Disentangle VAE for Molecular Generation

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Abstract

Automatic molecule generation plays an important role on drug discovery and has received a great deal of attention in recent years thanks to deep learning’s successful use. Graph-based neural network represents state-of-the-art methods on automatic molecule generation. However, it’s still challenging to generate molecule with desired properties, which is a core task in drug discovery. In this paper, we focus on this task and propose a Controllable Junction Tree Variational Autoencoder (C-JTVAE), adding an “extractor” module into VAE framework to describe some properties of molecule. Our method is able to generate similar molecular with desired property given an input molecule. Experimental results is encouraging.

1 Introduction

Automatic molecular generation has received much attention in recent years. One core task of molecule generation is to generate a molecule with desired property. For example, if we are given a molecule with low solubility as an input, we want to generate a molecule that is not only similar to the input molecule, but also has high solubility. There are two key factors that guarantee the success of such a process. That is, first, we want to generate a new molecule that is similar to the given molecule. Second, we want to control a certain property of the generated molecule.

2 Related Work

Regarding related studies, we review 2 research lines in automatic molecule generation. First is based on sequence representation of molecule. Second is graph representation.

Sequence-based methods One research line is to formulate the drug generation problem as a sequence generation problem. Most of these methods are based on the simplified molecular-input line-entry system (SMILES), a line notation describing the molecular structure using short ASCII strings Weininger (1988).

• Character Variational Auto-Encoder (C-VAE) generate SMILES string character-by-character Gómez-Bombarelli et al. (2018).
• Grammar VAE (G-VAE) generates SMILES following syntactic constraints given by a context-free grammar Kusner et al. (2017).
• Syntax-directed VAE (SD-VAE) that incorporates both syntactic and semantic constraints of SMILES via attribute grammar Dai et al. (2018).
• Das et al. (2018) proposed a method that is able to control the properties of the generated molecule based SMILES string generation.

Graph-based methods Another research line is based on graph structure of molecule Jin et al. (2018a, 2019), Fu et al. (2021), Xiao et al. (2020). Comparing sequence based method, this kind of method can capture graph-level information about molecule, which is usually lost in sequence-based method. Thus, graph-based models achieve state-of-the-art performance on this tasks.

• Junction Tree Variational Auto-Encoder (JT-VAE) generate tree-structured scaffold based on chemical substructures and then combine them into molecule Jin et al. (2018a).
• Motivated by machine translation model, Jin et al. (2019) proposed a graph-to-graph translation model, which is able to generate a new molecule with desired property based on pairs of molecules.

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| Part       | Notations | short explanation                   |
|------------|-----------|-------------------------------------|
| graph      | $V/E$     | set of vertex(atom) / edge(bond)    |
|            | $G = (V, E)$ | molecular graph                     |
|            | $N(x)$    | neighbor of vertex $x$              |
| junction tree | $T_G = (V, E, \mathcal{X})$ | junction tree                       |
|            | $V = \{C_1, \cdots, C_k\}$ | node set                            |
|            | $C_i = (V_i, E_i)$ | subgraph of $G$                     |
|            | $\mathcal{X}, |\mathcal{X}| = 780$ | vocabulary (bond / rings), union    |
|            | $\cup_i V_i = V, \cup_i E_i = E$ | one-hot label for $C_i$            |
|            | $x_i$     | directed Edge ($C_i$, $C_j$)        |
| Other      | $\tau(\cdot)$ | relu function                      |
|            | $\sigma(\cdot)$ | sigmoid function                  |

Table 1: Notations used in this paper and short descriptions.

The most relevant work is graph-to-graph translation model [Jin et al. (2018a, 2019); Hoang et al. (2019)]. It is able to translate the current molecule to a similar molecule with prespecified desired property (like drug-likeness). However, it has some limitations. It requires a large amount of paralleled molecule pairs to train a translation model for each desired property. Specifically, if the task is to improve the solubility of a molecule, the model requires $N$ data pairs $\{X_i, Y_i\}_{i=1}^N$, where $X_i$ is the input molecule with low solubility, $Y_i$ is the target molecule similar to $X_i$, but with high solubility.

In our setting, datasets consist of $\{X_i, c_i\}_{i=1}^N$, where $X_i$ is the $i$-th input molecule. $c_i$ is a vector, each dimension describes a specified property of $X_i$.

### 3 Method

In this section, we describe our method. We start from a brief introduction to Junction Tree Variational Auto-Encoder (JT-VAE) [Jin et al. (2018a)] because the proposed method relies heavily on it. Then we demonstrate controllable JT-VAE and the learning procedure. For ease of exposition, we list the important notations and their short explanations in Table 1.

#### 3.1 Junction Tree Variational Auto-Encoder (JT-VAE)

Our framework is based on Junction Tree Variational Auto-Encoder (JT-VAE) [Jin et al. (2018a)]. Thus, in this section, we provide a brief introduction to JT-VAE. Each molecule is represented by a graph $G = (V, E)$, where $V$ and $E$ are set of vertex (atom) and edge (bond), respectively. To construct cycle-free structure, junction tree $T_G^1$ is generated via decomposing graph $G$. It is mainly divided into following 4 parts, (i) graph encoder; (ii) tree encoder; (iii) tree decoder; (iv) graph decoder.

**Graph Encoder**

It uses Graph Message Passing Network (MPN) to encode the atom-level graph with $T$ steps of iterations as

$$\nu_{uv}^{(t)} = \tau(W_1^g x_u + W_2^g x_{uv} + W_3^g \sum_{w \in N(u) \setminus u} \nu_{wu}^{(t-1)}) \text{ for } t = 1, \cdots, T. \quad (1)$$

where $(u, v) \in E$ is edge in graph $G$, $x_u$ and $x_{uv}$ represent atom and bond type for node $u$ and edge $(u, v)$, respectively. Then the graph is encoded as average of atom-level encode.

$$h_u = \tau(U_1^g x_u + \sum_{v \in N(u)} U_2^g \nu_{uv}^{(T)}),$$

$$h_G = \frac{1}{|V|} \sum_{i \in V} h_i, \quad (2)$$

where $h_G$ is representation of $G$, the latent variable $z$ is sampled from a normal distribution parameterized by $G$.

$$z_G \sim \mathcal{N}(\mu(h_G), \sigma(h_G)). \quad (3)$$

$^1 T_G$ denotes the junction tree decomposed from graph $G$. 

\[ \begin{align*}
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Figure 1: Controllable Molecule Generation. Data corpus contains $N$ molecule and their labels $\{X_i, c_i\}_{i=1}^N$, $c_i \in \mathbb{R}^d$. Each dimension of $c$ represent one kind of score of molecule.

Tree Encoder
Then, to generate a cycle-free structure, graph is decomposed into “junction tree”. It encode junction tree via

$$m_{ij} = \text{GRU}(x_i, \{m_{ki}\}_{k \in N(i) \setminus j}),$$

where $m_{ij}$ is the message of directed edge $(C_i, C_j)$, $x_i$ represent one-hot label for $C_i$. Node and junction tree are respectively represented by

$$h_i = \tau(W^o x_i + \sum_{k \in N(i)} U^o m_{ki}),$$

$$h_{T_G} = h_{\text{root}}. \quad (5)$$

Latent variable $z_T \sim N(\mu(T_G), \sigma(T_G))$ is sampled from a normal distribution parameterized by $T_G$, represent junction tree $T_G$ in a continuous hidden space.

Tree Decoder
When decoding, for each node, the prediction is made based on 2-levels. First is a binary classification to predict whether it has leaf node

$$p_t = \sigma(u_d \cdot \tau(W_1^d x_i + W_2^d z_T + W_3^d \sum_{(k,i)} h_{(k,i)})),$$

where $u_d, W_1^d, W_2^d, W_3^d$ are parameters. Then if the node has leaf node, the task is to predict the label the its leaf node

$$q_j = \text{softmax}(U \tau(W_1 z_T + W_2 h_j)). \quad (7)$$

Graph Decoder
When learning, all possible substructure $G_i$ is enumerated and it is cast as a classification problem whose target is to maximize the scoring function of right structure.

$$\mathcal{L}_g = \sum_i f^a(G_i) - \log \sum_{G_i} \exp(f^a(G_i)), \quad (8)$$

where $f^a(G_i) = h_{G_i} \cdot z_G$ is a scoring function that measure the likelihood of the current substructure $G_i$. When sampling, graph decoder is to enumerate all possibly combinations, and pick the most likely structure in a greedy manner.

JTVAE learning objective
Combining the encoder and decoder steps for both tree and graph level, the learning objective $\mathcal{L}$ becomes

$$\mathcal{L} = \mathcal{L}_{KL} + \mathcal{L}_c + \mathcal{L}_g, \quad (9)$$

where $\mathcal{L}_{KL}$ is KL divergence loss for in tree and graph encoder. $\mathcal{L}_c$ is the cross entropy loss for two classification problems (Equation (6) and (7)). $\mathcal{L}_g$ is loss for scoring function in graph decoder, described in Equation (8). The whole loss is trained in end-to-end manner.
Algorithm 1 Controlled Molecule Generation

1: Let $X_i$ be input, $c_i$ be target, train Extractor using $\{X_i, c_i\}_{i=1}^N$ until convergence.
2: Train Encoder and Decoder using $\{X_i, c_i\}_{i=1}^N$ until convergence.
3: for epoch in $1, \cdots, K$ do
4: sample a minibatch $\{X_j, c_j\}_{j=1}^m$.
5: Minimize VAE loss, update encoder and decoder.
6: Get new data pairs, $\{z_j, c_j\}_{j=1}^m$, where $z_j \sim$ Encoder($X_j$).
7: Option I: Update decoder using soft decoding. # $[z, c] \rightarrow$ Decoder $\rightarrow \tilde{X} \rightarrow$ Extractor $\rightarrow \hat{c}$ via minimizing $\|c - \hat{c}\|_2^2$.
8: Option II: Update decoder using soft decoding. # $[z, c] \rightarrow$ Decoder $\rightarrow \tilde{X} \rightarrow$ Encoder $\rightarrow \hat{c}$ via minimizing $\|z - \hat{z}\|_2^2$.
9: end for

3.2 Controllable Molecule generation

In this section, we discuss controllable molecule generation procedure. First, we talk about key properties that we want to control. Second, we demonstrate how to realize it.

Properties of Molecule

In drug discovery, some properties are crucial in evaluating the effectiveness of generated drugs. In this paper, following Jin et al. (2019), we mainly focus on following three properties.

- **Drug likeness (QED)** [Bickerton et al. (2012)]. QED score of a compound ranges from 0 to 1. In drug discovery, we always want to generate a compound with higher QED score.

- **Dopamine Receptor (DRD2)** [Jin et al. (2018b); Huang et al. (2021); Fu et al. (2020)]. DRD2 score is to measure a molecule’s biological activity against a biological target named the dopamine type 2 receptor (DRD2). DRD2 score ranges from 0 to 1, and higher is better.

- **Penalized LogP**. The penalized logP score measures the solubility and synthetic accessibility of a compound. The oracle is calculated via RDKit.

Suppose we have $N$ molecules in training set, denoted $\{X_i\}_{i=1}^N$. We are interested in $d$ molecular properties, for example, if we want to control 3 properties mentioned above, then $d = 3$. For $i$-th molecule $X_i$, we define its score vector denoted $c_i \in \mathbb{R}^d$ to represent its score for different properties.

Extractor module

The framework is shown in Figure 1. It is built on the base of JTV AE. The difference is that it add an “extractor” module into the framework, which is described as follow.

Compared with JT-VAE, we add extractor module. It shares the same architecture with tree encoder except the output layer. But they are used to predict different target, so their parameters are not shared. Specifically, it represent junction tree as

$$h_u = \tau(U^1_u x_u + \sum_{v \in N(u)} U^2_v \nu^T_{vu}),$$

$$h_{\tau_G} = \sum_i h_i / |V|.$$ (10)

Then it add a fully-connected layer as

$$\hat{c} = W_c(h_{\tau_G}).$$ (11)

The whole extractor can be seen as a predictor. The input is molecule and the target is its properties. The learning objective is to minimize the difference between target $c$ and the prediction $\hat{c}$.

3.3 Learning Procedure

We train Extractor and VAE (encoder and decoder) independently. The main algorithm is listed in Algorithm 1.

4 Experiment

In this section, we describe our empirical procedures. We start with the description of experimental setup, including dataset description, preprocessing procedure, baseline methods and evaluation metrics, following Jin et al. (2018a, 2019); Xiao et al. (2020); Fu et al. (2021); Huang et al. (2020).
4.1 Experimental Setup

Dataset
First, we introduce the dataset that we are using. ZINC contains 250K drug molecules extracted from the ZINC database. It is available at Huang et al. (2021).

Preprocessing
We have $N$ data samples, $\{X_i, c_i\}_{i=1}^N$, where $X_i$ is the molecule, $c_i$ is vector, each dim of $c_i$ corresponds to one property. For each SMILES string in ZINC, we generate the QED, DRD2 and LogP scores using Rdkit package Landrum et al. (2006). For QED and DRD2 scores, their original score ranges from 0 to 1, so we don’t normalize them. For LogP score, we do normalization procedure to the raw score to make them lie in the interval $[0, 1]$ via clipping some extreme value (top 5% and bottom 5%) and then rescale to $[0, 1]$.

Baseline Methods
We compare our method with two important baseline methods, which represents state-of-the-art methods on this task.

- **JTVAE** Jin et al. (2018a). Our method is developed on basis of JTVAE. The difference is that JTVAE is totally unsupervised while our method uses property score as the guidance.
- **graph2graph** Jin et al. (2019). It requires data pairs for supervised graph2graph training, different from our method in architecture.

Evaluation
During evaluation procedure, we mainly focus on two evaluation metrics. First is the molecular similarity between the input molecule and the generated molecule, measured by Tanimoto similarity over Morgan fingerprints Rogers and Hahn (2010). The similarity between molecule $X$ and $Y$ is denoted $\text{sim}(X,Y)$, ranging from 0 to 1. Second metric is the improvement of scores on certain properties, including QED-score, DRD2-score and LogP-score.

4.2 Results

**single property control**
First, we study a simpler task, that is, the score vector $c \in \mathbb{R}$, the goal is to improve a single property score of a molecule. We test
Table 2: results of Similarity-Improvement (DRD2) for different methods. We can find that JTVAE can produce similar molecule, JTVAE+GAN can increase the desired property significantly, but will sacrifice the similarity.

| Model                | Similarity on average | Improvement of QED on average |
|----------------------|-----------------------|-------------------------------|
| JTVAE                | 0.635                 | 0.071                         |
| JTVAE + GAN          | 0.368                 | 0.754                         |
| ours [older]         | 0.640                 | 0.067                         |

DRD2 score here. For molecules \( \{X_j, c_j\}_{j=1}^{N'} \) (\( c_j \in \mathbb{R} \), size of test set is \( N' \)) in test set, we feed \( X_j \) forward encoder, get latent variable \( z_j \) (both graph and tree level), let \( c = 1 \), feed \( (z, c) \) to decoder and generate the new molecule \( Y_j \). We evaluate both similarity (i.e., \( \text{sim}(X_j, Y_j) \)) and improvement on desired property (i.e., \( \text{DRD2}(Y_j) - \text{DRD2}(X_j) \)). We plot all these values on Figure\(^6\) and report their average value in Table 2.

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