De Novo Structure-Based Drug Design Using Deep Learning

Authors: Sowmya Ramaswamy Krishnan, Navneet Bung, Sarveswara Rao Vangala, Rajgopal Srinivasan, Gopalakrishnan Bulusu, and Arijit Roy

Present by Yongxian Wu

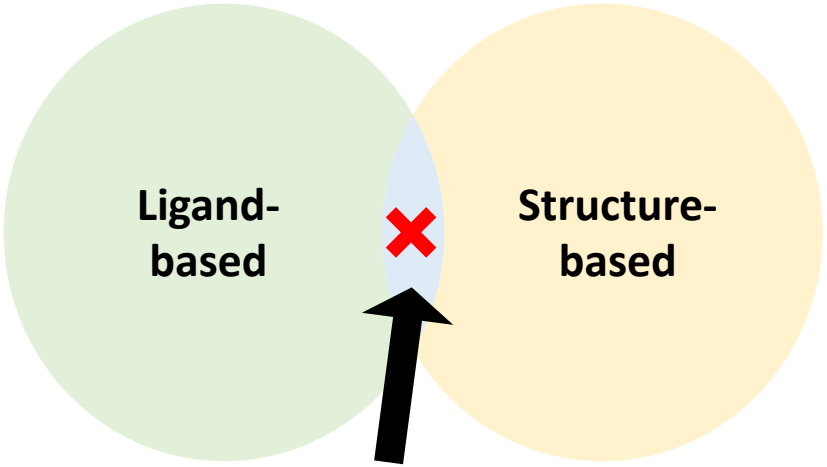
Outline

- Introduction of Drug Design
  - Background
  - Contributions of this paper
- Proposed Methodology
  - Model design
  - Training details
- Experiment Results
  - Generation results
  - Interpretation
- Rethinking and Discussion
  - Limitations on Generalization

Introduction of Drug Design

Ligand-based design:

- General Idea: Based on existed target-molecules data to train a molecule generator. Then apply it to new target.
- Pros:
  - Can provide reliable results
- Cons:
  - Cannot generalize to design drug for novel target



This paper lies in this field

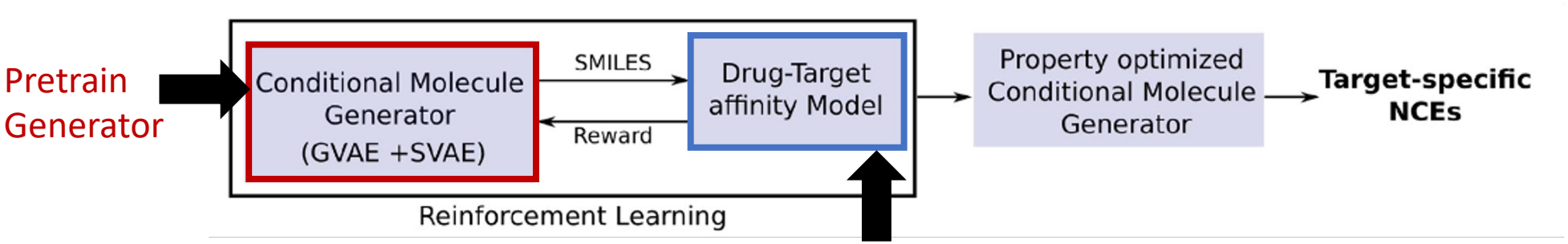
Structure-based design:

- General Idea: Directly capture the structure information to design
- Pros:
  - Structure is easier to be generalize to novel target
- Cons:
  - Should devise useful feature extraction method for structure information

Contributions:

- The first method which proposes to use binding site representation of target protein as structure information
- Get similar and identical design results on two well-studied target proteins: JAK2 and DRD2
- Give some interpretations on useful active sites from the trained deep learning model

Methodology Overview



GVAE:

- Pretrain active site graph VAE $\mathrm{Enc}^a, \mathrm{Dec}^a$
- Combine the structure information of target protein to design molecules
  - Construction of active site graph for target protein
  - Adopt Graphical neural network to capture the interaction between difference active sites

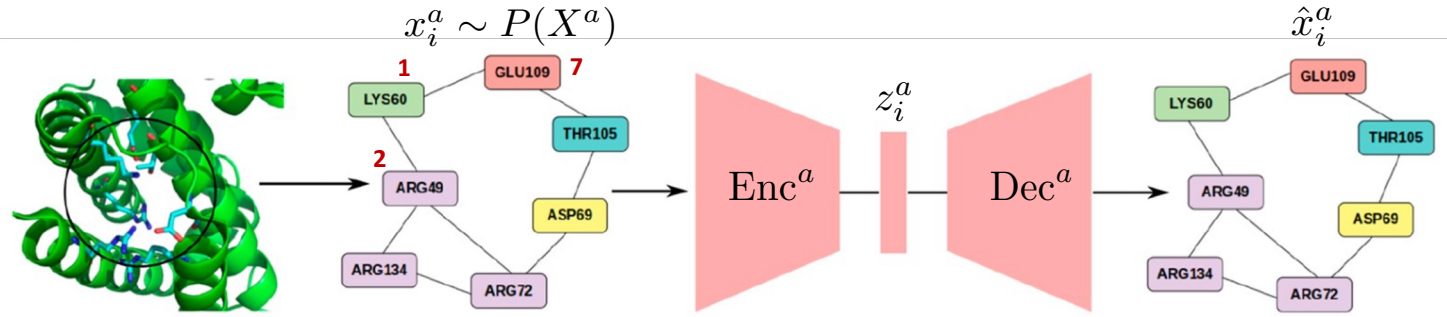
SVAE:

- Pretrain SMILES VAE $\mathrm{Enc}^s, \mathrm{Dec}^s$
- Conditioned on the target structure information, use pretrained molecule language model to generate appropriate drugs
  - Pretrain SMILES language model on the ChEMBL dataset in an unsupervised way
  - Fuse target information to finish conditional generation

Reinforcement Learning :

- Drug-Target affinity Model
- Use pretrain model to maximize conditional generation model
- Boost design performance with reinforcement learning
  - Use a pretrained affinity model as a reward function
  - Train the language model to achieve a high expected reward

Graph VAE

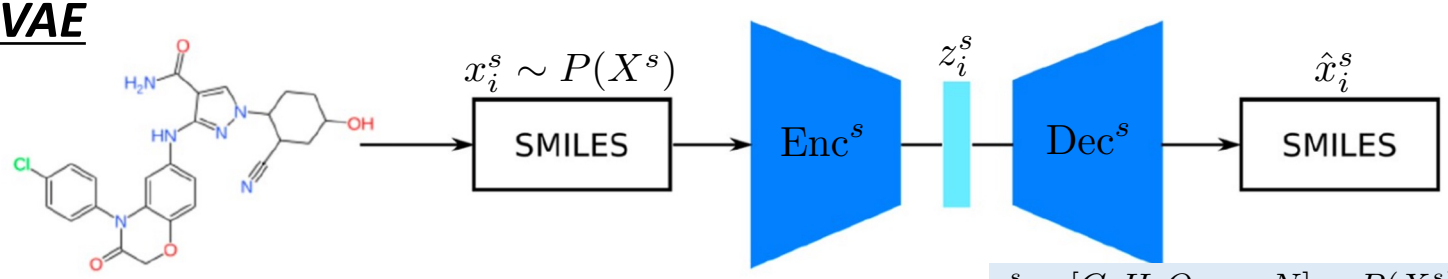


$$\text{Adjacency Matrix} = \begin{bmatrix} 0 & 1 & 0 & 0 & 0 & 0 & 1 \\ 1 & 0 & 1 & 1 & 0 & 0 & 0 \\ 0 & 1 & 0 & 1 & 0 & 0 & 0 \\ & & \cdots & & & & \\ 1 & 0 & 0 & 0 & 0 & 1 & 0 \end{bmatrix}$$

- Construct active site based on the target protein $x_i^a \sim P(X^a)$
  - How to construct? PDBbind and scPDB datasets
  - To consider the **structure information**, they use a **graph-based** neural network to model the **interaction** between different sites
- A Graph VAE is trained to reconstruct the adjacency matrix

$$z_i^a = \text{Enc}^a(x_i^a) \quad \hat{x}_i^a = \text{Dec}^a(z_i^a)$$
$$\mathcal{L} = \sum_i \text{CrossEntropy}(x_i^a, \hat{x}_i^a) + KL(q(z^a|x_i^a)||P(z))$$

Sequence VAE



$$x_i^s = [C, H, O, \ldots, N] \sim P(X^s) \quad P(x_i^s) = \prod_{j=1}^{L} P(x_{i,j}^s | x_{i,1:j-1}^s) P(x_{i,1}^s)$$

- Generating molecular is abstracted as a SMILES **language** generation problem
- Use the ChEMBL dataset, train a sequence generation model in **unsupervised** learning to predict the SMILES.

$$z_i^s = \text{Enc}^s(x_i^s) \quad \hat{x}_i^s = \text{Dec}^s(z_i^s)$$
$$\mathcal{L} = -\sum_i \log P(x_i^s) + KL(q(z^s|x_i^s)||P(z))$$

Decoding Use special token "!" as input, generate new token at time step t by samping from the distribution $P(\hat{x}_{i,t}^s | \hat{x}_{i,1:t-1}^s)$. Samplting methods include top-k or top-p.

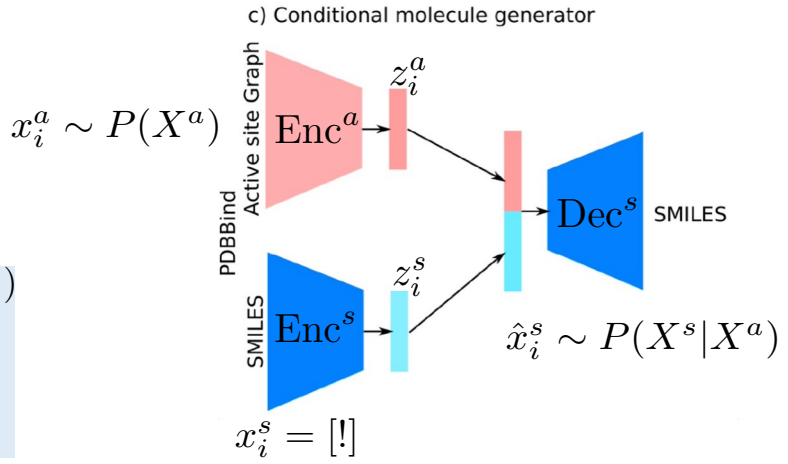
Kingma, Diederik P., and Max Welling. "Auto-encoding variational bayes." *arXiv preprint* arXiv:1312.6114 (**2013**)

Conditional Molecule Generation

- Generate appropriate molecule based on the target activate sites
- Given pairs of active site – molecule
  - PDBbind dataset $(x_i^a, x_i^s)\ \forall i \in [1, P]$
  - Pad the input smiles as special token (e.g. !)
  - Maximize the conditional log-likelihood

$$z_i^a = \mathrm{Enc}^a(x_i^a) \quad z_i^s = \mathrm{Enc}^s(x_i^s)$$
$$\hat{x}_i^s = \mathrm{Dec}^s([z_i^a, z_i^s])$$
$$\mathcal{L} = -\sum_i \log P(x_i^s | x_i^a)$$

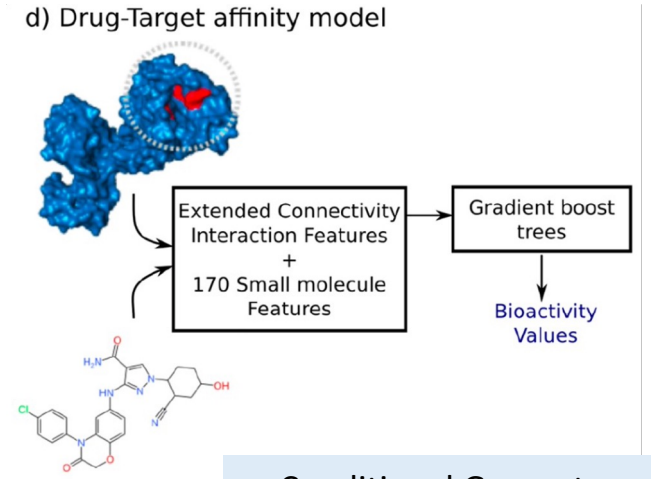
- This trained model is able to generate ligand based on input activate sites



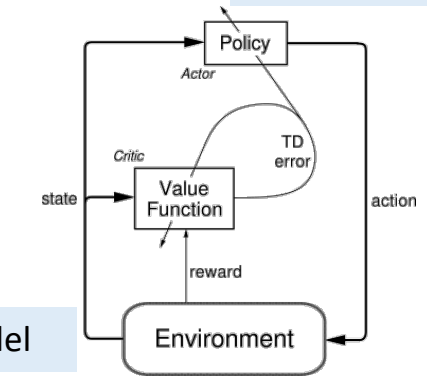
Reinforcement Learning with Drug-Target Affinity Score Model

- Test the bioactivity (Affinity) provided by the generator
  - The bioactivity can be determined through experiment but time consuming and indifferentiable $\mathrm{IC}_{50}, \mathrm{K}_i, \mathrm{K}_d$
    - PDBbind general set and refined set to experimentally determined
  - Use estimated model to predict the bioactivity of input
    - Adopt previous EDIF model (A kind of decision tree)

$$s = \mathrm{EDIF}(x^s, t)$$
$$r(s) = \exp(s/3)$$
$$J(\theta) = \max_\theta \mathbf{E}_{x^s \sim P(x^s|x^a)}[r(s)]$$



Conditional Generator



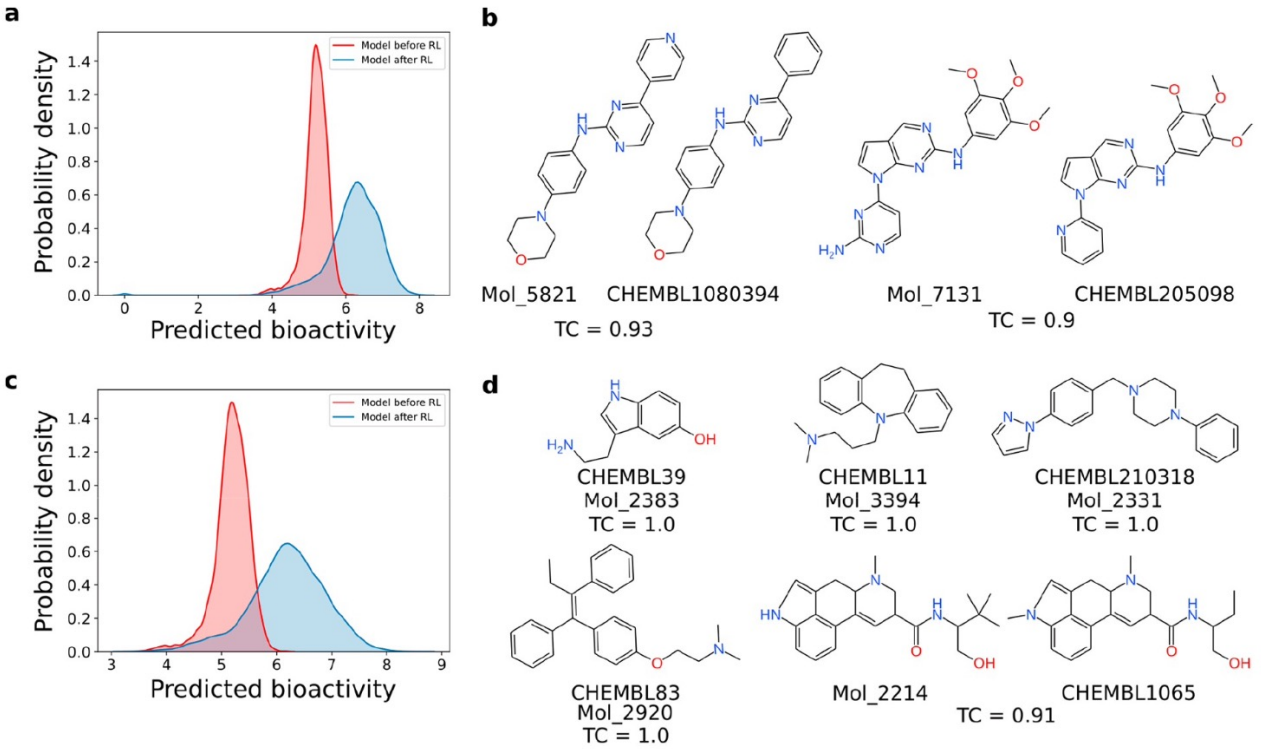
SMILES

DTA Model

Experiment Results

Conditional Molecule Generation

- Validation studies on two different target proteins: DRD2 and JAK2
  - For each target protein, use RL to do searching
- Generation of small molecules with high similarity to existing inhibitors



- Preservation of key pharmacophoric features required for efficient binding
- Generation of small molecules with high pharmacophore-level similarity compared to existing inhibitors

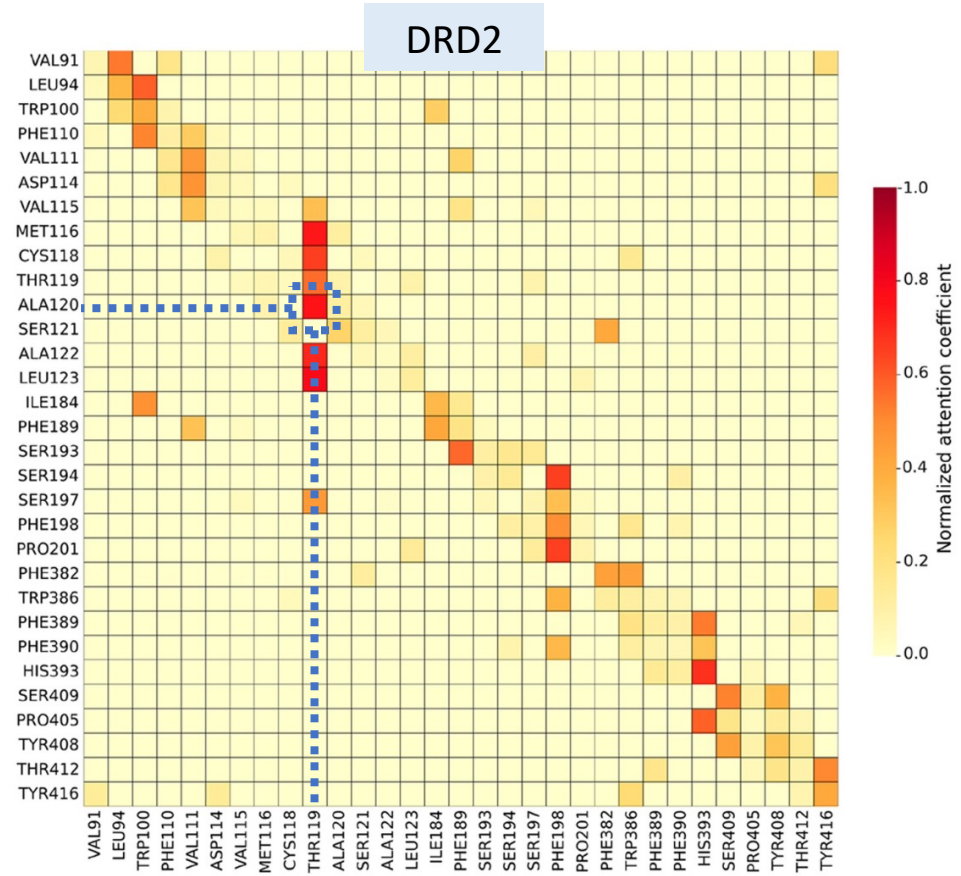
protein	pharmacophore	hits[b] (%)	screened count[c]	not screened count	screened by the other pharmacophore	not screened by both pharmacophores
DRD2 validation set	pharmacophore 1	97.26	4162	44	39	5
	pharmacophore 2	97.95	4158	48	43	
DRD2 generated set	pharmacophore 1	84.63	8475	761	329	432
	pharmacophore 2	85.09	8399	837	405	
JAK2 validation set	pharmacophore 1	99.72	1103	0	0	0
	pharmacophore 2	100	1103	0	0	
JAK2 generated set	pharmacophore 1	87.45	8577	27	15	12
	pharmacophore 2	94.76	8588	16	4	

[a]The percentage of hits, number of molecules screened by either pharmacophores, and molecules which are not screened by both the pharmacophores are provided. [b]Percentage of molecules with at least half the maximum overlap score are considered as hits. [c]Any molecule with a positive overlap score is considered as a screened molecule.

Understanding Graph Interaction

- Visualization methods: entropy histograms and attention coefficient heatmap
  - Interpretability of the model's learning process
- Explanation of attention coefficients
  - Role of specific residues and interactions in the active site
  - *17 of the 149 interactions* with attention weight greater than 0.5 (important)
  - Leu94, Trp100, Asp114, Thr119, Ile184, Phe198, His393, and Tyr416 are verified in the experiments

- Test interaction between generated molecules with target protein DRD2
  - These residues (Leu94, Trp100, Ile184, Phe110) form hydrophobic interactions with the generated molecules.
- Deep learning models are often criticized as black boxes, but the method proposed in this work could explain the importance of active site residues.



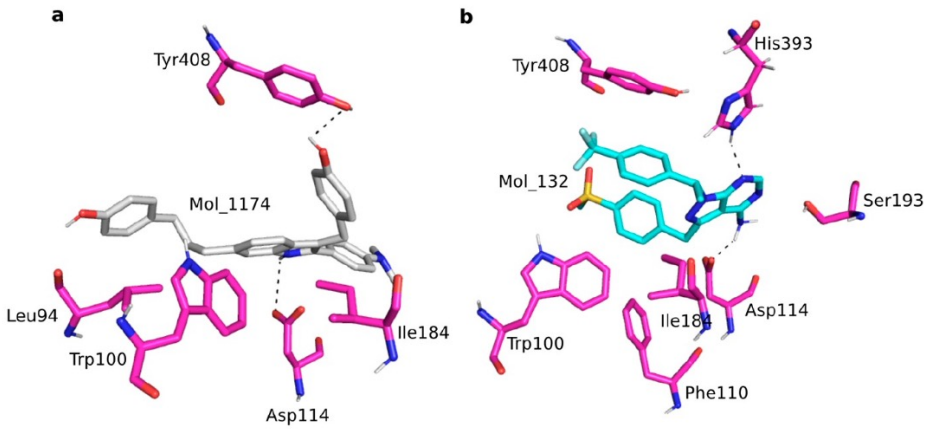


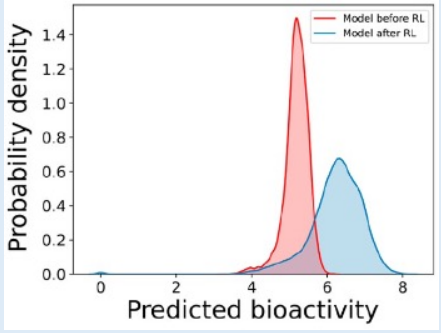
Figure 4. Interactions between key active site residues identified from attention coefficients and selected DRD2-specific generated small molecules: (a) Mol_1174 (white sticks) and (b) Mol_132 (cyan sticks). The residues forming hydrogen bond are shown as dotted lines.

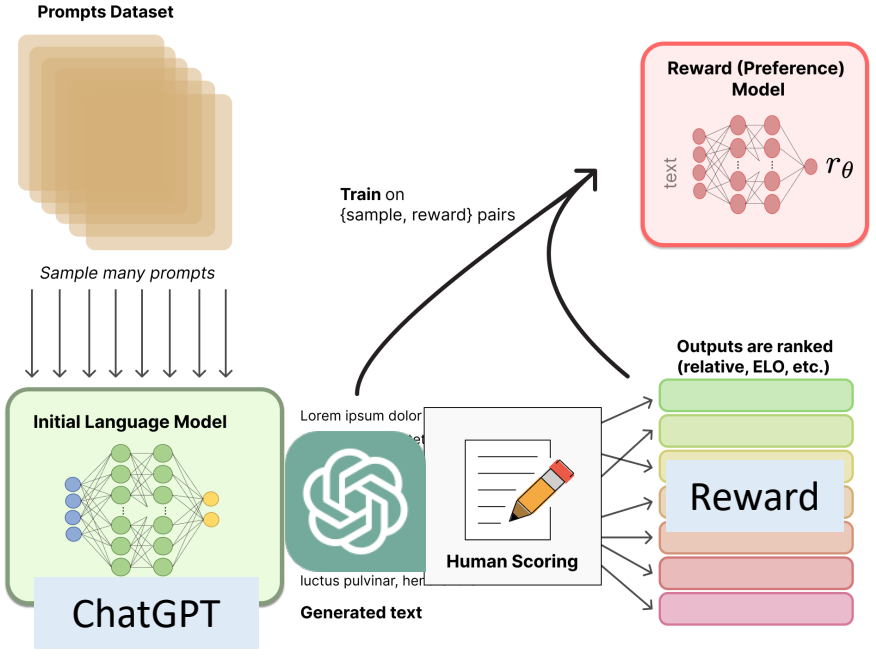
Limitations on Generalization

- In inference stage, an overfit problem is introduced in their method.
  - Individually consider one target protein leads the model overfit to this target on the affinity dataset and cannot be generalize to other target proteins
  - It ignores the conditional generation process $\hat{x}_i^s \sim P(X^s|X^a)$ ✖
- Take an essential training component (Reinforcement Learning Human Feedback, RLHF) in ChatGPT as an example. It is bad for the GPT can only produce good answer on one question.

Inference:

- Only *consider one target protein*, use RL to search until observed distribution shift (sampling)





Ref: https://huggingface.co/blog/rlhf

Proposal

- To fix the generalization, a straightforward method is improving the RL stage in a correct way (we should consider all target proteins instead of only one).
- The structure information considered in this paper is not enough:
  - Protein is in a 3D structure. We should consider the geometric information in the 3D space instead on only focusing 2D graph feature
  - For protein encoding and generation, we already have many much more powerful tools (e.g., Alpha Fold and Large Protein Language model). These tools can help us better understand the protein function and interaction.
- Benchmark dataset should be built
  - The evaluation method should be improved for better understand the algorithm performance

Thanks for Your Attention

Appendix

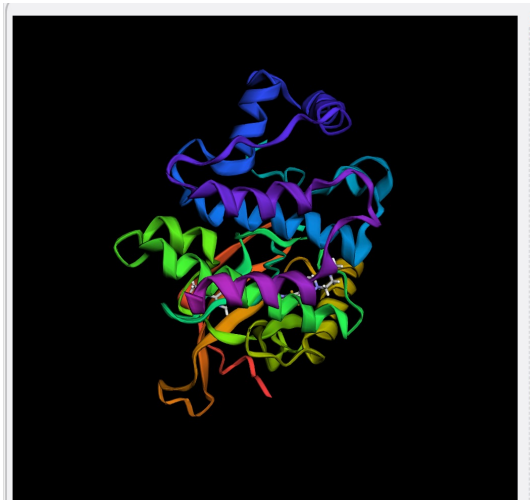
Databases Used in the Study

- ## ChEMBL Database
  - a manually curated database of bioactive molecules with drug-like properties. It brings together chemical, bioactivity and genomic data to aid the translation of genomic information into effective new drugs.
  - used in this study to train a sequence generation model in an unsupervised learning

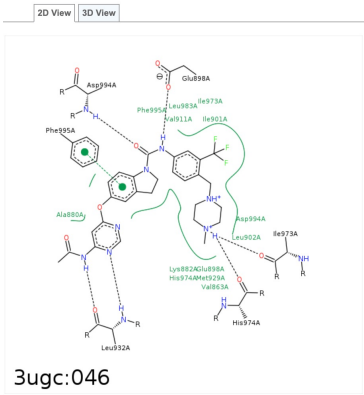
- ## PDBbind Database
  - a comprehensive collection of the binding data of all types of biomolecular complexes deposited in the Protein Data Bank (PDB)
  - used in this study to construct active site based on the target protein and to provide pairs of active site – molecule for maximizing the conditional log-likelihood

- ## scPDB Database
  - a database of 3D structures of binding sites found in the PDB
  - used in this study for the construction of active site graphs for target proteins

Parent Molecule ChEMBL ID	Parent Molecule Name	Parent Molecule Type	Max Phase	First Approval	USAN Stem	References
CHEMBL3622821	UPADACITINIB	Small molecule	4	2019	-tinib	FDA
CHEMBL4802163	NEZULCITINIB	Small molecule	2	No Data	-tinib	PubMed
CHEMBL4297507	DELGOCITINIB	Small molecule	3	No Data	-tinib	PubMed
CHEMBL3137308	PEFICITINIB	Small molecule	3	No Data	-tinib	Other, PubMed



Entry Information	
PDB ID	3ugc
Complex Type	Protein-Ligand
PDBbind Subset	general set
Protein Name	Tyrosine-protein kinase JAK2
Ligand Name	046
EC.Number	E.C.2.7.10.2
Resolution	1.34(Å)
Affinity (Kd/Ki/IC50)	IC50=0.947uM
Release Year	2012
Protein/NA Sequence	Check fasta file
Primary Reference	(2012) Cancer Discov Vol. 2: pp. 512-523
Ligand Properties	
Formula	$C_{28}H_{30}F_3N_7O_3$
Molecular Weight	569.578
Exact Mass	569.236

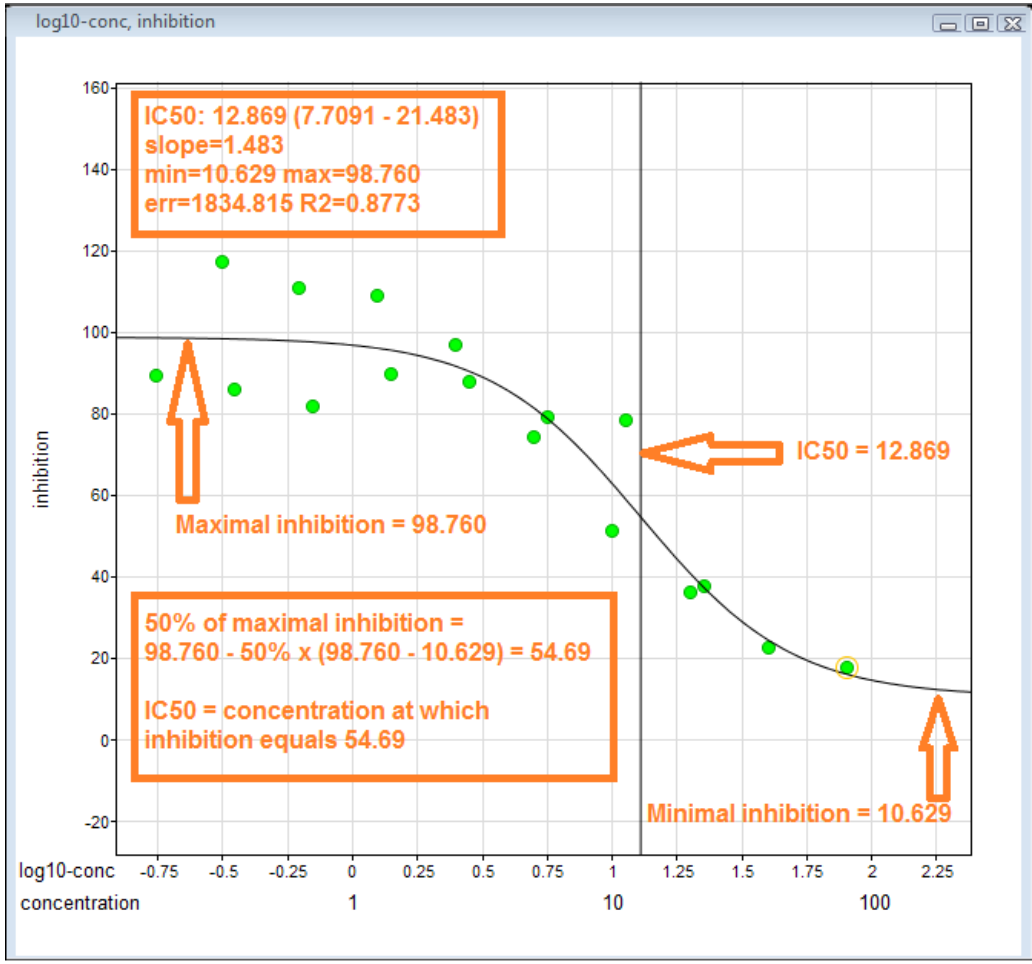


3ugc:046

Ligand Atom	Protein Atom	Protein Residue	Interaction Distance (Å)	Interaction Angle (°)	Interaction Type
C41	CD1	LEU- 855	3.99	0	Hydrophobic
C47	CD2	LEU- 855	3.99	0	Hydrophobic
C31	CG1	VAL- 863	4.31	0	Hydrophobic
C32	CG2	VAL- 863	3.9	0	Hydrophobic
C41	CB	ALA- 880	4.29	0	Hydrophobic
C22	CD	LYS- 882	3.76	0	Hydrophobic
C9	CG	GLU- 898	3.81	0	Hydrophobic
N14	OE2	GLU- 898	2.92	144.42	H-Bond (Ligand Donor)
C6	CG2	ILE- 901	4.17	0	Hydrophobic
C12	CD2	LEU- 902	3.69	0	Hydrophobic
C2	CD1	LEU- 905	4.29	0	Hydrophobic
F4	CG2	ILE- 910	3.47	0	Hydrophobic

Key Parameters in Protein Binding: IC50, Ki, and Kd

- IC50 (Half Maximal Inhibitory Concentration)
  - the concentration of a drug required to inhibit a biological function or a biochemical reaction by 50%
  - a measure of the potency of a drug
- Ki (Inhibition Constant)
  - the concentration of an inhibitor where the binding with the target is reduced by half while the target is at a constant concentration. Lower Ki values indicate higher affinity
  - a measure of the binding affinity of an inhibitor for its target
- Kd (Dissociation Constant)
  - the concentration of a drug at which half of the drug is bound to its target protein and half is free in solution. Lower Kd values indicate higher affinity.
  - a measure of the propensity of a larger object to separate (dissociate) reversibly into smaller components. In the context of drug-target interactions



https://en.wikipedia.org/wiki/IC50#/media/File:Example_IC50_curve_demonstrating_visually_how_IC50_is_derived.png

Ki (Inhibition Constant) & Kd (Dissociation Constant)

Ki (Inhibition Constant):

Definition:

- The inhibitory constant (Ki) is a type of equilibrium dissociation constant (Kd) that represents the equilibrium binding affinity for a ligand that reduces the activity of its binding partner. Ki represents the concentration at which the inhibitor ligand occupies 50% of the receptor sites when no competing ligand is present. **The smaller the Ki the greater the binding affinity** and the smaller the amount of ligand is needed to inhibit its binding partners activity.

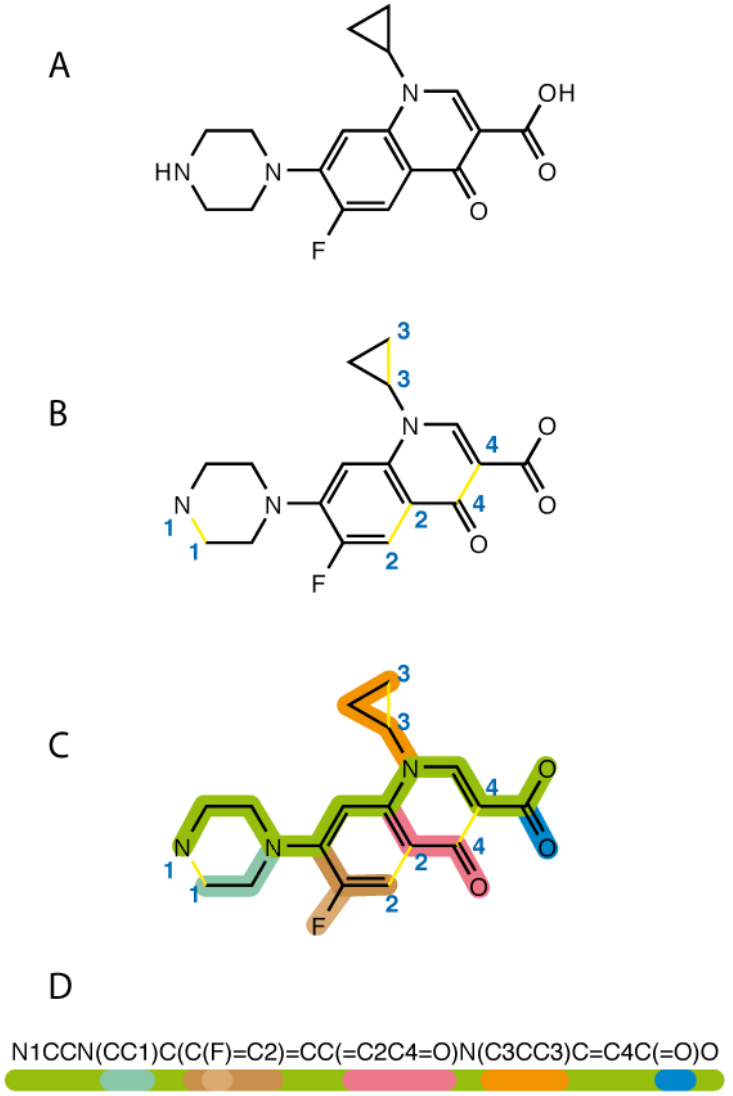
Kd (Dissociation Constant):

Definition:

- A measure of the tendency of a larger complex to separate (dissociate) into its smaller parts. For example, when a protein complex separates into its component proteins, or when a salt splits-up into its component ions. The dissociation reaction can be represented as AxBy ⇄ Ax + By and the equilibrium dissociation constant (Kd) is calculated as Kd =([Ax][By])/[AxBy] where [Ax], [By], and [AxBy] are the concentrations of each component and the fully formed complex at equilibrium.
- In receptor pharmacology, the dissociation constant is commonly used to describe the affinity between a ligand and its receptor. Therefore, Kd can be used as a measure of binding affinity (how tightly a ligand binds to a receptor). The ligand-receptor binding reaction can be represented as L + R ⇄ LR and Kd can be calculated as Kd =([L][R])/[LR]. In the case of ligand-receptor complexes, Kd represents the ligand concentration and should be calculated when 50% of the receptors are bound to ligands. **The smaller the Kd, the more tightly bound the ligand is** and therefore **the higher the affinity** between the ligand and the receptor.

SMILES Sequences in Molecular Representation

- Definition
  - SMILES (Simplified Molecular Input Line Entry System) is a line notation (a typographical method using printable characters) for entering and representing molecules and reactions. For a given molecule, it encodes the structure of the molecule as a string of printable characters.
- Components
  - A SMILES sequence typically includes atoms, bonds, ring closures, and branches. For example, the SMILES sequence for water is 'H2O', and for ethanol is 'CCO'.
- Application
  - In drug discovery and cheminformatics, SMILES is used as a compact notation for chemical structures. It's useful for database searches, and it's often used in machine learning models to predict properties of molecules.



https://en.wikipedia.org/wiki/Simplified_molecular-input_line-entry_system#/media/File:SMILES.png

Tanimoto Coefficient (TC)

- Definition
  - The Tanimoto Coefficient is calculated as the ratio of the intersection of two sets to the union of the two sets. In the context of molecular structures, these "sets" are often represented as binary vectors, where each element of the vector represents the presence (1) or absence (0) of a particular molecular feature.
- Interpretation
  - A Tanimoto Coefficient of 1 indicates that the two sets (or molecular structures) are identical, while a Tanimoto Coefficient of 0 indicates that the two sets have no elements in common.
- Application
  - In drug discovery, the Tanimoto Coefficient is used to compare the similarity of different compounds, helping researchers identify potential drug candidates that are similar to known effective compounds.

```
T = Nc / (Na + Nb - Nc)

where:
  Na is the number of elements in set A
  Nb is the number of elements in set B
  Nc is the number of elements that are shared in A and
```

For example, the Tanimoto coefficient of (A, B, C, D, E) and (I, H, G, F, E, D) is 2/9 = 0.22.

Why use JAK2 and DRD2?

JAK2 (Janus Kinase 2) and DRD2 (Dopamine Receptor D2) are often used in studies like this due to their well-characterized nature and relevance in drug discovery.

JAK2:

- This is a protein tyrosine kinase involved in a specific type of cell signaling pathway known as the JAK-STAT pathway. Mutations in JAK2 have been implicated in various types of leukemia and other cancers. Therefore, JAK2 is a significant target for cancer therapeutics, and studying it can help in the development of new cancer drugs.

DRD2:

- This is a receptor for dopamine, a crucial neurotransmitter in the brain. DRD2 plays a significant role in the function of the central nervous system, and it's a target for various drugs used to treat neurological and psychiatric disorders, including Parkinson's disease and schizophrenia. Studying DRD2 can contribute to the development of new treatments for these conditions.

By using these two well-studied proteins, the researchers can more easily interpret their results and compare them with existing data. Furthermore, any advancements made in designing drugs for these targets have the potential for immediate therapeutic applications.

Variational Auto Encoder

Consider observed N samples x_i under i.i.d. assumption from an unknown distribution $P(X)$, which means $x_i \sim P(X)$. To estimate the parameter of unknown $P(X)$ from observed samples, the log-likelihood is considered as

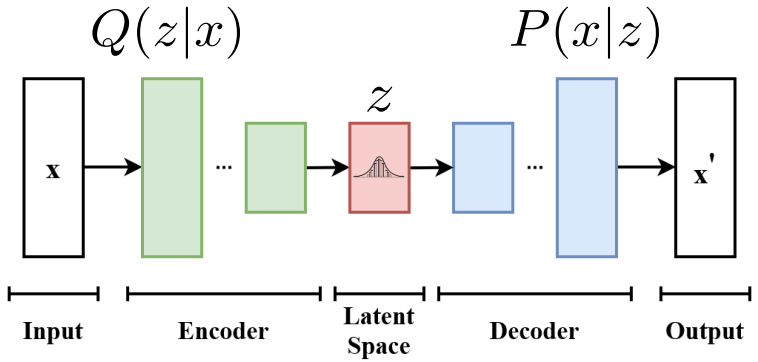
$$\log P(\{x_1, \ldots, x_N\}) = \sum_{i=1}^{N} \log P(x_i) \quad \text{(i.i.d. assumption)}$$
$$\log P(x_i) = KL(Q(z|x_i)||P(z|x_i)) + \mathbf{E}_{Q(z|x_i)}[\log \frac{P(x,z)}{Q(z|x)}]. \tag{1}$$

where we introduce the latent distribution of $Q(z|x)$.

Since the KL distance is always postive, therefore, the lowerbound of log-likelihood is

$$\log P(x_i) \geq \mathbf{E}_{Q(z|x_i)}[\log \frac{P(x,z)}{Q(z|x)}] \quad \text{(ELBO)}$$
$$\mathbf{E}_{Q(z|x_i)}[\log \frac{P(x,z)}{Q(z|x)}] = \mathbf{E}_{Q(z|x_i)}[\log P(x_i|z)] - KL(Q(z|x_i)||P(z)). \tag{2}$$

which means to maximize log-likelihood which equals to maximize the lower bound (ELBO).



E.g., SMILES VAE Training

$$z_i^s = \text{Enc}^s(x_i^s) \quad \hat{x}_i^s = \text{Dec}^s(z_i^s)$$
$$\mathcal{L} = -\sum_i \log P(x_i^s) + KL(q(z^s|x_i^s)||P(z))$$

Ref: Kingma, Diederik P., and Max Welling. "Auto-encoding variational bayes." arXiv preprint arXiv:1312.6114 (2013).

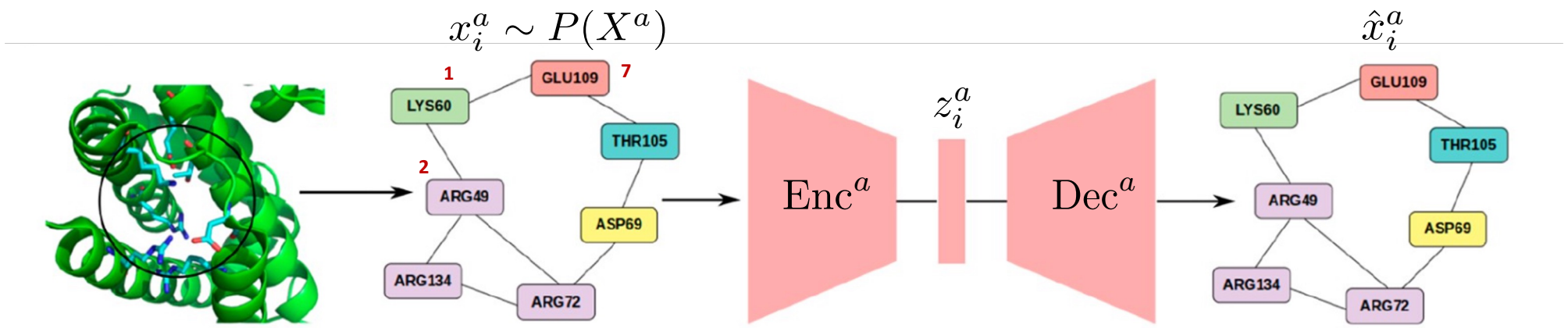
Methodology: Consider Target Structure

- Construct active site based on the target protein $x_i^a \sim P(X^a)$
  - How to construct? PDBbind and scPDB datasets
  - To consider the structure information, they use a graph-based neural network to model the interaction between different sites
- A Graph VAE is trained to reconstruct the adjacency matrix

$$z_i^a = \mathrm{Enc}^a(x_i^a) \quad \hat{x}_i^a = \mathrm{Dec}^a(z_i^a)$$

$$\mathcal{L} = \sum_i \mathrm{CrossEntropy}(x_i^a, \hat{x}_i^a) + KL(q(z^a|x_i^a)||P(z))$$

$$\text{Adjacency Matrix} = \begin{bmatrix} 0 & 1 & 0 & 0 & 0 & 0 & 1 \\ 1 & 0 & 1 & 1 & 0 & 0 & 0 \\ 0 & 1 & 0 & 1 & 0 & 0 & 0 \\ & & \cdots & & & & \\ 1 & 0 & 0 & 0 & 0 & 1 & 0 \end{bmatrix}$$



VAE Pretraining for Active Site

An active site graph can be represented as vertices $\mathcal{V} = \{v_1, \ldots, v_N\}$ and edges $e_{i,j} \in \mathcal{E}$

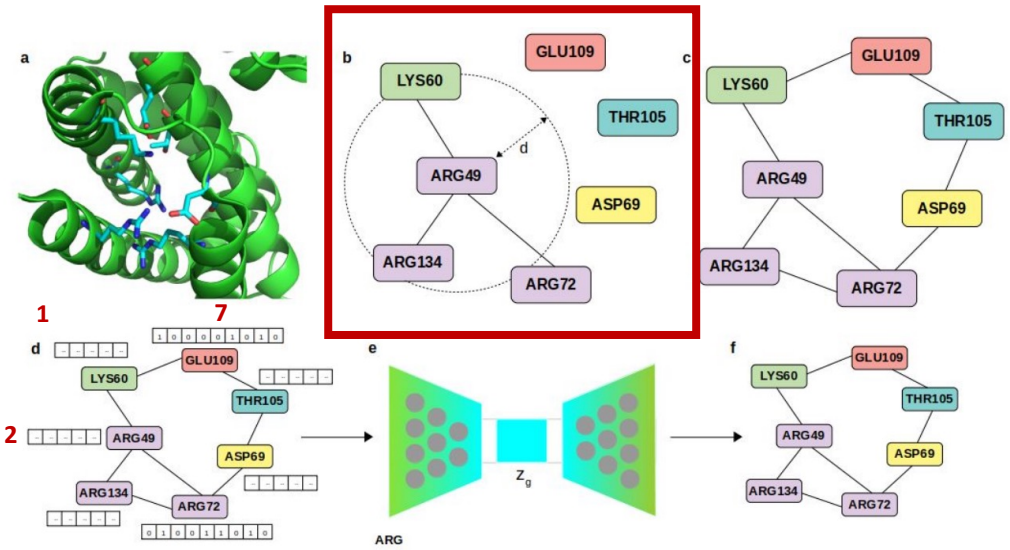
GAT Network Compute attention score $s_{i,j}$ between adjanced node embedding h_{v_i} and h_{v_j}:

$$s_{i,j} = \frac{\exp(Wh_{v_i} \cdot Wh_{v_j})}{\sum_{(i,k)\in\mathcal{E}} \exp(Wh_{v_i} \cdot Wh_{v_k})}$$
$$\hat{h}_{v_i} = \sum_{(i,k)\in\mathcal{E}} s_{i,k} h_{v_k} \quad (1)$$

Edge Reconstruction After encoded the graph feature, the decoder is asked to reconstruct adjacency matrix of $\mathcal{E}$ (connected edges means 1 otherwise 0) for each vertice v

$$z_i^a = \text{Enc}^a(x_i^a) \quad \hat{x}_i^a = \text{Dec}^a(z_i^a)$$
$$\mathcal{L} = \sum_i \text{CrossEntropy}(x_i^a, \hat{x}_i^a) + KL(q(z^a|x_i^a)||P(z)) \quad \text{(ELBO)} \quad (2)$$
$$\text{CrossEntropy} = -\sum_i x_i^a \log(\hat{x}_i^a)$$

Construct active site graph $d < 4\mathring{A}$



$$\text{Adjacency Matrix} = \begin{bmatrix} 0 & 1 & 0 & 0 & 0 & 0 & 1 \\ 1 & 0 & 1 & 1 & 0 & 0 & 0 \\ 0 & 1 & 0 & 1 & 0 & 0 & 0 \\ & & \cdots & & & & \\ 1 & 0 & 0 & 0 & 0 & 1 & 0 \end{bmatrix}$$

Methodology: Small Molecular Generation

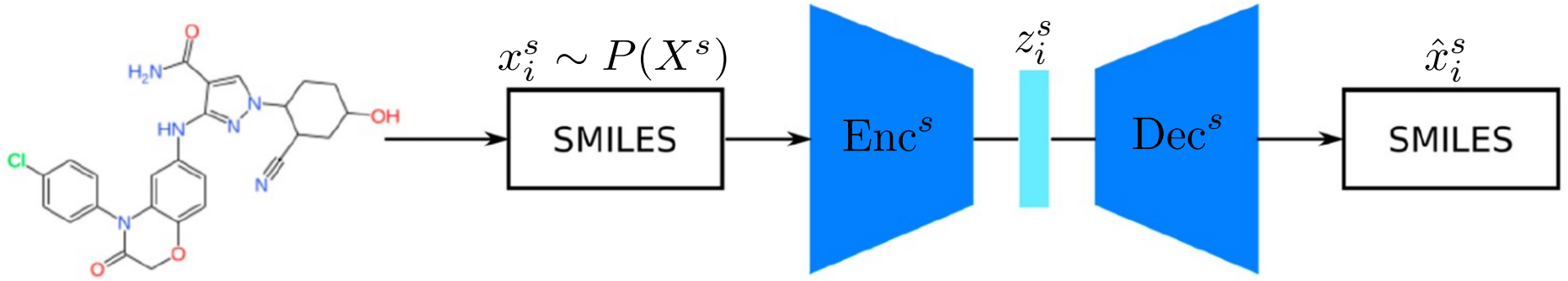
- Generating molecular is abstracted as a SMILES language generation problem $x_i^s = [C, H, O, \ldots, N] \sim P(X^s) \quad P(x_i^s) = \prod_{j=1}^{L} P(x_{i,j}^s | x_{i,1:j-1}^s) P(x_{i,1}^s)$

- Use the ChEMBL dataset, train a sequence generation model in unsupervised learning to predict the SMILES.

$$z_i^s = \mathrm{Enc}^s(x_i^s) \quad \hat{x}_i^s = \mathrm{Dec}^s(z_i^s)$$

$$\mathcal{L} = -\sum_i \log P(x_i^s) + KL(q(z^s|x_i^s)||P(z))$$

Decoding Use special token "!" as input, generate new token at time step t by samping from the distribution $P(\hat{x}_{i,t}^s | \hat{x}_{i,1:t-1}^s)$. Samplting methods include top-k or top-p.

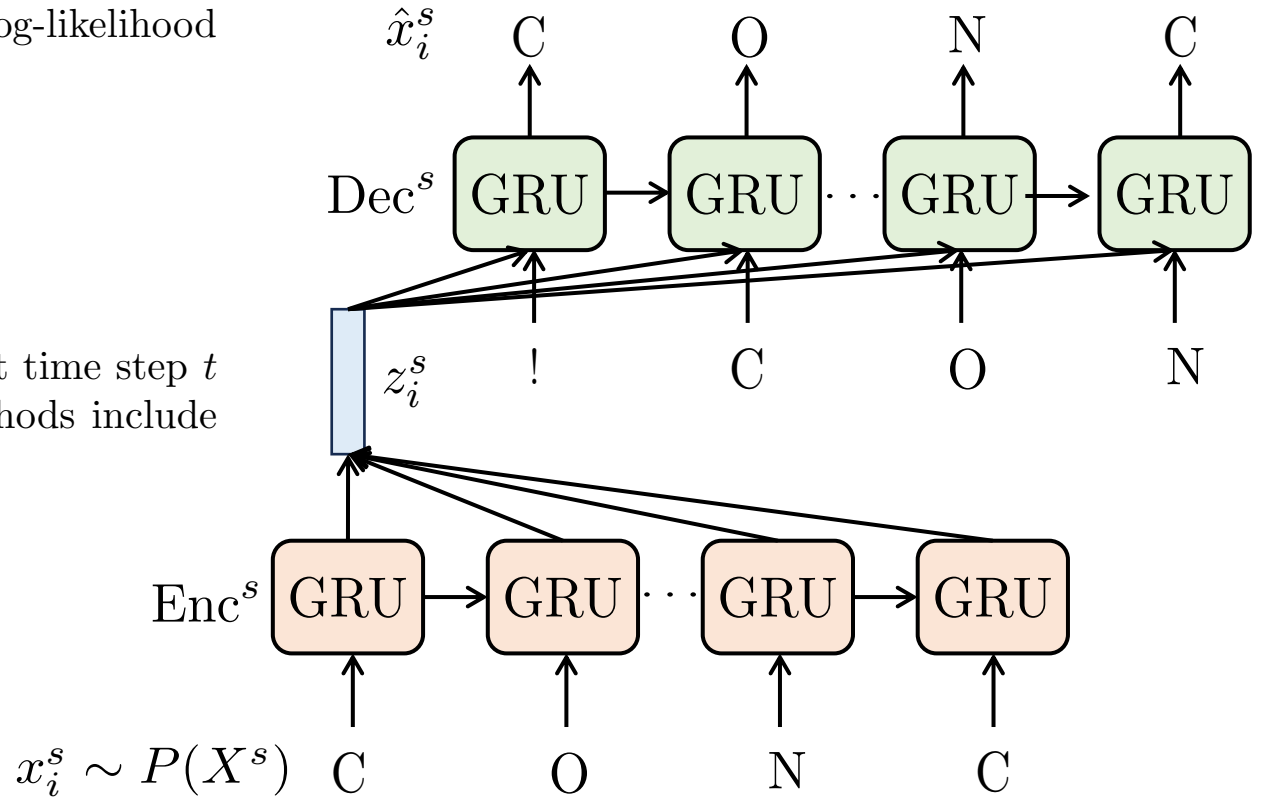


VAE Pretraining for SMILES Language Model

The SMILES sequence $x^s \sim P(X^s)$, therefore, the maximize log-likelihood can be defined as:

$$z_i^s = \text{Enc}^s(x_i^s) \quad \hat{x}_i^s = \text{Dec}^s(z_i^s)$$
$$\mathcal{L} = -\sum_i \log P(x_i^s) + KL(q(z^s|x_i^s)||P(z)) \quad \text{(ELBO)}.$$

Decoding Use special token "!" as input, generate new token at time step t by samping from the distribution $P(\hat{x}_{i,t}^s|\hat{x}_{i,1:t-1}^s)$. Samplting methods include top-k or top-p.



Joulin, Armand, and Tomas Mikolov. "Inferring algorithmic patterns with stack-augmented recurrent nets." *Advances in neural information processing systems 28* (**2015**).

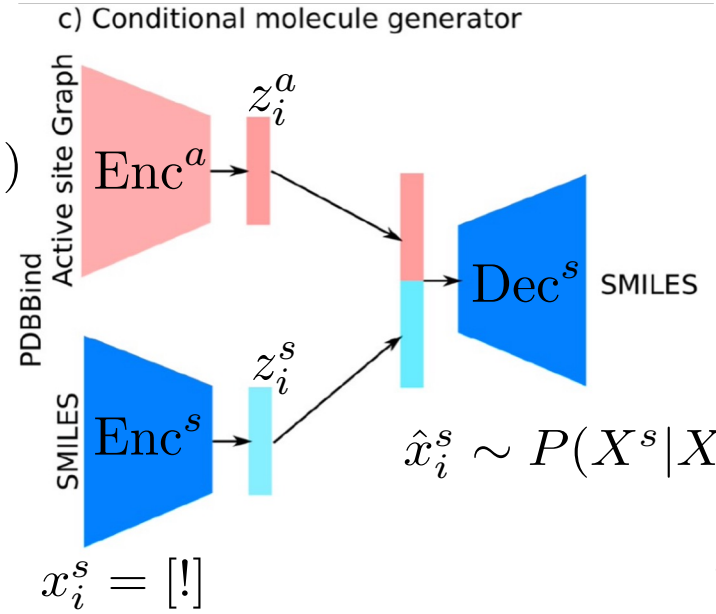
Methodology: Conditional Molecule Generation

- Generate appropriate molecule based on the target activate sites

- Given pairs of active site – molecule $(x_i^a, x_i^s)\ \forall i \in [1, P]$
  - PDBbind dataset
  - Pad the input smiles as special token (e.g. !)
  - Maximize the conditional log-likelihood

$$z_i^a = \mathrm{Enc}^a(x_i^a) \quad z_i^s = \mathrm{Enc}^s(x_i^s)$$
$$\hat{x}_i^s = \mathrm{Dec}^s([z_i^a, z_i^s])$$
$$\mathcal{L} = -\sum_i \log P(x_i^s | x_i^a)$$

- This trained model is able to generate according molecules based on input activate sites



Methodology Summary

Pretraining:

- Pretrain active site VAE and SMILES VAE

$$\mathrm{Enc}^a, \mathrm{Dec}^a, \mathrm{Enc}^s, \mathrm{Dec}^s$$

- Use pretrain model to maximize conditional generation model

$$(x_i^a, x_i^s)\ \forall i \in [1, P]$$

$$\hat{x}_i^s \sim P(X^s|X^a)$$

Reinforcement Learning:

- Construct affinity model as environment

$$s = \mathrm{EDIF}(x^s, t)$$

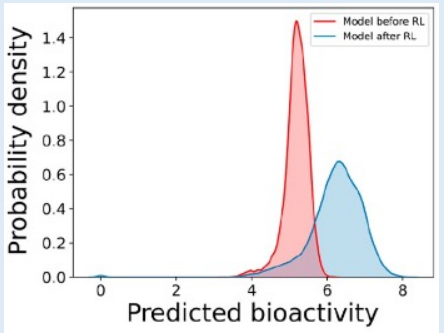
$$r(s) = \exp(s/3)$$

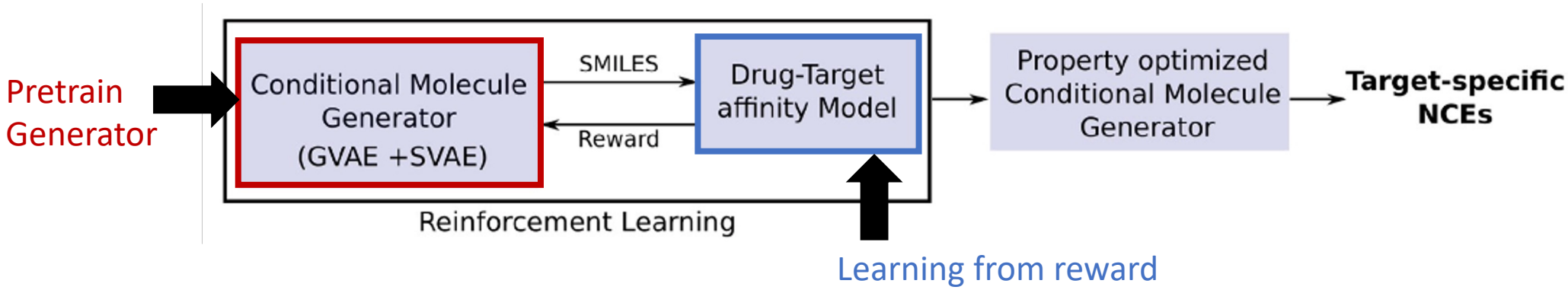
- Use pretrain model to maximize conditional generation model

$$\nabla_\theta J(\theta) = \mathbf{E}_{x^s \sim P(x^s|x^a)}[r(s)]$$

Inference:

- Only *consider one target protein*, use RL to search until observed distribution shift (sampling)





De Novo Structure-Based Drug Design Using Deep Learning

Authors: Sowmya Ramaswamy Krishnan, Navneet Bung, Sarveswara Rao Vangala, Rajgopal Srinivasan, Gopalakrishnan Bulusu, and Arijit Roy

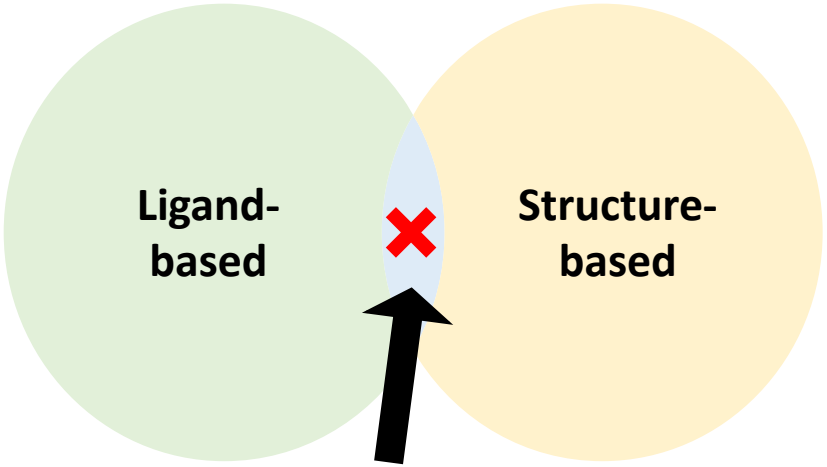
Outline

- Introduction of Drug Design
  - Background
  - Contributions of this paper
- Proposed Methodology
  - Model design
  - Training details
- Experiment Results
  - Generation results
  - Interpretation
- Rethinking and Discussion
  - Existed Problem on Generalization
- Conclusions

Introduction of Drug Design

Ligand-based design:

- General Idea: Based on existed target-molecules data to train a molecule generator. Then apply it to new target.
- Pros:
  - Can provide reliable results
- Cons:
  - Cannot generalize to design drug for novel target



This paper lies in this field

Structure-based design:

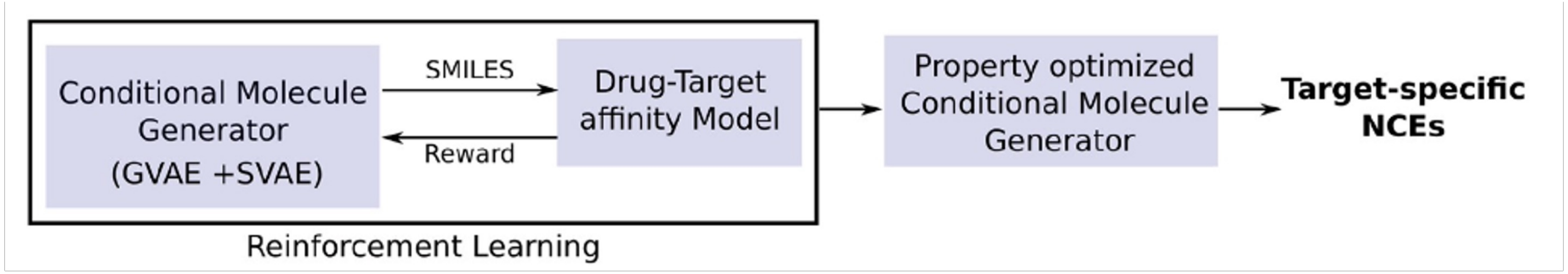
- General Idea: Directly capture the structure information to design
- Pros:
  - Structure is easier to be generalize to novel target
- Cons:
  - Should devise useful feature extraction method for structure information

- Contributions:
  - The first method which proposes to use binding site representation of target protein as structure information
  - Get similar and identical design results on two well-studied target proteins: JAK2 and DRD2
  - Give some interpretations on useful active sites from the trained deep learning model

Methodology

Methodology: Overview

- Combine the structure information of target protein to design molecules
  - Construction of active site graph for target protein
  - Adopt Graphical neural network to capture the interaction between difference active sites
- Conditioned on the target structure information, use pretrained molecule language model to generate appropriate drugs
  - Pretrain SMILES language model on the ChEMBL dataset in an unsupervised way
  - Fuse target information to finish conditional generation
- Boost design performance with reinforcement learning
  - Use a pretrained affinity model as a reward function
  - Train the language model to achieve a high expected reward



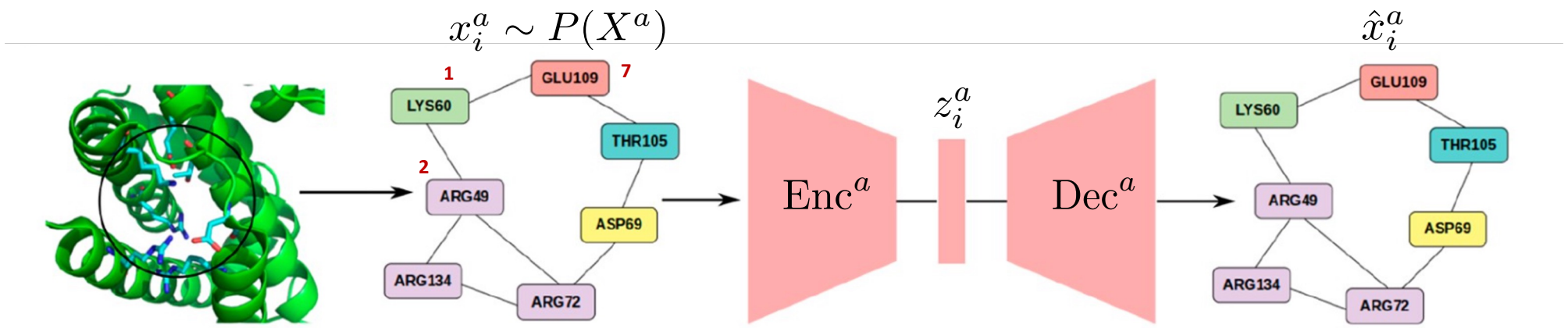
Methodology: Consider Target Structure

- Construct active site based on the target protein $x_i^a \sim P(X^a)$
  - How to construct? PDBbind and scPDB datasets
  - To consider the structure information, they use a graph-based neural network to model the interaction between different sites
- A Graph VAE is trained to reconstruct the adjacency matrix

$$z_i^a = \mathrm{Enc}^a(x_i^a) \quad \hat{x}_i^a = \mathrm{Dec}^a(z_i^a)$$

$$\mathcal{L} = \sum_i \mathrm{CrossEntropy}(x_i^a, \hat{x}_i^a) + KL(q(z^a|x_i^a)||P(z))$$

$$\text{Adjacency Matrix} = \begin{bmatrix} 0 & 1 & 0 & 0 & 0 & 0 & 1 \\ 1 & 0 & 1 & 1 & 0 & 0 & 0 \\ 0 & 1 & 0 & 1 & 0 & 0 & 0 \\ & & \cdots & & & & \\ 1 & 0 & 0 & 0 & 0 & 1 & 0 \end{bmatrix}$$



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$$\mathcal{L} = -\sum_i \log P(x_i^s) + KL(q(z^s|x_i^s)||P(z))$$

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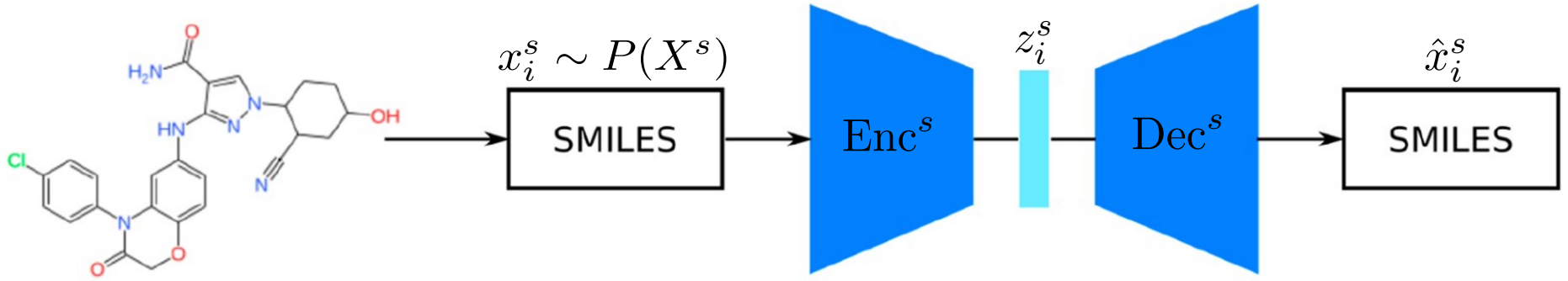

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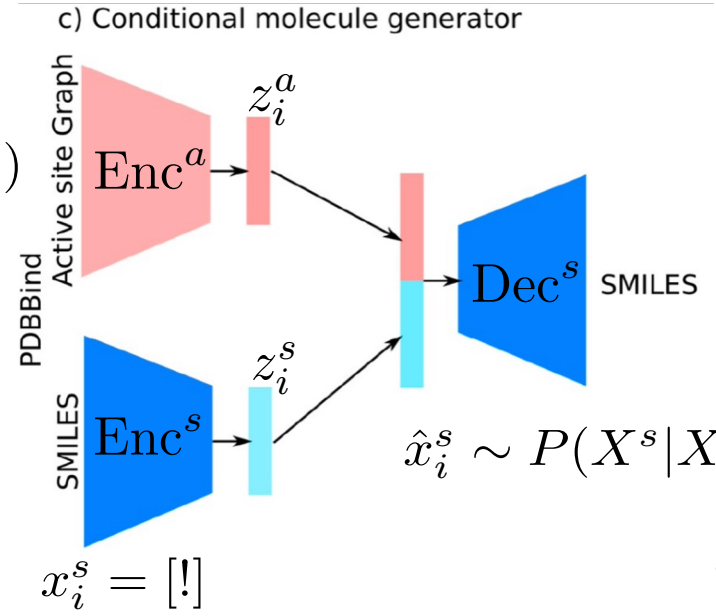
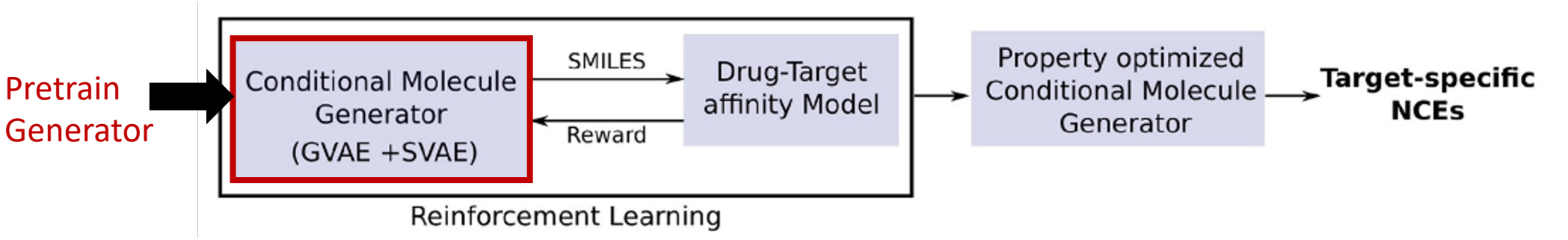
- This trained model is able to generate according molecules based on input activate sites



Methodology: Review the generator part



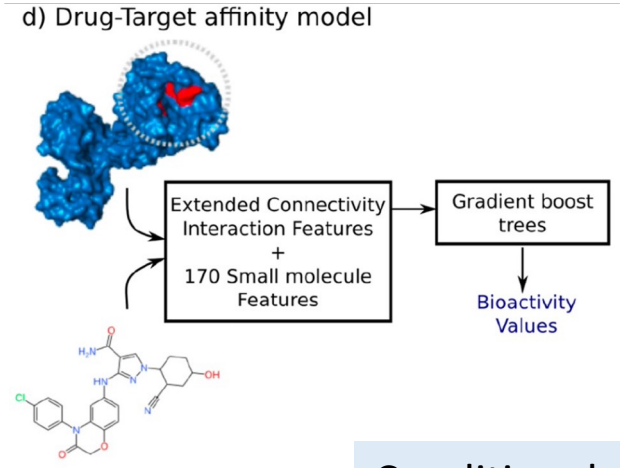
- Why we need pretraining?
  - Pretraining is essential to capture prior graph interaction semantics
  - Pretraining is essential to generate valid molecule sequence
- Next step
  - Further boost the drug design performance to achieve good affinity
  - Use reinforcement learning (RL) to judge the SMILES sequence produced by the conditional generator

Methodology: Drug-Target Affinity Score Model + RL

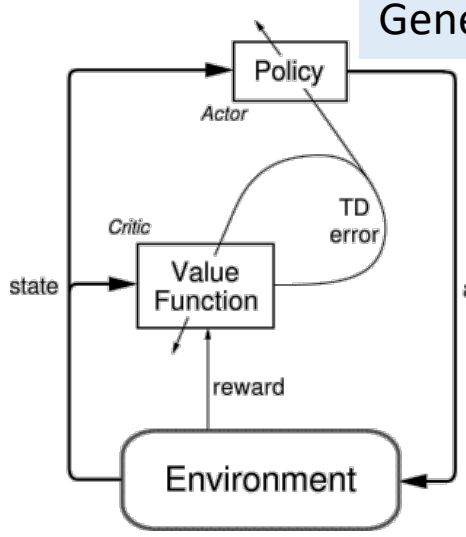
- Test the bioactivity (Affinity) provided by the generator
  - The bioactivity can be determined through experiment but time consuming and indifferentiable
    - PDBbind general set and refined set to experimentally determined $\mathrm{IC}_{50}, \mathrm{K}_i, \mathrm{K}_d$
  - Use estimated model to predict the bioactivity of input
    - Adopt previous EDIF model (A kind of decision tree)

$$s = \mathrm{EDIF}(x^s, t)$$
$$r(s) = \exp(s/3)$$
$$J(\theta) = \max_\theta \mathbf{E}_{x^s \sim P(x^s|x^a)}[r(s)]$$

$$\nabla_\theta J(\theta) = \mathbb{E}_{s_0, a_0, \ldots, s_t, a_t}[\sum_{t=0}^{T-1} \nabla_\theta \log \pi_\theta(a_t|s_t)] Q_w(s_t, a_t)$$
$$= \mathbb{E}_\tau[\sum_{t=0}^{T-1} \nabla_\theta \log \pi_\theta(a_t|s_t) Q_w(s_t, a_t)]$$



Conditional Generator



SMILES

DTA Model

Methodology: Summary

Pretraining:

- Pretrain active site VAE and SMILES VAE

$$\mathrm{Enc}^a, \mathrm{Dec}^a, \mathrm{Enc}^s, \mathrm{Dec}^s$$

- Use pretrain model to maximize conditional generation model

$$(x_i^a, x_i^s)\ \forall i \in [1, P]$$

$$\hat{x}_i^s \sim P(X^s|X^a)$$

Reinforcement Learning:

- Construct affinity model as environment

$$s = \mathrm{EDIF}(x^s, t)$$

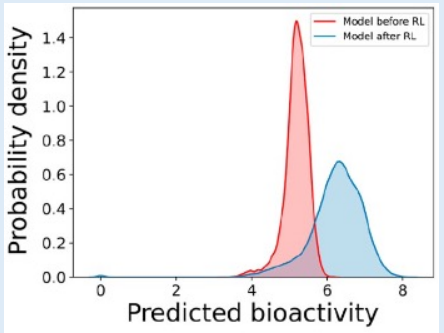
$$r(s) = \exp(s/3)$$

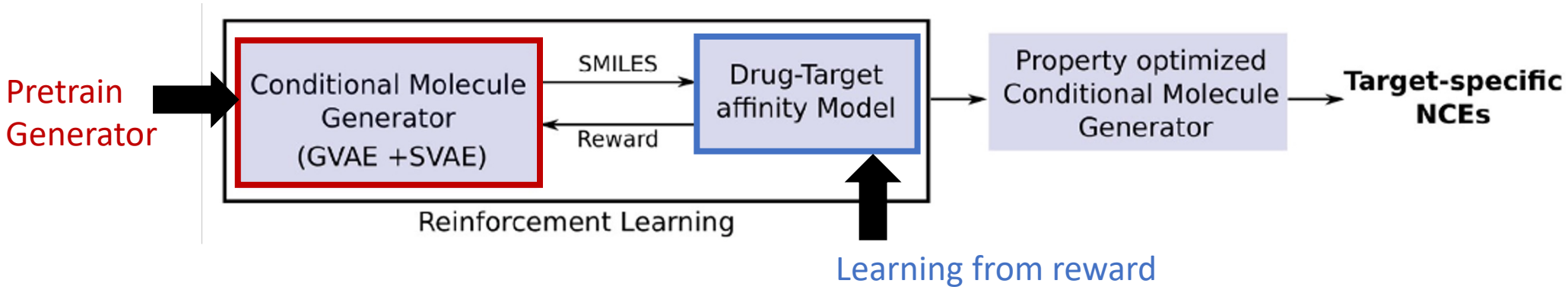
- Use pretrain model to maximize conditional generation model

$$\nabla_\theta J(\theta) \quad \text{policy gradient}$$

Inference:

- Only *consider one target protein*, use RL to search until observed distribution shift (sampling)

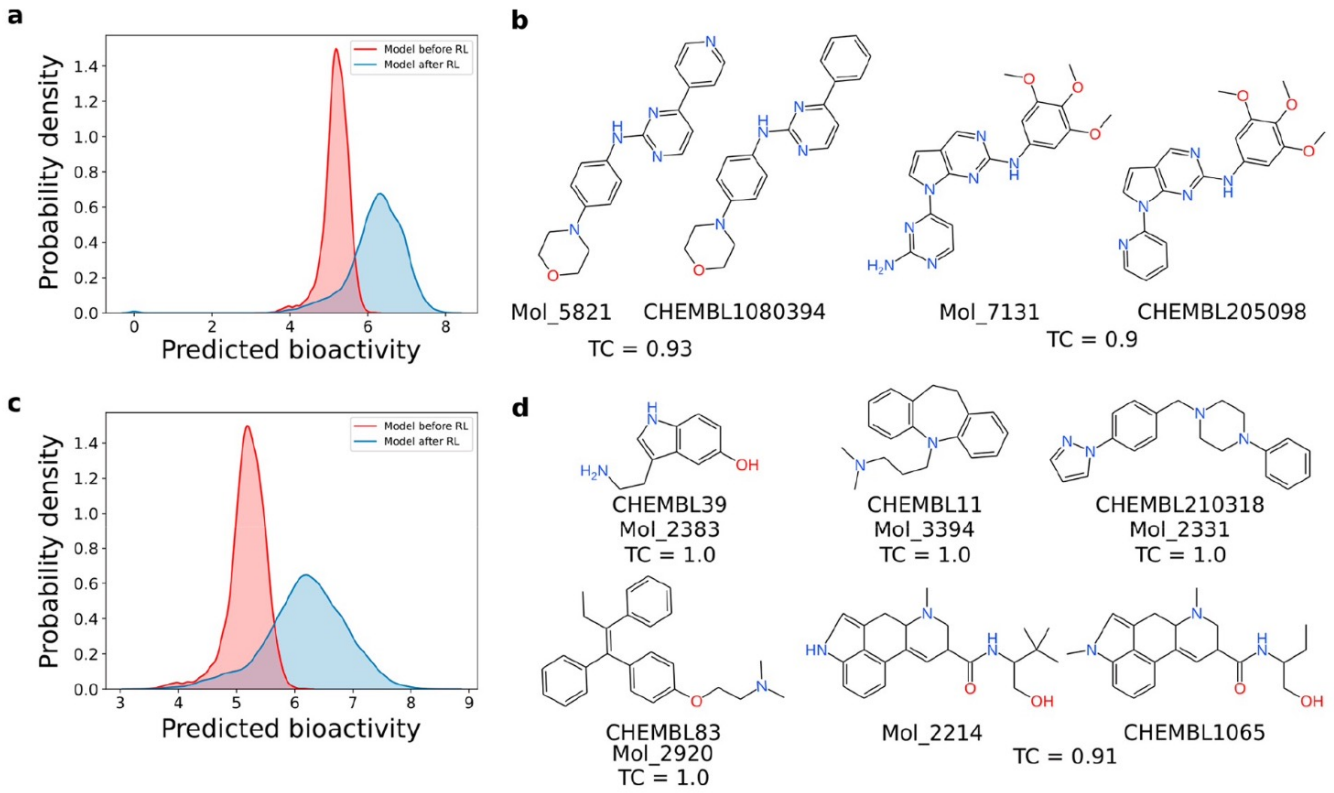




Experiment Results

Validation: Generated Results

- Validation studies on two different target proteins: DRD2 and JAK2
  - For each target protein, use RL to do searching
- Generation of small molecules with high similarity to existing inhibitors



Validation: Generated Results

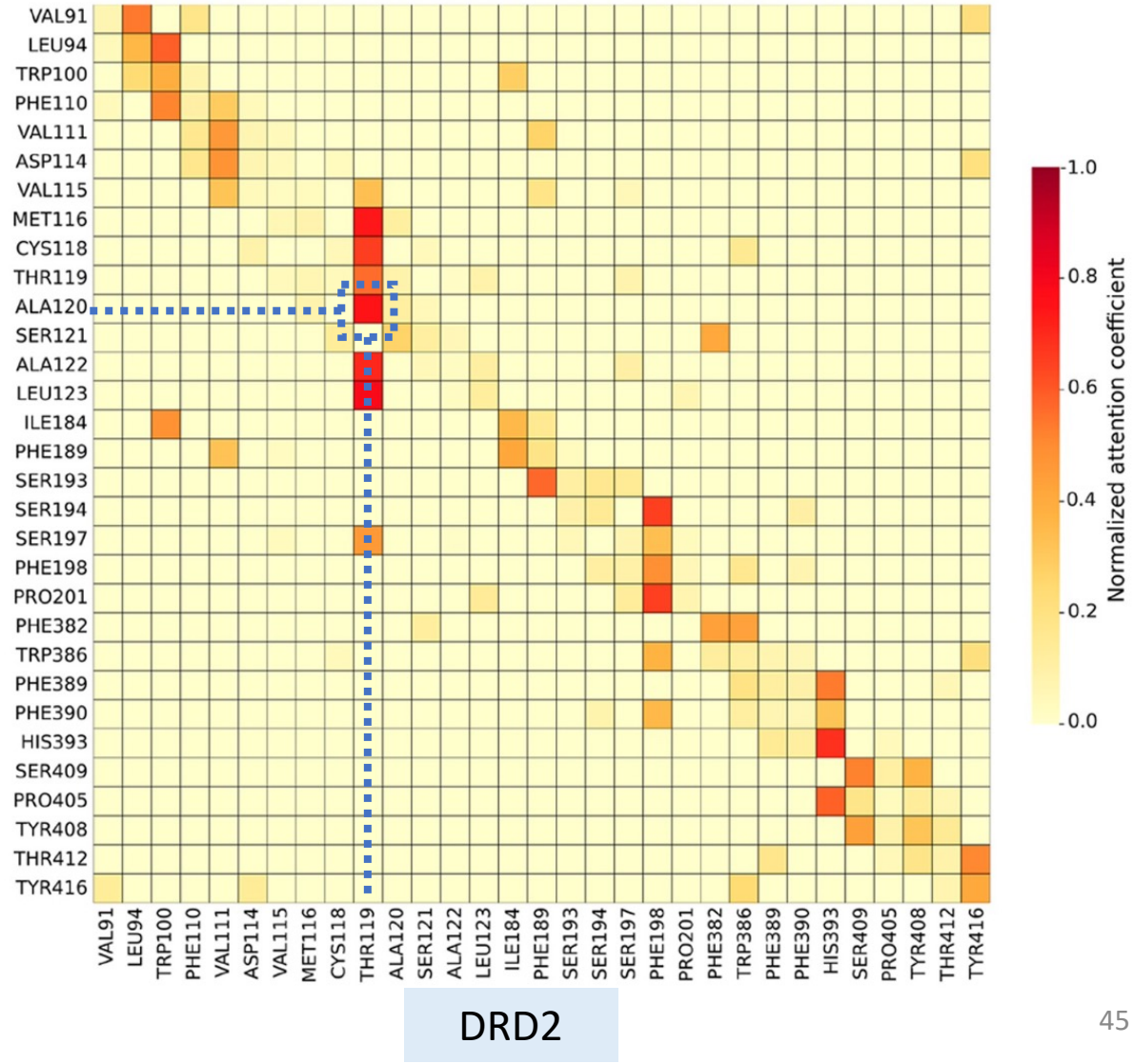
- Preservation of key pharmacophoric features required for efficient binding
- Generation of small molecules with high pharmacophore-level similarity compared to existing inhibitors

protein	pharmacophore	hits[b] (%)	screened count[c]	not screened count	screened by the other pharmacophore	not screened by both pharmacophores
DRD2 validation set	pharmacophore 1	97.26	4162	44	39	5
	pharmacophore 2	97.95	4158	48	43	
DRD2 generated set	pharmacophore 1	84.63	8475	761	329	432
	pharmacophore 2	85.09	8399	837	405	
JAK2 validation set	pharmacophore 1	99.72	1103	0	0	0
	pharmacophore 2	100	1103	0	0	
JAK2 generated set	pharmacophore 1	87.45	8577	27	15	12
	pharmacophore 2	94.76	8588	16	4	

[a]The percentage of hits, number of molecules screened by either pharmacophores, and molecules which are not screened by both the pharmacophores are provided. [b]Percentage of molecules with at least half the maximum overlap score are considered as hits. [c]Any molecule with a positive overlap score is considered as a screened molecule.

Understanding Graph Interaction

- Visualization methods: entropy histograms and attention coefficient heatmap
  - Interpretability of the model's learning process
- Explanation of attention coefficients
  - Role of specific residues and interactions in the active site
  - *17 of the 149 interactions* with attention weight greater than 0.5 (important)
  - Leu94, Trp100, Asp114, Thr119, Ile184, Phe198, His393, and Tyr416 are verified in the experiments



DRD2

Understanding Target-molecule Interaction

- Test interaction between generated molecules with target protein DRD2
  - These residues (Leu94, Trp100, Ile184, Phe110) form hydrophobic interactions with the generated molecules.
- Deep learning models are often criticized as black boxes, but the method proposed in this work could explain the importance of active site residues.

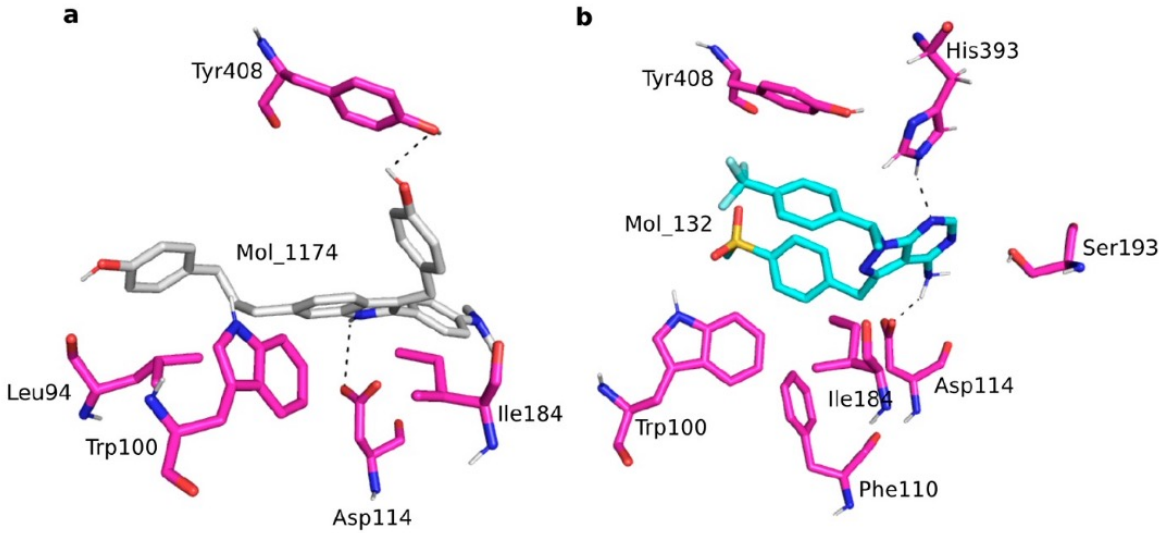


Figure 4. Interactions between key active site residues identified from attention coefficients and selected DRD2-specific generated small molecules: (a) Mol_1174 (white sticks) and (b) Mol_132 (cyan sticks). The residues forming hydrogen bond are shown as dotted lines.

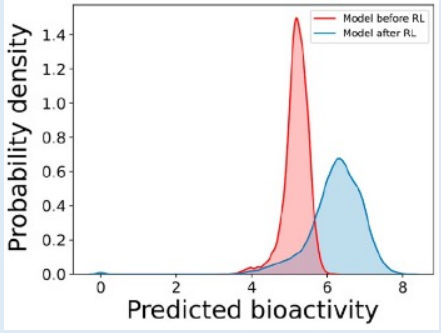
Rethinking and Discussion

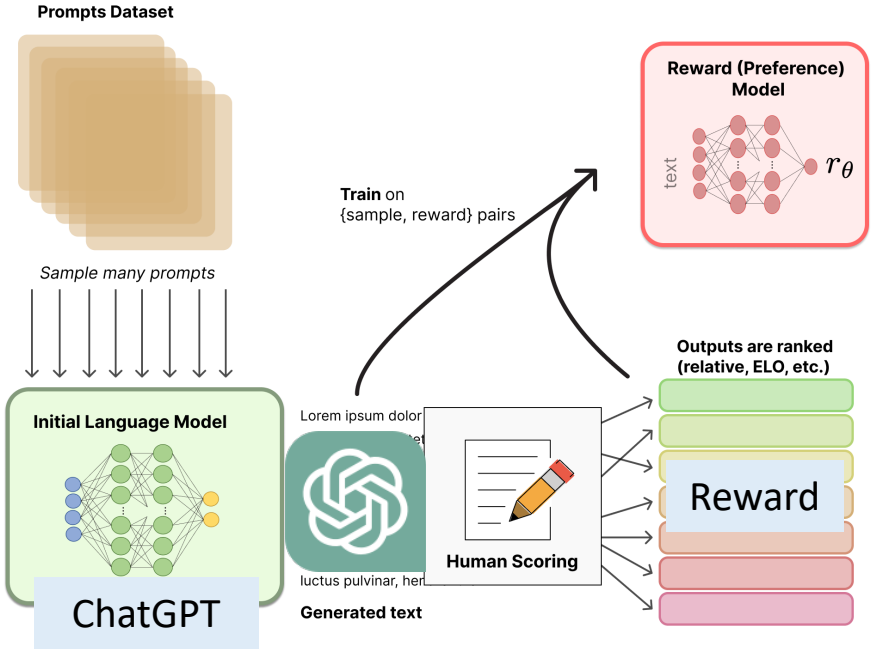
Existed Problem on Generalization

- In inference stage, an overfit problem is introduced in their method.
  - Individually consider one target protein leads the model overfit to this target on the affinity dataset and cannot be generalize to other target proteins
  - It ignores the conditional generation process $\hat{x}_i^s \sim P(X^s|X^a)$ ✗
- Take an essential training component (Reinforcement Learning Human Feedback, RLHF) in ChatGPT as an example. It is bad for the GPT can only produce good answer on one question.

Inference:

- Only *consider one target protein*, use RL to search until observed distribution shift (sampling)





Ref: https://huggingface.co/blog/rlhf

Conclusion

- Recap of the study and the novel structure-based method for small molecule generation
- Importance of distinguishing key residues and interactions in the active site
- Implications for more efficient, cost-effective drug discovery
- Problematic RL method leads to bad generalization ability

Thanks for Your Attention

Appendix

Variational Auto Encoder

Consider observed N samples x_i under i.i.d. assumption from an unknown distribution $P(X)$, which means $x_i \sim P(X)$. To estimate the parameter of unknown $P(X)$ from observed samples, the log-likelihood is considered as

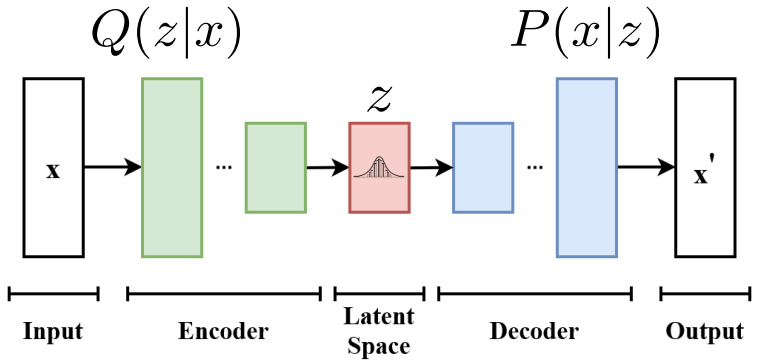
$$\log P(\{x_1, \ldots, x_N\}) = \sum_{i=1}^{N} \log P(x_i) \quad \text{(i.i.d. assumption)}$$
$$\log P(x_i) = KL(Q(z|x_i)||P(z|x_i)) + \mathbf{E}_{Q(z|x_i)}[\log \frac{P(x,z)}{Q(z|x)}]. \tag{1}$$

where we introduce the latent distribution of $Q(z|x)$.

Since the KL distance is always postive, therefore, the lowerbound of log-likelihood is

$$\log P(x_i) \geq \mathbf{E}_{Q(z|x_i)}[\log \frac{P(x,z)}{Q(z|x)}] \quad \text{(ELBO)}$$
$$\mathbf{E}_{Q(z|x_i)}[\log \frac{P(x,z)}{Q(z|x)}] = \mathbf{E}_{Q(z|x_i)}[\log P(x_i|z)] - KL(Q(z|x_i)||P(z)). \tag{2}$$

which means to maximize log-likelihood which equals to maximize the lower bound (ELBO).



E.g., SMILES VAE Training

$$z_i^s = \text{Enc}^s(x_i^s) \quad \hat{x}_i^s = \text{Dec}^s(z_i^s)$$
$$\mathcal{L} = -\sum_i \log P(x_i^s) + KL(q(z^s|x_i^s)||P(z))$$

Ref: Kingma, Diederik P., and Max Welling. "Auto-encoding variational bayes." arXiv preprint arXiv:1312.6114 (2013).

VAE Pretraining for Active Site

An active site graph can be represented as vertices $\mathcal{V} = \{v_1, \ldots, v_N\}$ and edges $e_{i,j} \in \mathcal{E}$

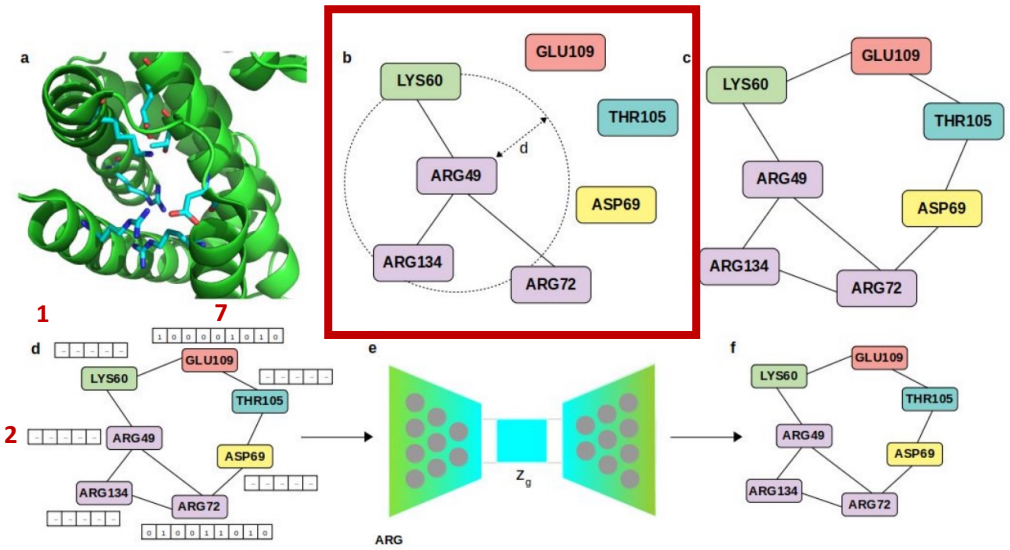
GAT Network Compute attention score $s_{i,j}$ between adjanced node embedding h_{v_i} and h_{v_j}:

$$s_{i,j} = \frac{\exp(Wh_{v_i} \cdot Wh_{v_j})}{\sum_{(i,k)\in\mathcal{E}} \exp(Wh_{v_i} \cdot Wh_{v_k})}$$
$$\hat{h}_{v_i} = \sum_{(i,k)\in\mathcal{E}} s_{i,k} h_{v_k} \quad (1)$$

Edge Reconstruction After encoded the graph feature, the decoder is asked to reconstruct adjacency matrix of $\mathcal{E}$ (connected edges means 1 otherwise 0) for each vertice v

$$z_i^a = \text{Enc}^a(x_i^a) \quad \hat{x}_i^a = \text{Dec}^a(z_i^a)$$
$$\mathcal{L} = \sum_i \text{CrossEntropy}(x_i^a, \hat{x}_i^a) + KL(q(z^a|x_i^a)||P(z)) \quad \text{(ELBO)} \quad (2)$$
$$\text{CrossEntropy} = -\sum_i x_i^a \log(\hat{x}_i^a)$$

Construct active site graph $d < 4\mathring{A}$



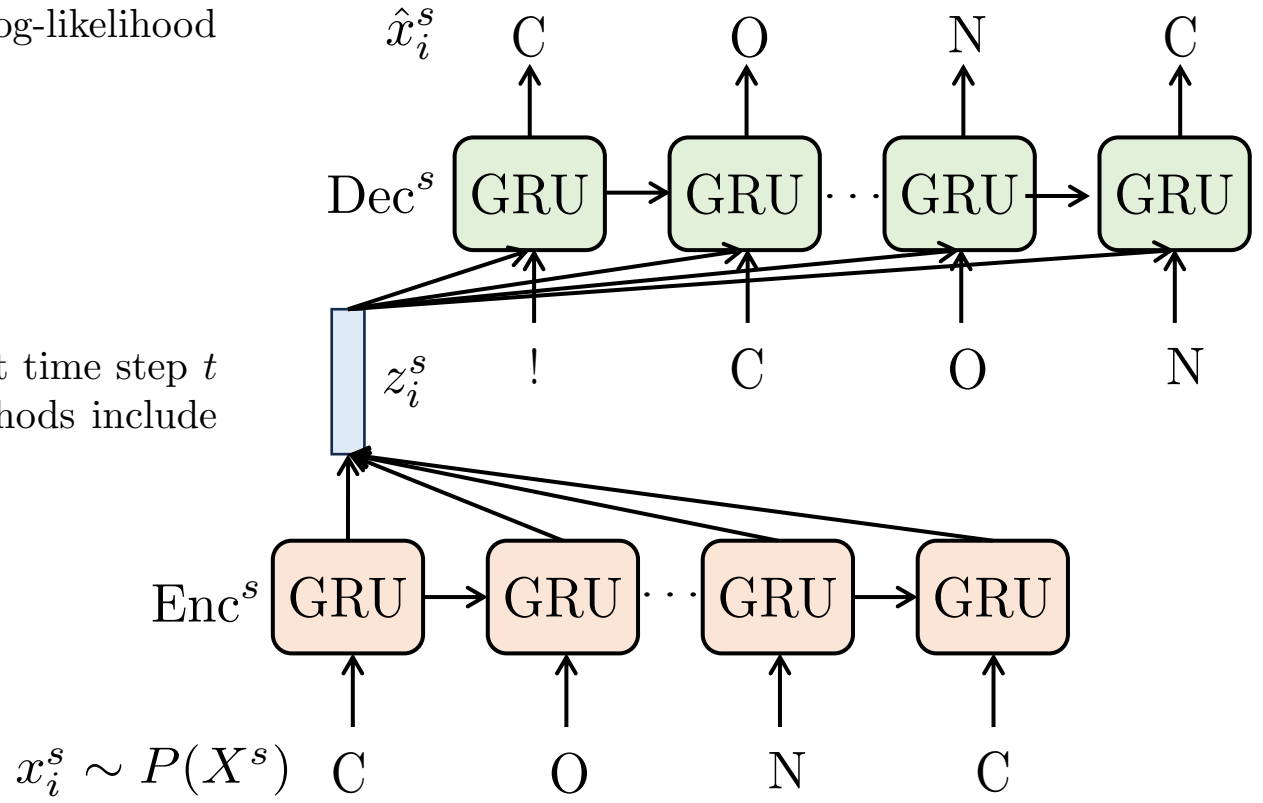
$$\text{Adjacency Matrix} = \begin{bmatrix} 0 & 1 & 0 & 0 & 0 & 0 & 1 \\ 1 & 0 & 1 & 1 & 0 & 0 & 0 \\ 0 & 1 & 0 & 1 & 0 & 0 & 0 \\ & & \cdots & & & & \\ 1 & 0 & 0 & 0 & 0 & 1 & 0 \end{bmatrix}$$

VAE Pretraining for SMILES Language Model

The SMILES sequence $x^s \sim P(X^s)$, therefore, the maximize log-likelihood can be defined as:

$$z_i^s = \text{Enc}^s(x_i^s) \quad \hat{x}_i^s = \text{Dec}^s(z_i^s)$$
$$\mathcal{L} = -\sum_i \log P(x_i^s) + KL(q(z^s|x_i^s)||P(z)) \quad \text{(ELBO)}.$$

Decoding Use special token "!" as input, generate new token at time step t by samping from the distribution $P(\hat{x}_{i,t}^s|\hat{x}_{i,1:t-1}^s)$. Samplting methods include top-k or top-p.



Ref: Joulin, Armand, and Tomas Mikolov. "Inferring algorithmic patterns with stack-augmented recurrent nets." Advances in neural information processing systems 28 (2015).