Goal directed molecule generation using Monte Carlo Tree Search

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Abstract
One challenging and essential task in biochemistry is the generation of novel molecules with desired properties. Novel molecule generation remains a challenge since the molecule space is difficult to navigate through, and the generated molecules should obey the rules of chemical valency. Through this work, we propose a novel method, which we call unitMCTS, to perform molecule generation by making a unit change to the molecule at every step using Monte Carlo Tree Search. We show that this method outperforms the recently published techniques on benchmark molecular optimization tasks such as QED and penalized logP. We also demonstrate the usefulness of this method in improving molecule properties while being similar to the starting molecule. Given that there is no learning involved, our method finds desired molecules within a shorter amount of time.

1 Introduction
One of the fundamental problems in chemistry is the design of novel molecules with specific properties. Molecule generation is essential for drug design and material science. Nevertheless, the task remains a difficult one due to the vastness of the chemical space. It is estimated that the number of drug-like molecules is around $10^{23} \to 10^{60}$ [Polishchuk et al., 2013]. Also, the chemical space is discrete with high sensitivity of properties to molecular structure. Hence, there is an increasing need for efficient models focussed on specific applications that guide molecule generation.

In recent years, various ML approaches have been deployed in molecular design. Generally, molecules are represented as SMILES strings [Gómez-Bombarelli et al., 2016, Blaschke et al., 2018] (a linear string notation), fed as input to the model. One of the primary challenges with the SMILES notation is to ensure the validity of generated strings since the generated strings may or may not correspond to a molecule. A better way of representing molecules is with molecular graphs where a node represents an atom, and an edge represents a bond. This method’s advantage is the stepwise generation of molecular graphs [Li et al., 2018], which is valid at every step. One common strategy for molecular graph generation is using a generative model such as Generative Adversarial Network or Variational Auto Encoder. Although generative models seem a viable option for generation, these models cannot optimize for a particular property. Hence, an additional step is usually employed that involves optimization in the latent space of the model using a property-oriented decoder [Samanta et al., 2019], Particle Swarm Optimization [Winter et al., 2019], or Bayesian Optimization [Jin et al., 2018]. Non-convexity and high dimensionality of the latent space usually render the task of optimization...
highly difficult. A second strategy is based on reinforcement learning, which involves an agent that interacts with the environment to learn and make decisions that maximize the cumulative reward. Again, the featurization of molecules here can be done with SMILES representation. Using RL techniques with SMILES representation [Guimaraes et al., 2018; Olivecrona et al., 2017] struggle in generating valid molecules. However, search-based techniques such as MCTS with SMILES can help maintain chemical validity [Yang et al., 2017] by removing invalid SMILES strings. Using molecular graphs representation with RL provides 100% validity [You et al., 2018]. However, all of the methods mentioned above involves the use of a dataset. Zhou et al. [Zhou et al., 2019] pursued a different approach by constructing a Markov Decision Process with unit modification to a molecule as actions and used DQN to approximate the molecules’ value. Molecules are represented using fingerprints, and this method learns to generate molecules without the help of a dataset. Gottipati et al. [Gottipati et al., 2020] propose multiple modifications to an existing molecule at every step. This method constitutes an MDP with valid reactions as possible actions, while reactants and products are the states. We follow the MDP structure defined by Zhou et al. [Zhou et al., 2019]; however, we do not allow bridge atoms so that the generated molecules look feasible.

2 Markov Decision Process

We define the generation process for our method using the MDP $M = (S, A, R, P)$ which is defined as follows.

State space, $S$ consists of all valid molecules, $s \in S$. At $t = 0$, $s_0$ begins with nothing or a specific molecule (for constrained optimization), and at every step, the molecule is modified. The number of steps allowed from the starting state is limited according to the task at hand.

Action space, $A$ consists of all possible modifications that can be performed on a molecule. Given any molecule, all modifications that can be applied to it falls under one of four categories;

- Atom addition - Let $K$ be the set of atoms that are allowed for addition. For any given molecule $M$, all atoms in set $K$ are added to molecule $M$ at every location that results in a chemically valid bond. These additions result in several possible new molecules.
- Bond addition - Any two atoms $a$ and $b$ that allow for a valid addition of bond in molecule $M$ is included in this list of molecules
- Bond removal - Any two atoms $a$ and $b$ connected by a bond in Molecule $M$ can be removed and included in this list of molecules.
- Bond replacement - Any two atoms $a$ and $b$ connected by a bond can be replaced with another bond subject to valency conditions. All valid replacements are included in this list of molecules.

Atom removal is not included here since when an atom becomes disconnected from a molecule, it is automatically removed. Together all these modifications correspond to actions that can be performed on the existing molecule $M$. We do not allow modifications that introduce bridge atoms in the molecule.

Reward, $R$ associated with the generated molecule is used as feedback. We do not reward the system at every step. After each episode, properties associated with the final generated molecule are used to update the nodes’ value.

Transition probability, $P$ - Since the MDP is deterministic, each action can correspond to a single new state. Hence, the probability of reaching that state is one while all other states are zero.

3 Proposed method

In a regular tree search, one evaluates a node, its descendants, and so on until a final solution is obtained. However, this brute force search is not efficient for tasks that exponentially increase the number of nodes as we go further down the tree. One such example that has a vast number of possibilities is the game of Go. However, humans have achieved a state of the art performance
MCTS makes the tree search faster by arriving at a policy that gives more importance to favorable descendants while lesser importance to others. This way, only a minimal number of nodes are explored in order to obtain the optimal solution.

Monte Carlo Tree Search consists of four steps, which are repeated for a certain number of times. The four steps are:

- **Selection** - This step involves selecting a node that favors both exploration and exploitation among all descendants of a parent. The strategy used to select the node is called tree policy and is defined in Equation (1).
- **Expansion** - Once we reach the tree’s leaf node, possible future states of the node are added to the tree, thus expanding it.
- **Simulation** - After a new node is added, a simulation is performed for a specified rollout depth using a simple rollout policy.
- **Backpropagation** - The resulting state’s value is then used to update \( V \) and \( n \) of nodes in the selected path of the tree.

\[
\text{child} = \arg\max_i \frac{V_i}{n_i} + c\sqrt{\frac{\ln N_i}{n_i}} \tag{1}
\]

where \( V_i \) is the value of the node, \( n_i \) and \( N_i \) are the numbers of times the node, and its parent have been visited, and \( c \) is a hyperparameter that decides the importance of exploration and exploitation.

**Algorithm 1: unitMCTS**

for each mcts step do
  while not leaf do
    Select - Pick a child node based on tree policy in Equation (1)
  end
  Expand - Add top \( k \) children to the tree and initialize the number of visits, \( n \), with one and value, \( V \), with reward obtained by \( \epsilon \)-greedy policy for each new node. Backpropagate value and visits till the root of the tree.
  Simulation - Simulate with rollout policy until rollout depth and pick the final molecule.
  while not root do
    Backpropagate - Scale the reward exponentially using a scaling factor \( \alpha \). Increment \( V \) and \( n \) of the node in the selected path by the scaled reward of molecule and one, respectively. Move to the parent of the node.
  end
end

4 Results & Discussion

Setup - RDKit [Landrum, 2016] is used for the molecule environment. The maximum steps per episode are 38 for all molecular optimization tasks starting from scratch and 20 for constrained optimization tasks, being set similar to Zhou et al. [Zhou et al., 2019] for a fair comparison. unitMCTS uses three atoms, i.e., Carbon, Nitrogen, and Oxygen for molecule generation. We optimize for two metrics, namely Quantitative Estimate of Drug Likeness (QED) and Penalized logP. QED is a weighted sum of a molecule’s fundamental properties, such as its solubility, molecular weight, etc. It has a bounded range of \([0, 1]\). Penalized logP is the logarithm of the partition ratio of solute between octanol and water subtracted by synthetic accessibility score and long cycles. It has a range of \((-\infty, \infty)\).

Baselines - We compare our method with the following baselines. JTVAE [Jin et al., 2018] uses a graph representation of molecules combined with Variational Auto Encoder for generating molecular graphs and Bayesian Optimization on latent space for optimizing property scores. ORGAN [Guimaraes et al., 2018] follows a text representation of molecules coupled with RL based generation. ChemTS [Yang et al., 2017] uses the Monte Carlo Tree Search for SMILES generation with RNN
Table 1: Top 3 molecules obtained by each method on QED and Penalized logP tasks

| Method                | Penalized logP | QED |
|-----------------------|----------------|-----|
|                       | 1st | 2nd | 3rd | 1st | 2nd | 3rd |
| ORGAN                 | 3.63| 3.49| 3.44| 0.896| 0.824| 0.82 |
| JTV AEE               | 5.3 | 4.93| 4.49| 0.925| 0.911| 0.91 |
| ChemTS                | 6.56| 6.43| 6.34| —    | —    | —    |
| GCPN                  | 7.98| 7.85| 7.8 | 0.948| 0.947| 0.946|
| MolDQN-bootstrap      | 11.84| 11.84| 11.82| 0.948| 0.944| 0.943|
| Ours (unitMCTS)       | 12.63| 12.6 | 12.55| 0.948| 0.948| 0.948|

(a) QED optimization  (b) Penalized logP optimization

Figure 1: Top molecules generated by our method

To evaluate the effectiveness of molecule generation using MCTS, we have evaluated our approach on two standard tasks, namely Property optimization and Constrained optimization.

4.1 Property optimization

This task aims to generate molecules with high QED and Penalized logP scores. Table 1 summarizes the property optimization results obtained by our method compared to other approaches. Our method outperforms all the baselines with an average improvement of 60% over GCPN and 6% over MolDQN-bootstrap on the Penalized logP task. Our method outperforms the baselines on the QED task as well. All of our generated molecules for both QED and Penalized logP tasks look realistic and are displayed in Figure 1. Given that only valid molecules are added to the tree, our method’s validity is 100%.

4.2 Constrained optimization

In this task, we chose 800 molecules with the lowest Penalized logP scores in the ZINC [Irwin et al., 2012] dataset and performed a search to improve the Penalized logP while maintaining similarity with the starting molecule at various thresholds. Table 2 summarizes the performance of our method compared to the baselines. Our method outperforms the baselines at all thresholds. The tree expansion for this task is slightly different from the above tasks since only the top $k$ molecules that pass the similarity check are added to the tree. Hence, the success rate of our method is 100%.
Table 2: Mean and S.D. of Penalized logP improvement in constrained optimization tasks

| δ  | JT-VAE       | GCPN       | MolDQN-bootstrap | Ours (unitMCTS) |
|----|-------------|------------|------------------|-----------------|
| 0.0| 1.91 ± 2.04 | 4.20 ± 1.28| 7.04 ± 1.42      | 9.47 ± 2.38     |
| 0.2| 1.68 ± 1.85 | 4.12 ± 1.19| 5.06 ± 1.79      | 8.21 ± 1.99     |
| 0.4| 0.84 ± 1.45 | 2.49 ± 1.30| 3.37 ± 1.62      | 6.21 ± 1.15     |
| 0.6| 0.21 ± 0.71 | 0.79 ± 0.63| 1.86 ± 1.21      | 3.44 ± 1.80     |

5 Future work

Our work primarily deals with unit modification to a molecule at every step. Hence, we have not compared our method with techniques [Gottipati et al., 2020] [Winter et al., 2019] that perform multiple modifications starting from an existing molecule. The generated molecules from these methods require more than 38 steps with unit changes. Our future work in this area is to propose MolMCTS that adds molecules at every step, similar to MDP proposed by [Gottipati et al., 2020].

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