Functional-Group-Based Diffusion for Pocket-Specific Molecule Generation and Elaboration

Haitao Lin, Yufei Huang, Odin Zhang, Yunfan Liu, Lirong Wu, Siyuan Li, Zhiyuan Chen, Stan Z. Li
AI Lab, Research Center for Industries of the Future, Westlake University

Introduction

Most of AI-assisted structure-based drug design methods are atom-level-based, which consider atoms as basic components and generate atom positions and types. In this way, however, it is hard to generate realistic fragments with complicated structures. To solve this, we propose D3FG, a functional-group-based diffusion model for pocket-specific molecule generation and elaboration. It decomposes molecules into two categories of components: functional groups defined as rigid bodies and linkers as mass points. The two kinds of components can together form complicated fragments that enhance ligand-protein interactions.

Methods

Generating targets. For the functional groups, D3FG aims to generate its type s_i, center 3D position x_i and the local frames orientation O_i, while for the single atom which we called linker, it aims to generate its type s_j and position x_i.

Forward diffusion process. Let s_j^t as the one-hot encoding of the type of a single functional group or linker in the timestep t, the forward process transits it into the abosorbing state as Eq. (1). For the positions x_j^t, its transition distributions are Gaussian as Eq. (2). For the functional group orientation, SO(3) diffusion is used, which employ isotropic Gaussian distribution on SO(3) to formulate the process, as shown in Eq. (3).

$$q(s_j^t|s_j^{t-1}) = \text{Multinomial}\left(s_j^{t-1}\boldsymbol{Q}^t\right)$$
$$q(s_j^t|s_j^0) = \text{Multinomial}\left(s_j^0\bar{\boldsymbol{Q}}^t\right) \quad (1)$$

$$q(\boldsymbol{x}_j^t|\boldsymbol{x}_j^{t-1}) = \mathcal{N}\left(\boldsymbol{x}_j^t|\sqrt{1-\beta_{\text{pos}}^t}\cdot\boldsymbol{x}_j^{t-1}, \beta_{\text{pos}}^t\boldsymbol{I}\right);$$
$$q(\boldsymbol{x}_j^t|\boldsymbol{x}_j^0) = \mathcal{N}\left(\boldsymbol{x}_j^t|\sqrt{\bar{\alpha}_{\text{pos}}^t}\cdot\boldsymbol{x}_j^0, (1-\bar{\alpha}_{\text{pos}}^0)\boldsymbol{I}\right), \quad (2)$$

$$q(\boldsymbol{O}_j^t|\boldsymbol{O}_j^0) = \mathcal{IG}_{\text{so(3)}}\left(\boldsymbol{O}_j^t|\lambda_{\text{ori}}(\bar{\alpha}_{\text{ori}}^t, \boldsymbol{O}_j^0), (1-\bar{\alpha}_{\text{ori}}^t)\right), \quad (3)$$

Backward generative process. A transformer-based equivariant graph neural networks is used to formulate the backward process as a denoiser. Three heads parameterized with MLP are stacked after several layers of transformers update the node embedding for updating the three variables as Eq. (5).

$$p(s_j^{t-1}|\mathcal{M}^t, \mathcal{P}) = \text{Multinomial}\left(F(\mathcal{M}^t, \mathcal{P})[j]\right).$$
$$p(\boldsymbol{x}_j^{t-1}|\mathcal{M}^t, \mathcal{P}) = \mathcal{N}\left(\boldsymbol{x}_j^{t-1}|\boldsymbol{\mu}_{\text{pos}}(\mathcal{M}^t, \mathcal{P}), \beta_{\text{pos}}^t\boldsymbol{I}\right) \quad (5)$$
$$p(\boldsymbol{O}_j^{t-1}|\mathcal{M}^t, \mathcal{P}) = \mathcal{IG}_{\text{so(3)}}\left(\boldsymbol{O}_j^{t-1}|H(\mathcal{M}^t, \mathcal{P})[j], \beta_{\text{ori}}^t\right)$$

Two types of generation schemes. (i) In joint scheme, we regard amino acids, functional groups, and linkers at the same level, and use one single neural network to predict the three variables and update them. (ii) In two-stage scheme, we regard amino acids and functional groups at the fragment level, and linkers at the atom level, and use two different neural networks to parameterize the transition distribution. In the first stage, the functional groups are generated, and then single atoms as linkers will be generated to connect the generated functional groups as a full molecule. (Fig. 1)

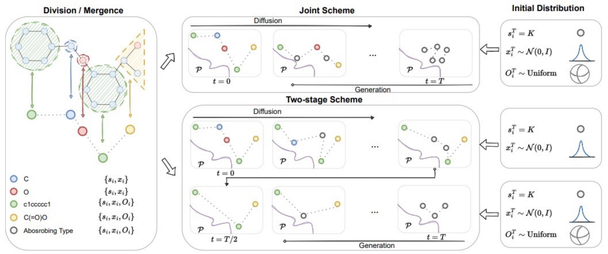
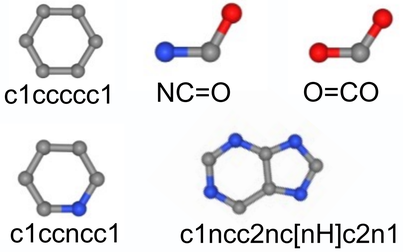


Fig. 1 Two generation schemes.

Experiments

Functional group repository is established based on the most frequent functional groups occurring in the CrossDock2020.



Structure analysis. D3FG has superiority in generating molecules with realistic drug structures since distributions of the functional groups in generated molecules are more similar to the real drug molecules'. Besides, in the molecule geometries like atom type, bond distance, bond angle, dihedral and atom type distribution, D3FG also achieves the competitive performance with sota methods.

Drug property comparison. Experiments on molecule generation and elaboration are conducted. (i) D3FG of the two-stage scheme achieves competitive affinity scores, comparable to TargetDiff and much better than D3FG of the joint scheme. (ii) Two variants of D3FG achieve overall best performance in the metrics. (iii) In the molecule elaboration task, D3FG(EHot) tends to generate molecules with higher affinity, while molecules elaborated by D3FG(ECold) show tiny differences in binding affinity from the raw references.

Table. 1 Comparison on Drug Properties

	Vina Score (↓)	Vina ΔAffinity (↑)	Gnina Score (↑)	Gnina ΔAffinity(↑)	QED (↑)	SA (↑)	LogP	Lipinski (↑)
Ref. (Test)	-7.06	-	5.37	-	0.471	0.725	0.818	4.247
LiGAN	-6.17	21.24%	4.29	21.68%	0.382	0.584	-0.138	4.046
GraphBP	-6.36	27.41%	4.52	26.54%	0.437	0.502	3.024	4.448
3DSBDD	-6.12	20.73%	4.48	19.22%	0.426	0.625	0.266	4.735
Pocket2Mol	-6.92	45.86%	5.34	40.68%	**0.543**	0.746	1.584	4.904
TargetDiff	**-7.11**	**49.52%**	**5.41**	**42.40%**	0.474	0.581	1.402	4.487
DiffSBDD	-6.37	31.32%	4.63	27.96%	0.494	0.343	-0.157	4.895
D3FG (Joint)	-6.89	37.32%	5.30	33.45%	**0.507**	**0.832**	2.796	**4.943**
D3FG (Stage)	**-6.96**	**45.88%**	**5.43**	**43.36%**	0.501	**0.840**	2.821	**4.965**
D3FG (EHot)	-7.19	51.78%	5.51	56.53%	0.482	0.731	0.814	4.330
D3FG (ECold)	-7.02	44.03%	5.16	32.69%	0.476	0.707	0.820	4.228