De Novo molecular design with Deep Reinforcement Learning

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About me

Ph.D. in Chemistry (computational)

Minor in CS/ML

Worked in Federal research lab on HPC & GPU computing to solve chemical problems

Now I am faculty at the University of North Carolina, Chapel Hill

We use ML & AI to solve challenging problems in chemistry

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A public–private partnership that supports the discovery of new medicines through open access research

www.thesgc.org
The Long and Winding Road to Drug Discovery

Data Science approaches useful across the pipeline, but very different techniques aim for success, but if not: fail early, fail cheap.
The graph illustrates the internal rate of return (IRR) for the investment in Pharma R&D over the years 1990 to 2020. The IRR analysis shows a steady decline, indicating that the returns are already below the cost of capital in 2017 and are projected to reach 0% by 2020. The source of this information is Endpoints News (https://endpts.com).

Source: Endpoints News
https://endpts.com
Drowning in Data

...but starving for Knowledge
The growing appreciation of molecular modeling and informatics
“Behold the rise of the machines”
## Summary of recent AI-based studies on chemical library design

<table>
<thead>
<tr>
<th>Molecular representations</th>
<th>Generative models</th>
<th>Method of biasing generated compounds</th>
</tr>
</thead>
<tbody>
<tr>
<td>• Fingerprints</td>
<td>• Autoencoders</td>
<td>• None</td>
</tr>
<tr>
<td>• SMILES</td>
<td>• Generative</td>
<td>• Latent space optimization</td>
</tr>
<tr>
<td>• Graphs</td>
<td>• adversarial</td>
<td>• Fine-tuning on small subset of</td>
</tr>
<tr>
<td></td>
<td>• models (GANs)</td>
<td>molecules with the desired property</td>
</tr>
<tr>
<td></td>
<td>• Recurrent neural</td>
<td>• Reinforcement Learning</td>
</tr>
<tr>
<td></td>
<td>• networks (RNNs)</td>
<td></td>
</tr>
<tr>
<td></td>
<td>• Convolutional</td>
<td></td>
</tr>
<tr>
<td></td>
<td>• neural networks</td>
<td></td>
</tr>
<tr>
<td></td>
<td>(CNNs)</td>
<td></td>
</tr>
</tbody>
</table>
De Novo molecular design with Deep Reinforcement Learning

General Approach

Application to Molecular design

Patent pending

arXiv:1711.10907
Drug discovery pipeline

- Chemical structures
- Chemical descriptors
- Predictive QSAR models
- Property/activity
- QSAR magic
- Virtual screening
- Hits (confirmed actives)
- Inactives (confirmed inactives)

Chemical database

~10^6 – 10^9 molecules
Design of the ReLeaSE* method

Challenges:

• Generate chemically feasible SMILES
• Develop SMILES-based QSAR model
• Employ Predictive ML model to bias library generation

Language of SMILEs

Clc1cc(C(c3ccccc3)=NCC(N2C)=O)c2cc1

A

B

C

D

N1CCN(C(C)=C)=C(F)=C=C(C=C)=O|N=C=C(N3)C=C4O=O
Generative model

1.5M molecules from ChEMBL

RNN: \{W_1^0, ..., W_2^0\}

c1ccc(O)cc1

Did the training converge?

NO

RNN: \{W_1^*, ..., W_2^*\}

YES

RNN: \{W_1^*, ..., W_2^*\}

+ loss

Softmax loss

\texttt{<START>c1ccc(O)cc1<END>}

\texttt{c1ccc(F)cc1<END>}

\texttt{<START>c1ccc(O)cc1}
Reinforcement learning for chemical design

Generative model

\[
0c(cc1cc2)c(c(cCl)c(Cl)c3)cncnc2c1
\]

\[
RNN: \{W_1, ..., W_n\}
\]

\[<\text{START}>\]

Predictive model

\[
RNN = \{\sigma, W_h, W_x\}
\]

\[c1cccccl\]

Reinforcement learning for chemical design

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Generative model

RNN:
\{W_1, ..., W_n\}

<START>

Predictive model

RNN = \{\sigma, W_h, W_x\}

c1cccccl

Reinforcement learning for chemical design

Technical details

• Models were trained on Nvidia Titan X and Titan V GPUs
• Training generative model on ChEMBL took ~ 25 days
• Training predictive models took ~ 2 hours
• Biasing generative model with reinforcement learning for one property ~ 1 day
• Generative model produces 1000s compounds per minute
Results: Biasing target properties in the designed libraries

JAK2 (Kinase) inhibition

**CAS 236-084-2** (buffer reagent)

**ZINC37859566**

**NEW CHEMOTYPE**

**SIMILAR SCAFFOLDS**

**Train data distribution**
**Maximized property distribution**
**Minimized property distribution**

arXiv:1711.10907
Results: analysis of similarity

Distribution of Tanimoto similarity to the nearest neighbor in training dataset for compounds predicted to be active for EGFR by consensus of QSAR models:

- Similarity = 0.57
- Similarity = 0.69
- Similarity = 0.86
Results: Synthetic accessibility score* of the designed libraries

Target predictions for generated compounds using SEA*

<table>
<thead>
<tr>
<th>Query</th>
<th>Target Key</th>
<th>Target Name</th>
<th>Description</th>
<th>P-Value</th>
<th>MaxTC</th>
</tr>
</thead>
<tbody>
<tr>
<td>EGFR_HUMAN+5</td>
<td>EGFR</td>
<td></td>
<td>Epidermal growth factor receptor</td>
<td>8.688e-244</td>
<td>0.61</td>
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<tr>
<td>ERBB2_HUMAN+5</td>
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<td>Receptor tyrosine-protein kinase erbB-2</td>
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<tr>
<td>ERBB2_RAT+5</td>
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<td>5.893e-87</td>
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<tr>
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<td>Vascular endothelial growth factor receptor 2</td>
<td>6.294e-65</td>
<td>0.58</td>
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<tr>
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<td>Receptor tyrosine-protein kinase erbB-4</td>
<td>1.354e-64</td>
<td>0.49</td>
</tr>
</tbody>
</table>

Target predictions for generated compounds using SEA*

<table>
<thead>
<tr>
<th>Query</th>
<th>Target Key</th>
<th>Target Name</th>
<th>Description</th>
<th>P-Value</th>
<th>MaxTC</th>
</tr>
</thead>
<tbody>
<tr>
<td>NPM_HUMAN+5</td>
<td>NPM1</td>
<td>Nucleophosmin</td>
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<td>3.118e-74</td>
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<tr>
<td>CCNH_HUMAN+5</td>
<td>CCNH</td>
<td>Cyclin-H</td>
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<td>2.571e-32</td>
<td>0.38</td>
</tr>
<tr>
<td>PAK1_HUMAN+5</td>
<td>PAK1</td>
<td>Serine/threonine-protein kinase PAK1</td>
<td></td>
<td>5.277e-24</td>
<td>0.39</td>
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<tr>
<td>ALK_HUMAN+5</td>
<td>ALK</td>
<td>ALK tyrosine kinase receptor</td>
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<td>3.714e-23</td>
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<tr>
<td>JAK2_HUMAN+5</td>
<td>JAK2</td>
<td>Tyrosine-protein kinase JAK2</td>
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<td>1.136e-21</td>
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<tr>
<td>INSR_HUMAN+5</td>
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<td>Insulin receptor</td>
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<tr>
<td>CCNB1_HUMAN+5</td>
<td>CCNB1</td>
<td>G2/mitotic-specific cyclin-B1</td>
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<td>2.22e-16</td>
<td>0.38</td>
</tr>
</tbody>
</table>

Model visualization for JAK2 (projection using t-SNE)

Examples of Stack-RNN cells with interpretable gate activations

a) Chemically-sensible neurons

Carbonyl group activation

Aromatic moiety activation

Heterocyclic Nitrogen

b) Syntactic neurons

Symbol after round brackets deactivation

End of molecule

Summary

• AI methods coupled with SMILES representation afford biased libraries generation
• The system naturally embeds reinforcement to produce novel structure with the desired property
• The system can be tuned to bias libraries towards specific property ranges
• Next phase is experimental validation of hits by UNC SGC team