classic interpretable models, such as linear regression, decision trees, and naive Bayes classifiers, are always an alternative as long as the certainty remains that they will not be replaced later.

5 | DISCUSSION

In this review, application advances of deep learning methods are summarized for de novo drug design and molecular dynamics (MD) simulation. De novo drug design supplies a stationary way for drug design, and it can grow the novel ligands based on atoms or fragments in the receptor pocket. However, de novo drug design cannot consider the dynamical vibration, rotations, and translation of atoms in receptor and ligand. MD simulations supply a dynamical way to precisely optimize the ligand pose in the receptor pocket through the dynamical vibration, rotations, and translation of atoms based on molecular force fields. De novo drug design and MD simulation have been widely applied in drug design field and promoted the process of drug discovery. With the development of artificial intelligence, promising deep learning methods have emerged in the studies of de novo drug design and MD simulation. Deep learning methods can improve the precision and accuracy of de novo drug design and force fields for MD simulation. Although deep learning is a new way for de novo drug design and MD simulation, it is still developed along the research direction of classical de novo drug design and MD simulation. First, the conventional classical de novo drug design methods can be generally divided into two categories based on 2D and 3D molecular generation. Deep learning is also developed for de novo drug design on basis of 2D and 3D molecular generation. Most of current deep learning studies of de novo drug design focus on the 2D molecular generation. Although some studies¹⁵³ use the 3D information of protein pocket as the conditions to control molecular generation, it cannot still obtain the suitable poses of ligand in the receptor pocket, directly. The 3D drug design via deep learning has become an interesting and challenging problem for drug design. In this article, the related progress of 3D drug design is separately listed in the part of de novo drug design by deep learning models. As reported in the literature,⁷³ the density grids of receptor and ligand which are encoded and trained by convolutional neural networks, supply a promising way for 3D de novo drug design.

Second, for in silico drug design process, MD simulation can provide a dynamical and reliable way to design and optimize drugs after the stationary de novo drug design. Deep learning can enhance the efficiency and precision of MD simulation from two aspects: one is dimension reduction, the other is accuracy improvement of force field parameters. Even though deep learning methods reduce the high dimensional structure space, they can still achieve acceptable accuracy according to the reported studies.²⁶ For parameters of force field, deep learning can reach ab initio calculation level that cannot be carried out by classical MD simulation. Deep learning can help MD simulation to improve the accuracy and efficiency for studying the dynamical interaction mechanism between drugs and receptors. At last, deep learning models have many parameters and hidden layers that are hard to be understandable and interpretive. Rational de novo drug design and MD simulation require deep learning models to be interpretable and transparent. Hence, interpretable machine learning (IML) is introduced for the deep learning models of de novo drug design and MD simulation in our review. IML is mainly divided into model-specific and model-agnostic methods. Model-agnostic methods are easier to interpret any type of model than model-specific methods. Even though IML in de novo drug design and MD simulation is a very immature field, we still summarize model-agnostic methods such as Shapley values, integrated gradients, and graph-convolution-based methods from a few examples in the reported literature. Because IML can explore which parts of deep learning models have more contribution for de novo drug design and MD simulations, it will be beneficial to rational drug design.

Generally, de novo drug design, MD simulation, and IML describe drug design blueprints from stationary, dynamical, and interpretable properties. Deep learning models can improve the accuracy and efficiency of stationary de novo

drug design as well as drug MD simulation. IML can be further used to explain deep learning models of de novo drug design and MD simulation.

6 | CONCLUSION

Deep learning studies about de novo drug design and MD simulation have grown quickly over the past few years. The arrangement of major workflow and components of de novo drug design and MD simulation can further promote the technology development of drug discovery, as they are based on the current reported classical and deep learning methods. It is of great interest to review the common workflows of deep learning for de novo drug design and MD simulations. This article summarizes two major routes for de novo drug design: one being ligand growth in the confined pocket of the receptor by using deep learning methods or classical algorithm, the other being ligand virtual screening following the step of ligand generation using deep learning methods or classical algorithm. There are currently only few free and available soft tools for de novo drug design. On the contrary, there are many research reports and source codes of deep learning involving de novo drug design, which reveals that it is a promising method for de novo drug design with a great deal of potential. Besides, the deep learning studies are reviewed for MD simulation. Deep learning methods can train the models to predict the potential energy, force field, and so on. Expressly, deep learning can learn the parameters of energies and forces with near ab-initio accuracy at a low cost. It can solve the quantum-mechanical problem that cannot be represented by empirical force fields. In addition, the end-to-end differentiable simulations based on deep learning can recover the parameters of the force field from a short MD trajectory, which would be impossible to achieve using traditional MD source codes. Furthermore, IML provides a way forward regarding the interpretability of deep learning models of de novo drug design and MD simulations. It is believed that IML can help deep learning models to find the key features and guide rational drug design. With a great deal of data accumulation, the availability of large amounts of high-quality molecular data becomes more and more important to how the performance and reliability of deep learning models are affected in the future. Indeed, the constantly developing deep learning technology and IML will play a more pivotal role in de novo drug design and MD simulation alike.

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CONFLICT OF INTEREST

All authors have declared no conflicts of interest for this article.

AUTHOR CONTRIBUTIONS

Qifeng Bai: Conceptualization (lead); data curation (equal); funding acquisition (lead); methodology (equal); resources (equal); supervision (equal); validation (equal); visualization (equal); writing – original draft (equal); writing – review and editing (equal). **Shuo Liu:** Data curation (equal); validation (equal); visualization (equal); writing – original draft (equal). **Yanan Tian:** Data curation (equal); resources (equal); writing – original draft (equal). **Tingyang Xu:** Funding acquisition (equal); methodology (equal); supervision (equal); writing – original draft (equal). **Antonio Jesús Banegas-Luna:** Data curation (equal); writing – original draft (equal). **Horacio Pérez-Sánchez:** Methodology (equal); supervision (equal); writing – review and editing (equal). **Junzhou Huang:** Validation (equal); writing – review and editing (equal). **Huanxiang Liu:** Methodology (equal); resources (equal). **Xiaojun Yao:** Conceptualization (equal); writing – review and editing (equal).

DATA AVAILABILITY STATEMENT

Data sharing is not applicable to this article as no new data were created or analyzed in this study.

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