Guiding Deep Molecular Optimization With Genetic Exploration

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Overview

- Mission
- Introduction
- Related Work
- Solution (P1, P2, P3)
- Experiments (P1, P2, P3)
- Conclusion & Broader Impacts
- Discussion
Mission:
Focus on improving “de novo” molecular design
The ability to create new molecular structures from scratch for useful application (Drug discovery, material design, etc)
Molecules are unpredictable in nature due to mutations and crossovers.
QUESTION

How can we control nature?
Introduction

- **Deep Neural Networks (DNNs)**
  - demonstrated successful results for solving de novo molecular design

- Other related works focus on the problem of drug design creation

**The question:**

- As there are new frontiers with DNNs with optimizing the outcomes of the desired molecular structure

- How can we validate the molecular structure for its desired outcome?
Related Work

Other technology explored

• Deep Reinforcement Learning:
  • Model Adaptation = Reward of desired outcomes
  • Applications: Protein Structure Design, Biological Sequences

• Deep Embedding Optimization:
  • Having neural networks learn from characteristics (Embeddings) from DNNs and apply them on a universal stand
  • Applications: Particle Swarm Optimization, Bayesian Optimizations

• Genetic Algorithms:
  • Search over molecular space, looking over mutations and crossover (Evolution based)
  • Applications: Optimization problems
Solution

Genetic Expert Guided Learning (GEGL)

• Deep Reinforcement Learning Framework

• Premise:

  • To award the Desired outcome of the molecular design

  • From the initial (Apprentice) stage to the final (expert) stage

• 3 steps:

  • 1.) Apprentice stage: the DNN takes in the molecules with a given space and compares

  • 2.) Expert Policy: Checks the queue to match what the desired molecule is in a given space

  • 3.) The parameters are optimized in the apprentice stage to obtained the desired outcome

Figure 1: Illustration of the proposed genetic expert-guided learning (GEGL) framework.
Solution (P2)

Genetic Expert Guided Learning (GEGL)

Deep Reinforcement Learning Framework

- $x$  
  A given molecule
- $r(x)$  
  The desired reward molecule
- $\Theta$  
  The DNN’s Parameters (able to adjust within a space
- $Q$  
  Queue
- $Q_{ex}$  
  The Expert Queue
- $Q_{app} \cup Q_{ex}$  
  The Union of Apprentice Queue and Expert Queue
- $\pi(x; \Theta)$  
  The neural apprentice policy
- $\pi_{ex}(x; Q)$  
  The expert apprentice policy
- $K$  
  Constant representing size
- $\sum_{x \in Q_{app} \cup Q_{ex}} \ log \pi(x; \Theta)$  
  The sum of all policies the molecule endured for the desired max output
Solution (P3)

Genetic Expert Guided Learning (GEGL)

• Deep Learning Framework:

• Set at initial stage (with each instance of time)

• As there are more samples

• Queue is being updated with each policy, checking for desired output

• While new samples are generated, the queue will be updated for each molecule

• While the expert queue is being updated for the size, being less than the minimal reward function

• The algorithm ends when all policies have been met with the desired matches from the apprentice queue

Algorithm 1 Genetic expert-guided learning (GEGL)

1: Set \( Q \leftarrow \emptyset, Q_{ex} \leftarrow \emptyset \). \( \triangleright \) Initialize the max-reward priority queues \( Q \) and \( Q_{ex} \).
2: for \( t = 1, \ldots, T \) do
3:     for \( m = 1, \ldots, M \) do
4:         Update \( Q \leftarrow Q \cup \{ x \} \), where \( x \sim \pi(\cdot; \theta) \).
5:         If \( |Q| > K \), update \( Q \leftarrow Q \setminus \{ x_{\text{min}} \} \), where \( x_{\text{min}} = \arg \min_{x \in Q} \tau(x) \).
6:     end for
7:     for \( m = 1, \ldots, M \) do \( \triangleright \) Step B: add \( M \) samples generated by \( \pi_{\text{ex}} \) into \( Q_{ex} \).
8:         Update \( Q_{ex} \leftarrow Q_{ex} \cup \{ x \} \), where \( x \sim \pi_{\text{ex}}(\cdot; Q) \).
9:         If \( |Q_{ex}| > K \), update \( Q_{ex} \leftarrow Q_{ex} \setminus \{ x_{\text{min}} \} \), where \( x_{\text{min}} = \arg \min_{x \in Q_{ex}} \tau(x) \).
10:    end for
11:    Maximize \( \sum_{x \in Q \cup Q_{ex}} \log \pi(x; \theta) \) over \( \theta \). \( \triangleright \) Step C: train \( \pi \) with imitation learning.
12: end for
13: Report \( Q \cup Q_{ex} \) as the output. \( \triangleright \) Output the highly-rewarding molecules.
Algorithm 1 Genetic expert-guided learning (GEGL)

1: Set $\mathcal{Q} \leftarrow \emptyset$, $\mathcal{Q}_{\text{ex}} \leftarrow \emptyset$. \quad \triangleright Initialize the max-reward priority queues $\mathcal{Q}$ and $\mathcal{Q}_{\text{ex}}$.
2: for $t = 1, \ldots, T$ do
3: \hspace{1em} for $m = 1, \ldots, M$ do \quad \triangleright Step A: add $M$ samples generated by $\pi$ into $\mathcal{Q}$.
4: \hspace{2em} Update $\mathcal{Q} \leftarrow \mathcal{Q} \cup \{\mathbf{x}\}$, where $\mathbf{x} \sim \pi(\mathbf{x}; \theta)$.
5: \hspace{2em} If $|\mathcal{Q}| > K$, update $\mathcal{Q} \leftarrow \mathcal{Q} \setminus \{\mathbf{x}_{\text{min}}\}$, where $\mathbf{x}_{\text{min}} = \arg \min_{\mathbf{x} \in \mathcal{Q}} r(\mathbf{x})$.
6: \hspace{1em} end for
7: \hspace{1em} for $m = 1, \ldots, M$ do \quad \triangleright Step B: add $M$ samples generated by $\pi_{\text{ex}}$ into $\mathcal{Q}_{\text{ex}}$.
8: \hspace{2em} Update $\mathcal{Q}_{\text{ex}} \leftarrow \mathcal{Q}_{\text{ex}} \cup \{\mathbf{x}\}$, where $\mathbf{x} \sim \pi_{\text{ex}}(\mathbf{x}; \mathcal{Q})$.
9: \hspace{2em} If $|\mathcal{Q}_{\text{ex}}| > K$, update $\mathcal{Q}_{\text{ex}} \leftarrow \mathcal{Q}_{\text{ex}} \setminus \{\mathbf{x}_{\text{min}}\}$, where $\mathbf{x}_{\text{min}} = \arg \min_{\mathbf{x} \in \mathcal{Q}_{\text{ex}}} r(\mathbf{x})$.
10: \hspace{1em} end for
11: Maximize $\sum_{\mathbf{x} \in \mathcal{Q} \cup \mathcal{Q}_{\text{ex}}} \log \pi(\mathbf{x}; \theta)$ over $\theta$. \quad \triangleright Step C: train $\pi$ with imitation learning.
12: end for
13: Report $\mathcal{Q} \cup \mathcal{Q}_{\text{ex}}$ as the output. \quad \triangleright Output the highly-rewarding molecules.
Experiment (P1)

Overview of

• Comparison study of GEGL

• Algorithms of DRL, DEO, DSL, and GA

• penalized log $p$ = testing ground for molecule optimization models

• Penalized log $p = \log P(x) - \text{SynthehticAccessiblity}(x) - \text{RingPenalty}(x)$

• Comparison of 8,192 molecules—unrealistic results

• Penalized log $p$ vs. Penalized log $p$ with similarity constraints
### (a) PenalizedLogP

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<td>GEGL† (Ours)</td>
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### (b) Similarity-constrained PenalizedLogP

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Experiment (P2)

GuacaMol Benchmark

- Designed as a benchmark performance of de novo molecular design and various tasks
- Appendix E
- Luckily, with the benchmark GEGL achieves the highest score when comparing different algorithms
- 19/20 tasks of recognizing different de Novo Molecules
- Ranolazine MPO, Sitagliptin MP, and Zaleplon MPO tasks
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Experiment (P3)

Ablation studies

• Comparison study of GEGL
• Focus on max-reward priority queue
• Same types of tasks from the GuacAMl benchmark
• Compare the benchmarks of the GuacMolScores relative to the apprentice queue and the union of the two queue

\[ \text{GuacamolScore}(Q) / \text{GuacaMolScore}(Q \cup Q_{ex}) \]
Figure 6: Illustration of ablation studies for (a, b) investigating contribution from DNN and genetic operator, and (c, d) separate evaluation of max-reward priority queues.
Conclusion & Broader Impacts

• The team created a new framework of DNNs to solve the design problem of molecular structures

• Optimization for a DRL framework for molecular design

• The algorithm is expected to perform well for domains of genetic algorithms

• Helping to design desire outcomes of “designer drugs”

• Relative to crossovers & Mutations
Thank you
Further Reading

Schrödinger
What is Life?

The Code Breaker
Jennifer Doudna, Gene Editing, and the Future of the Human Race
Walter Isaacson
Discussion

1. What are your thoughts on creating new drug designs?

2. Based on the team’s efforts what are some suggestions to improve?

3. What are some future directions you would suggest or think of?