# Molecule Generation for Drug Design: a Graph Learning Perspective

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## Abstract

Machine learning, particularly graph learning, is gaining increasing recognition for its transformative impact across various fields. One such promising application is in the realm of molecule design and discovery, notably within the pharmaceutical industry. Our survey offers a comprehensive overview of state-of-the-art methods in molecule design, particularly focusing on *de novo* drug design, which incorporates (deep) graph learning techniques. We categorize these methods into three distinct groups: *i) all-at-once, ii) fragment-based,* and *iii) node-by-node.* Additionally, we introduce some key public datasets and outline the commonly used evaluation metrics for both the generation and optimization of molecules. In the end, we discuss the existing challenges in this field and suggest potential directions for future research.

# 1 Introduction

In recent years, machine learning based drug discovery has been more and more conspicuous since it greatly reduces time, money and labor costs for developing novel drugs [34, 87, 43]. Among the processes of drug development, generating chemical molecules with good quality and optimizing chemical molecules for desired properties are of particular importance. So the challenge lies in how to apply machine learning methods to generate "good" molecules with or without additional constraints. Different approaches and models have been designed till now, including including those based on variational autoencoder (VAE) [44], generative adversarial networks (GAN) [27], reinforcement learning (RL) [39], and more.

To characterize molecules, several types of molecular representations are devised, ranging from Simplified Molecular Input Line Entry System (SMILES) strings [75] to manually predefined molecular features [60]. Among them, SMILES-based and graph-based representation methods are the most widely used in molecular generation tasks. Early molecular generation methods are SMILES-based. SMILES can be seen as a type of 1D text representation. These SMILES-based methods cannot ensure 100% chemical validity [16] unless complicated constraints are added. Meanwhile, molecules can naturally be represented using graphs, which are essentially a type of 2D representation. Recently, an increasing number of methods have shifted towards graph-based approaches. Unlike the 1D SMILES-based methods, 2D molecule generation approaches can easily ensure that the generated molecules are 100% chemically valid. Additionally, graph-based representation has the ability to accurately depict the inherent structure of molecules. In light of the fact that graph-based representation is currently the mainstream method, this study will specifically concentrate on existing graph-based methodologies.

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There also exist surveys on molecule generation and optimization. [31] and [18] both provide a comprehensive overview of the literature in the field of deep generative models for graph generation. But they do not focus on molecules only. Apart from molecules, they also present deep generative models designed for other domains, such as social networks. As for [16, 2], they both put emphasis on the four architectures often utilized for molecule design methods. It is also worth mentioning that [16, 2, 31, 18] all discuss molecule design methods based on different molecular representations, including SMILES, 2D representation referring to connectivity graph and 3D representation that contains coordinates of the atoms within a molecule. As previously noted, despite the extensive literature on SMILES-based generative models [26, 41, 59, 29, 28], these methods have fallen out of mainstream use. Additionally, there is a noticeable disparity in the volume of research between 3D-generative methods for molecules and the more prevalent 2D graph-based methods. For readers interested in 3D-based methods, existing representative works like G-SchNet [22], E-NF [21], GEN3D [61] and G-SphereNet [51] are recommended.

Different from the existing surveys mentioned above, our survey solely focuses on the drug design tasks and conducts a comprehensive overview of the state-of-the-art molecular design methods based on the 2D representation, i.e., only from a graph learning perspective. Additionally, compared to other surveys and an earlier version of our own survey, we include some more recent methods, particularly some diffusion-based methods, which were not covered in previous surveys.

In this survey, we provide a comprehensive review of the latest graph-based methods for molecule generation and optimization. These methods are classified into three categories based on their generation strategies: *all-at-once*, *fragment-based*, and *node-by-node*. The survey also covers key public datasets and standard evaluation metrics used in this field. Additionally, we delve into an in-depth analysis of the current challenges faced in this area and proposes three promising directions for future research.

## 2 Preliminaries and Problem Formulation

In this section, we first introduce graph-based molecule representation. Then, we formally formulate the problem of molecule generation task.

#### 2.1 Graph-based Molecule Representation

In the field of Graph-based molecule representation [80, 32, 81], it is common to use a graph G = (V, E) to model a molecule, where V is the graph's node set mapping to atoms constituting a molecule and E is denotes the graph's edge set mapping to chemical bonds, with |V| = n and |E| = m. In molecule graph, nodes are sometimes representing atomic types from the periodic table, or representing certain kinds of molecule fragments. The node feature matrix **X** characterizes the property of each node while the adjacency matrix **A** characterizes the relationships between each node. Let the number of edge types be b and the number of node types be c, then we have  $\mathbf{A} \in \{0,1\}^{n \times n \times b}$  and  $\mathbf{X} \in \{0,1\}^{n \times c}$ , where  $\mathbf{A}_{ijk} = 1$  when there exists an edge with type k between the  $i^{th}$  and  $j^{th}$  nodes, otherwise 0. We can also represent the molecular graph using the node feature matrix **X** and the adjacency matrix **A**, i.e.,  $G = (\mathbf{A}, \mathbf{X})$ .

#### 2.2 Problem Formulation

Generation tasks aim to generate novel samples from a similar distribution as the training data [18]. A molecule generation method intends to generate novel, diverse molecules which follow the unknown data distribution p(G) provided by a set of graphs  $D_G$ . A machine learning method towards this problem usually proposes a model to learn form large scales of data which either obtains an implicit strategy or estimates the p(G) directly and then samples from the distribution to generate new molecules.

# **3** Generation Strategies

For classifying existing methods of *de novo* molecule generation or molecule optimization, in this paper we propose to base on their generation granularity level as shown in Fig. 1: *i*) using an all-at-



Figure 1: Three typical molecule generation strategies.

one generation or optimization strategy; *ii*) adopting rational substructures as editing blocks; or *iii*) building graphs in a node-by-node setting. We describe their main features as summarized in Table 1.

#### 3.1 Generation Strategy I: All-at-once

There are a number of deep graph generators to generate the entire molecular in one shot, which we call "*all-at-once*".

VGAE [46], built upon a variational autoencoder (VAE) [44], is a framework designed for unsupervised learning with graph-based data. VGAE leverages latent variables and is trained to learn interpretable latent representations, which are then used to generate new molecular graphs. Unlike VGAE, which can only learn from a single input graph, GraphVAE [69] is another VAE-based generative model that can learn from a set of graphs. The encoder of GraphVAE uses a graph convolutional network (GCN) [85] to embed the input molecular graph into a continuous representation z while the decoder of GraphVAE outputs a probabilistic fully-connected graph constrained by a predefined maximum size, from which discrete samples are drawn. However, GraphVAE encounters challenges in effectively aligning with the training data distribution and relies on an expensive graph matching procedure. In order to address these issues, MPGVAE [19] integrates a message passing neural network (MPNN) [25] to the encoder and decoder of the GraphVAE. Furthermore, [53] proposes a specialized regularization framework for training VAEs that encourages the satisfaction of validity constraints for molecules, i.e. the number of bonding-electron pairs must not exceed the valence of an atom.

In addition to the aforementioned VAE-based methods, there are also approaches that utilize other generative models, such as MolGAN [12] and GraphNVP [54]. MolGAN proposes an implicit generative model for molecular graphs, which adapts generative adversarial networks (GAN) [27] for graph-structured data and integrates a reinforcement learning objective to encourage the generation of molecules with desired properties. GraphNVP is the first known molecule generation model based on invertible normalizing flow [13, 45]. It performs *dequantization* technique [13, 45] to transform discrete adjacency tensor A and node label matrix X into continuous variables and then uses coupling layers to obtain latent representations  $z_A, z_X$ .  $z_A$  and  $z_X$  are concatenated together to obtain the final latent representation and splitting z into  $z_A$  and  $z_X$ . GraphNVP takes two steps to generate a molecule. The first is generating a graph structure A from  $z_A$  and the second is generating node attributes X based on the structure A from  $z_X$ . Furthermore, GraphNVP trains a linear regressor on the latent vector of a randomly selected molecule along the direction of the desired property, as learned through linear regression, thereby facilitating molecular optimization.

In recent developments, innovative approaches to molecular generation have emerged, building upon a class of advanced generative model known as diffusion models [33, 70]. GDSS [38], for instance, introduces a novel graph diffusion process to model the joint distribution of nodes and edges, utilizing a system of stochastic differential equations (SDEs). Subsequently, GDSS formulates specialized score matching objectives tailored to this diffusion process to estimate the gradient of the joint log density for each component. Moreover, it introduces a novel solver for the SDE system to facilitate efficient sampling from the reverse diffusion process. It is essential to emphasize that GDSS embeds graphs into a continuous space and introduces Gaussian noise to the node features and the graph adjacency matrix. However, this approach removes the inherent sparsity of graphs, resulting in entirely noisy graphs where structural information, such as connectivity or cycle counts, remains undefined. Consequently, the continuous diffusion process can present challenges for the denoising network in capturing the structural properties of the data. In contrast, inspired by Discrete Denoising Diffusion Probabilistic Models (D3PMs) [4], a newly method DiGress [74] adopts a discrete diffusion process that systematically modifies graphs with noise. This process involves the addition or removal of edges and changes in categories. Additionally, DiGress employs a noise model that preserves the marginal distribution of node and edge types during the diffusion process. Furthermore, it introduces an innovative guidance procedure for conditioning graph generation on graph-level properties and enhances the input of the denoising network with auxiliary structural and spectral features. While DiGress has made notable advancements compared to GDSS, it still faces challenges in accurately estimating the joint distribution of measurements derived from node features and molecular graph structures. This challenge primarily arises from the approach of deriving separate embeddings for nodes and edges, treating them as distinct entities. Therefore, a more recent diffusion-based method called Wave-GD [11] has been introduced. Wave-GD harnesses the spectral dependencies between node and edge signals to more effectively characterize their joint distributions through a score-based diffusion model. By capturing their multi-resolution coherence, this model demonstrates the capability to generate high-fidelity molecules while preserving the frequency characteristics observed in the training samples.

#### 3.2 Generation Strategy II: Fragment-based

Numerous methods have been proposed that utilize rational substructures, also known as fragments, as building blocks to generate high-quality molecules, which are categorized as "*fragment-based*" here.

Among these methods, a considerable number are based on the variational autoencoder. An earlier typical work proposes a model named JT-VAE [35] which first decomposes the molecular graph G into its junction tree  $\mathcal{T}$ , where each node in the tree represents a substructure of the molecule. JT-VAE then encodes both the junction tree and molecular graph into their latent embeddings  $\mathbf{z}_{\mathcal{T}}$  and  $\mathbf{z}_{G}$ , respectively. As for the decoding phase, JT-VAE first reconstructs junction tree from  $\mathbf{z}_{\mathcal{T}}$  then generates molecule graph from the predicted junction tree by a graph decoder which learns how to assemble subgraphs.

JT-VAE achieved a landmark 100% validity, thanks to the implementation of a junction tree representation. This approach simplifies the process, as creating a tree structure is less complex compared to generating a general graph with degree constraints. Meanwhile, MHG-VAE [40] refers to the scenario where the decoder produces invalid molecules as a *decoding error issue*. While the tree representation effectively mitigates the *decoding error issue*, it does come with certain limitations. This representation focuses only on connections at the fragment level and fails to define the specific atoms within the fragments that should be connected. Moreover, due to its lack of specificity at the atom level, information regarding stereochemistry is not retained. To compensate, all potential configurations are enumerated, and one is selected through the training of auxiliary neural networks. In contrast, MHG-VAE can address the *decoding error issue* without the auxiliary neural networks. MHG-VAE's key innovation lies in its molecular hypergraph grammar (MHG), derived from the hyperedge replacement grammar (HRG) [14]. In MHG, an atom is depicted as a hyperedge, while a bond is represented by a node. HRG generates a hypergraph by substituting a non-terminal hyperedge with another hypergraph. Integrating HRG with MHG allows for atom-level connections, and the stereochemistry can be seamlessly integrated into the grammar. Additionally, this approach respects the number of nodes linked to each hyperedge, which corresponds to the valency of atoms in molecular structures. Consequently, these principles facilitate the generation of valid molecules using a single VAE architecture.

HierVAE [36], another VAE-based model designed by the same authors as JT-VAE, introduces larger and more flexible graph motifs as building blocks, exhibiting enhanced performance when dealing with larger molecules. The encoder of HierVAE generates a multi-resolution representation for each molecule, progressing in a fine-to-coarse fashion from atoms to connected motifs. Each hierarchical level in this model integrates the encoding of its lower-level constituents with the graph structure at that level. The autoregressive coarse-to-fine decoder of HierVAE adds motifs sequentially, one at a time. This process interweaves the selection of a new motif with the task of determining how it connects to the evolving molecular structure.

In the realm of drug discovery, there's often a necessity for a specific scaffold to be included in the synthesized molecule. MoLeR [56], also based on VAE, has been developed to cater to this need, facilitating the extension of partial molecules. MoLeR integrates motifs (molecule fragments) into its atom-by-atom generation process. When dealing with atoms that are part of a motif, MoLeR concatenates the initial chemically relevant features with the motif embedding. For atoms not associated with a motif, a special embedding vector is employed to indicate the absence of a motif. To define a concrete generation sequence, MoLeR initially opts for an initial atom selection. Subsequently, for each partial molecule, it proceeds to select the next atom from those that are adjacent to the atoms previously generated. Following each selection, in cases where the presently chosen atom is part of a motif, MoLeR incorporates the entire motif into the partial graph at once. Furthermore, MoLeR enhances its molecular generation of the molecular structures.

Previous methods like JT-VAE and HierVAE constructed the vocabulary of molecular fragments using simple hand-crafted rules, which may not effectively reveal frequent patterns in datasets. Besides, in previous *fragment-based* methods, subgraph prediction and assembly are conducted either autoregressively, as in HierVAE, or according to a pre-defined tree structure, as in JT-VAE. However, both approaches have inherent limitations: each newly predicted subgraph can only attach to a local set of previously generated subgraphs, leading to inflexibility. To overcome these issues, PS-VAE [47] has been developed. PS-VAE begins by creating a vocabulary of molecular fragments from a given dataset, starting with distinct atoms and progressively merging neighboring fragments to update the vocabulary. This merge-and-update strategy leads to the formation of principal subgraphs, a novel concept introduced in this paper, which represent frequent and significant repetitive patterns in molecules. PS-VAE also theoretically ensures that any *principal subgraph* can be covered by the developed vocabulary. Additionally, PS-VAE introduces a two-step subgraph assembling strategy: it initially predicts a set of fragments sequentially and subsequently performs a global assembly of all generated subgraphs. This method reduces dependency on permutation and places more emphasis on global connectivity, offering a more robust approach compared to traditional fragment-based methods.

In the original paper of MiCaM [23], another method based on VAE, the authors also highlight the crucial importance of developing an effective motif vocabulary. Accordingly, MiCaM devises an algorithm that identifies the most prevalent substructures based on their frequency within the molecule library. It scans the entire library to detect fragment pairs that frequently occur adjacent to each other within molecular graphs and subsequently merge these pairs into larger fragments. This merging process is repeated for a pre-determined number of steps, accumulating fragments to form a comprehensive motif vocabulary. The obtained motifs retain their structural connectivity information. Therefore, they are referred to as *connection-aware motifs* in the paper. The generator of MiCaM operates by concurrently selecting motifs to be added and specifying their connection modes. During each step of the generation process, MiCaM concentrates on a nonterminal connection, presenting two alternatives: (1) opting for a connection from the motif vocabulary, indicating the addition of a new motif, or (2) choosing a connection from the current molecular structure, a move that leads to the cyclization of the molecule.

Modof [10] stands as another advanced deep generative method designed for molecule optimization. It operates by predicting a single disconnection site within a molecule and subsequently modifying the molecule by altering the fragments at that site, including elements such as ring systems, linkers, and side chains. What sets Modof apart from existing molecule optimization methods is its approach to learning from and encoding the disparities between molecules before and after optimization at a single disconnection site. When it comes to modifying a molecule, Modof generates only one fragment that represents the anticipated difference. This is achieved by decoding a sample obtained from the latent

*difference* space. Subsequently, Modof removes the original fragment at the disconnection site and replaces it with the newly generated fragment. Its model training also employs the VAE objective.

MoleculeChef [8] has highlighted a significant issue in previous molecular generation methods. These earlier methods often failed to provide instructions on how to synthesize the molecules they generated. This lack of synthesis guidance implies that there are no assurances that the molecules produced by these methods can be practically synthesized in real-world laboratory scenarios. In contrast to prior research, MoleculeChef generates novel molecules by simulating virtual chemical reactions, closely mimicking the discovery process of molecules in the lab. n MoleculeChef, the encoder is responsible for mapping a multiset of reactants to a probability distribution in latent space, while the decoder generates this multiset of reactants sequentially using a RNN [57]. The resulting set of reactants is then processed through a reaction predictor to produce a final product. Notably, MoleculeChef employs the Molecular Transformer [67] as the chosen implementation for the reaction predictor. The paper acknowledges the possibility of utilizing a Variational Autoencoder (VAE) objective for training MoleculeChef. However, due to the inherent complexity of MoleculeChef's decoder, continuing to use the VAE objective would pose significant training challenges. As a solution, MoleculeChef ultimately opts to utilize the Wasserstein autoencoder (WAE) [72] objective. This decision is made to address the aforementioned training challenges associated with the VAE objective effectively.

There also exist several works using reinforcement learning (RL) to optimize the properties of generated molecules. An earlier work GCPN [84] stands out as a representative goal-directed 2D molecule generation approach. Compared with graph generative models struggling to incorporate desired molecular properties or constraints, RL excels at representing such hard constraints and desired properties by designing environment dynamics and reward functions. Besides, RL enables active exploration of the molecule space beyond the samples found in a dataset while the exploration capabilities of generative models are constrained by the limitations of the training dataset. GCPN formulates the graph generation task as a Markov Decision Process (MDP), where a molecule is constructed sequentially. This construction process involves either adding a bond to connect existing atoms within the graph or connecting a new fragment with the current molecular graph. The intermediate rewards include step-wise validity rewards and adversarial rewards, while the final rewards are computed as a sum over domain-specific rewards and adversarial rewards. The domain-specific rewards comprise the combination of final property scores, whereas the adversarial rewards are defined through a GAN. DeepGraphMolGen [42] builds upon the foundation of GCPN and takes a further step in addressing the challenge of generating novel molecules with desired interaction properties. In DeepGraphMolGen, interaction binding models are learned from binding data using GCNs. Recognizing that experimentally obtained property scores may contain potentially significant errors, DeepGraphMolGen incorporates a robust loss for the model. Notably, in contrast to GCPN, the final reward in DeepGraphMolGen includes the pKi value [15] of the final molecule as predicted by the trained model.

While GCPN and DeepGraphMolGen are capable of generating molecules with desired properties, it remains challenging for them to generate molecules that simultaneously satisfy many property constraints. RationaleRL [37], an RL-based 2D molecule generation method, has been introduced to specifically tackle this limitation. Its core idea involves composing molecules from a vocabulary of substructures known as *molecular rationales*. The first step of RationaleRL is extracting rationales that are likely accountable for each property from molecules by Monte Carlo Tree Search (MCTS) [9] and combining them for multiple properties. Specifically, during search process, each state in the search tree means a subgraph of the molecule and the property score of the subgraph indicates the reward. Then RationaleRL uses graph generative models to expand the rationales into full molecules. To generate realistic compounds, the graph generator is trained in two phases, namely pre-training phase and fine-tuning phase. After pre-training on a large set of real molecules, the graph generator is fine-tuned on property-specific rationales through multiple iterations using policy gradient.

Previous RL-based methods for goal-directed molecular design often emphasized relatively straightforward objectives, such as QED [17]. However, achieving high scores in these simple molecular properties does not necessarily ensure drug-likeness or therapeutic potential, underscoring the importance of adopting more relevant design objectives in generative tasks. In contrast, another RL-based approach known as FREED [82] places its focus on a more meaningful optimization target, namely, the docking score. This choice is made because docking simulations [65, 79] provide a more direct and practical proxy for assessing therapeutic potential, making it a valuable metric in the context of molecular design. FREED adopts a strategy for generating molecules that involves attaching a chemically realistic and pharmacochemically acceptable fragment unit to a given sub-graph at each step. Importantly, the model is enforced to create new bonds only at attachment sites that are considered suitable based on the fragment library preparation step. These strategies effectively leverage prior knowledge in medicinal chemistry, ensuring that molecule generation remains confined within the chemical space conducive to drug design. Additionally, FREED explores various explorative algorithms, incorporating curiosity-driven learning and prioritized experience replay (PER) [63]. In particular, FREED introduces an innovative PER method that defines priority based on the novelty of experiences, estimated by the predictive error or uncertainty of the auxiliary reward predictor's outcome. This approach is designed to mitigate the lack of robustness observed in previous methods and to encourage the exploration of diverse solutions during the molecular generation process.

Recently, a novel generative approach known as GFlowNet [6] has emerged, with close ties to RL. GFlowNet is designed to tackle the challenge of learning a stochastic policy for generating an object, such as a molecular graph, through a sequence of actions. The primary objective is to ensure that the probability of generating an object is directly proportional to a specified positive reward assigned to that object. GFlowNet views the generative process as a flow network, making it particularly adept at handling scenarios where various trajectories lead to the same final state. For instance, in molecular graph generation, there are multiple ways to sequentially add atoms to a molecule. In this context, GFlowNet conceptualizes the set of trajectories as a flow and transforms the flow consistency equations into a learning objective. This approach is analogous to how Bellman equations are utilized in Temporal Difference methods [71]. Within the flow network framework, nodes represent states, and edges represent actions. GFlowNet finds practical application in molecule generation, where the 'state' corresponds to the current molecule, and the 'action' involves adding a fragment from a predefined vocabulary of fragments to the current molecule or terminating the generation process.

Another emerging line considers molecule generation as a sampling procedure. One noteworthy method in this category is MARS [78]. The core concept of MARS involves initiating the process from a seed molecule and continually generating candidate molecules by making modifications to fragments of molecular graphs from previous iterations. In MARS, the task of molecular design is framed as an iterative editing process, with the overall objective being composed of multiple property scores. To search for optimal chemical compounds, MARS employs the annealed Markov Chain Monte Carlo (MCMC) sampling [24] technique. This approach allows for the exploration of chemicals with novel and diverse fragments. MARS utilizes graph neural networks (GNNs) to represent proposals for modifying molecular fragments. These GNNs adaptively learn their parameters to propose fragment modifications. While MPNNs are used in practice, other GNN architectures can also be integrated into the framework. Moreover, MARS leverages the sample paths generated on-the-fly to adaptively train the proposal network, eliminating the need for external annotated data. This adaptive learnable proposal mechanism enables MARS to continuously enhance the quality of molecule generation throughout the process.

MIMOSA is another molecule generation approach built on the MCMC sampling method. MIMOSA unfolds in three distinct stages. Initially, MIMOSA focuses on training a pair of property-neutral GNNs. These networks are tasked with the prediction of molecular topologies and substructure types. These substructures encompass atoms and rings. This step is crucial for improving the embeddings of molecules, aiding in the later stage of sampling. Subsequently, MIMOSA leverages these predictions to conduct three core substructure manipulations: ADDITION, REPLACEMENT, and REMOVAL to generate new molecule candidates. In its final stage, MIMOSA evaluates these newly generated molecules, assigning them weights based on criteria such as structural resemblance and drug property constraints. Molecules that fulfill these specified criteria are then chosen for additional processing rounds.

There's another fragment-based method called DEG [30], which is also related to sampling. This method seeks to resolve two primary challenges. Existing methods predominantly rely on deep neural networks, necessitating extensive training on vast datasets, often comprising tens of thousands of examples. Contrarily, real-world scenarios usually present significantly smaller, class-specific chemical datasets, often just a few dozen samples, primarily due to the labor-intensive nature of experimentation and data acquisition. This limited dataset size presents a substantial challenge for deep learning-based generative models in effectively capturing the full scope of the molecular design landscape. In response, DEG emerges as a generative model optimized for data efficiency, capable of learning from much smaller datasets compared to standard benchmarks. Its core mechanism involves a learnable graph grammar, which generates molecules following a series of production rules. These

Model	Generation Strategy	Methodology	Venue	
VGAE	all-at-once	VAE-based	NeurIPS workshop 2016	
GraphVAE	all-at-once	VAE-based	ICANN 2018	
MPĜVAE	all-at-once	VAE-based	arXiv 2020	
Regularized VAE	all-at-once	VAE-based	NeurIPS 2018	
MolGAN	all-at-once	GAN-based	ICML workshop 2018	
GraphNVP	all-at-once	Flow-based	arXiv 2019	
GDSS	all-at-once	Diffusion-based	ICML 2022	
DiGress	all-at-once	Diffusion-based	ICLR 2023	
Wave-GD	all-at-once	Diffusion-based	NeurIPS 2023	
JT-VAE	fragment-based	VAE-based	ICML 2018	
MHGVAE	fragment-based	VAE-based	ICML 2019	
HierVAE	fragment-based	VAE-based	ICML 2020	
MoleculeChef	fragment-based	VAE-based	NeurIPS 2019	
MoLeR	fragment-based	VAE-based	ICLR 2022	
PS-VAE	fragment-based	VAE-based	NeurIPS 2022	
MiCaM	fragment-based	VAE-based	ICLR 2023	
Modof	fragment-based	VAE-based	Nature Machine Intelligence 2021	
GCPN	fragment-based	RL-based	NeurIPS 2018	
DeepGraphMolGen	fragment-based	RL-based	Journal of Cheminformatics 2020	
RationaleRL	fragment-based	RL-based	ICML 2020	
FREED	fragment-based	RL-based	NeurIPS 2021	
GFlowNet	fragment-based	GFlowNet-based	NeurIPS 2021	
MARS	fragment-based	Sampling-based	ICLR 2021	
MIMOSA	fragment-based	Sampling-based	AAAI 2021	
DEG	fragment-based	sampling-based	ICLR 2022	
Mol-CycleGAN	fragment-based	GAN-based	Journal of Cheminformatics 2020	
CGVAE	node-by-node	VAE-based	NeurIPS 2018	
SbMolGen	node-by-node	VAE-based	Chemical Science 2020	
GraphAF	node-by-node	Flow-based	ICLR 2020	
GraphDF	node-by-node	Flow-based	ICML 2021	
STGG	node-by-node	Spanning-tree-based	ICLR 2022	

Table 1: Recent representative works of 2D molecule generation.

rules are autonomously derived from the training data, requiring no manual intervention. Additionally, the model undergoes further refinement through grammar optimization, facilitating the integration of extra chemical insights. Training of the DEG model is conducted through Monte Carlo (MC) sampling [58] and the REINFORCE algorithm [76].

Additionally, it's noteworthy to mention a GAN-based method designed for molecular optimization, Mol-CycleGAN[55]. More specifically, it employs the CycleGAN [88] architecture. A key strength of Mol-CycleGAN lies in its capacity to discern and learn transformation rules from compound sets, based on their desired and undesired property values. It functions within a latent space, which is trained by another model. Specifically, in the case of Mol-CycleGAN, this latent space is derived from the JT-VAE model we discussed earlier. The capability of Mol-CycleGAN to generate molecules with particular desired properties is well-demonstrated, particularly in terms of structural and physicochemical attributes. Notably, the molecules produced by this model closely resemble their initial forms, with a tunable degree of similarity, adjustable through a designated hyperparameter.

#### 3.3 Generation Strategy III: Node-by-node

In addition to synthesizing molecules directly or employing substructures as foundational building blocks, recent advancements have introduced alternative methodologies for molecular generation. These novel approaches, often referred to as "*node-by-node*", involve constructing molecules at the most fundamental level, atom by atom.

CGVAE [50] is an VAE-based generative model which builds gated graph neural networks (GGNN) [48] into the encoder and decoder. CGVAE uses GGNN to embed each node in the input graph G to a latent vector sampled from a diagonal normal distribution. The decoder of CGVAE initializes nodes with latent variables and generates edges between these nodes sequentially based on two decision functions: FOCUS and EXPAND. Specifically, the FOCUS function determines which node to visit and the EXPAND function decides which edges to add from the focus node in each step.

Dataset	Description	Number of molecules	Link
QM9	Stable small organic molecules made up of CHONF atoms	133,885	http://quantum-machine.org/datasets/
GDB-17	Enumeration of small organic molecules up to 17 atoms	>166,000,000,000	http://gdb.unibe.ch/downloads/
ZINC15	Commercially available compounds	> 750,000,000	http://zinc15.docking.org/
ChEMBL	Bioactive molecules with drug-like properties	> 2,000,000	https://www.ebi.ac.uk/chembl/
PubChemQC	Compounds with quantum chemistry estimated property based on density functional theory	3, 981, 230	http://pubchemqc.riken.jp/
DrugBank	FDA-approved drugs and other drugs public available	> 14,000	https://www.drugbank.ca/

Table 2: Representative datasets for 2D molecule generation.

The procedure will terminate when meeting the stop criteria. Notably, during the generation, all node representations should be updated once the generated subgraph changes. Furthermore, EXPAND function applies valency masking to guarantee chemical validity. CGVAE utilizes gradient ascent in the continuous latent space to optimize these molecules based on specific numerical properties.

Lim et al. propose another VAE-based method which is able to generate molecules with target properties while maintaining an arbitrary input scaffold as a substructure. In our survey, we refer to their method as SbMolGen. Its encoder adopts a variant of interaction network [5, 25] to encode one complete molecule graph G into a latent vector z, from which the decoder is trained to recover molecules. Specifically, the decoder takes a scaffold S as input and sequentially adds nodes and edges to S based on three loop stages namely NODE\_ADDITION, EDGE\_ADDITION, NODE\_SELECTION and a extra final stage named ISOMER\_SELECTION. Furthermore, we can concatenate the whole-molecule properties vector and scaffold properties vector with z sampled from latent space to condition the decoding process.

We have previously introduced two VAE-based methods for molecule generation in a node-by-node fashion. Additionally, there are flow-based methods available for generating molecules. GraphAF [68] is a representative flow-based model, whose concept is actually similar to the previously introduced GCPN. Both formulate the problem of molecular graph generation as a sequential decision process. Specifically, beginning with an empty graph, GraphAF sequentially generates a new node at each step, which is based on the structure of the current sub-graph. Subsequently, the edges connecting this newly added node with the existing ones are systematically formed, taking into account the existing graph structure. This iterative process continues until the generation of all nodes and edges is complete. The core concept of GraphAF involves defining an invertible transformation from a base distribution (like a multivariate Gaussian) to a molecular graph structure G = (A, X). In every round of generation, GraphAF, given the existing sub-graph structure, employs a stack of multiple layers of a modified version of Relational GCN [64] to derive the embeddings for each node. Following this, a sum-pooling operation is applied to these node embeddings to obtain the embedding of the entire sub-graph. This sub-graph embedding is then set as the mean and standard deviations of Gaussian distributions, which are subsequently used to generate the nodes and edges. Additionally, GraphAF suggests that the molecule generation process can be refined through reinforcement learning, aiming to optimize the properties of the molecules generated.

It's important to recognize that, akin to GraphNVP [54], GraphAF also converts discrete graph data into continuous data through the addition of real-valued noise, a technique known as *dequantization*. However, this *dequantization* process hinders the models' ability to accurately represent the original discrete distribution of graph structures. This presents a significant challenge in model training, as it impedes the capability to accurately capture the true distribution of graph structures, resulting in a diverse range of molecules generated. To address the challenges posed by *dequantization*, GraphDF [52], a novel approach building upon GraphAF, introduces the generation of molecular graphs using discrete latent variables. In GraphDF, all latent variables are discrete and sampled from multinomial distributions. We use a discrete flow model to reversibly map discrete latent variables to new nodes and edges. The discrete transform used in the discrete flow is a modulo shift transform. Apart from employing discrete latent variables, the process of molecule generation of GraphDF is similar to GraphAF.

STGG [1] stands out from prior VAE-based and flow-based methods as the first framework to utilize a spanning tree-based approach for molecular graph generation. This unique methodology conceptualizes the generation of molecular graphs through the construction of a spanning tree along with residual edges. This approach leverages the inherent sparsity found in molecular graphs, enabling

the use of efficient tree-constructive operations to establish molecular graph connectivity. STGG ensures that the generated molecular graphs adhere to chemical valence rules by applying constraints based on the intermediate graph structure formed during the construction process. Additionally, STGG introduces an innovative Transformer [73] architecture, incorporating tree-based relative positional encodings, to effectively facilitate the tree construction procedure.

#### 3.4 Discussion

The generation at different levels can have different advantages in specific applications. While in general, the fine-grained level manipulation at node level is flexible, while it may be less efficient for generation and has difficulty in modeling higher-level (sub)structure information. While the fragment-based pipeline allows edition of sub-structures of a molecule, which can be often meaningful to some specific functionality and reaction. Finally, the once-for-all scheme can be efficient while it may sometimes lack enough flexibility for incremental generation and optimization.

# **4** Datasets and Evaluation Metrics

**Datasets** We present a compilation of prominent publicly accessible datasets, commonly employed in molecule generation and optimization endeavors, as depicted in Table 2. Among them, ChEMBL and DrugBank are continually evolving, with periodic updates to their contents.

**Evaluation Metrics** Generation and optimization for molecules adopt two different sets of evaluation metrics. Molecule generation evaluates the overall quality of generated molecules from a statistical perspective in terms of these metrics, including *validity* (the percentage of generated molecules that are chemically valid), *novelty* (the fraction of generated molecules not appearing in the training data), *diversity* (the pairwise molecular distance among generated molecules), *uniqueness* (ratio of unique molecules) and *reconstruction* (the percentage of molecules which can be reconstructed from their latent variables). For molecule optimization, it adopts another set of metrics for evaluation on the basis of multi-property of generated molecules , such as quantitative estimate of drug-likeness (QED) [17], synthetic accessibility (SA) [7], octanol-water partition coefficients (logP) [62] and so on.

# 5 Challenges and Future Directions

Despite the significant achievements of graph-based deep learning in automating molecule design, the complexity of molecular structures presents ongoing challenges. In this section, we suggest three future directions for further research.

**Macro-molecules Design** The current body of research primarily concentrates on the design of small molecules, and its effectiveness diminishes considerably when applied to the design of larger molecules such as polymers. The complexity of large molecular systems is inherently much greater than that of small molecular systems, naturally leading to increased modeling difficulties. The failure also stems from the many generation steps required to realize larger molecules and the associated challenges with gradients across the iterative steps [36]. Therefore, it is imperative to devise novel approaches specifically tailored to handle larger molecules.

**3D Drug Discovery** The generation of 3D molecular geometries is an area that has not been extensively explored. Compared to 1D SMILES-based and 2D graph-based representations, the addition of a third dimension considerably broadens the molecular space to be examined, thereby raising the level of complexity [83]. Nonetheless, the generation of 3D molecules is both meaningful and necessary, given that accurate 3D coordinates are crucial for precise prediction of quantum properties [66]. Despite its importance, there are relatively few studies focused on this aspect, highlighting a need for further research and development in this field.

**Structure-based Drug Design** Chemical space is vast, yet the subset of molecules with certain desirable properties is much smaller by contrast, e.g. activity against a given target, that makes them well suited for the discovery of drug candidates [86]. Structure-based drug discovery aims to

design small-molecule ligands that bind with high affinity and specificity to pre-determined protein targets [3], which is a fundamental and challenging task in drug discovery, essentially sampling compounds from promising sub-regions of chemical space. Nevertheless, the successful application of machine learning to the problem of structure-based drug design remains relatively limited in the current literature. This highlights a substantial challenge and, simultaneously, presents a significant opportunity for breakthroughs and progress in future research within this domain.

# 6 Conclusion

The generation of molecules with desired properties holds paramount importance, particularly in the pharmaceutical industry. In this context, we have introduced a broad array of graph-based deep learning models for molecular deisgn, categorizing them into three distinct groups based on their generative strategies. Additionally, we have compiled a comprehensive overview of public datasets and the evaluation metrics widely used in this field. In the end, we delve into the challenges and prospective future developments in this dynamic and evolving area.

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