Reward Conditioned Policy for Molecular Optimization

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Abstract

This paper suggests a novel deep reinforcement learning method for *de novo* molecular generation, which is a representative computational chemistry task to automatically discover a new drug with a special property. The *de novo* generation can be cast as reinforcement learning (RL), where policy explores finding high-quality molecules in the massive chemical space. The chemical space is composed of *graph* structures, where the atom is a node and chemical bonding is an edge. Therefore, combining RL with graph representation learning is a crucial technique, getting considerable attention. However, those techniques have a significant limitation where the reward function for molecule generation is very extensive and has high uncertainty. To tackle these limitations, we suggest utilizing offline pre-collected data (which is highly reliable) for *de novo* molecular generation. To this end, we propose reward conditioned policy that can generate high-quality molecule graphs leveraging offline pre-collected data, with two novel auto-encoder structures: *generator-AE*, and *plugin-CVAE*. The generator-AE is designed to reconstruct molecular graphs. The plugin-CVAE, which is a reward-conditioned variational auto-encoder is designed to reconstruct the latent vector of *generator-AE* under the condition of reward. In the test phase, our method has three following steps: (a) we input high rewards and normal distributed latent into the decoder of plugin-CVAE, (b) the latent vector (for *generator-AE*) generated from plugin-CVAE becomes input of *generator-AE* decoder, (c) finally, *generator-AE* decoder generate high-quality molecular graph. Our method has two benefits: (a) it can be used as an offline-RL method, which only utilizes pre-collected offline datasets without an online oracle, and (b) it can be used as a sample-efficient online-RL where it extends offline datasets using online exploration. Experiment results show that the proposed method makes the state-of-the-art result of penalized octanol-water partition coefficient optimization task.

1 Task Description

1. **Dataset.** We have chemical dataset **ZINC250K** [1].
2. **Oracles.** We have chemical oracles (i.e. reward metric) as panelized logp (**PlogP**:water-solubility), **QED** (toxic screening) and **GuacaMol** [2] benchmarks.
3. **Offline Setting.** We only provide oracle values for **ZINC250K** for offline training. The major purpose is to design new molecules having maximum oracle value *without online oracle calls*.

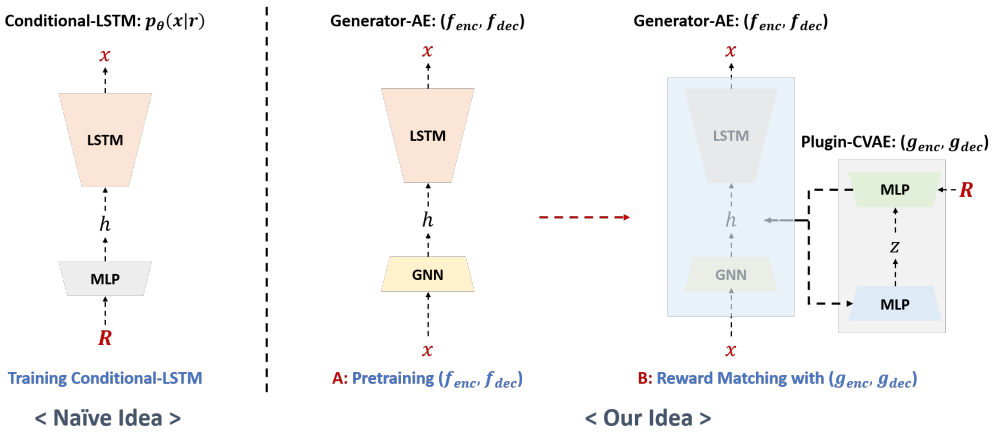


Figure 1: An overview of our idea

4. **Online Sample Efficient Setting.** We also validate the online adaptability of the offline model with *limited* oracle call (inspired by [3]). The major purpose is to design new molecules having maximum oracle value.

2 Idea Sketch

2.1 Notations

1. Molecule Graph: $\boldsymbol{x} = \{\mathcal{V}, \mathcal{E}\}$. The $\mathcal{V}$ contains atoms and $\mathcal{E}$ contains bonds between atoms.
2. Reward: $\boldsymbol{R}$.
3. Dataset for online oracle round t: $\mathcal{D}_t$. The $\mathcal{D}_0$ indicates an offline dataset.

Note that molecule graph $\boldsymbol{x}$ can be represented with a Simplified molecular-input line-entry system (SMILES) [4], which is sequential data. Therefore, we handle SMILES-LSTM [5] as generating neural networks for $\boldsymbol{x}$.

2.2 Naiive Reward Conditioned Policy with SMILES LSTM

The most representative reward conditioning method directly maps reward value into latent space such as the *decision-transformer* [6]. Therefore we suggest *conditional-LSTM* as our baseline which is reward conditioned policy with SMILES LSTM. As shown in Fig. 1, we iteratively train *conditional-LSTM*, $p_\theta(\boldsymbol{x}|\boldsymbol{R})$ as follows:

1. Samples data from offline dataset: $(\boldsymbol{x}, \boldsymbol{R}). \sim \mathcal{D}_0$.
2. Maximize likelihood to produce $\boldsymbol{x}$ for $p_\theta(\boldsymbol{x}|\boldsymbol{R})$ using cross-entropy loss.

2.3 Our Idea

Our major idea is utilizing two auto-encoding scheme: *Generator-AE* and *Plugin-CVAE*. The *Generator-AE* (f_{enc}, f_{dec}) is trained to reconstruct $\boldsymbol{x}$. The *Plugin-CVAE*, which is R conditioned variational auto-encoder (g_{enc},g_{dec}), is trained to reconstruct $\boldsymbol{h}$. As shown in Fig. 1, we train our scheme as:

1. **Phase A.**: Pretrain *Generator-AE*: $f_{dec}(f_{enc}(\boldsymbol{x})) \approx \boldsymbol{x}$ using reconstruction loss.
2. **Phase B.**: Finetunes *Plugin-CVAE*: $g_{dec}(g_{enc}(\boldsymbol{h}, \boldsymbol{R})) \approx \boldsymbol{h} = f_{enc}(\boldsymbol{x})$ using VAE loss. In this process, the *Generator-AE* is not updated.

After training, our generative model p is composited as: $p(\boldsymbol{x}|\boldsymbol{R}) = f_{dec}(g_{dec}(\boldsymbol{z}|\boldsymbol{R}))$, where $\boldsymbol{z} \sim \mathcal{N}(0, I)$.

Benefit of our model. Our model is beneficial with generalization capability with limited reward data because we designed a compact reward matching system using *Plugin-CVAE* (excluding SMILES LSTM in the reward matching process which is expensive to train).

3 Preliminary Experimental Results

3.1 Training Results of *Generator-AE*

This section gives experimental results of the **Phase A** of Section 2.3: training of *Generator-AE*. Specifically, this task aims to reconstruct a molecular graph, using a sequential decoder (i.e. SMILES LSTM). To evaluation reconstruction performances, we report two metrics: sequence accuracy and element accuracy. Let N be the number of the input molecular graphs, and $\{K_i\}_{i=1}^{N}$ be the length of each SMILES string of the corresponding molecular graph.

Sequence Accuracy. The sequence accuracy acc_{seq} is evaluated as:

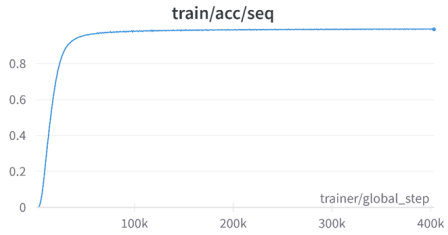
$$acc_{seq} = \frac{1}{N} \sum_{i=1}^{N} 1_{\{f_{dec}(f_{enc}(x))=x\}} \tag{1}$$

Sequence accuracy is metric to measure how many SMILES sequences were perfectly reconstructed.

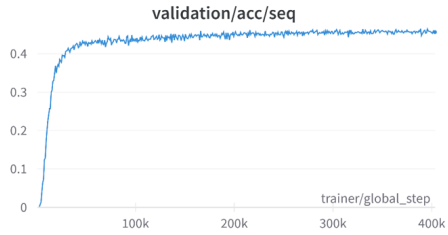
Element Accuracy. The element accuracy acc_{elem} is evaluated as:

$$acc_{elem} = \frac{1}{N} \frac{1}{\sum_i K_i} \sum_{i=1}^{N} \sum_{j=1}^{K_i} 1_{\{f_{dec}(f_{enc}(x))_j=x_j\}} \tag{2}$$

The element accuracy is a more generous metric than the sequence accuracy, where it measures the number of *element* which reconstructed successfully.

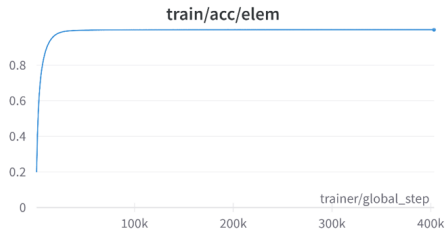


(a) Sequence accuracy on training.



(b) Sequence accuracy on validation.

Figure 2: Training and validation graph of sequence accuracy.



(a) Element accuracy on training.

(b) Element accuracy on validation.

Figure 3: Training and validation graph of element accuracy.

Reconstruction Results. As shown in Fig. 2 and Fig. 3, both sequential accuracy and element accuracy give high reconstruction quality, except the fact that the validation reconstruction only

Table 1: Performance evaluation of **PlogP**. Types of methods are indicated by deep reinforcement learning (DRL), deep embedding optimization (DEO), genetic algorithm (GA), and offline reinforcement learning (Off-RL).

Methods	Type	Objective	Num Online shot
GVAE+BO [9]	DEO	2.87	∞
SD-VAE [10]	DEO	3.50	∞
ORGAN [11]	DRL	3.52	∞
VAE+CBO [12]	DEO	4.01	∞
ChemGE [13]	GA	4.53	∞
CVAE+BO [14]	DEO	4.85	∞
JT-VAE [15]	DEO	4.90	∞
ChemTS [16]	DRL	5.60	∞
GCPN [17]	DRL	7.86	∞
MRNN [18]	DRL	8.63	∞
MolDQN [19]	DRL	11.84	∞
GraphAF [20]	DRL	12.23	∞
GB-GA [21]	GA	15.76	∞
DA-GA [22]	GA	20.72	∞
MSO [23]	DEO	26.1	∞
PGFS [24]	DRL	27.22	∞
GEGL [5]	DRL	31.40	∞
R-cond-policy-offline (ours)	Off-RL	20.10*	0
R-cond-policy-online (ours)	DRL	**77.12**	4,000

reaches about 0.5. Increasing the reconstruction accuracy is a crucial challenge for the molecule generation community, not only for the molecule optimization community; improving reconstruction accuracy may improve optimization quality also. We leave it for further research; next section, we show our framework can compete with the state-of-the-art, even though we use a poor auto-encoder model.

3.2 Performance Evaluation on *Water-solubility*

This section measures *panalized octanol-water partition coefficient* (**PlogP**) as an evaluation metric. The **PlogP** is the most widely used metric for *de novo* molecular optimization. However, several works [7, 8] have pointed out that the **PlogP** metric is ill-defined as a molecule scoring function; this metric assign a high score for **unrealistic** molecules which is unstable.

In this work, we show that the proposed method can make state-of-the-art results on **PlogP** task, only using few shot online adaptation. We compare with several online baselines where the scores are measured without considering sample efficiency (see Table 1).

Furthermore, our framework can avoid generating **unrealistic** molecules as it can control generation quality using input query of reward-conditioned policy $p(\boldsymbol{x}|\boldsymbol{R})$. Specifically, we can adjust $\boldsymbol{R}$ to get enough score **realistic** molecules to contrast with the existing online search method that just aims to maximize the score (We will experiment with this until final reports).

4 Future Direction

1. Ablation Studies.
2. Evaluating performance on various chemical metrics.
3. Evaluating sample efficiency of the offline dataset.

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