Deep Generative Models for Graphs
VAEs, GANs, and reinforcement learning for de novo drug discovery

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MSc Thesis presentation
The drug design processes

Which problem do we want to solve?

- **Drug design** is the process of finding new drugs

![Diagram showing the drug design process]

- The first step is **Drug Discovery**
  - screening large compound libraries
  - designing of **new unknown molecules** (*de novo*)
Our contributions

How others proposed to study the problem?

- Generating **SMILES** representations [Gómez-Bombarelli et al., 2016]
- Generating **labeled graphs** [Simonovsky and Komodakis, 2018]

How do we study the problem?

- Using **labeled graphs**
- **Likelihood-based vs. likelihood-free** methods (VAE vs. GAN)
- Biasing the process using **reinforcement learning**
Background
Variational Auto-Encoders

Likelihood-based generative process [Kingma and Welling, 2013]

[Hafner, 2018]
Likelihood-free generative process [Goodfellow et al., 2014]

Figure: Schema of GAN architecture.
Models
Vectorial representation of graphs

Figure: The molecule (a) is represented as an labeled graph (b) which can be encoded into an adjacency tensor $A$ and an annotation matrix $X$. 
The reconstruction loss is a sum of two **categorical cross entropy** losses.
Molecular graph GAN

\[ p(z) \xrightarrow{G_\theta} \sim A \xrightarrow{\sim} \tilde{A} \xrightarrow{\sim} \tilde{X} \xrightarrow{D_\phi} 0/1 \]

From generator to discriminator with **differentiable sampling**.
Molecular graph GAN with RL

Figure: Schema of MolGAN from our previous work [De Cao and Kipf, 2018].
Experiments
Experiments

Which questions we would like to answer?

- likelihood-based vs. likelihood-free (VAEs vs. GANs)
- the effect of RL towards chemical objectives
- Is generating a graph better than a SMILES representation?
VAEs train an **encoder**!

**VAE objective:** reconstruction loss and divergence

**RL objective:** sampled molecules should maximize a score

There is a **mismatch between these two!**
Trade-off between WGAN and RL

<table>
<thead>
<tr>
<th>Method</th>
<th>validity</th>
<th>uniqueness</th>
<th>QED</th>
</tr>
</thead>
<tbody>
<tr>
<td>$\lambda = 0.0$ (full RL)</td>
<td>100.00</td>
<td>3.16</td>
<td>0.61</td>
</tr>
<tr>
<td>$\lambda = 0.125$</td>
<td>100.00</td>
<td>7.21</td>
<td>0.61</td>
</tr>
<tr>
<td>$\lambda = 0.25$</td>
<td>99.80</td>
<td>10.16</td>
<td>0.61</td>
</tr>
<tr>
<td>$\lambda = 0.375$</td>
<td>99.90</td>
<td>11.11</td>
<td>0.60</td>
</tr>
<tr>
<td>$\lambda = 0.5$</td>
<td>99.40</td>
<td>31.29</td>
<td>0.56</td>
</tr>
<tr>
<td>$\lambda = 0.625$</td>
<td>97.20</td>
<td>49.69</td>
<td>0.51</td>
</tr>
<tr>
<td>$\lambda = 0.75$</td>
<td>93.70</td>
<td>64.35</td>
<td>0.51</td>
</tr>
<tr>
<td>$\lambda = 0.875$</td>
<td>89.40</td>
<td>69.69</td>
<td>0.50</td>
</tr>
<tr>
<td>$\lambda = 1.0$ (no RL)</td>
<td>90.10</td>
<td>63.91</td>
<td>0.50</td>
</tr>
</tbody>
</table>

Table: WGAN and RL objectives trade-off.
Figure: WGAN matches the data distribution of the synthetic accessibility score.
Figure: WGAN in combination with RL push the distribution of the synthetic accessibility score (SAS) to be as low as possible.
### Comparison with VAE based methods

<table>
<thead>
<tr>
<th>Method</th>
<th>validity</th>
<th>uniqueness</th>
<th>novelty</th>
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</thead>
<tbody>
<tr>
<td>CharacterVAE</td>
<td>10.3</td>
<td>67.5</td>
<td>90.0</td>
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<tr>
<td>GrammarVAE</td>
<td>60.2</td>
<td>9.3</td>
<td>80.9</td>
</tr>
<tr>
<td>GraphVAE</td>
<td>55.7</td>
<td>76.0</td>
<td>61.6</td>
</tr>
<tr>
<td>GraphVAE/imp</td>
<td>56.2</td>
<td>42.0</td>
<td>75.8</td>
</tr>
<tr>
<td>GraphVAE NoGM</td>
<td>81.0</td>
<td>24.1</td>
<td>61.0</td>
</tr>
<tr>
<td>Our VAE</td>
<td>61.5</td>
<td><strong>97.6</strong></td>
<td>69.1</td>
</tr>
<tr>
<td>Our VAE with RL</td>
<td><strong>89.1</strong></td>
<td>11.1</td>
<td><strong>92.3</strong></td>
</tr>
<tr>
<td>Our WGAN</td>
<td><strong>89.2</strong></td>
<td>26.5</td>
<td>55.7</td>
</tr>
<tr>
<td>Our WGAN with RL</td>
<td><strong>99.6</strong></td>
<td>14.5</td>
<td><strong>97.7</strong></td>
</tr>
</tbody>
</table>

Table: Baseline results from GraphVAE [Simonovsky and Komodakis, 2018].
Comparison with a GAN based method

<table>
<thead>
<tr>
<th>Method</th>
<th>validity</th>
<th>SAS</th>
<th>time</th>
</tr>
</thead>
<tbody>
<tr>
<td>ORGAN</td>
<td>96.5</td>
<td>0.83</td>
<td>8.7</td>
</tr>
<tr>
<td>OR(W)GAN</td>
<td>97.6</td>
<td>0.75</td>
<td>9.6</td>
</tr>
<tr>
<td>Naive RL</td>
<td>97.7</td>
<td>0.83</td>
<td>10.6</td>
</tr>
<tr>
<td>Our VAE with RL</td>
<td>89.6</td>
<td>0.71</td>
<td>0.09</td>
</tr>
<tr>
<td>Our VAE with RL (full QM9)</td>
<td>94.0</td>
<td>0.86</td>
<td>2.2</td>
</tr>
<tr>
<td>Our WGAN with RL</td>
<td>100.0</td>
<td>0.70</td>
<td>0.15</td>
</tr>
<tr>
<td>Our WGAN with RL (full QM9)</td>
<td>99.8</td>
<td>0.92</td>
<td>3.3</td>
</tr>
</tbody>
</table>

**Table:** Baseline results from ORGAN [Guimaraes et al., 2017].
Conclusion and future work
Conclusion

Considering experimental, we identify these further contributions:

- recurrent SMILES generation is more computational expensive
- likelihood-based models are difficult to be optimized with RL

... but keeping in mind and these limitations:

- we experimented using compounds of at most 9 atoms
- models are susceptible to mode collapse
Future work

We identify four principal directions for future work:

- address **mode collapse** [Srivastava et al., 2017]
- combine **variational** approaches with **adversarial** learning to benefit from both approaches [Mescheder et al., 2017, Rosca et al., 2017]
- train our models on **ChEMBL** [Gaulton et al., 2011]
- more **realistic reward** functions [Li et al., 2018]


