Full-Atom Peptide Design with Geometric Latent Diffusion

Xiangzhe Kong, Yinjun Jia, Wenbing Huang, Yang Liu

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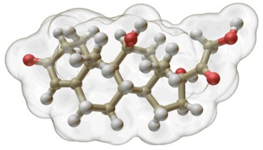
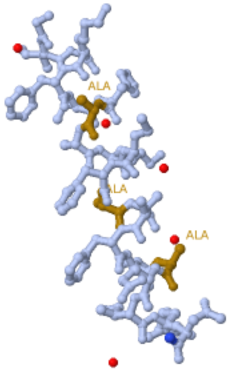
Why Peptide?



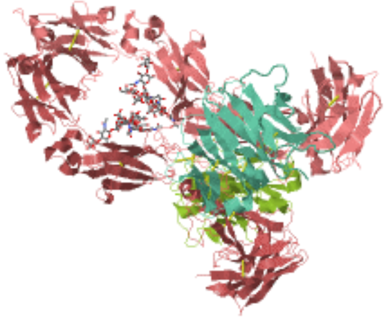
Small Molecule

V.S.



Peptide

V.S.



Antibody

Small Molecule – Drawbacks

- Low specificity
- Toxicity
- Low synthesizability

Peptide – Advantages

- High specificity
- Good safety
- High synthesizability

Peptide – Advantages

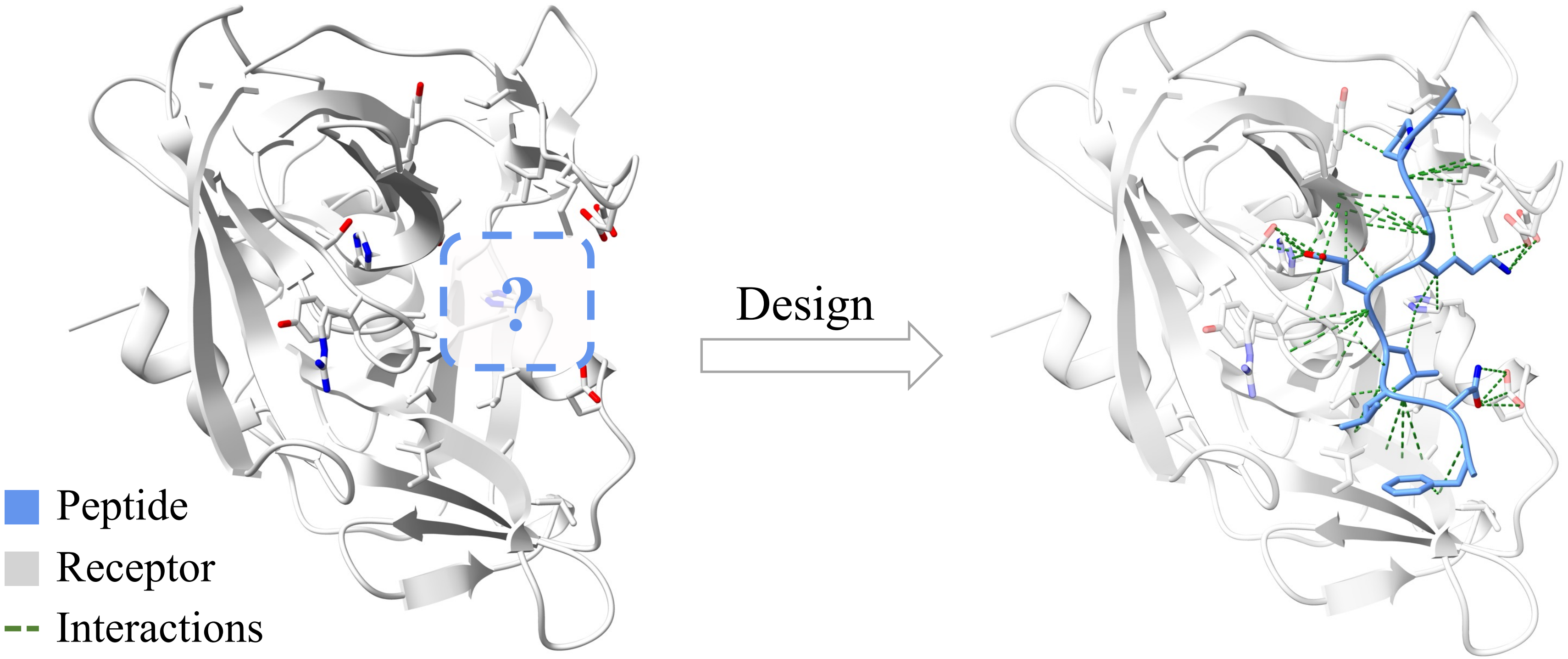
- High cell permeability
- Oral availability
- Low cost

Antibody – Drawbacks

- Low cell permeability
- Injection
- High cost

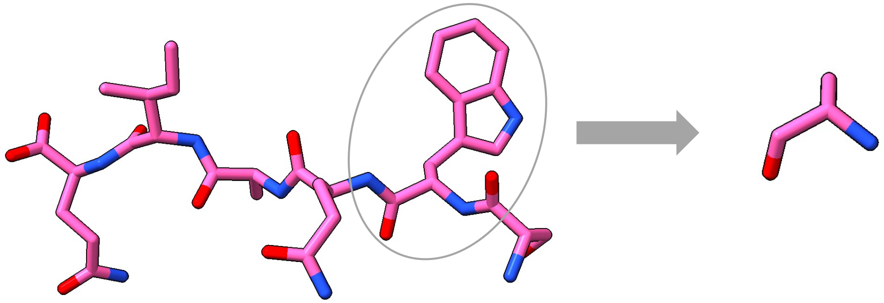
Therapeutic peptides: current applications and future directions. *Signal transduction and targeted therapy* 7.1 (2022): 48.

Peptide Design: Given the binding site $\mathcal{G}_b = \{(x_i, \overrightarrow{X_i})\}$, the model is required to generate the full-atom structure of a peptide binder $\mathcal{G}_p = \left\{\left(x_j, \overrightarrow{X_j}\right)\right\}$, where x and $\vec{X}$ denote the amino acid type and the coordinates of all atoms in the amino acid.



Challenges

Variable Data Length

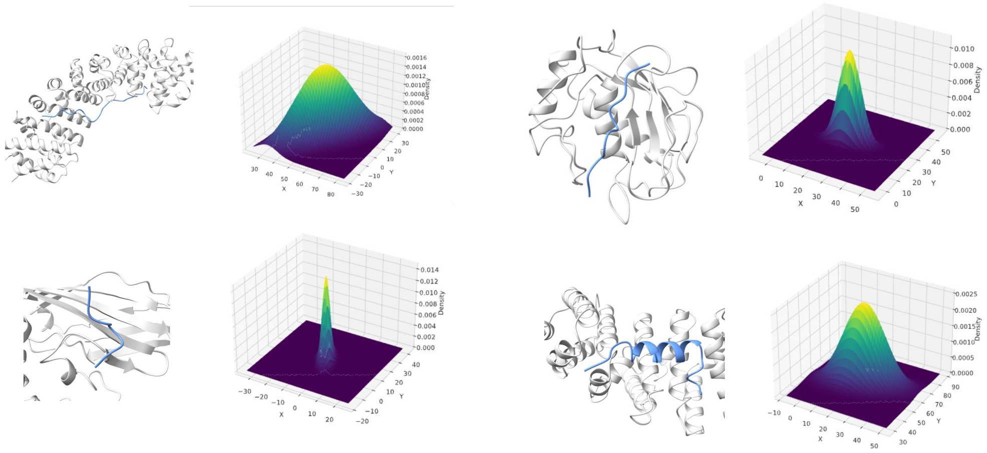


$$x_j^t = W \quad \longrightarrow \quad x_j^{t-1} = A$$

$$\vec{X}_j^t \in \mathbb{R}^{14\times3} \quad \longrightarrow \quad \vec{X}_j^{t-1} \in \mathbb{R}^{5\times3}$$

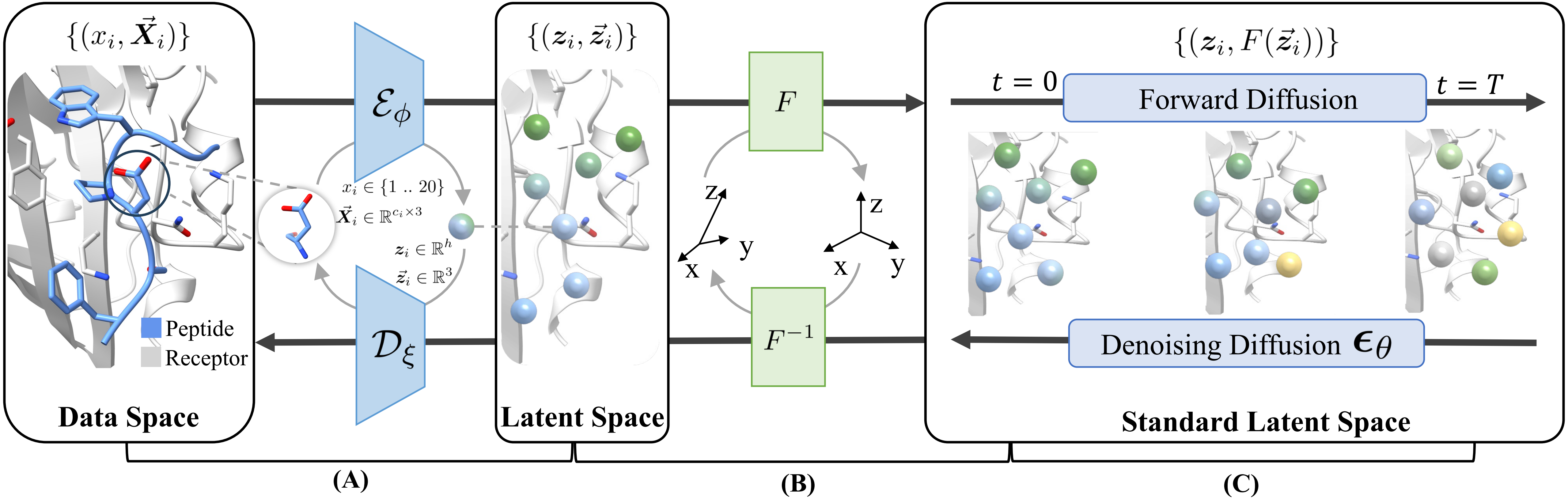
- Different amino acids have different number of atoms
- Denosing amino acid types result in abrupt changes in the number of atoms (i.e. data length), which is not compatible with current diffusion framework.

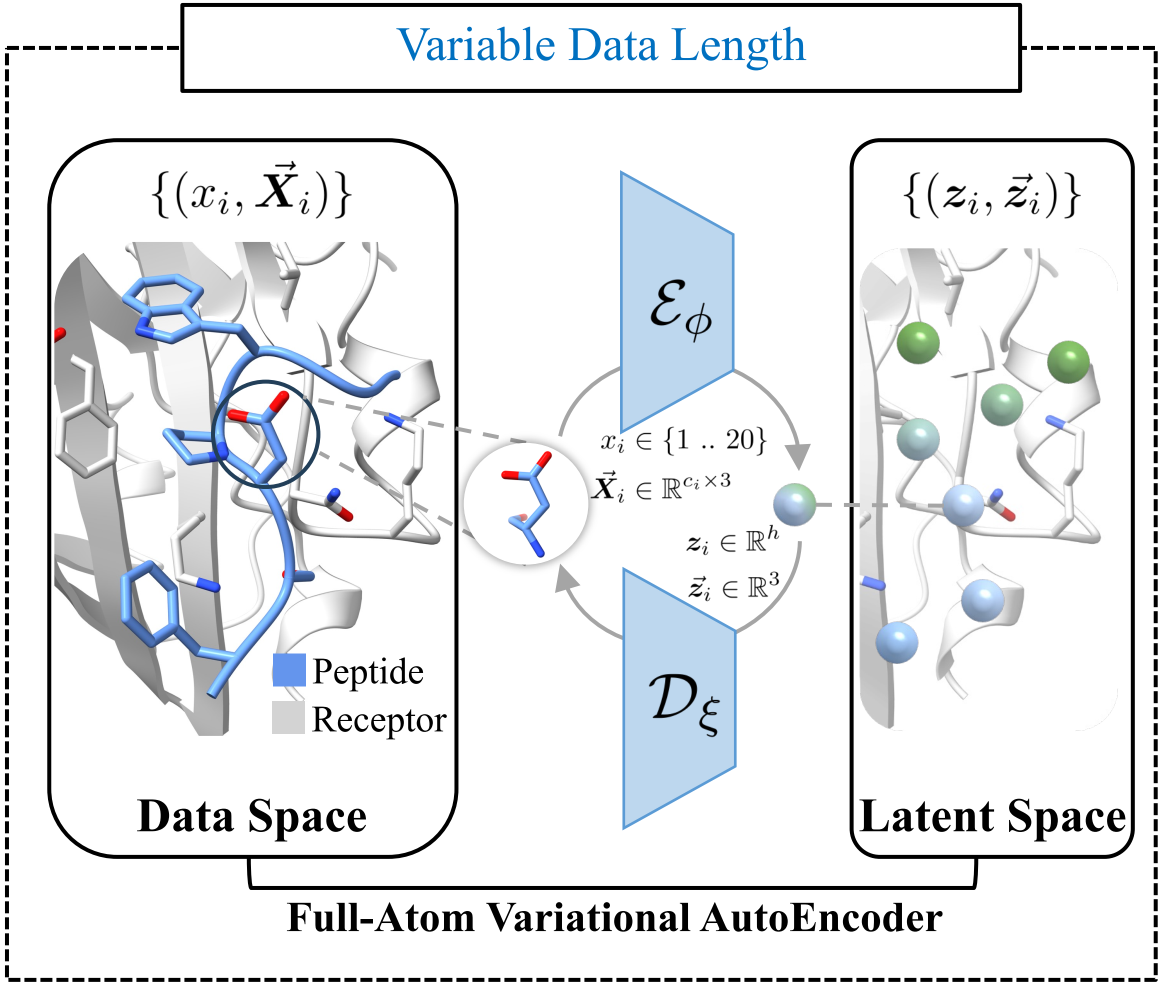
Diverse Pocket Geometry



- $\vec{x} \sim \mathcal{N}(\vec{\mu}, \Sigma)$ with diverse expectation and covariance, leading to poor generalizability
- Current diffusion models tend to produce exploding coordinates for some binding sites in the test set.

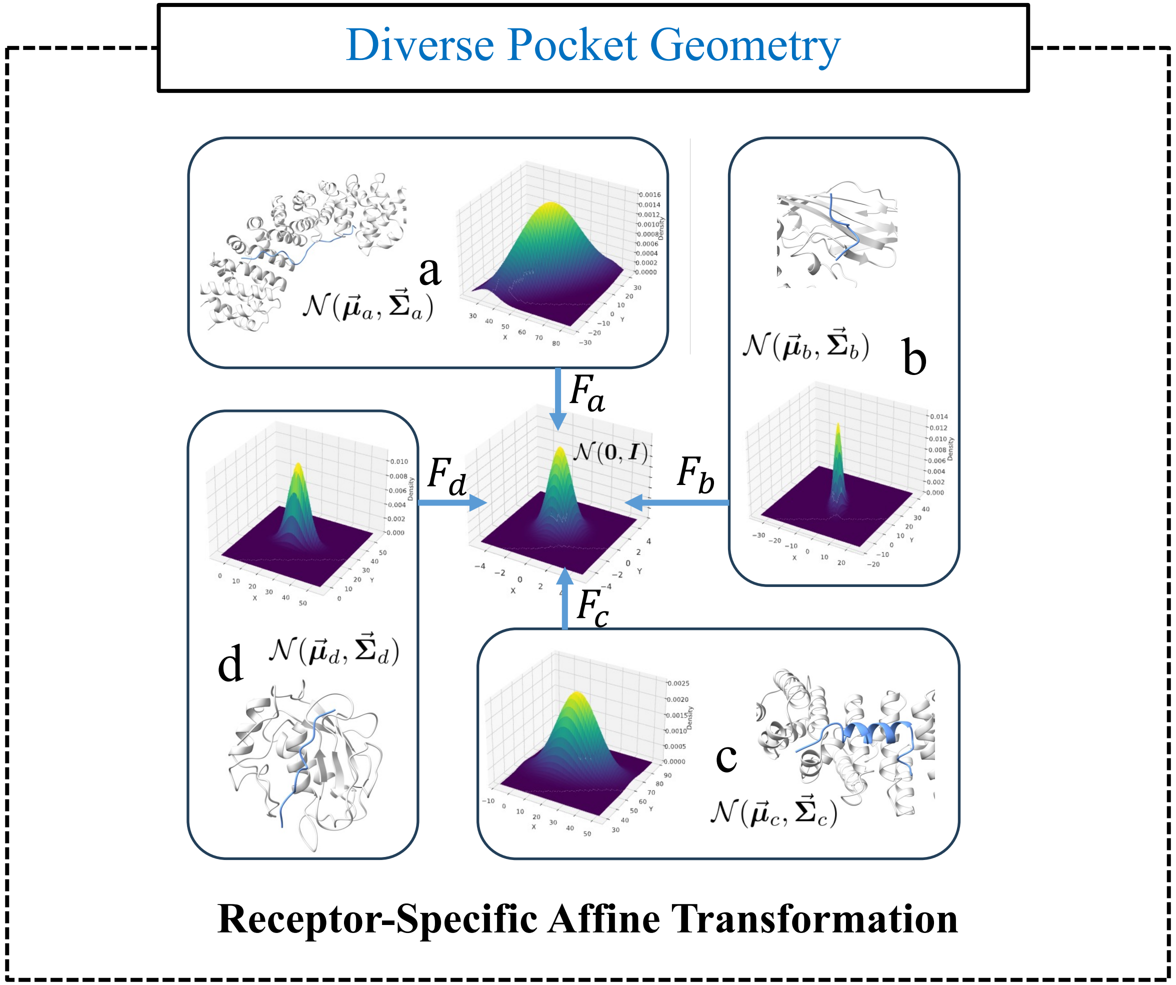
Peptide Design with Geometric LAtent Diffusion (PepGLAD)


$\{(x_i, \vec{\boldsymbol{X}}_i)\}$
Peptide
Receptor
Data Space
$\mathcal{E}_\phi$
$\mathcal{D}_\xi$
$x_i \in \{1 \,..\, 20\}$
$\vec{\boldsymbol{X}}_i \in \mathbb{R}^{c_i \times 3}$
$\boldsymbol{z}_i \in \mathbb{R}^h$
$\vec{\boldsymbol{z}}_i \in \mathbb{R}^3$
$\{(\boldsymbol{z}_i, \vec{\boldsymbol{z}}_i)\}$
Latent Space
F
F^{-1}
z
y
x
z
x
y
$\{(\boldsymbol{z}_i, F(\vec{\boldsymbol{z}}_i))\}$
$t = 0$
Forward Diffusion
$t = T$
Denoising Diffusion $\boldsymbol{\epsilon}_\theta$
Standard Latent Space
(A)
(B)
(C)


Variable Data Length

$\{(x_i, \vec{\boldsymbol{X}}_i)\}$
$\mathcal{E}_\phi$
$\{(\boldsymbol{z}_i, \vec{\boldsymbol{z}}_i)\}$
$x_i \in \{1 \; .. \; 20\}$
$\vec{\boldsymbol{X}}_i \in \mathbb{R}^{c_i \times 3}$
$\boldsymbol{z}_i \in \mathbb{R}^h$
$\vec{\boldsymbol{z}}_i \in \mathbb{R}^3$
$\mathcal{D}_\xi$
Peptide
Receptor
Data Space
Latent Space

Full-Atom Variational AutoEncoder


Diverse Pocket Geometry

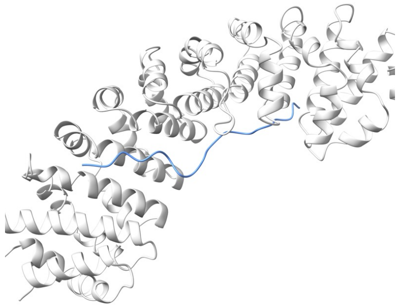
a
$\mathcal{N}(\vec{\boldsymbol{\mu}}_a, \vec{\boldsymbol{\Sigma}}_a)$
F_a
$\mathcal{N}(\vec{\boldsymbol{\mu}}_b, \vec{\boldsymbol{\Sigma}}_b)$
b
F_d
$\mathcal{N}(\boldsymbol{0}, \boldsymbol{I})$
F_b
F_c
d
$\mathcal{N}(\vec{\boldsymbol{\mu}}_d, \vec{\boldsymbol{\Sigma}}_d)$
c
$\mathcal{N}(\vec{\boldsymbol{\mu}}_c, \vec{\boldsymbol{\Sigma}}_c)$

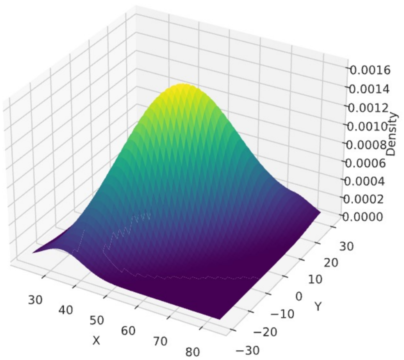
Receptor-Specific Affine Transformation

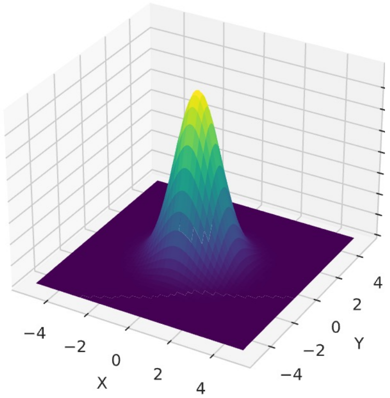
Receptor-Specific Affine Transformation

easily invertible normalization trick

$$\begin{tikzcd} \mathcal{N}(\vec{\mu}, \vec{\Sigma}) \arrow[r, bend left, "F(\vec{\boldsymbol{x}}) = \vec{\boldsymbol{L}}^{-1}(\vec{\boldsymbol{x}} - \vec{\boldsymbol{\mu}})"] & \mathcal{N}(\mathbf{0}, \boldsymbol{I}) \arrow[l, bend left, "F^{-1}(\vec{\boldsymbol{x}}) = \vec{\boldsymbol{L}}\vec{\boldsymbol{x}} + \vec{\boldsymbol{\mu}}"] \end{tikzcd}$$







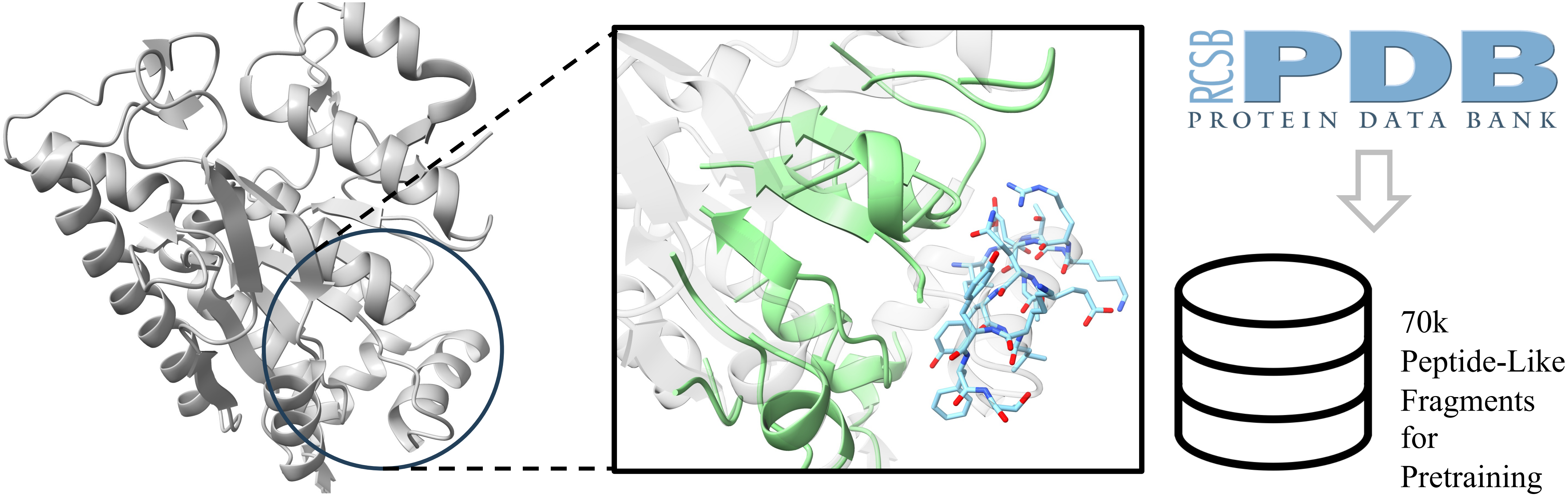
Cholesky Decomposition

$$\vec{\boldsymbol{\Sigma}} = \vec{\boldsymbol{L}}\vec{\boldsymbol{L}}^{\top}, \vec{\boldsymbol{L}} \in \mathbb{R}^{3\times 3}$$

$$\begin{bmatrix} l_{11} & 0 & 0 \\ l_{21} & l_{22} & 0 \\ l_{31} & l_{32} & l_{33} \end{bmatrix}\begin{bmatrix} l_{11} & l_{21} & l_{31} \\ 0 & l_{22} & l_{32} \\ 0 & 0 & l_{33} \end{bmatrix}$$

Dataset: ProtFrag

70K peptide-like fragments within monomers for training the full-atom variational autoencoder



70k Peptide-Like Fragments for Pretraining

Dataset: PepBench

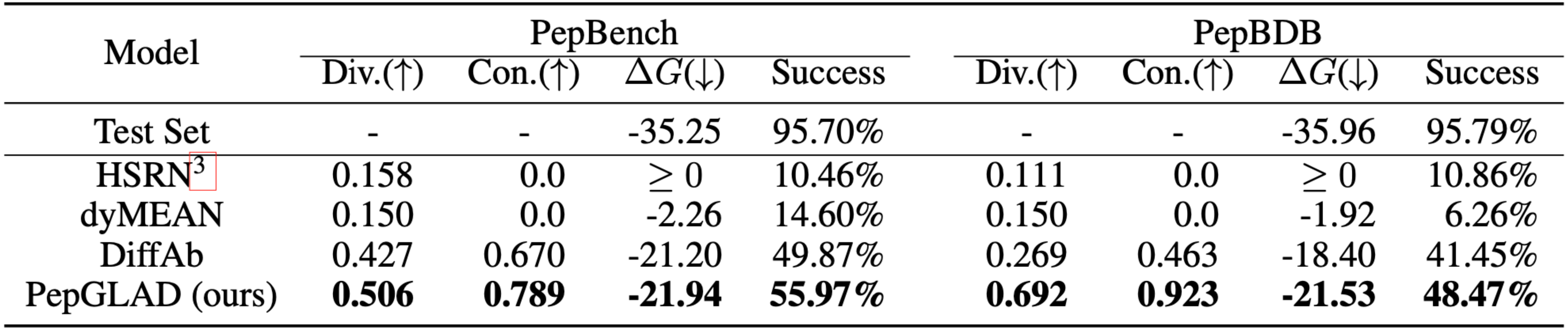
- **Training/Validation:** 6K cleaned non-redundant peptides (4-25 residues) from PDB
- **Test:** 93 complexes curated by experts from existing literature[1]
- **Split:** Cluster all complexes with target proteins sequence identity above 40%, and remove the complexes sharing the same clusters with those from the test set. Such split test the generalization ability of the generative models with respect to different target proteins.
- Url: https://doi.org/10.5281/zenodo.13358010

[1] Tsaban, Tomer, et al. "Harnessing protein folding neural networks for peptide–protein docking." *Nature communications* 13.1 (2022): 176.

Exp1: Sequence-Structure Co-Design

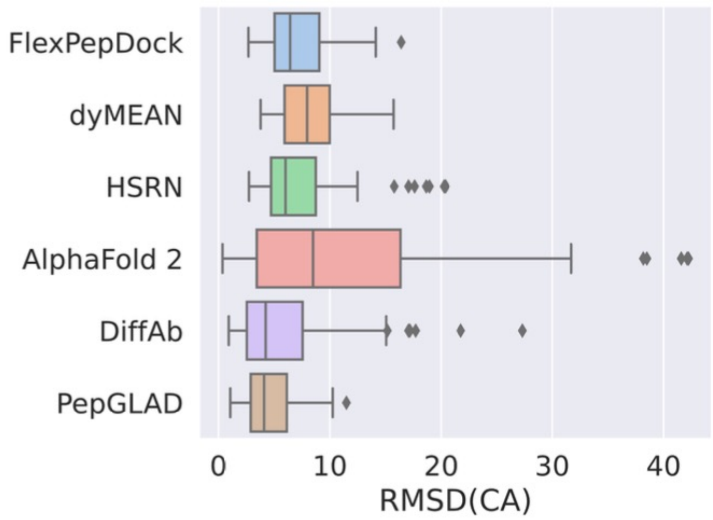
Metrics:

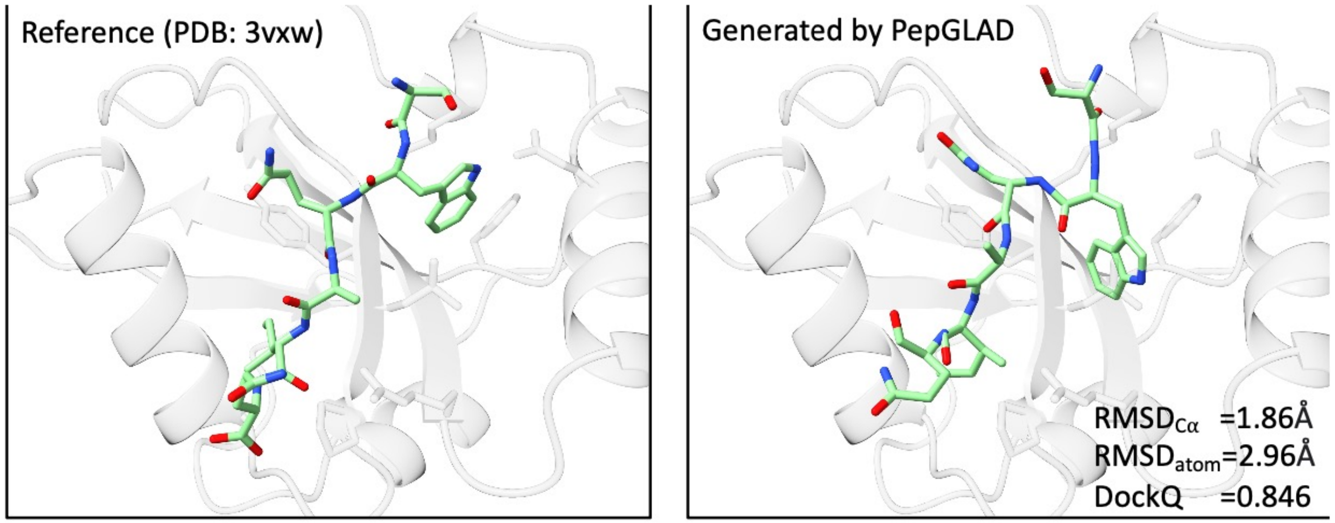
- **Diversity:** Ratio of unique clusters of sequence-structure clustering
- **Consistency:** Association between sequence clusters and structure clusters (similar sequences should lead to similar structures)
- **ΔG**: Binding energy measured by Rosetta
- **Success:** Ratio of ΔG < 0



Model	PepBench				PepBDB			
	Div.(↑)	Con.(↑)	ΔG(↓)	Success	Div.(↑)	Con.(↑)	ΔG(↓)	Success
Test Set	-	-	-35.25	95.70%	-	-	-35.96	95.79%
HSRN[3]	0.158	0.0	≥ 0	10.46%	0.111	0.0	≥ 0	10.86%
dyMEAN	0.150	0.0	-2.26	14.60%	0.150	0.0	-1.92	6.26%
DiffAb	0.427	0.670	-21.20	49.87%	0.269	0.463	-18.40	41.45%
PepGLAD (ours)	**0.506**	**0.789**	**-21.94**	**55.97%**	**0.692**	**0.923**	**-21.53**	**48.47%**

Exp2: Binding Conformation Generation




Reference (PDB: 3vxw)

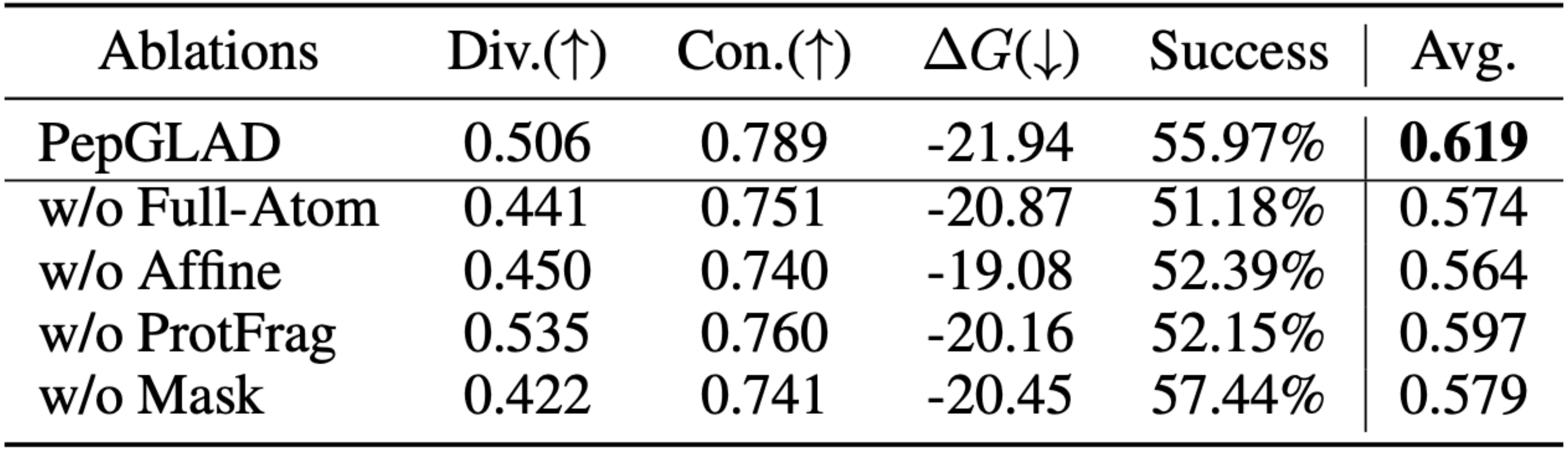
Generated by PepGLAD

Model	PepBench			PepBDB		
	RMSD$_{C_\alpha}$(↓)	RMSD$_{atom}$(↓)	DockQ(↑)	RMSD$_{C_\alpha}$(↓)	RMSD$_{atom}$(↓)	DockQ(↑)
FlexPepDock	6.43	7.52	0.393	-	-	-
AlphaFold 2	8.49	9.20	0.355	-	-	-
dyMEAN	7.96	8.35	0.374	17.64	17.56	0.142
HSRN	6.02	7.59	0.508	9.28	9.72	0.394
DiffAb	4.23	7.60	0.586	13.96	13.12	0.236
PepGLAD (ours)	**4.09**	**5.30**	**0.592**	**8.87**	**8.62**	**0.403**

Ablation Study

Significance:

Affine Transformation > Full-Atom Modeling > Masked Autoencoder > Protein Fragments Training



Ablations	Div.(↑)	Con.(↑)	$\Delta G(\downarrow)$	Success	Avg.
PepGLAD	0.506	0.789	-21.94	55.97%	**0.619**
w/o Full-Atom	0.441	0.751	-20.87	51.18%	0.574
w/o Affine	0.450	0.740	-19.08	52.39%	0.564
w/o ProtFrag	0.535	0.760	-20.16	52.15%	0.597
w/o Mask	0.422	0.741	-20.45	57.44%	0.579

Conclusion

- PepGLAD: full-atom model for peptide design given the binding site on the target protein
- We curate PepBench with carefully selected test complexes and split criterion to test the generalization ability across different target proteins
- We curate ProtFrag of 70K peptide-like fragments for data augmentation, which may facilitate future research on peptide design
- PepGLAD surpasses state-of-the-art models in terms of sequence-structure co-design and binding conformation generation

Thank you for your attention!

Paper Link

Code Link