Deep Generative Model for
De Novo Drug Design

2019/11/14
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Drug discovery

Flow chart of drug discovery process

- Compound library is used to screen hit compound.
- Good hit compound reduces time and money.
- **Diverse** and **high-quality** compound library is needed.
Chemical space is vast, and only a tiny fraction was collected as compound libraries.

Construction of virtual library

- Building block
  
- Genetic algorithm
  
- Reaction-based rule

References:

Deep generative model

- Generative model generates realistic data from feature of data.

→ Drug-like molecules can be generated by generative model learning features of biologically-active compounds.
1. Deep learning methods in drug design
   - RNN
   - RNN with RL (ReLeaSE)
   - VAE
   - Graph / GAN (MolGAN)

2. Application in drug discovery (GENTRL)

3. Summary
Examples of SMILES representation

- **Caffeine**: CN1c2ncn(C)c2C(=O)N(C)C1=O
- **Ibuprofen**: CC(C)Cc1ccc(cc1)C(C)C(O)=O
- **Morphine**: [H][C@]12C=C[C@H](O)[C@@H]3Oc4c5c(C[C@H]1N(C)CC[C@@@]235)ccc4O

De novo drug design by RNN

- **Generation of sentence**
  - Input: Chemistry is ...
  - Output:
    - Chemistry is “important”
    - Chemistry is “fascinating”
    - Chemistry is “potato”
    - Chemistry is “runs”
  - Learn English grammar

- **Generation of chemical structure**
  - Input: c (SMILES)
  - Output: c1cccccc1

De novo drug design by RNN

Examples of generated novel molecules

- 976327 molecules were generated.
- 847955 molecules were novel.
- 75% of new molecules were highly scored (“core” or “backup”) by AstraZeneca filter.

De novo design cycle

Scheme

“Synthesis” ... molecule generation
“Virtual Assay” ... best molecule selection by machine learning
“Design” ... retraining RNN model by best molecules

6% of known active molecules were re-generated.

De novo drug design by RNN

RNN

Data 541555 bioactive molecules

Fine-tune 25 molecules with known agonistic activity on RXR (retinoid X receptor) and/or PPAR (peroxisome proliferator-activated receptor)

Result 1000 molecules (90% were valid and novel)

5 molecules were synthesized and tested in vitro.

G. Schneider et al., Mol. Inf., 2018, 37, 1700153.
De novo drug design by RNN

Synthesized novel molecules and these bioactivity

<table>
<thead>
<tr>
<th>Compound no.</th>
<th>RXRα</th>
<th>RXRβ</th>
<th>RXRγ</th>
<th>PPARα</th>
<th>PPARγ</th>
<th>PPARδ</th>
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<tbody>
<tr>
<td>1</td>
<td>0.13 ± 0.01</td>
<td>1.1 ± 0.3</td>
<td>0.06 ± 0.02</td>
<td>inactive</td>
<td>2.3 ± 0.2</td>
<td>inactive</td>
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<tr>
<td>2</td>
<td>13.0 ± 0.1</td>
<td>9 ± 2</td>
<td>8.0 ± 0.7</td>
<td>inactive</td>
<td>2.8 ± 0.3</td>
<td>inactive</td>
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<tr>
<td>3</td>
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<td>inactive</td>
<td>inactive</td>
<td>4.0 ± 1.0</td>
<td>10.1 ± 0.3</td>
<td>inactive</td>
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<tr>
<td>4</td>
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<td>inactive</td>
<td>inactive</td>
<td>inactive</td>
<td>9 ± 3</td>
<td>14 ± 2</td>
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<tr>
<td>5</td>
<td>inactive</td>
<td>inactive</td>
<td>inactive</td>
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<tr>
<td>reference agonists a)</td>
<td>0.033 ± 0.002</td>
<td>0.024 ± 0.004</td>
<td>0.025 ± 0.002</td>
<td>0.006 ± 0.002</td>
<td>0.6 ± 0.1</td>
<td>0.5 ± 0.1</td>
</tr>
</tbody>
</table>

a) Reference agonists, literature data: bexarotene\textsuperscript{[17]} for RXRs, GW7647\textsuperscript{[16]} for PPARα, pioglitazone\textsuperscript{[19]} for PPARγ, L165,041\textsuperscript{[19]} for PPARδ

G. Schneider et al., Mol. Inf., 2018, 37, 1700153.
De novo drug design by RNN

Pros

- Diverse set of molecules could be generated.
- Generated molecules had drug-like properties.

Cons

- Chemical space was restricted by training set.
- Properties of generated molecules couldn’t be controlled.

Reinforcement Learning (RL)
Reinforcement Learning (RL)

Scheme of Reinforcement Learning

- Agent
- Reward
- Action
- Environment
- State

Application

AlphaGo
De novo drug design by RL

Scheme of “ReLeaSE”

## De novo drug design by RL

### Target Properties
- **Tm** (Melting point)
- **logP** (n-octanol / water partition coefficient)
- **pIC$_{50}$** for **JAK2** (Janus protein kinase 2)

### Distribution of predicted properties

De novo drug design by RL

Analysis of generated molecules

<table>
<thead>
<tr>
<th>Property</th>
<th>Valid molecules (%)</th>
<th>Mean SAS</th>
<th>Mean molar mass</th>
<th>Mean value of target property</th>
</tr>
</thead>
<tbody>
<tr>
<td>$T_m$</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Baseline</td>
<td>95</td>
<td>3.1</td>
<td>435.4</td>
<td>181</td>
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<tr>
<td>Minimized</td>
<td>31</td>
<td>3.1</td>
<td>279.6</td>
<td>137</td>
</tr>
<tr>
<td>Maximized</td>
<td>53</td>
<td>3.4</td>
<td>413.2</td>
<td>200</td>
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<tr>
<td>Inhibition of JAK2</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Baseline</td>
<td>95</td>
<td>3.1</td>
<td>435.4</td>
<td>5.70</td>
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<tr>
<td>Minimized</td>
<td>60</td>
<td>3.85</td>
<td>481.8</td>
<td>4.89</td>
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<tr>
<td>Maximized</td>
<td>45</td>
<td>3.7</td>
<td>275.4</td>
<td>7.85</td>
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<tr>
<td>LogP</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Baseline</td>
<td>95</td>
<td>3.1</td>
<td>435.4</td>
<td>3.63</td>
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<tr>
<td>Range-optimized</td>
<td>70</td>
<td>3.2</td>
<td>369.7</td>
<td>2.58</td>
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</tbody>
</table>

(SAS = synthetic accessibility score)

With reinforcement learning, the proportion of valid molecules was lowered.

De novo drug design by VAE

Variational Autoencoder jointly-trained on properties

Continuous variable representation for:
- Interpolation
- Optimization
- Exploration

SMILES Encoder Latent Space Decoder SMILES

Generated

Encoder and Decoder

1. VAE learns about characteristic feature of a training set.
2. Similar molecules were mapped close together in latent space.

VAE was jointly trained with Predictor.

7,500,000 molecules were generated from 250,000 samples.

De novo drug design by VAE

- VAE optimized \((5 \times \text{QED} - \ast \text{SAS})\).
  
  \((\text{QED} = \text{Qualitative Estimate of Drug-likeness}, \text{SAS} = \text{Synthetic Accessibility Score})\)

- Molecular optimization was achieved efficiently by gradient-based search.

Problems of SMILES representation

- SMILES is not designed to capture molecular similarity.

  ![Chemical structures and SMILES representations]

  
  Cc1cn(CN(C)C(=O)c3ccc(F)cc3C)c(C)c(C)nc2s1  
  Cc1cc(F)ccc1C(=O)N(C)Cc1c(C)nc2scC(c)n12

- SMILES is not robust to small molecules.

  ![Chemical structures and SMILES representations]

  
  CN1c2ncn(C)c2C(=O)N(C)C1=O  
  CN1c2ncn(C)c2C(=O)N(C)C=O
MolGAN

Scheme of MolGAN

Generate new molecules

Predict properties

Judge valid or invalid

arXiv:1805.11973
Graph representation

Chemical Structure

Molecular Graph

- **Graph** ... collection of **nodes** and **edges**

- Machine learning model **don’t have to learn rules** of molecular representations.
Graph convolution

- New vector = self + adjacent vector
  
  → New vector includes the information of the surrounding environment.

GAN

Scheme of Generative Adversarial Network (GAN)

Manufacture of counterfeit money vs Police
GAN

https://arxiv.org/abs/1809.11096

BW to Color

https://arxiv.org/abs/1611.07004

Edges to Photo

https://arxiv.org/abs/1611.07004
GAN

Scheme of Generative Adversarial Network (GAN)

**Generator** : generate molecules similar to training set

**Discriminator** : discriminate generated molecules from training set

arXiv:1805.11973
Reward network

Scheme of Reinforcement Learning (RL)

Reward: Valid, Drug-likeness, Synthesizability, Solubility

Generated molecules or Training set?

arXiv:1805.11973
## Performance of MolGAN

### Results

<table>
<thead>
<tr>
<th>Objective</th>
<th>Algorithm</th>
<th>Valid (%)</th>
<th>Unique (%)</th>
<th>Druglikeness</th>
<th>Synthesizability</th>
<th>Solubility</th>
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</thead>
<tbody>
<tr>
<td>Druglikeness</td>
<td>ORGAN</td>
<td>88.2</td>
<td>69.4</td>
<td>0.52</td>
<td></td>
<td></td>
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<tr>
<td></td>
<td>Naive RL</td>
<td>97.1</td>
<td>97.1</td>
<td>0.57</td>
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<td></td>
<td><strong>MolGAN</strong></td>
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<td><strong>2.0</strong></td>
<td><strong>0.61</strong></td>
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<td>Synthesizability</td>
<td>ORGAN</td>
<td>96.5</td>
<td>45.9</td>
<td></td>
<td>0.83</td>
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<td>Naive RL</td>
<td>97.7</td>
<td>13.6</td>
<td></td>
<td>0.83</td>
<td></td>
</tr>
<tr>
<td></td>
<td><strong>MolGAN</strong></td>
<td><strong>99.4</strong></td>
<td><strong>2.1</strong></td>
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<td><strong>0.95</strong></td>
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<tr>
<td>Solubility</td>
<td>ORGAN</td>
<td>94.7</td>
<td>54.3</td>
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<td></td>
<td>Naive RL</td>
<td>92.7</td>
<td>100.0</td>
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<td>0.78</td>
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<td><strong>MolGAN</strong></td>
<td><strong>99.8</strong></td>
<td><strong>2.3</strong></td>
<td></td>
<td><strong>0.89</strong></td>
<td></td>
</tr>
<tr>
<td>All</td>
<td>ORGAN</td>
<td>96.1</td>
<td>97.2</td>
<td>0.52</td>
<td>0.71</td>
<td>0.53</td>
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<tr>
<td></td>
<td><strong>MolGAN</strong></td>
<td><strong>97.4</strong></td>
<td><strong>2.4</strong></td>
<td><strong>0.47</strong></td>
<td><strong>0.84</strong></td>
<td><strong>0.65</strong></td>
</tr>
</tbody>
</table>

ORGAN (SMILES instead of graph), Naïve RL (without GAN)

- MolGAN beats other models in terms of optimizing property.
- Unique score of generated molecules was very low.

arXiv:1805.11973
Identification of DDR1 kinase inhibitor by GENTRL

- Day 19 ... 30000 molecules were generated by GENTRL.
- **Day 23** ... 6 molecules were **selected** by prioritization.
- Day 35 ... Synthesis was completed.
- **Day 46** ... Activities of synthesized molecules were confirmed in cell-based assay.

**Creation of chemical space**

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Molecular generation by Reinforcement Learning

Reinforcement Learning
Agent: generator
State: generated molecules
Reward: novelty, kinase inhibition activity, DDR1 inhibition activity
SOM: predict properties of molecules

Selected molecules and inhibitory activity in vitro and vivo

Chemical Space
- Chemical space is vast (~10^60) compared to compound library size (~10^6, 10^8).
- Generative model can generate 10^3 ~ 10^5 drug-like compounds.
- Generative model can control properties of generated molecules by RL.
- The role of generative model is to capture the underlying rules of a data distribution.
- Generative model only reconstruct the training data set.

Molecular representation
- SMILES is not robust to small changes or mistakes.
- By using graph representations, generative model don’t need to learn complex syntax, but this method is not perfect.
- There is still a need for research on the optimal molecular representation.
  - Junction Tree (arXiv:1802.04364)
  - 3D (arXiv:1810.11347)
Summary

Evaluation of Model

- The performance of each generative model is evaluated by different methods.
  - Number of generated molecules
  - Distribution on 2D map.
  - Properties of generated molecules.
  - Experimental activity.
- Evaluation method of model is needed.
- Several benchmarks are being developed. (J. Chem. Inf. Model, 2019, 59, 1096)

Application in drug discovery

- The generated molecules must be reduced to the number that can be synthesized.
- The generated molecules are necessarily synthesizable.
- SAS (synthetic accessibility score) may prevent generation of molecular diversity.
- Generative model may prove valuable in combination with retrosynthesis AI or virtual screening AI.
AZ filter

Class 1: bland structures
  - Fewer than 4 carbon atoms etc.
Class 2: reactive structures
  - Anhydride etc.
Class 3: frequent hitters
  - Nitrophenols etc.
Class 4: dye-like structures
Class 5: unlike drug candidates or unsuitable fragments
Class 6: difficult series or natural compounds
Class 7: general ugly halogenated structures
Class 8: general ugly oxygen
Class 9: general ugly nitrogen
Class 10: general ugly sulphur