



Generalist Equivariant Transformer Towards 3D Molecular Interaction Learning

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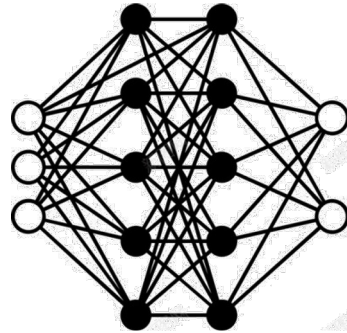
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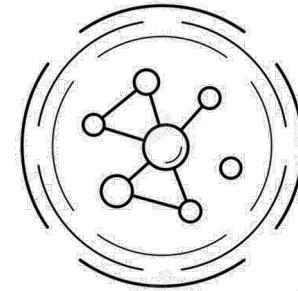
Data Matters



Data



Model



Optimization

Scarcity of Data

Affinity Prediction

- Protein - Small Molecule: 5316
- Protein - Protein: 2852
- Protein - RNA/DNA: 1052
- RNA/DNA - Small Molecule: 149



Data are hard to obtain

- Wet-lab experiments are costly
- It's hard to find new complexes in some domains

Is it possible to transfer knowledge
from data in different domains?

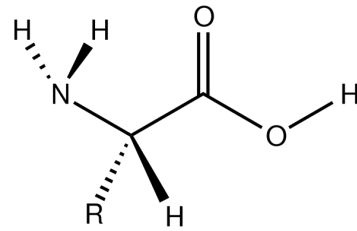
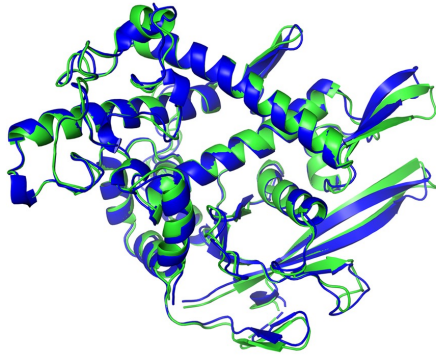
Representations of Different Molecules

Molecule Type

Building Block

Different building blocks lead to different representation unit

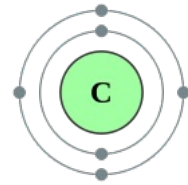
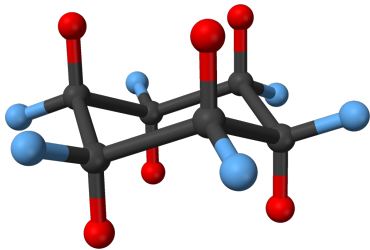
Protein



Amino Acid

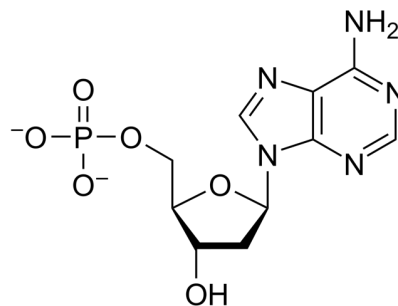
However, the basic units are always atoms and the essence of molecular interactions/structures is secondary-bonding between atoms (e.g. hydrogen bond, π - π interaction), regardless of the building blocks.

Small Molecule

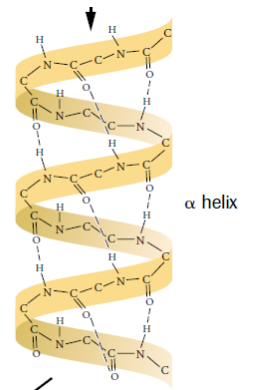
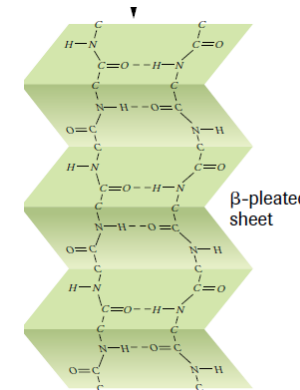


Atom

RNA/DNA



Nucleotide



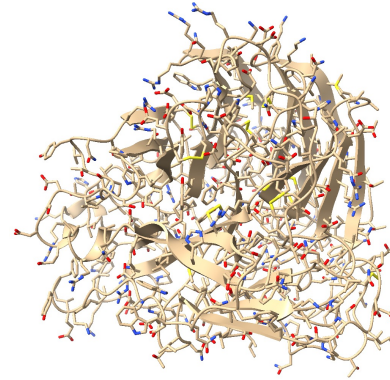
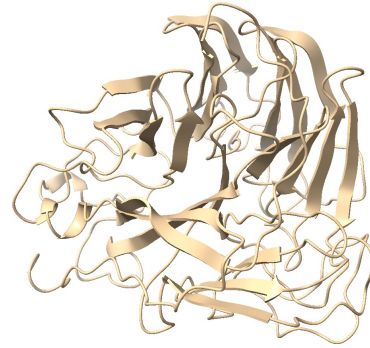
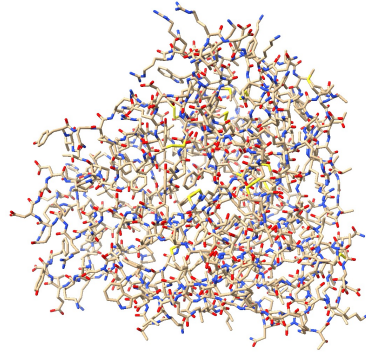
Naive Unified Representation

Atom-level
(fine-grained)

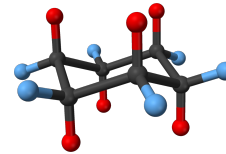
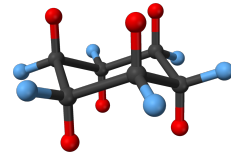
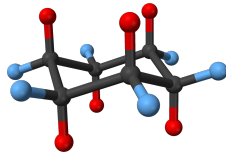
Block-level
(coarse-grained)

Unified Representation?

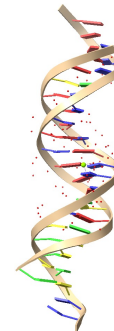
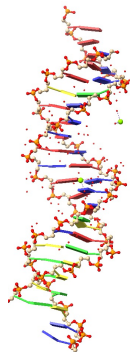
Protein



Small Molecule



RNA/DNA



Is it possible to maintain both
the atom-level instances and the
heuristics of building blocks?

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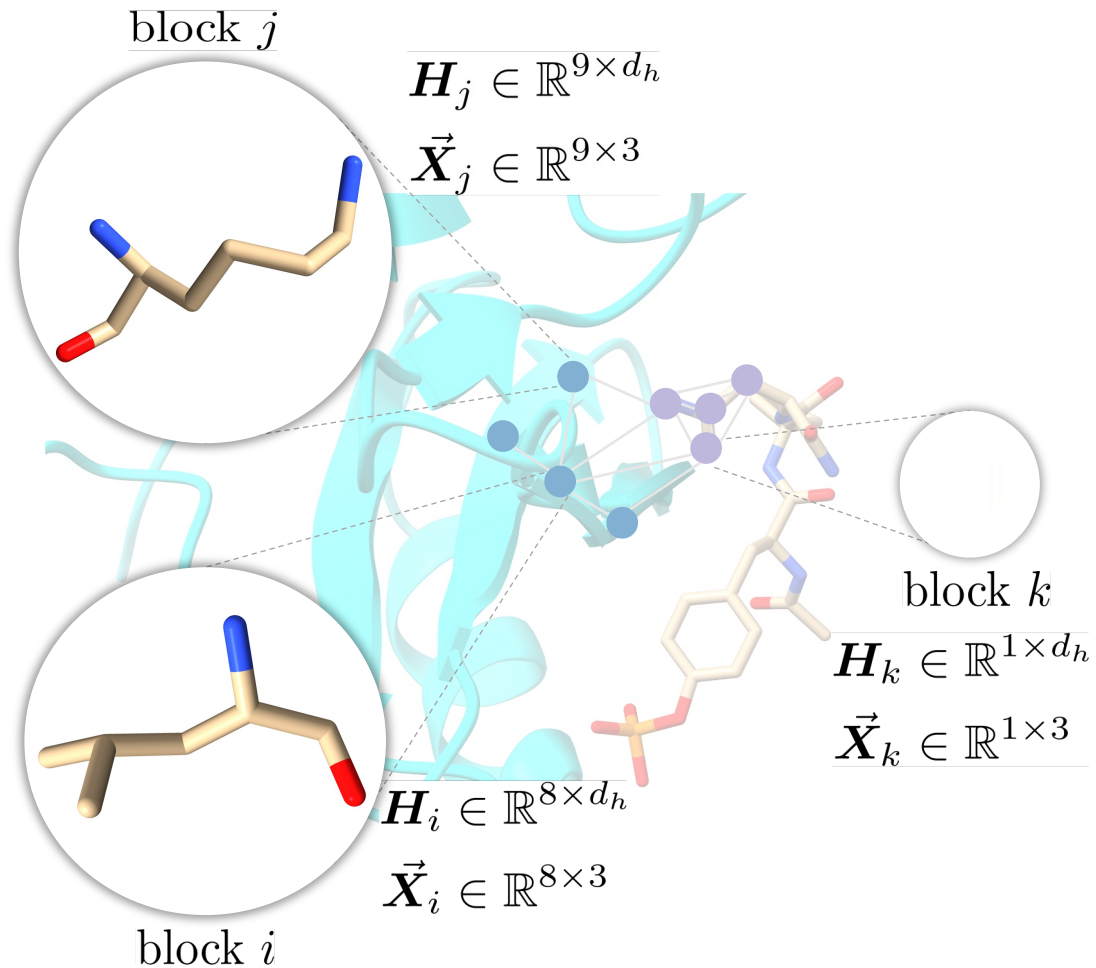
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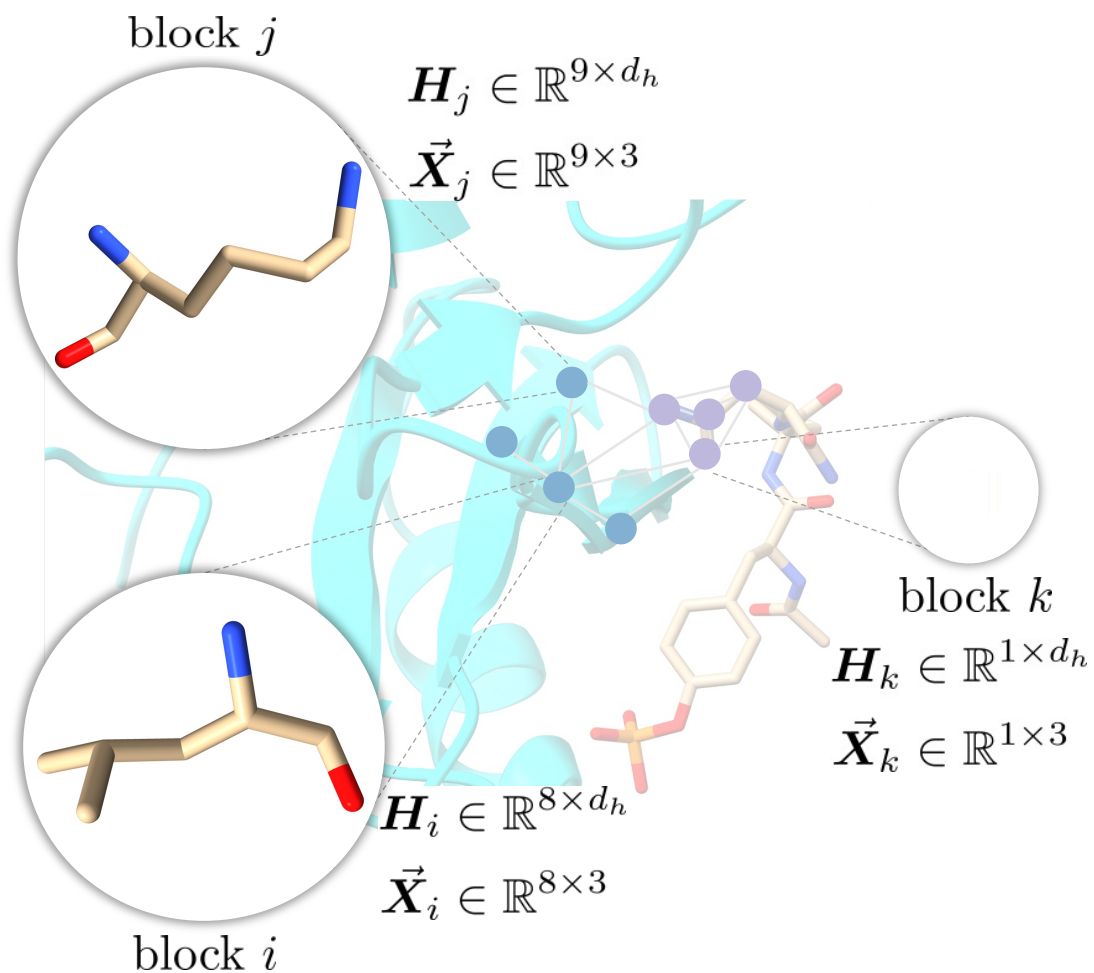
4. Future Plan

Geometric Graph of Sets: Definition



How are about a geometric graph where each node (block) contains a set of atoms?

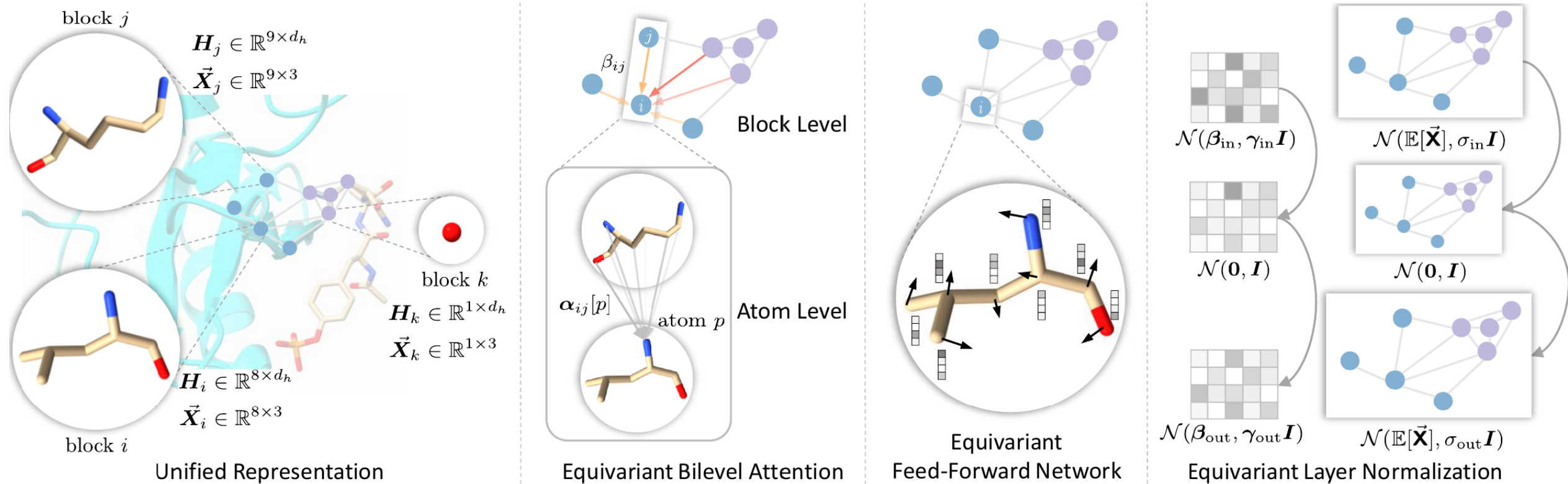
Geometric Graph of Sets: Challenge



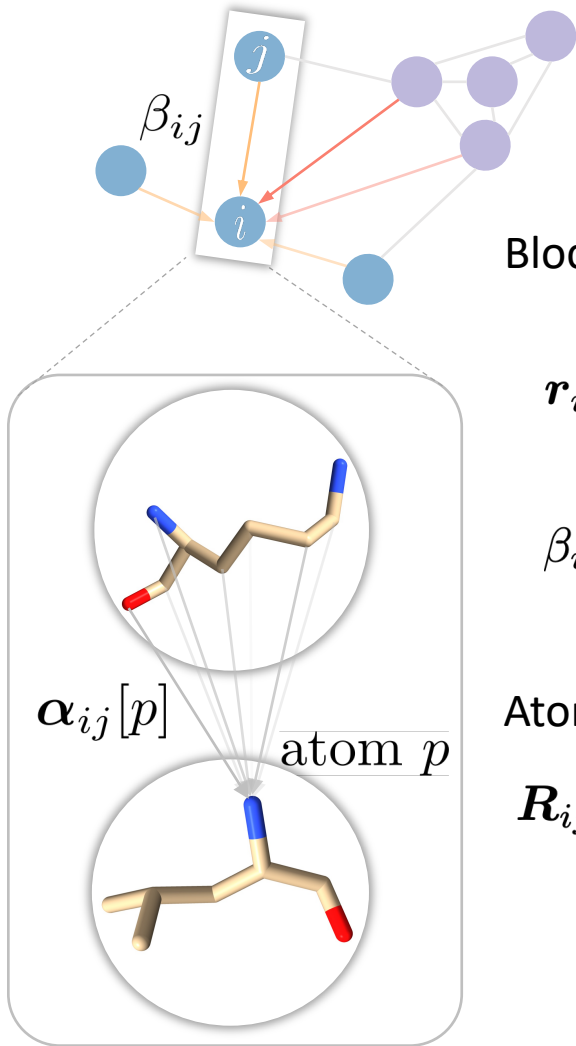
Challenges for designing a corresponding model

- Node features / coordinates are matrices with **variable number of rows!**
- Still, **E(3)-equivariance** is important!
- Moreover, **intra-block permutation invariance** is also important since the atoms within a block are unordered

Overview



Equivariant Bilevel Attention



Block Level

$$\mathbf{r}_{ij} = \frac{1}{n_i n_j} \sum_{p=1}^{n_i} \sum_{q=1}^{n_j} \mathbf{R}_{ij}[p, q]$$

$$\beta_{ij} = \frac{\exp(\mathbf{r}_{ij} \mathbf{W}_B)}{\sum_{j \in \mathcal{N}(i)} \exp(\mathbf{r}_{ij} \mathbf{W}_B)}$$

Atom Level

$$\mathbf{R}_{ij}[p, q] = \phi_A(\mathbf{Q}_i[p], \mathbf{K}_j[q], \text{RBF}(\mathbf{D}_{ij}[p, q]), \mathbf{e}_{ij}),$$

$$\alpha_{ij} = \text{Softmax}(\mathbf{R}_{ij} \mathbf{W}_A)$$

$$\mathbf{Q}_i = \mathbf{H}_i \mathbf{W}_Q, \quad \mathbf{K}_j = \mathbf{H}_j \mathbf{W}_K, \quad \mathbf{V}_j = \mathbf{H}_j \mathbf{W}_V,$$

$$\vec{\mathbf{X}}_{ij}[p, q] = \vec{\mathbf{X}}_i[p] - \vec{\mathbf{X}}_j[q], \quad \mathbf{D}_{ij}[p, q] = \|\vec{\mathbf{X}}_{ij}[p, q]\|_2$$

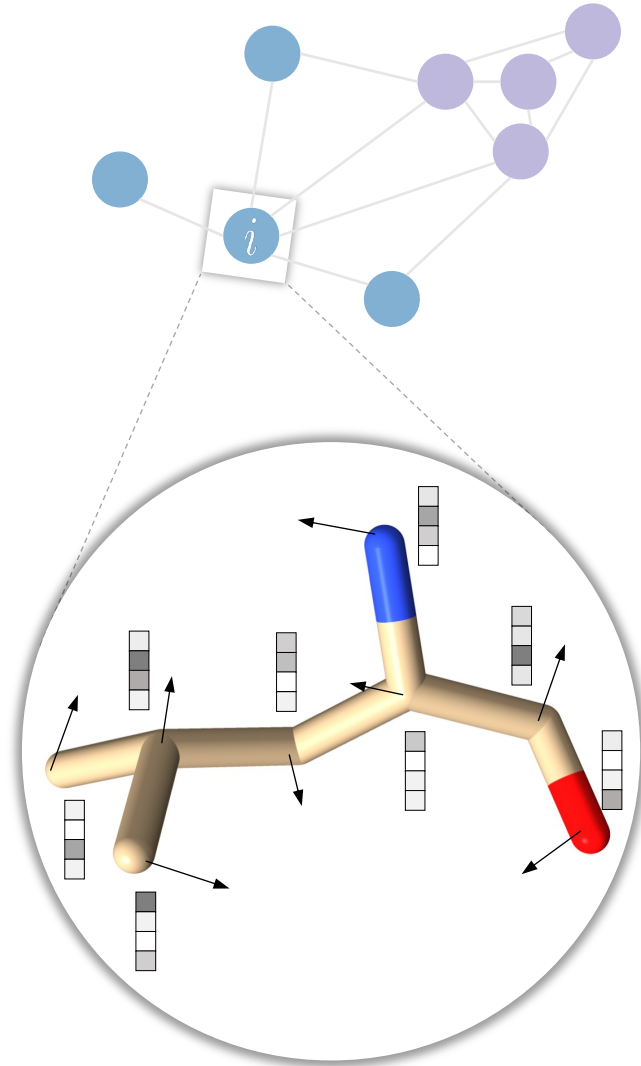
$$\mathbf{m}_{ij,p} = \alpha_{ij}[p] \cdot \phi_v(\mathbf{V}_j \parallel \text{RBF}(\mathbf{D}_{ij}[p]))$$

$$\vec{\mathbf{m}}_{ij,p} = \alpha_{ij}[p] \cdot (\vec{\mathbf{X}}_{ij}[p] \odot \sigma_v(\mathbf{V}_j \parallel \text{RBF}(\mathbf{D}_{ij}[p])))$$

$$\mathbf{H}'_i[p] = \mathbf{H}_i[p] + \sum_{j \in \mathcal{N}(i)} \beta_{ij} \phi_m(\mathbf{m}_{ij,p}),$$

$$\vec{\mathbf{X}}'_i[p] = \vec{\mathbf{X}}_i[p] + \sum_{j \in \mathcal{N}(i)} \beta_{ij} (\sigma_m(\mathbf{m}_{ij,p}) \cdot \vec{\mathbf{m}}_{ij,p}),$$

Equivariant Feed-Forward Network



$$\mathbf{h}_c = \text{centroid}(\mathbf{H}_i), \quad \vec{\mathbf{x}}_c = \text{centroid}(\vec{\mathbf{X}}_i).$$

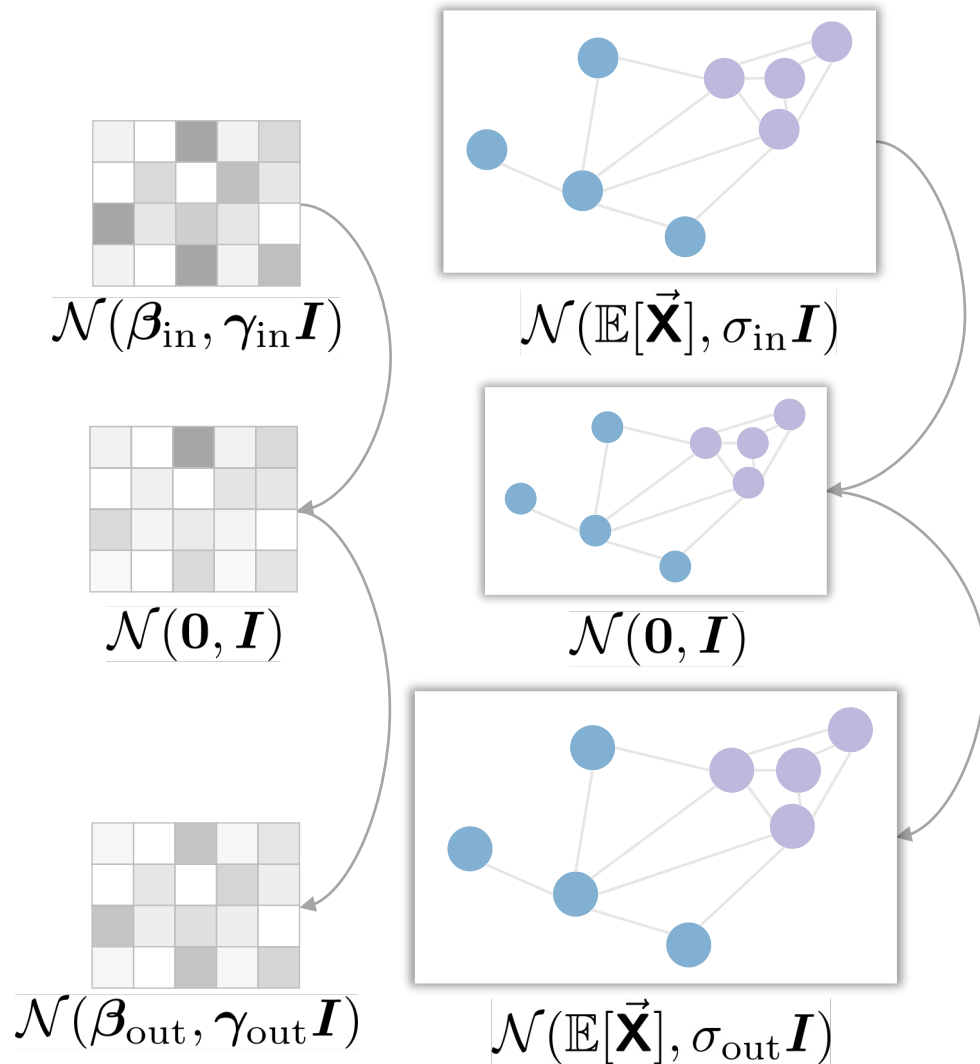
$$\Delta\vec{\mathbf{x}} = \vec{\mathbf{x}} - \vec{\mathbf{x}}_c, \quad \mathbf{r} = \text{RBF}(\|\Delta\vec{\mathbf{x}}\|_2),$$

$$\mathbf{h}' = \mathbf{h} + \phi_h(\mathbf{h}, \mathbf{h}_c, \mathbf{r}),$$

$$\vec{\mathbf{x}}' = \vec{\mathbf{x}} + \Delta\vec{\mathbf{x}}\phi_x(\mathbf{h}, \mathbf{h}_c, \mathbf{r}),$$

Local (intra-block) adjustments

Equivariant Layer Normalization



$$\mathbf{h} = \frac{\mathbf{h} - \mathbb{E}[\mathbf{h}]}{\sqrt{\text{Var}[\mathbf{h}]} } \cdot \gamma + \beta,$$

$$\vec{\mathbf{x}} = \frac{\vec{\mathbf{x}} - \mathbb{E}[\vec{\mathbf{X}}]}{\sqrt{\text{Var}[\vec{\mathbf{X}} - \mathbb{E}[\vec{\mathbf{X}}]]}} \cdot \sigma + \mathbb{E}[\vec{\mathbf{X}}],$$

Contents

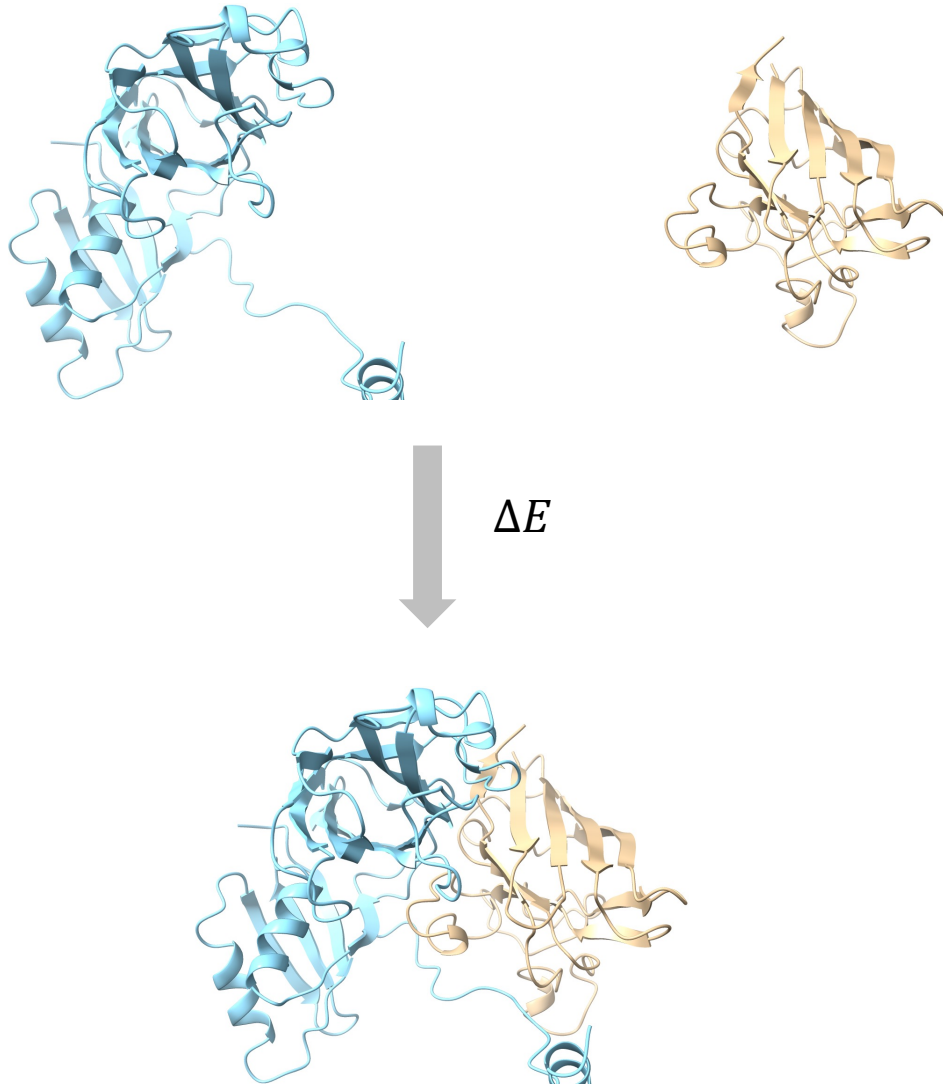
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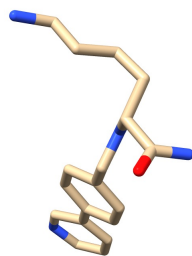
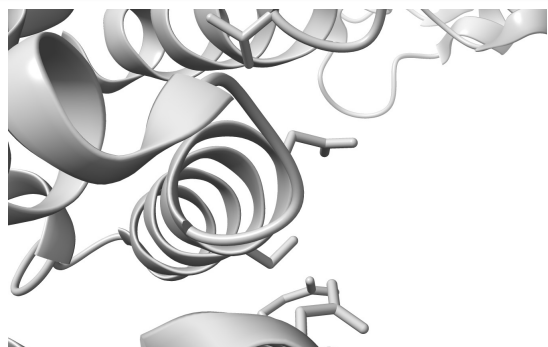
4. Future Plan

Protein-Protein Affinity

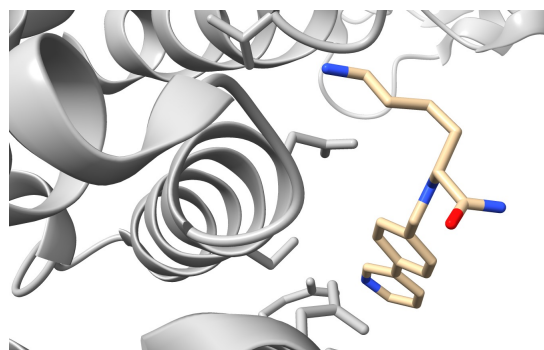


Repr.	Model	Rigid	Medium	Flexible	All
Spearman \uparrow					
Block	SchNet	0.476 \pm 0.015	0.520 \pm 0.013	0.068 \pm 0.009	0.427 \pm 0.012
	DimeNet++	0.466 \pm 0.088	0.368 \pm 0.037	0.171 \pm 0.054	0.317 \pm 0.031
	EGNN	0.364 \pm 0.043	0.455 \pm 0.026	0.080 \pm 0.038	0.382 \pm 0.022
	ET	0.552 \pm 0.039	0.482 \pm 0.025	0.090 \pm 0.062	0.415 \pm 0.027
	GemNet	0.420 \pm 0.072	0.446 \pm 0.059	0.066 \pm 0.058	0.393 \pm 0.027
	MACE	0.596 \pm 0.047	0.450 \pm 0.014	<u>0.306 \pm 0.029</u>	0.466 \pm 0.011
	Equiformer	0.560 \pm 0.015	<u>0.530 \pm 0.017</u>	0.251 \pm 0.002	<u>0.496 \pm 0.007</u>
	LEFTNet	0.515 \pm 0.039	0.492 \pm 0.020	0.193 \pm 0.023	0.452 \pm 0.013
Atom	SchNet	0.546 \pm 0.005	0.512 \pm 0.007	0.028 \pm 0.032	0.404 \pm 0.016
	DimeNet++	OOM			
	EGNN	0.450 \pm 0.042	0.438 \pm 0.021	0.027 \pm 0.030	0.349 \pm 0.009
	ET	0.582 \pm 0.025	0.487 \pm 0.002	0.117 \pm 0.008	0.436 \pm 0.004
	GemNet	OOM			
	MACE	<u>0.619 \pm 0.037</u>	0.487 \pm 0.049	0.221 \pm 0.064	0.449 \pm 0.052
	Equiformer	OOM			
	LEFTNet	0.524 \pm 0.074	0.508 \pm 0.038	0.189 \pm 0.066	0.431 \pm 0.046
Hierarchical	SchNet	0.476 \pm 0.017	0.523 \pm 0.014	0.072 \pm 0.021	0.424 \pm 0.016
	DimeNet++	OOM			
	EGNN	0.387 \pm 0.023	0.461 \pm 0.020	0.078 \pm 0.043	0.390 \pm 0.016
	ET	0.547 \pm 0.045	0.516 \pm 0.019	0.100 \pm 0.111	0.438 \pm 0.029
	GemNet	OOM			
	MACE	0.580 \pm 0.075	0.476 \pm 0.048	0.282 \pm 0.036	0.470 \pm 0.016
	Equiformer	OOM			
	LEFTNet	0.476 \pm 0.082	0.494 \pm 0.037	0.151 \pm 0.019	0.446 \pm 0.029
Unified	GET (ours)	0.622 \pm 0.030	0.533 \pm 0.014	0.363 \pm 0.017	0.533 \pm 0.011

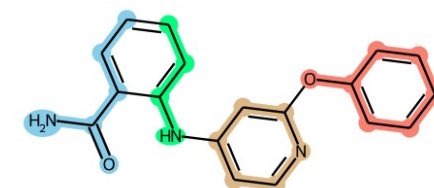
Protein-Ligand Affinity



ΔE



Repr.	Model	LBA		
		RMSE↓	Pearson↑	Spearman↑
Block	SchNet	1.406 ± 0.020	0.565 ± 0.006	0.549 ± 0.007
	DimeNet++	1.391 ± 0.020	0.576 ± 0.016	0.569 ± 0.016
	EGNN	1.409 ± 0.015	0.566 ± 0.010	0.548 ± 0.012
	ET	1.367 ± 0.037	0.599 ± 0.017	0.584 ± 0.025
	GemNet	1.393 ± 0.036	0.569 ± 0.027	0.553 ± 0.026
	MACE	1.385 ± 0.006	0.599 ± 0.010	0.580 ± 0.014
	Equiformer	1.350 ± 0.019	0.604 ± 0.013	0.591 ± 0.012
	LEFTNet	1.377 ± 0.013	0.588 ± 0.011	0.576 ± 0.010
Atom	SchNet	1.357 ± 0.017	0.598 ± 0.011	0.592 ± 0.015
	DimeNet++	1.439 ± 0.036	0.547 ± 0.015	0.536 ± 0.016
	EGNN	1.358 ± 0.000	0.599 ± 0.002	0.587 ± 0.004
	ET	1.381 ± 0.013	0.591 ± 0.007	0.583 ± 0.009
	GemNet	OOM	OOM	OOM
	MACE	1.411 ± 0.029	0.579 ± 0.009	0.563 ± 0.012
	Equiformer	OOM	OOM	OOM
	LEFTNet	1.343 ± 0.004	0.610 ± 0.004	0.598 ± 0.003
Hierarchical	SchNet	1.370 ± 0.028	0.590 ± 0.017	0.571 ± 0.028
	DimeNet++	1.388 ± 0.010	0.582 ± 0.009	0.574 ± 0.007
	EGNN	1.380 ± 0.015	0.586 ± 0.004	0.568 ± 0.004
	ET	1.383 ± 0.009	0.580 ± 0.008	0.564 ± 0.004
	GemNet	OOM	OOM	OOM
	MACE	1.372 ± 0.021	0.612 ± 0.010	0.592 ± 0.010
	Equiformer	OOM	OOM	OOM
	LEFTNet	1.366 ± 0.016	0.592 ± 0.014	0.580 ± 0.011
Unified	GET (ours)	<u>1.327 ± 0.005</u>	<u>0.620 ± 0.004</u>	<u>0.611 ± 0.003</u>
	GET-PS (ours)	1.309 ± 0.012	0.633 ± 0.008	0.642 ± 0.009

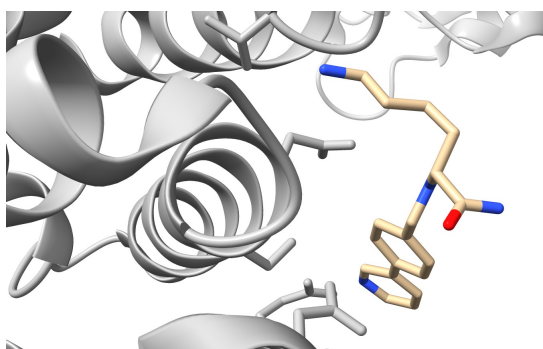
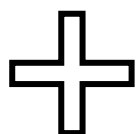
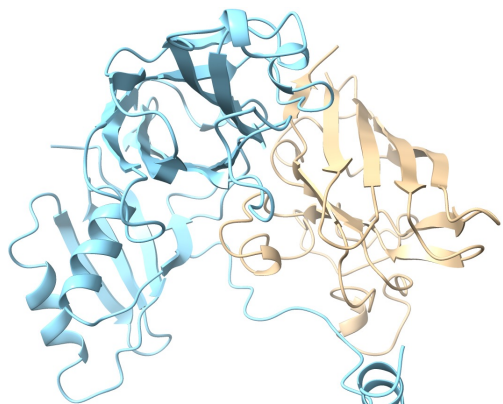


Molecule Generation by
Principal Subgraph
Mining and Assembling
(NeurIPS 2022)

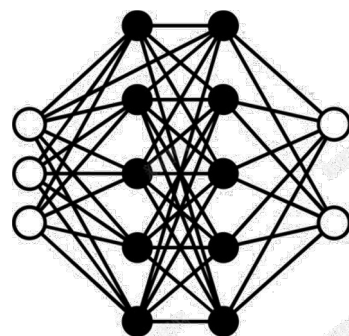
Can we really **transfer** knowledge between **different** domains?

Mixed Training – Mutual Enhancements

Protein - Protein



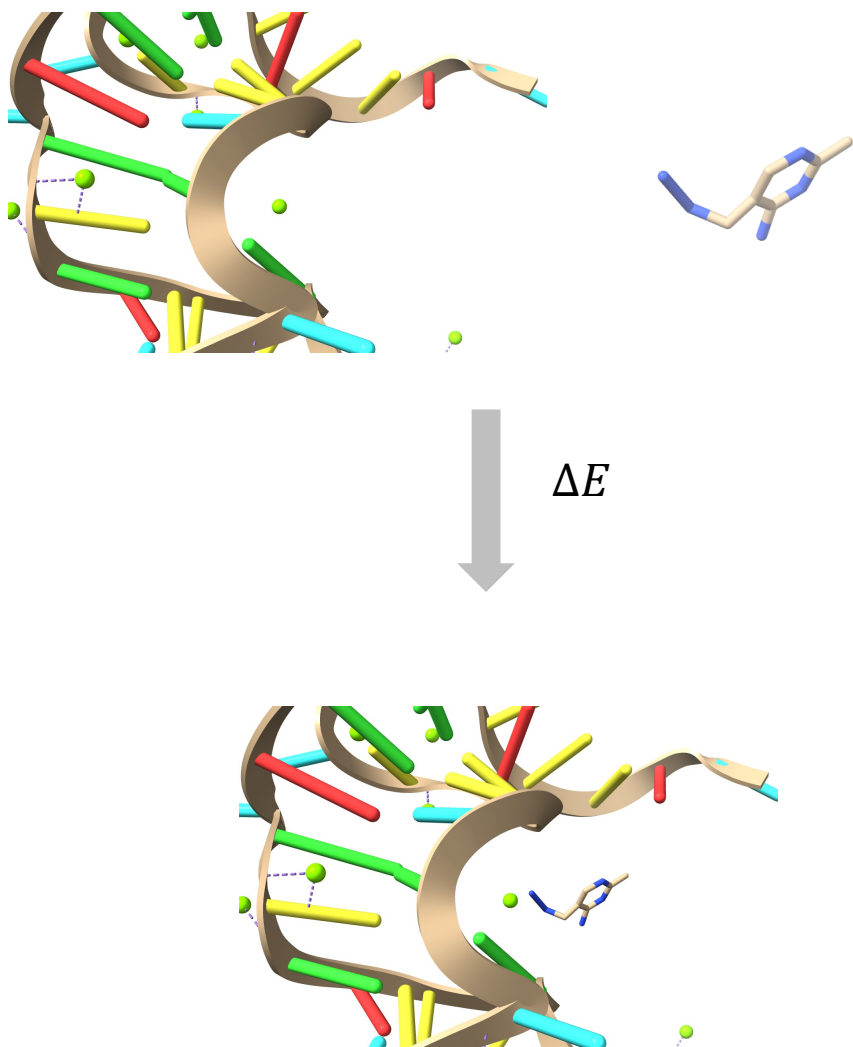
Protein - Small Molecule



GET

Repr.	Model	PPA-All	LBA
Block	ET	0.424 ± 0.021	0.599 ± 0.017
	ET-mix	0.457 ± 0.011	0.586 ± 0.012
	MACE	0.470 ± 0.015	0.599 ± 0.010
	MACE-mix	0.372 ± 0.042	0.590 ± 0.018
	LEFTNet	0.452 ± 0.013	0.588 ± 0.011
	LEFTNet-mix	0.450 ± 0.008	0.543 ± 0.005
Atom	ET	0.401 ± 0.005	0.591 ± 0.007
	ET-mix	0.382 ± 0.029	0.566 ± 0.061
	MACE	0.463 ± 0.052	0.579 ± 0.009
	MACE-mix	0.444 ± 0.024	0.580 ± 0.030
	LEFTNet	0.448 ± 0.046	0.610 ± 0.004
	LEFTNet-mix	0.476 ± 0.023	0.579 ± 0.014
Hier.	ET	0.438 ± 0.026	0.580 ± 0.008
	ET-mix	0.412 ± 0.035	0.569 ± 0.017
	MACE	0.466 ± 0.020	0.612 ± 0.010
	MACE-mix	0.324 ± 0.076	0.588 ± 0.011
	LEFTNet	0.445 ± 0.024	0.592 ± 0.014
	LEFTNet-mix	0.472 ± 0.020	0.556 ± 0.001
Unified	GET (ours)	0.514 ± 0.011	0.620 ± 0.004
	GET-mix (ours)	0.519 ± 0.004	0.622 ± 0.006

Zero-Shot DNA/RNA-Ligand Affinity!



Zero-shot inference on 149 DNA/RNA-ligand affinity exhibit **moderate** correlation!

Repr.	Model	Pearson \uparrow	Spearman \uparrow
Block	ET	0.217 ± 0.059	0.185 ± 0.051
	MACE	0.004 ± 0.045	0.045 ± 0.034
	LEFTNet	0.279 ± 0.127	0.252 ± 0.082
Atom	ET	0.150 ± 0.034	0.198 ± 0.043
	MACE	-0.005 ± 0.079	0.027 ± 0.083
	LEFTNet	0.271 ± 0.062	0.279 ± 0.062
Hierarchical	ET	0.348 ± 0.047	0.302 ± 0.028
	MACE	0.002 ± 0.055	0.041 ± 0.030
	LEFTNet	0.279 ± 0.122	0.259 ± 0.077
Unified	GET	0.450 ± 0.054	0.362 ± 0.041

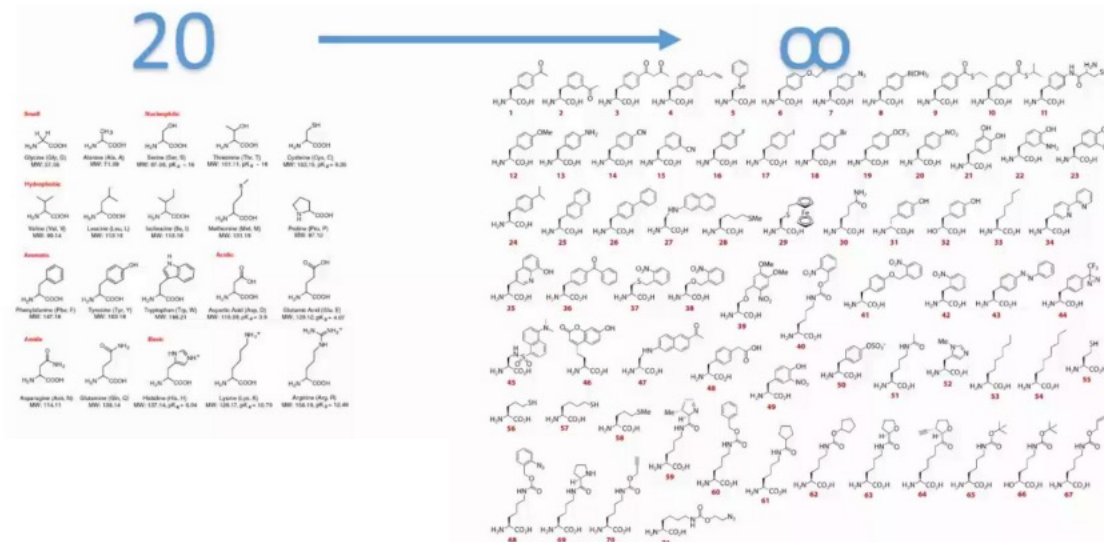
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Future Plan

We can do a lot of things with this unified representation!

- One pretrained model for all kinds of biomolecules!
- Fragment-based small molecule segmentation?
- Non-canonical amino acids (think it as out-of-vocabulary problem)



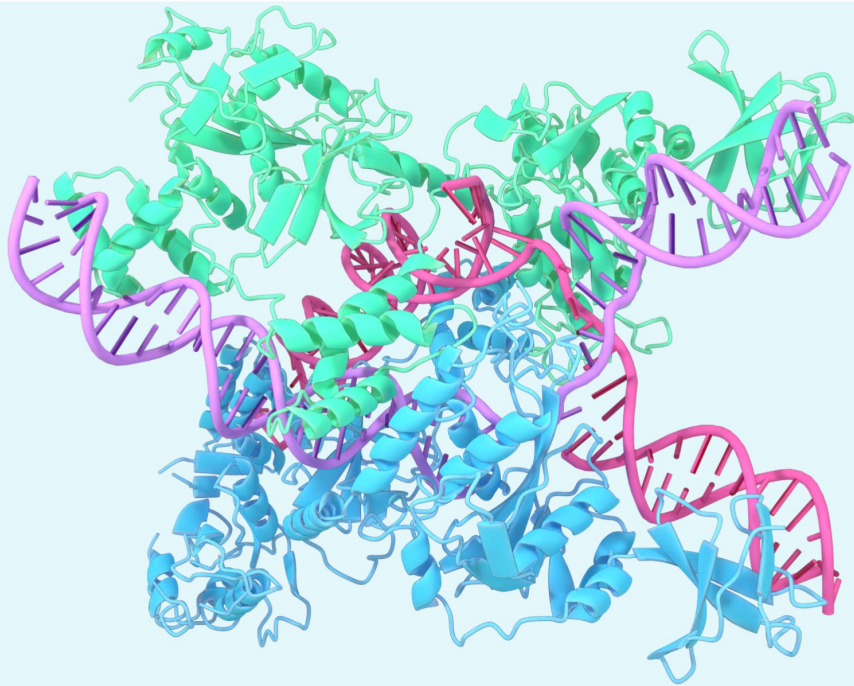
Future Plan

A glimpse of the next generation of AlphaFold

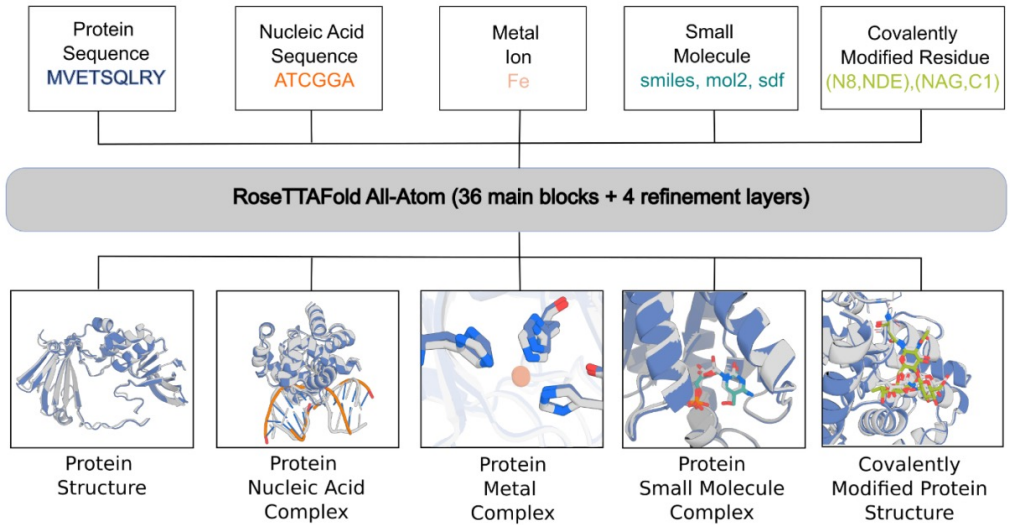
31 OCTOBER 2023

Google DeepMind AlphaFold team and Isomorphic Labs team

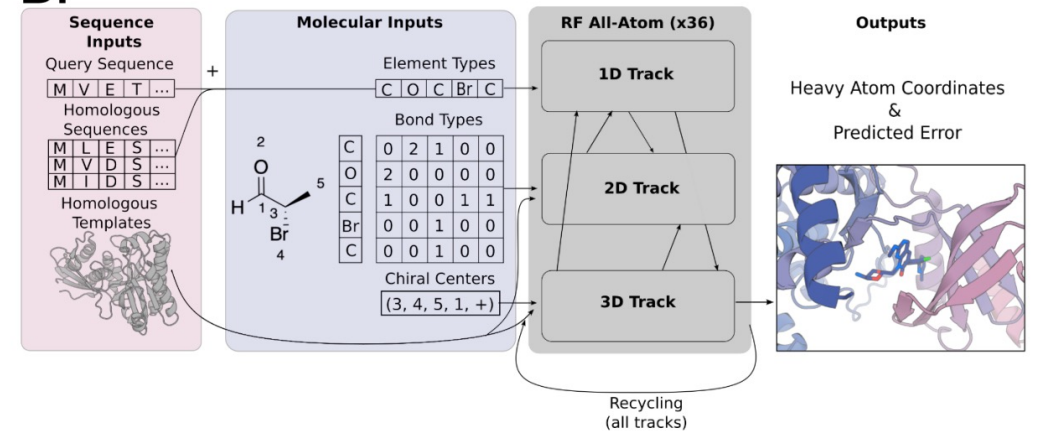
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A.



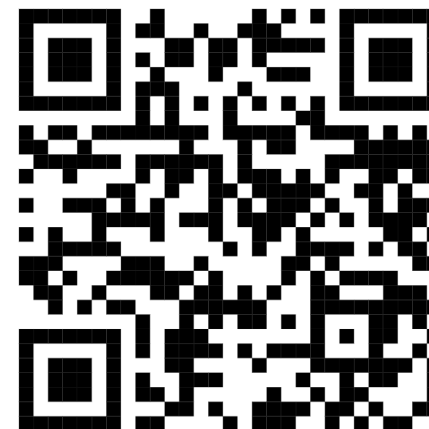
B.



Thank you for your attention!



Paper Link



Code Link