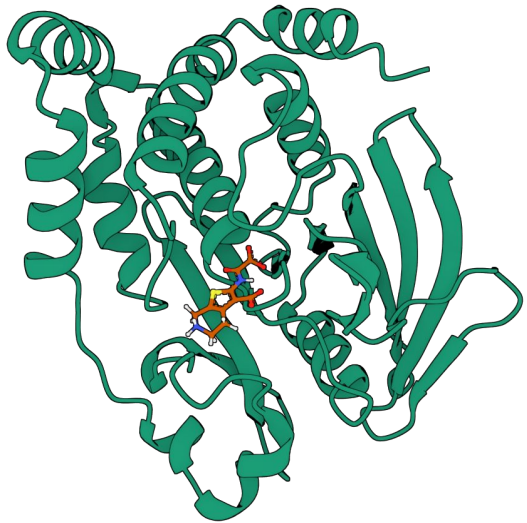
University of Missouri

Dissertation Defense

Geometric Deep Learning & Generative Modeling of 3D Biomolecules

Alex Morehead, PhD Candidate
University of Missouri, April 28th, 2025



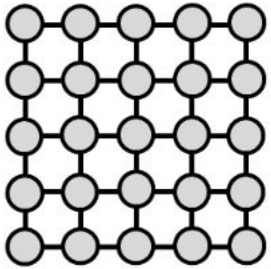
Presentation Overview

Geometric Deep Learning
(e.g., AlphaFold 2, *Geometric Transformer*, *GCPNet*)

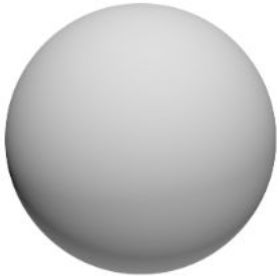
Generative Models
(e.g., AlphaFold 3, *GCDM*, *FlowDock*)

Biomolecule Design
(e.g., RFdiffusionAA, *GCDM-SBDD*, *PoseBench*)

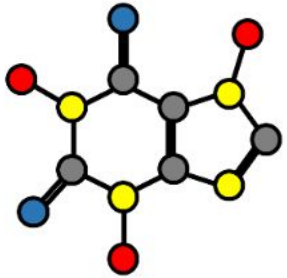
In this defense, we discuss three synergistic research areas that have recently experienced *huge* growth



Grids



Groups



Graphs

Geodesics & Gauges

What is Geometric Deep Learning?

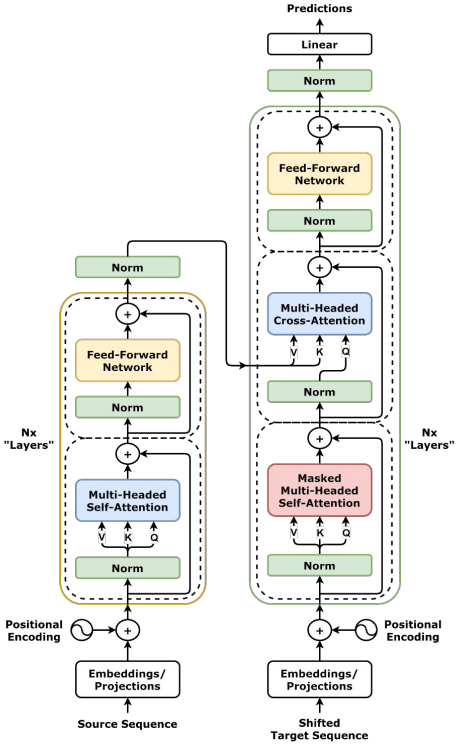
Reference: Bronstein et al. 2025, MIT Press

Key Ideas

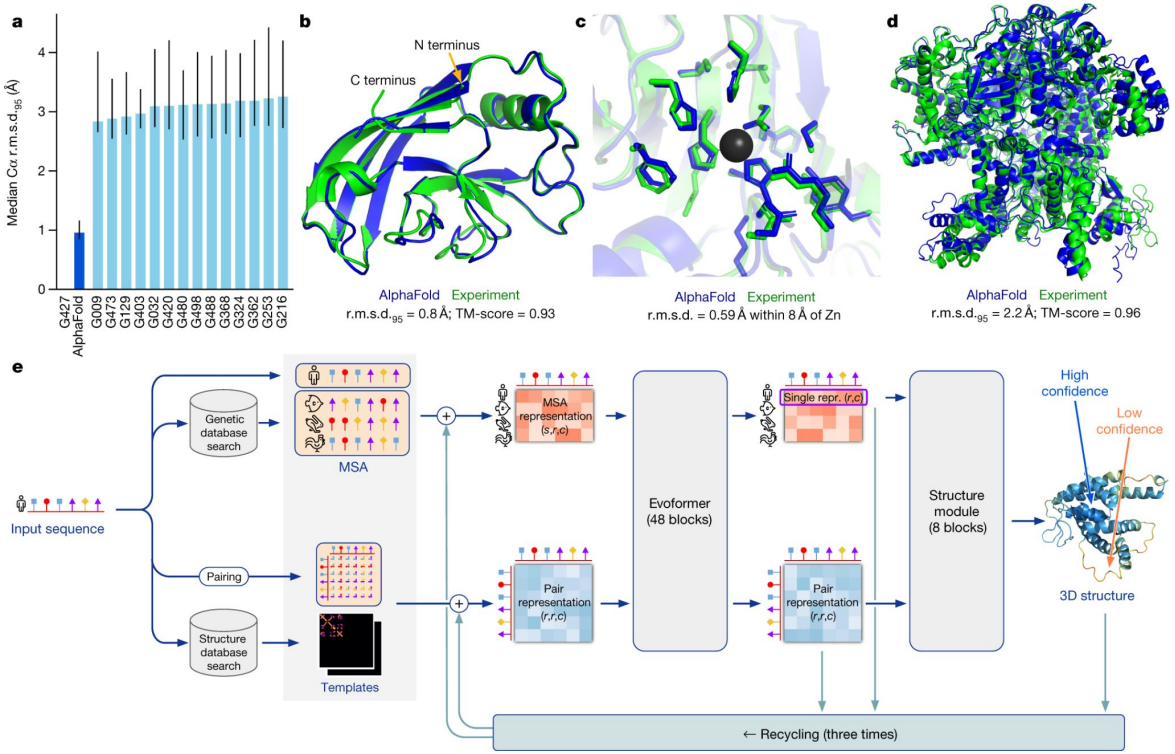
1. Symmetries in nature can be modeling precisely using bespoke neural networks

2. Many of the most common types of AI algorithms (e.g., Transformers) are symmetric

3. Modeling real-world data with geometric deep learning has yielded compelling results



Geometric Deep Learning Case Study (AlphaFold 2)

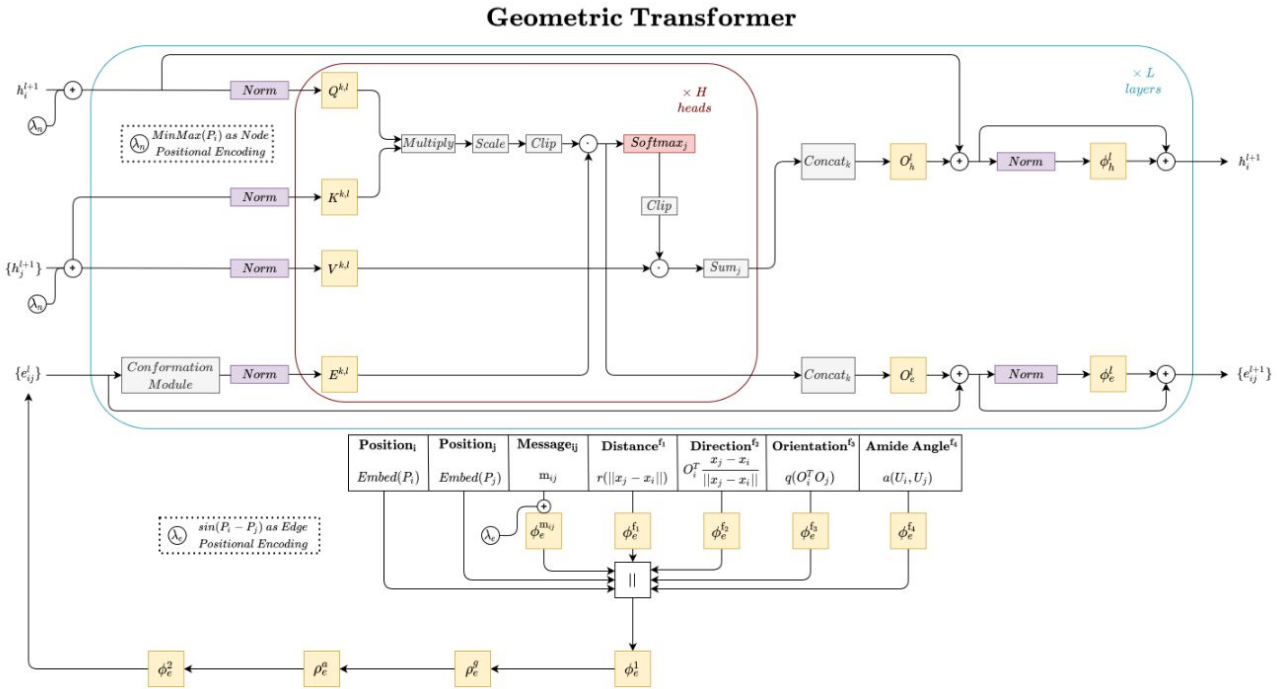


A prime example of **AI4Science**!

Reference: Jumper et al. 2021, Nature

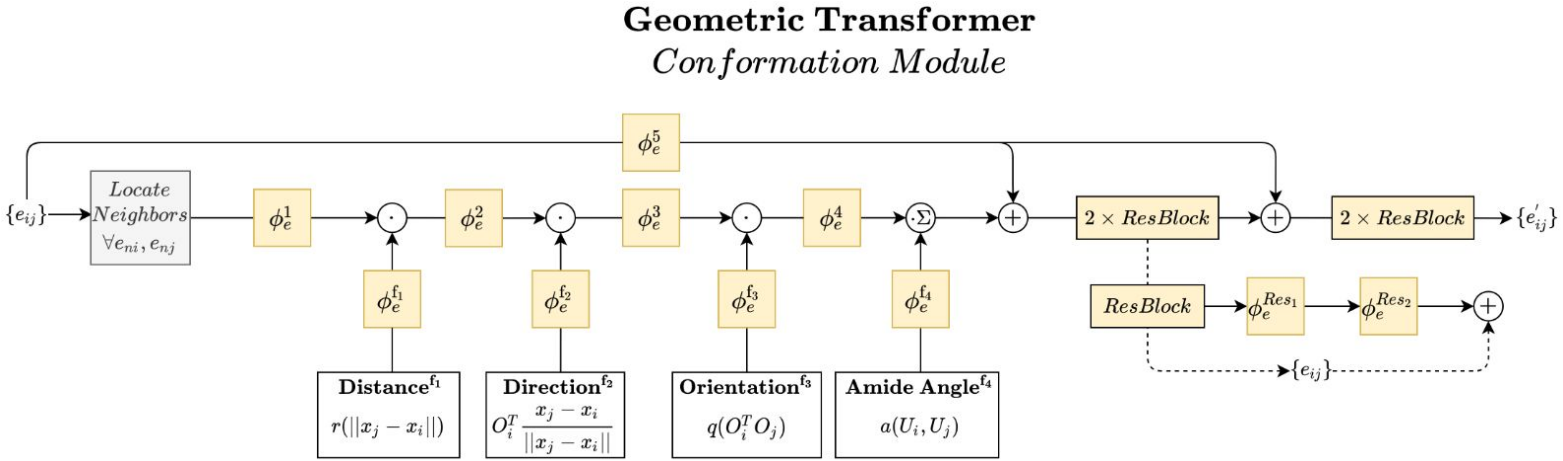
Geometric Deep Learning Case Study (Geometric Transformer)

Deep graph learning for **biomolecules**



Reference: **Morehead** et al. 2022, ICLR

Geometric Deep Learning Case Study (Geometric Transformer - Conformation Module)



- The model uniquely learns representations of **geometric line graphs** for downstream predictions!

Reference: **Morehead** et al. 2022, ICLR

Geometric Deep Learning Case Study (Geometric Transformer)

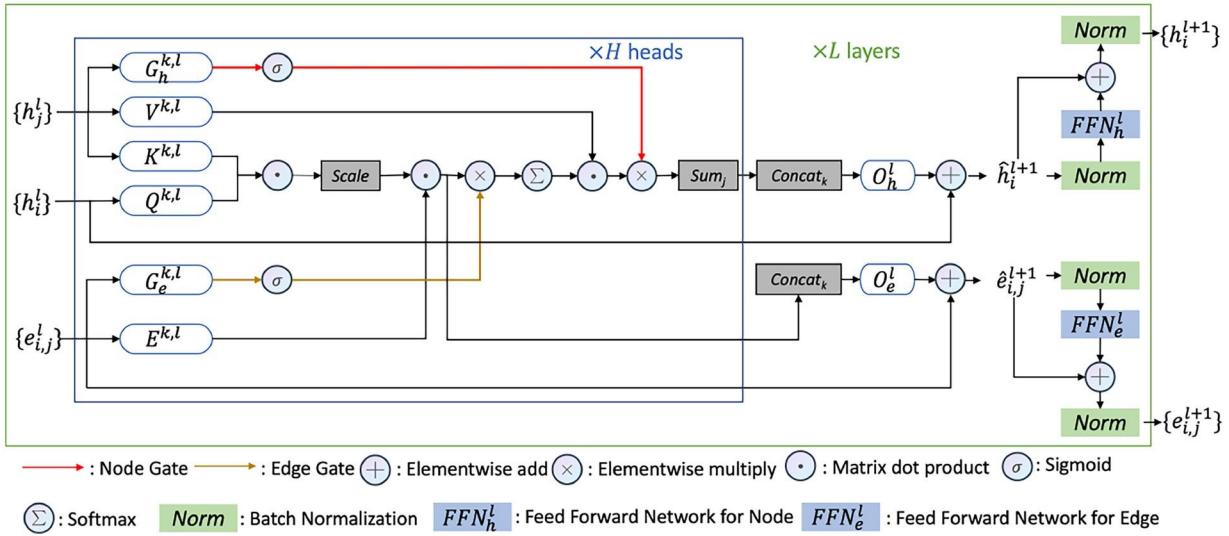
	19 (Both Types)					
Method	P@10	P@L/10	P@L/5	R@L	R@L/2	R@L/5
BI	0.01	0	0.01	0.02	0.01	0.001
DI (GCN)	0.12 (0.04)	0.10 (0.05)	0.09 (0.04)	0.11 (0.001)	0.06 (0.01)	0.02 (0.01)
DI (GT)	0.10 (0.03)	0.09 (0.03)	0.08 (0.02)	0.11 (0.02)	0.06 (0.01)	0.02 (0.01)
DI (GeoT w/o EPE)	0.13 (0.02)	0.14 (0.03)	0.13 (0.02)	0.12 (0.01)	0.07 (0.01)	0.03 (0.01)
DI (GeoT w/o GFG)	0.11 (0.01)	0.12 (0.02)	0.10 (0.02)	0.11 (0.01)	0.06 (0.01)	0.03 (0.01)
DI (GeoT)	**0.21 (0.01)**	**0.19 (0.01)**	**0.14 (0.01)**	**0.13 (0.02)**	**0.08 (0.01)**	**0.04 (0.003)**

- **Geometric** priors consistently improve predictions of atomic protein-protein interactions!

Reference: **Morehead** et al. 2022, ICLR

EPE: Edge Position Encoding; GFG: Geometric Feature Gating

Geometric Deep Learning Case Study (Gated Graph Transformer)

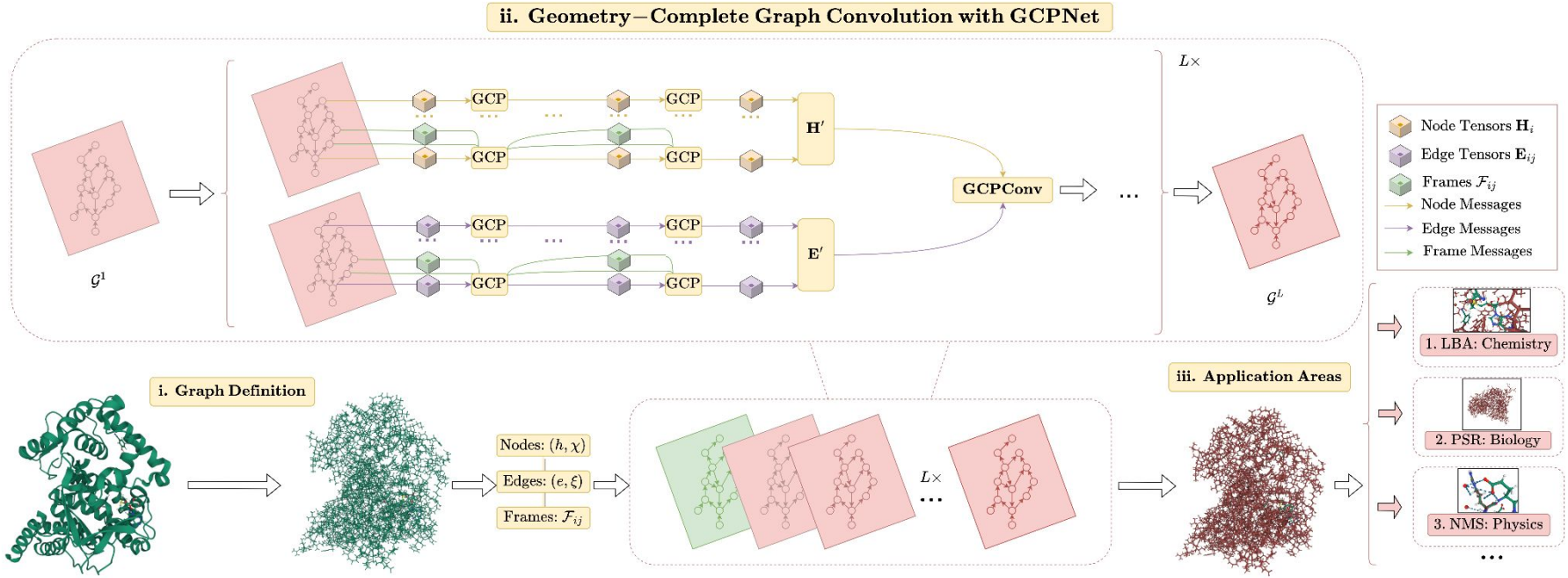


- **Learnable gating** also played an important role in follow-up work on (multi-chain) protein representation learning

Reference: Chen*, **Morehead***, et al. 2023, ISMB
*equal contribution

h: Node-Level Features; e: Edge-Level Features

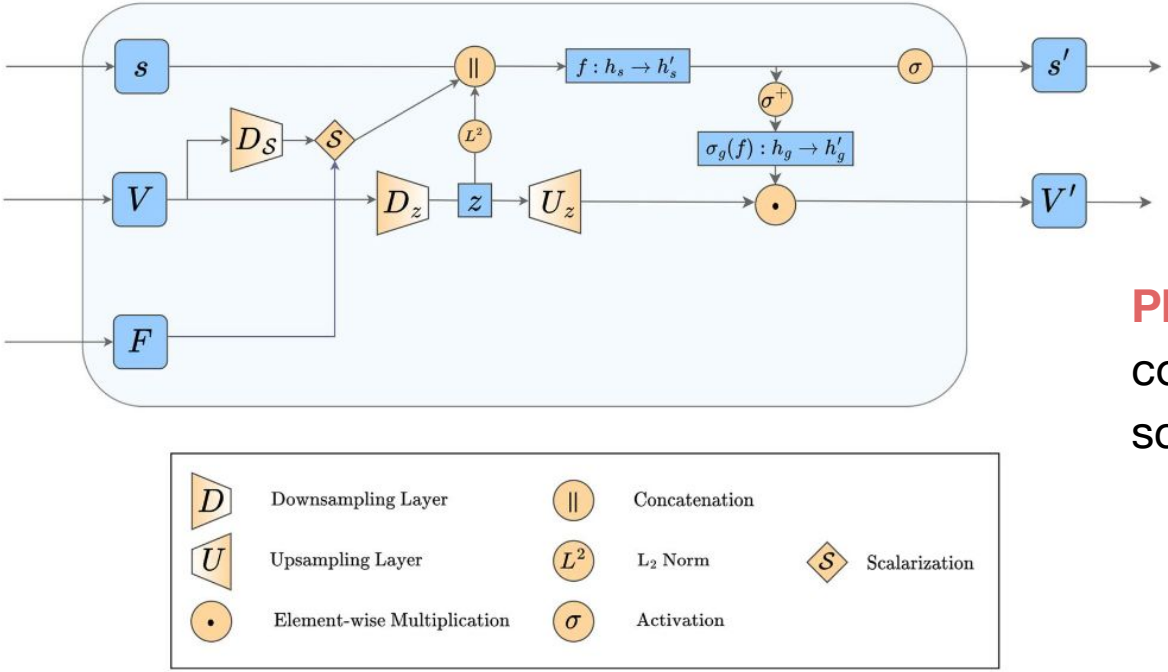
Geometric Deep Learning Case Study (GCPNet)



A **broadly applicable** geometric graph neural network

Reference: **Morehead** et al. 2024, Bioinformatics

Geometric Deep Learning Case Study (GCPNet - GCP Module)



Physical priors come from scalarization!

Reference: **Morehead** et al. 2024, Bioinformatics

Geometric Deep Learning Case Study (GCPNet - Forward Pass)

Algorithm 1. GCPNET

Require: $(h_i \in \mathbf{H}, \chi_i \in \boldsymbol{\chi})$, $(e_{ij} \in \mathbf{E}, \xi_{ij} \in \boldsymbol{\xi})$, $x_i \in \mathbf{X}$, graph $\mathcal{G}$

Initialize $\mathbf{X}^0 = \mathbf{X}^C \leftarrow \text{Centralize}(\mathbf{X})$

$\mathcal{F}_{ij} = \text{Localize}(x_i \in \mathbf{X}^0, x_j \in \mathbf{X}^0)$

Project $(h_i^0, \chi_i^0), (e_{ij}^0, \xi_{ij}^0) \leftarrow \mathbf{GCP}_e((h_i, \chi_i), (e_{ij}, \xi_{ij}), \mathcal{F}_{ij})$

for $l = 1$ **to** L **do**

    $(h_i^l, \chi_i^l), x_i^l = \text{GCPConv}^l((h_i^{l-1}, \chi_i^{l-1}), (e_{ij}^0, \xi_{ij}^0), x_i^{l-1}, \mathcal{F}_{ij})$

end for

if Updating Node Positions **then**

    $\mathcal{F}_{ij}^L = \text{Localize}(x_i \in \mathbf{X}^l, x_j \in \mathbf{X}^l)$

    Finalize $(\mathbf{X}^L) \leftarrow \text{Decentralize}(\mathbf{X}^l)$

else

    $x_i^L = x_i^0$

end if

Project $(h_i^L, \chi_i^L), (e_{ij}^L, \xi_{ij}^L) \leftarrow \mathbf{GCP}_p((h_i^l, \chi_i^l), (e_{ij}^0, \xi_{ij}^0), \mathcal{F}_{ij}^L)$

Ensure: $(h_i^L, \chi_i^L), (e_{ij}^L, \xi_{ij}^L), x_i^L$

So how does this model work?

Reference: **Morehead** et al. 2024, Bioinformatics

Geometric Deep Learning Case Study (GCPNet)

Type	Method	Symmetries	R/S Accuracy (%) ↑
INN	ChIRo (Schneuing *et al.* 2022)	SE(3)	98.5
	SchNet (Schneuing *et al.* 2022)	E(3)	54.4
	DimeNet++ (Schneuing *et al.* 2022)	E(3)	65.7
	SphereNet (Schneuing *et al.* 2022)	SE(3)	98.2
ENN	EGNN (Schneuing *et al.* 2022)	E(3)	50.4
	SEGNN (Schneuing *et al.* 2022)	SE(3)	83.4
Ours	GCPNet w/o Frames	E(3)	50.2 ± 0.6
	GCPNet	SE(3)	**98.7 ± 0.1**

- **Physical** priors are necessary for geometric neural networks to understand molecular chirality!

Reference: **Morehead** et al. 2024, Bioinformatics

Frames: Local Coordinate Frames; R/S: Right/Left

Geometric Deep Learning Case Study (GCPNet)

Method	ES(5)	ES(20)	G+ES(20)	L+ES(20)	Average
GNN (Du *et al.* 2022)	0.0131	0.0720	0.0721	0.0908	0.0620
TFN (Du *et al.* 2022)	0.0236	0.0794	0.0845	0.1243	0.0780
SE(3)-Transformer (Du *et al.* 2022)	0.0329	0.1349	0.1000	0.1438	0.1029
Radial Field (Du *et al.* 2022)	0.0207	0.0377	0.0399	0.0779	0.0441
PaiNN	0.0158	N/A	N/A	N/A	N/A
ET	0.1653	0.1788	0.2122	0.2989	0.2138
EGNN (Du *et al.* 2022)	0.0079	0.0128	0.0118	0.0368	0.0173
ClofNet (Du *et al.* 2022)	**0.0065**	0.0073	**0.0072**	0.0251	0.0115
GCPNet w/o Frames	0.0067	0.0074	0.0074	0.0200	0.0103
GCPNet w/o ResGCP	0.0090	0.0135	0.0099	0.0278	0.0150
GCPNet w/o Scalars	0.0119	0.0173	0.0170	0.0437	0.0225
GCPNet	0.0070	**0.0071**	0.0073	**0.0173**	**0.0097**

- For complex physical (many-body) systems, **learnable geometric frames** enable more precise point predictions

Reference: **Morehead** et al. 2024, Bioinformatics

Frames: Local Coordinate Frames; R/S: Right/Left

Geometric Deep Learning Case Study (GCPNet)

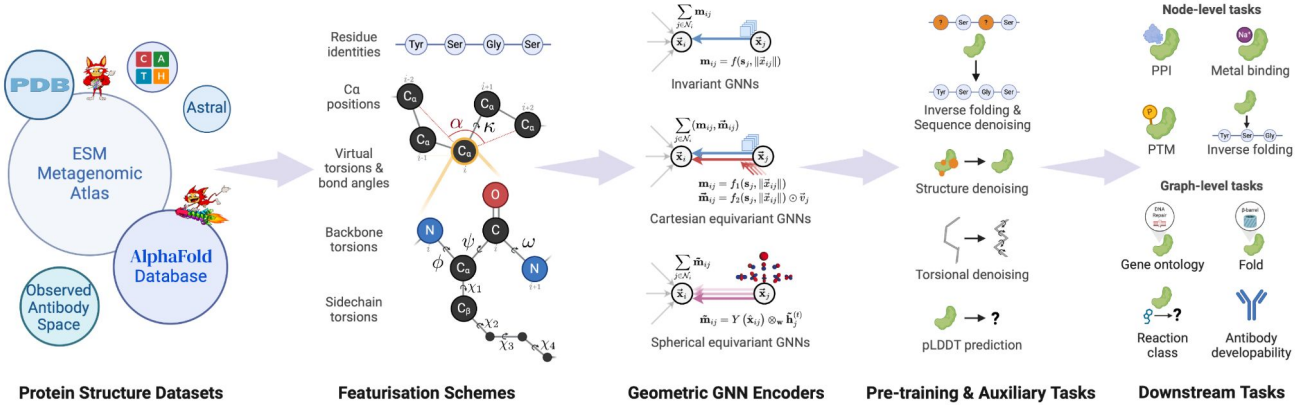
Type	Method	RMSE ↓	p ↑	Sp ↑
CNN	3DCNN (Wang *et al.* 2023b)	1.416 ± 0.021	0.550	0.553
	DeepDTA (Wang *et al.* 2023b)	1.866 ± 0.080	0.472	0.471
	DeepAffinity (Aykent and Xia 2022)	1.893 ± 0.650	0.415	0.426
RNN	Bepler and Berger (Wang *et al.* 2023b)	1.985 ± 0.006	0.165	0.152
	TAPE (Wang *et al.* 2023b)	1.890 ± 0.035	0.338	0.286
	ProtTrans (Wang *et al.* 2023b)	1.544 ± 0.015	0.438	0.434
GNN	GCN (Wang *et al.* 2023b)	1.601 ± 0.048	0.545	0.533
	DGAT (Aykent and Xia 2022)	1.719 ± 0.047	0.464	0.472
	DGIN (Aykent and Xia 2022)	1.765 ± 0.076	0.426	0.432
	DGAT-GCN (Aykent and Xia 2022)	1.550 ± 0.017	0.498	0.496
	MaSIF (Wang *et al.* 2023b)	1.484 ± 0.018	0.467	0.455
	IEConv (Wang *et al.* 2023b)	1.554 ± 0.016	0.414	0.428
	Holoprot-Full Surface (Wang *et al.* 2023b)	1.464 ± 0.006	0.509	0.500
	Holoprot-Superpixel (Wang *et al.* 2023b)	1.491 ± 0.004	0.491	0.482
	ProNet-Amino-Acid (Wang *et al.* 2023b)	1.455 ± 0.009	0.536	0.526
	ProNet-Backbone (Wang *et al.* 2023b)	1.458 ± 0.003	0.546	0.550
	ProNet-All-Atom (Wang *et al.* 2023b)	1.463 ± 0.001	0.551	0.551
	GeoSSL-DDM (Liu *et al.* 2023)	1.451 ± 0.030	0.577	0.572
ENN	Cormorant (Aykent and Xia 2022)	1.568 ± 0.012	0.389	0.408
	PaiNN	1.698 ± 0.050	0.366	0.358
	ET	1.490 ± 0.019	0.564	0.532
	GVP (Aykent and Xia 2022)	1.594 ± 0.073	0.434	0.432
	GBP (Aykent and Xia 2022)	1.405 ± 0.009	0.561	0.557
Ours	GCPNet w/o Frames	1.485 ± 0.015	0.521	0.504
	GCPNet w/o ResGCP	1.514 ± 0.008	0.471	0.468
	GCPNet w/o Scalars	1.685 ± 0.000	0.050	0.000
	GCPNet w/o Vectors	1.727 ± 0.005	0.270	0.304
	GCPNet	**1.352 ± 0.003**	**0.608**	**0.607**

- **Each model component** is important for accurately predicting protein-ligand binding affinities

Reference: **Morehead** et al. 2024, Bioinformatics

Frames: Local Coordinate Frames; ResGCP: ResidualGCP

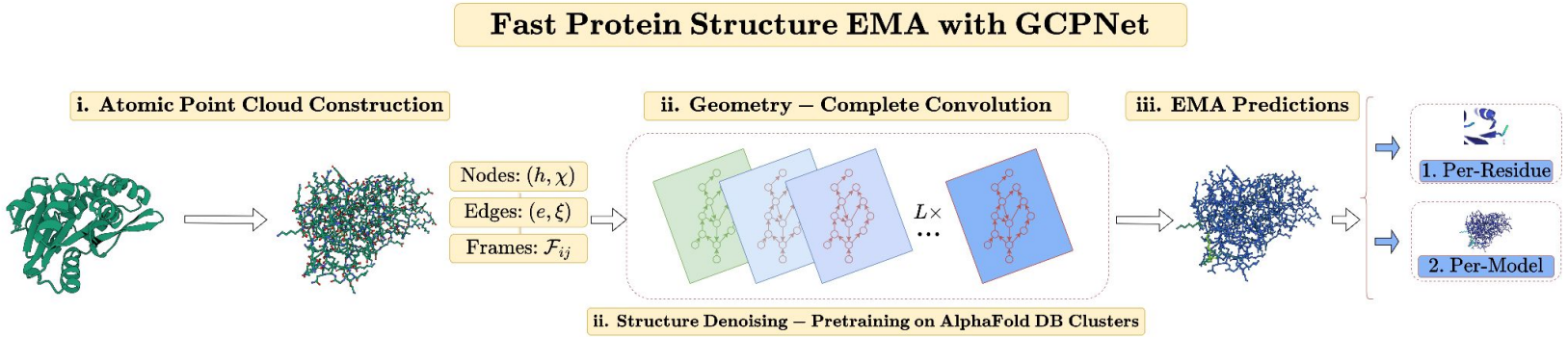
Geometric Deep Learning Case Study (ProteinWorkshop)



- GCPNet yielded excellent performance for **inverse folding** and **protein-protein interaction prediction** in a new standardized deep learning benchmark for protein representation learning

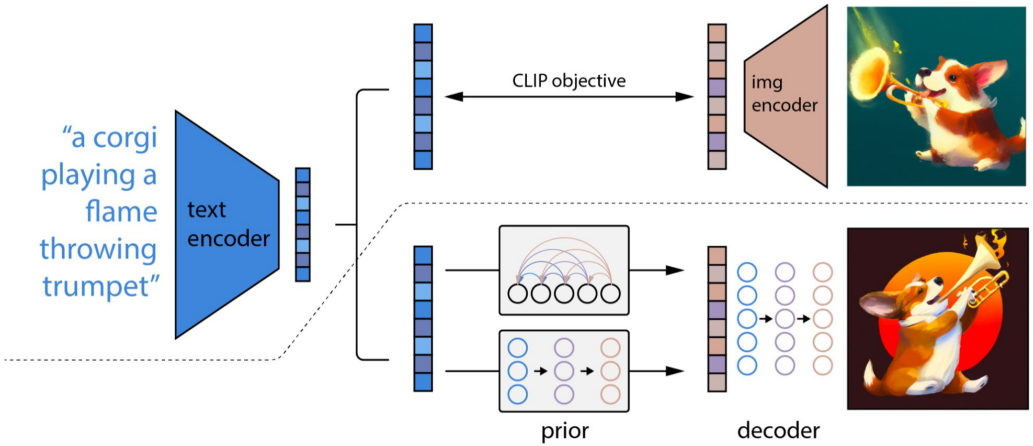
Reference: Jamasb*, **Morehead***, et al. 2024, ICLR
*equal contribution

Geometric Deep Learning Case Study (GCPNet-EMA)



- GCPNet has since also been adapted as a state-of-the-art **estimator** of the **model accuracy (EMA)** of predicted protein structures

Reference: **Morehead** et al. 2024, Protein Science



What about Generative Modeling?

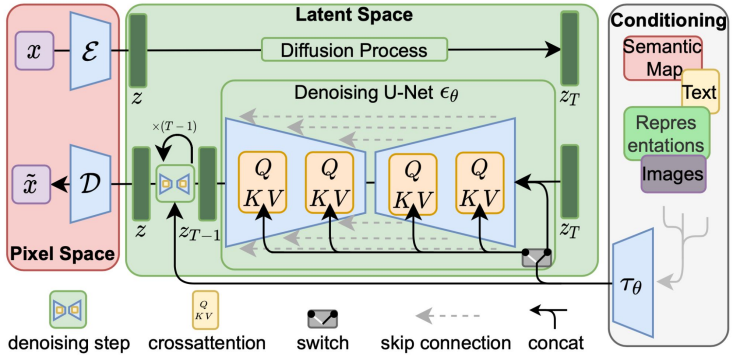
Reference: Ramesh et al. 2022, arXiv

Key Ideas

1. Most datasets can become the basis of a powerful generative model of that domain

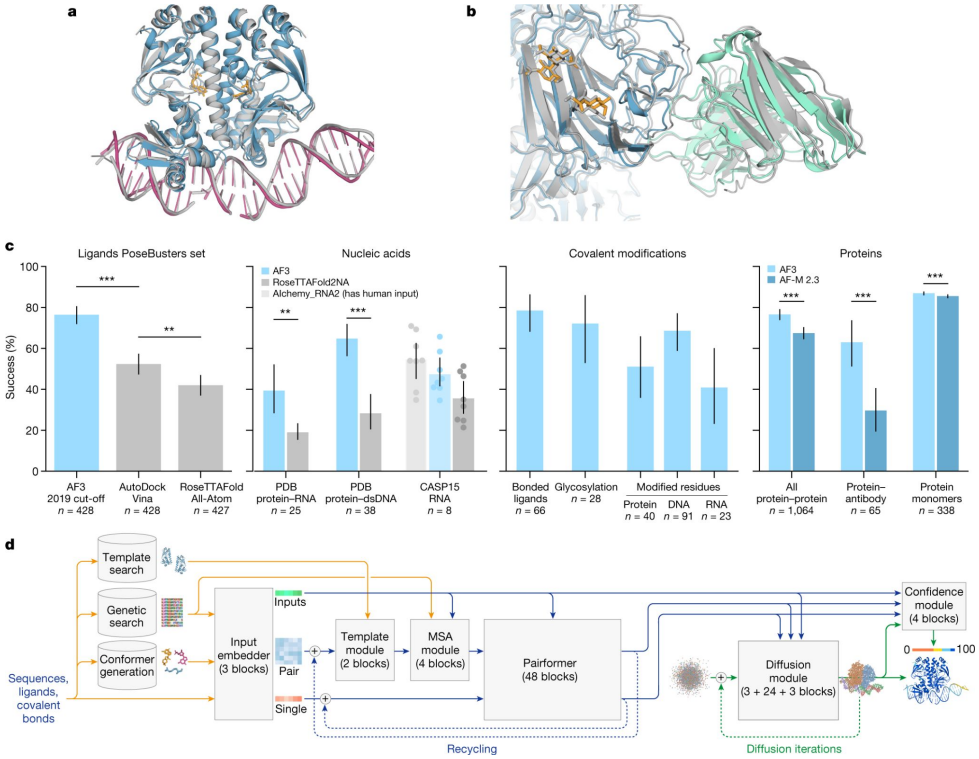
2. Once trained, such a generative model can generate new (similar yet distinct) examples

3. Importantly, these algorithms can enable complex data analysis within scientific pipelines



Reference: Rombach et al. 2022, CVPR

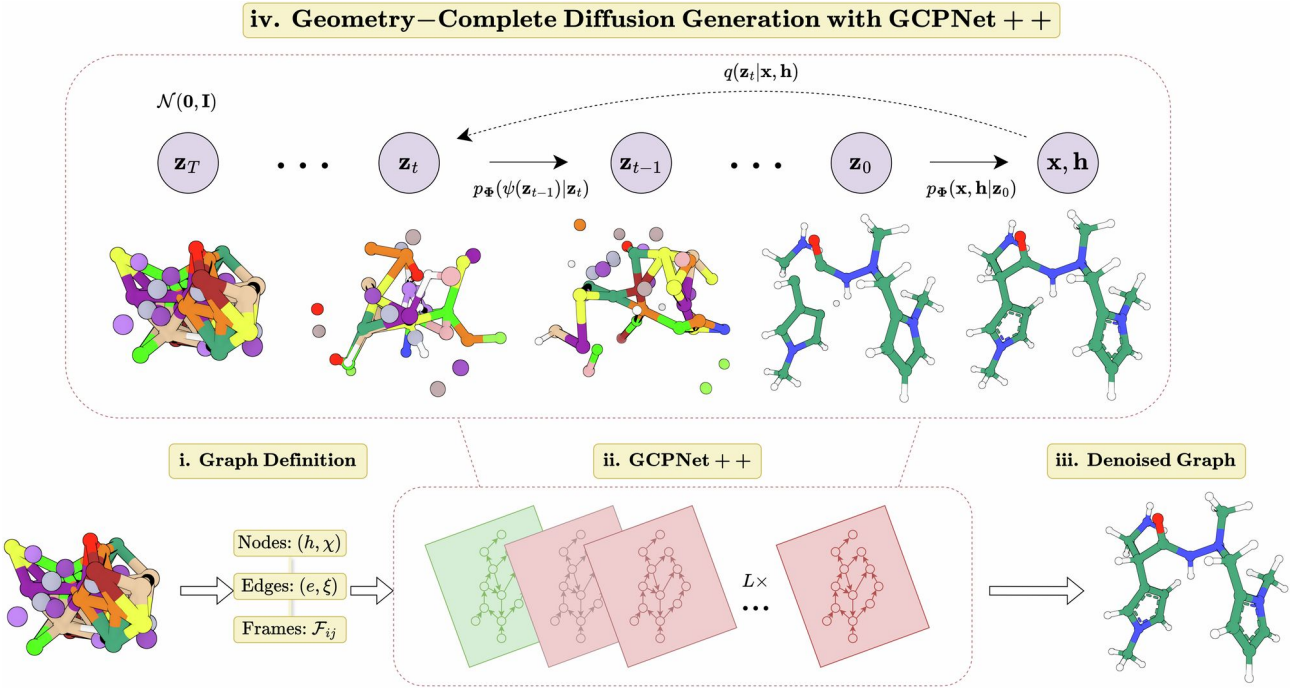
Generative Modeling Case Study (AlphaFold 3)



Representing all of life's molecules with **denoising diffusion**

Reference: Abramson et al. 2024, Nature

Generative Modeling Case Study (GCDM)



Learning geometric (vector) features for diffusion generation

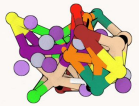
Reference: **Morehead** et al. 2024, Nature CommsChem

Generative Modeling Case Study (GCDM)

Task	$\alpha\downarrow$	$\Delta\epsilon\downarrow$	$\epsilon_{HOMO}\downarrow$	$\epsilon_{LUMO}\downarrow$	$\mu\downarrow$	$C_v\downarrow$
Units	Bohr^3	meV	meV	meV	D	$\frac{cal}{mol}$K
Naive (Upper-bound)	9.01	1470	645	1457	1.616	6.857
# Atoms	3.86	866	426	813	1.053	1.971
EDM	2.76	655	356	584	1.111	1.101
GeoLDM	2.37	**587**	**340**	522	1.108	1.025
GCDM	**1.97**	602	344	**479**	**0.844**	**0.689**
QM9 (Lower-bound)	0.10	64	39	36	0.043	0.040

Task	$\alpha\downarrow$	$\Delta\epsilon\downarrow$	$\epsilon_{HOMO}\downarrow$	$\epsilon_{LUMO}\downarrow$	$\mu\downarrow$	$C_v\downarrow$
Units	Bohr^3	meV	meV	meV	D	$\frac{cal}{mol}$K
GeoLDM	2.77 ± 0.12	655 ± 20.57	357 ± 5.68	565 ± 10.62	1.089 ± 0.02	1.070 ± 0.04
GCDM	**1.99** ± 0.01	**595** ± 14.34	**346** ± 1.23	**480** ± 6.58	**0.855** ± 0.00	**0.698** ± 0.01

- **Neural network expressiveness** enables more precise 3D molecule generation for property conditioning



Reference: **Morehead** et al. 2024, Nature CommsChem

Generative Modeling Case Study (GCDM)

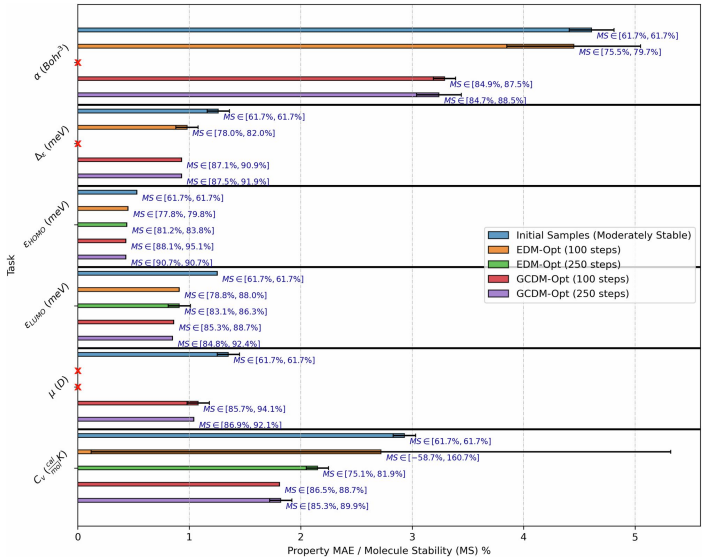
Type	Method	NLL ↓	AS (%) ↑	MS (%) ↑
NF	E-NF	–	75.0	0.0
DDPM	GDM	−14.2	75.0	0.0
	GDM-aug	−58.3	77.7	0.0
	EDM	−137.1	81.3	0.0
	Bridge	–	81.0 ± 0.7	0.0
	Bridge + Force	–	82.4 ± 0.8	0.0
LDM	GraphLDM	–	76.2	0.0
	GraphLDM-aug	–	79.6	0.0
	GeoLDM	–	84.4	0.0
GC-DDPM—Ours	GCDM w/o Frames	769.7	88.0 ± 0.3	3.4 ± 0.3
	GCDM w/o SMA	3505.5	43.9 ± 3.6	0.1 ± 0.0
	GCDM	**−234.3**	**89.0** ± 0.8	**5.2** ± 1.1
Data			86.5	2.8

Method	NLL ↓	AS (%) ↑	MS (%) ↑	Val (%) ↑	Val and Uniq (%) ↑	Novel (%) ↑	PB-Valid (%) ↑
GeoLDM	–	84.4 ± 0.1	0.6 ± 0.1	**99.5** ± 0.1	**99.4** ± 0.1	–	38.3 ± 0.5
GCDM	**−215.1** ± 3.8	**88.1** ± 0.1	**4.3** ± 0.4	95.5 ± 0.1	95.5 ± 0.1	**95.5** ± 0.1	**77.0** ± 0.1

- **Neural network expressiveness** for the first enables diffusion models to generate a sizeable fraction of valid large 3D molecules!

Reference: **Morehead** et al. 2024, Nature CommsChem

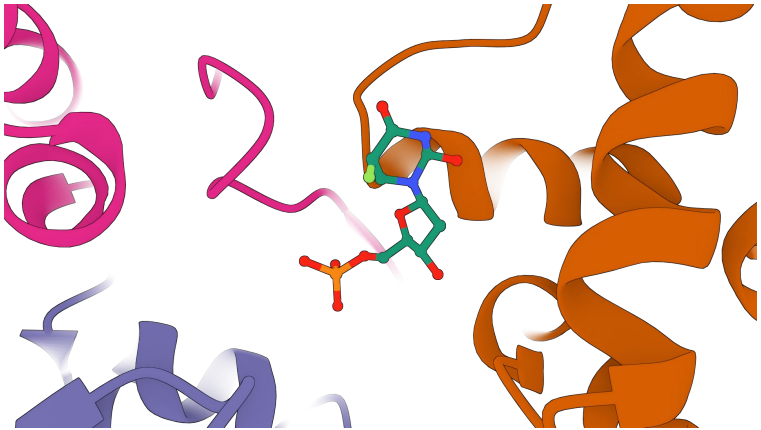
Generative Modeling Case Study (GCDM)



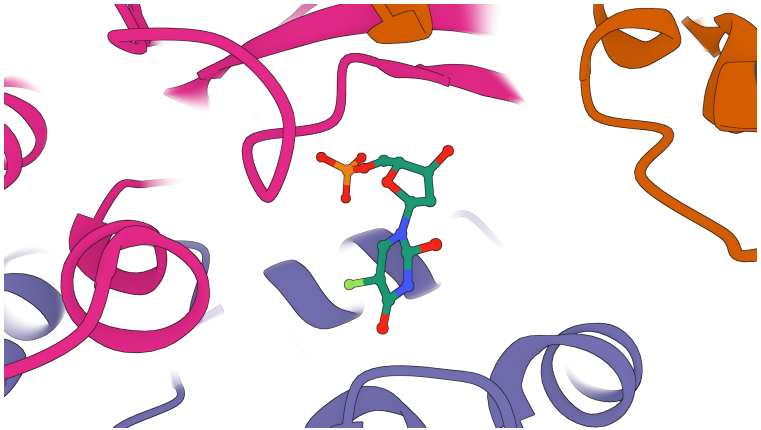
- **Neural network expressiveness** also yields consistent improvements in 3D molecule optimization of molecular properties

Reference: **Morehead** et al. 2024, Nature CommsChem

Generative Models Capture Molecular Details



DiffDock-L (Corso et al. 2024)

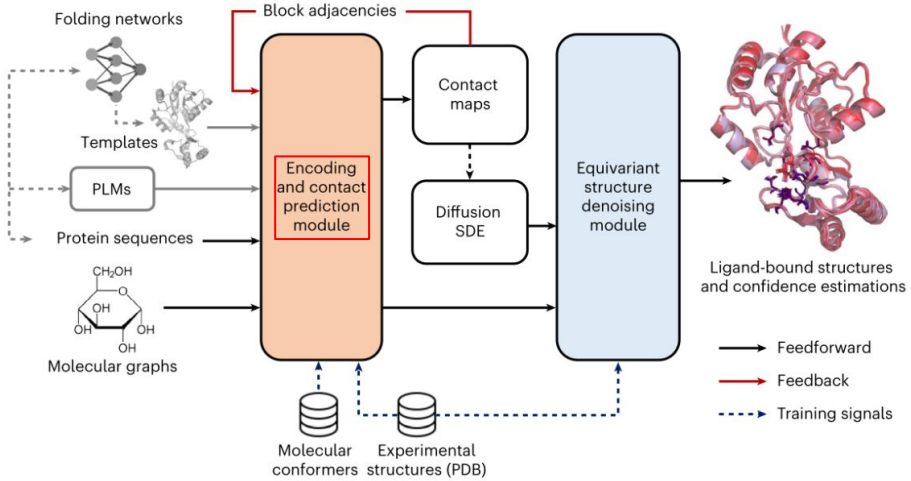


NeuralPLexer (Qiao et al. 2024)

In the past two years, deep generative models have demonstrated the ability to produce **realistic** protein-binding conformations of ligand molecules

References: Corso et al. 2024, ICLR; Qiao et al. 2024, NMI

Do Generative Models Learn Meaningful Features?



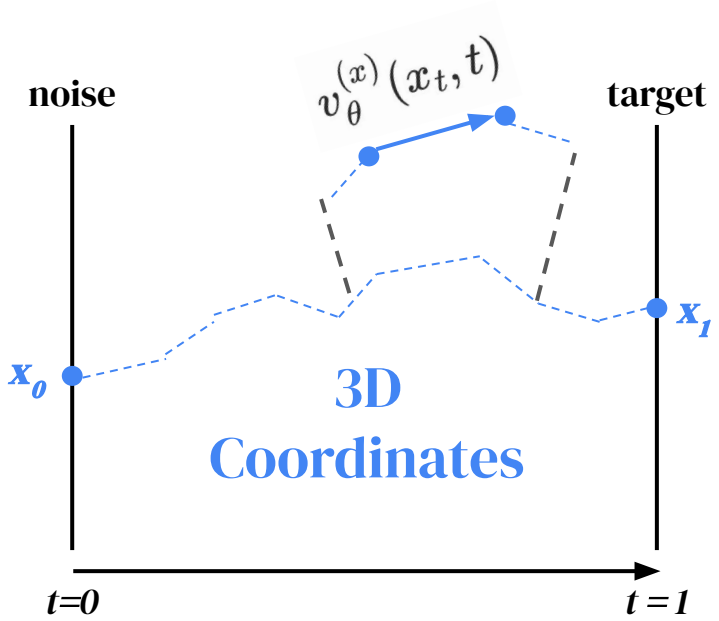
NeuralPLexer (Qiao et al. 2024)

Key Insight: Generative structure prediction models, when pre-trained on large datasets of biomolecules, learn meaningful features that are **readily** adapted for binding affinity estimation

Reference: Qiao et al. 2024, NMI

But What about Docking State Transitions?
→ Flow Matching in 3D

The denoiser v_θ predicts
3D coordinate updates



We fine-tune
NeuralPLexer as
our denoiser v_θ

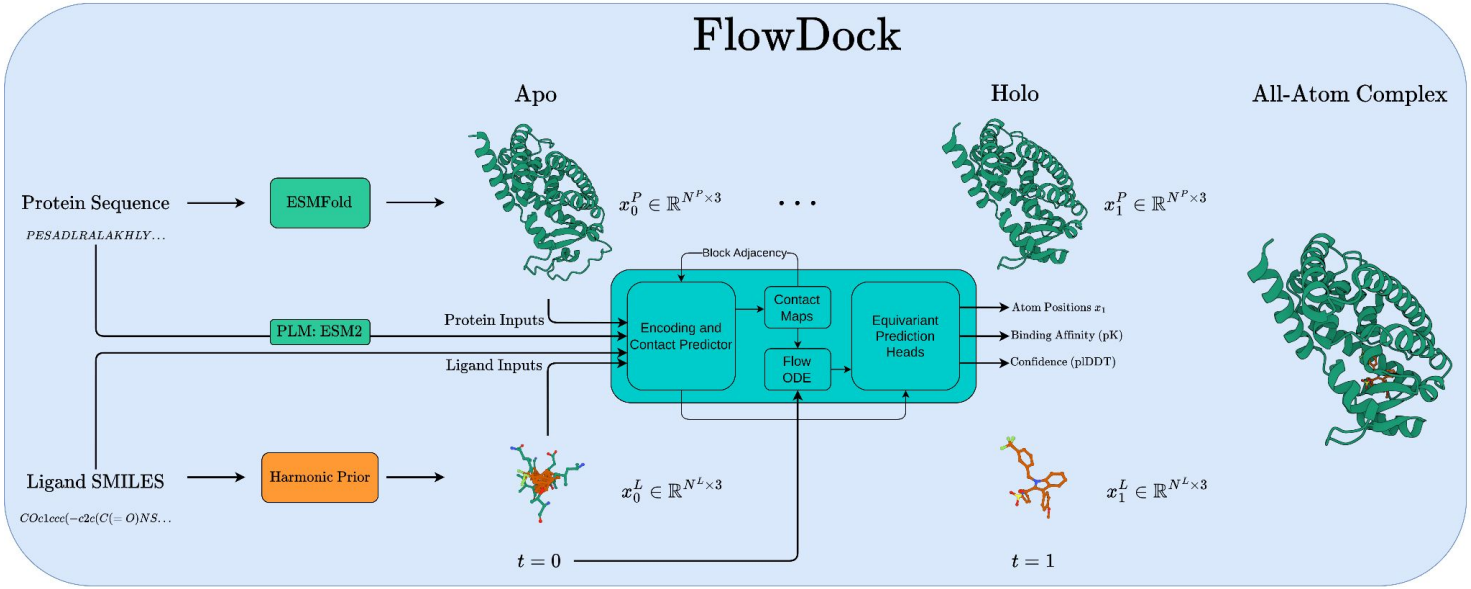
References: Chen et al. 2024, ICLR; Jing et al. 2024, ICML

Another Angle on Flow Matching

Gaussian flow matching → a kingdom of potatoes?

References: Fjelde et al. 2024, Blog Post; Esser et al. 2024, ICML

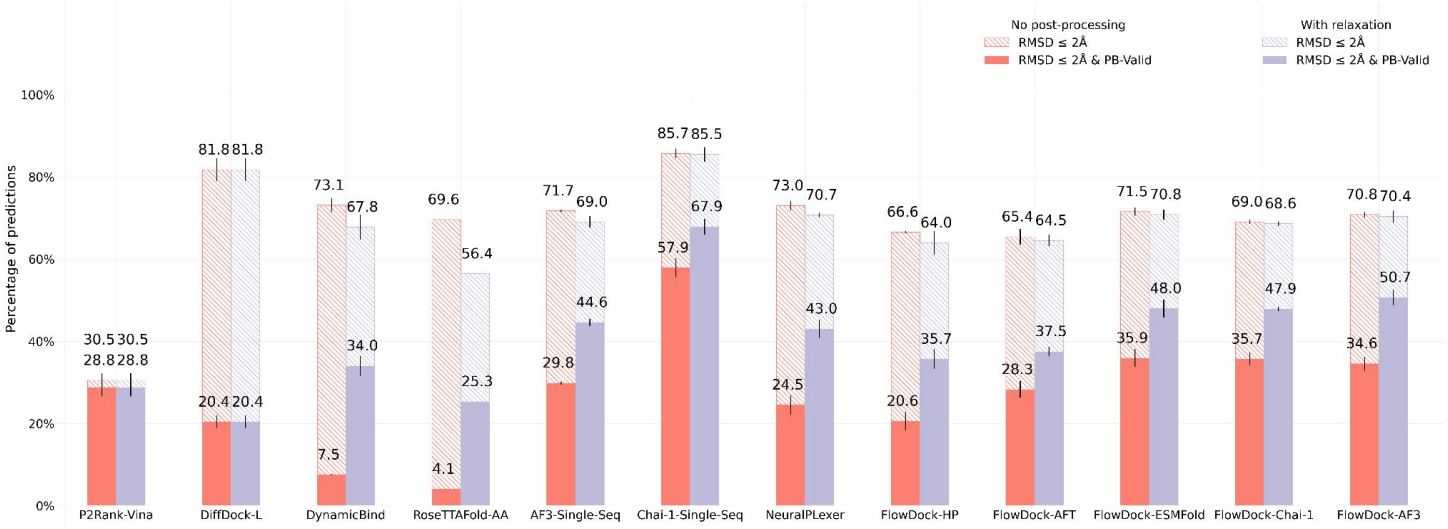
Generative Modeling Case Study (FlowDock)



The first available deep learning (blind) docking method based on **conditional flow matching**

Reference: **Morehead** et al. 2025, ISMB

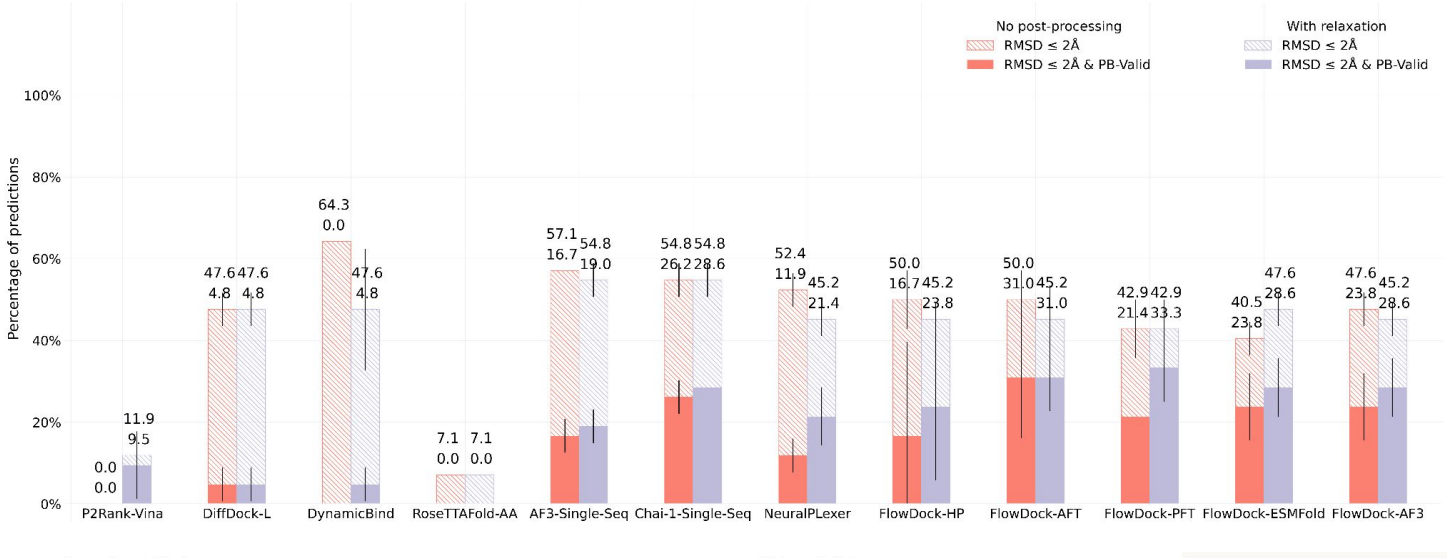
Generative Modeling Case Study (FlowDock - PoseBusters)



- FlowDock debuts as a lightweight and accurate **generative model of biomolecular structures**

Reference: **Morehead** et al. 2025, ISMB

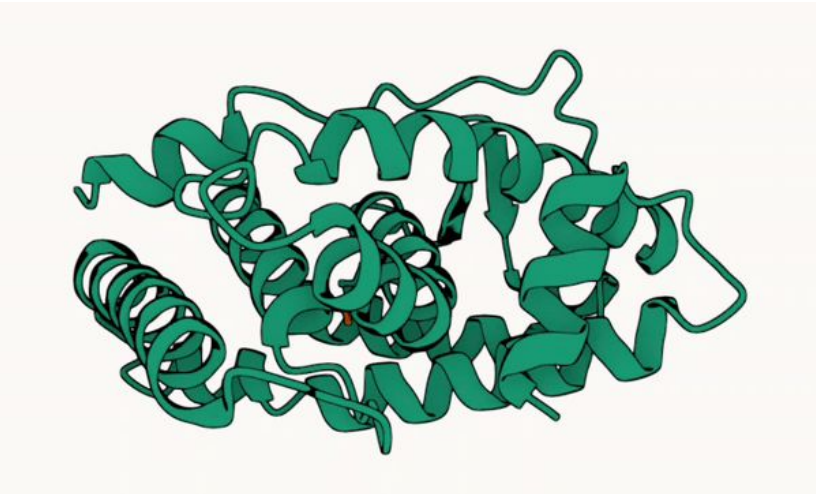
Generative Modeling Case Study (FlowDock - DockGen)



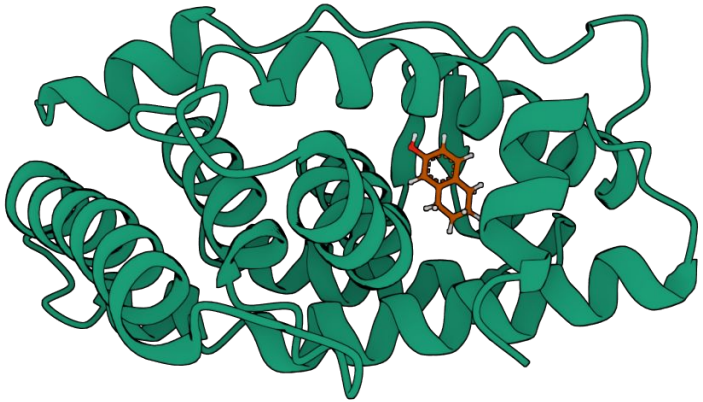
- FlowDock matches or exceeds the **generalization capabilities** of previous state-of-the-art methods

Reference: **Morehead** et al. 2025, ISMB

Accurate Sampling Trajectories



Generated Structure of PDBBind 6I67
(Predicted Affinity: 6.05)



Crystal Structure of PDBBind 6I67
(True Affinity 6.70)

Flow matching enables flexible docking via deep learning

Reference: **Morehead** et al. 2025, ISMB

Generative Modeling Case Study (FlowDock - PDBBind)

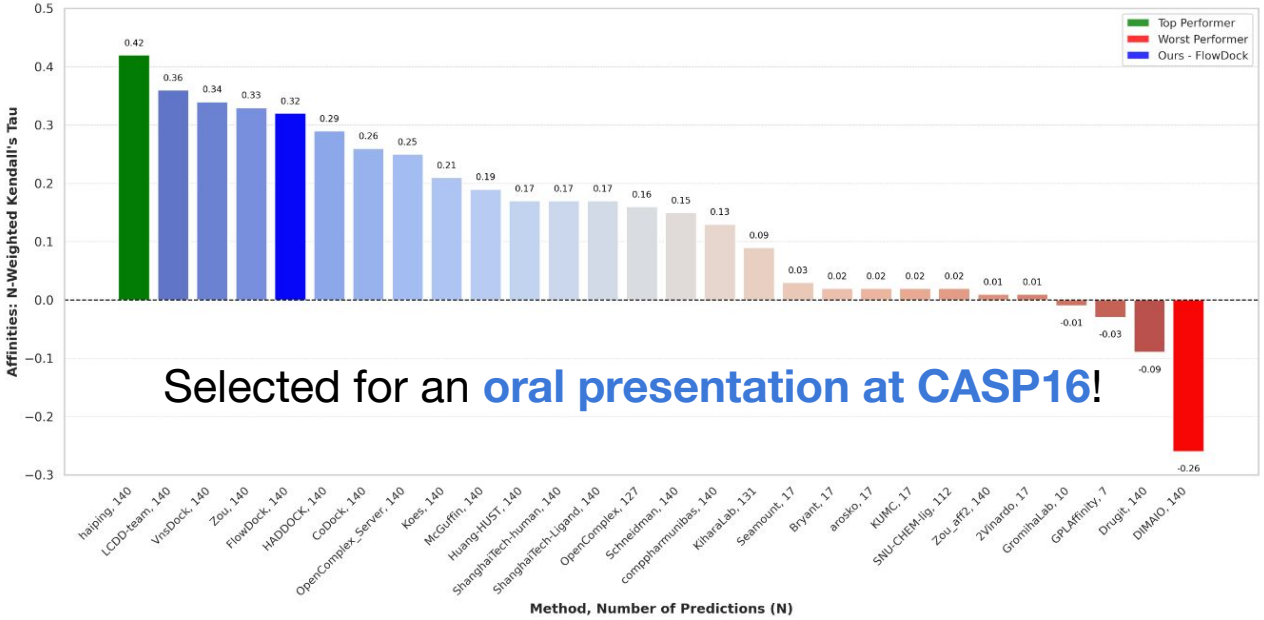
Method	Pearson (↑)	Spearman (↑)	RMSE (↓)	MAE (↓)
GIGN	0.286	0.318	1.736	1.330
TransformerCPI	0.470	0.480	1.643	1.317
MONN	0.545	0.535	1.371	1.103
TankBind	0.597	0.610	1.436	1.119
DynamicBind (One-Shot)	0.665	0.634	1.301	1.060
FlowDock-HP	0.577 ± 0.001	0.560 ± 0.001	1.516 ± 0.001	1.196 ± 0.002
FlowDock-AFT	0.663 ± 0.003	0.624 ± 0.003	1.392 ± 0.005	1.113 ± 0.003
FlowDock	$\mathbf{0.705 \pm 0.001}$	$\mathbf{0.674 \pm 0.002}$	1.363 ± 0.003	1.067 ± 0.003

Method	Runtime (s)	CPU Memory Usage (GB)	GPU Memory Usage (GB)
P2Rank-Vina	1,283.70	9.62	0.00
DiffDock-L	88.33	8.99	70.42
DynamicBind	146.99	5.26	18.91
RoseTTAFold-All-Atom	3,443.63	55.75	72.79
AF3	3,049.41	-	-
AF3-Single-Seq	58.72	-	-
Chai-1-Single-Seq	114.86	58.49	56.21
NeuralPLexer	29.10	11.19	31.00
FlowDock	39.34	11.98	25.61

- This (fast) model can accurately predict both biomolecular structures **and binding affinities**!

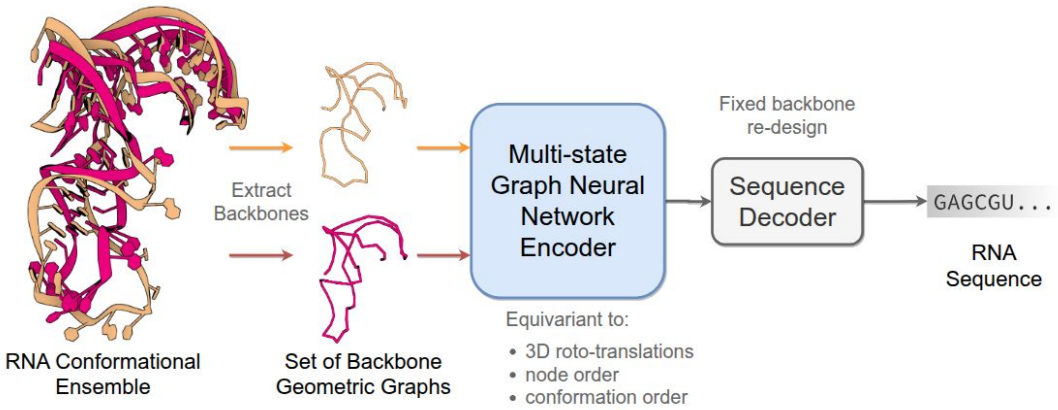
Reference: **Morehead** et al. 2025, ISMB

Generative Modeling Case Study (FlowDock - CASP16)



Selected for an **oral presentation at CASP16**!

Reference: **Morehead** et al. 2025, ISMB



How does this impact Biomolecule Design?

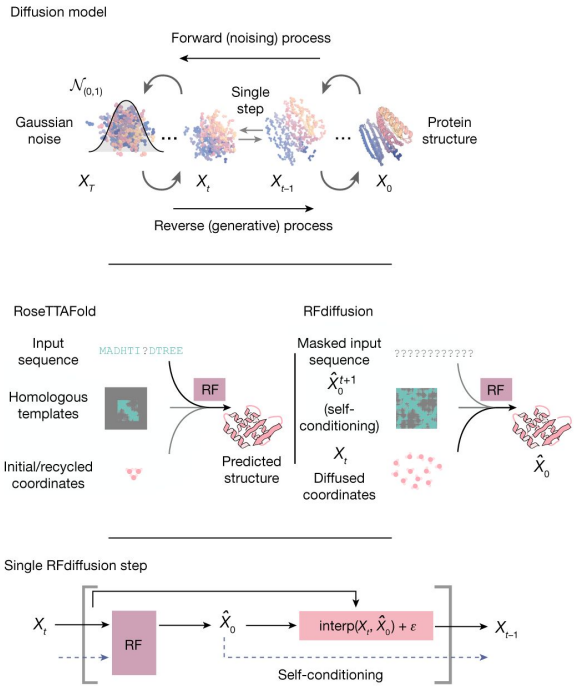
Reference: Joshi et al. 2025, ICLR

Key Ideas

1. As geometric and generative models become more powerful, the number of promising biomolecule design use cases grows

2. Nonetheless, data quality (1) and quantity (2) can be rate limiters of successful design efforts

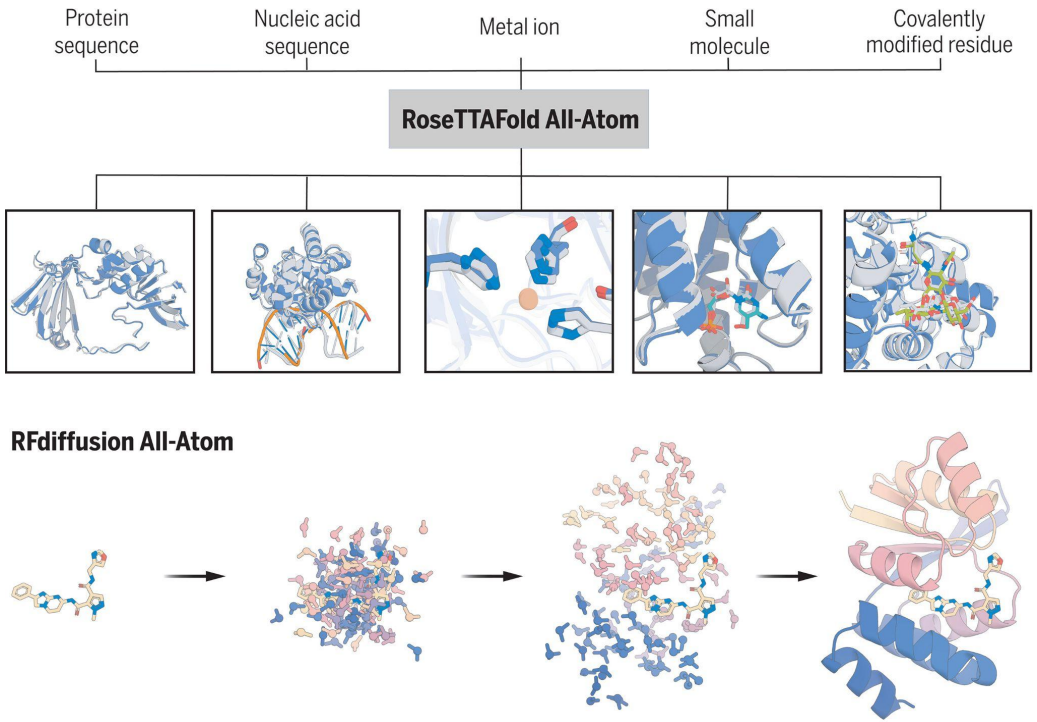
3. Pre-training on large (related) datasets can be a useful way to initialize a generative design model



Reference: Watson et al. 2023, Nature

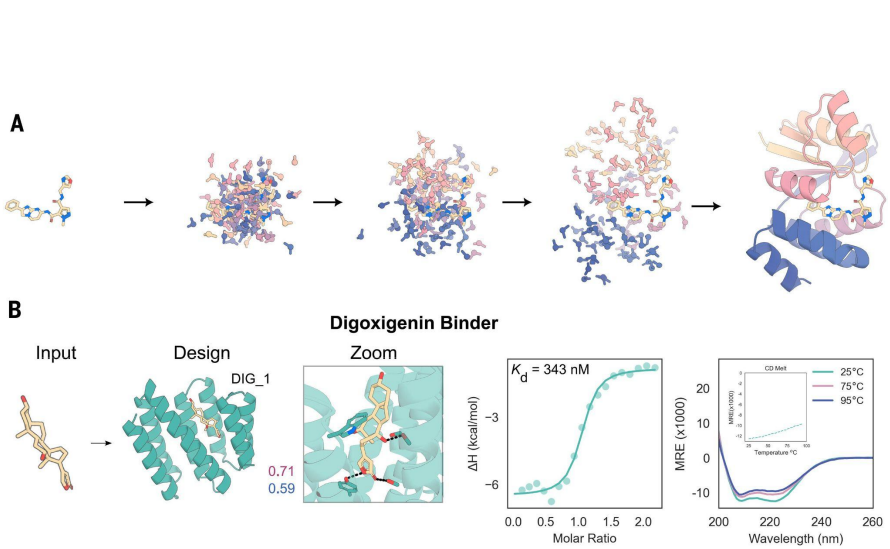
Biomolecule Design Case Study (RoseTTAFoldAA & RFdiffusionAA)

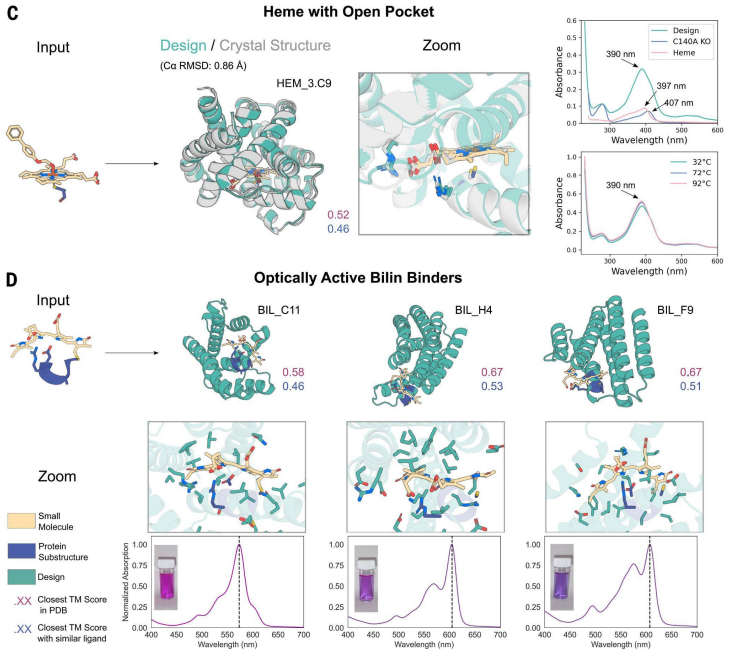
Atomic biomolecule design is here!



Reference: Krishna et al. 2024, Science

Biomolecule Design Case Study (RoseTTAFoldAA & RFdiffusionAA)

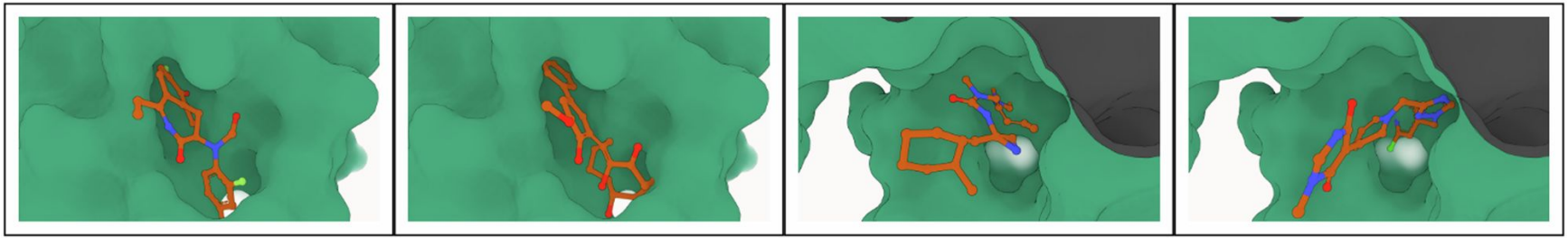




Reference: Krishna et al. 2024, Science

Experimentally characterizing proteins designed for specific small molecules

Biomolecule Design Case Study (GCDM-SBDD)

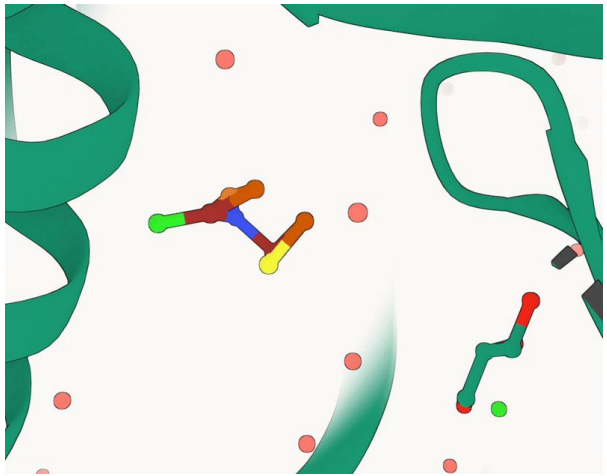


(a) 2FKY: -8.7 Vina (b) 2FKY: -9.7 Vina (c) 4Z2G: -8.2 Vina (d) 4Z2G: -8.7 Vina

- Finding: Molecule generation models can readily be repurposed as structure-based drug designers

Reference: **Morehead** et al. 2024, Nature CommsChem

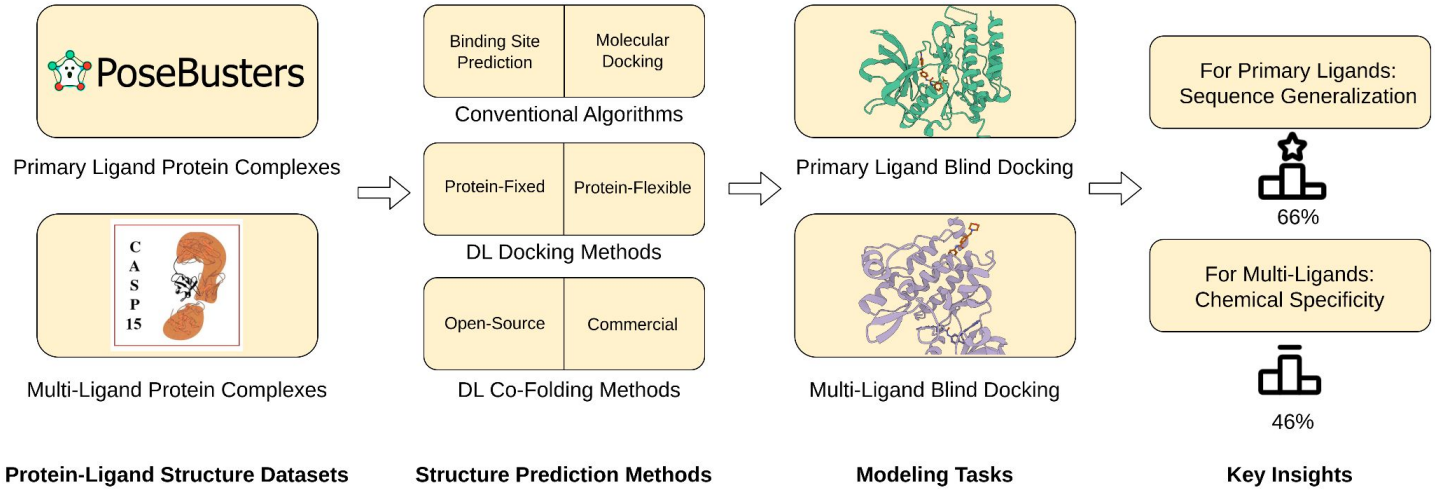
Biomolecule Design Case Study (GCDM-SBDD)



- Note: Most structure-based drug design methods based on generative modeling are primarily challenged with pocket design specificity

Reference: **Morehead** et al. 2024, Nature CommsChem

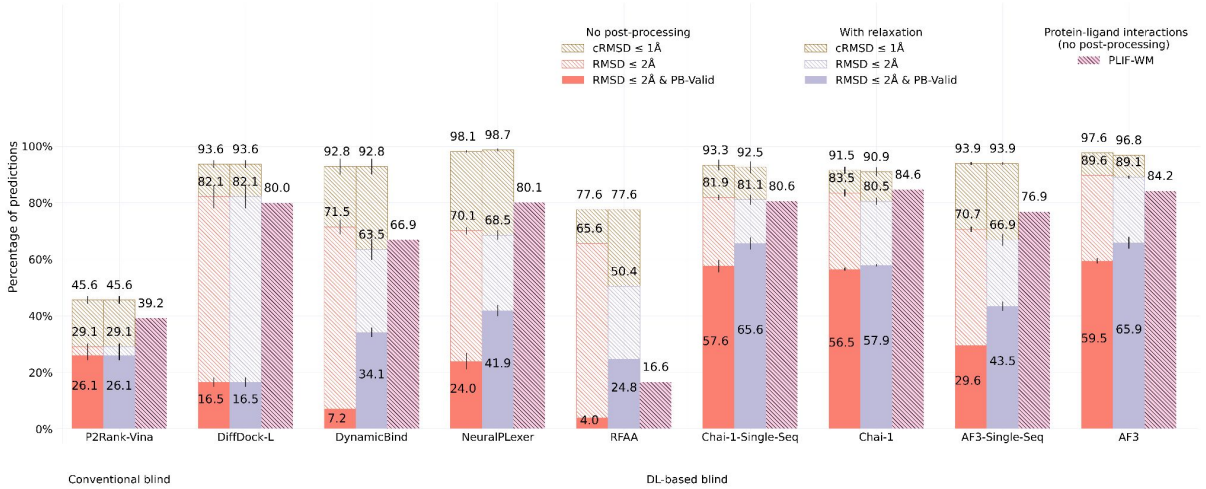
Biomolecule Design Case Study (PoseBench)



- Intuition: An algorithm must be an accurate structure predictor before design is tractable

Reference: **Morehead** et al. 2024, ICML AI4Science (Spotlight)

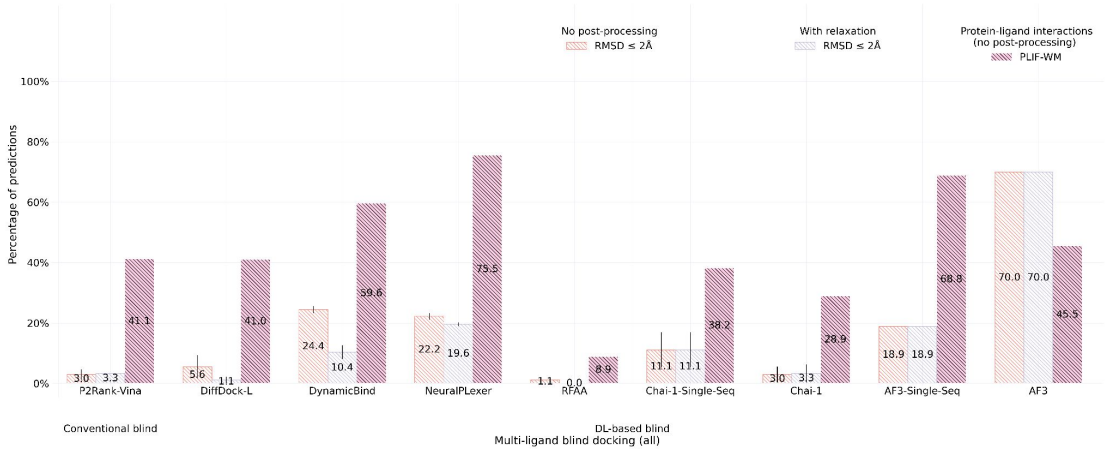
Biomolecule Design Case Study (PoseBench - PoseBusters Benchmark)



- Benchmarking results: AlphaFold 3 is currently the best structure predictor around, but not by a lot (and only with high-quality multiple sequence alignment inputs)

Reference: **Morehead** et al. 2024, ICML AI4Science (Spotlight)

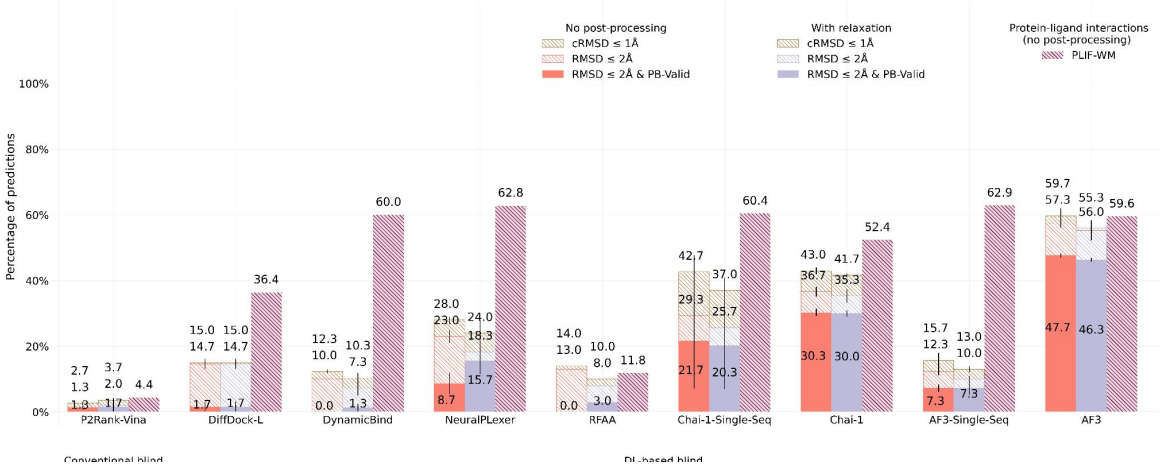
Biomolecule Design Case Study (PoseBench - CASP16 Benchmark)



- Benchmarking results: In diverse (multi-molecule) use cases, AlphaFold 3 shines, yet it is still challenged to faithfully model crystalized protein-ligand interactions

Reference: **Morehead** et al. 2024, ICML AI4Science (Spotlight)

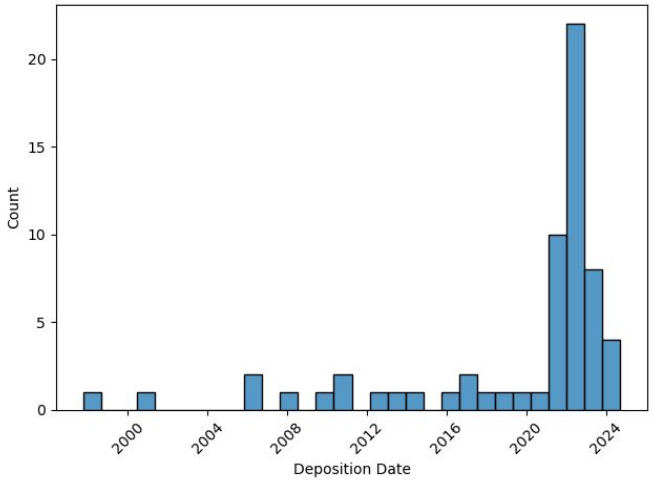
Biomolecule Design Case Study (PoseBench - DockGen-E Benchmark)



- Benchmarking results: Even for datasets overlapping with AlphaFold 3's training data, uncommon prediction targets highlight the model's room for improvement

Reference: **Morehead** et al. 2024, ICML AI4Science (Spotlight)

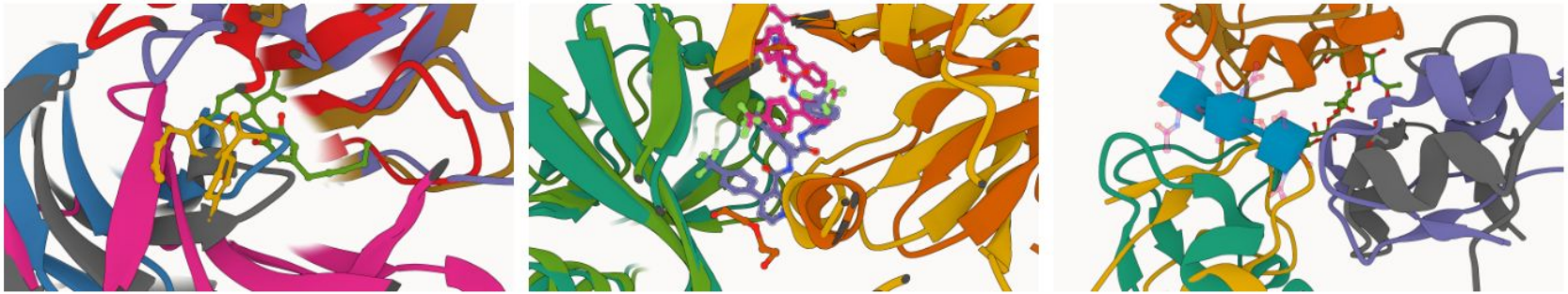
Biomolecule Design Case Study (PoseBench - Failure Modes Analysis)



- Analysis: Most of the time when AlphaFold 3 makes an inaccurate prediction, the prediction target is evolutionarily distinct from what the model has seen

Reference: **Morehead** et al. 2024, ICML AI4Science (Spotlight)

Biomolecule Design Case Study (PoseBench - Common Failure Modes)

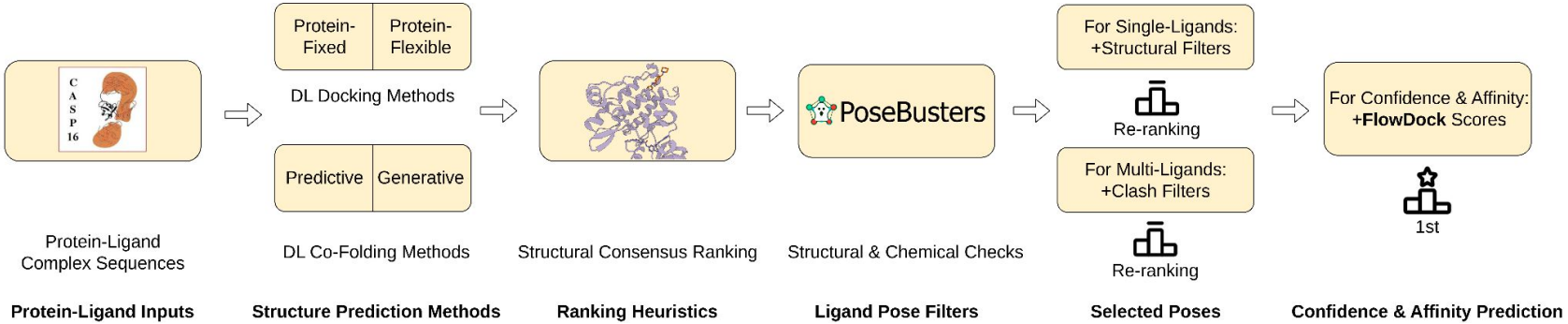


(a) Biosynthetics (RFAA) (b) Immune Proteins (AF3) (c) Novel Proteins (AF3)

- Analysis: Even the best structure prediction methods such as AlphaFold 3 have trouble predicting several important classes of proteins

Reference: **Morehead** et al. 2024, ICML AI4Science (Spotlight)

Biomolecule Design Case Study (MULTICOM_ligand)



- Finding: An unsupervised best-of-N deep learning ensemble performs remarkably well compared to specialist (singular) prediction algorithms

Reference: **Morehead** et al. 2025, Proteins (CASP16-Invited Issue)

Biomolecule Design Case Study (MULTICOM_ligand)

Algorithm 1 MULTICOM_ligand for protein-ligand structure and affinity prediction

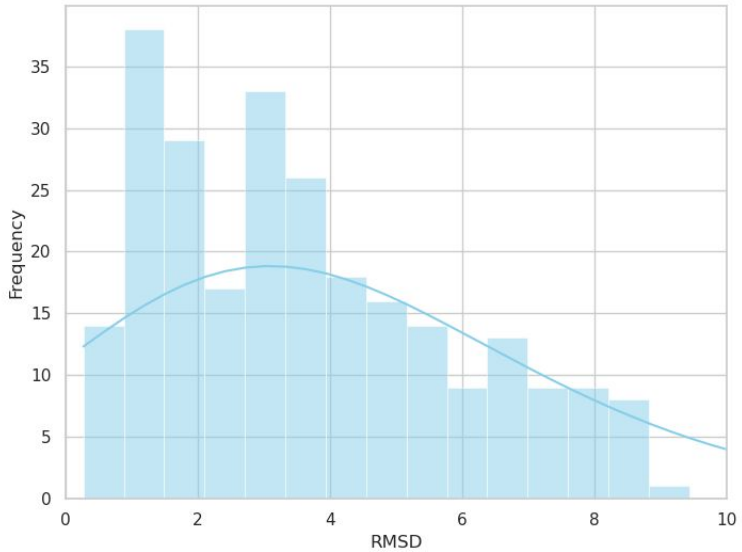
Notation: (X: intermediate protein or protein-ligand structure; $\hat{X}$: final protein-ligand structure; $\hat{B}$: binding affinity, $\hat{C}$: confidence score)

Input: Protein sequence and ligand SMILES string (S, M)
Predict $X^{init} \leftarrow \text{ESMFold}(S)$
Sample $X^{dd} \leftarrow \text{DiffDock-L}(S, M, X^{init})$
Sample $X^{db} \leftarrow \text{DynamicBind}(S, M, X^{init})$
Sample $X^{np} \leftarrow \text{NeuralPLexer}(S, M, X^{init})$
Predict $X^{rfaa} \leftarrow \text{RoseTTAFold-All-Atom}(S, M)$
Rank $X^{con} \leftarrow \text{StructureConsensus}(X^{dd,db,np,rfaa})$
Bust $X^{bust} \leftarrow \text{PoseBustersFilters}(X^{con})$
if Is Multi-Ligand **then**
    Clash Bust $X^{bust} \leftarrow \text{ClashFilters}(X^{bust})$
end if
Finalize $\hat{X}, \hat{C}, \hat{B} \leftarrow \text{FlowDockAssess}(S, M, X^{bust})$
Output: Sampled top-5 heavy-atom structures $\hat{X}$ with confidence scores $\hat{C}$ and binding affinities $\hat{B}$

- Overview: How does this ensemble work?

Reference: **Morehead** et al. 2025, Proteins (CASP16-Invited Issue)

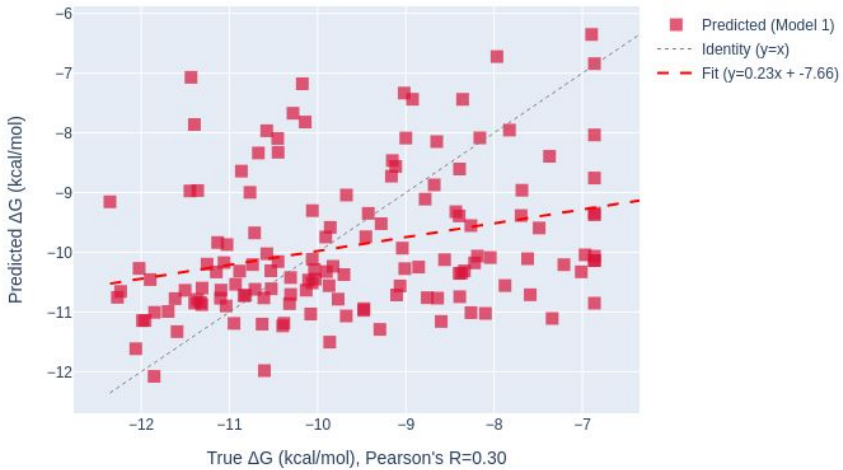
Biomolecule Design Case Study (MULTICOM_ligand)



- Evaluation: How well does this ensemble do in a (CASP16) blind assessment?

Reference: **Morehead** et al. 2025, Proteins (CASP16-Invited Issue)

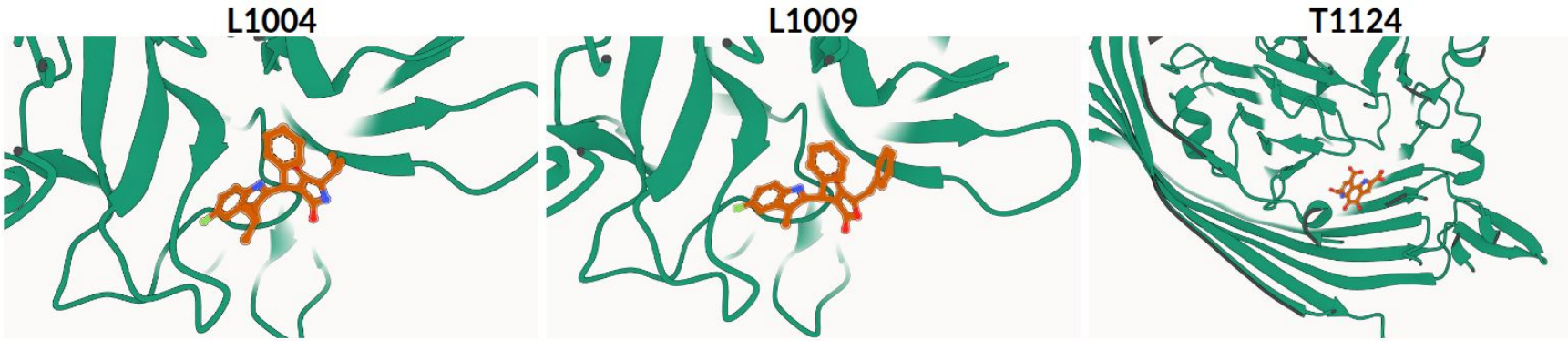
Biomolecule Design Case Study (MULTICOM_ligand)



- Capabilities: How well can this method predict binding affinities?

Reference: **Morehead** et al. 2025, Proteins (CASP16-Invited Issue)

Biomolecule Design Case Study (MULTICOM_ligand)



(a) RMSD=0.510 (b) RMSD=0.603 (c) RMSD=4.244

- Analysis: How do this method's (best and worst) predictions look?

Reference: **Morehead** et al. 2025, Proteins (CASP16-Invited Issue)

Interdisciplinary Challenges

1. Developing proper benchmarks and evaluation metrics for deep learning-based structure prediction and design methods requires **dual** computing and life science expertise

2. Evaluating the performance of structure-based drug design methods is **bottlenecked** by the rate of wet lab experiments a group can complete

3. Whether, and the extent to which, deep learning methods for biochemical data can generalize to novel types of biomolecules are open questions for the field

Future Directions

1. **Exploring** the design space of biomolecular diffusion models could be a powerful new means of drug discovery

2. Neural network expressiveness could be more strongly characterized and **linked** to the (in)capabilities of today's bio-generative models

3. Generative modeling is primed for innovation from the perspective of biophysical priors and conditional flow matching

Dissertation Outcomes (1)

1. This PhD dissertation has yielded **8 first-author publications** (with **3** additional papers either currently in review or released as a preprint) and has contributed to **20+** peer-reviewed works overall (including **one** NIH grant proposal)

2. These first-author (+co-first-author) publications include **2** (+**2**) works presented at top CS conferences (according to **CSRankings**) including the International Conference on Learning Representations (**ICLR**) and Intelligent Systems for Molecular Biology (**ISMB**) and **2** works published in **Nature Portfolio** journals

Dissertation Outcomes (2)

1. To date, this dissertation's associated papers have garnered 450+ citations and inspired multiple follow-up works in machine learning (GearNet - ICLR 2023 2023) and generative modeling (RNA-FrameFlow - ICML 2024 SPIGM)

2. Further, this dissertation has been awarded the Berkeley Lab's **2025 Admiral Grace Hopper Postdoctoral Fellowship** in Computing Sciences

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17. Jamasb*, A. R., **Morehead***, A., et al. "Evaluating Representation Learning on the Protein Structure Universe." International Conference on Learning Representations (ICLR 2024).
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20. Joshi, Chaitanya K., et al. "gRNAde: Geometric Deep Learning for 3D RNA inverse design." International Conference on Learning Representations (ICLR 2025).
21. **Morehead**, Alex, and Jianlin Cheng. "FlowDock: Geometric Flow Matching for Generative Protein-Ligand Docking and Affinity Prediction." Bioinformatics 39.Supplement_1 (ISMB 2025): i308-i317.
22. **Morehead**, Alex, et al. "Protein-ligand structure and affinity prediction in CASP16 using a geometric deep learning ensemble and flow matching." Proteins: Structure, Function, and Bioinformatics (2025).
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* denotes co-first-authorship (equal contribution)

National Institutes of Health

Thank you!

Website

GitHub

Summary

- **Geometric deep learning** is a widely applicable toolkit for computational modeling of physical phenomena.
- **Geometric** and **generative models** are accelerating biochemical science.
- Large-scale deep learning efforts are poised to introduce new modalities for scientific inquiry within drug discovery and beyond.