PILOT: Equivariant Diffusion for Target-Aware De Novo Ligand Generation with Multi-Objetive Guidance via Importance Sampling

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- 1. Prior works utlizing equivariant autoregressive or difusion models for target-aware 3D ligand design demonstrated suboptimal performance regarding synthetic accessibility. Is there a way to alleviate this issue? learning models. Thus, designing ligands from scratch without addressing these critcal Prior works utilizing equivariant autoregressive or diffusion models for target-aware 3D $\overline{3}$. However, can use mathematic during the hit expansion phase of drug discovery. The hit expansion phase of drug discovery. The hit expansion phase of drug discovery. The hit expansion phase of drug discovery $\overline{$
- 2. How can we design molecules that have optimized pharmacological properties specifically tailored to given protein targets?
- 3. Can we increase performance and generality by pre-training the diffusion model on large corpora of unconditional molecular data derived at a low level of theory? How does this transfer to target-conditioned drug design?

We introduce PILOT, a novel de novo generative model, denoted as $p_{\theta}(M|P,c)$, de- $\lim_{x \to \infty} \int_{0}^{x} \int_{0}^{x} e^{i\theta} \, dx$ igands represented by $x = (\mathbf{H}, \mathbf{X}, \mathbf{E})$, with $\mathbf{H} \in \{0, 1\}^{N \times K_a}, \mathbf{E} \in \{0, 1\}^{N \times K_a}$ $(0,1\}^{N \times N \times K_b}$, $\mathbf{X} \in \mathbb{R}^{N \times 3}$. This model processes both continuous and discrete variables and is conditoned on a specifc protein pocket *P*. We propose trajectory-based importance sampling to conditoned on a specifc protein pocket *P*. We propose trajectory-based importance sampling to optimize multiple objectives, including synthetic accessibility, docking score, and predicted halfmaximal inhibitory concentration (IC_{50}), thereby enhancing the targeted design of ligands. signed for generating 3D ligands represented by $x = (\mathbf{H}, \mathbf{X}, \mathbf{E})$, with $\mathbf{H} \in \{0, 1\}^{N \times K_a}, \mathbf{E} \in$ $\{0,1\}^{N \times N \times K_b}$, $\mathbf{X} \in \mathbb{R}^{N \times 3}$. This model processes both continuous and discrete variables and is

POTENCY OPTIMIZATION BondAnglesW¹ ↓ 0.42*±*0*.*⁰³ 1.86*±*0*.*⁰⁶ 0.52*±*0*.*⁰³ 0.92*±*0*.*⁰² 0.95*±*0*.*⁰² 1.07*±*0*.*⁰⁶

Performance comparison among unconditional and pIC50-conditional sampling using the Kinodata3D rest set comprising 10 kinase targets for 100 sampled ligands each. Evaluation based on mean docking score as proxy for omding anning using Qv and, predicted providence with NDKR-based chemical scores for α properties the drug meness ore as proxy for binding affinity using QVina2, EQGAT*^x*0*,f t disc* (*ws*(*t*)) 95.65*±*0*.*¹² 99.66*±*0*.*¹⁰ 0.11*±*0*.*⁰ 1.55*±*0*.*²¹ $N_{\rm N}$ cased enermodel and show that the generation $S_{\rm N}$ $\left(\frac{\omega_{1}}{\omega_{2}} \right)$ Performance comparison among unconditional and pIC50-condi Most set comprising to kinase targets for two sampled inguites \mathbf{c} .
Secore as provy for binding affinity using OVina? predicted pl Score as proxy for ointing allinity using Q vinaz, predicted process (OFD) and studies \blacksquare 85.15.85.15.85 properties like drug-likeness (QED) and synth Sing the Kinodata3D
ased on mean docking \overrightarrow{D} Kit-based chemical TargetDif -7.318*±*2*.*⁴⁷ -9.669*±*2*.*⁵⁵ 0.483*±*0*.*²⁰ 0.584*±*0*.*¹³ 4.594*±*0*.*⁸³ 0.718*±*0*.*⁰⁹ Performance comparison among unconditional and pIC50-conditional sampling using the Kinodata3D test set comprising 10 kinase targets for 100 sampled ligands each. Evaluation based on mean docking score as proxy for binding affinity using QVina2, predicted pIC50 and other RDKit-based chemical properties like drug-likeness (QED) and synthetic accessibility (SA)

Overview Navariant

Experiments lack of specifcity and result in inefectve drug candidates. Moreover, drug candidates must

THE EFFECT OF IMPORTANCE SAMPLING

Performance comparison among unconditional, SA-conditional, and SA-docking-conditional sampling using the CrossDocked 2020 test set comprising 100 protein targets for 100 sampled ligands each. Evaluation based on mean docking score as proxy for binding affinity using QVina2 and other RDKitbased chemical properties like drug-likeness (QED) and ligands. mance comparison among uncor $\frac{3.1}{100}$ However, can we use the hit expansion phase of drug discovery. The highest phase of drug discovery $\frac{1}{100}$ and $\frac{1}{100}$ and $\frac{1}{100}$ and $\frac{1}{100}$ and $\frac{1}{100}$ and $\frac{1}{100}$ and $\frac{1}{100}$ T and T can be involved as T is a proxy for official and T and T and T and T and T are T are T and T and T are T are T are T and T are T and T are T are T and T are T and T ar α and α increase the properties through high-throughput symmetre accessionity α Performance comparison among unconditional, SA-conditional, and SA-docking-conditional sampling using the CrossDocked2020 test set comprising 100 protein targets for 100 sampled ligands each. Evaluation based on mean docking score as proxy for binding affinity using QVina2 and other RDKitbased chemical properties like drug-likeness (QED) and synthetic accessibility (SA)

seally procedure procedure terms in the sealing of the SA-conditional model is scores for all sampled ligands across test targets for unconditional. SA-conditional and dockingconditional sampling Red rectangles within these plots highlight regions where sampled ligands $\frac{1}{2}$ assessing drug-like is frequently referenced, which is frequently referenced, which includes criteria is frequently referenced, which includes criteria is frequently referenced, which includes criteria is $\frac{1}{$ Scatter plots with Gaussian kernel density estimation illustrating the evolution of QED, SA and docking scores for all sampled ligands across test targets for unconditional, SA-conditional and dockingconditional samplingRed rectangles within these plots highlight regions where sampled ligands demonstrate superior QED, SA, and docking scores compared to the test set

Motivation and Background

Iert: Density plot comparing unconditional with pIC50-conditional sampling **left**: Density plot comparing unconditional with pIC RSE **1.1** α 1.18*z*⁰.000 0.85*±0.000 1.2000 1.2000 1.2000 1.2000 1.45⁰.000 1.48<i>±0.*00 **discute the-discute inconduction in the act of the state-of-the-**
discussed to other (SO₁ conductional with pIC50-conditional with pIC50-conditional with pIC50-conditional staterecent Density proceduring difusional with press conditions. **left**: Density plot comparing unconditional with pIC50-conditional sampling

right: Scatter heatmap overlap of unconditional and pIC50-conditional sampling comparing docking $\frac{1}{2}$ scores and predicted pIC50 values T_{SUSL} and T_{SUSL} and T_{SUSL} $\text{FUSL}}$ FUSL

Research Questons: MOTIVATION AND BACKGROUND exhibit favorable absorpton, distributon, metabolism, excreton (ADME), and toxicity profles

In the upper panel of Fig. 8, we demonstrate how ensemble modeling significantly improves the stability and generality of pIC50 predictions. Here, we employ an ensemble of expert models for CDK2 - EXAMPLES

lack of specifcity and result in inefectve drug candidates. Moreover, drug candidates must

Our proposed EQGAT*x*⁰

DIFUSION
TRAINING AND INFERENCE