UniMoMo: Unified Generative Modeling of 3D Molecules for *De Novo* Binder Design

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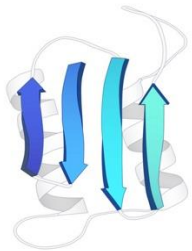
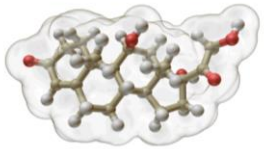
Jianzhu Ma, Wenbing Huang, Kai Liu, Yang Liu



Contents

Different Types of Molecules Serve Different Purposes



Therapeutic Areas

Neurological diseases

Infectious diseases

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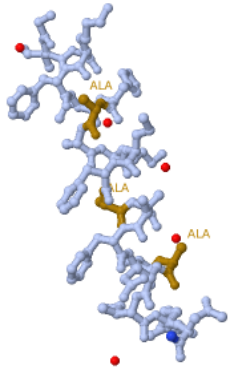
Small Molecule

√ good

- Oral bioavailability
- Cell permeability

× bad

- Specificity
- Mutation resistance



Therapeutic Areas

Metabolic diseases

Cardiovascular conditions

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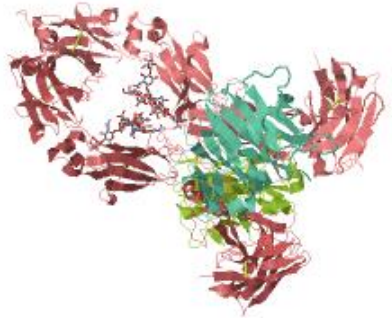
Peptide

√ good

- Safety (lower toxicity)
- Modulating protein-protein interactions

× bad

- Half-life
- Tissue penetration



Therapeutic Areas

Cancer

Autoimmune diseases

…

Antibody

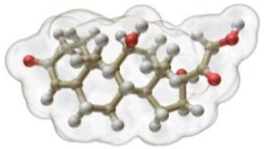
√ good

- Specificity
- Half-life

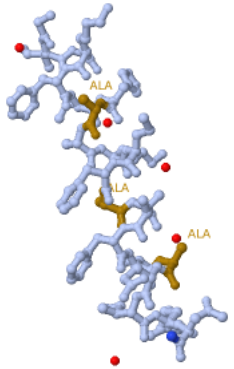
× bad

- Cell permeability
- Oral bioavailability

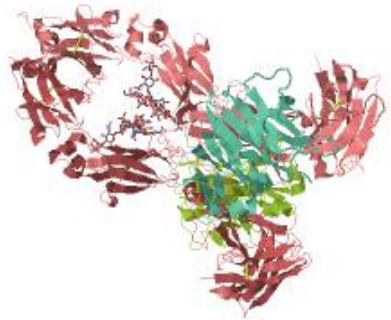
Current Paradigm: Domain-Specific Models



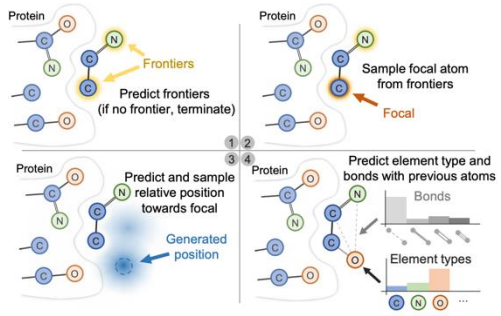
Small Molecule

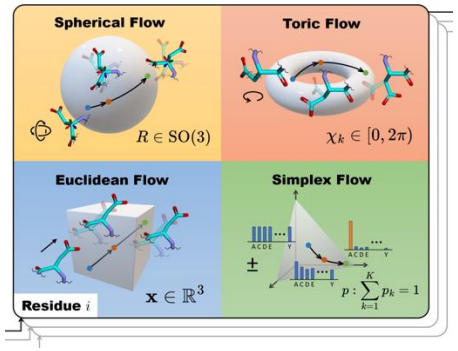


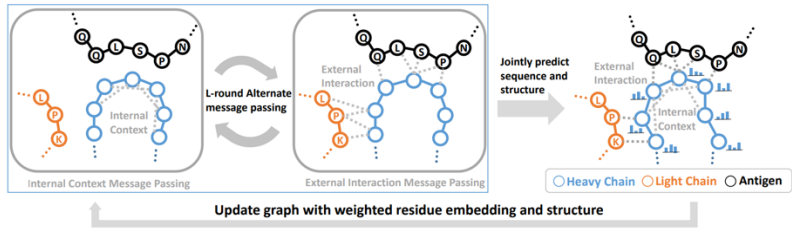
Peptide



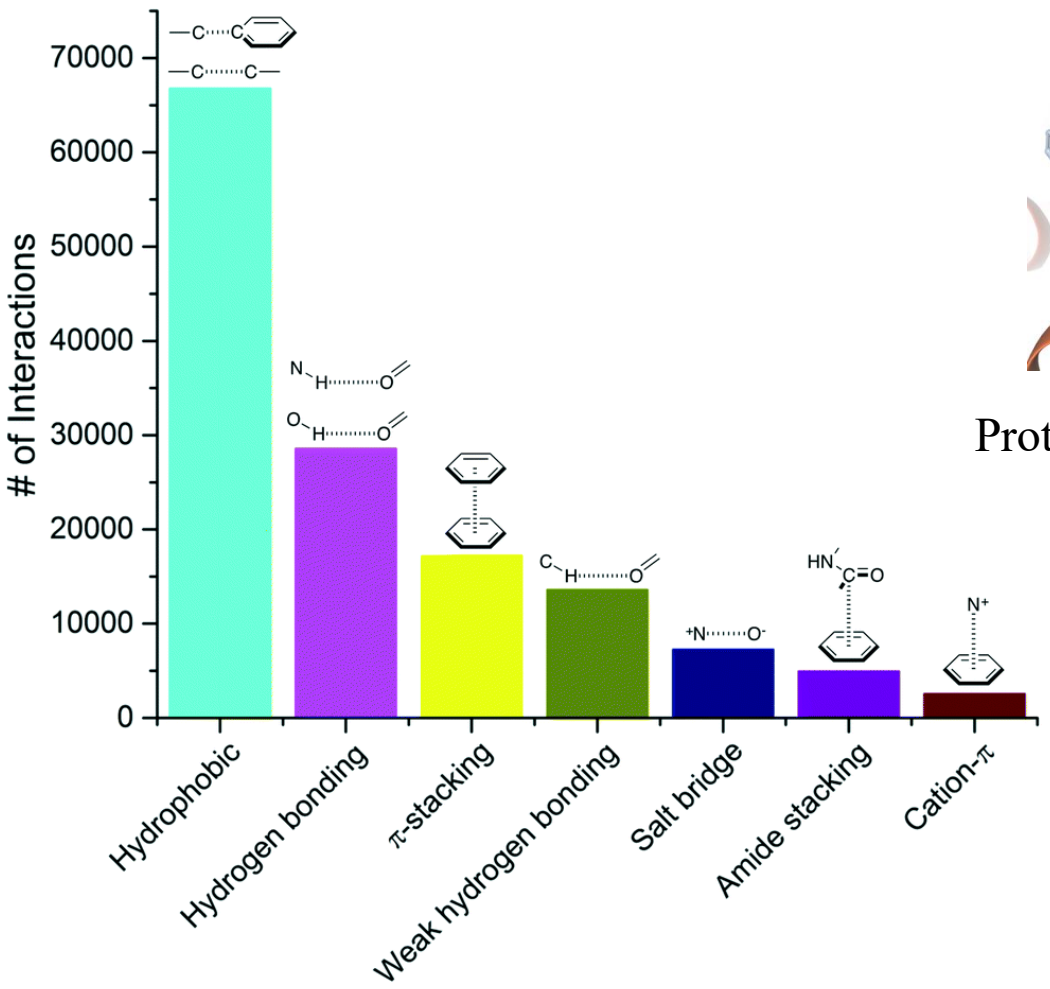
Antibody

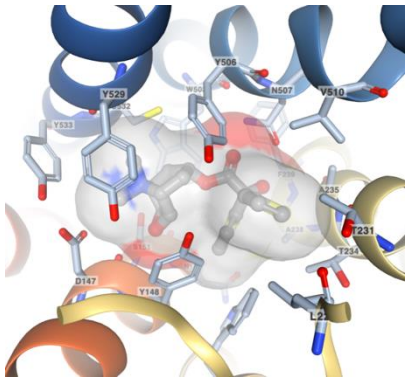




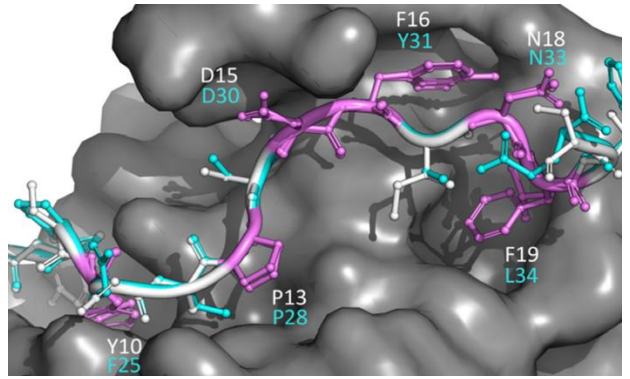


Reason 1 for a Unified Model: Shared Interaction Patterns

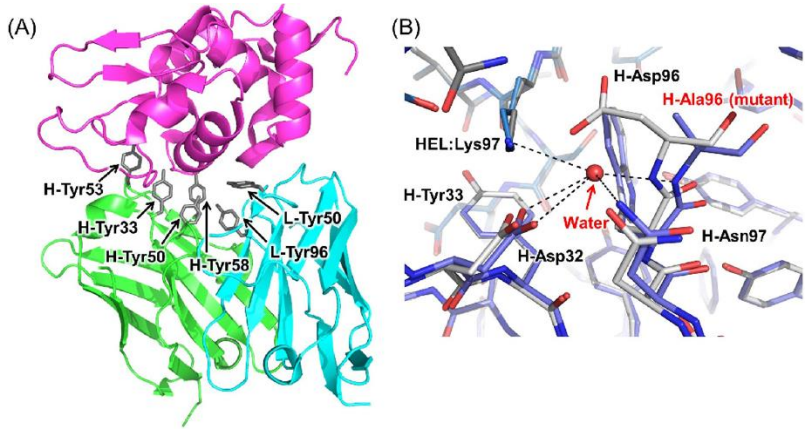




Protein & Small Molecule

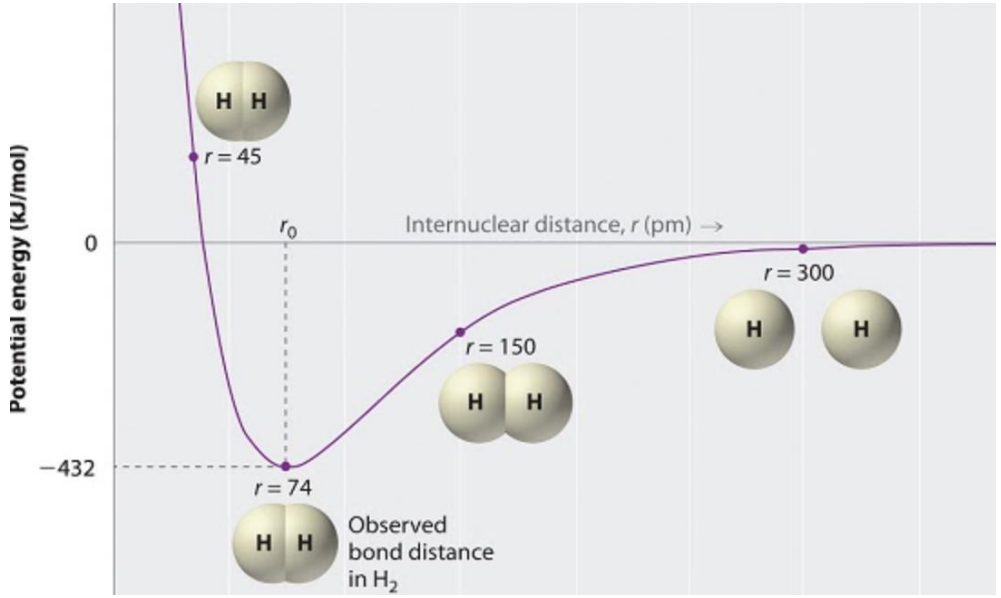


Protein & Peptide

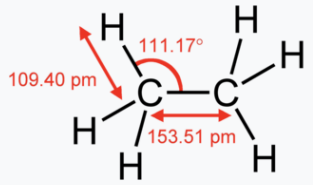
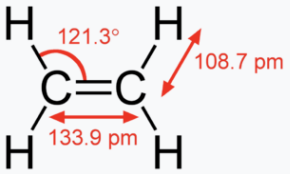
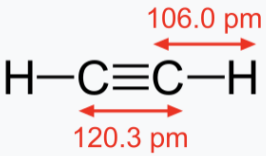


Protein & Antibody

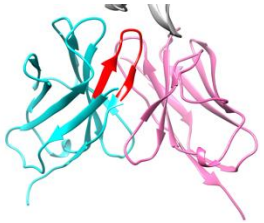
Reason 2 for a Unified Model: Shared Physical Constraints



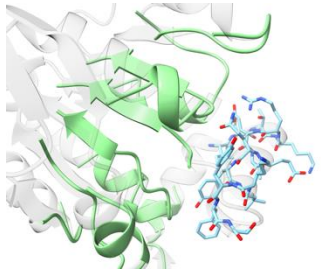
Comparison of bond lengths in simple hydrocarbons[5]

Molecule	Ethane	Ethylene	Acetylene
Formula	C_2H_6	C_2H_4	C_2H_2
Class	alkane	alkene	alkyne
Structure			
Hybridisation of carbon	sp^3	sp^2	sp
C-C bond length	**153.5 pm**	**133.9 pm**	**120.3 pm**
Proportion of C-C single bond	100%	87%	78%
Structure determination method	microwave spectroscopy	microwave spectroscopy	infrared spectroscopy

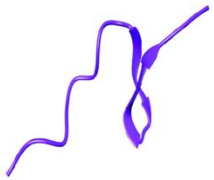
Unifying Molecules into One Generative Model



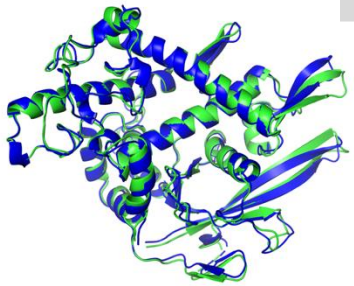
Antibody



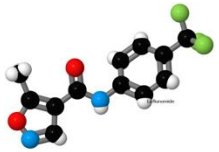
Fragments



Peptide



Protein



Small Molecule

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Unified Generative Model

Application Standpoint

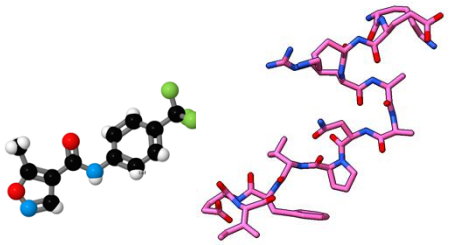
Enables the exploration of multiple drugs spanning diverse molecular types for a single target, addressing varied therapeutic needs.

Machine Learning Standpoint

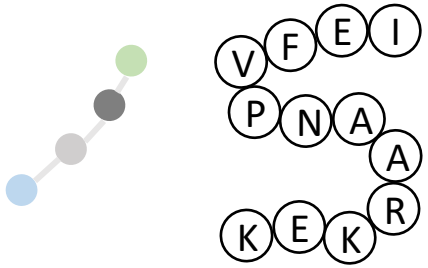
Leverages larger and more diverse datasets, better exploiting available data for learning generalizable patterns.

Representation: Atom or Block?

Atom Level

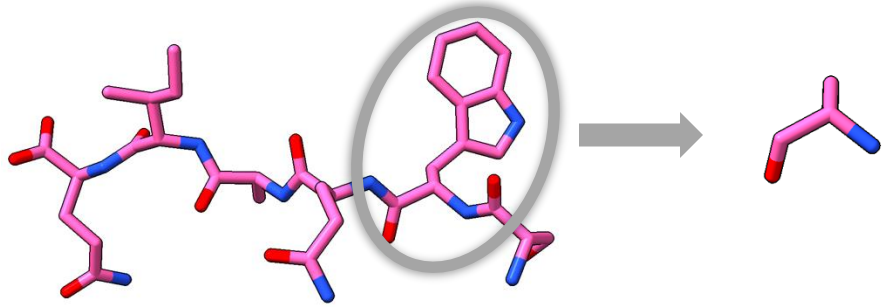


Block Level



- Atom-level representation ignores the intrinsic hierarchical priors and leads to high complexity.
- Block-level representation lacks transferability, which is defined on atom-level details.

Diffusion: Variable Data Length



$x_j^t = W$

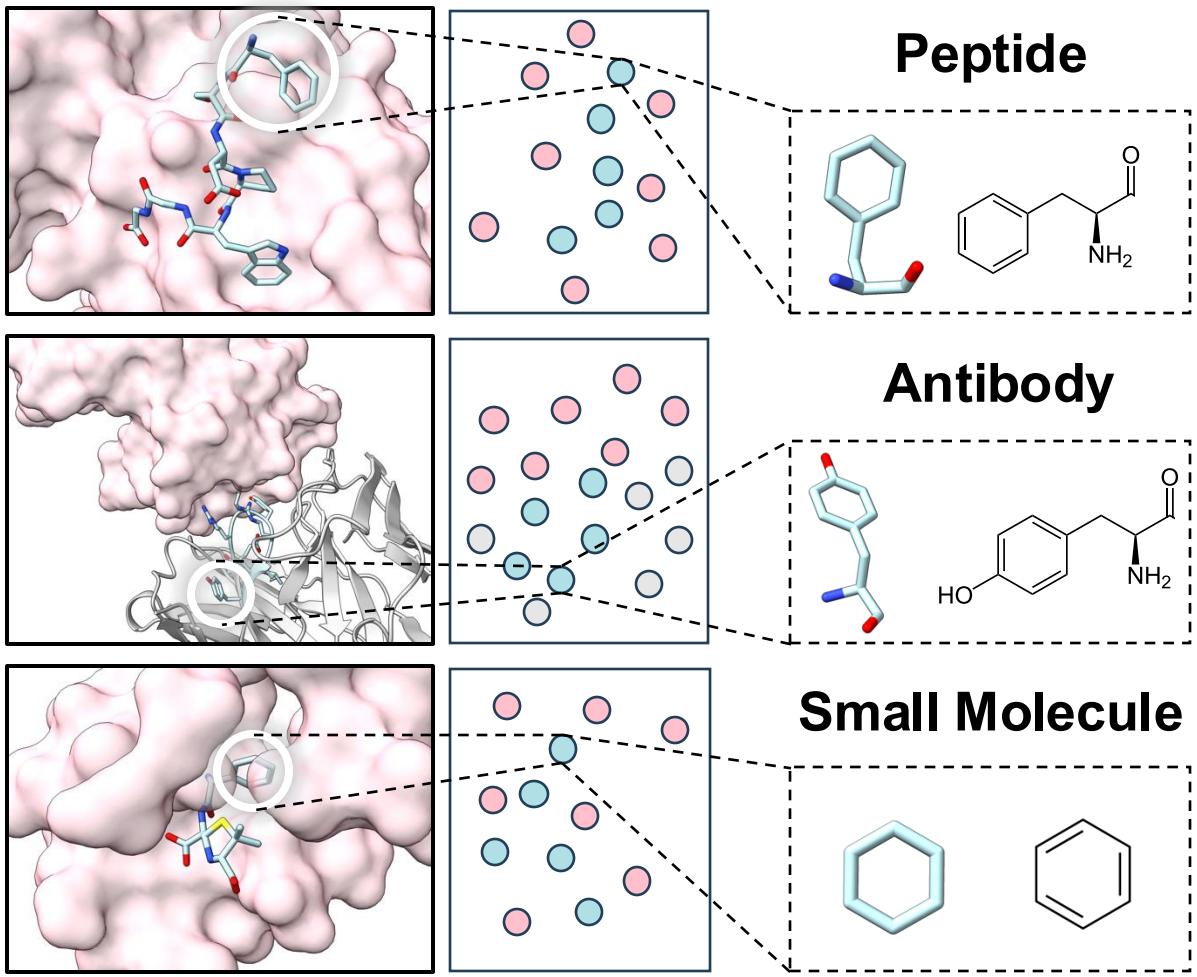
$\vec{X}_j^t \in \mathbb{R}^{14\times 3}$

$x_j^{t-1} = A$

$\vec{X}_j^{t-1} \in \mathbb{R}^{5\times 3}$

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

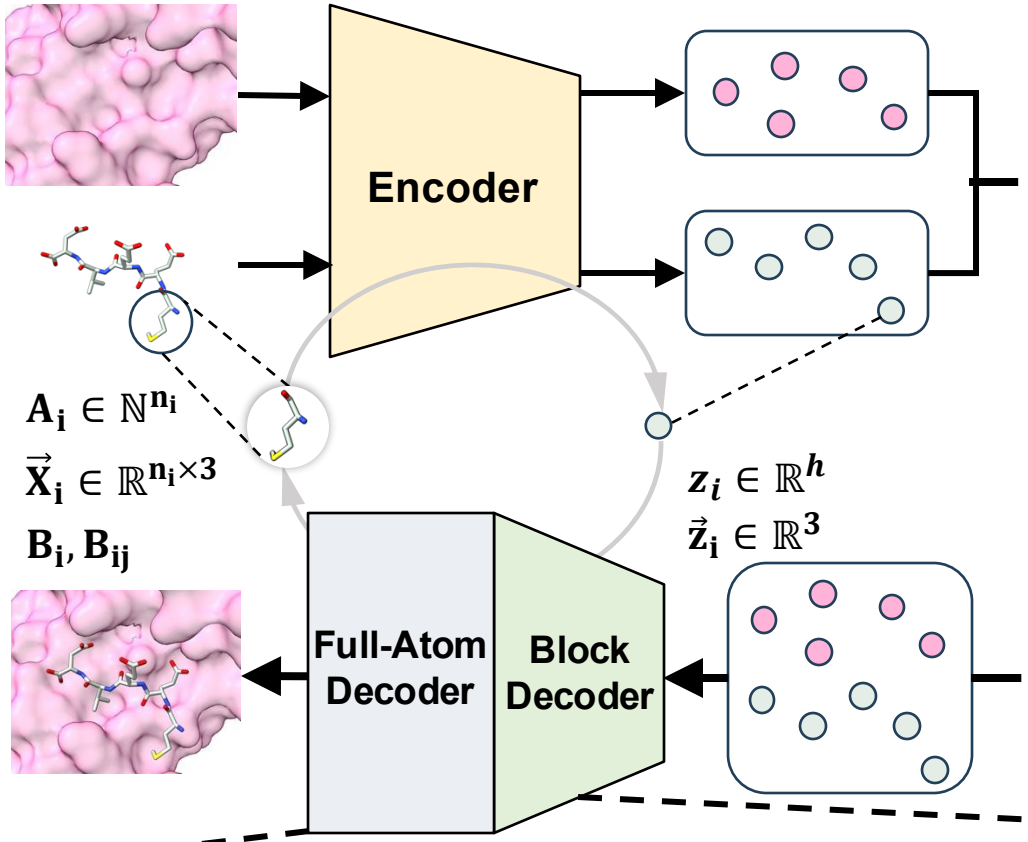
Unified Representation – Graph of Atomic Subgraphs (Blocks)



Type	Block
Peptide/Antibody/Protein	Amino Acid
Small Molecule	Fragment (PS)
Non-Canonical Amino Acid	Fragment (PS)

Molecule Generation by **Principal Subgraph** Mining and Assembling (NeurIPS 2022)

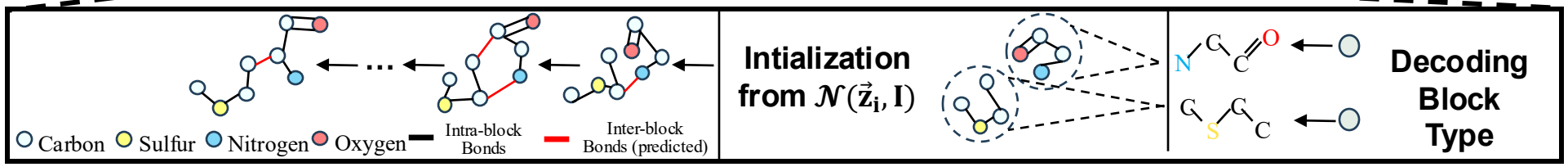
Unified Generation – Atomic VAE



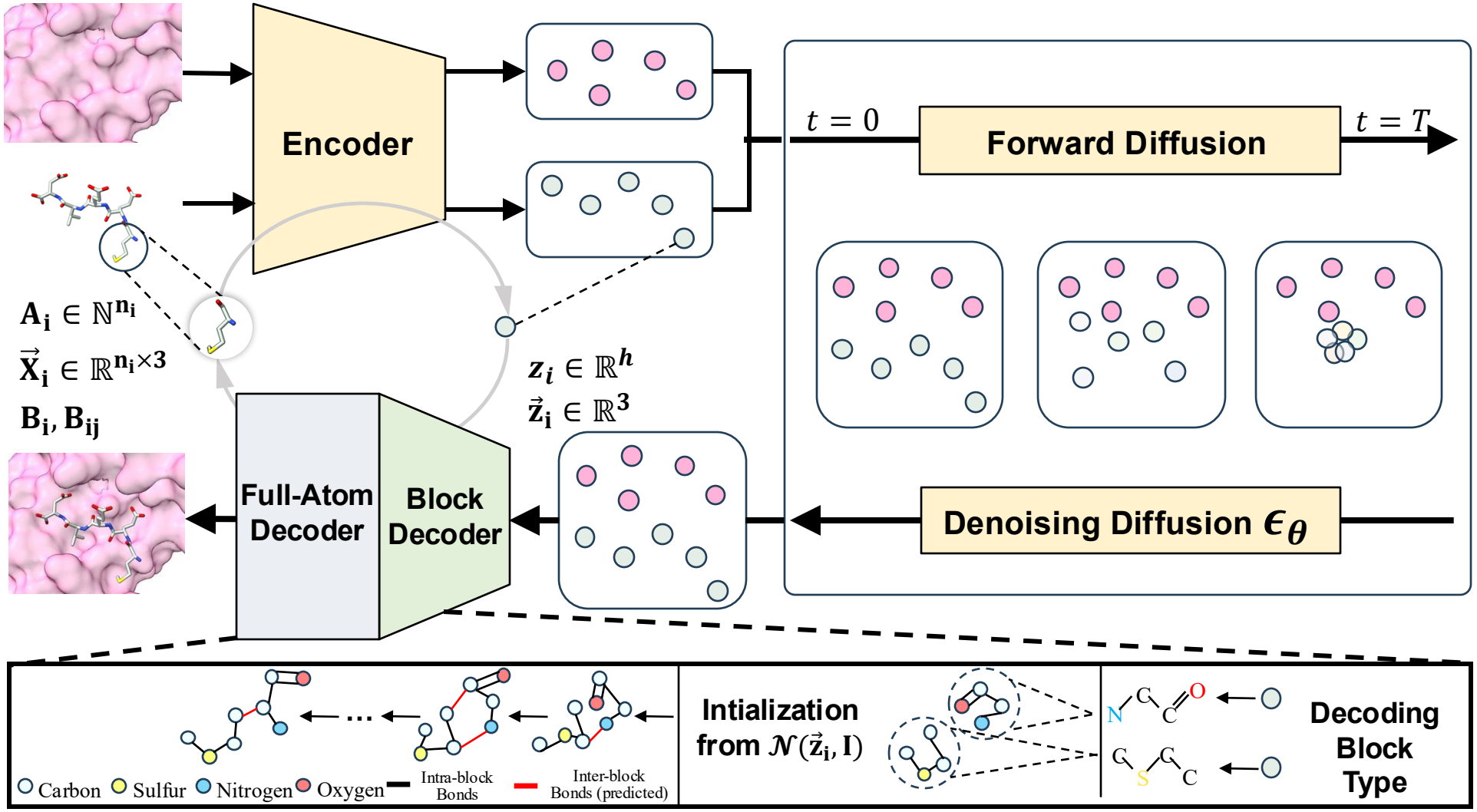
Iterative Full-Atom VAE

Compresses each block into a latent representation consisting of a low-dimensional hidden state and a spatial coordinate, then reconstruct the full-atom geometries from the latent point cloud with two-stage decoding.

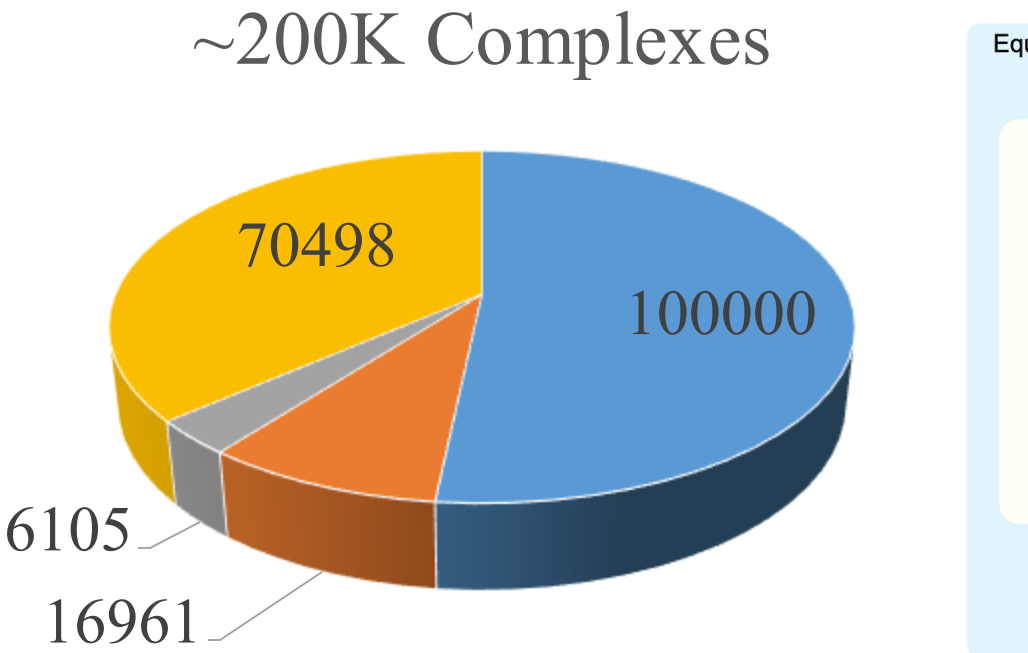
- Decoder is a **short-path flow matching**, leading to high-resolution atomic reconstruction.
- The VAE creates **a regular continuous space** for the implementation of generative models.

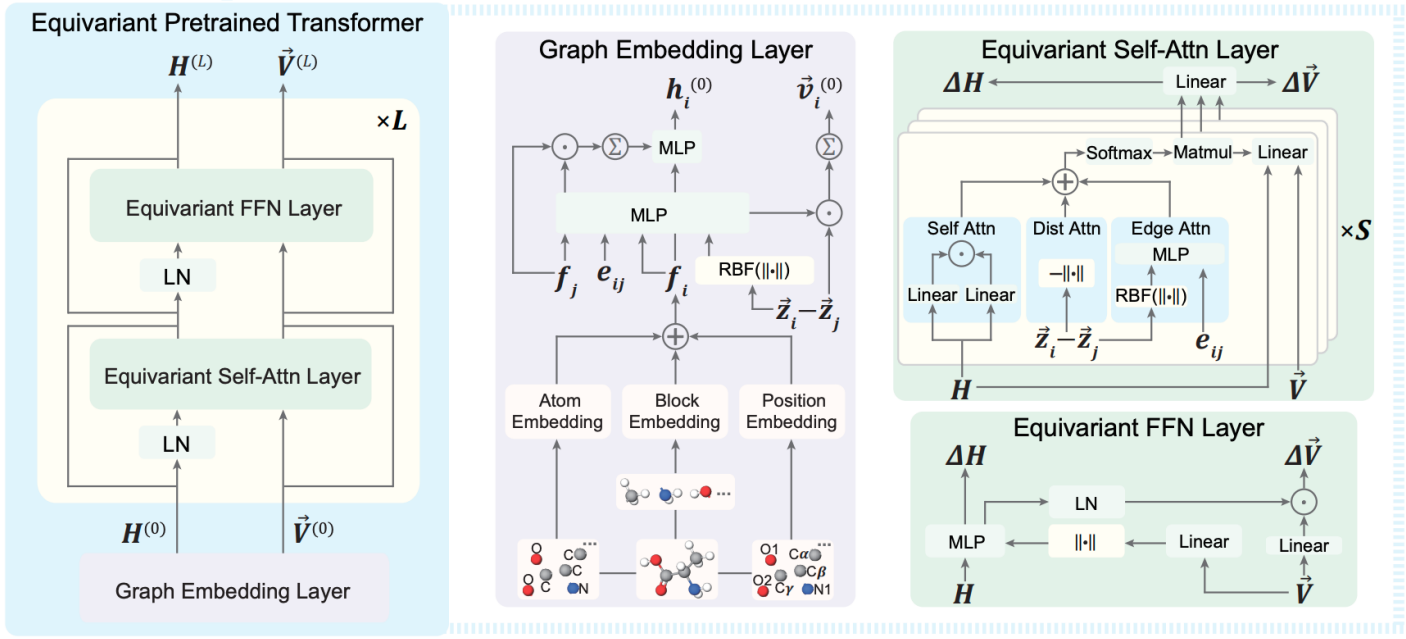


Unified Generation – Latent Diffusion



Equivariant Transformer for Scalability





Equivariant Pretrained Transformer for Unified Geometric Learning on Multi-Domain 3D Molecules (preprint)

Peptide

- **Higher recovery** of native binding conformation (C-RMSD, L-RMSD)
- Better **binding energy** (dG, IMP)
- More **reasonable geometry** (Clash, JSD of dihedral angles)
- Unified model achieves much better performance than single-domain counterparts

Table 1. Results for *de novo* peptide design.

Model	Recovery			Empirical Energy		Rationality				Diversity	
	AAR	C-RMSD	L-RMSD	ΔG	IMP	$Clash_{in}$	$Clash_{out}$	JSD_{bb}	JSD_{sc}	Seq.	Struct.
Reference	-	-	-	-37.25	-	0.31%	0.88%	-	-	-	-
RFDiffusion	34.68%	4.69	1.88	-13.47	5.38%	**0.06%**	13.58%	0.273	0.798	0.155	0.616
PepFlow	35.47%	2.87	1.79	-21.71	15.22%	2.72%	4.62%	0.240	0.693	0.530	0.507
PepGLAD	38.62%	2.74	1.60	-23.12	18.28%	1.82%	1.66%	0.474	0.398	**0.687**	**0.698**
UniMoMo (single)	37.59%	2.48	1.48	-28.72	29.03%	1.53%	0.94%	0.390	0.365	0.626	0.629
UniMoMo (all)	**39.45%**	**2.19**	**1.27**	**-34.35**	**40.86%**	0.45%	**0.93%**	**0.205**	**0.180**	0.617	0.573

Antibody

- **Higher recovery** of native CDRs (AAR, RMSD)
- Better **binding energy** (IMP)
- More **reasonable geometry** (Clash, JSD of dihedral angles)
- Unified model achieves much better performance than single-domain counterparts

Table 3. Results of rationality for antibody design on CDR-H3.

Model	$Clash_{in}$	$Clash_{out}$	JSD_{bb}	JSD_{sc}
Reference	0.08%	0.02%	-	-
MEAN	0.96%	0.16%	0.529	-
dyMEAN	1.02%	2.98%	0.542	0.702
GeoAB-R	0.59%	0.11%	0.529	-
DiffAb	0.31%	0.25%	0.268	-
GeoAB-D	0.75%	0.07%	0.430	-
UniMoMo (single)	0.25%	0.06%	0.278	0.284
UniMoMo (all)	**0.18%**	**0.03%**	**0.224**	**0.221**

Table 2. Results of recovery for antibody design on CDR-H3.

Model	#Generation	AAR	RMSD	IMP
Predictive				
MEAN	1	29.13%	1.87	6.67%
dyMEAN	1	31.65%	8.21	11.86%
GeoAB-R	1	32.04%	1.67	6.67%
Generative				
DiffAb	1	24.60%	2.77	10.34%
	10	38.42%	2.08	34.48%
	100	49.74%	1.46	60.34%
GeoAB-D	1	29.74%	1.73	6.67%
	10	38.20%	1.58	20.00%
	100	45.96%	1.50	40.00%
UniMoMo (single)	1	20.44%	2.71	15.00%
	10	39.04%	1.90	35.00%
	100	48.78%	1.39	63.33%
UniMoMo (all)	1	21.44%	2.52	13.33%
	10	42.05%	1.44	41.67%
	100	**52.34%**	**1.04**	**65.00%**

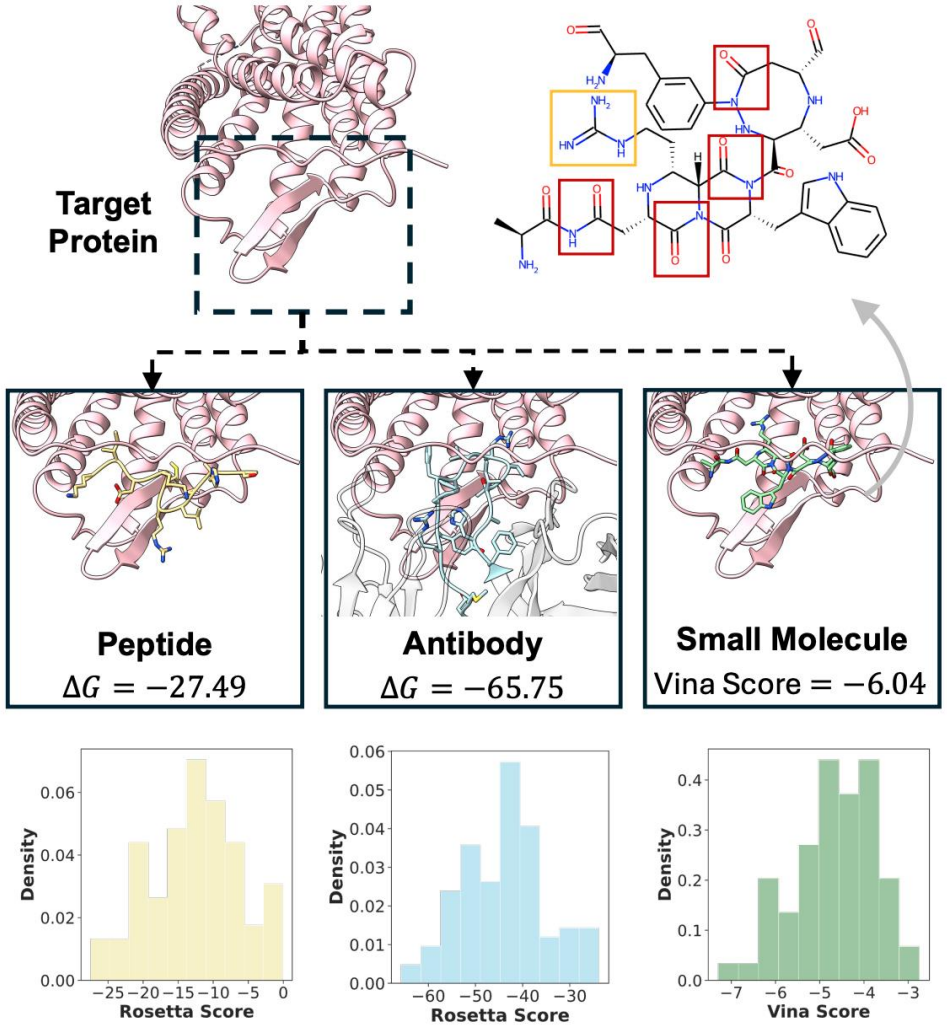
Small Molecule

Table 4. Overall comparisons for *de novo* small molecule design.

Model	substruct. 0.2	Chem. 0.2	Interact. 0.4	Geom. 0.2	Weighted Score	Rank
LIGAN	1.13	1.40	**4.27**	1.25	8.05	6
3DSBDD	1.13	1.60	2.23	0.70	5.67	9
GraphBP	0.17	1.50	0.37	0.10	2.13	14
Pocket2Mol	0.73	1.25	2.83	0.70	5.52	10
TargetDiff	1.77	1.50	3.50	1.70	8.47	5
DiffSBDD	0.77	1.75	1.20	0.95	4.67	12
DiffBP	0.27	1.10	2.10	1.35	4.82	11
FLAG	0.70	1.40	1.40	0.60	4.10	13
D3FG	1.47	**2.25**	1.80	0.70	6.22	8
DecompDiff	1.90	1.80	2.50	1.80	8.00	7
MolCRAFT	1.93	1.55	3.93	**2.20**	9.62	2
VoxBind	1.53	2.00	3.83	2.00	9.37	3
UniMoMo (single)	2.23	2.15	2.70	1.95	9.03	4
UniMoMo (all)	**2.27**	**2.25**	3.47	**2.20**	**10.38**	**1**

- Better fidelity to natural substructures
- Better chemical properties
- Good interaction patterns
- More reasonable geometry
- Best overall scores
- Unified model achieves much better performance than single-domain counterparts

Case Study on GPCR



- Good empirical **binding energy distribution** for different molecular types
- Mimicking **peptide scaffolds** to support large small molecules (red)
- Mimicking natural amino acids to form **interactions** (orange)

Conclusion

- UniMoMo: a unified generative model for all molecular types
- Joint training all data from different domains helps with each other
- UniMoMo surpasses state-of-the-art models, including domain-specific models in terms of binder design
- UniMoMo learns to borrow patterns from other domains to generate better binders

Thank you for your attention!

Paper Link

Code Link