Multimodal deep learning for protein engineering

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Microsoft Research New England
@KevinKaichuang

Proteins are biology’s actuators

- Human cells contain 1-3 billion proteins each
- Structure, metabolism, and signaling

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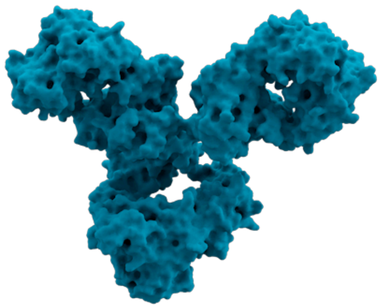

IgG

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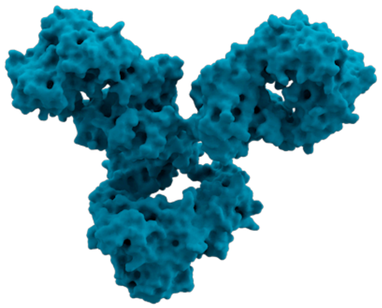

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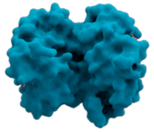

hemoglobin

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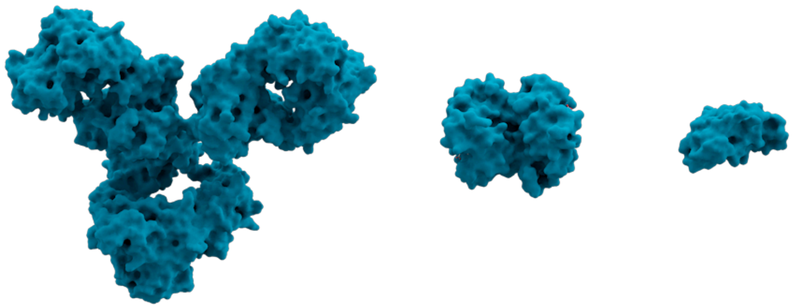

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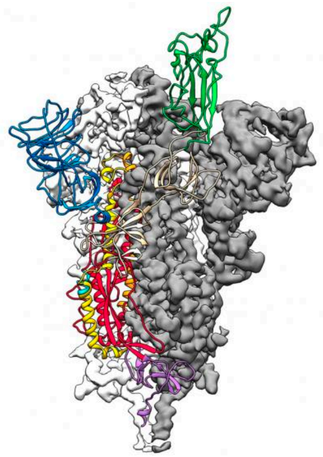
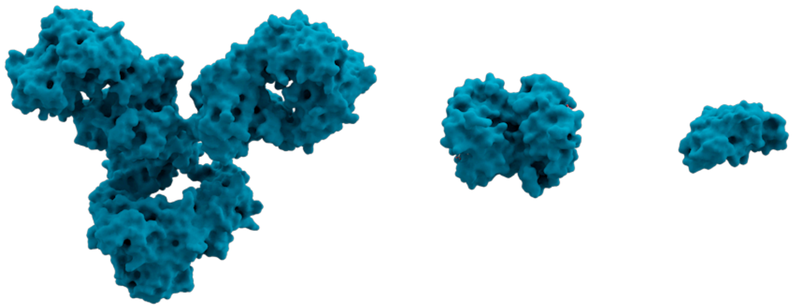


coronavirus spike protein



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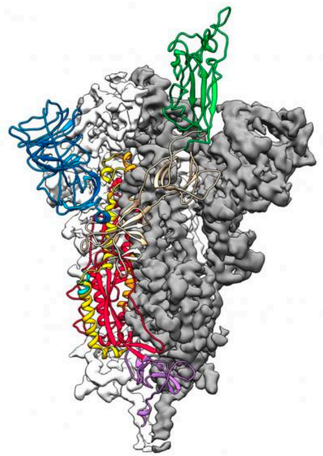

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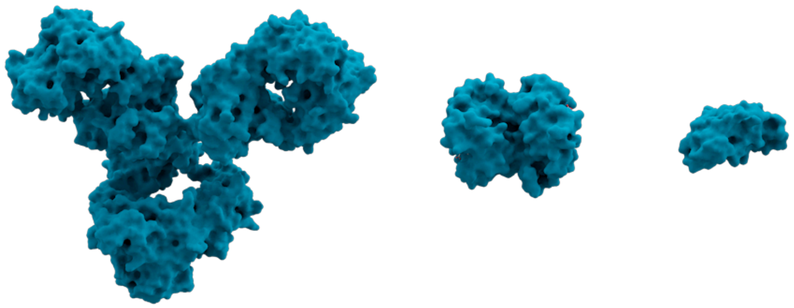

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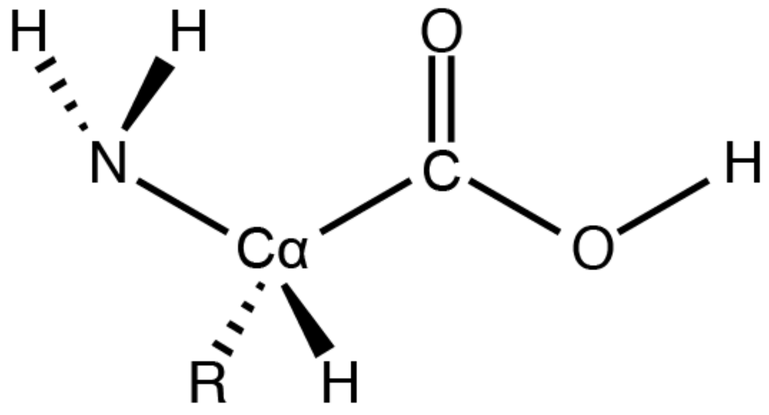
Diversity arises from 20 building blocks



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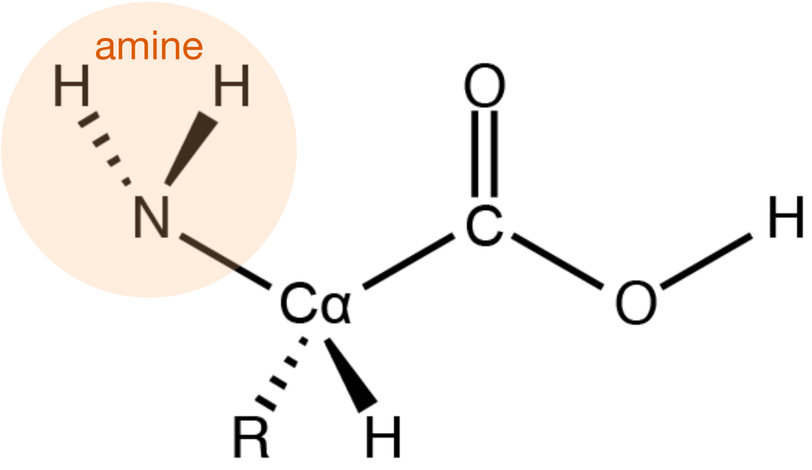

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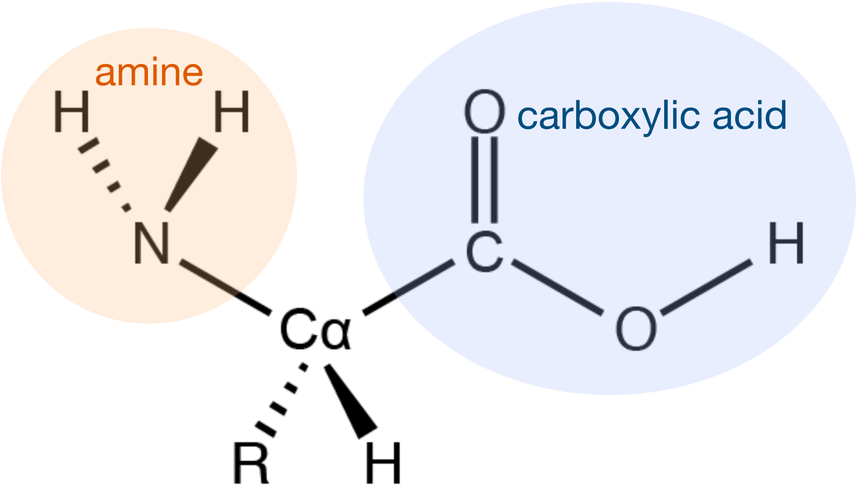

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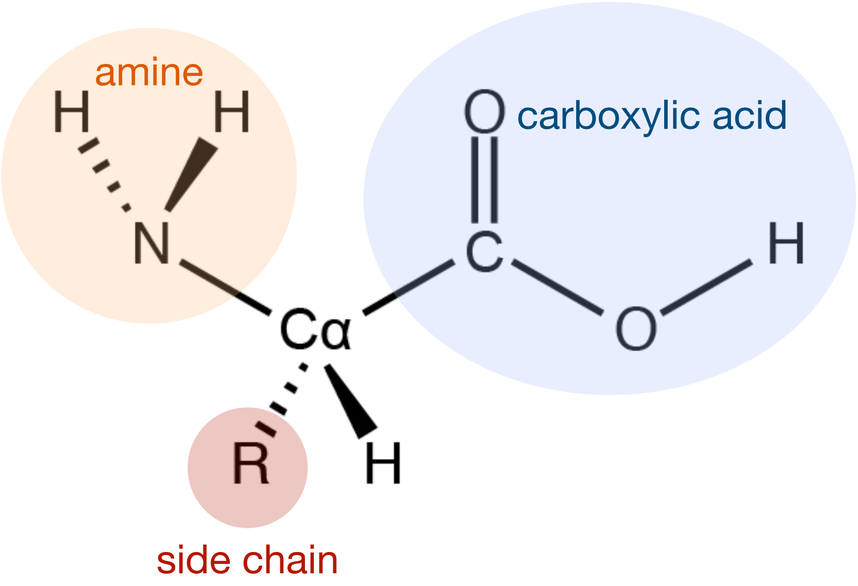

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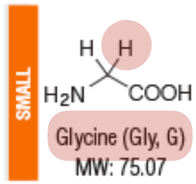

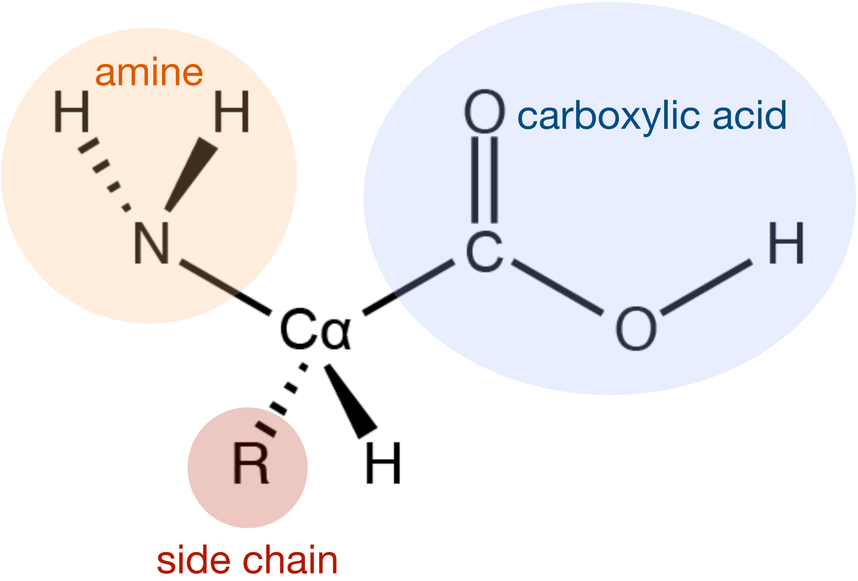

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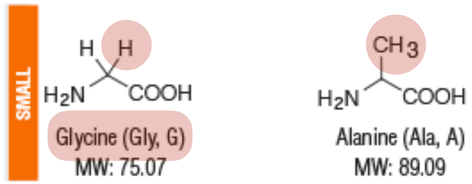

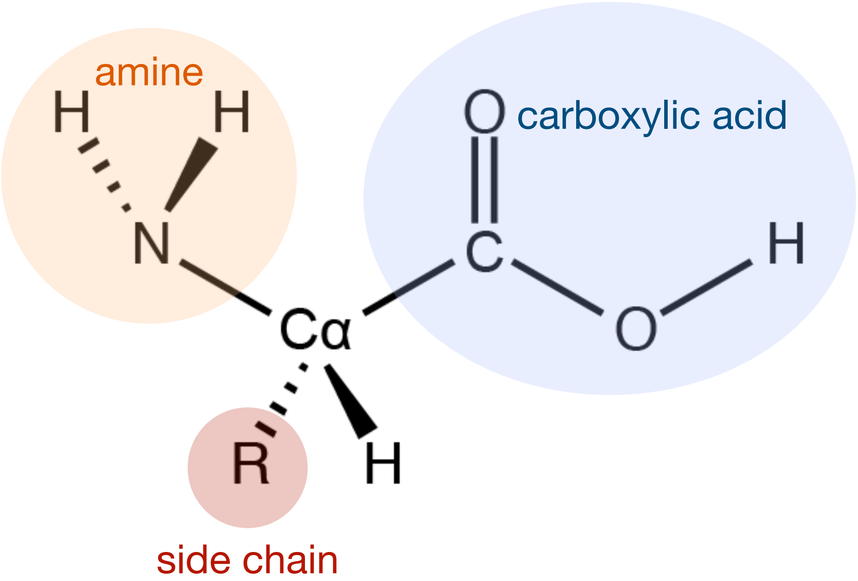

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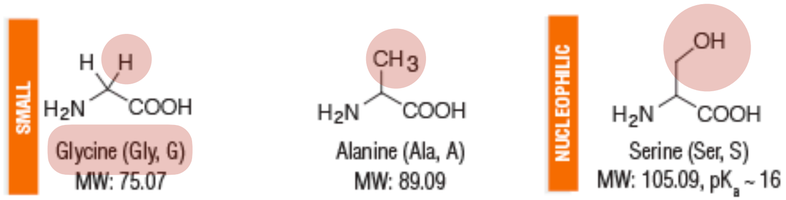

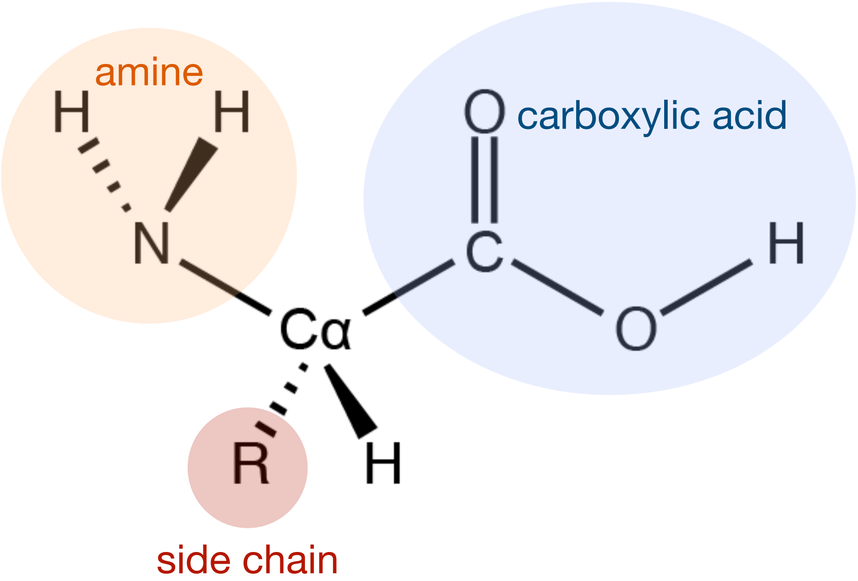

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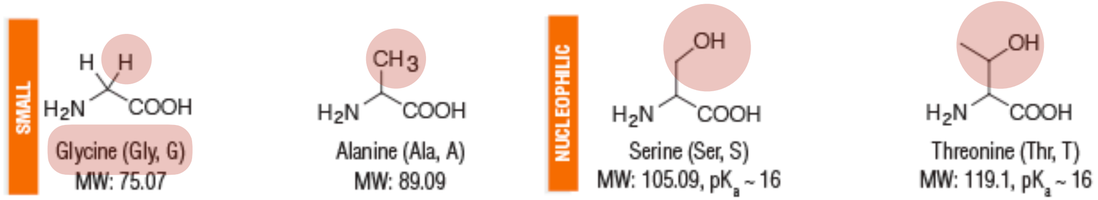

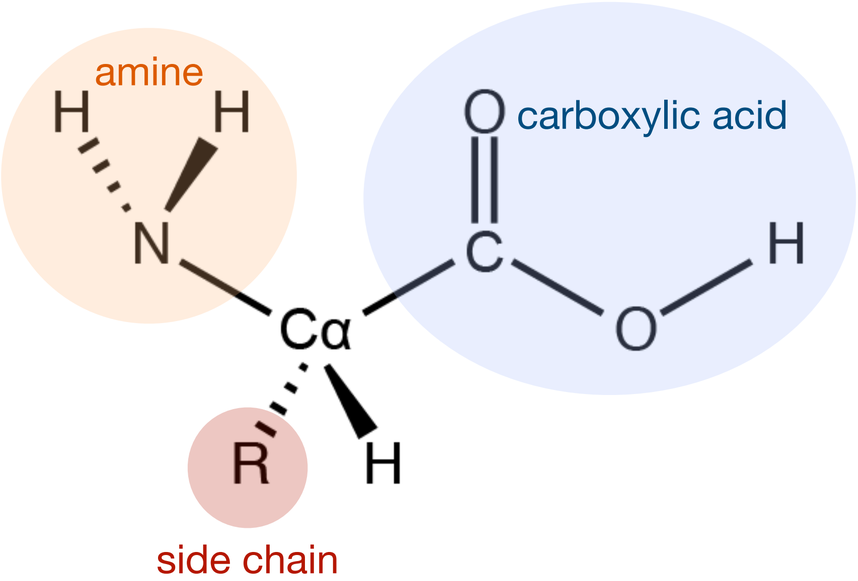

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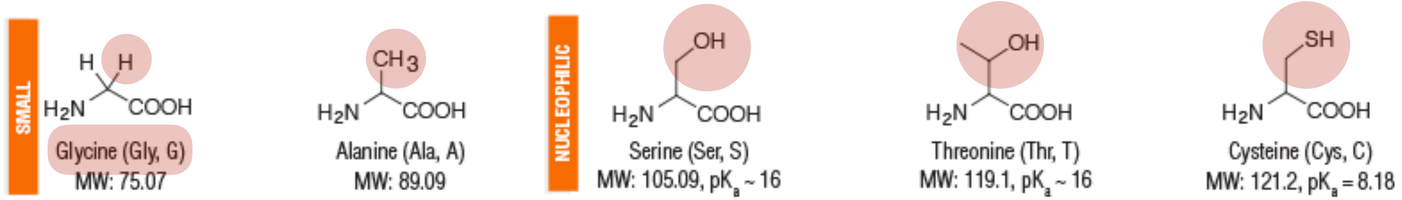

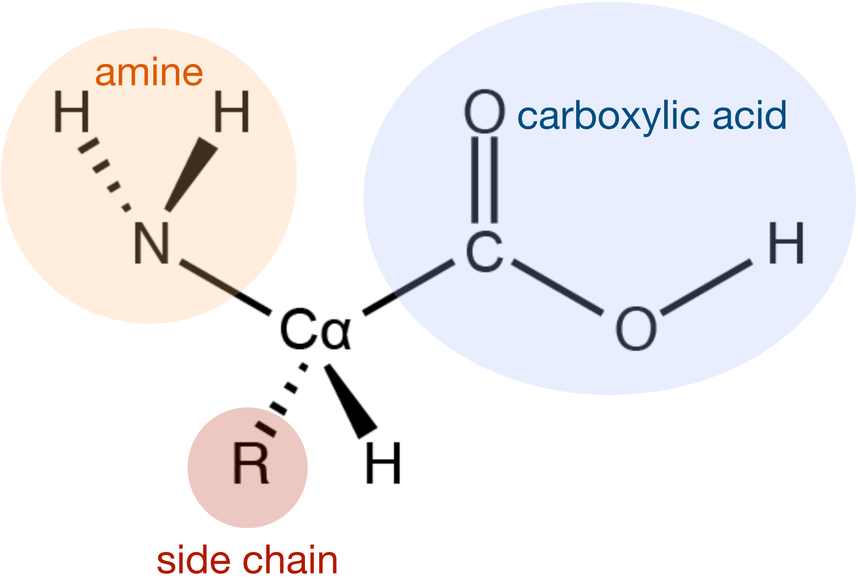

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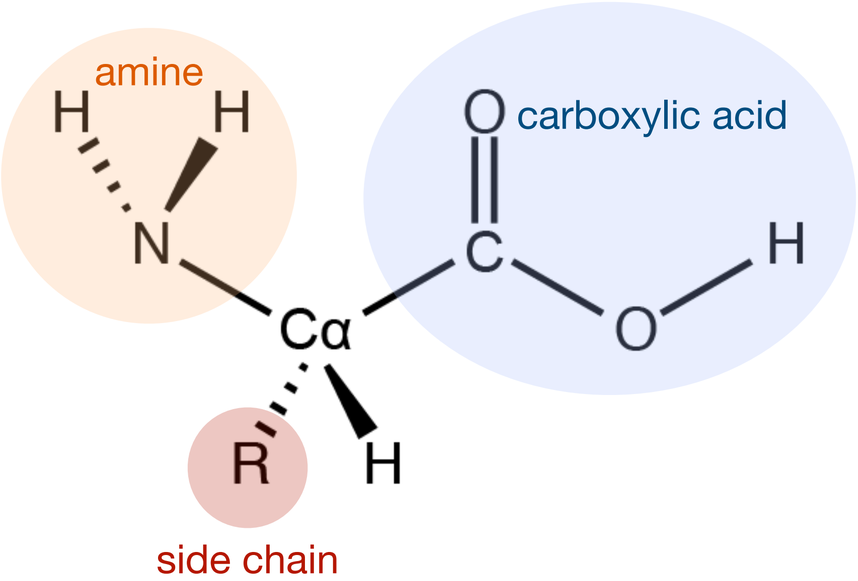

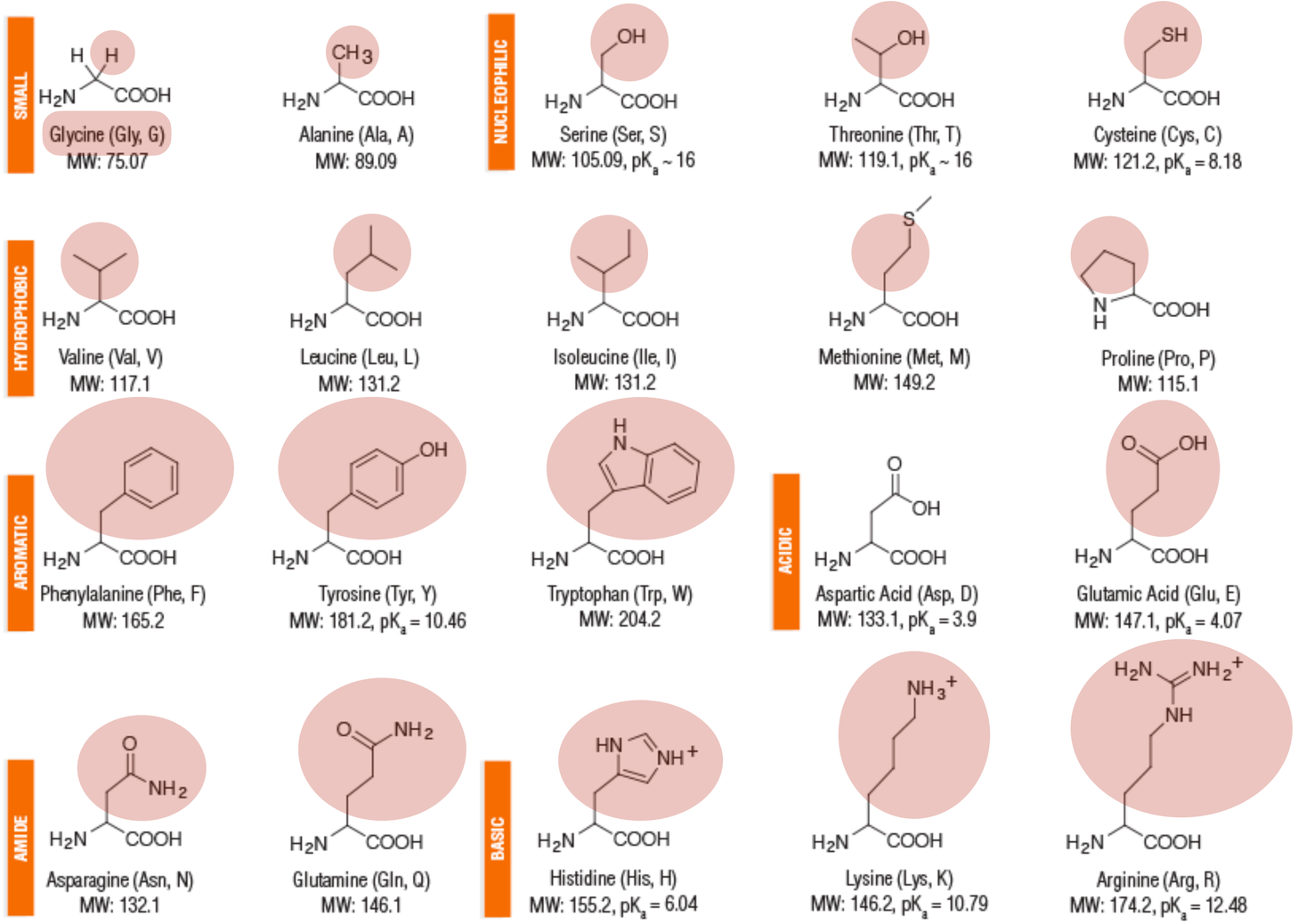

Why design proteins?

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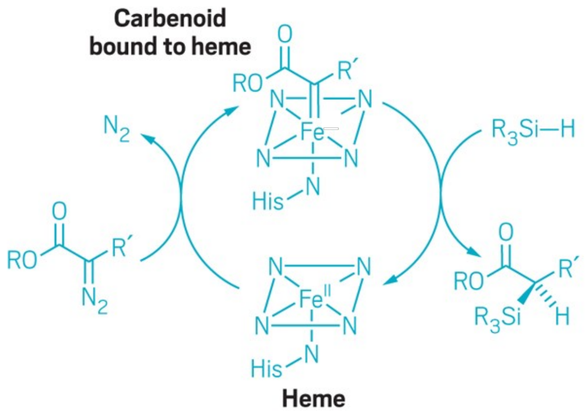

new chemistry

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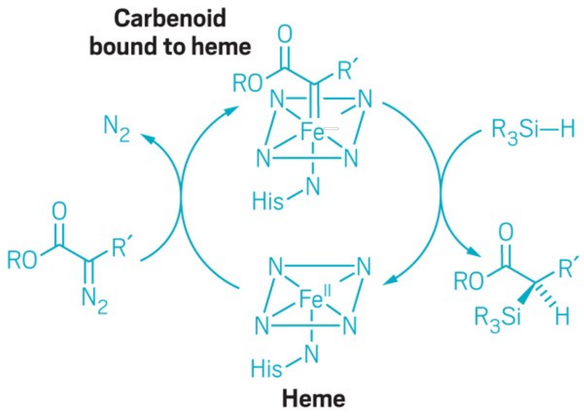

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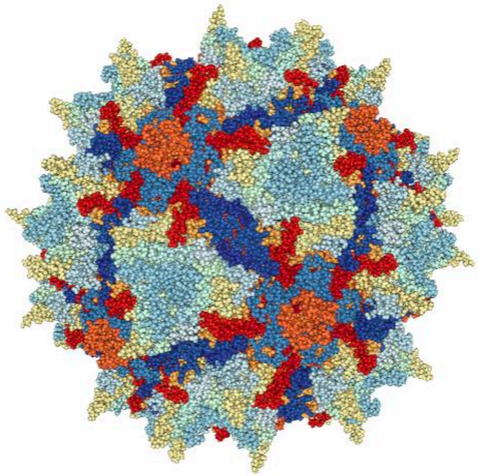

understand function

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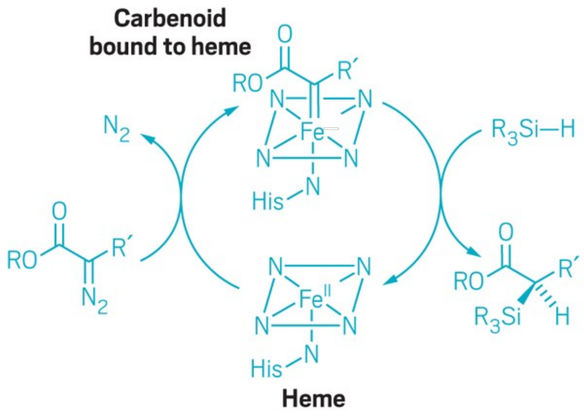

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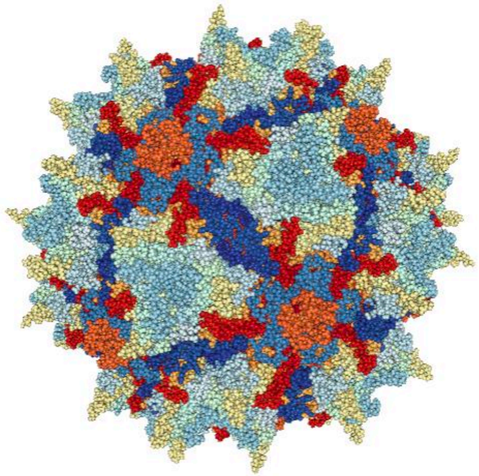

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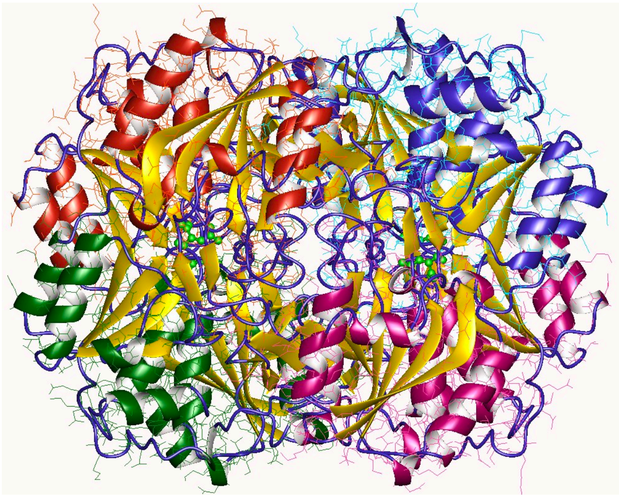

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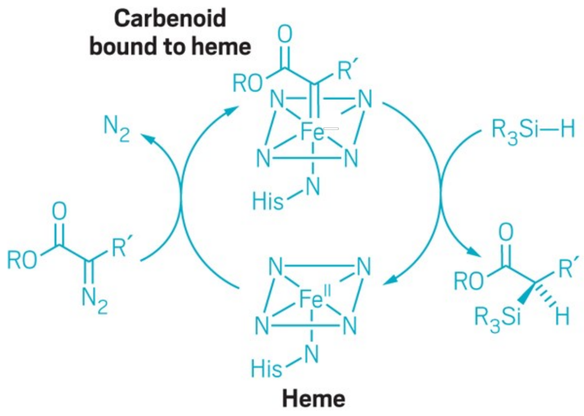

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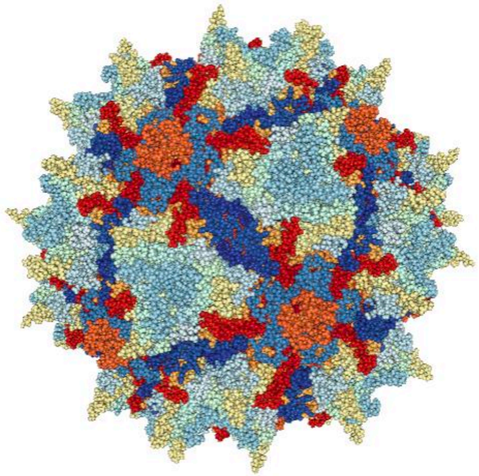

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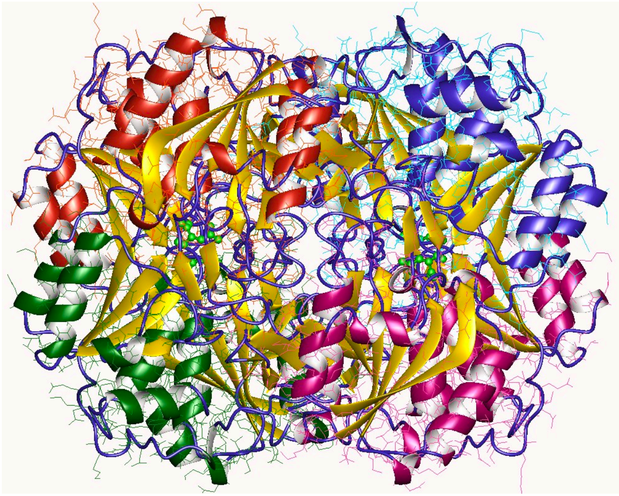

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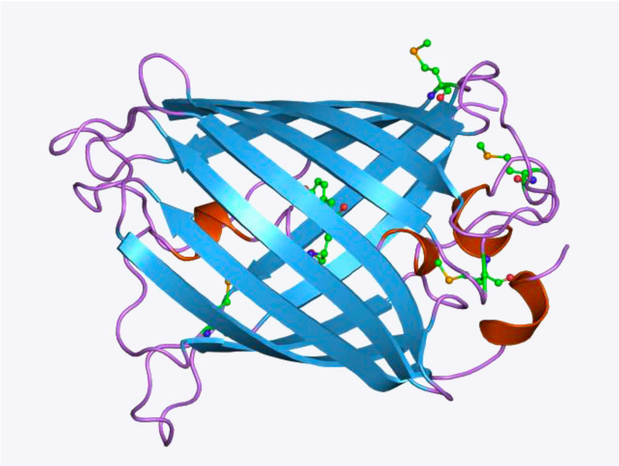
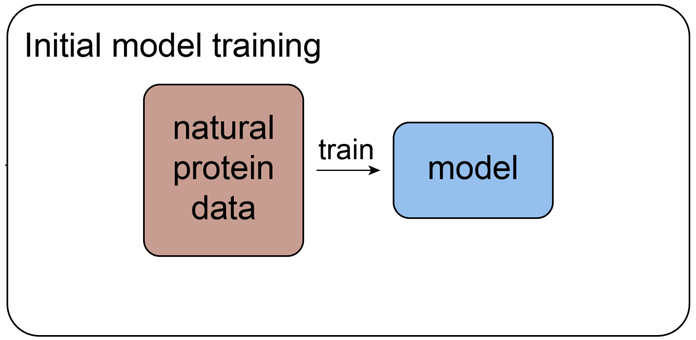


molecular tools

Use multiple data modalities to discover and design proteins



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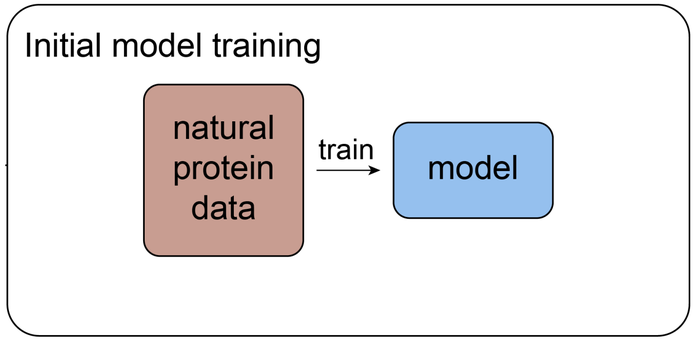

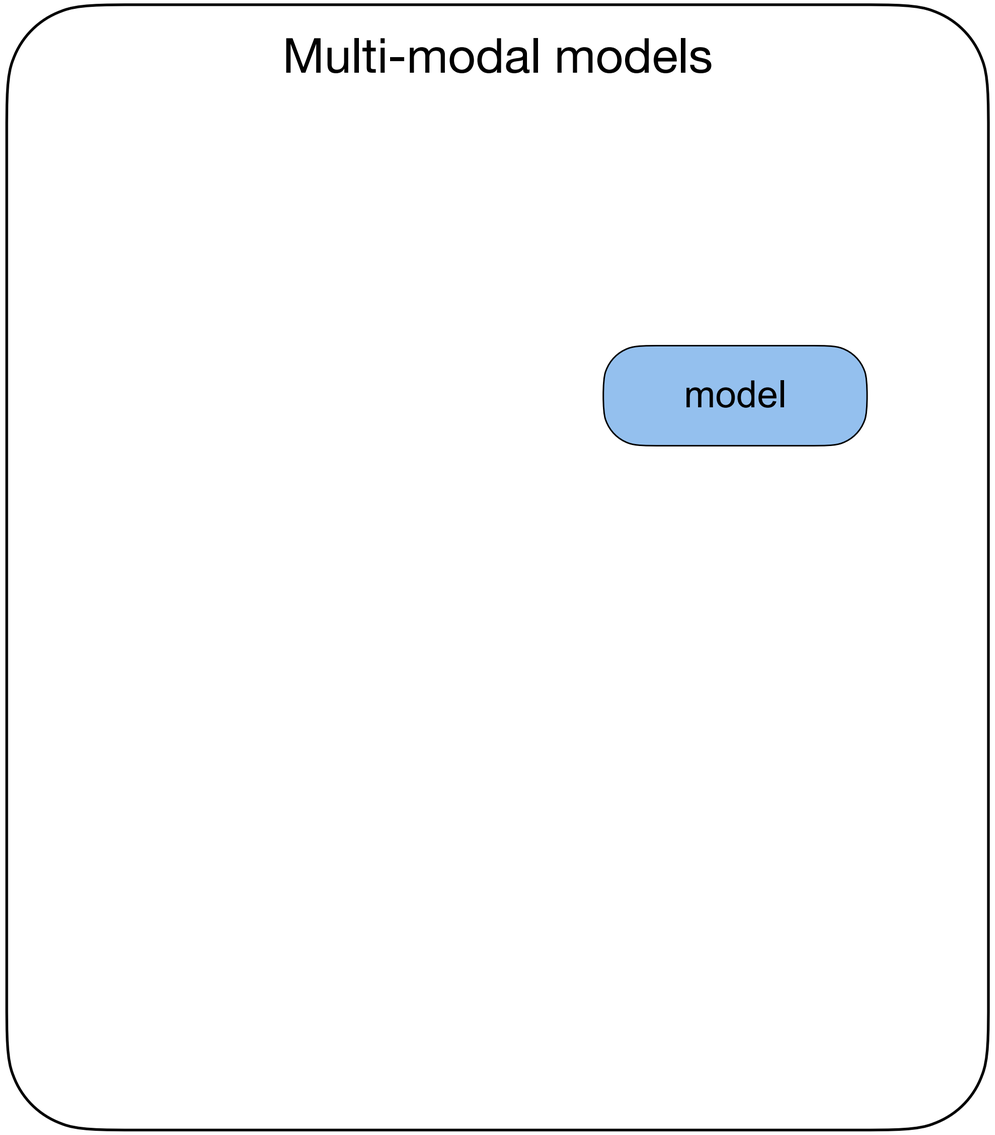

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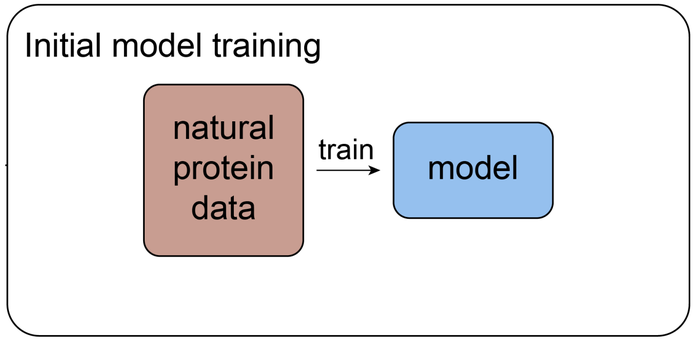

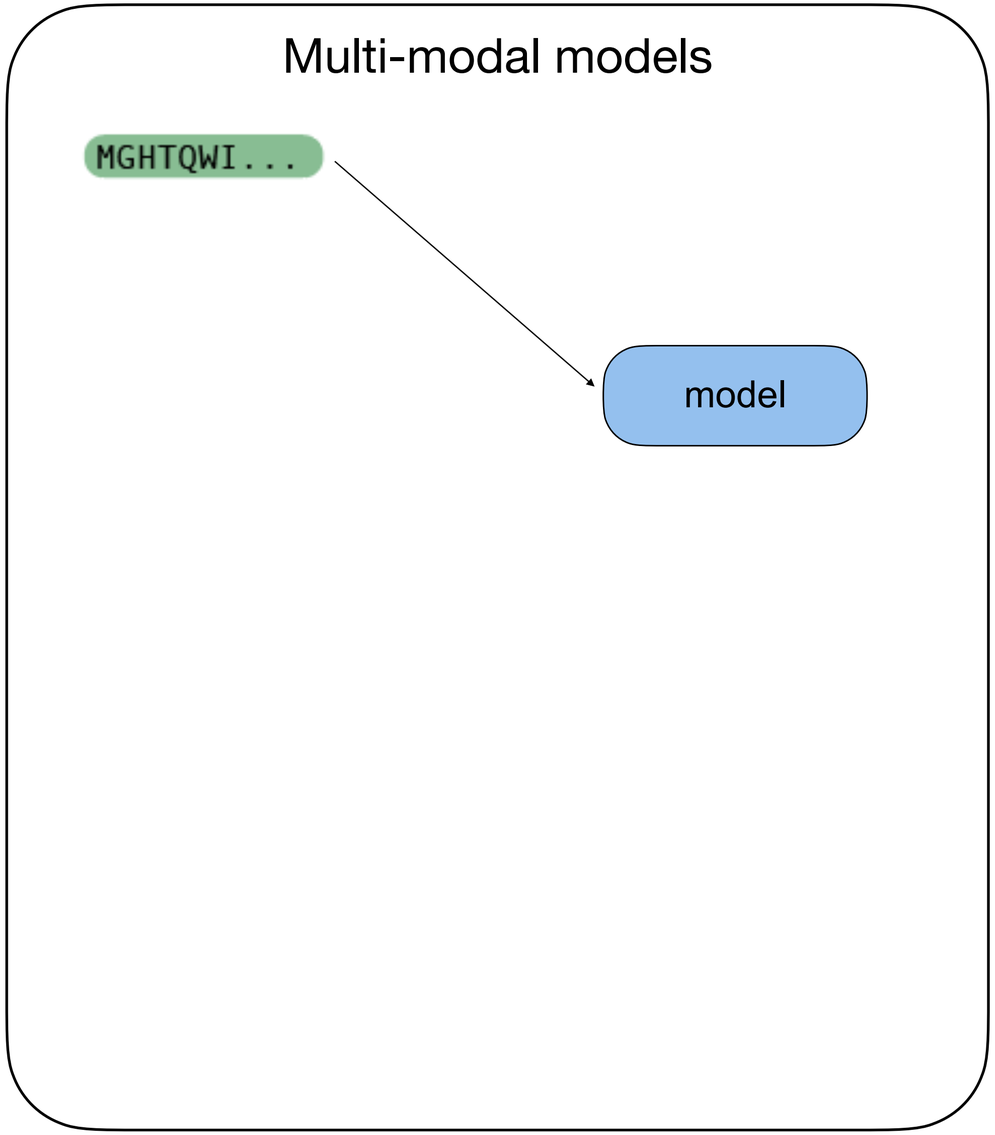

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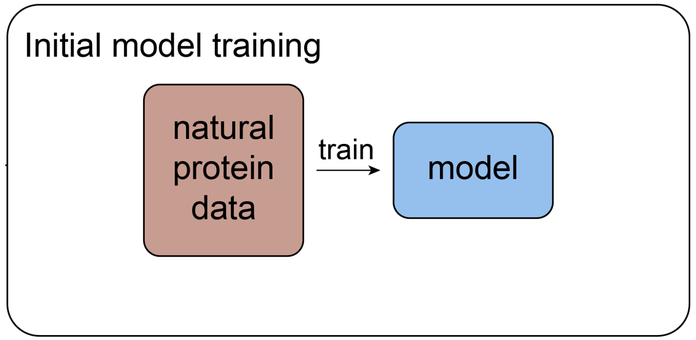

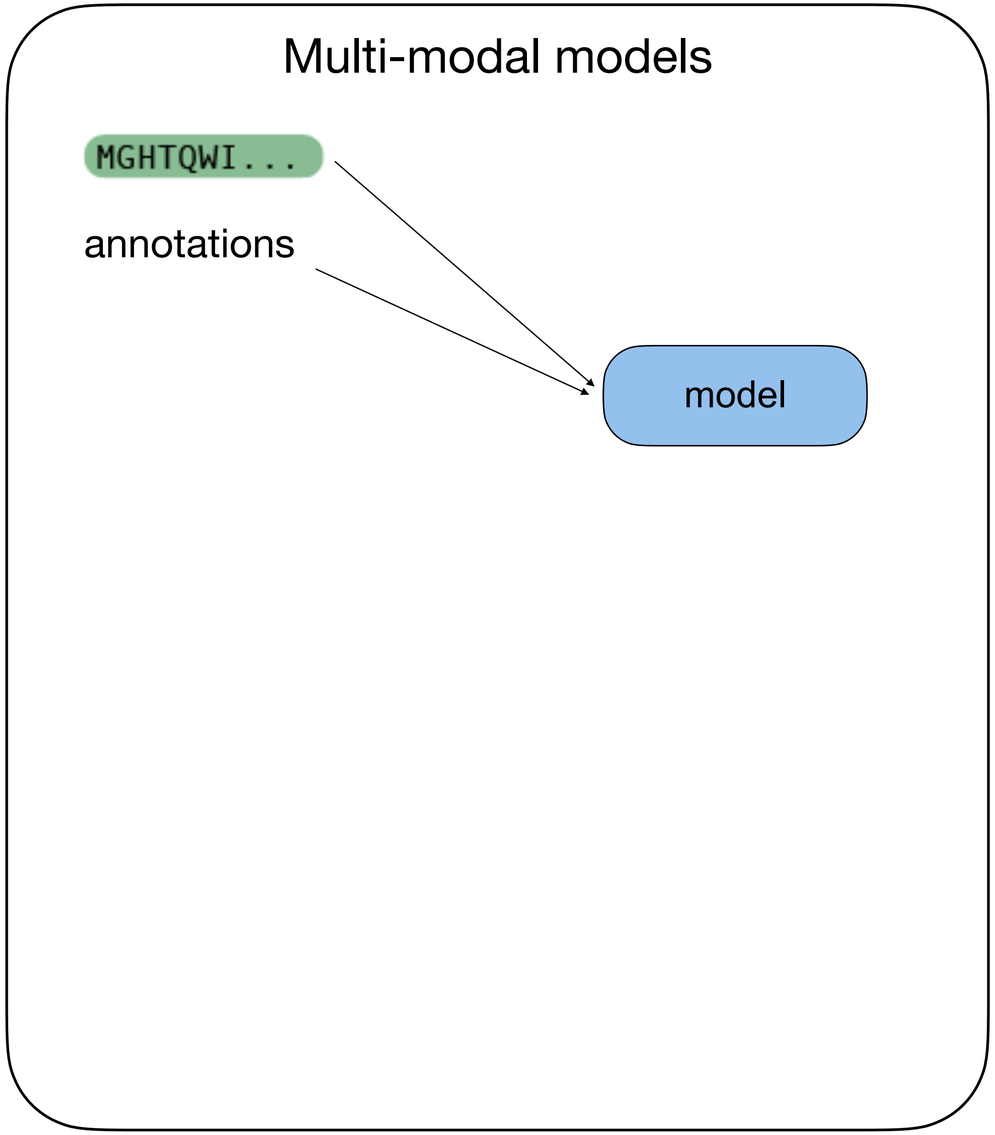

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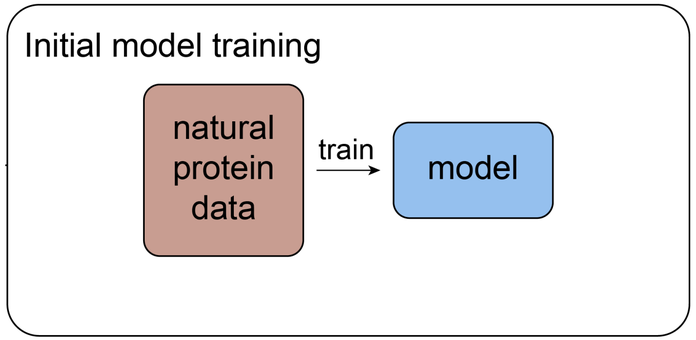

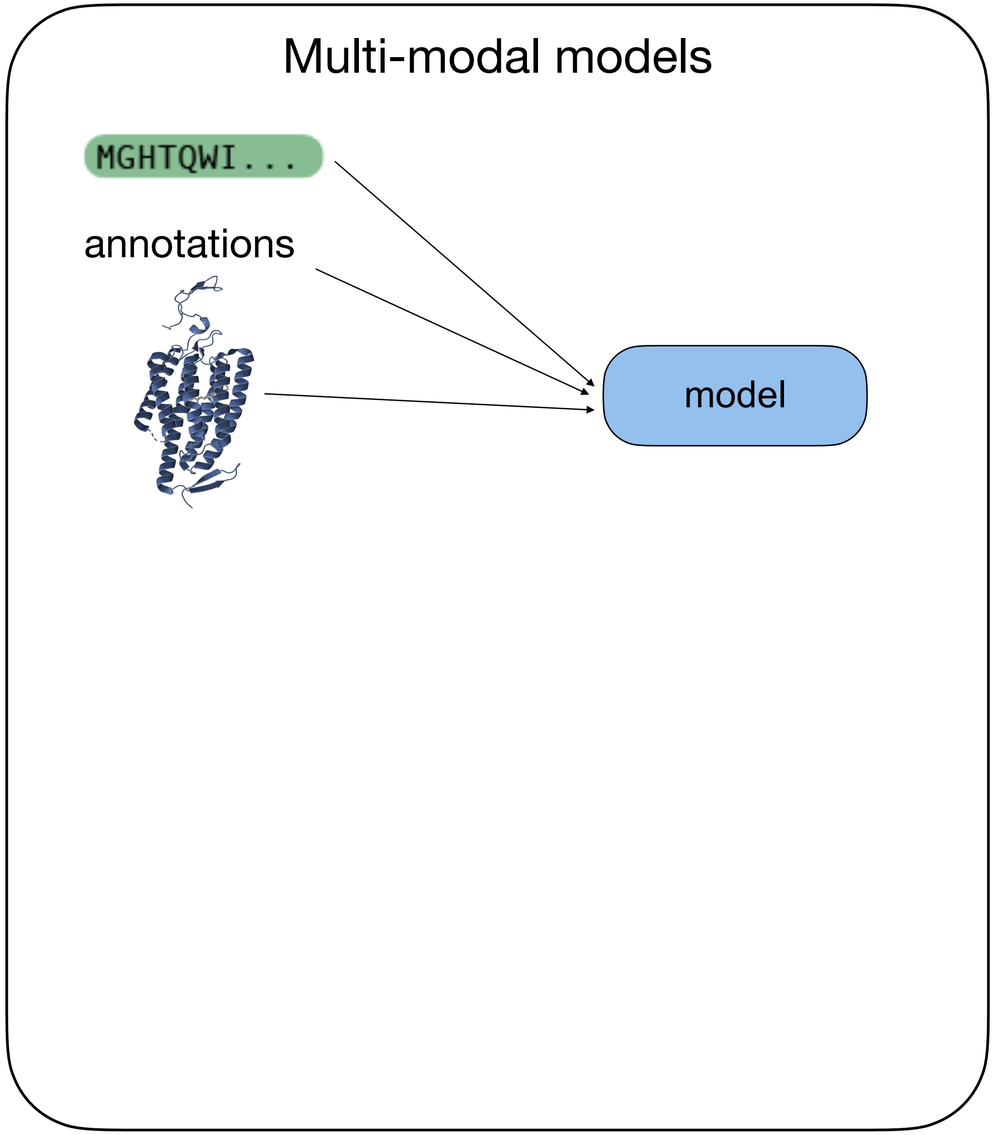

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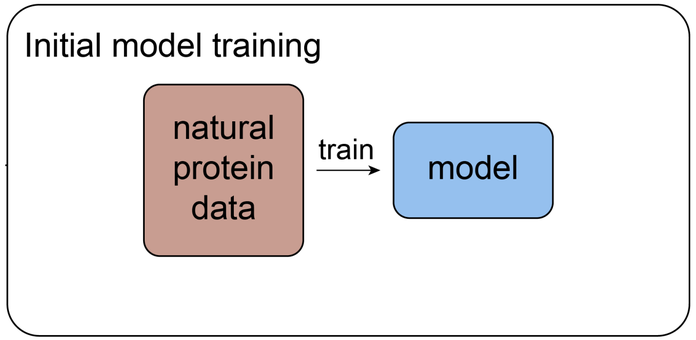

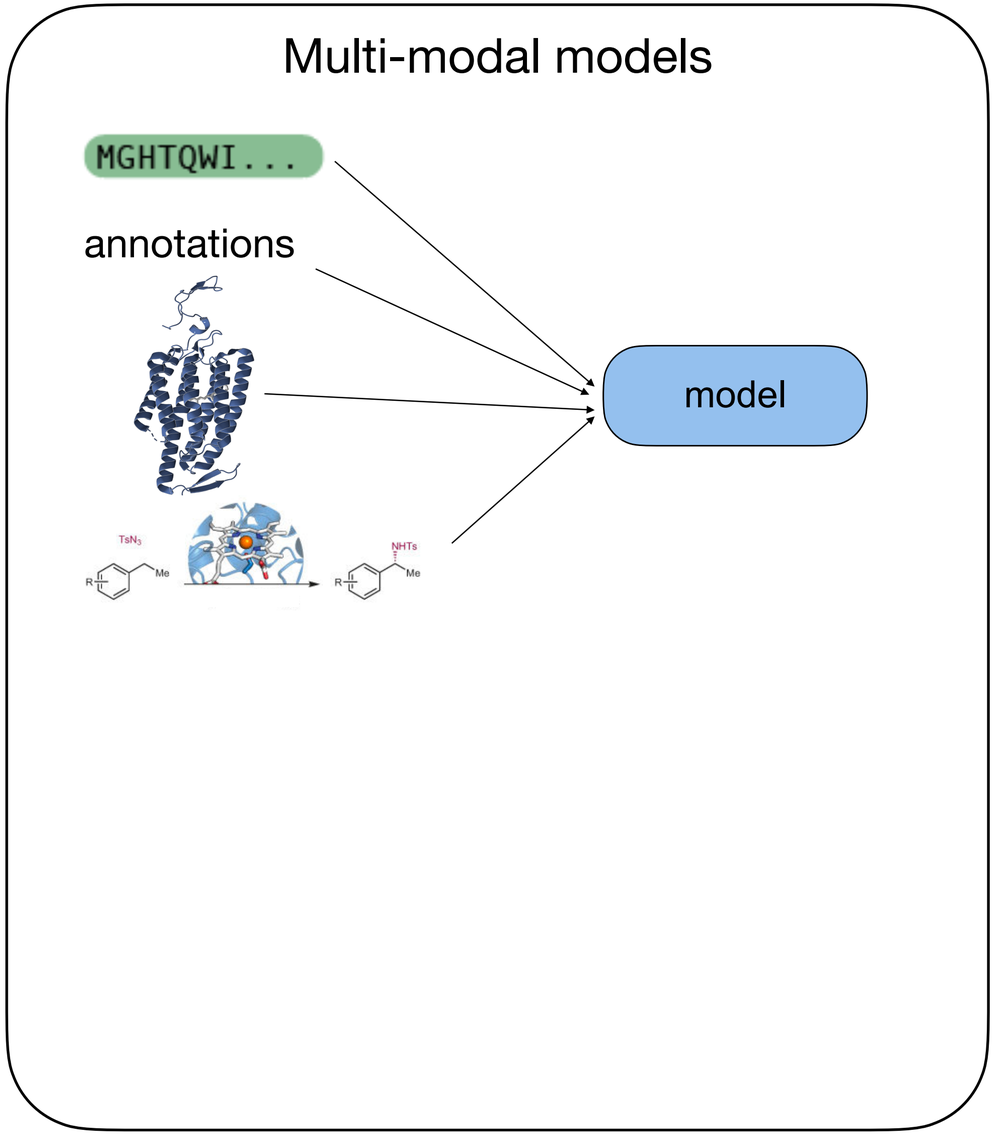

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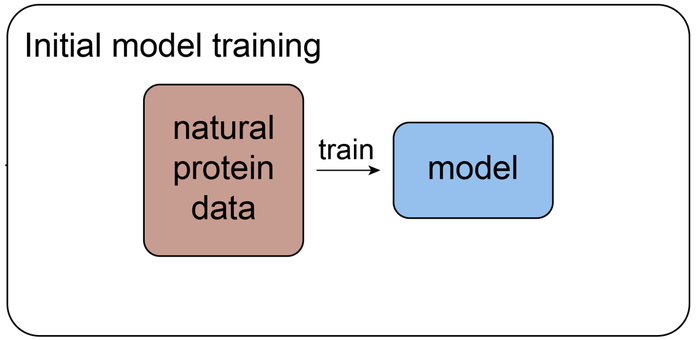

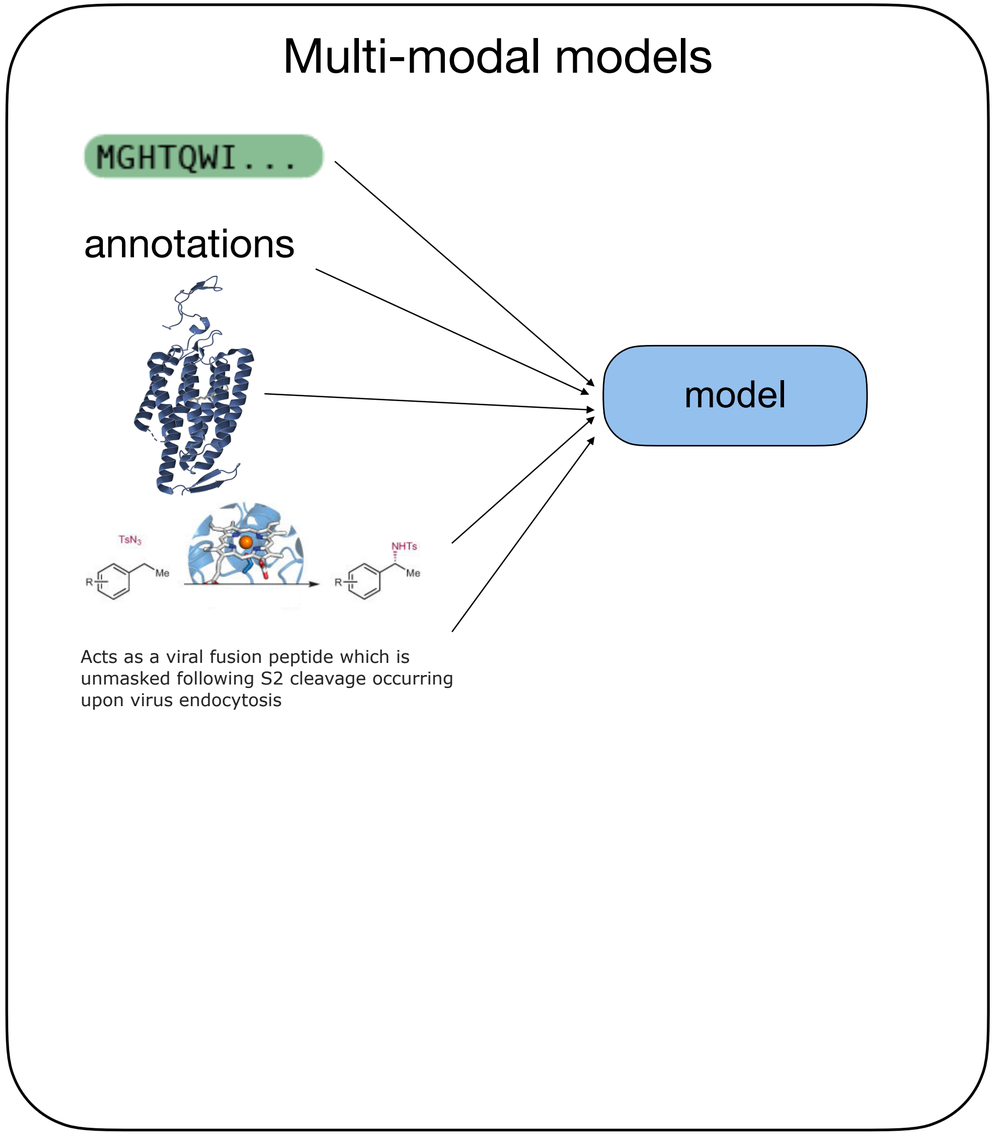

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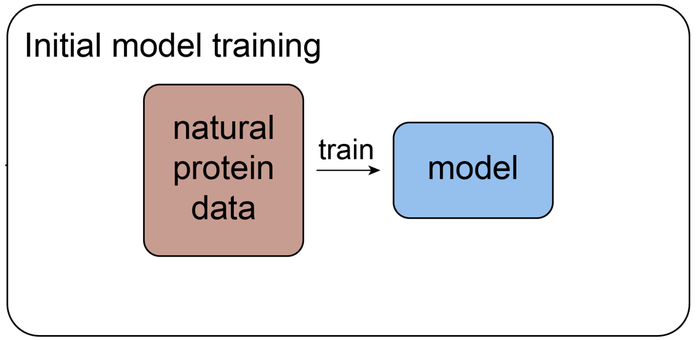

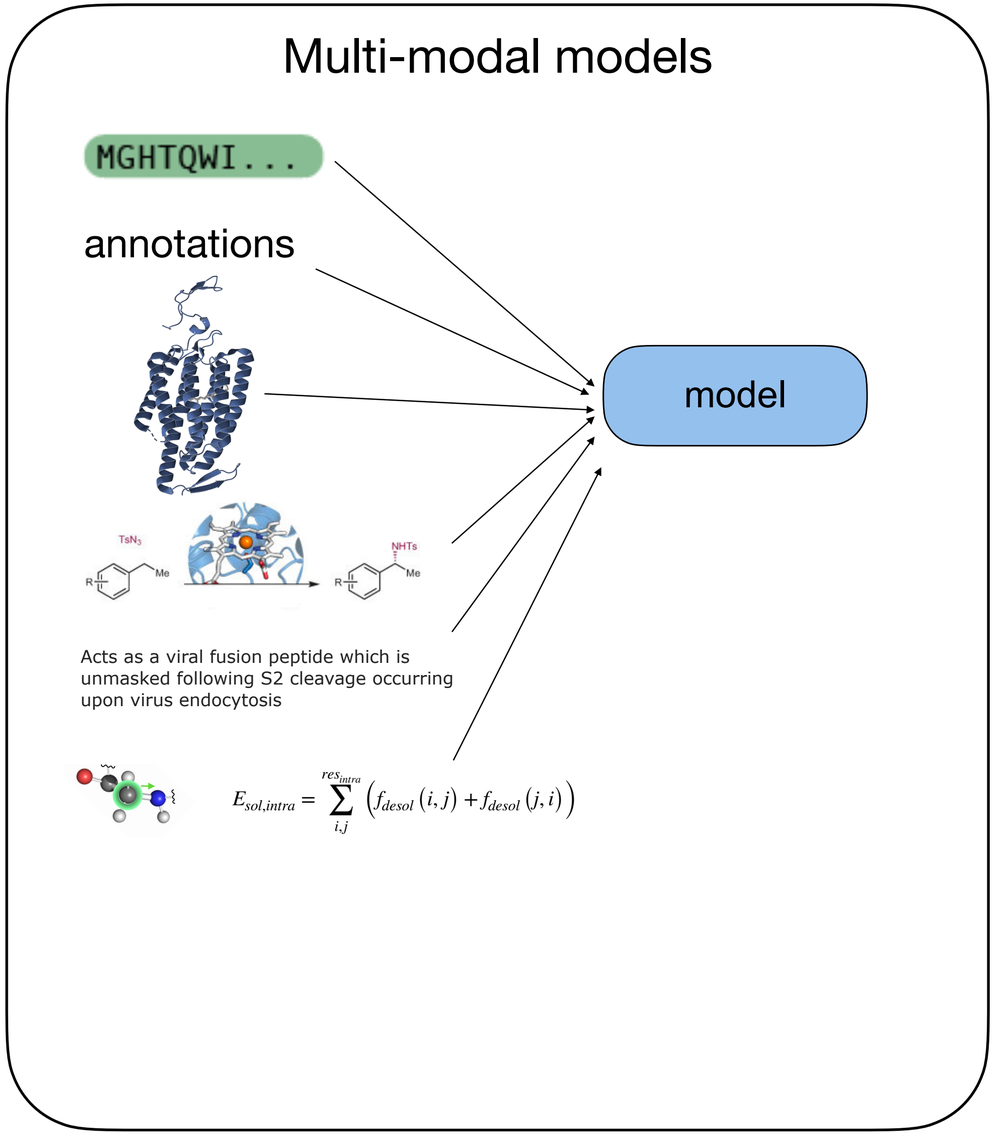

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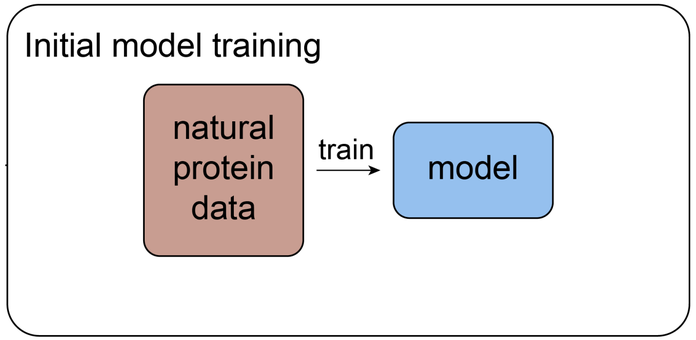

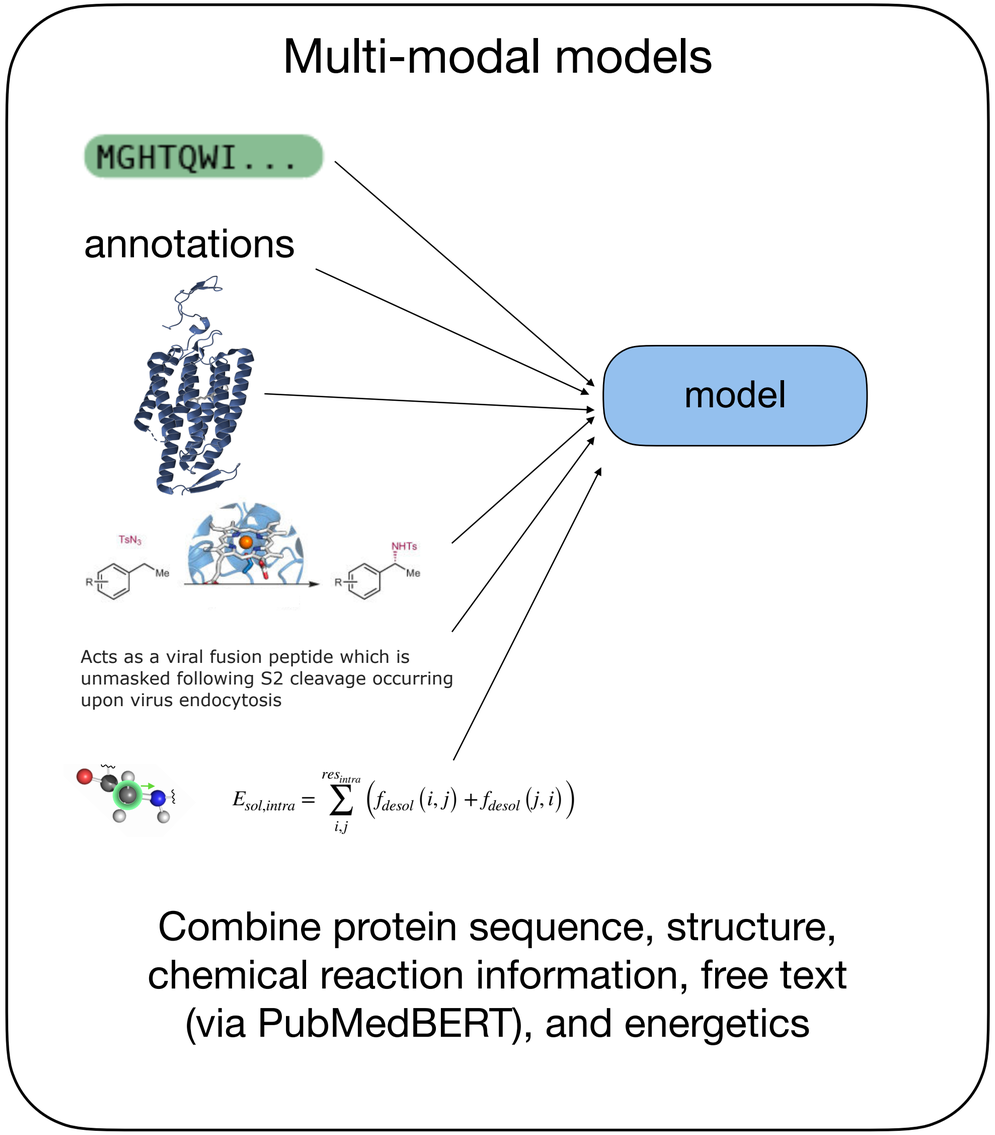

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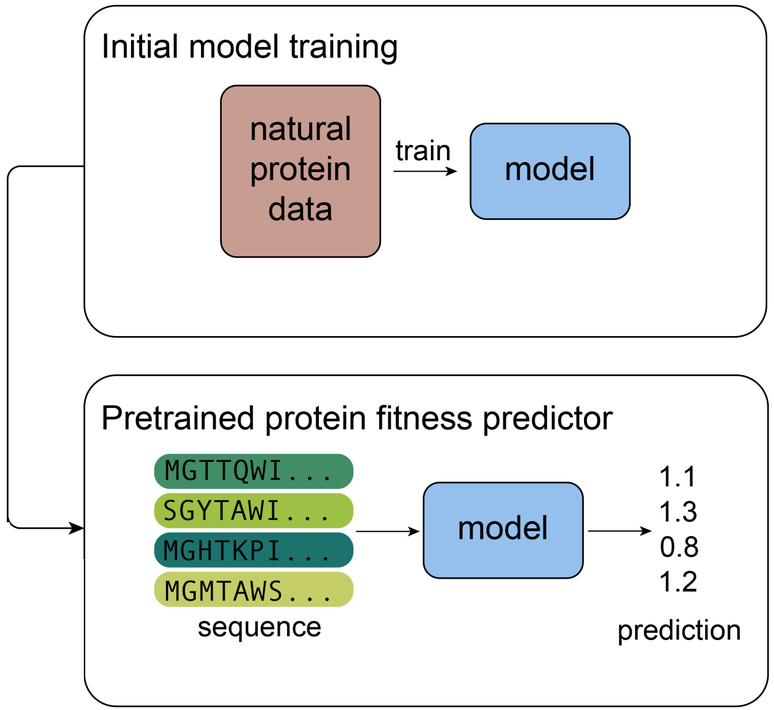

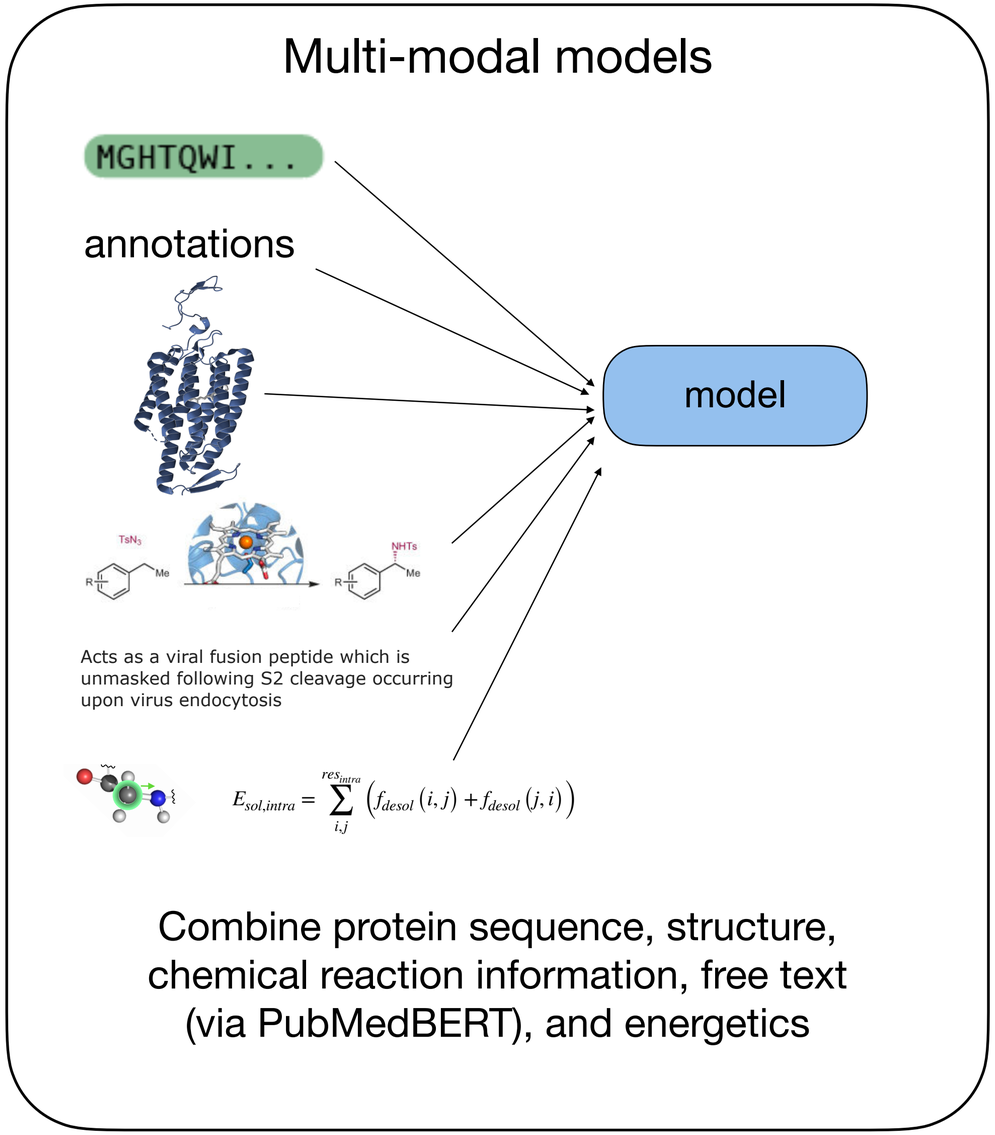

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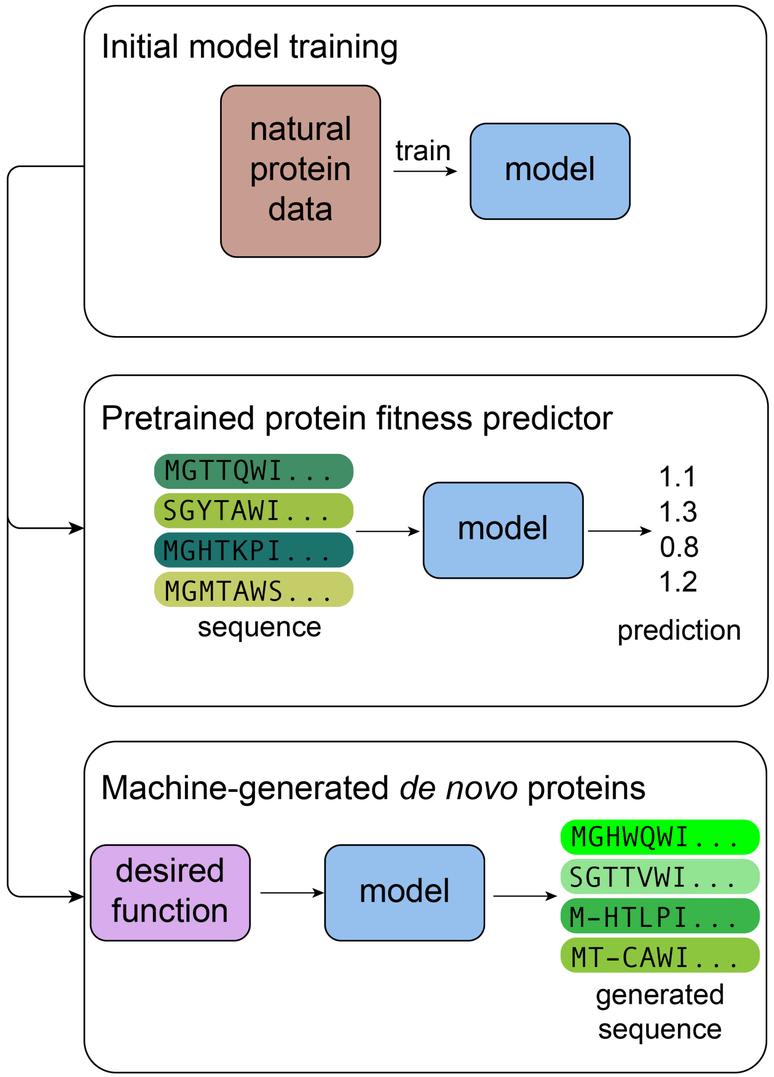

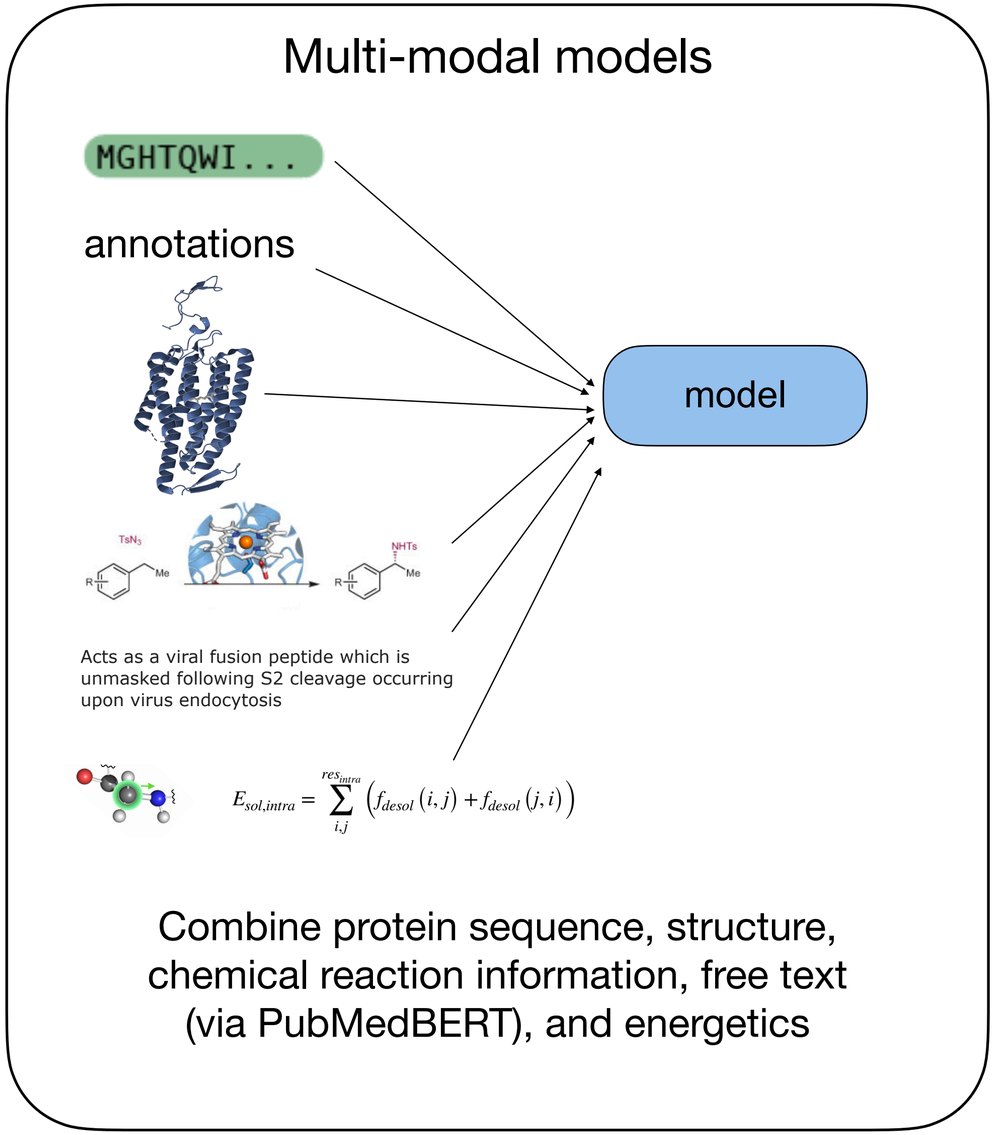

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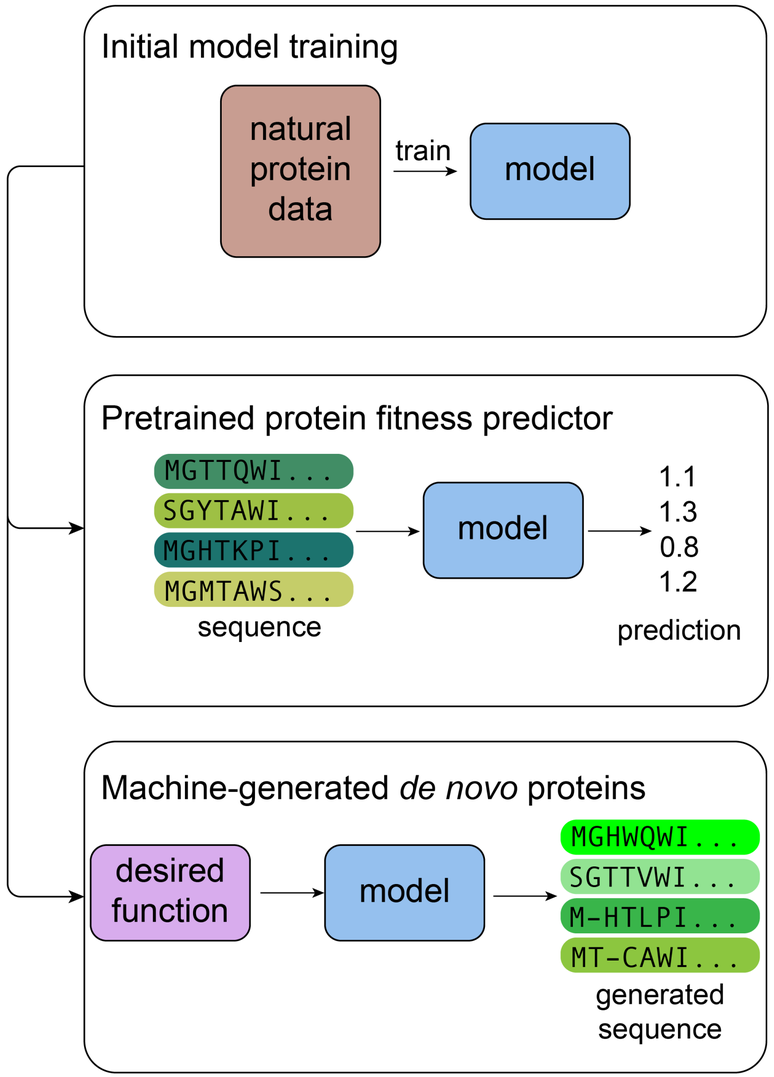

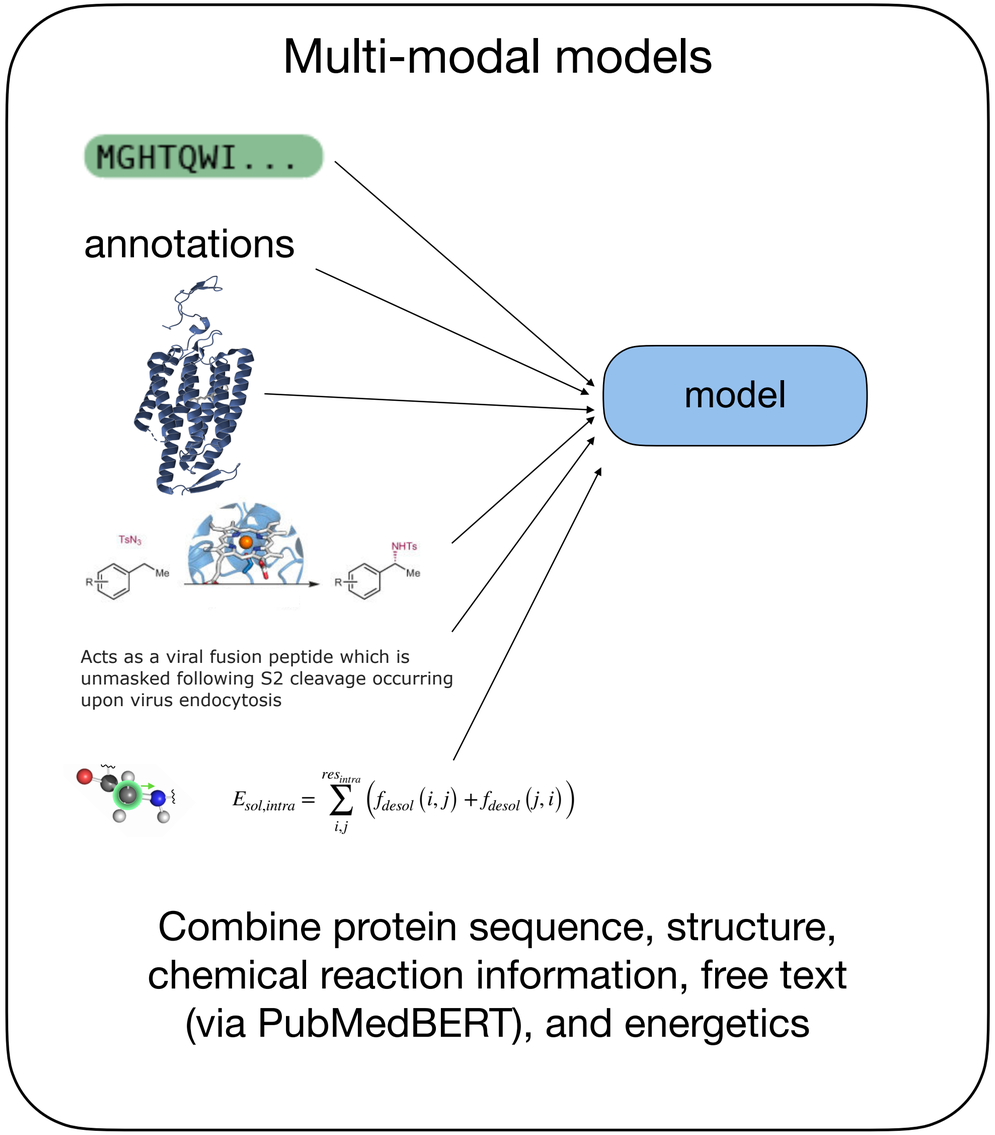

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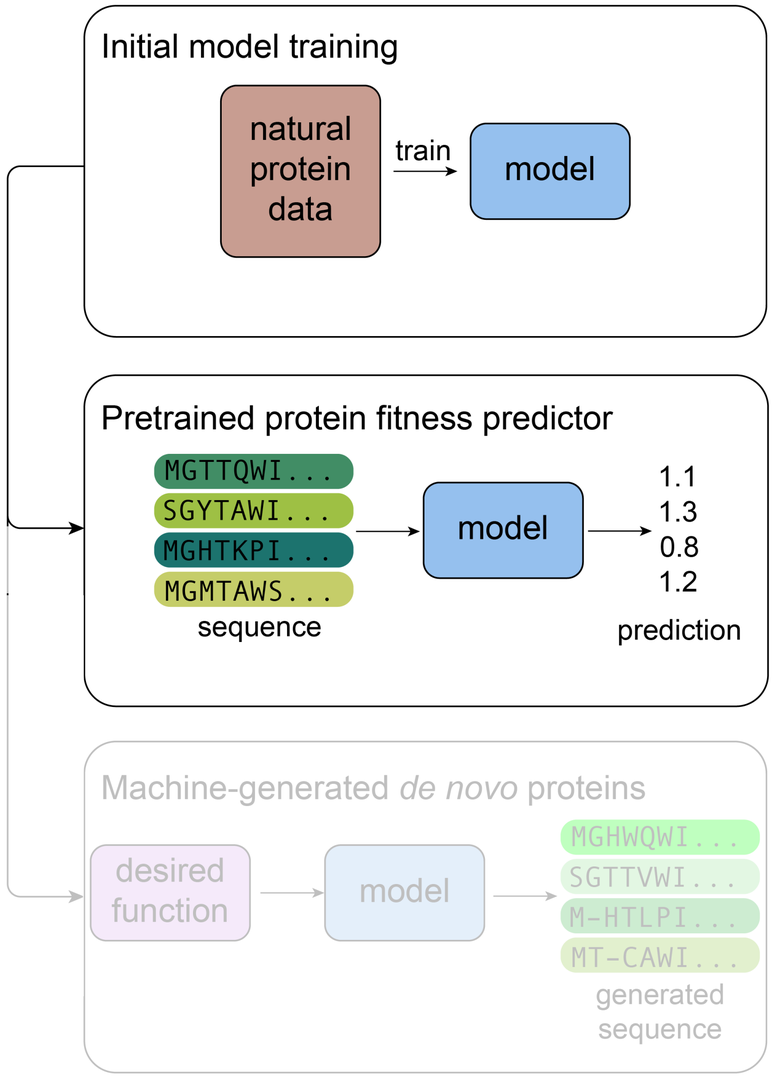
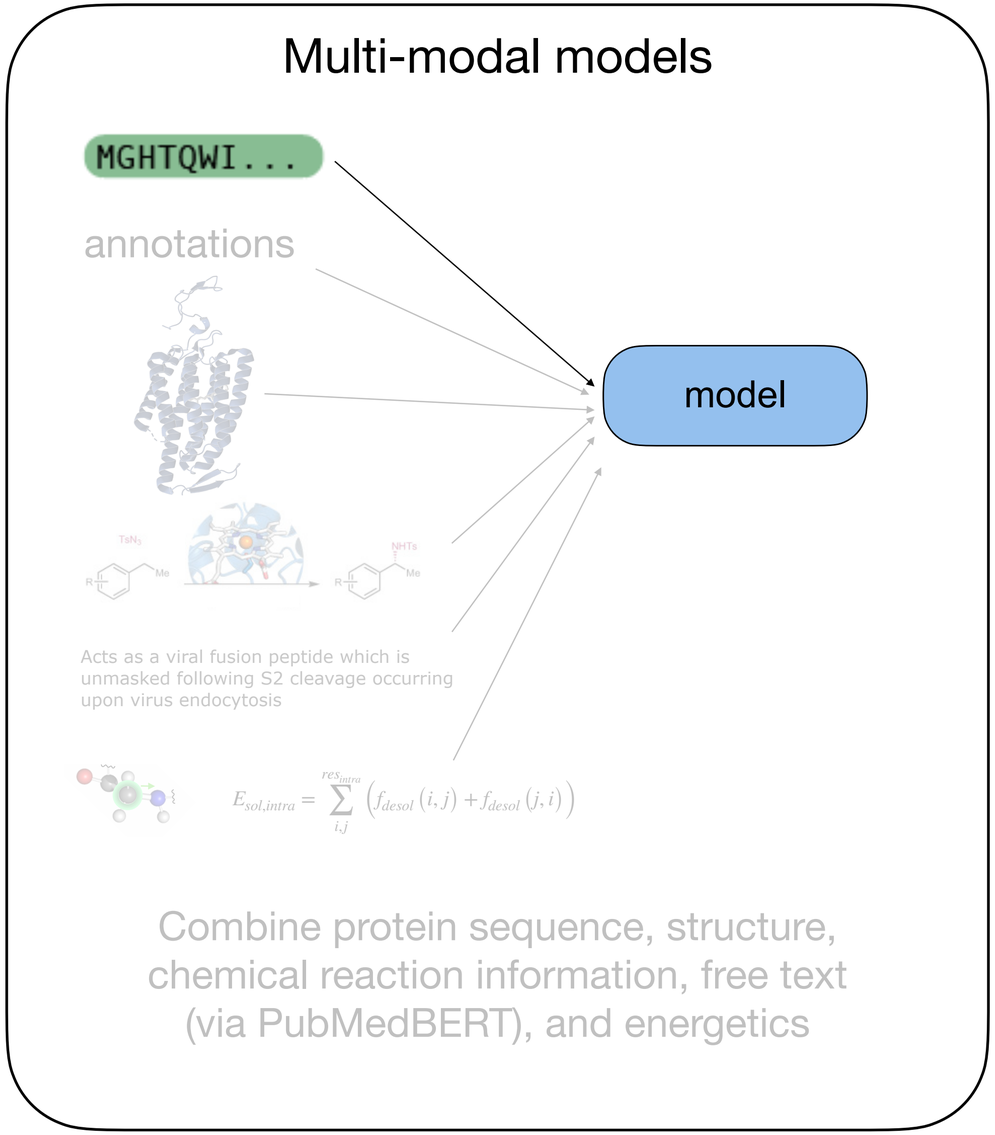
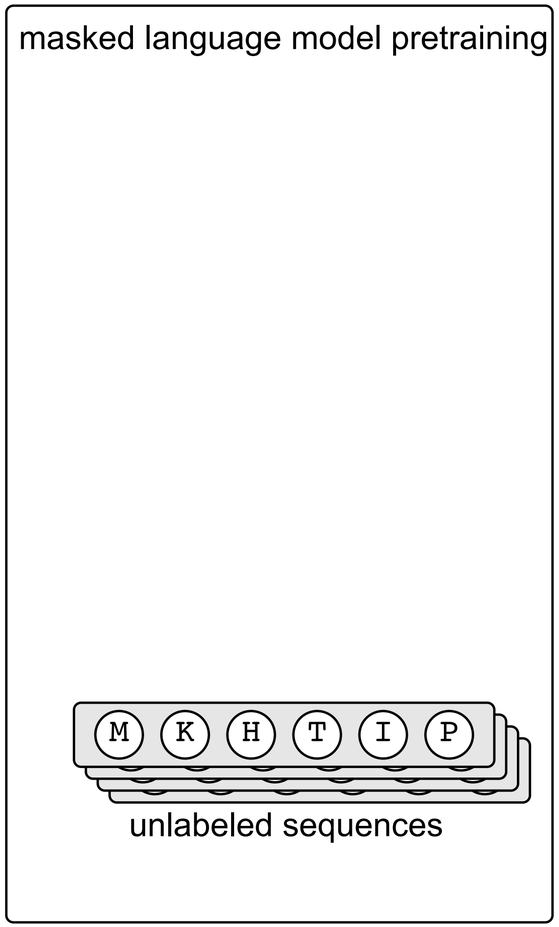




Use pretraining to leverage unlabeled sequences



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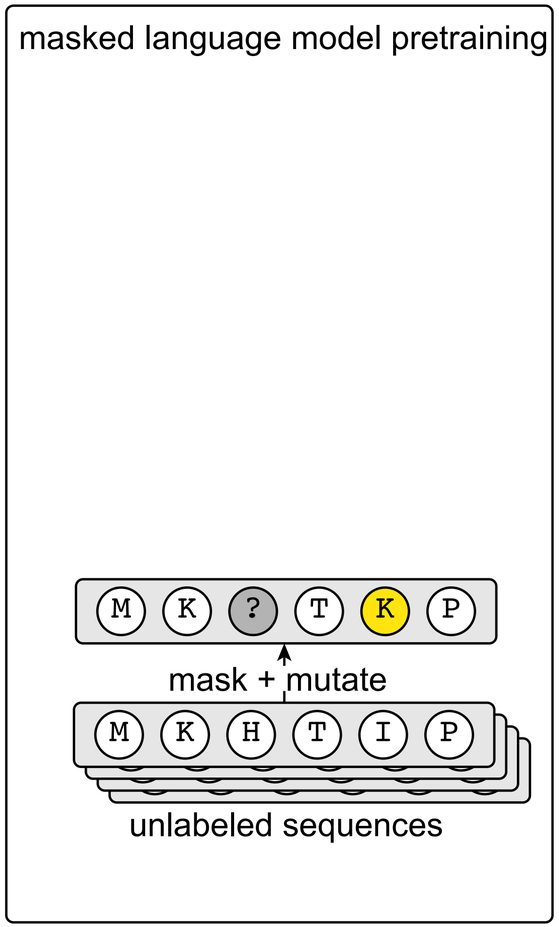

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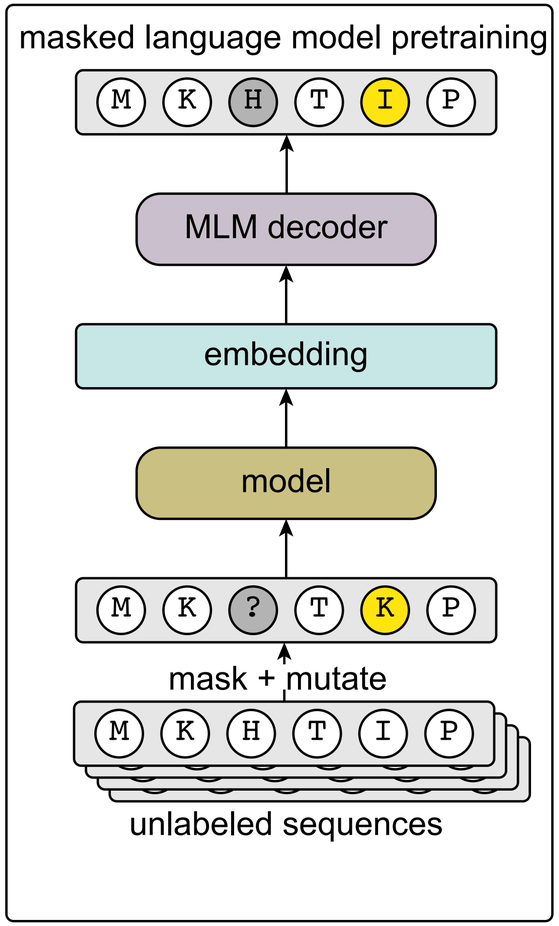

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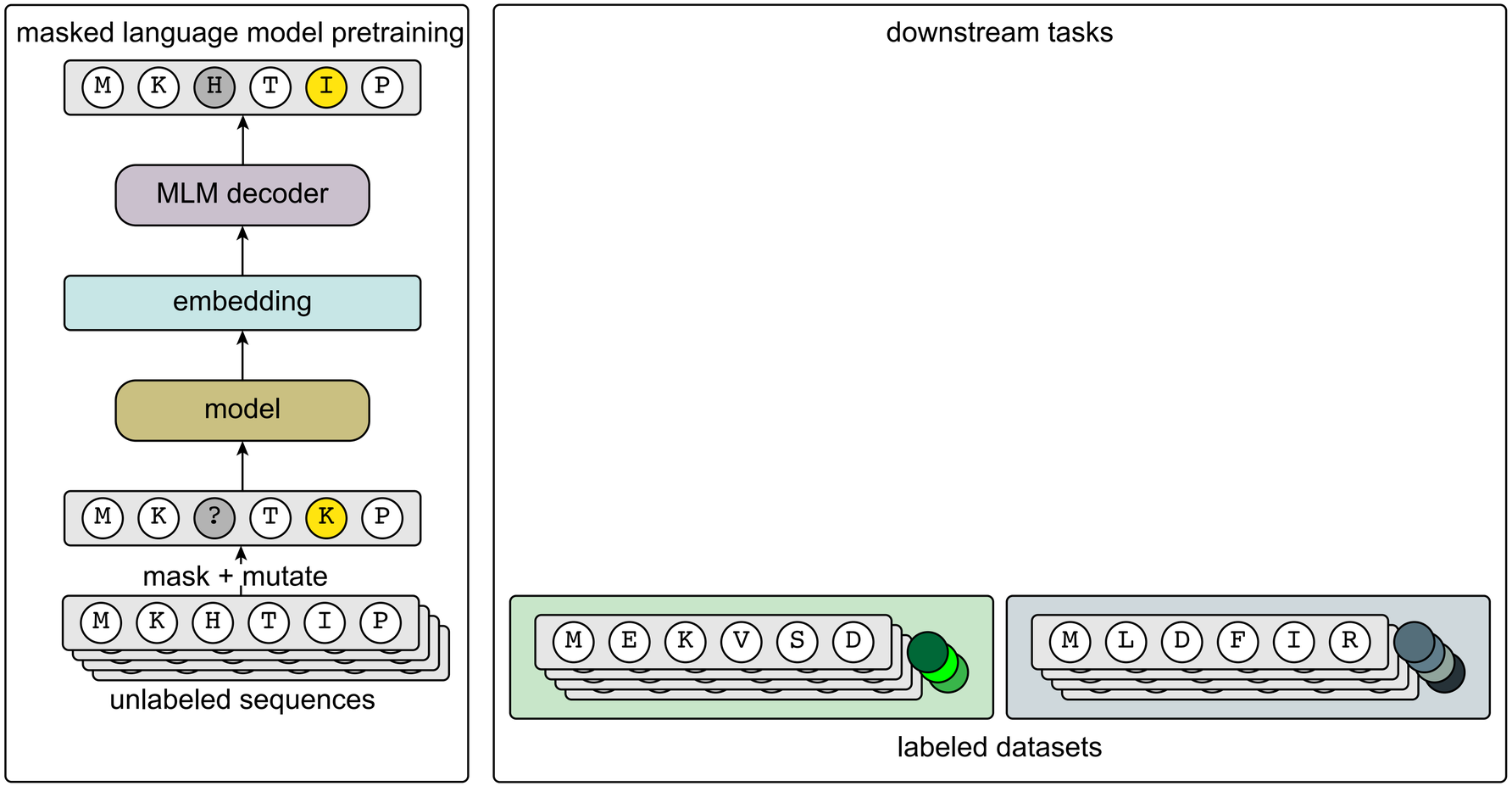

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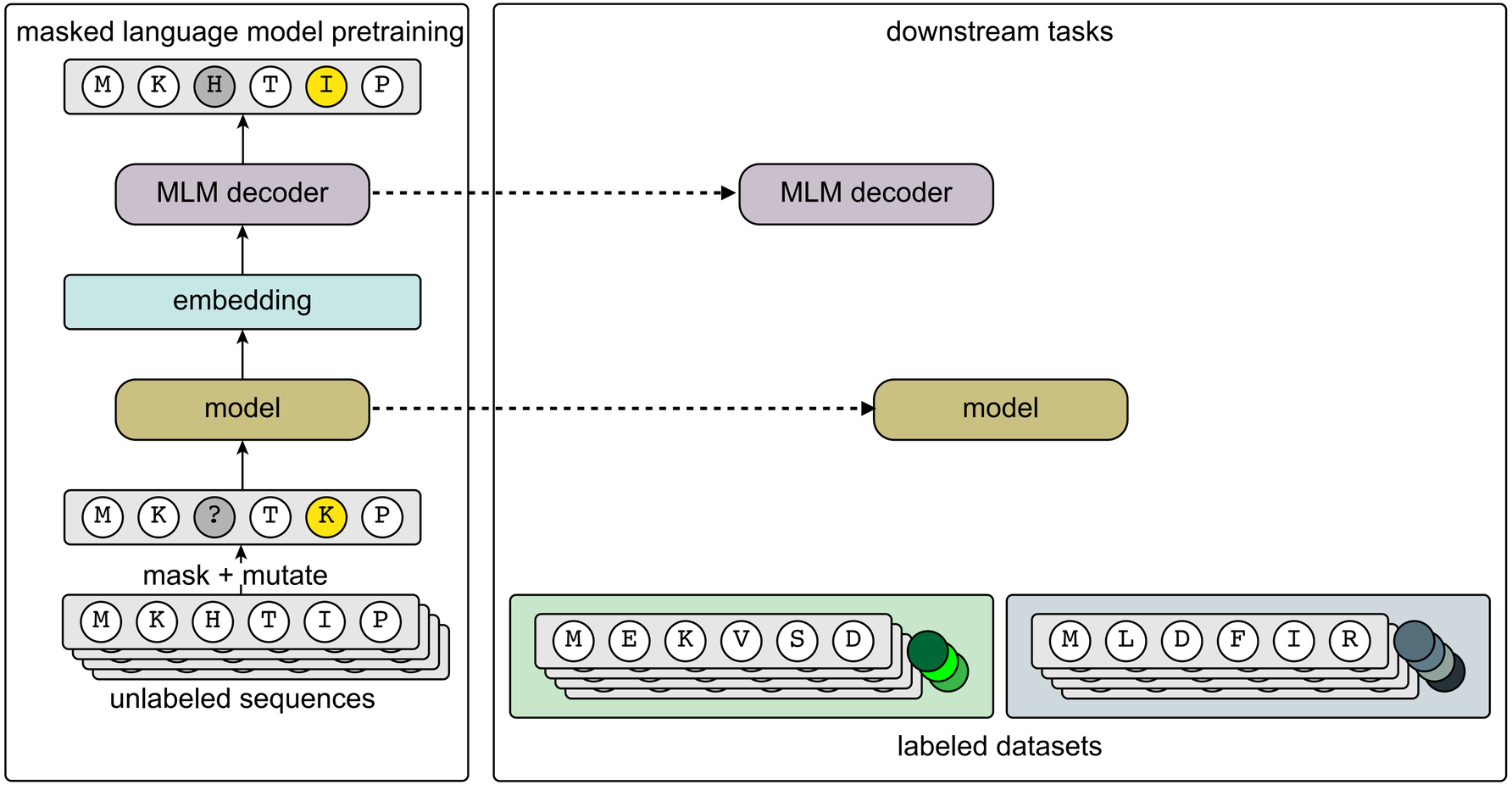

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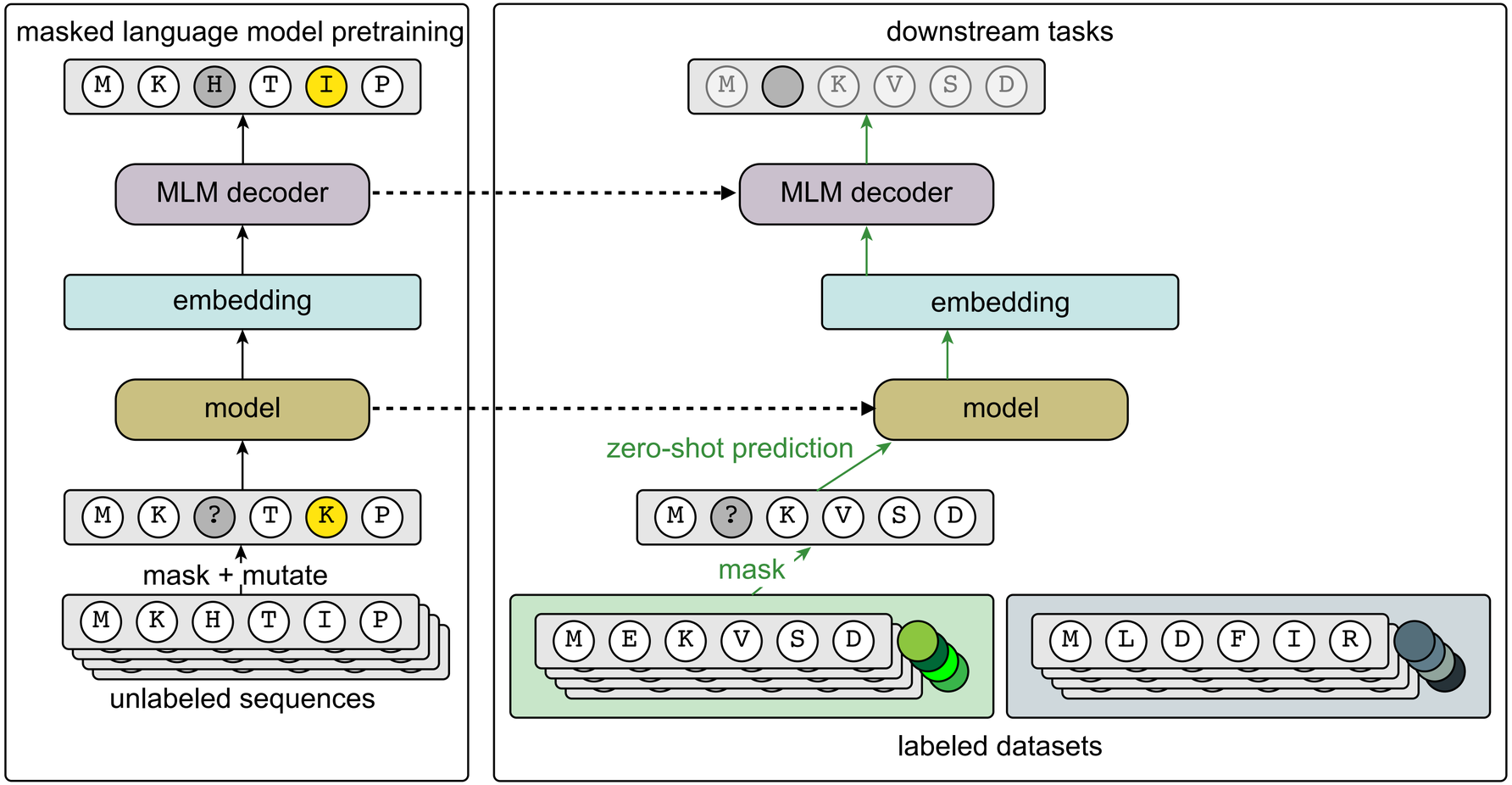

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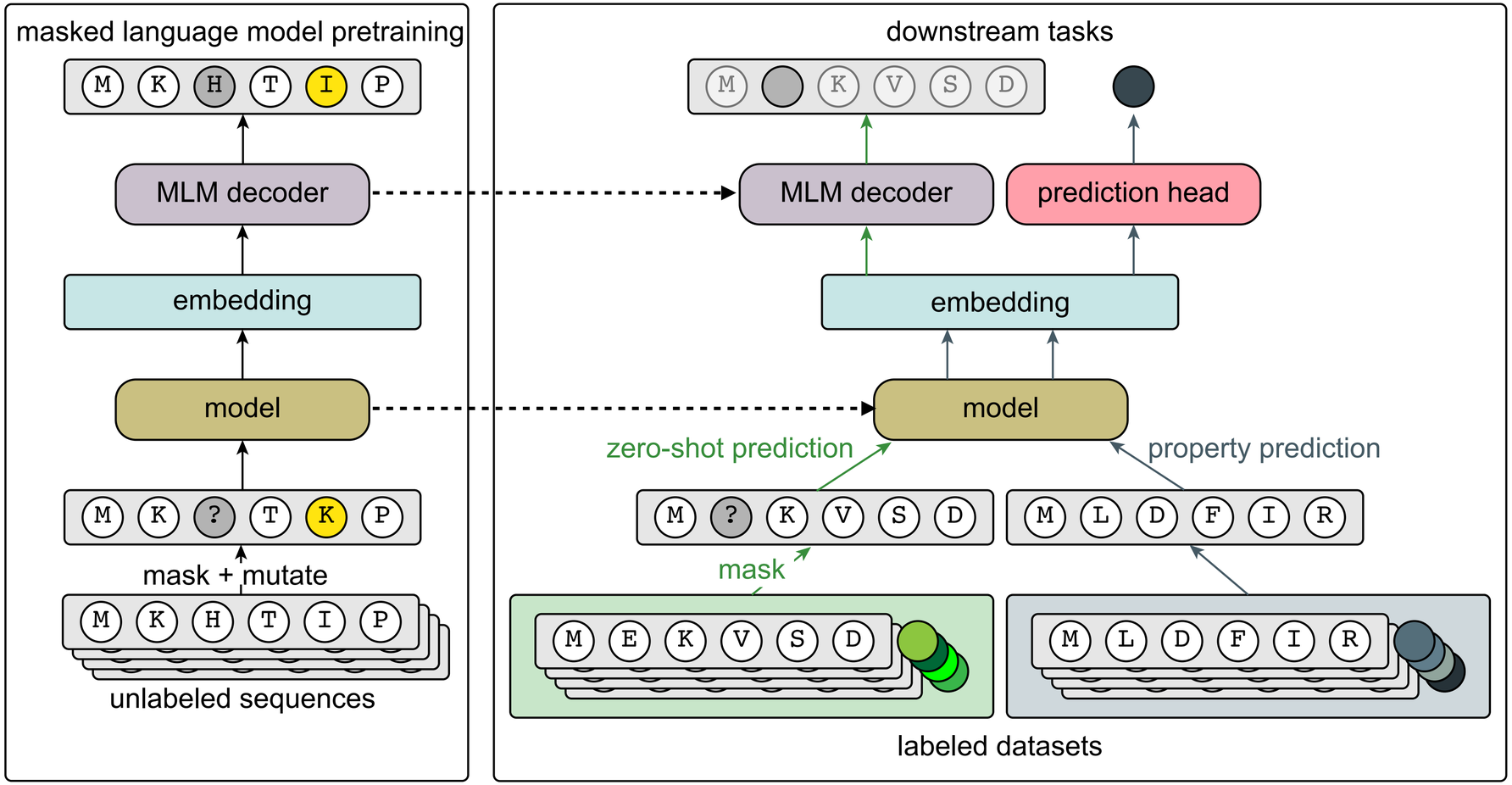

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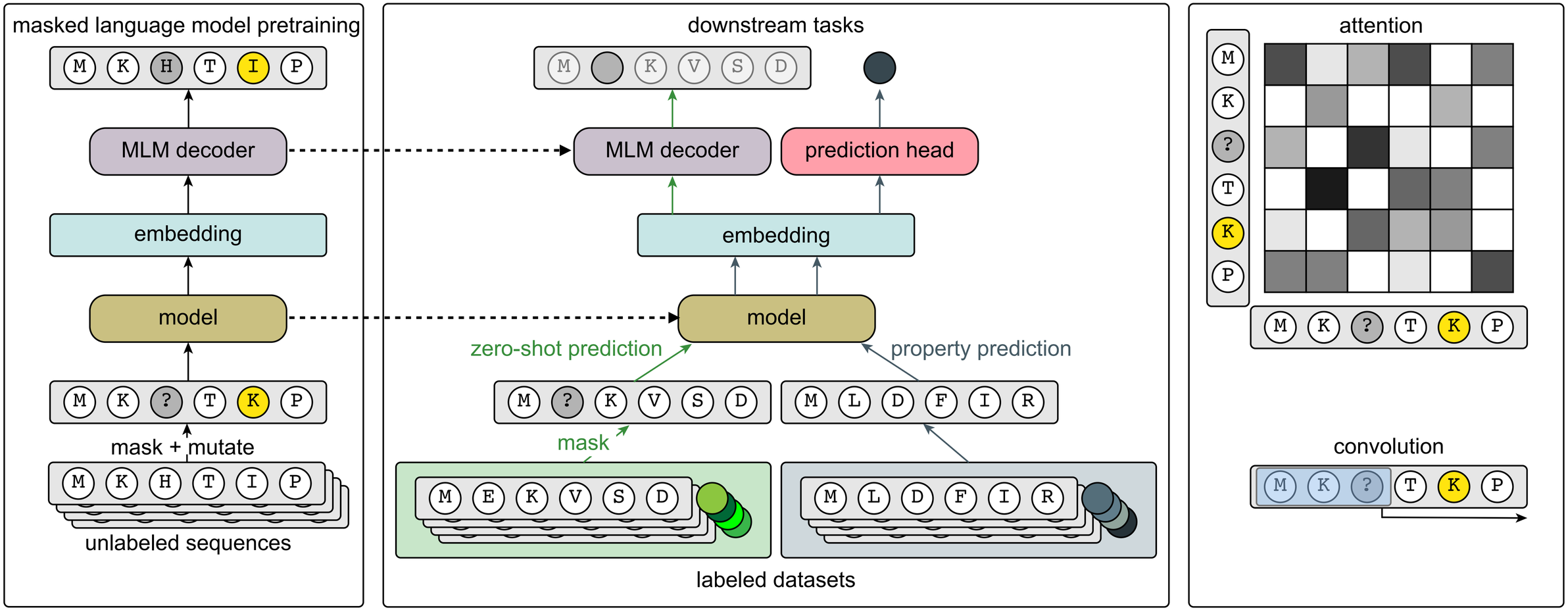

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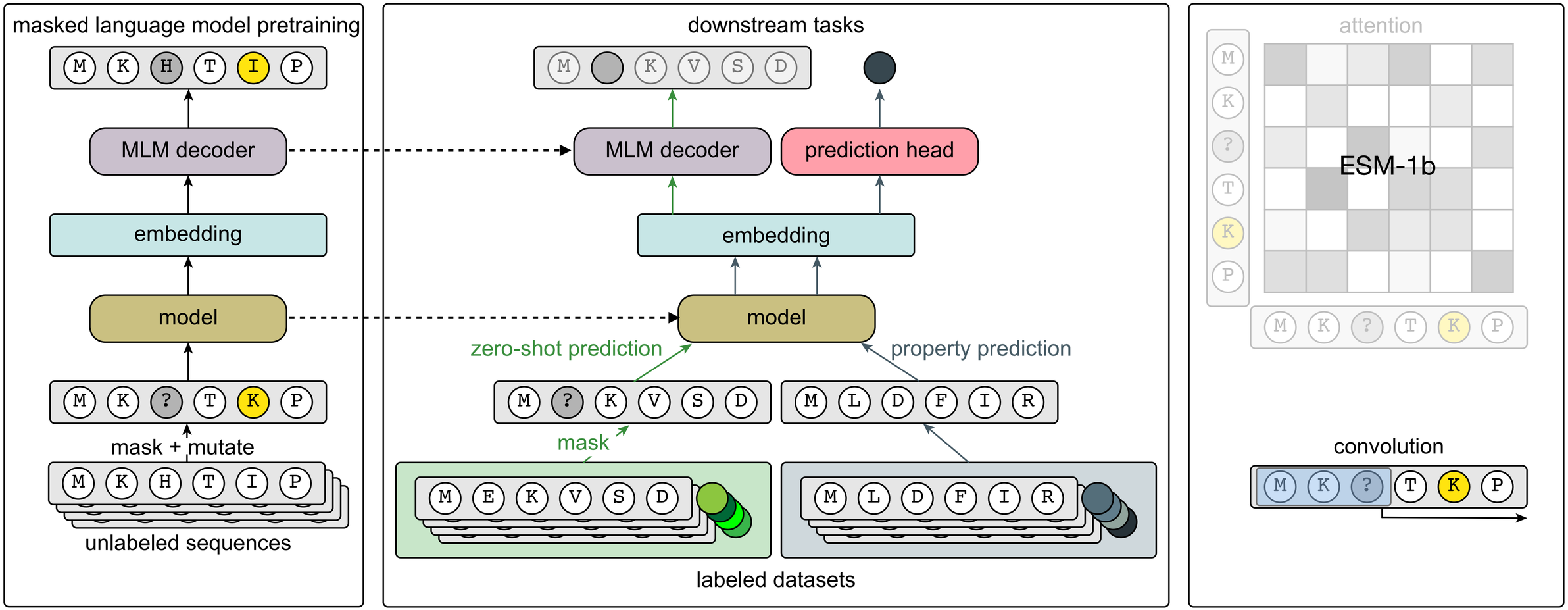

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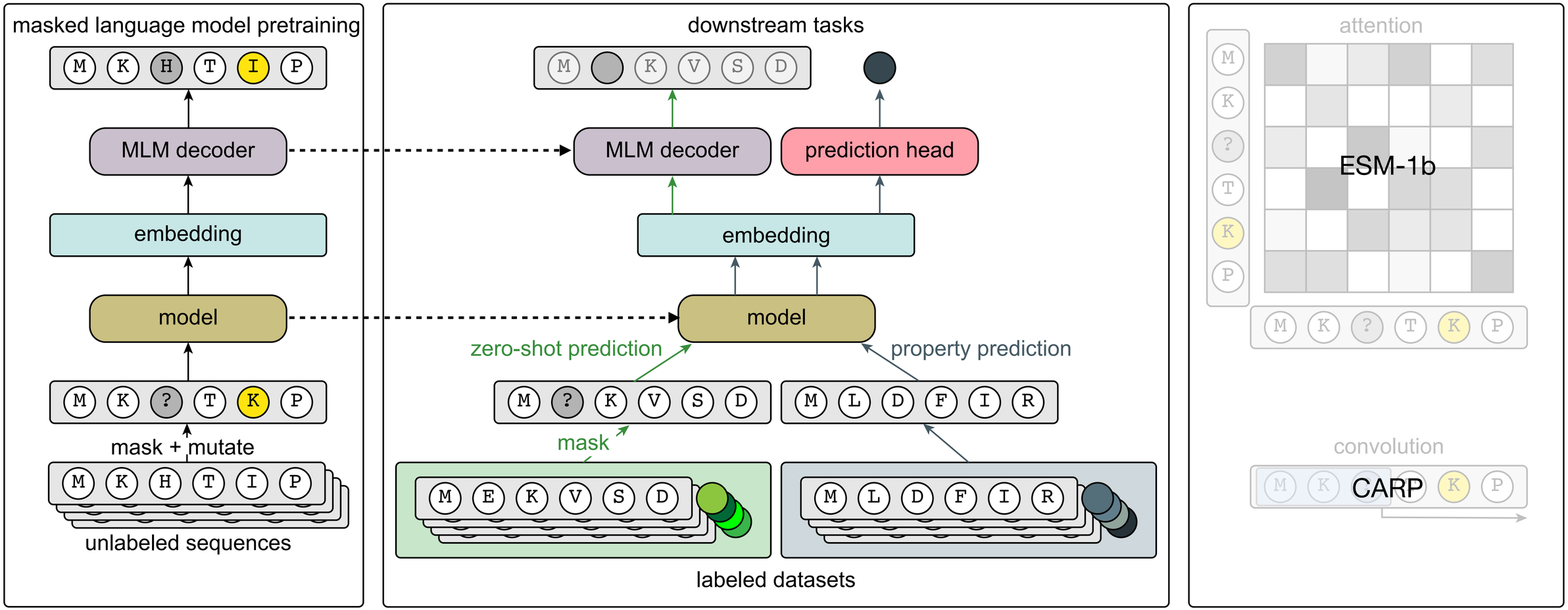

Pretrained models are zero-shot fitness predictors

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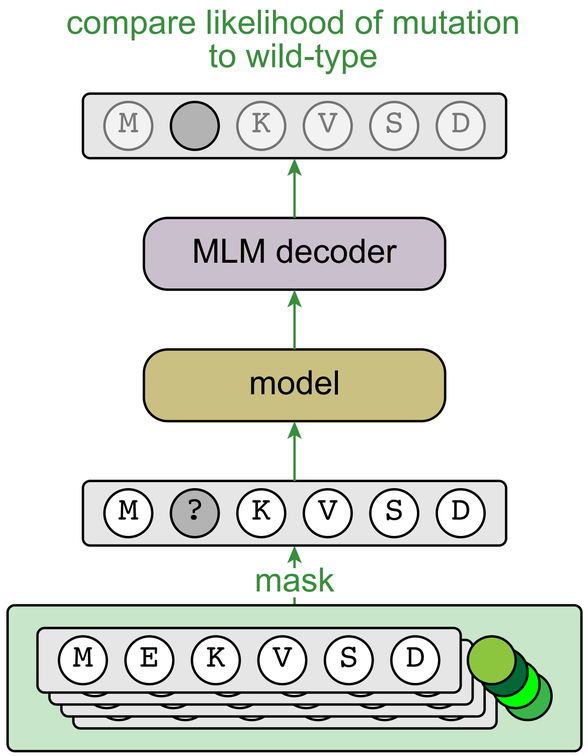

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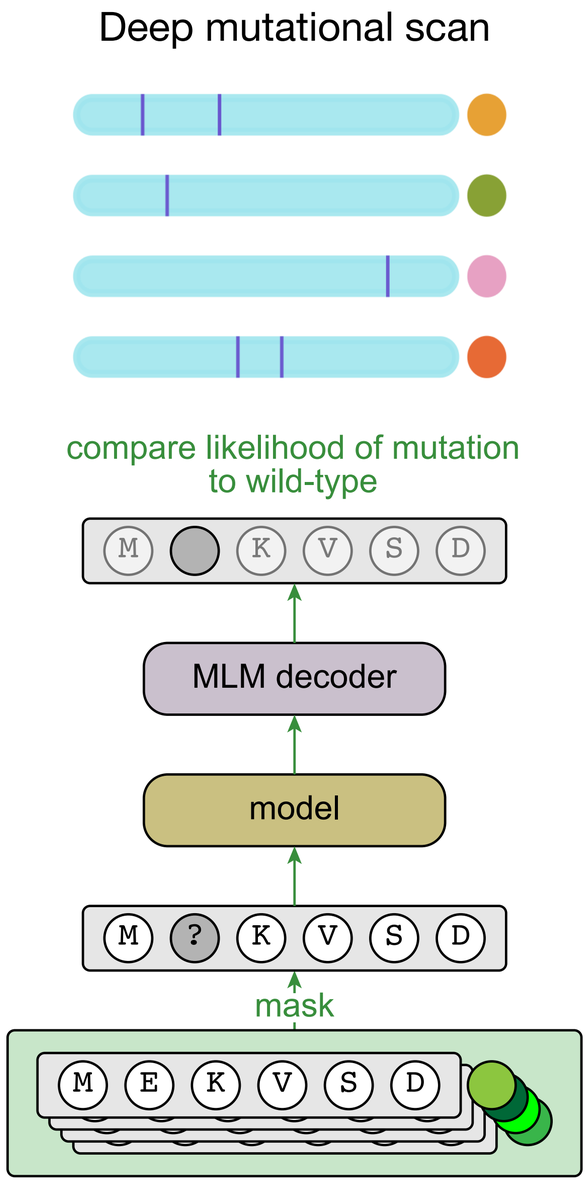

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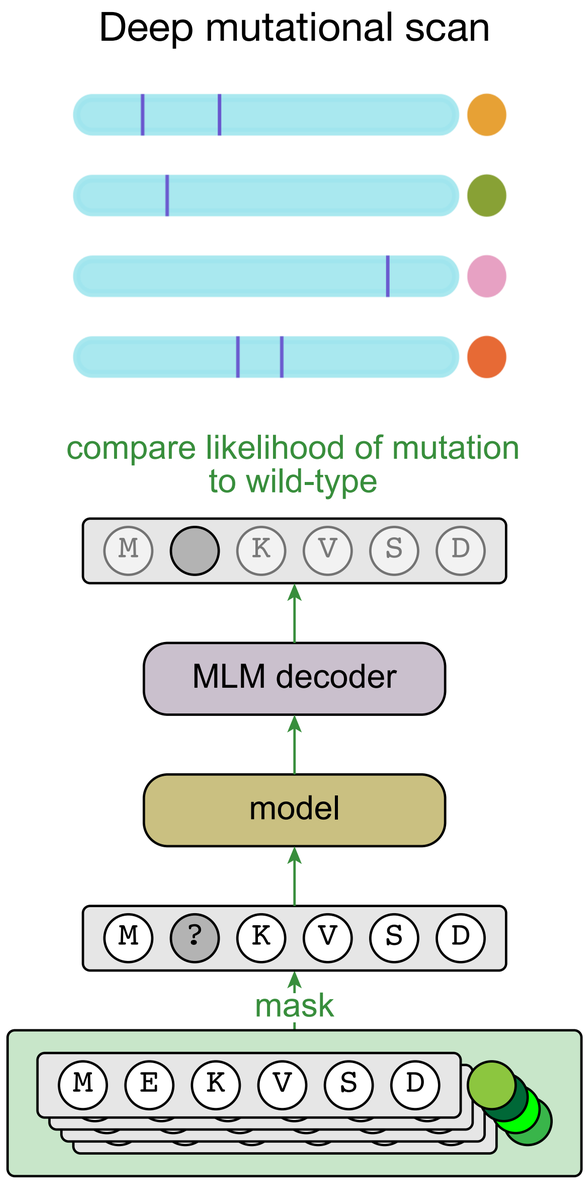

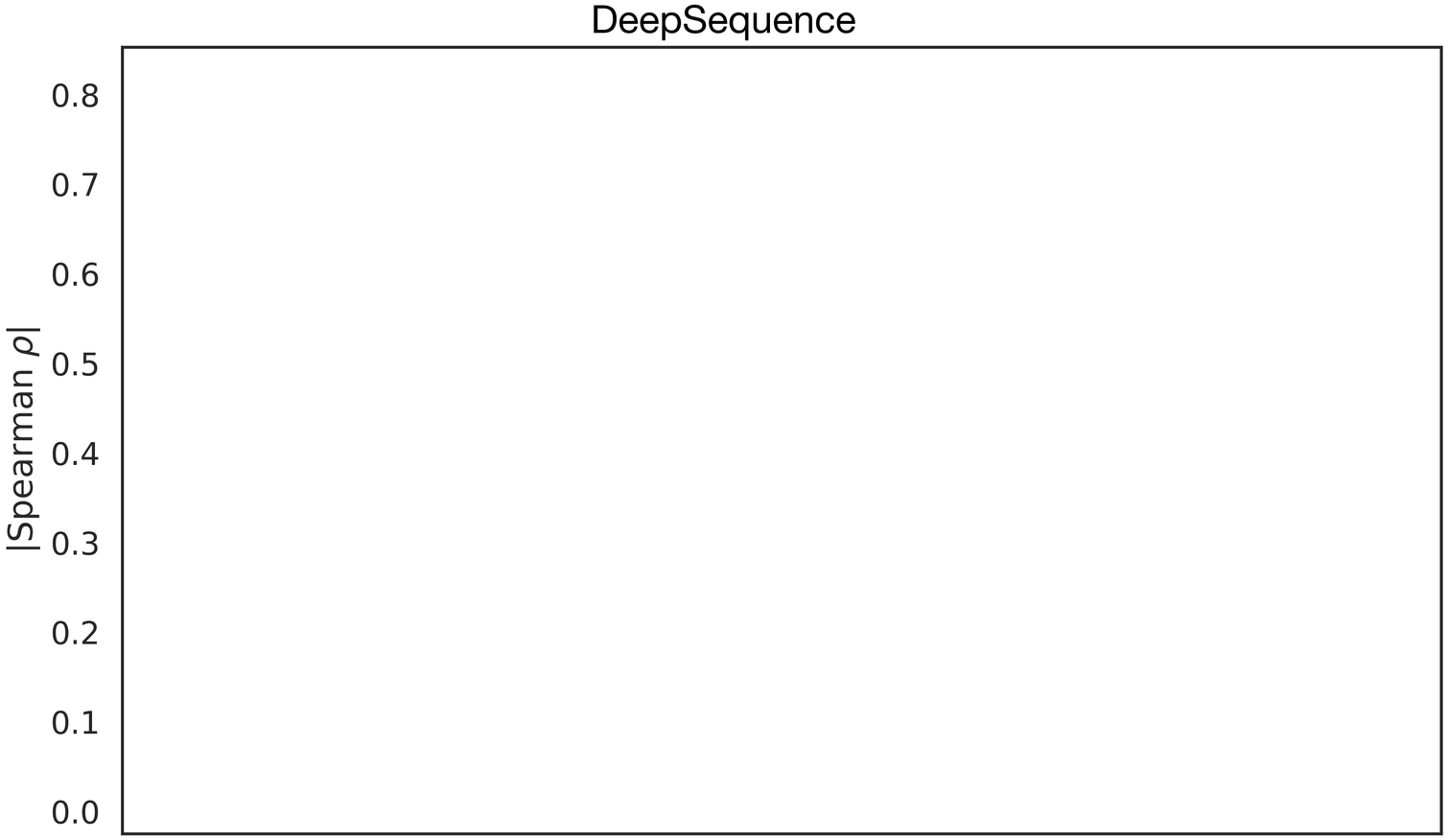

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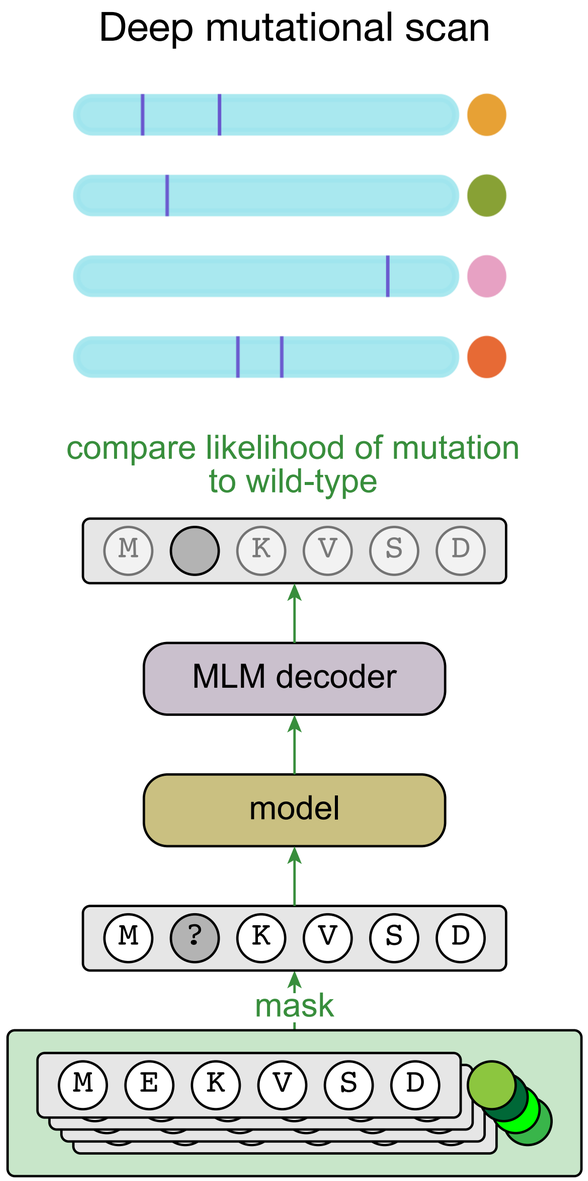

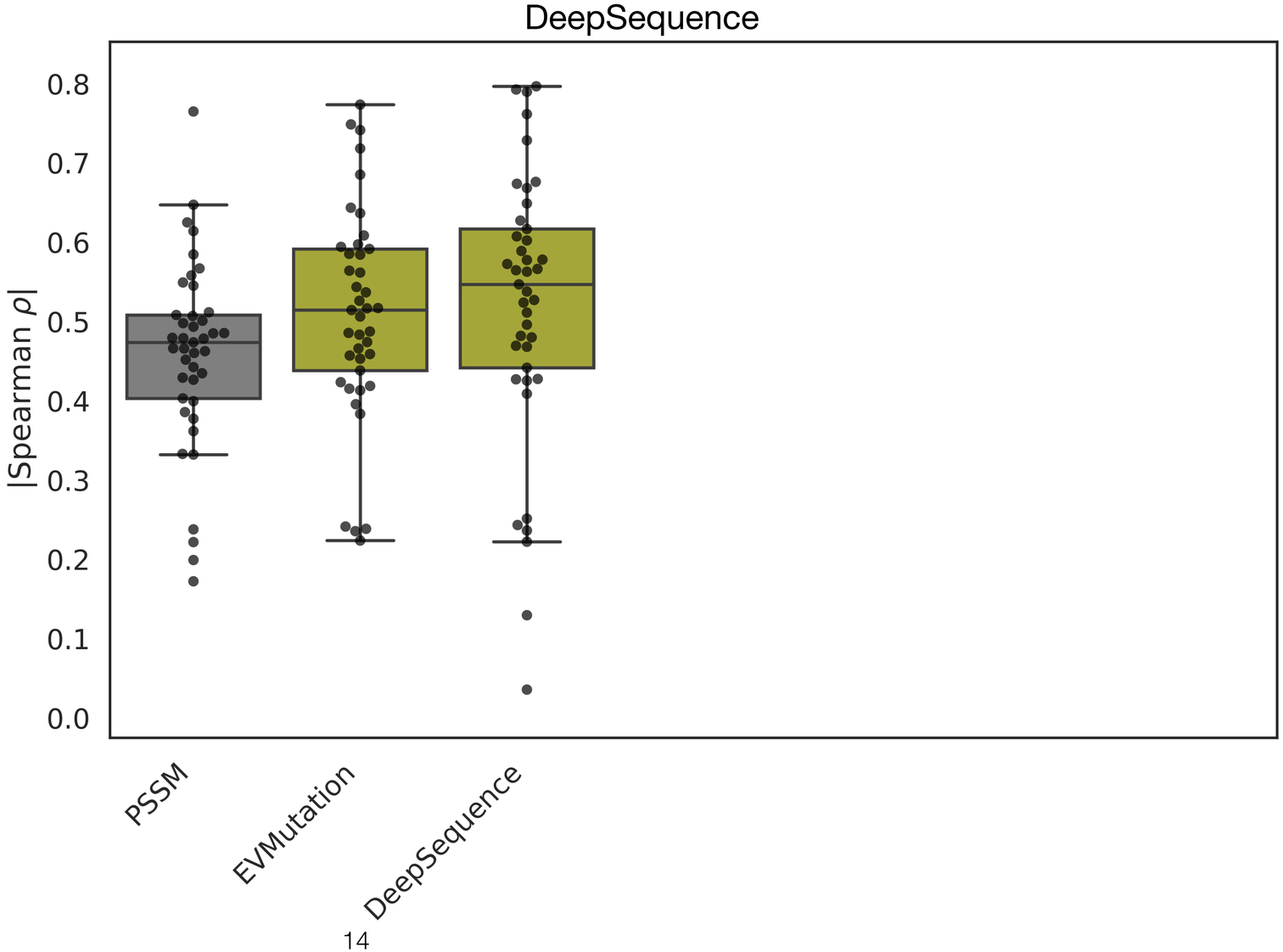

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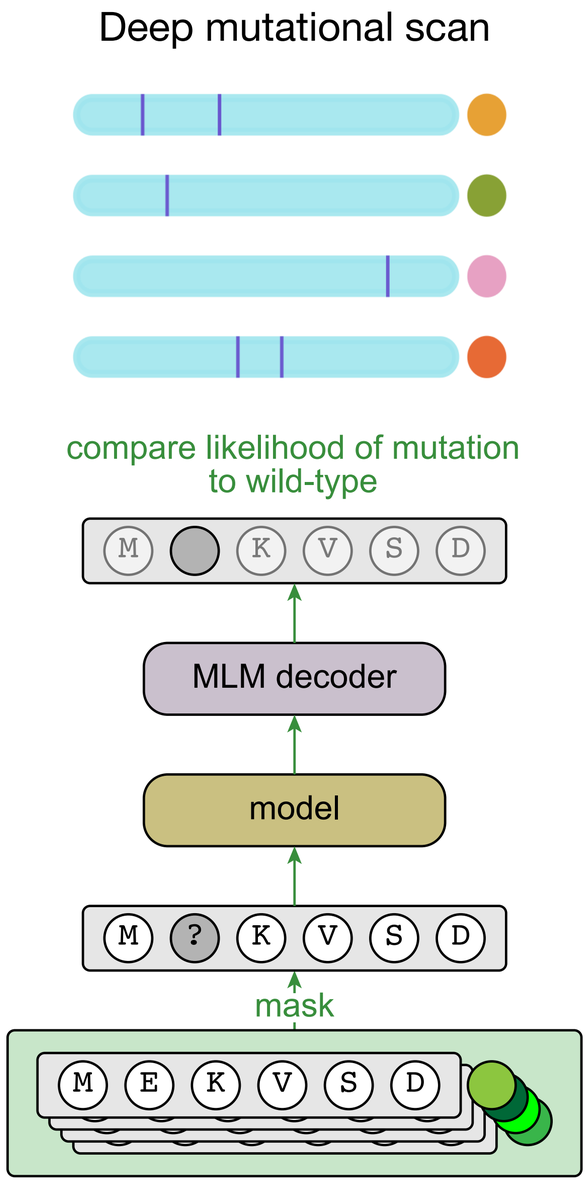

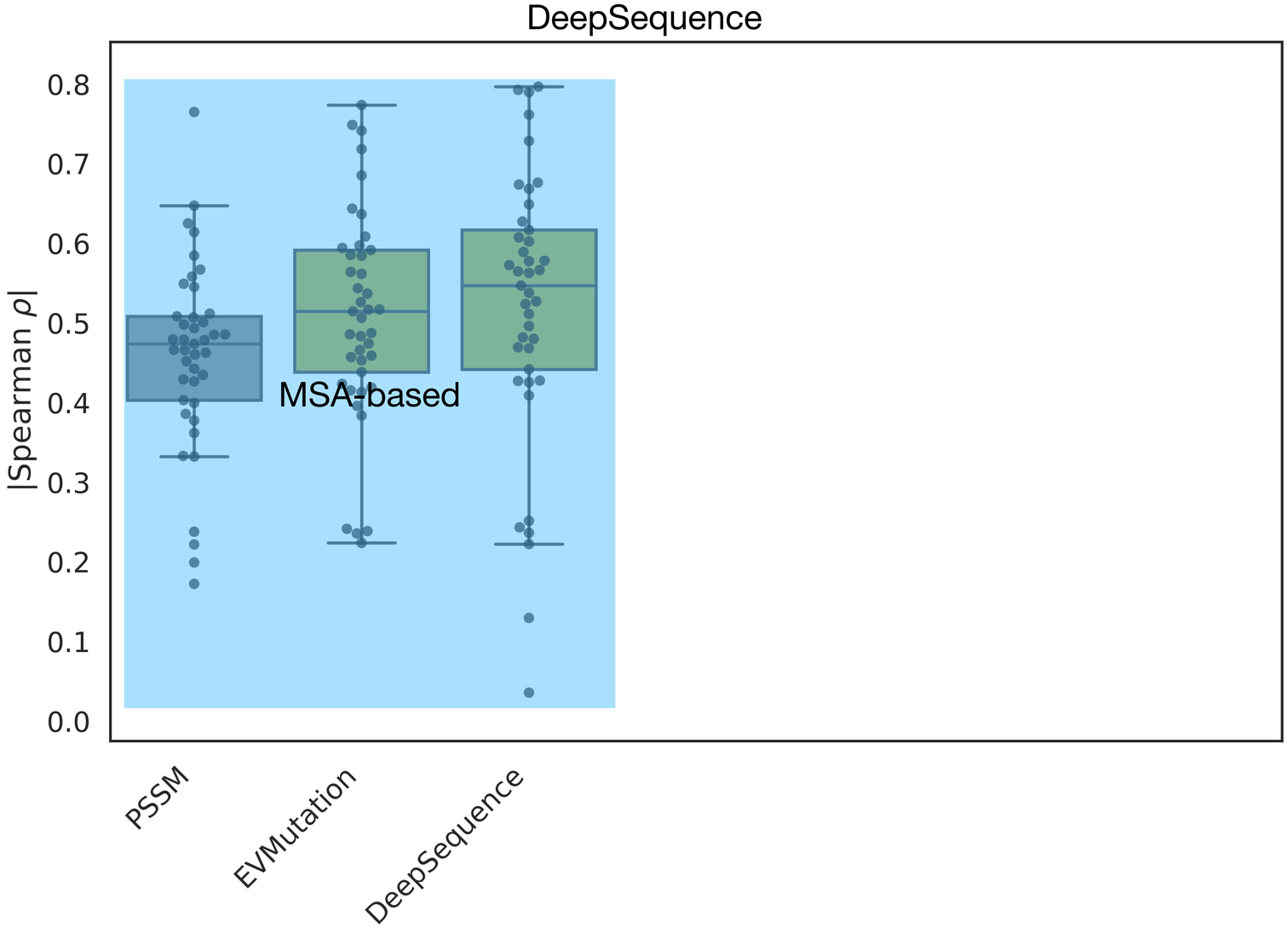

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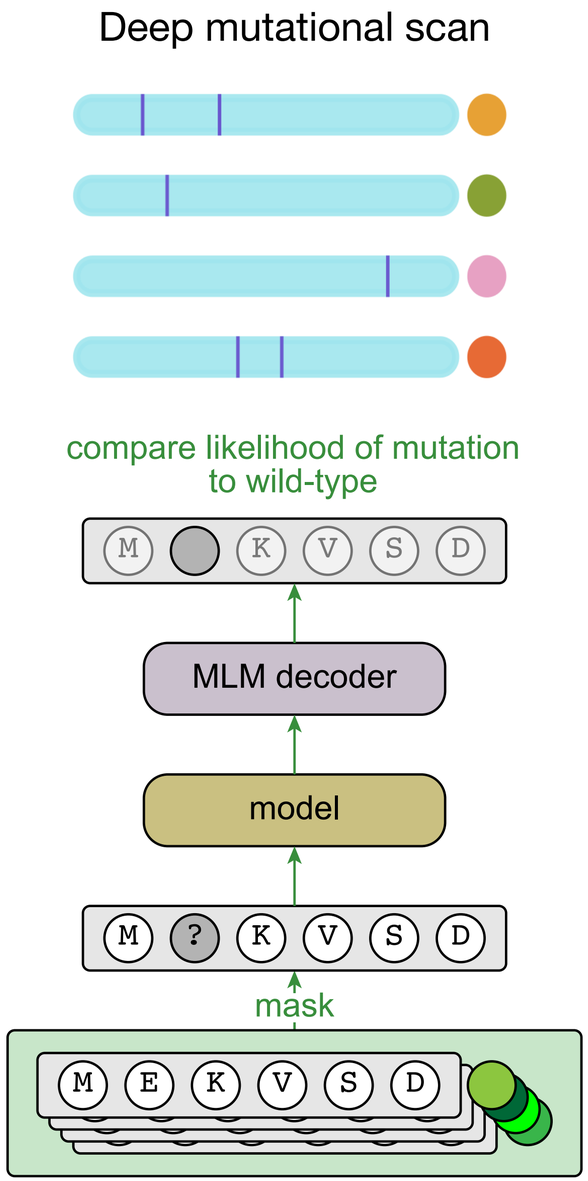

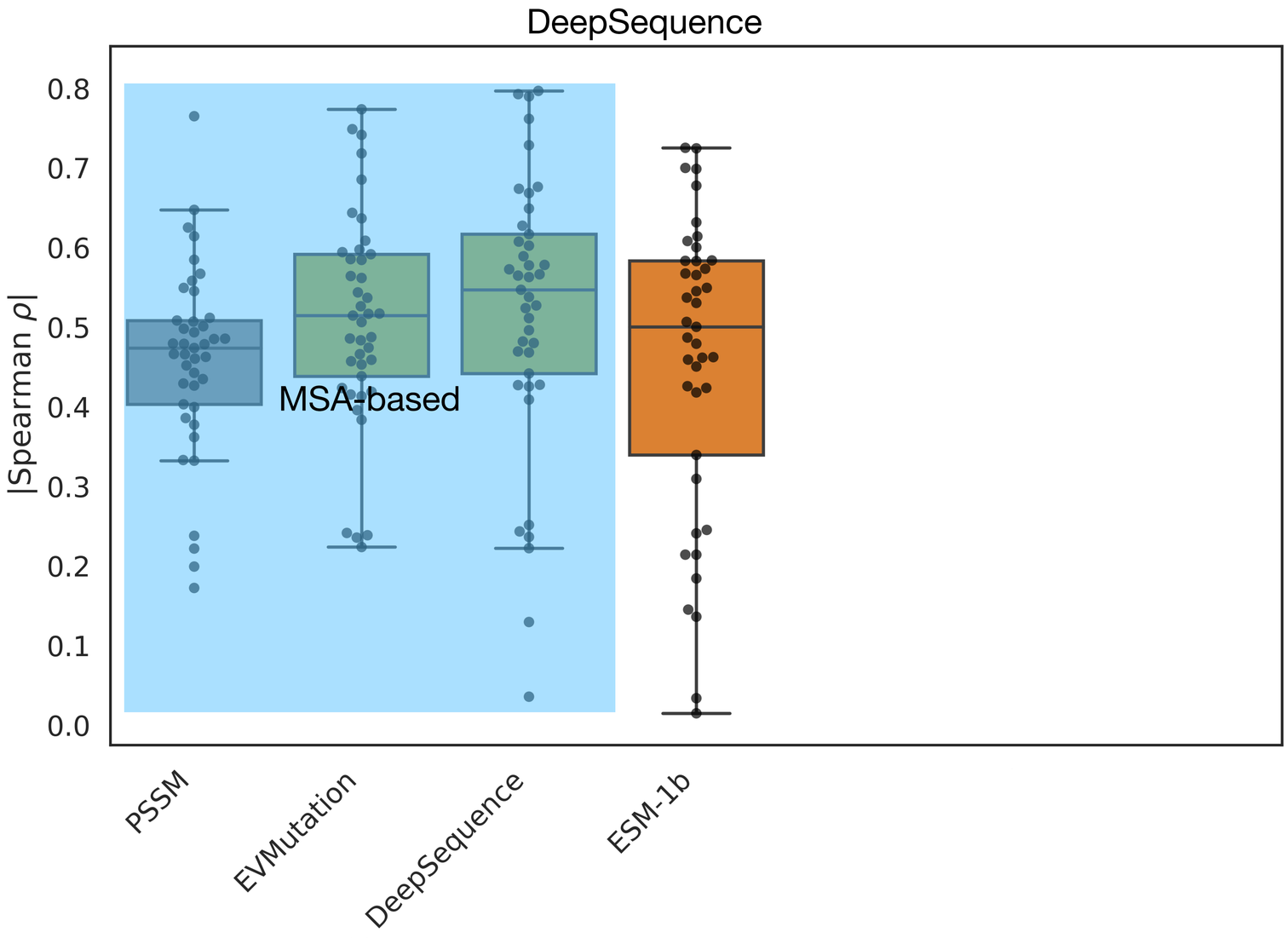

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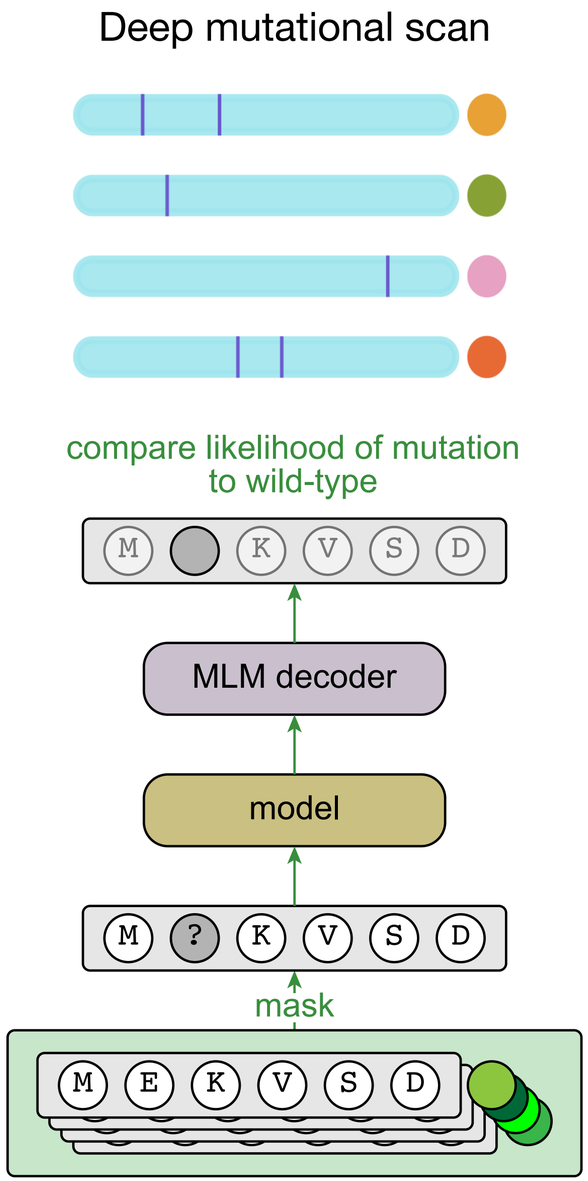

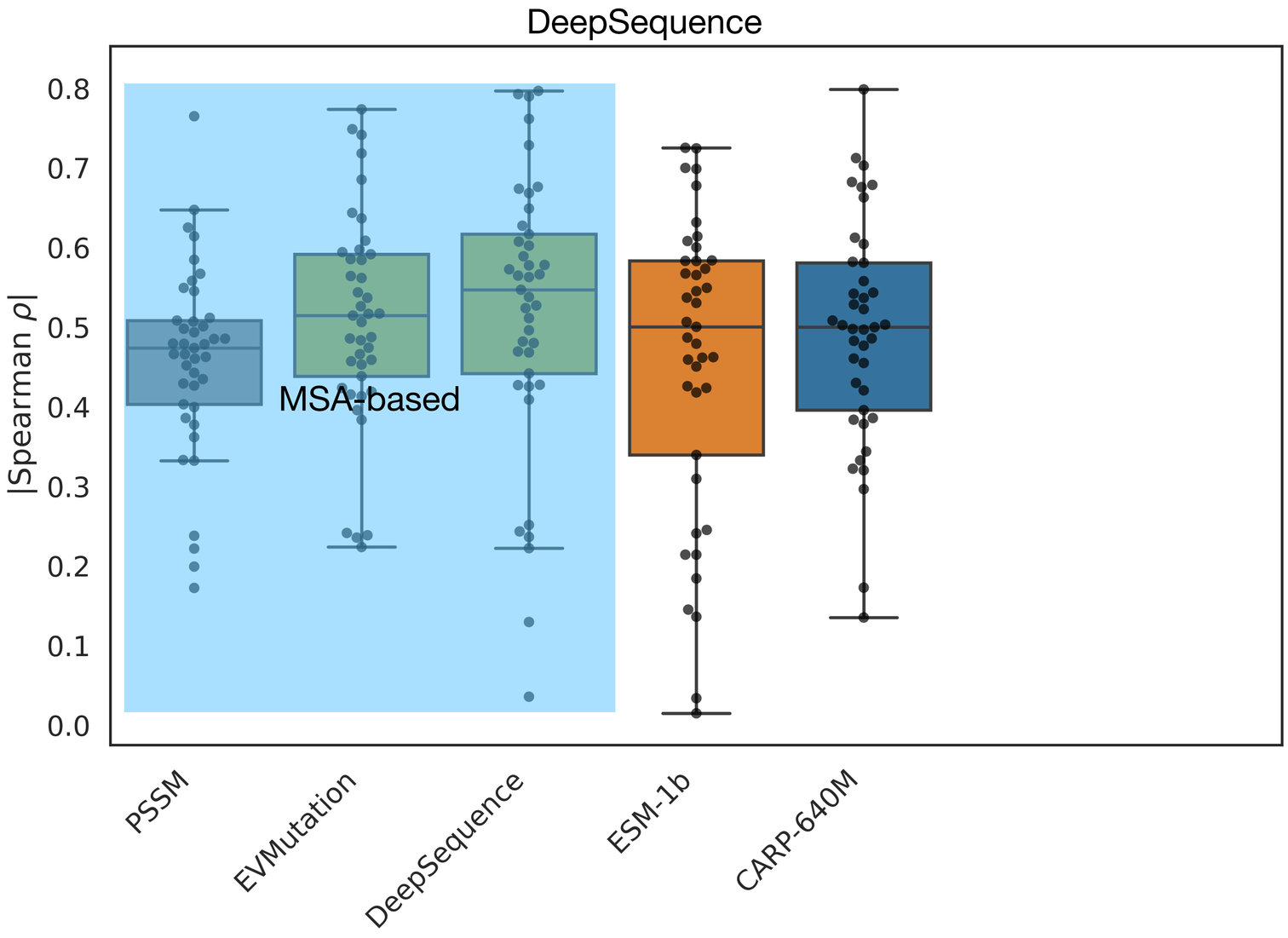

Structure predictions improve smoothly with pretraining

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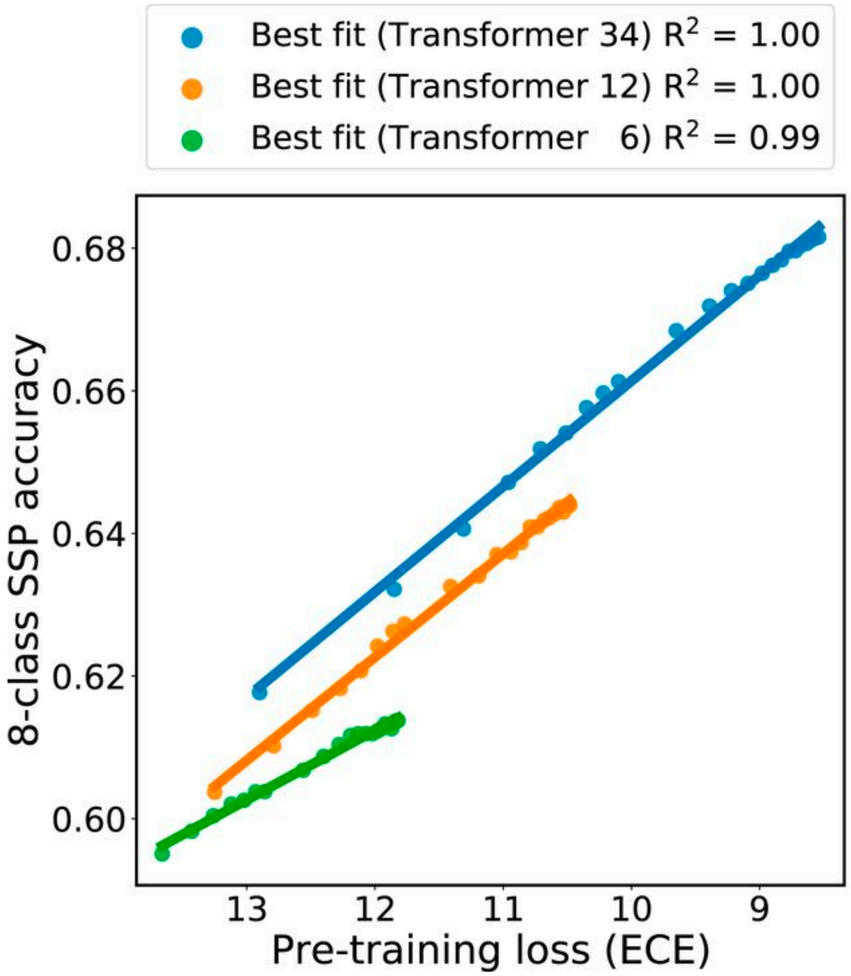

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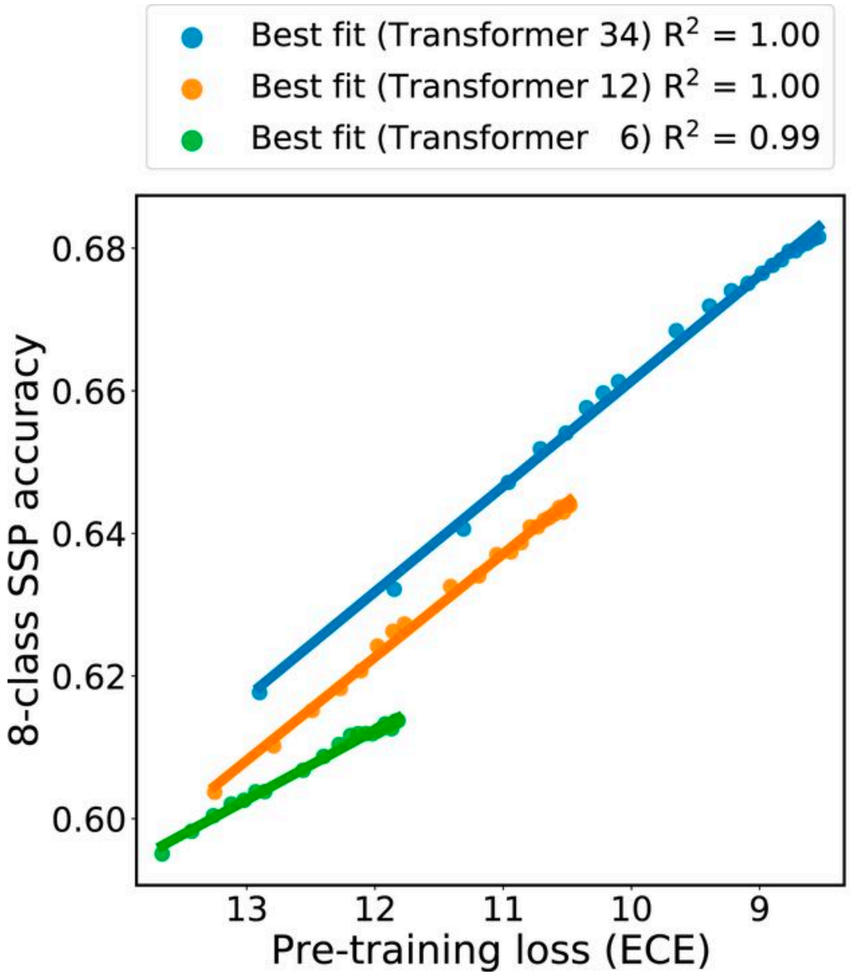

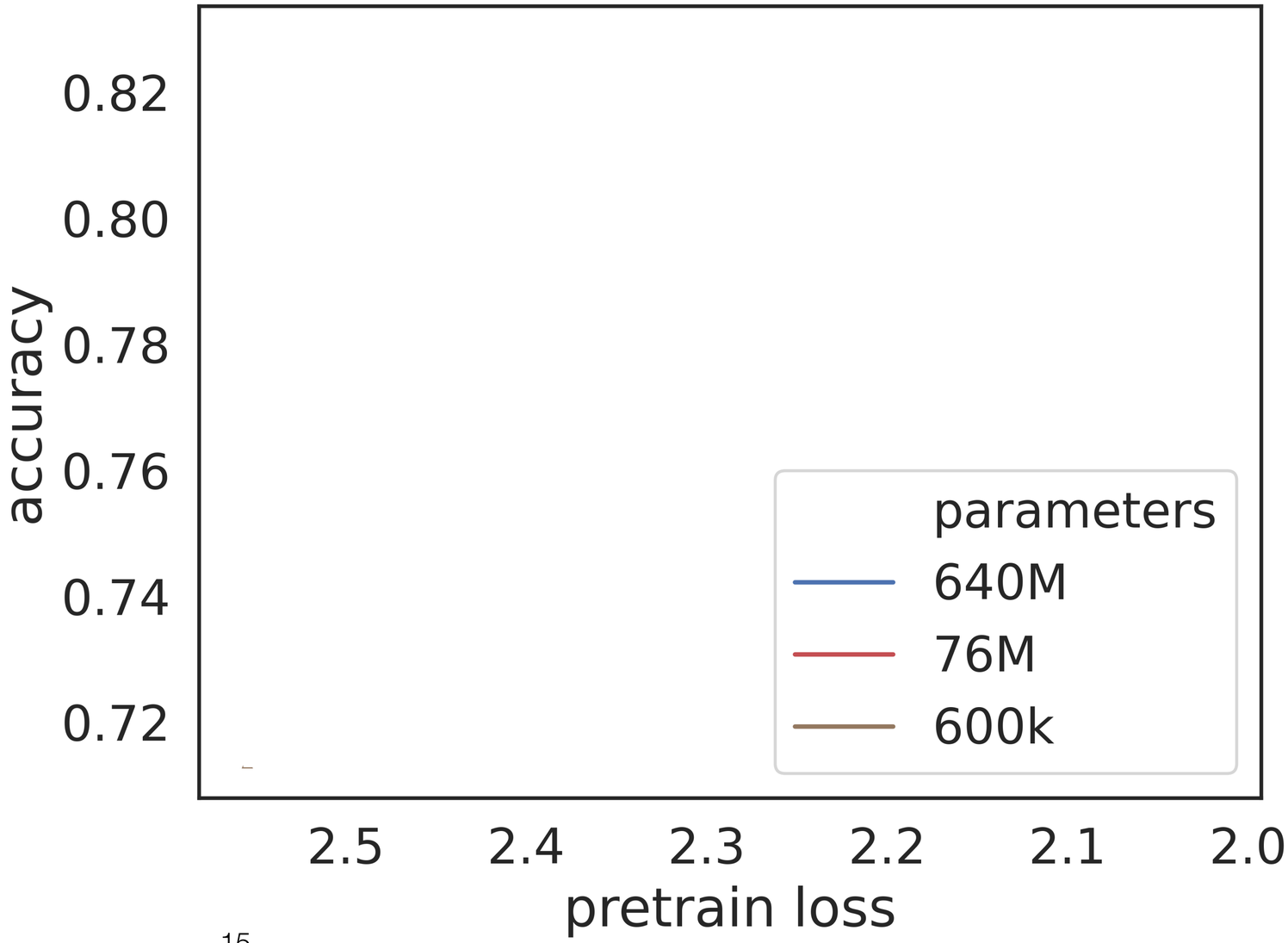

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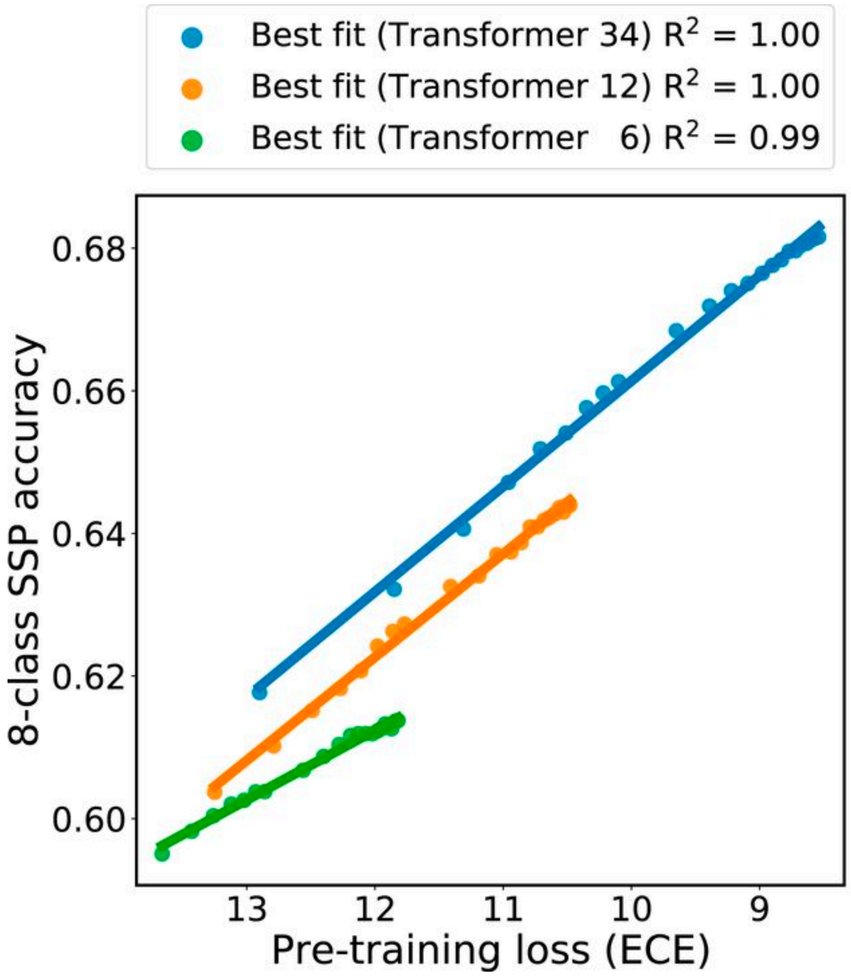
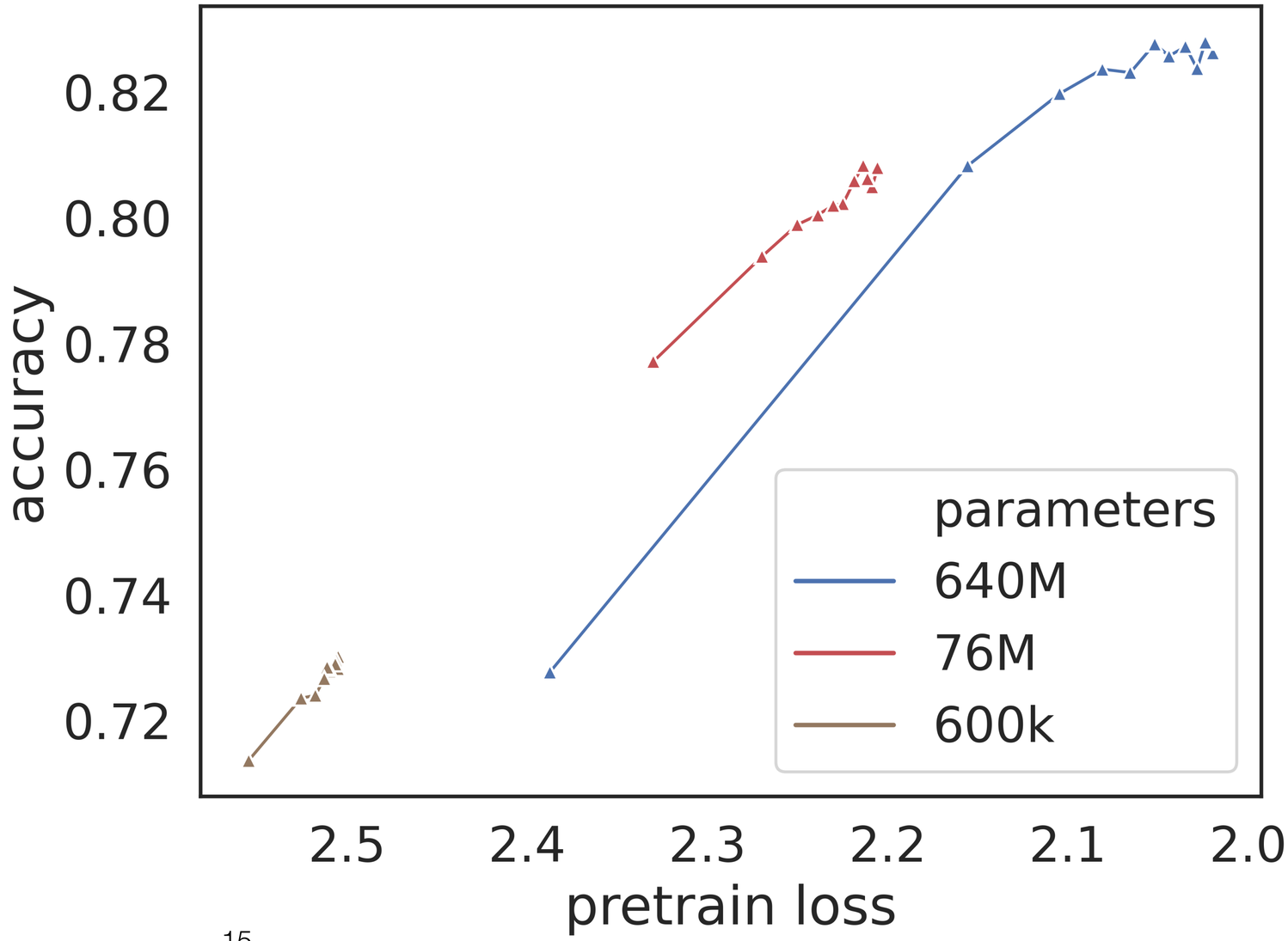
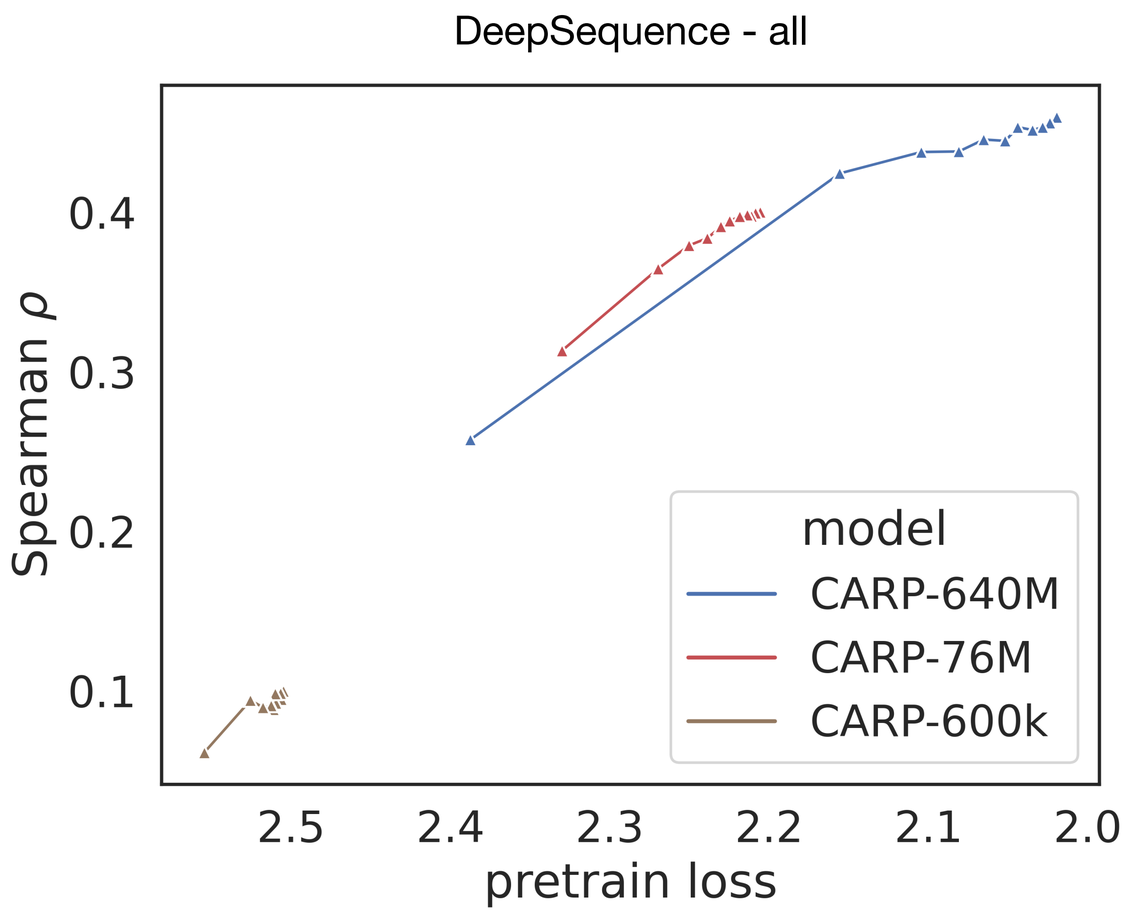




Zero-shot performance mostly improves with pretraining



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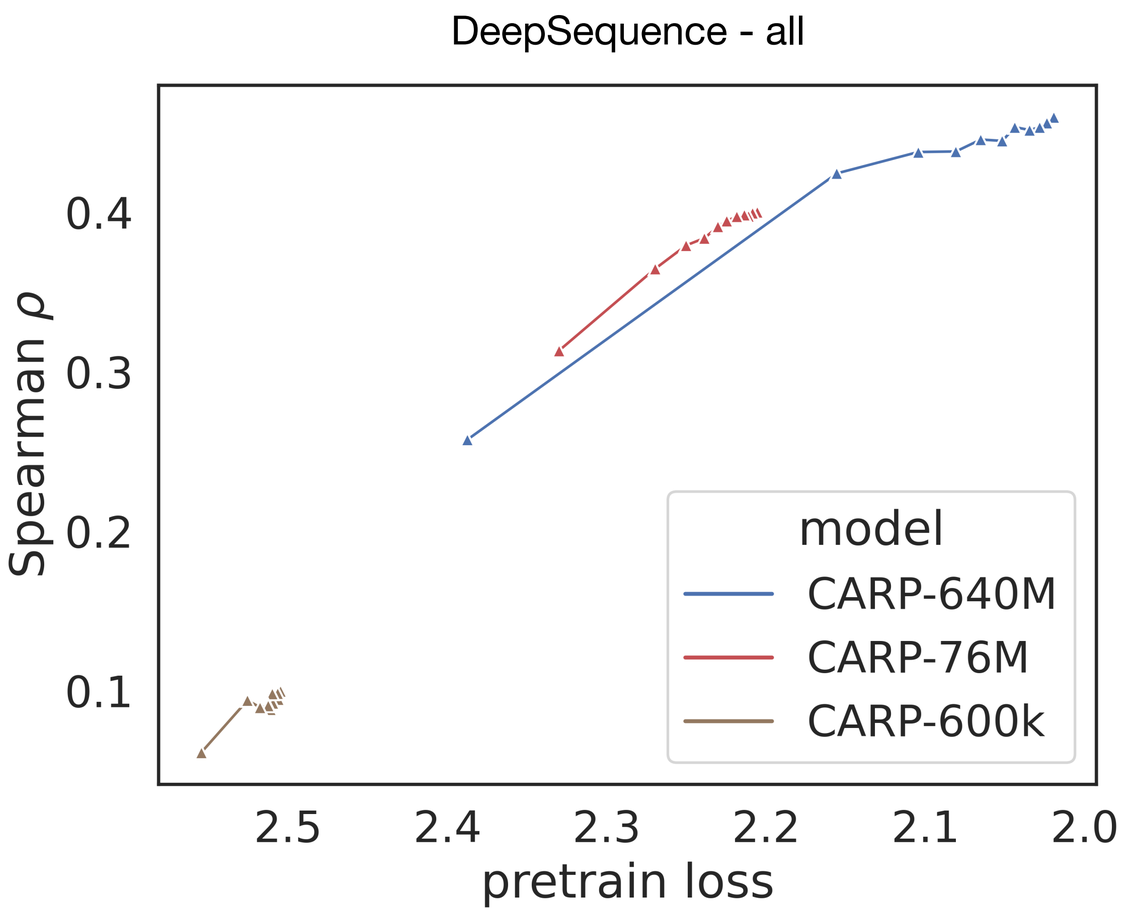

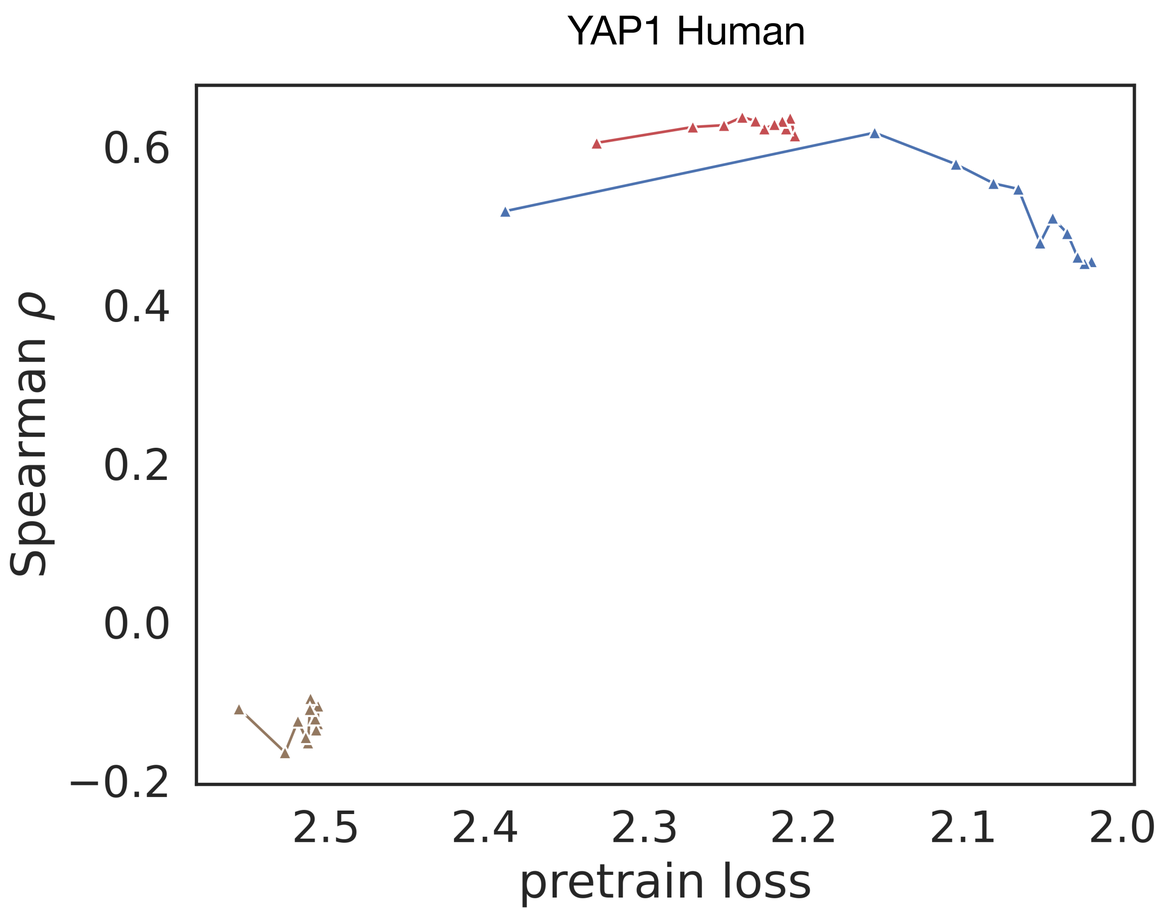

Protein engineering campaigns require out-of-domain generalization

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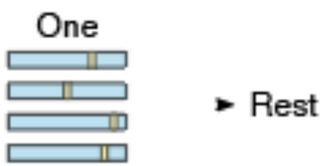

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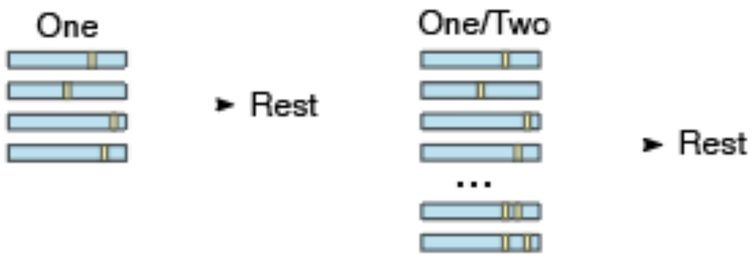

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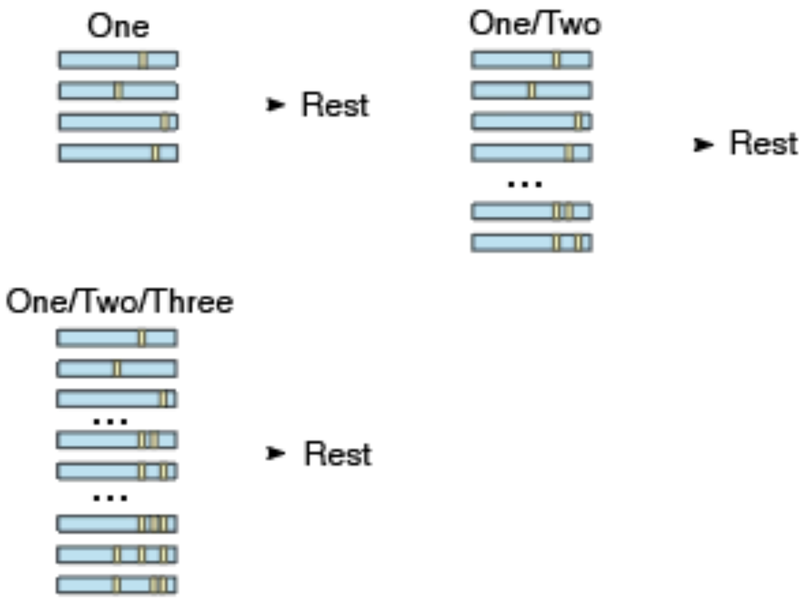

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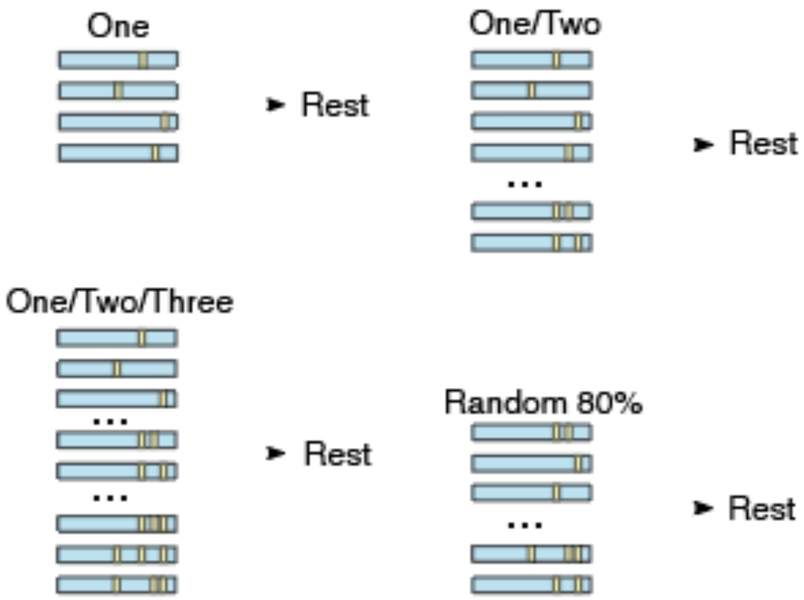

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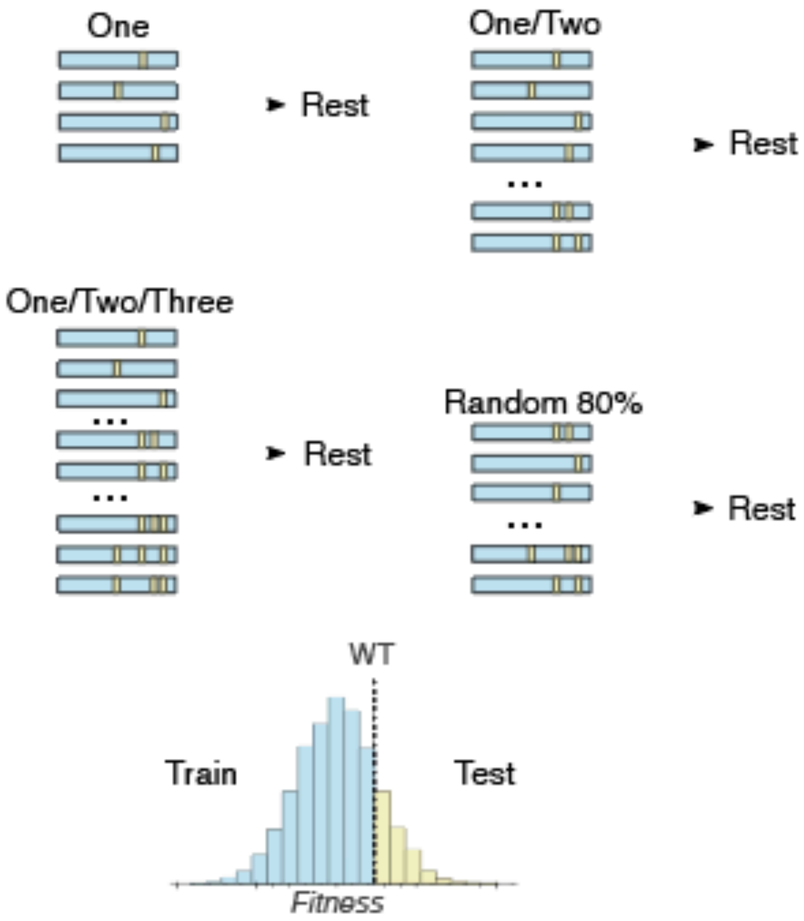

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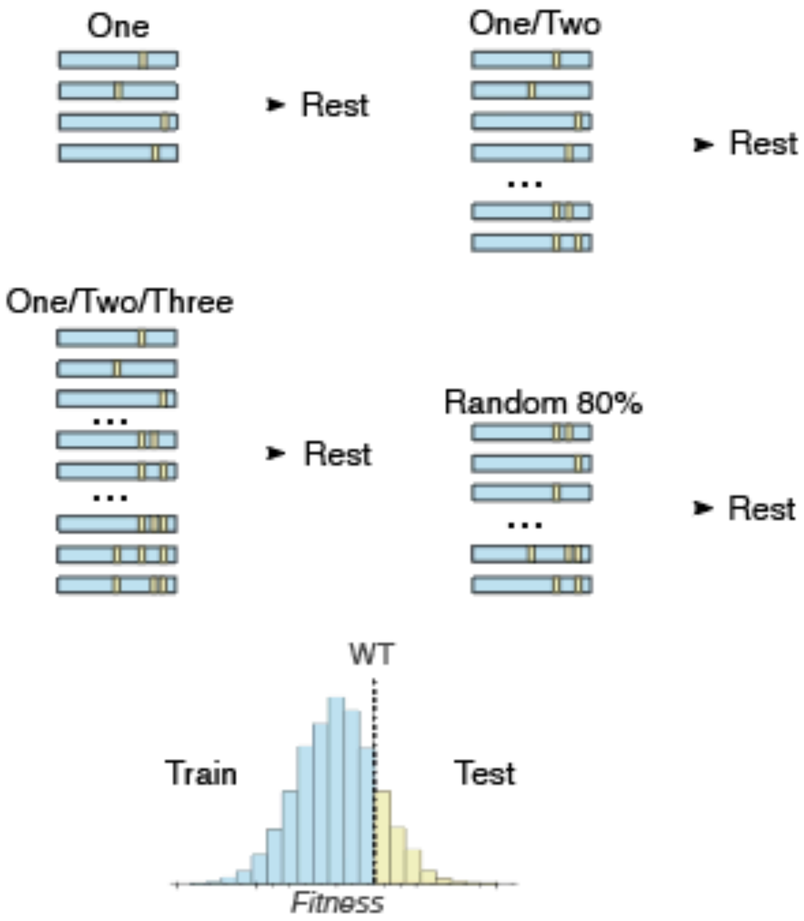
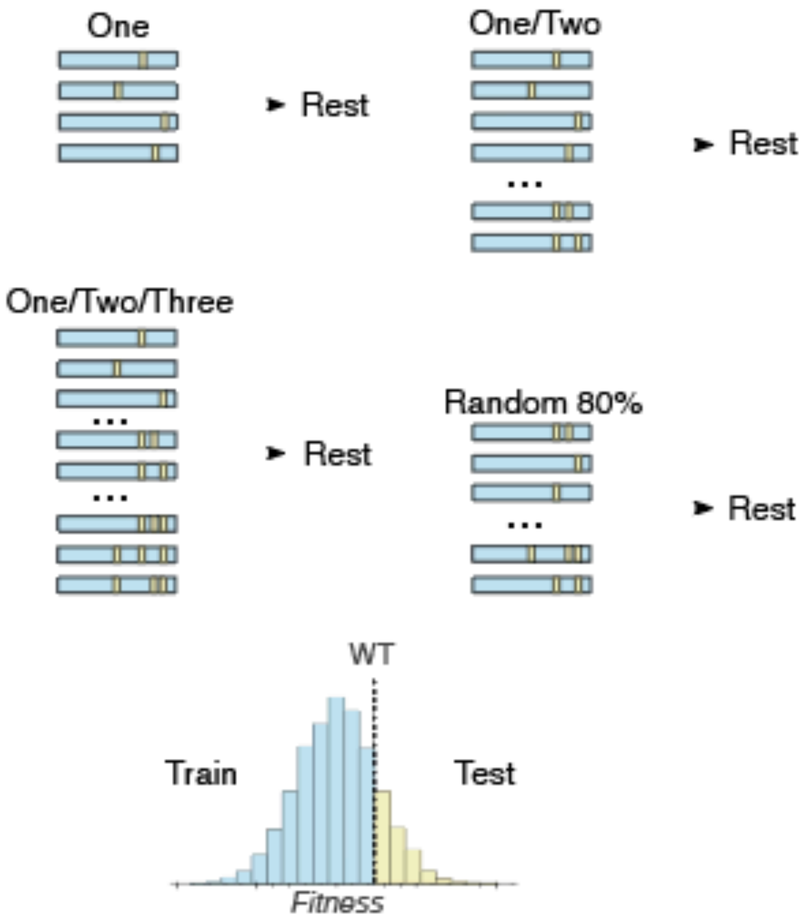


Can usually measure all single mutants

Protein engineering campaigns require out-of-domain generalization



Can usually measure all single mutants

Naively screen bigger spaces
->
mostly non-functional

Protein engineering campaigns require out-of-domain generalization

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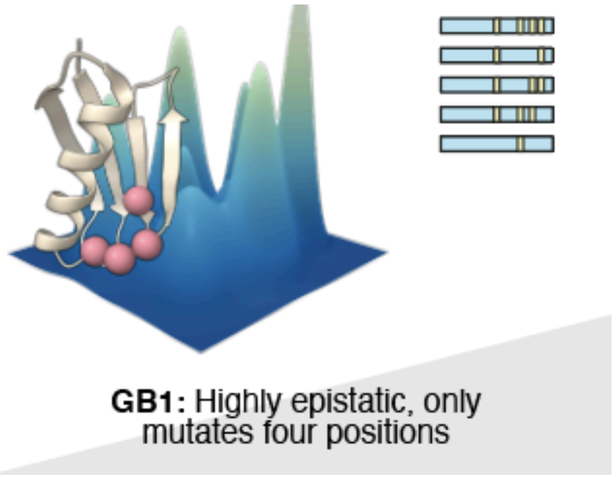

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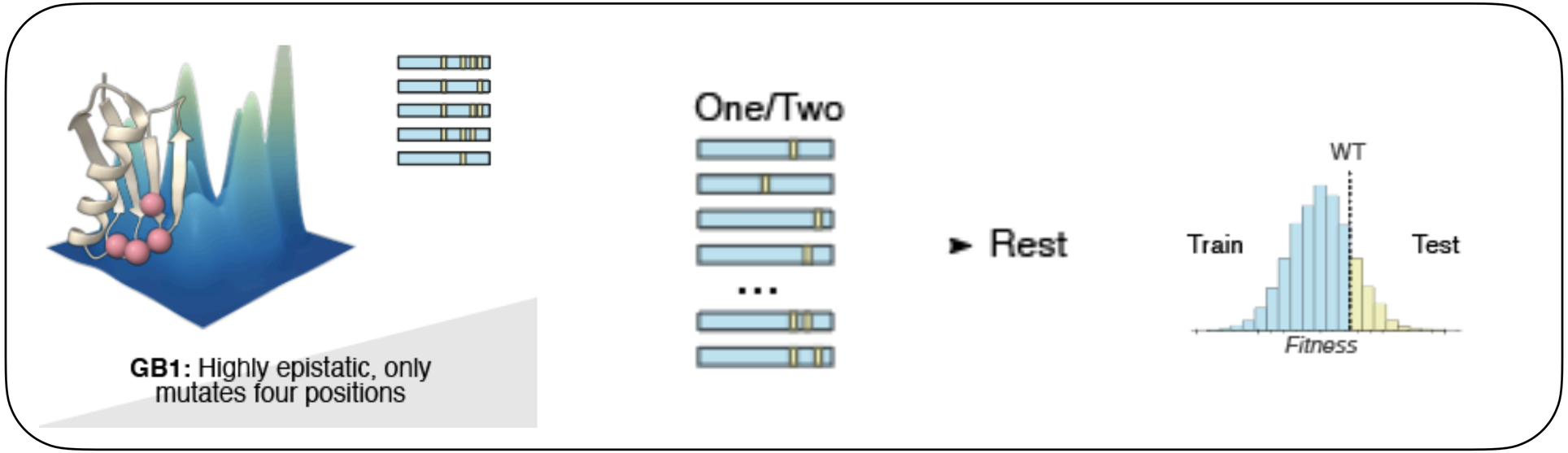
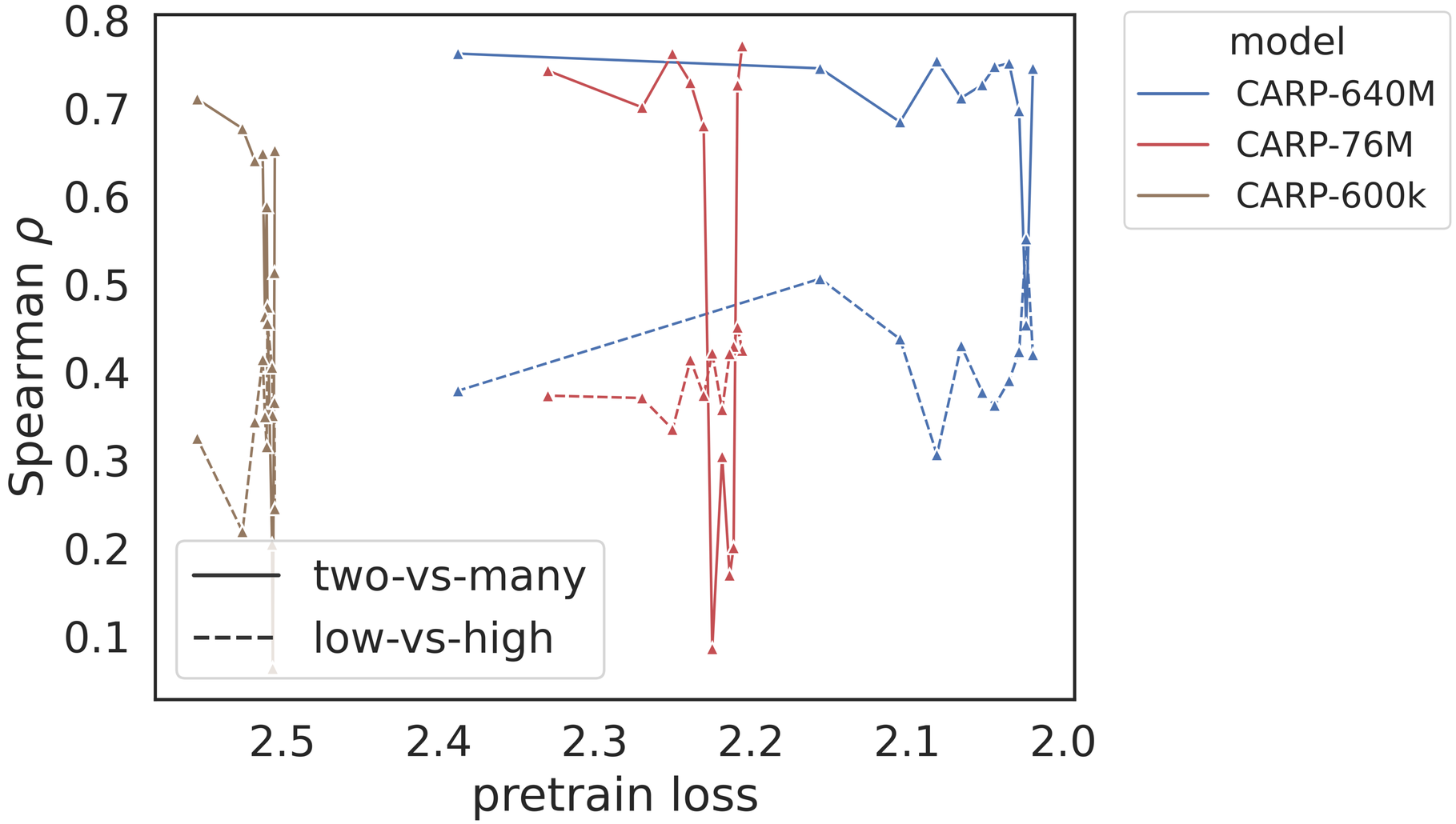
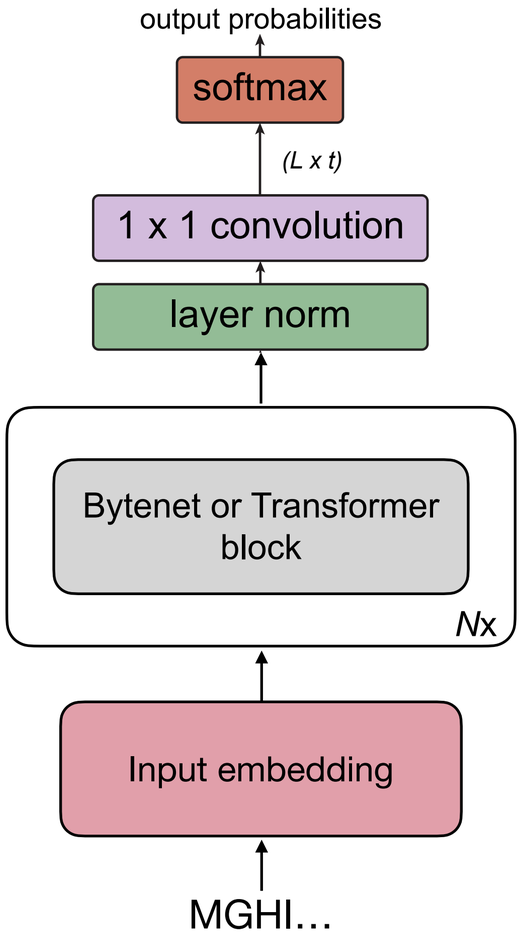


OOD performance does not improve with more pretraining



Not all layers are necessary for transfer



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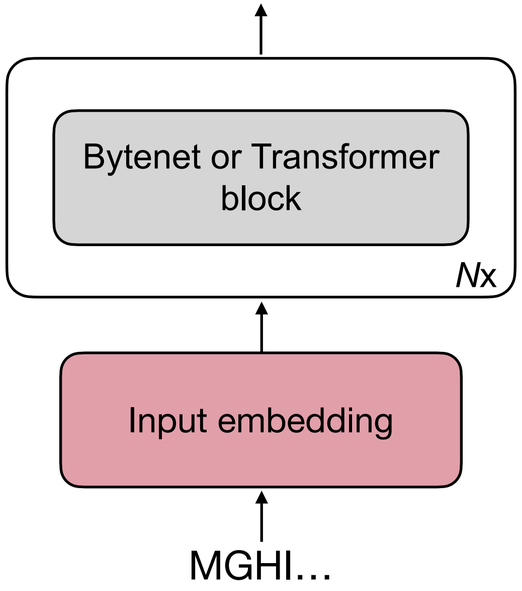

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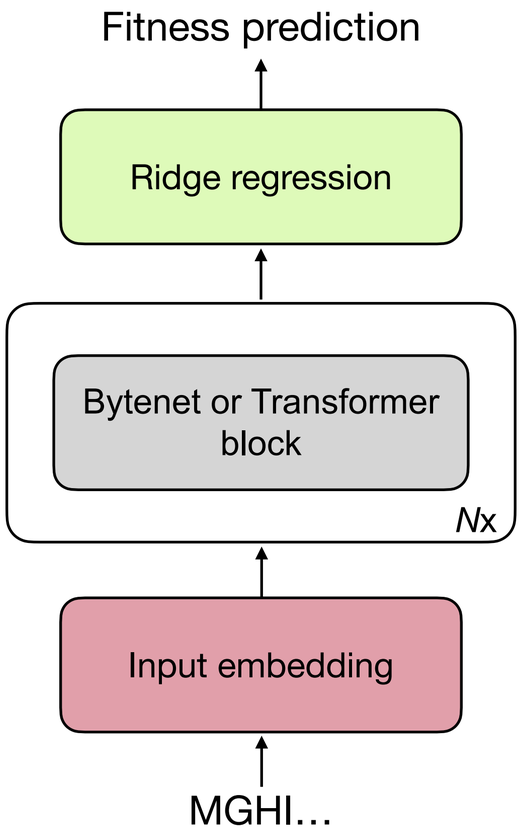

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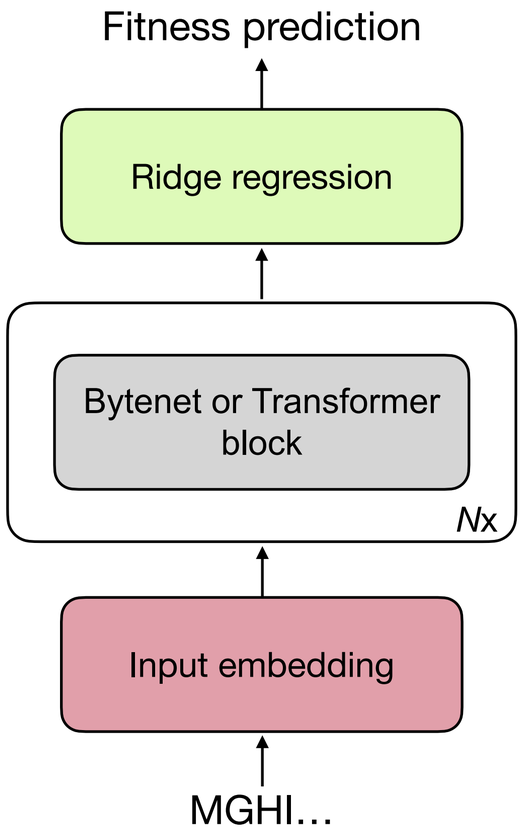

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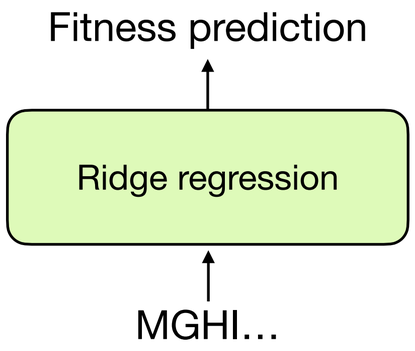

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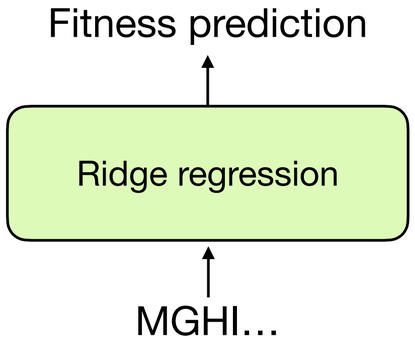

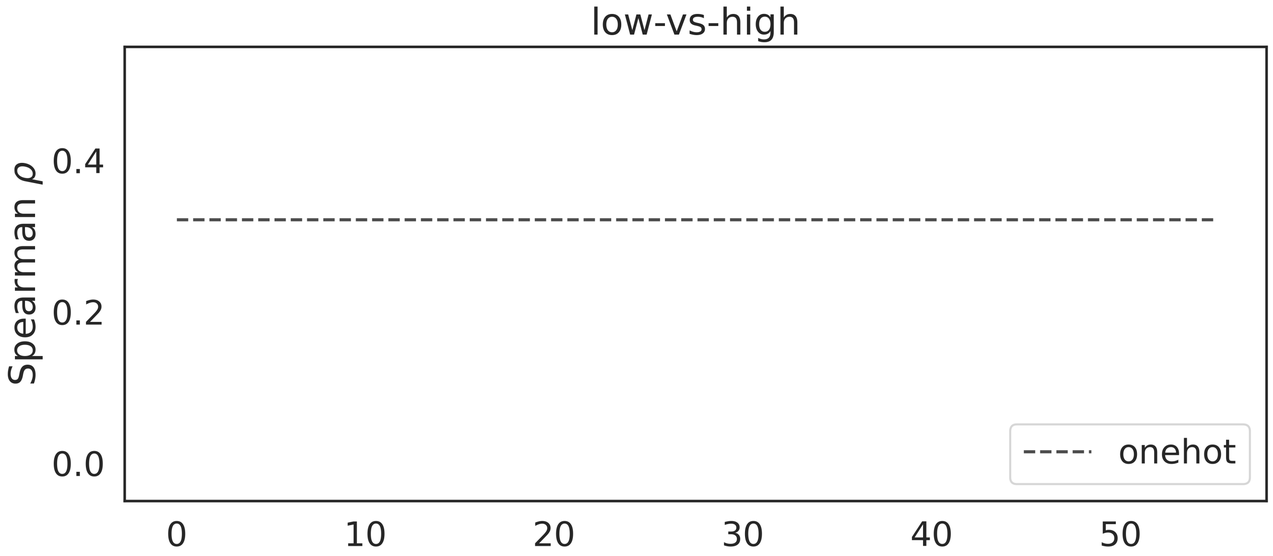

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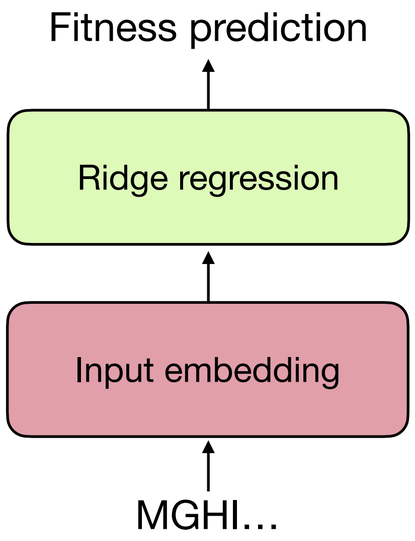

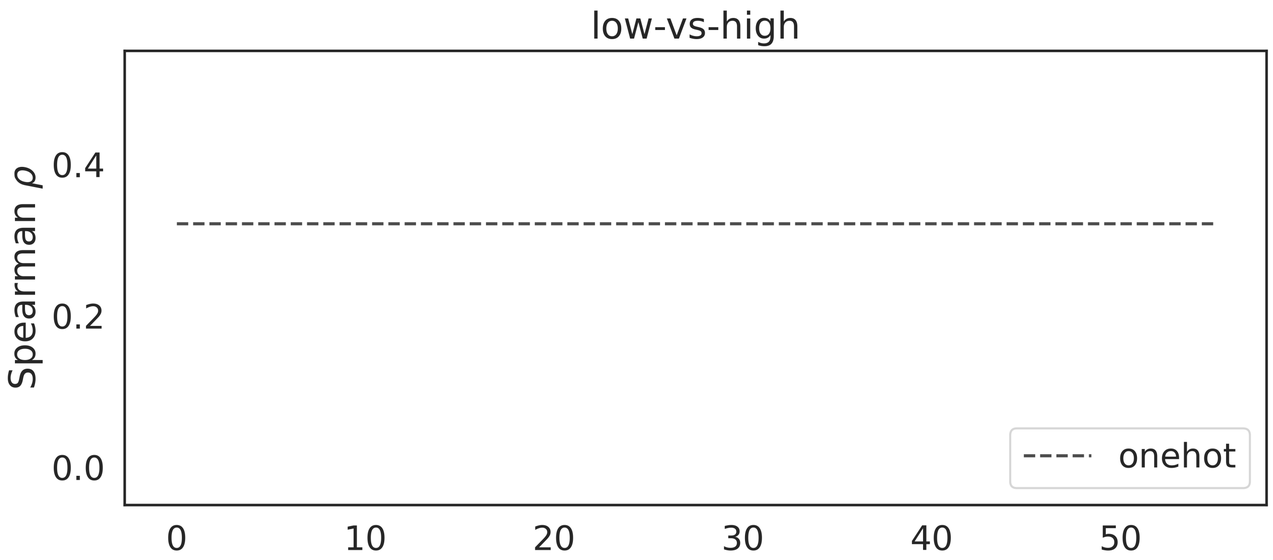

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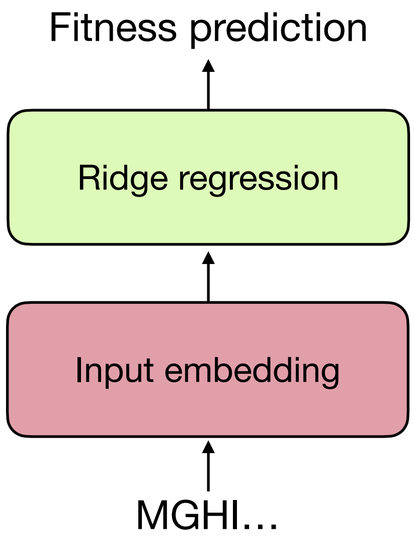

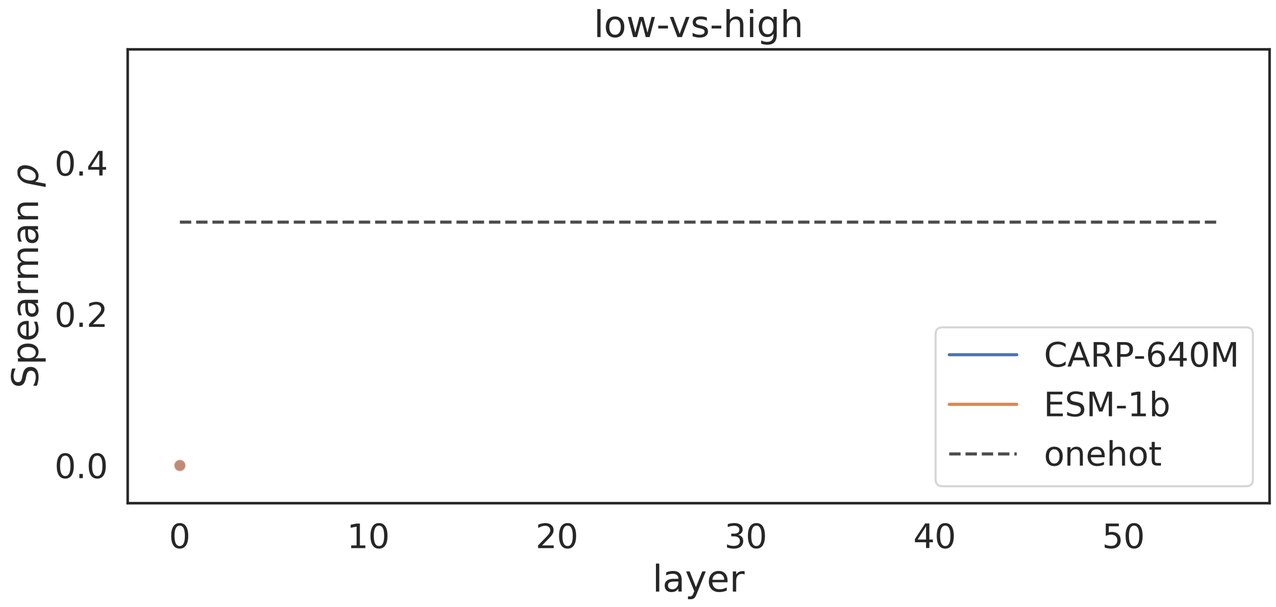

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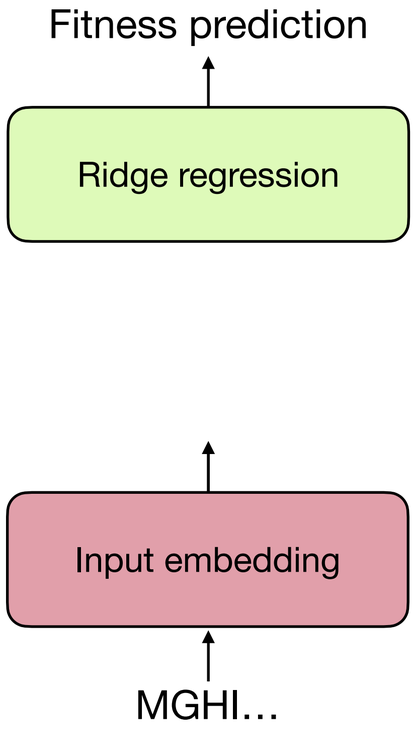

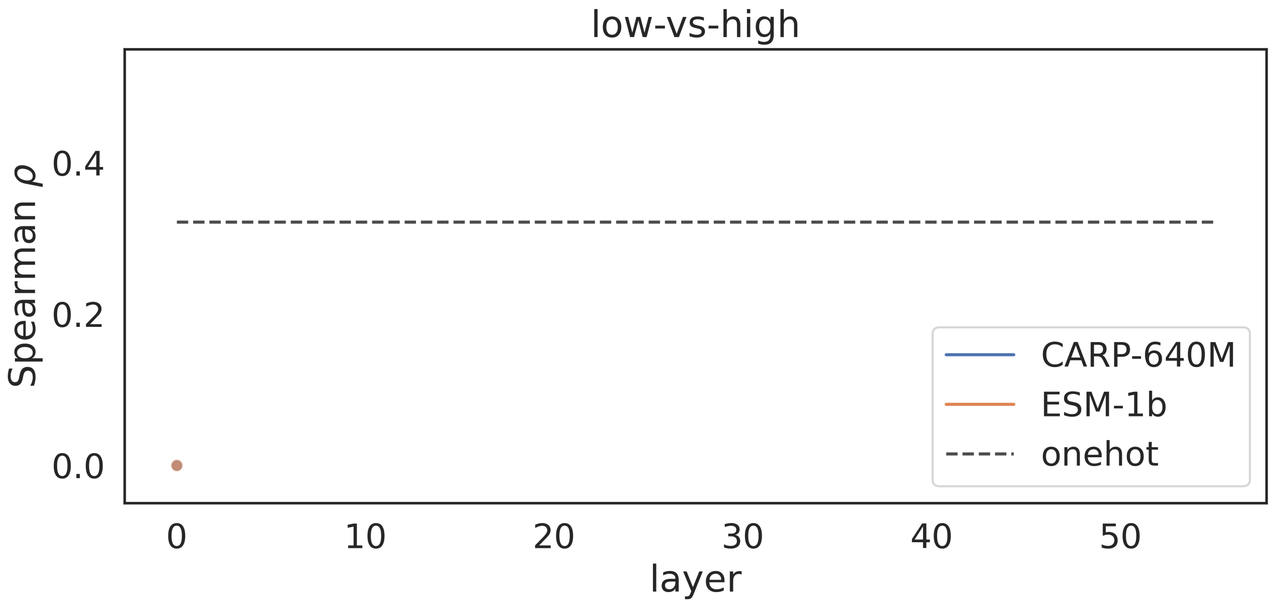

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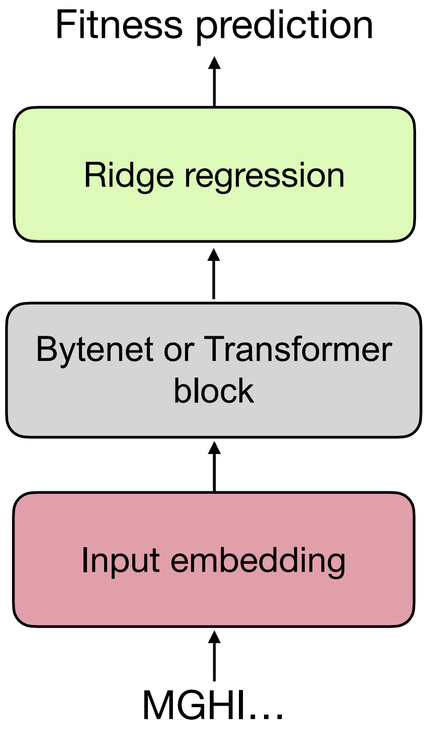

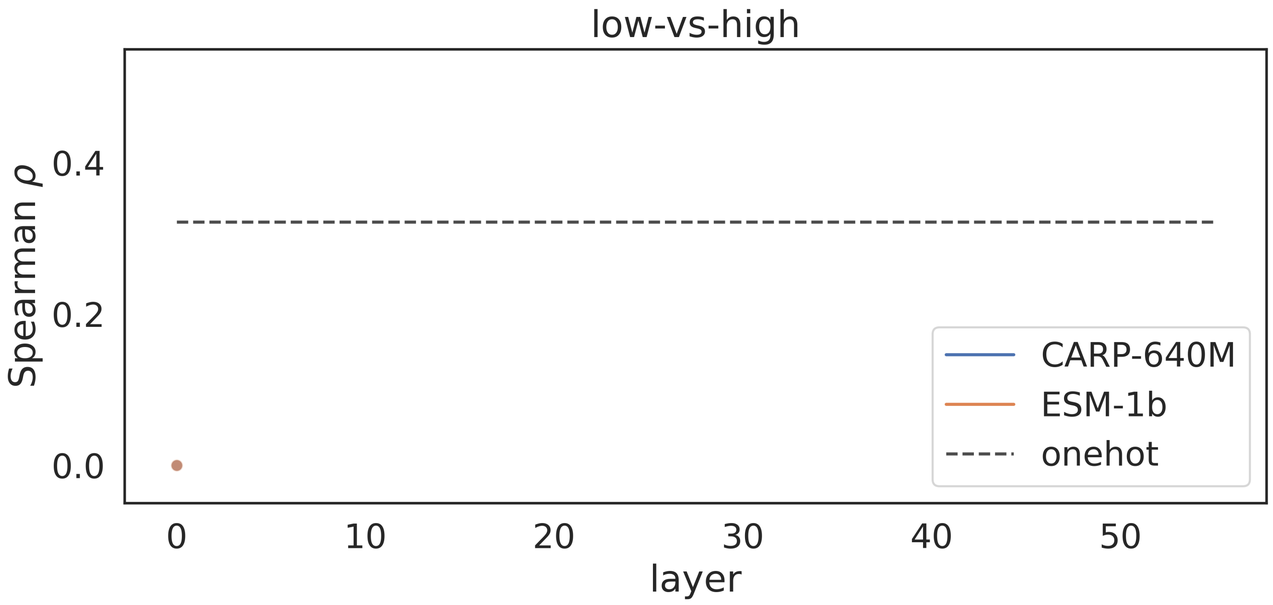

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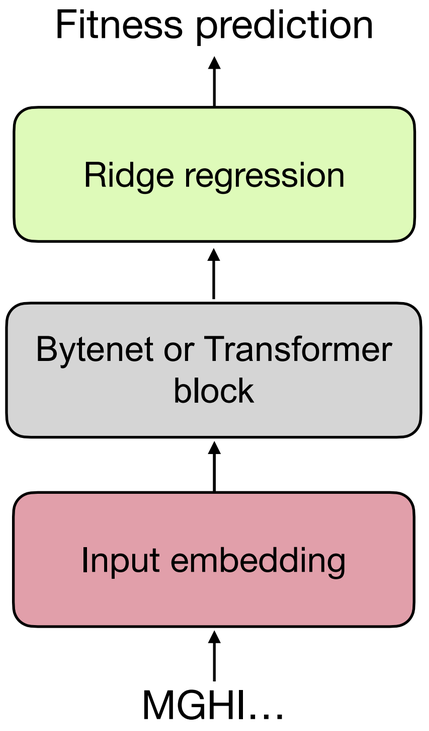

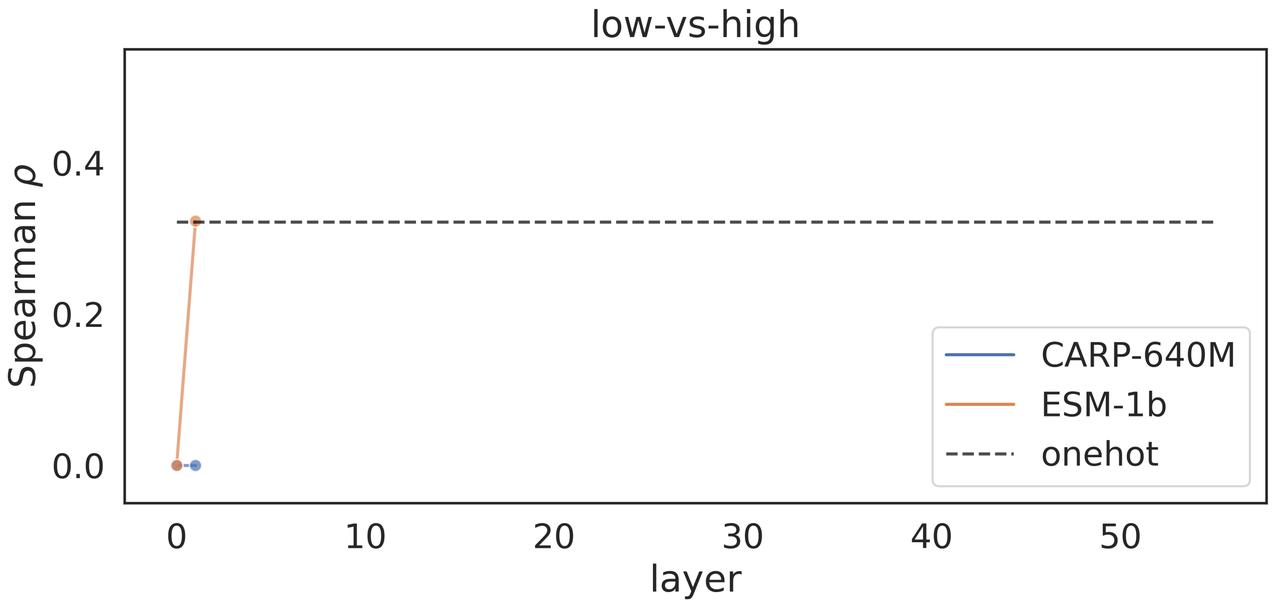

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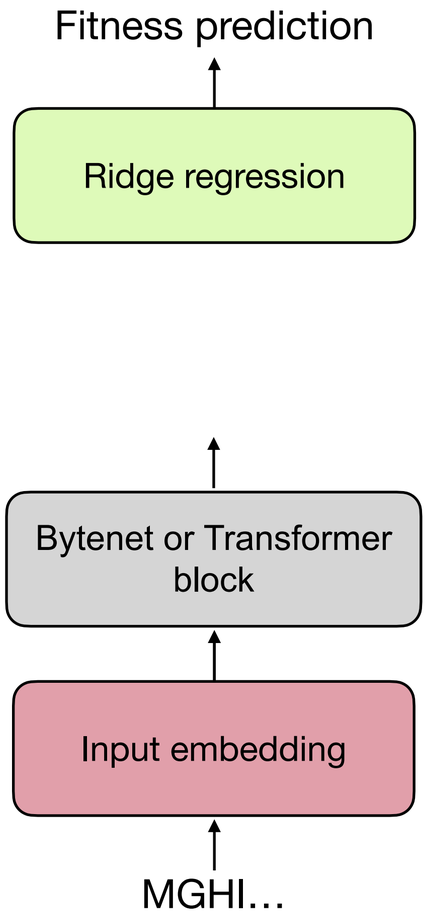

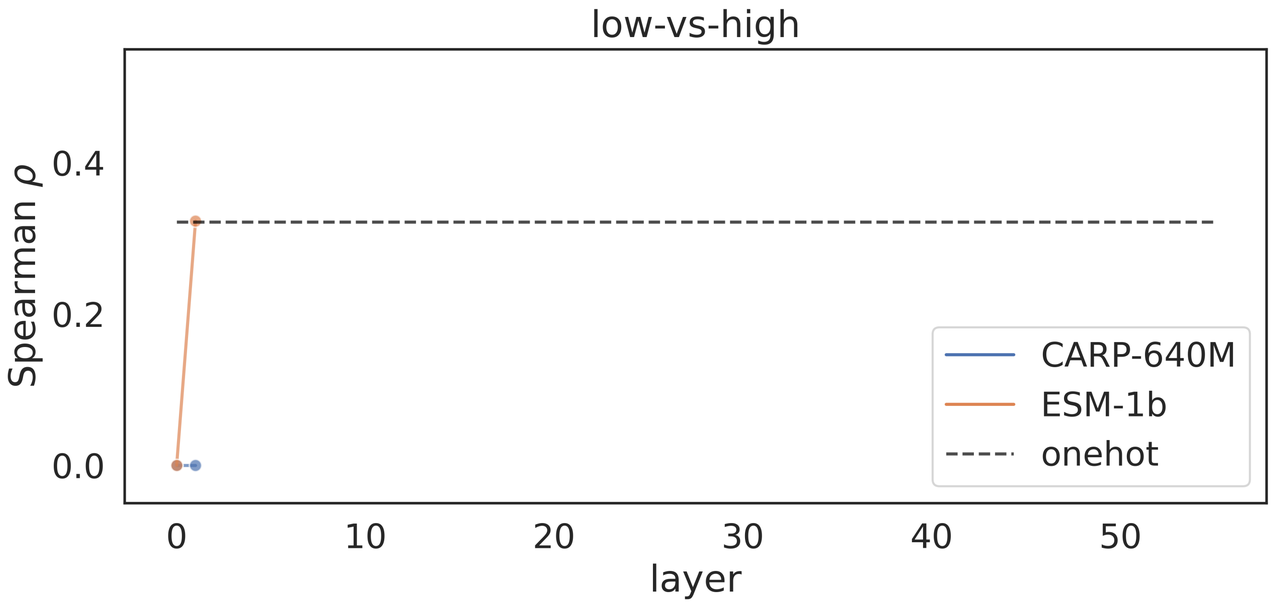

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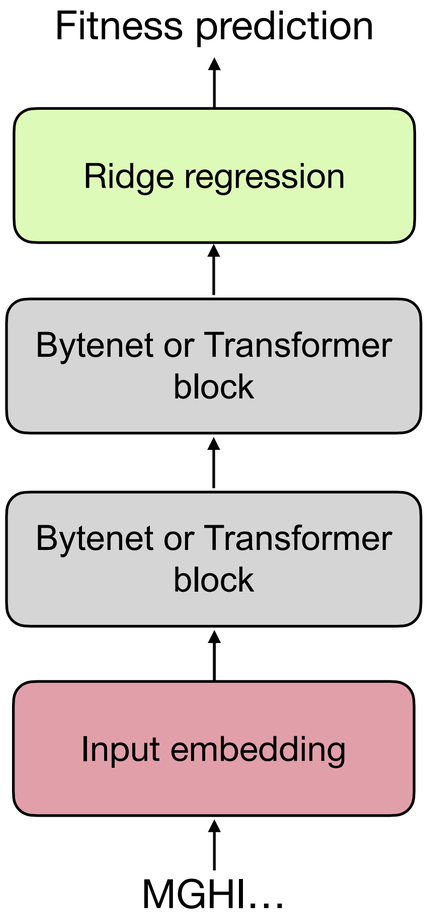

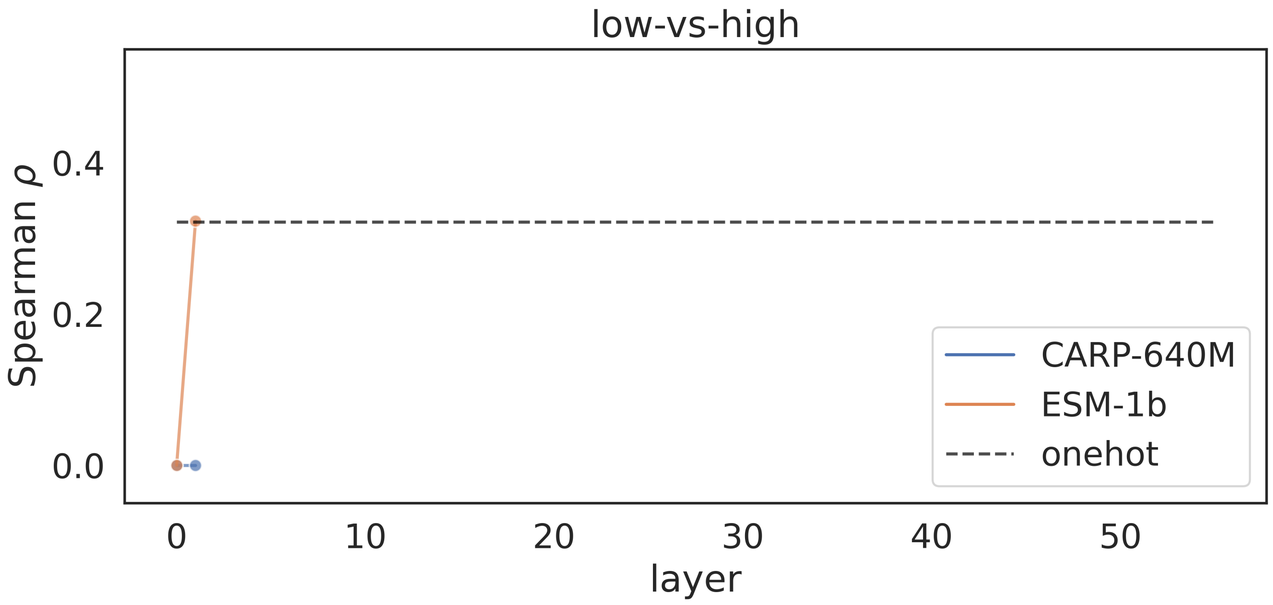

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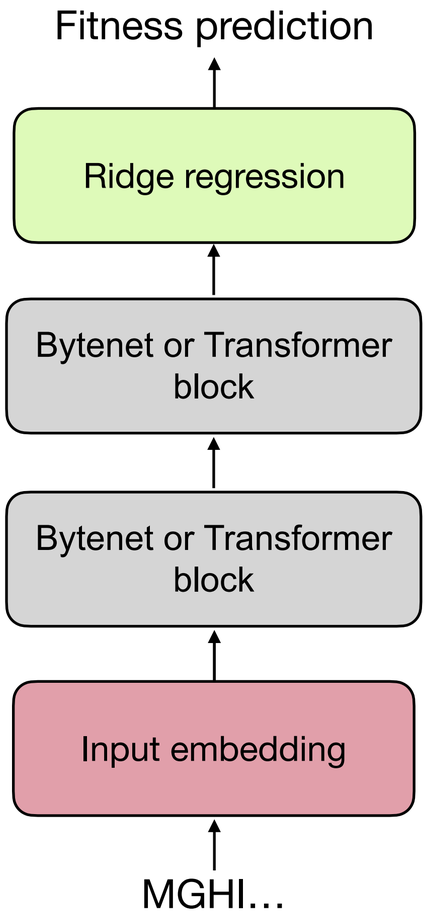

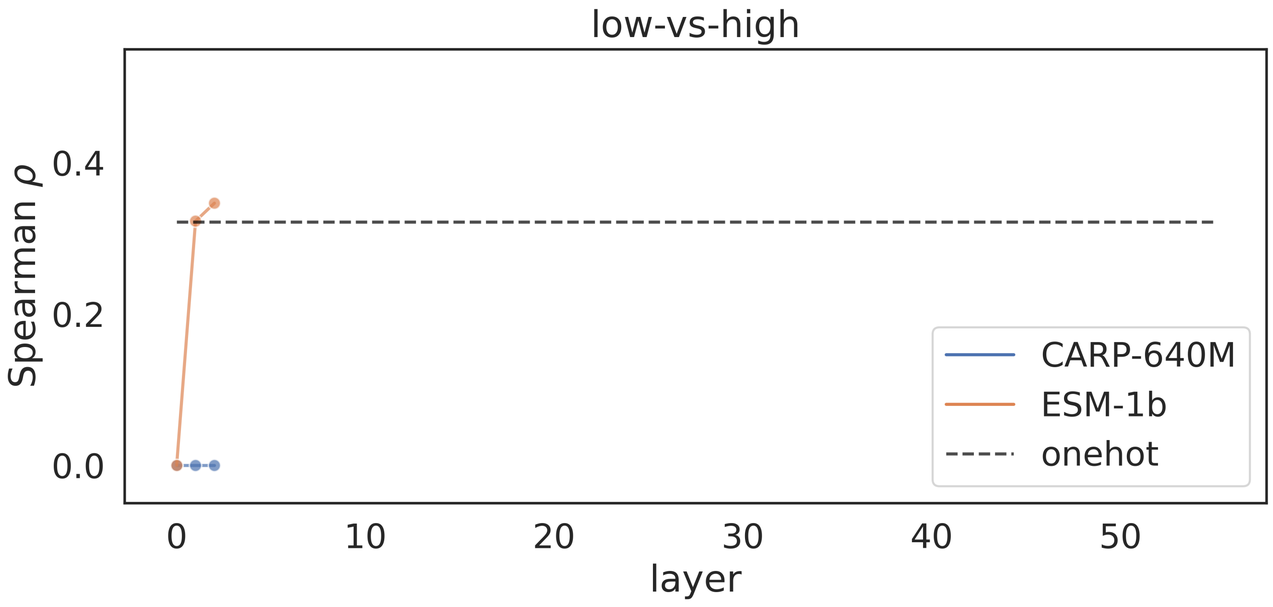

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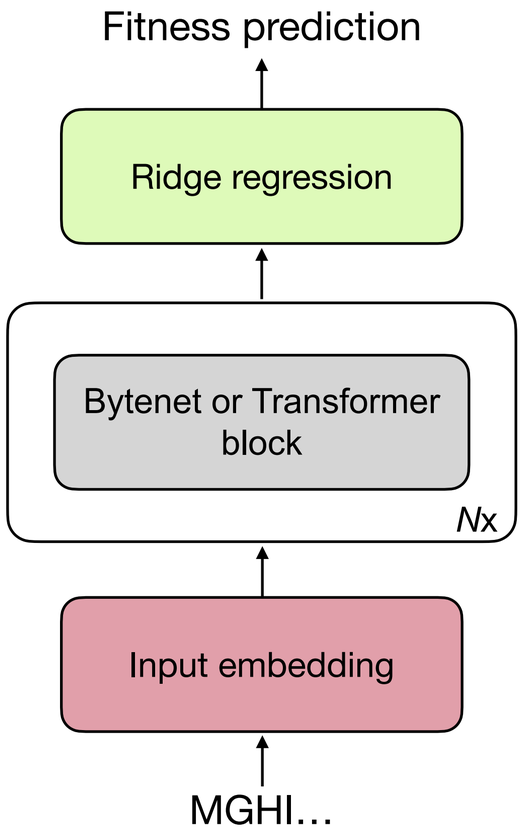

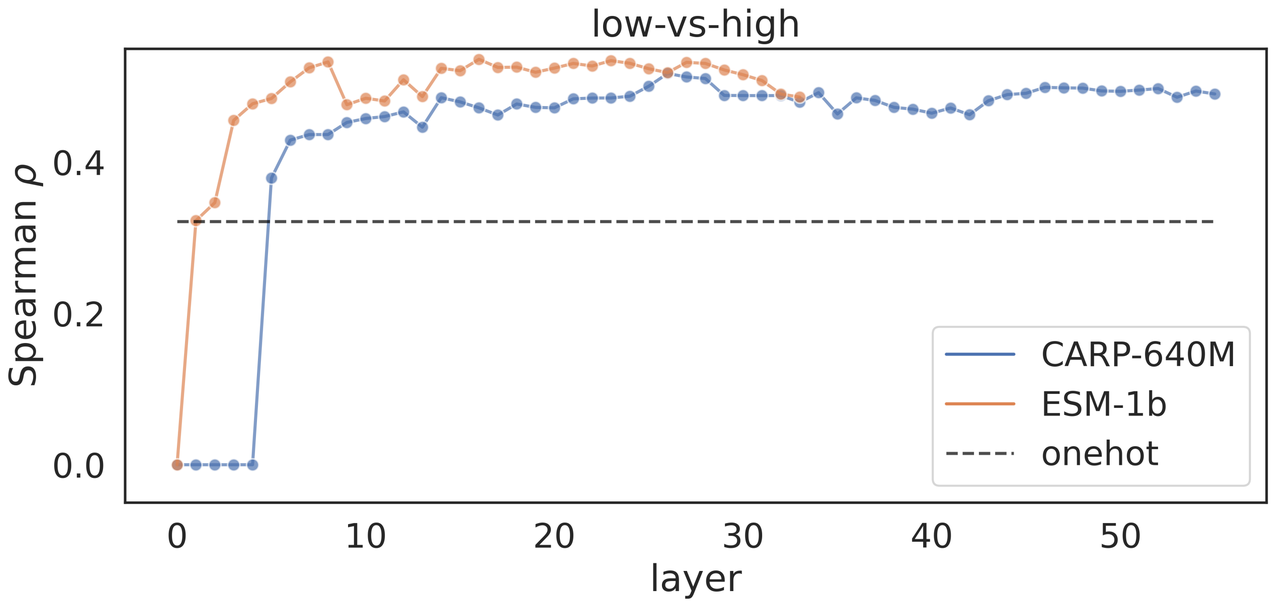

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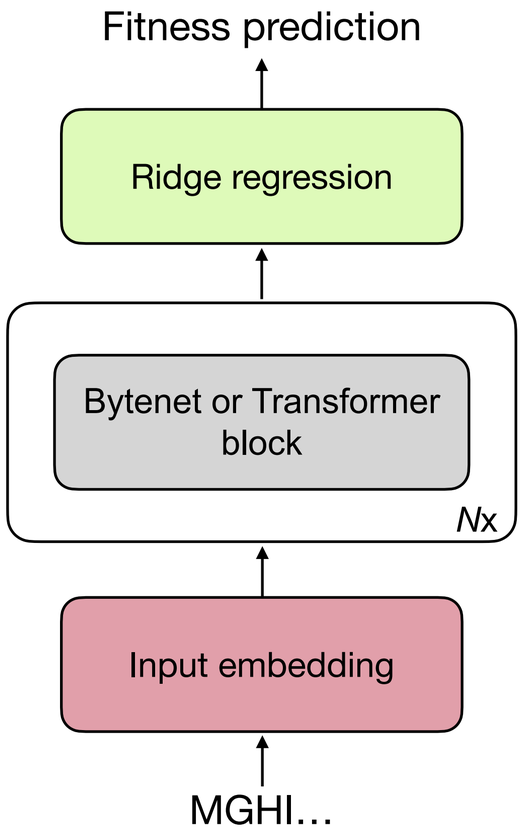
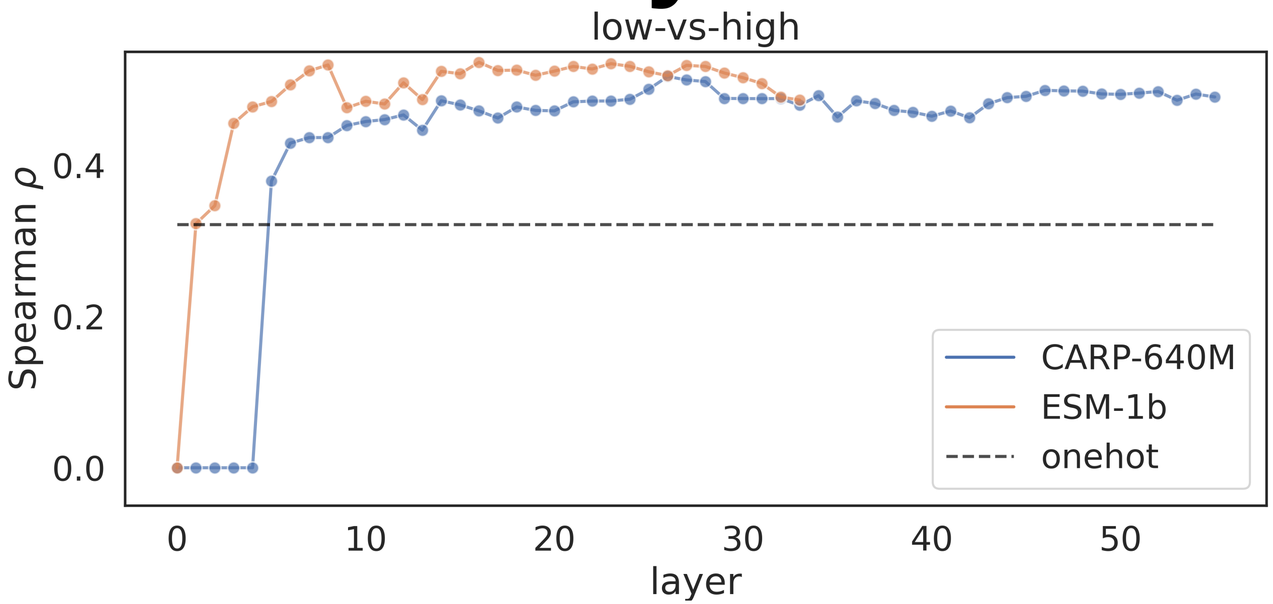
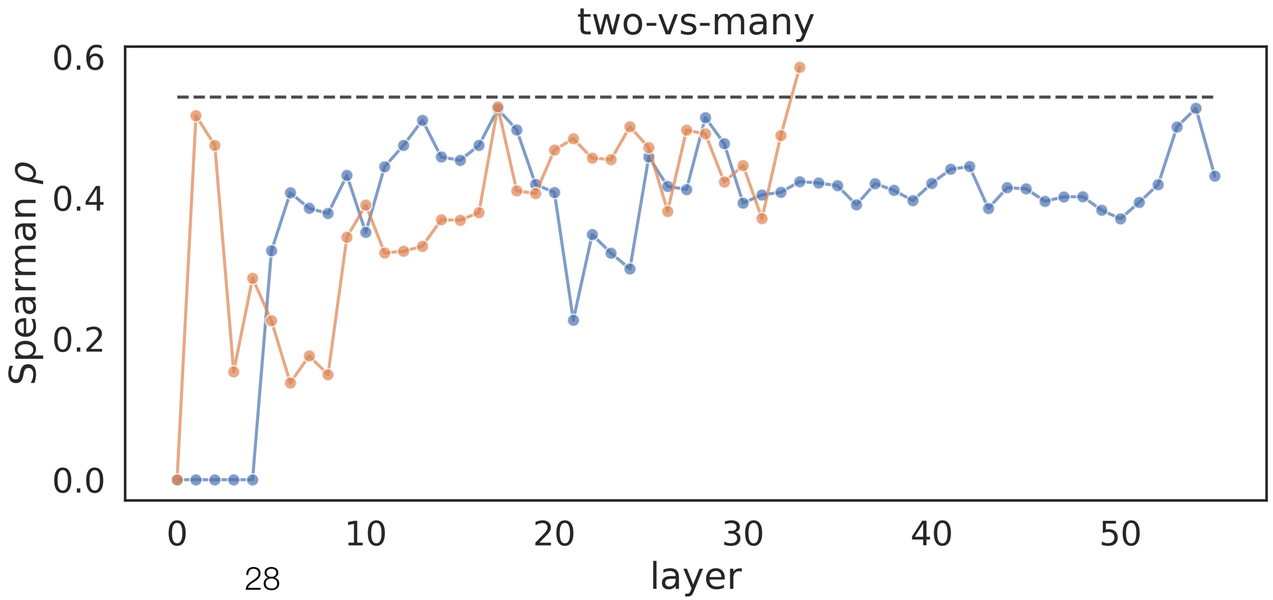
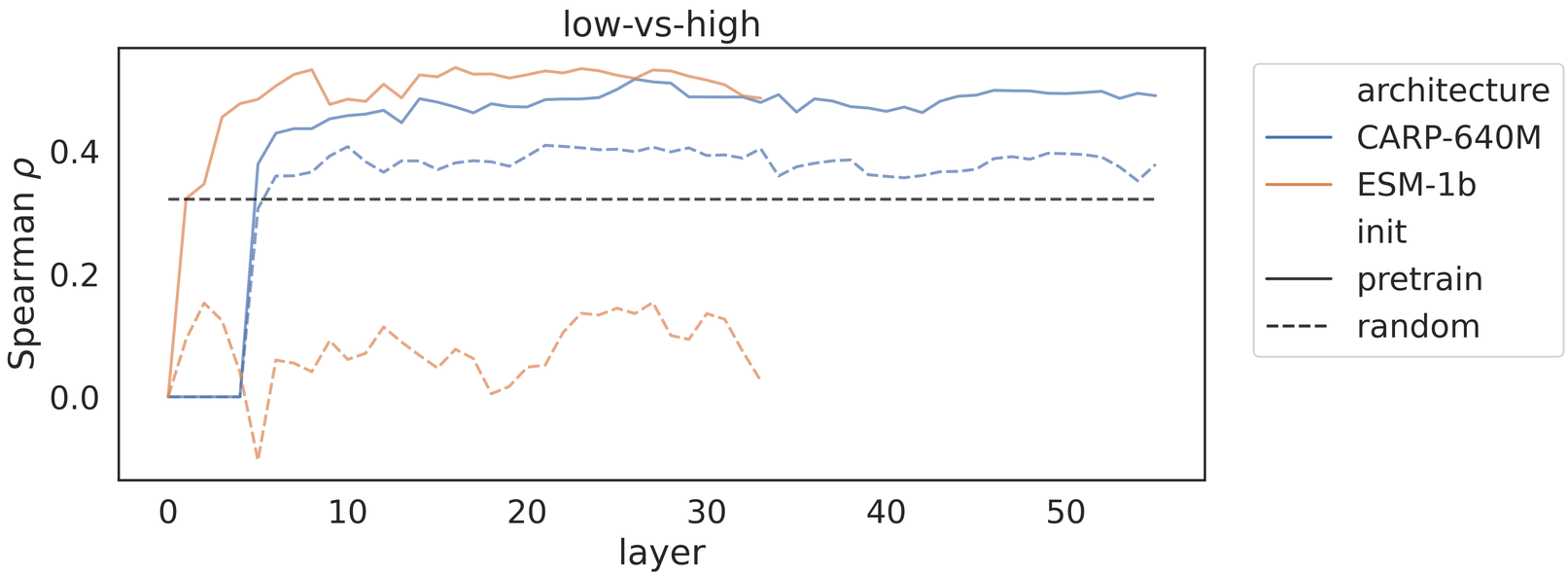






Pretraining helps beyond the architecture



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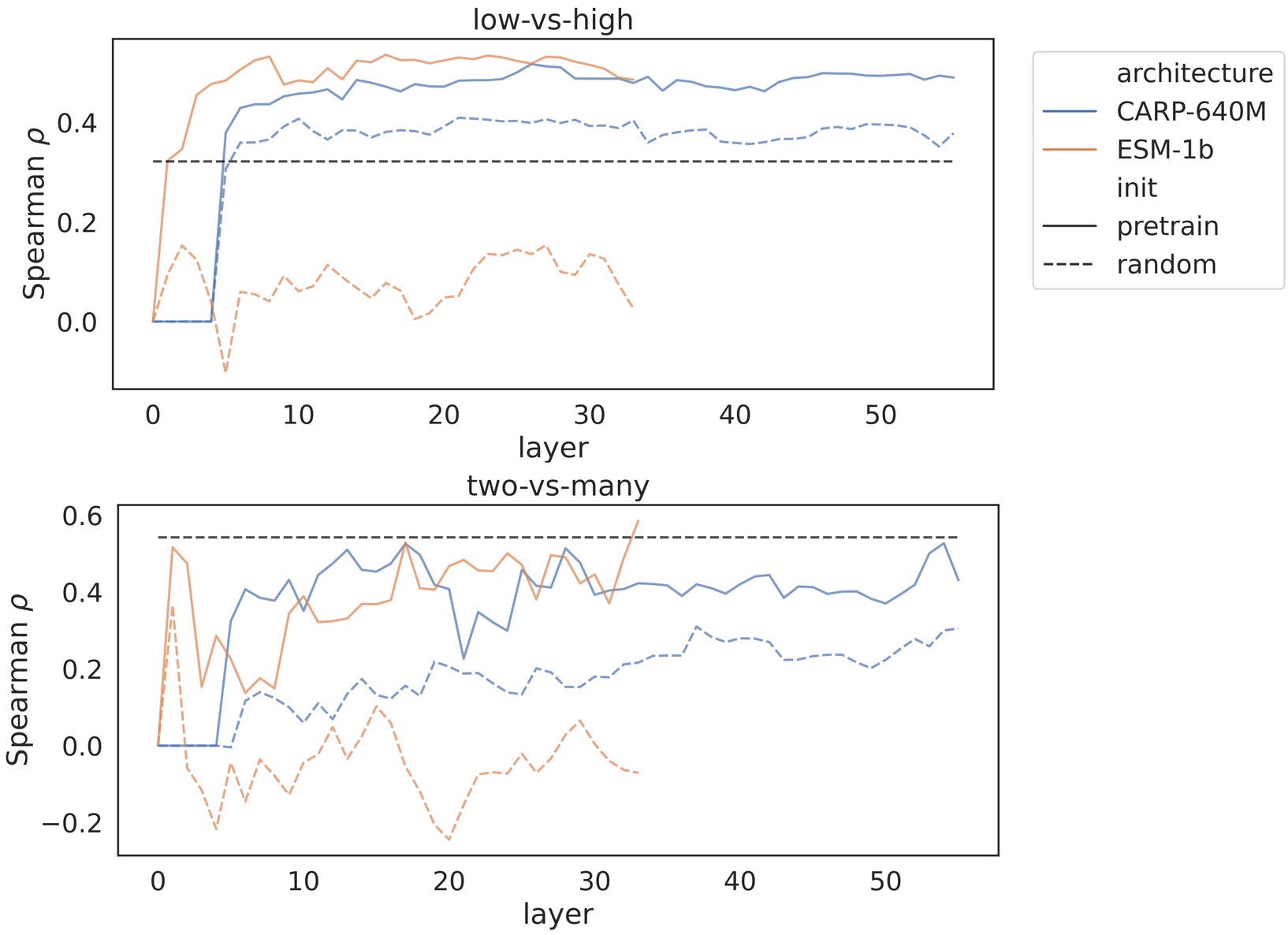
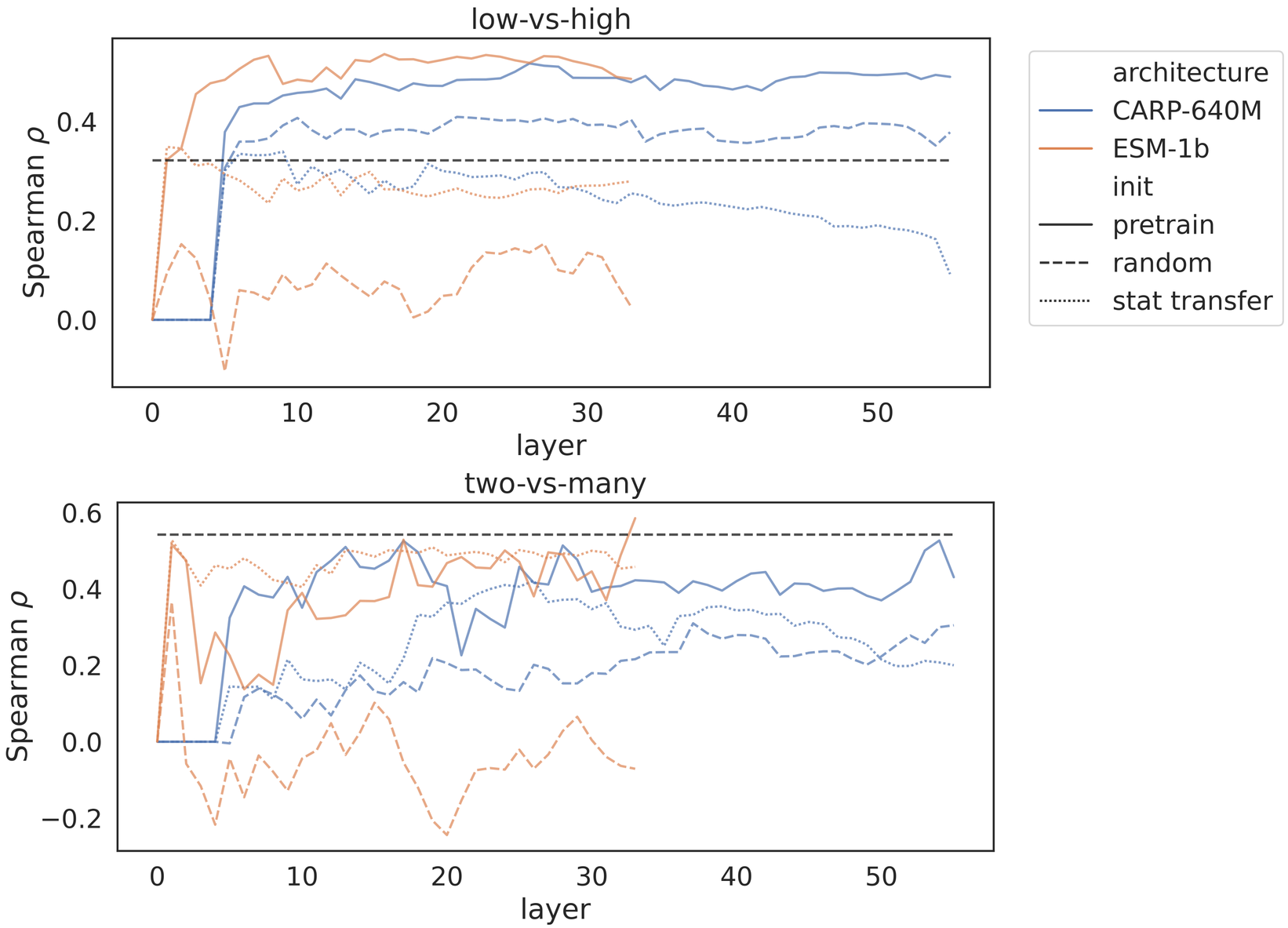
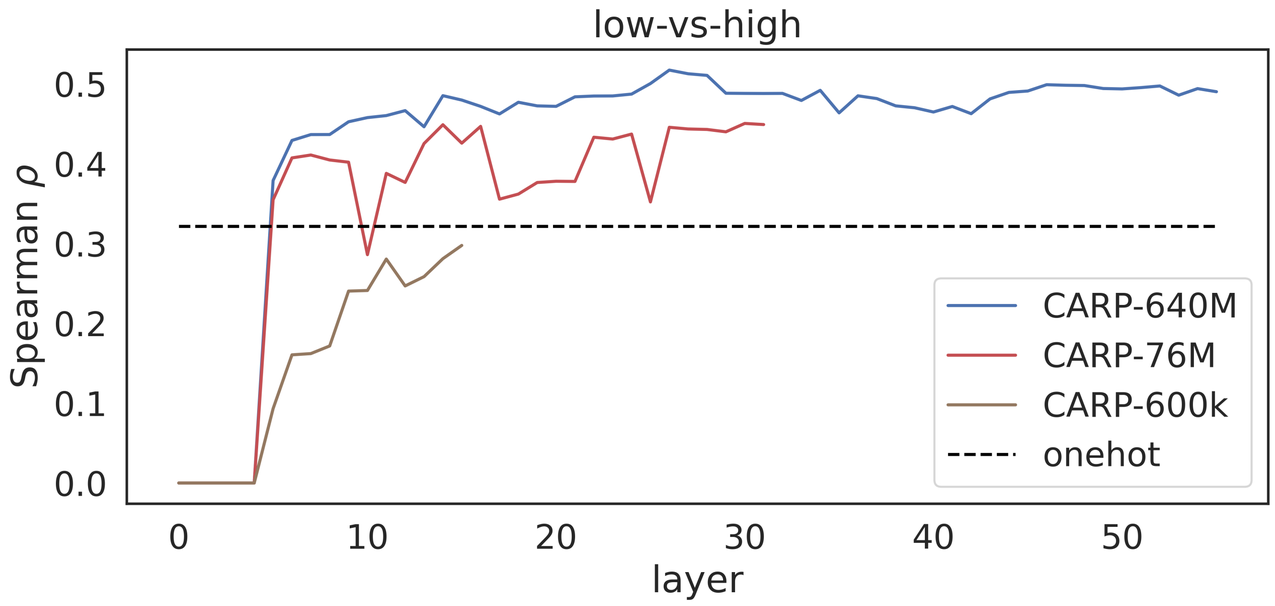


Sometimes, shuffled weights work too



Bigger models do not always help



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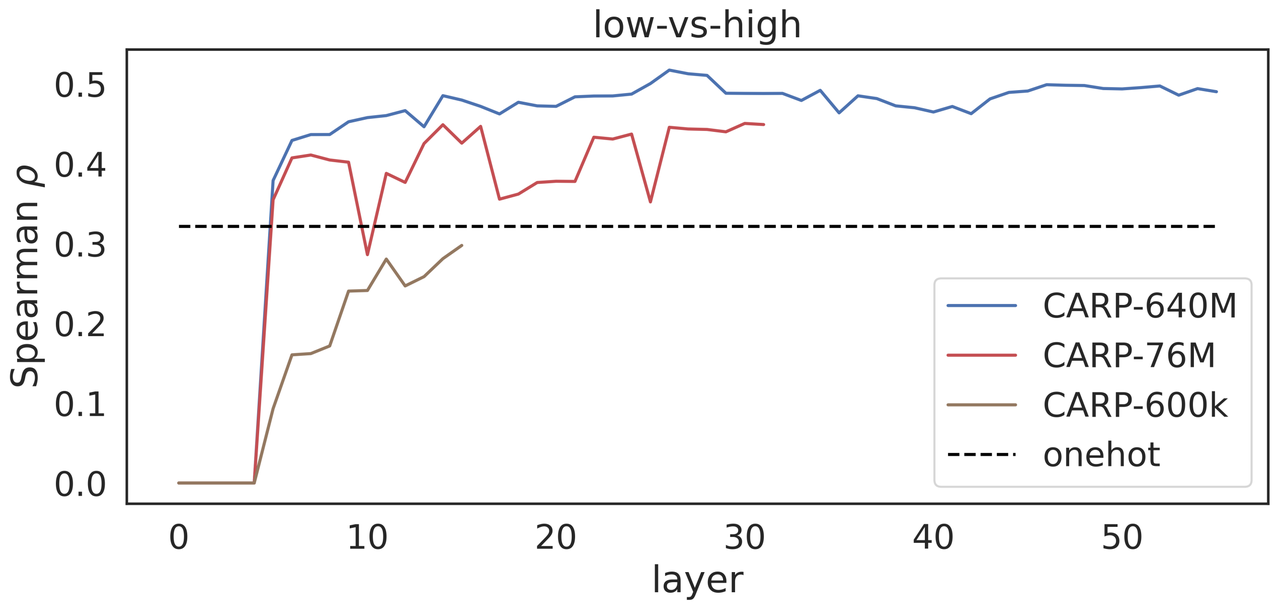
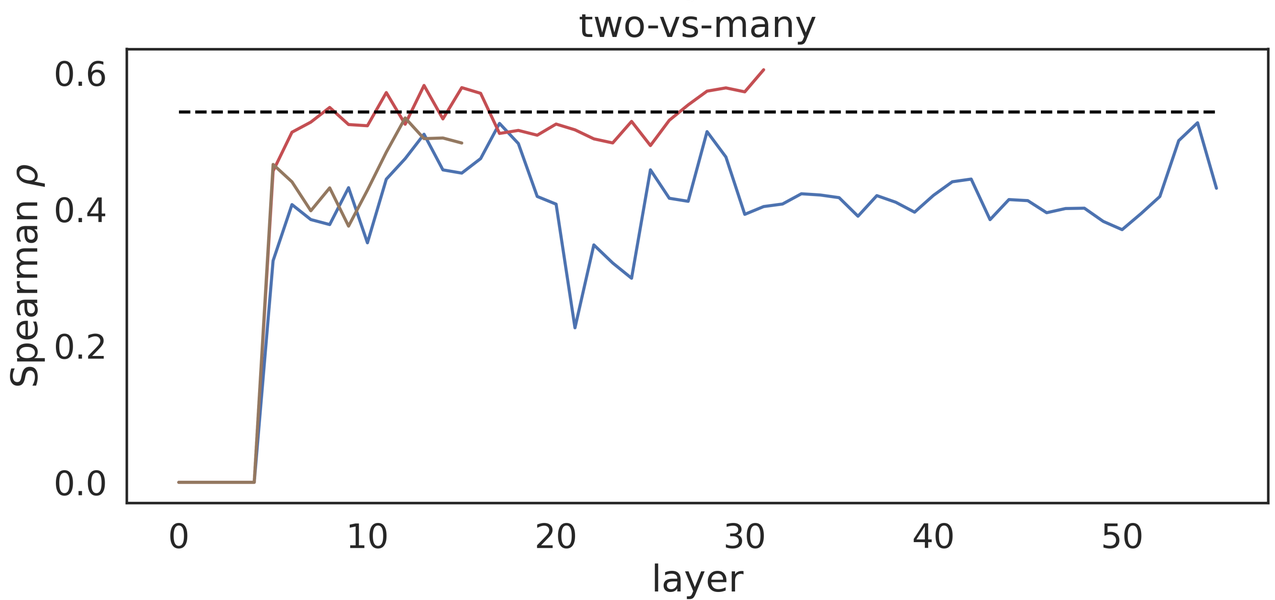
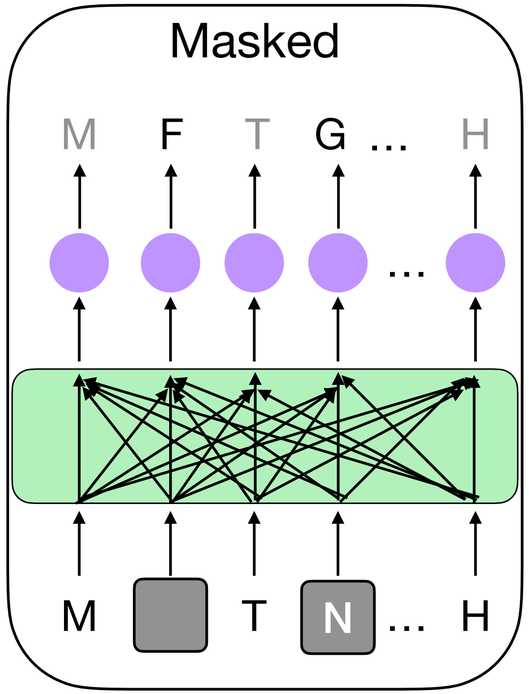
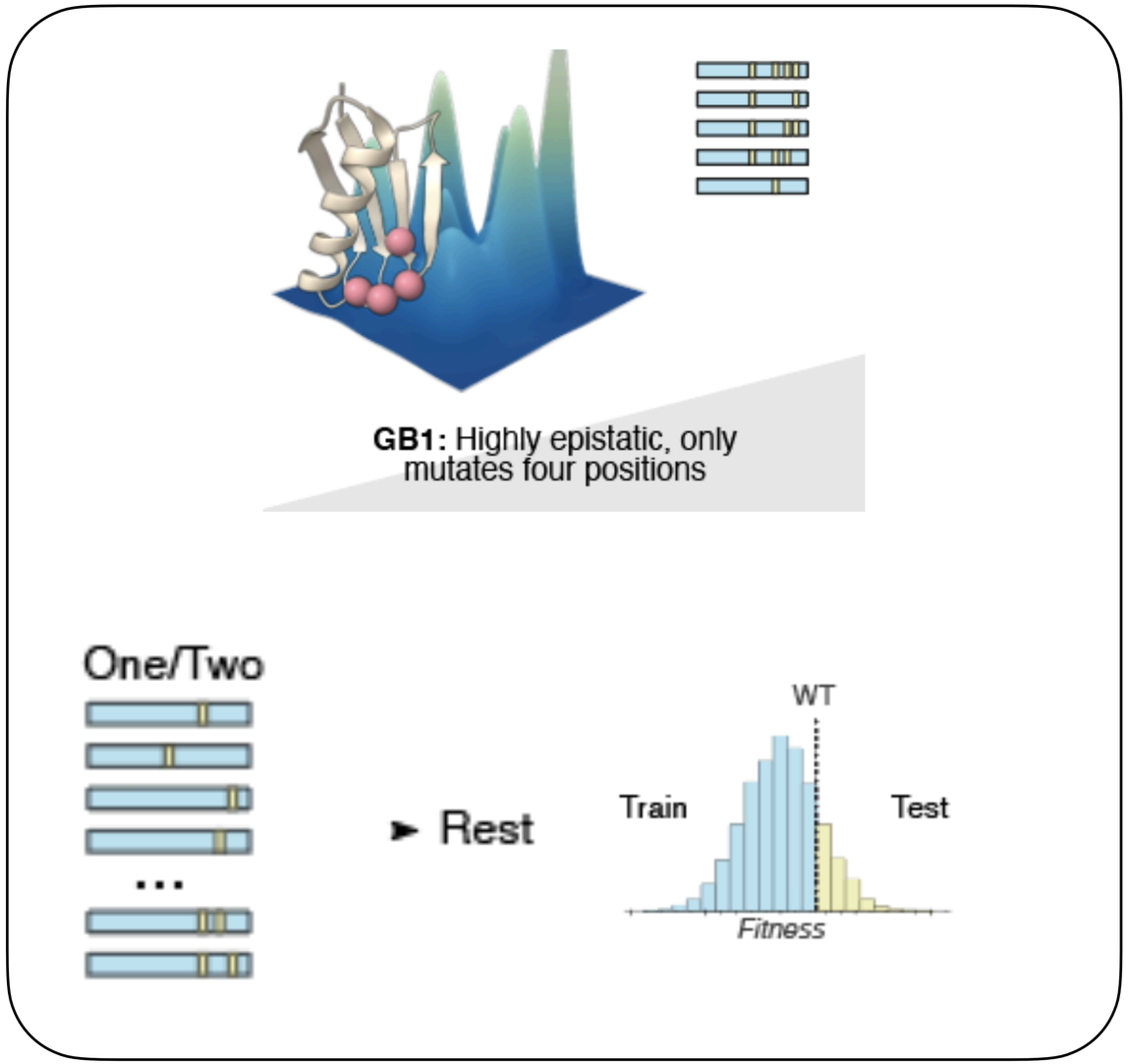


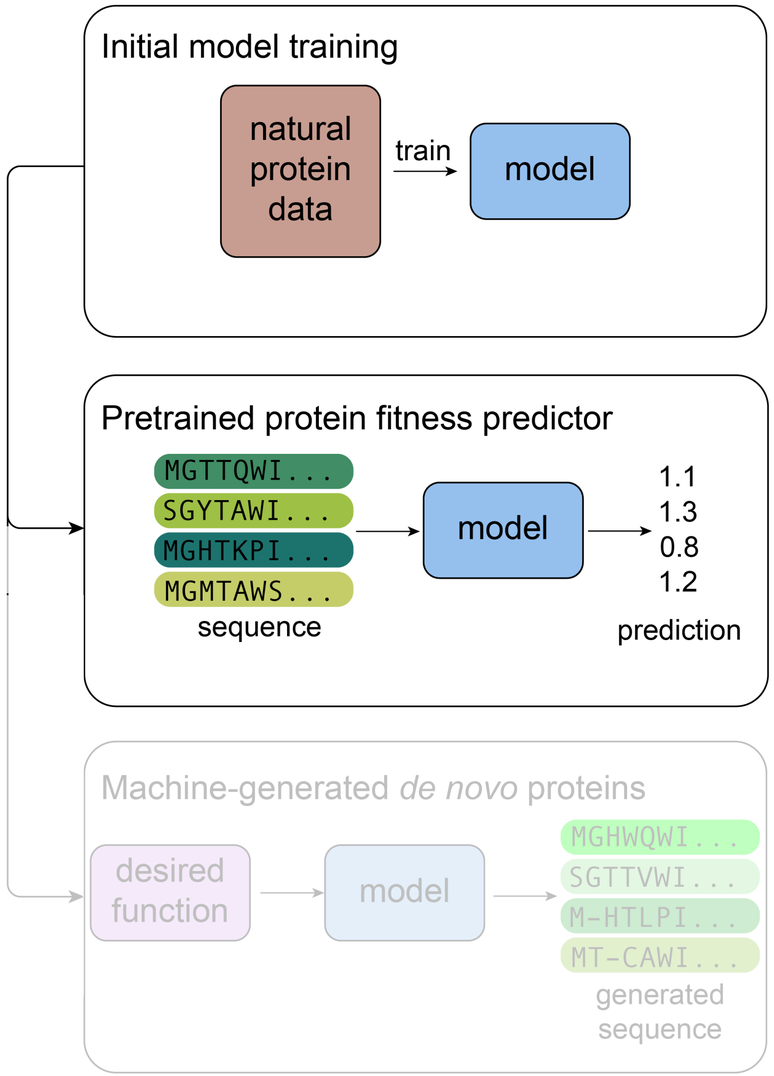


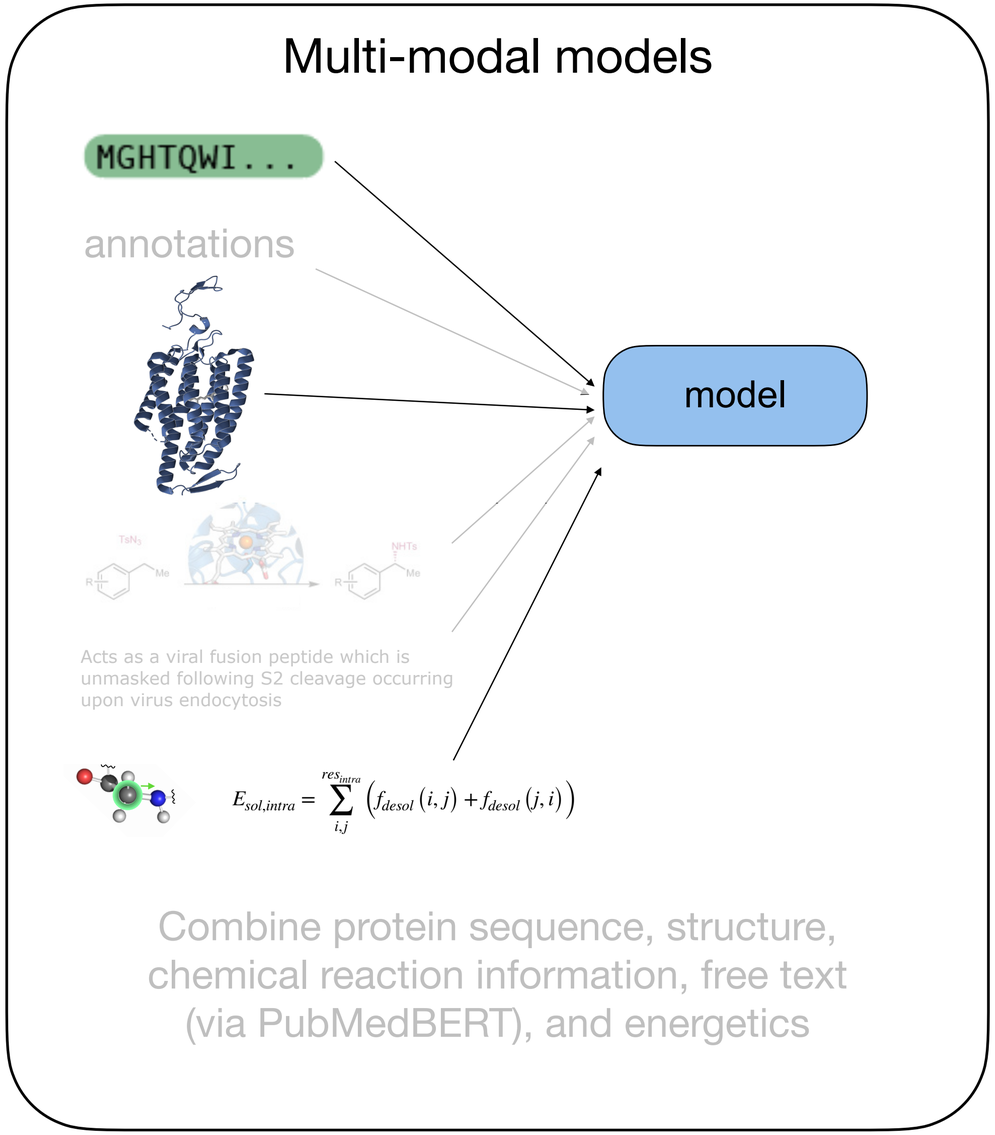
Pretrain and downstream tasks are mismatched





Use energetic features as inputs





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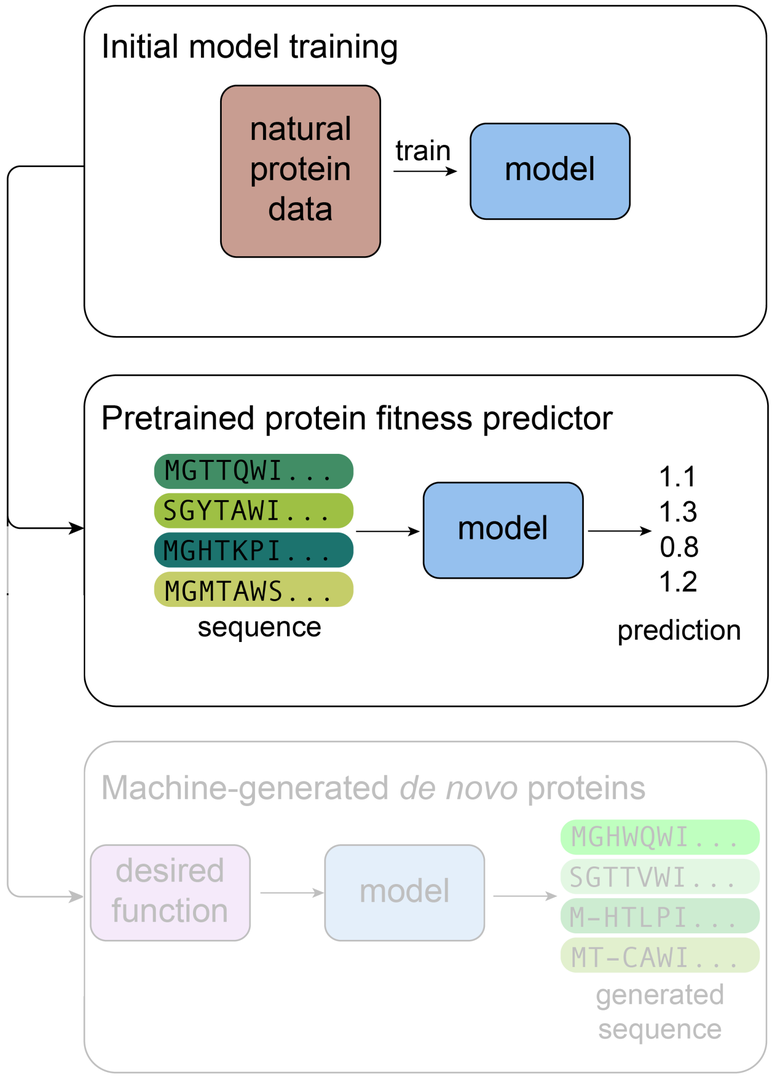

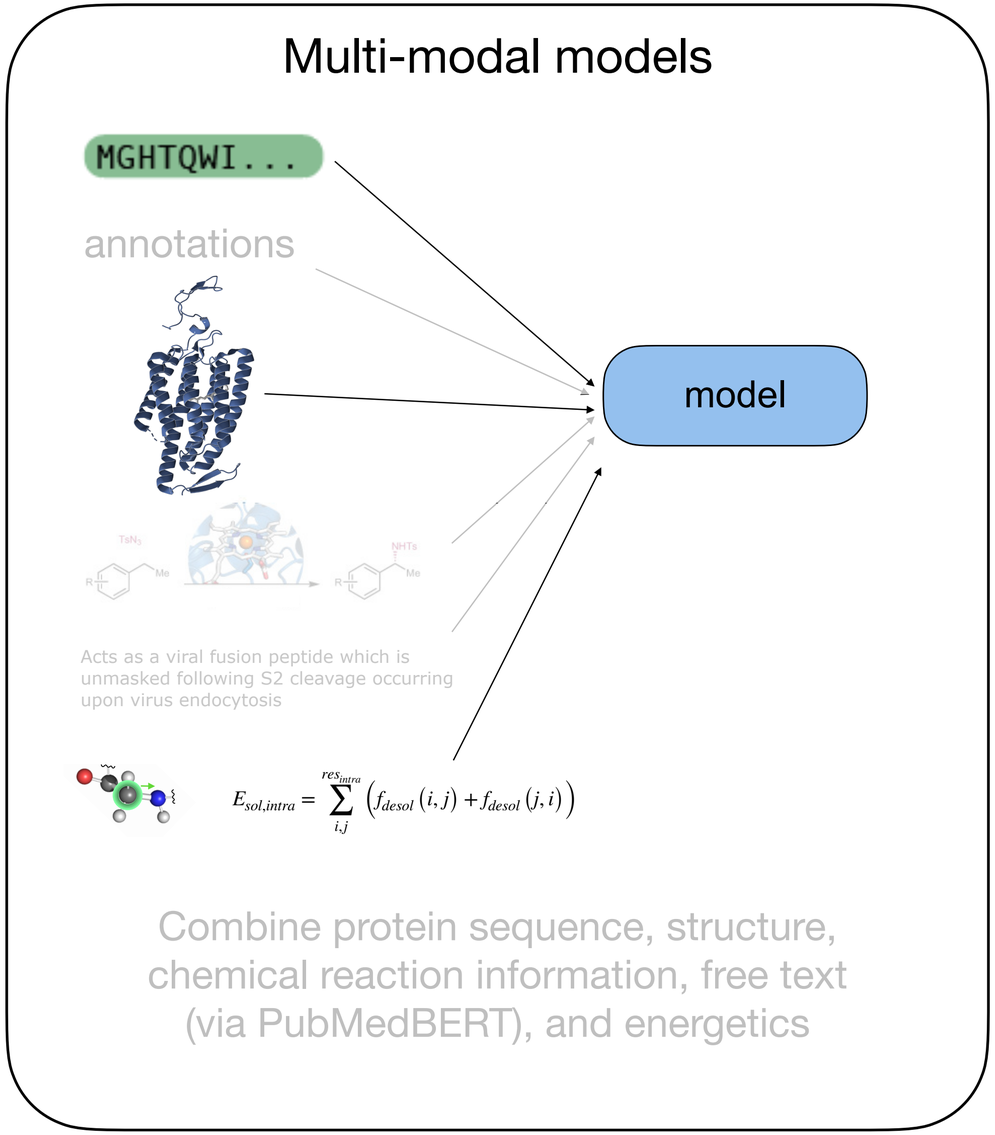

Use precomputed physics-based energies as input features

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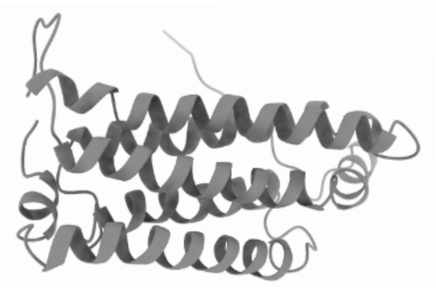
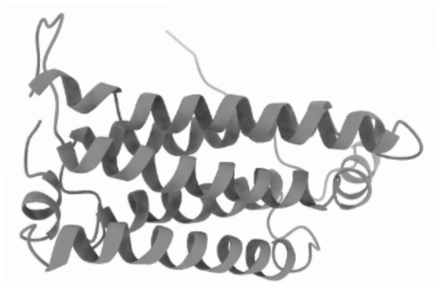
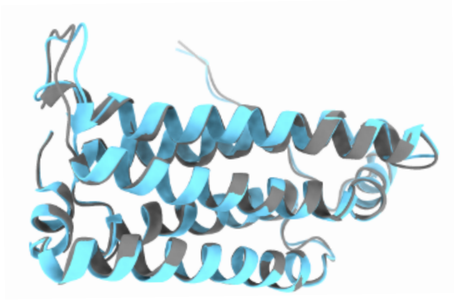


Reference protein

Use precomputed physics-based energies as input features



Reference protein



Protein variant: L10E

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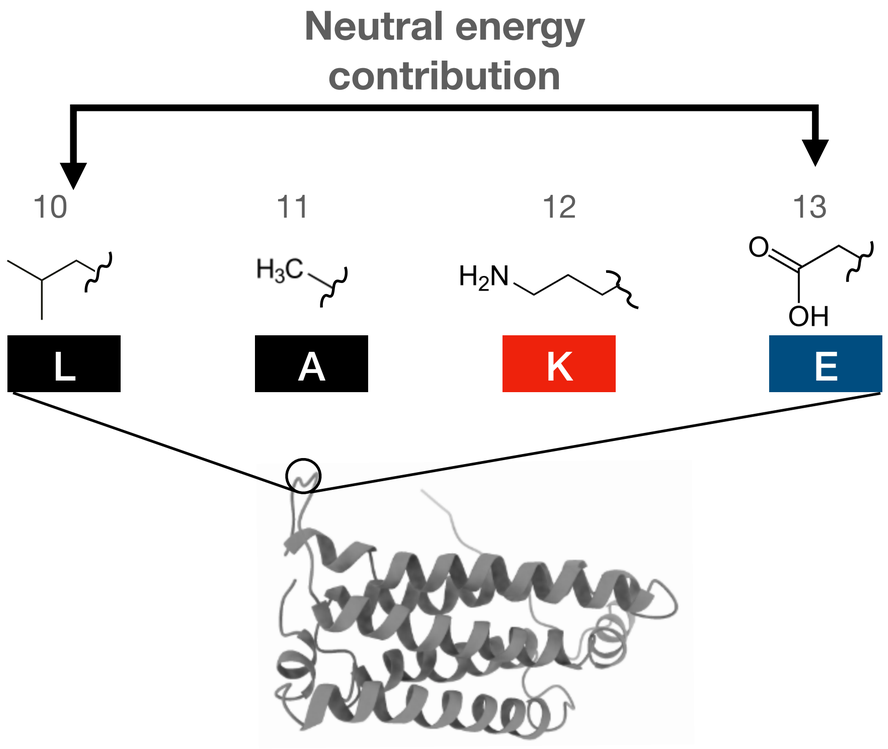

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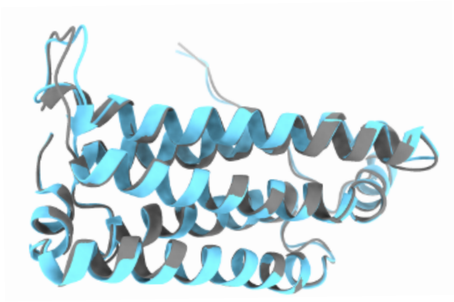

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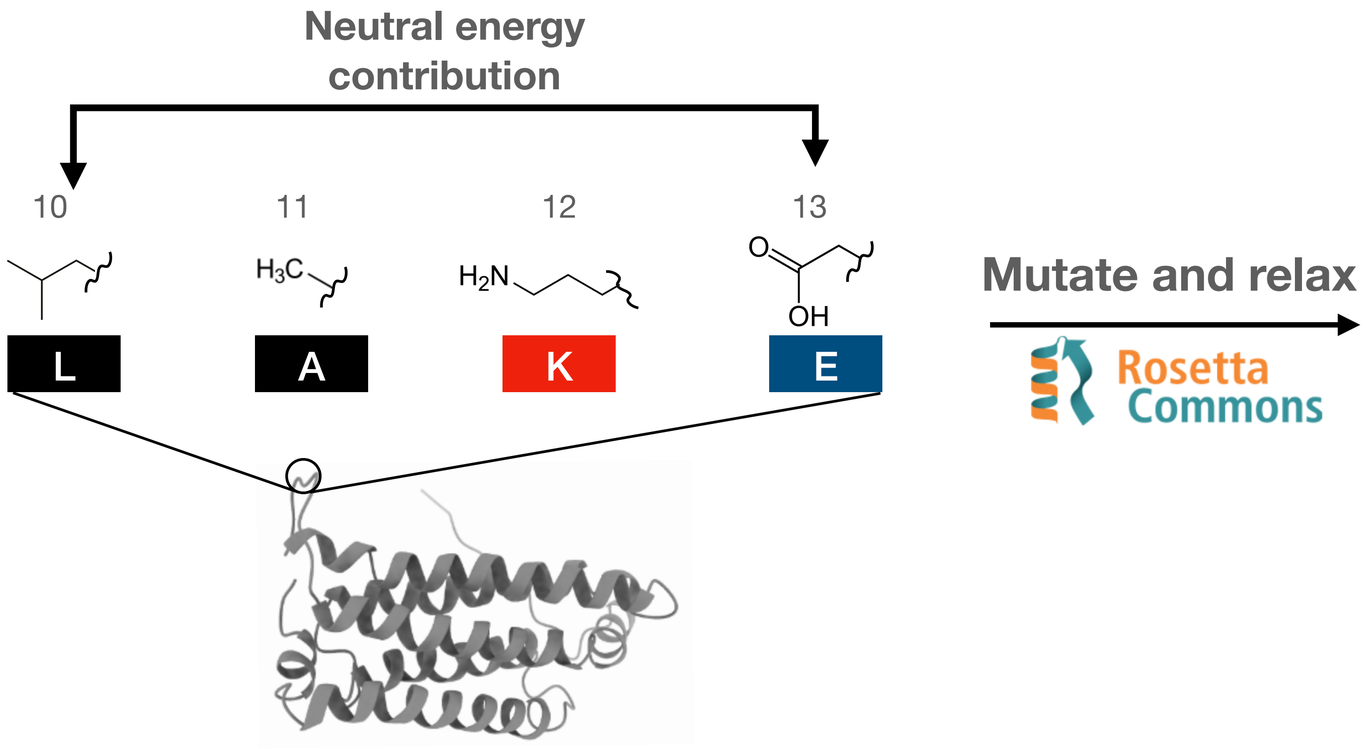

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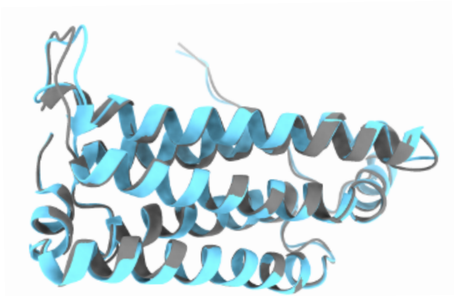

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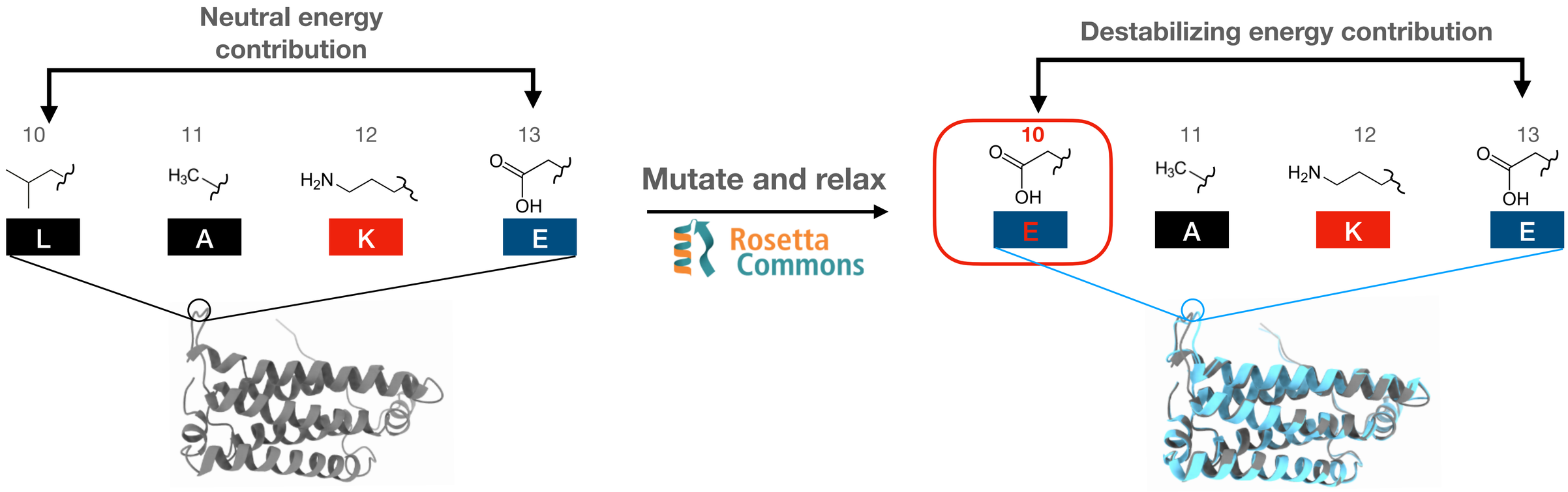
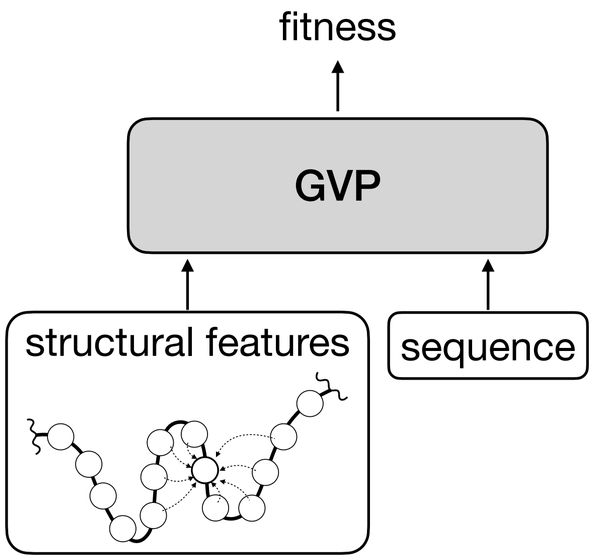


Reference protein

Protein variant: L10E

Energetics features improve performance in low-data regimes



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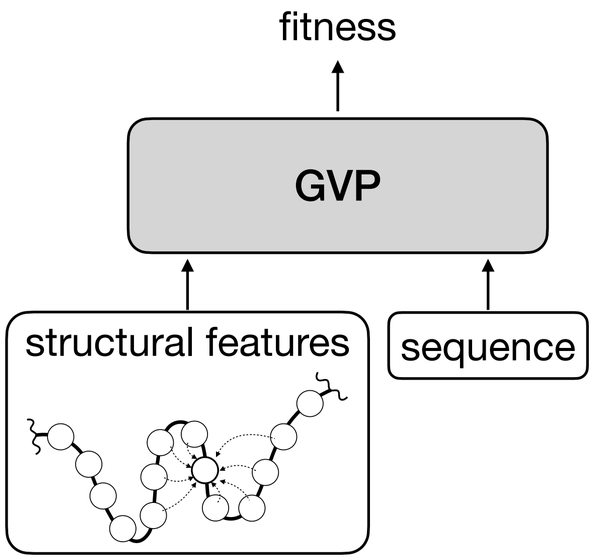

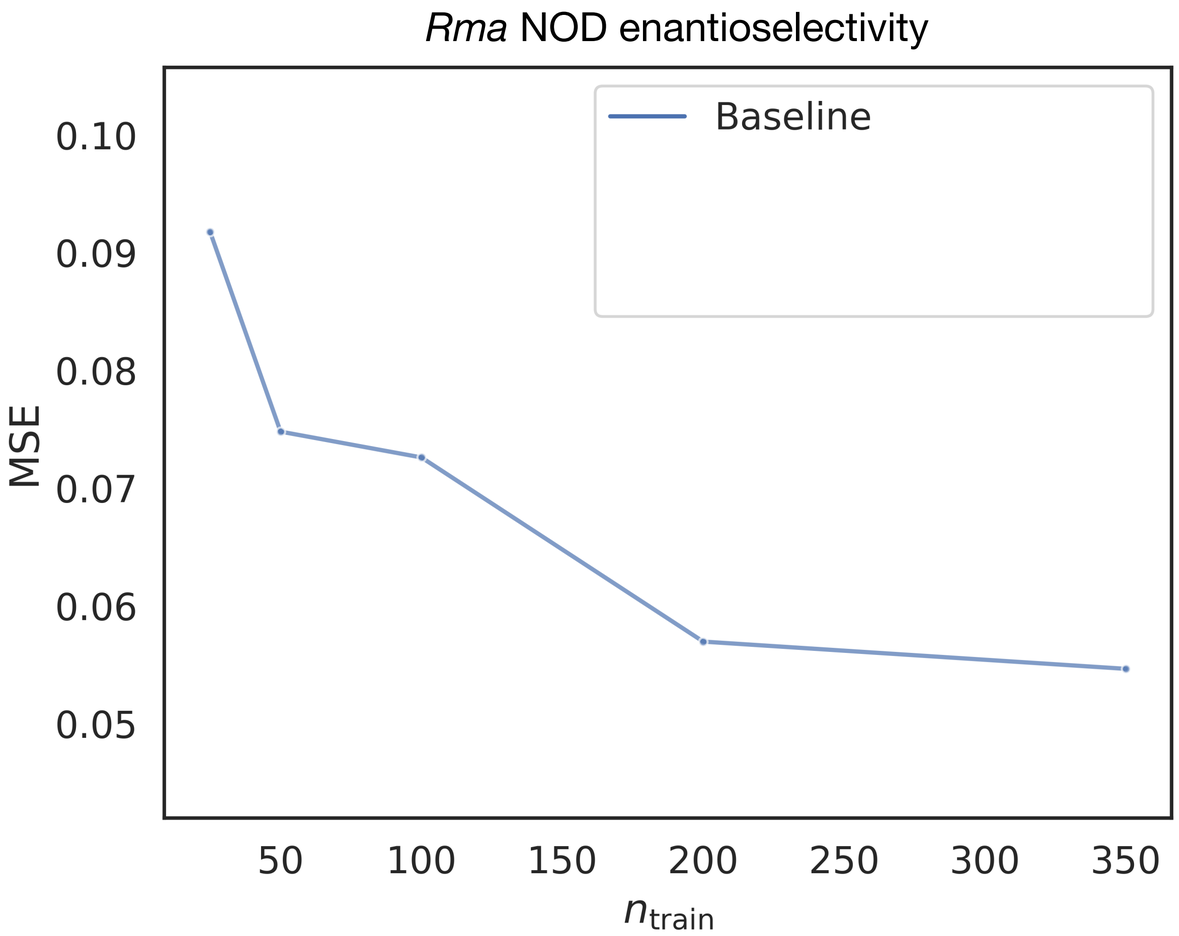

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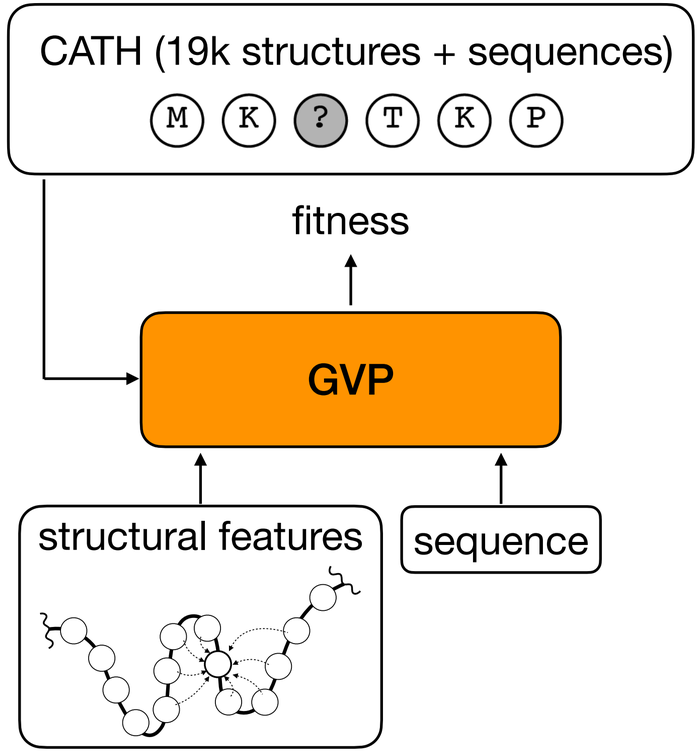

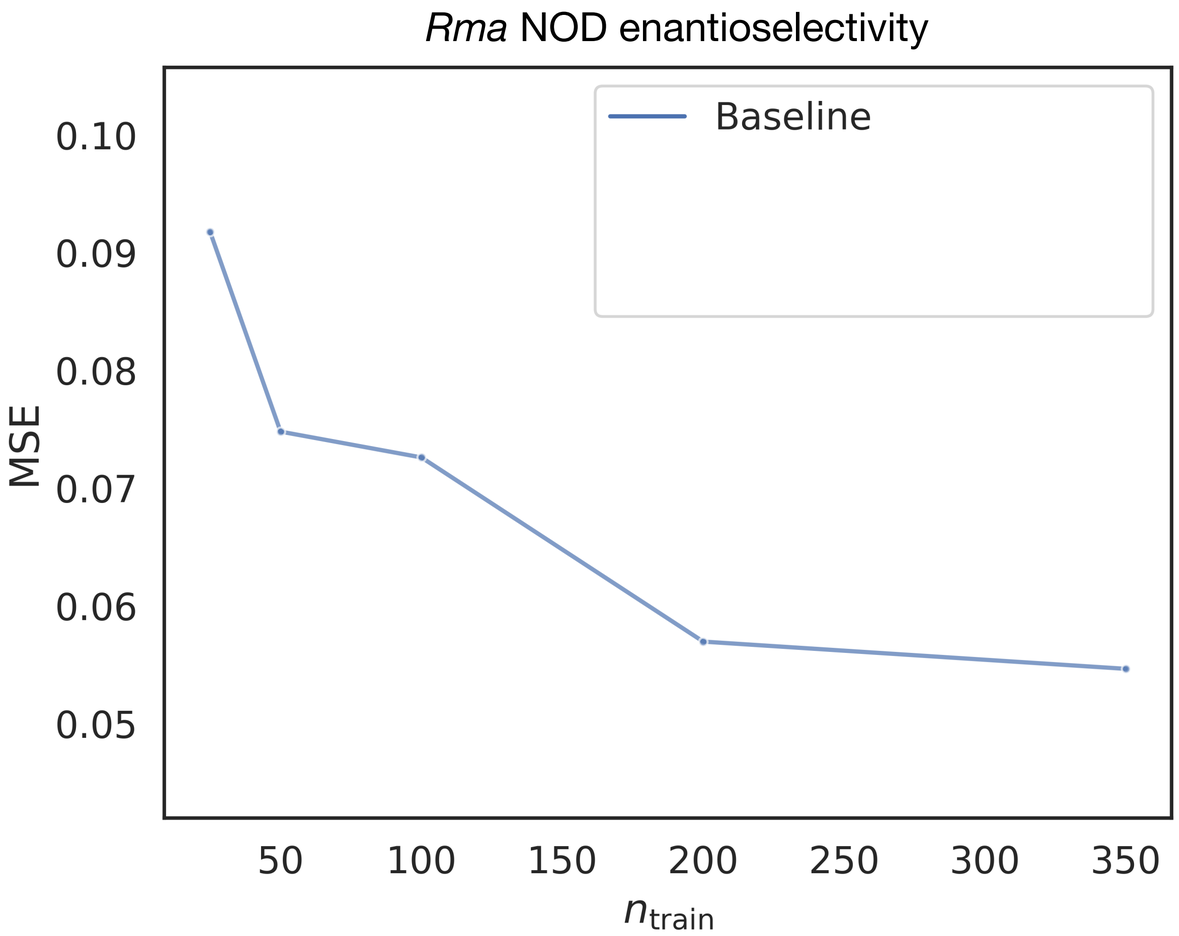

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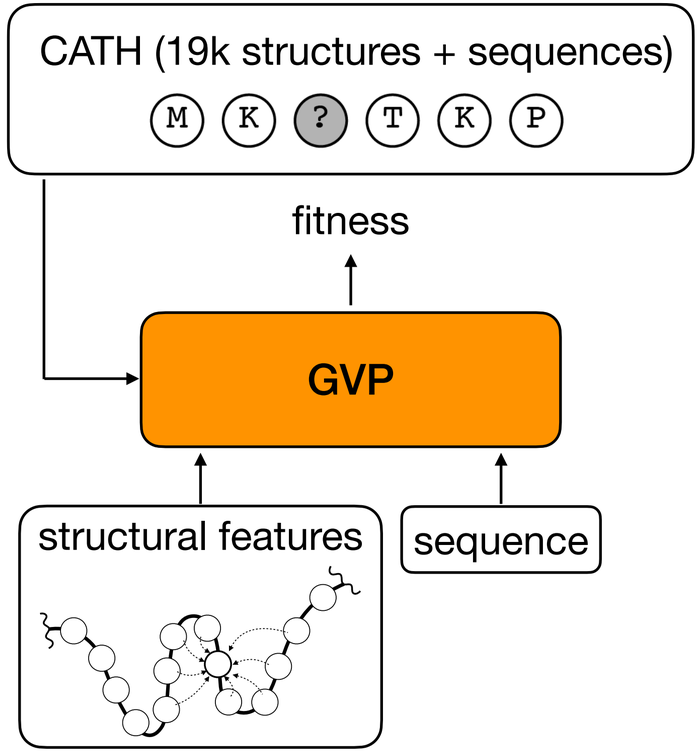

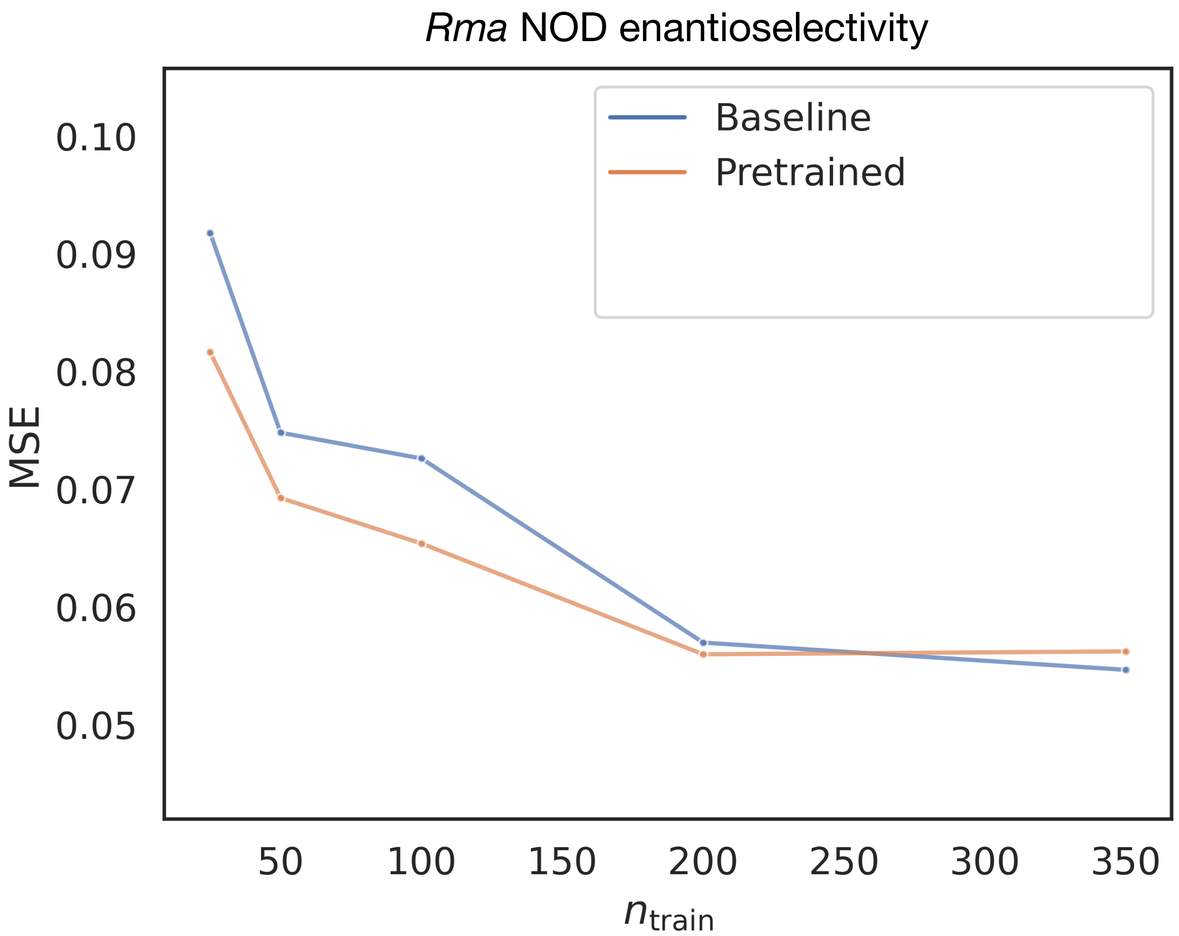

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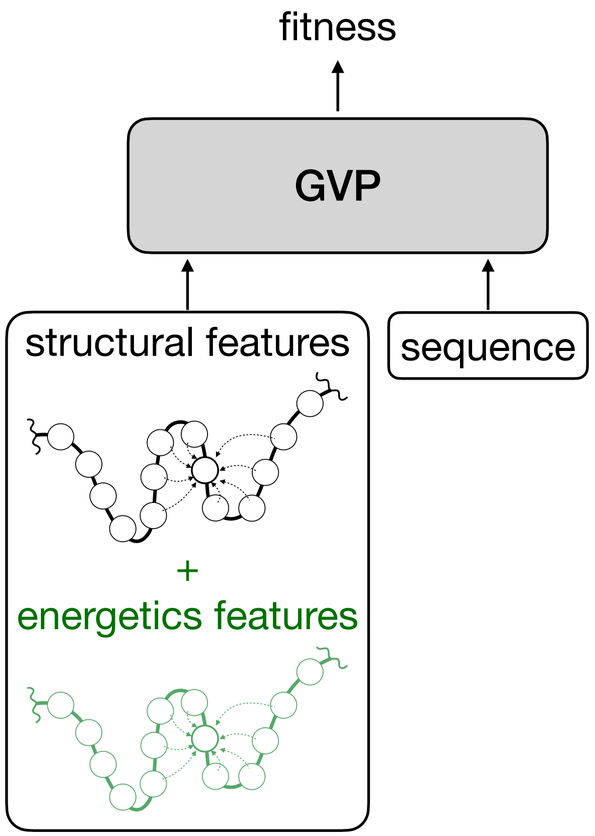

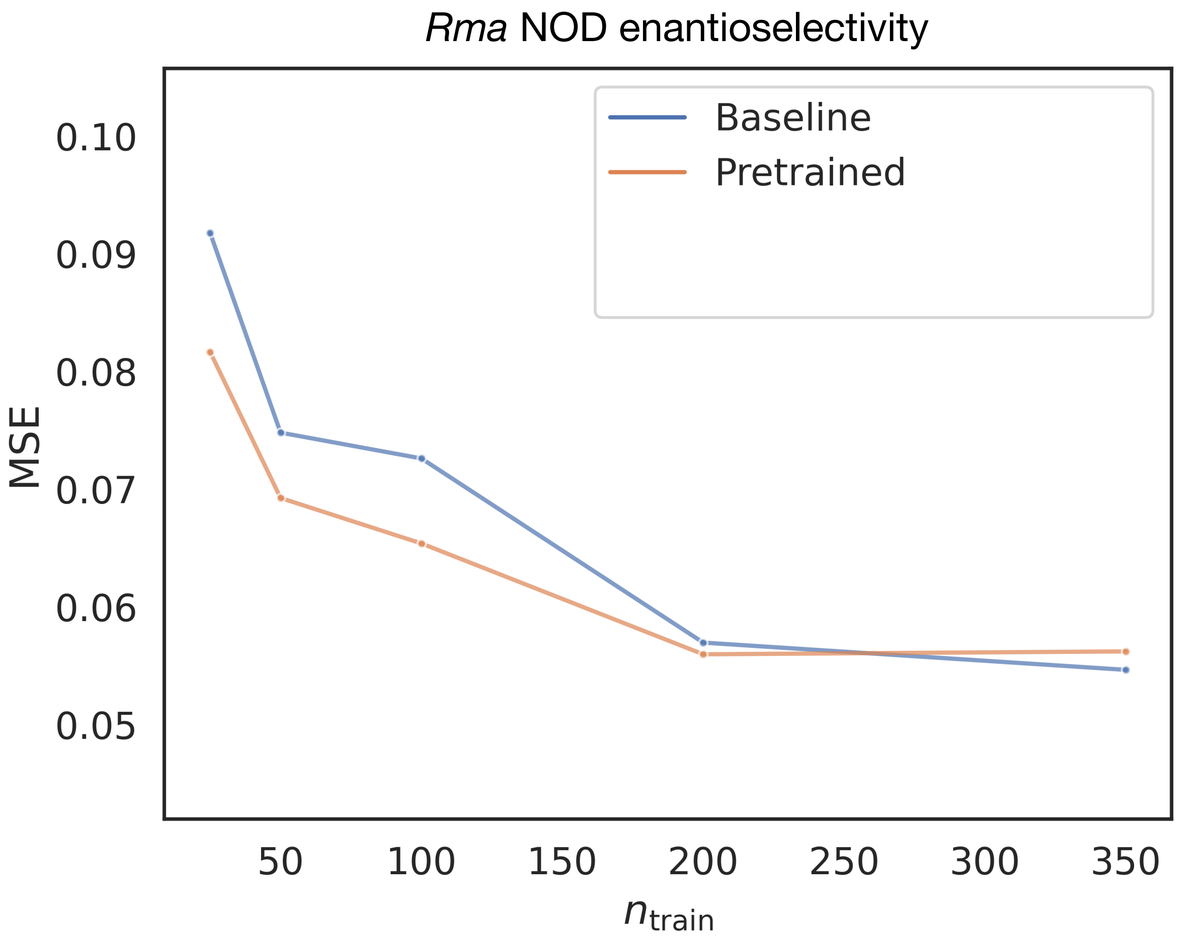

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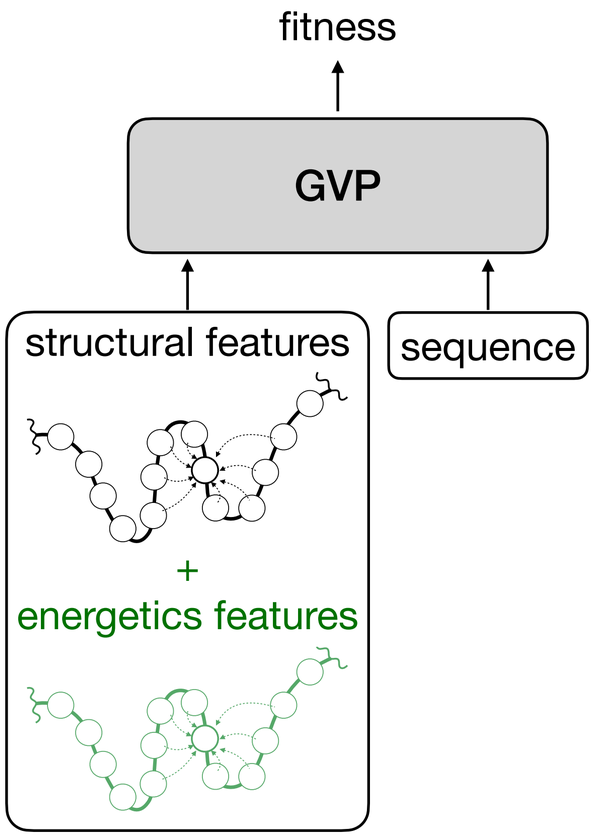

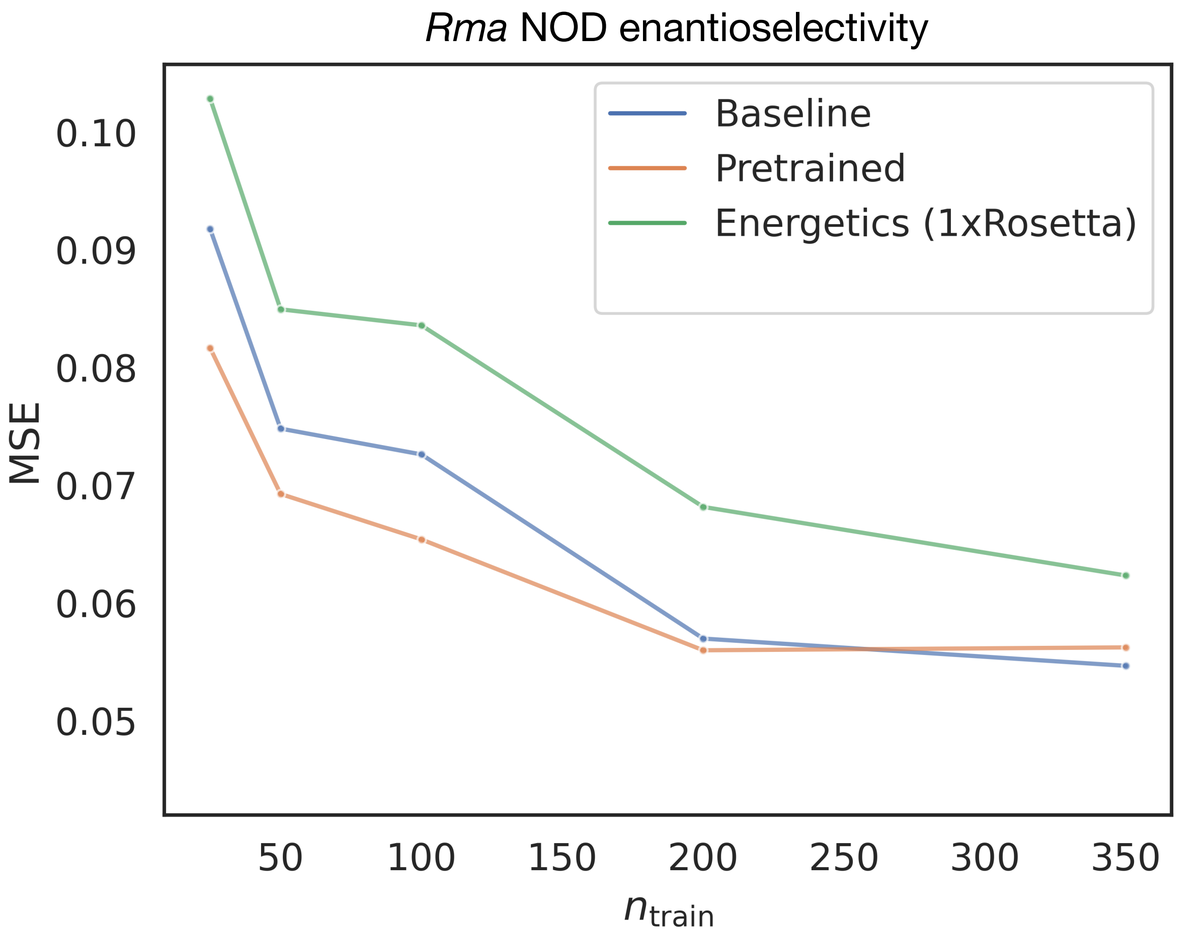

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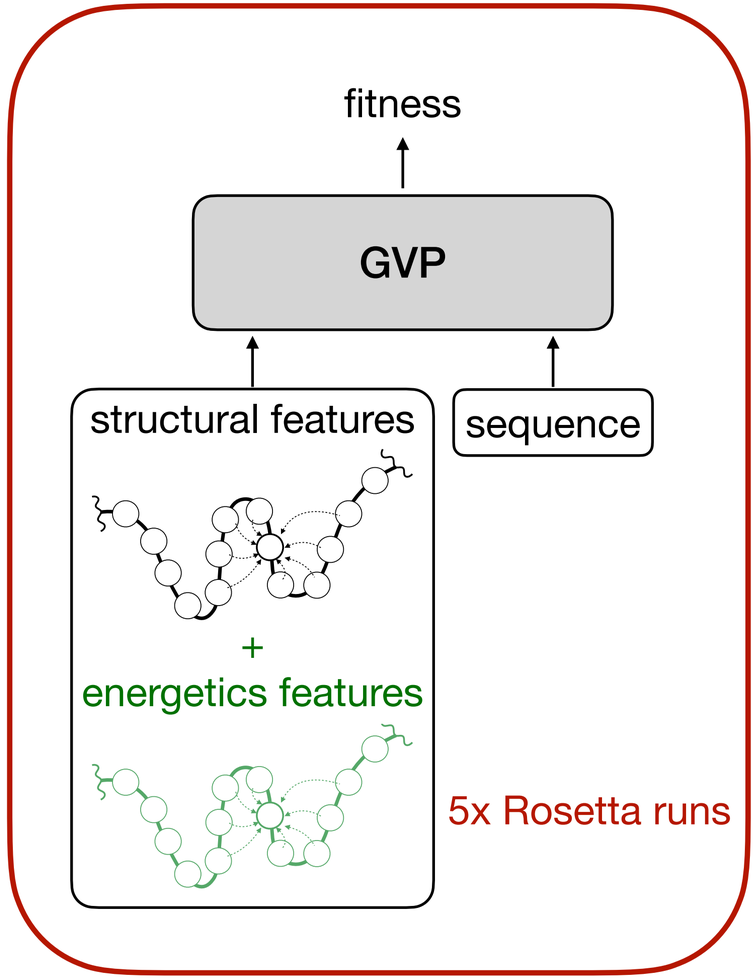

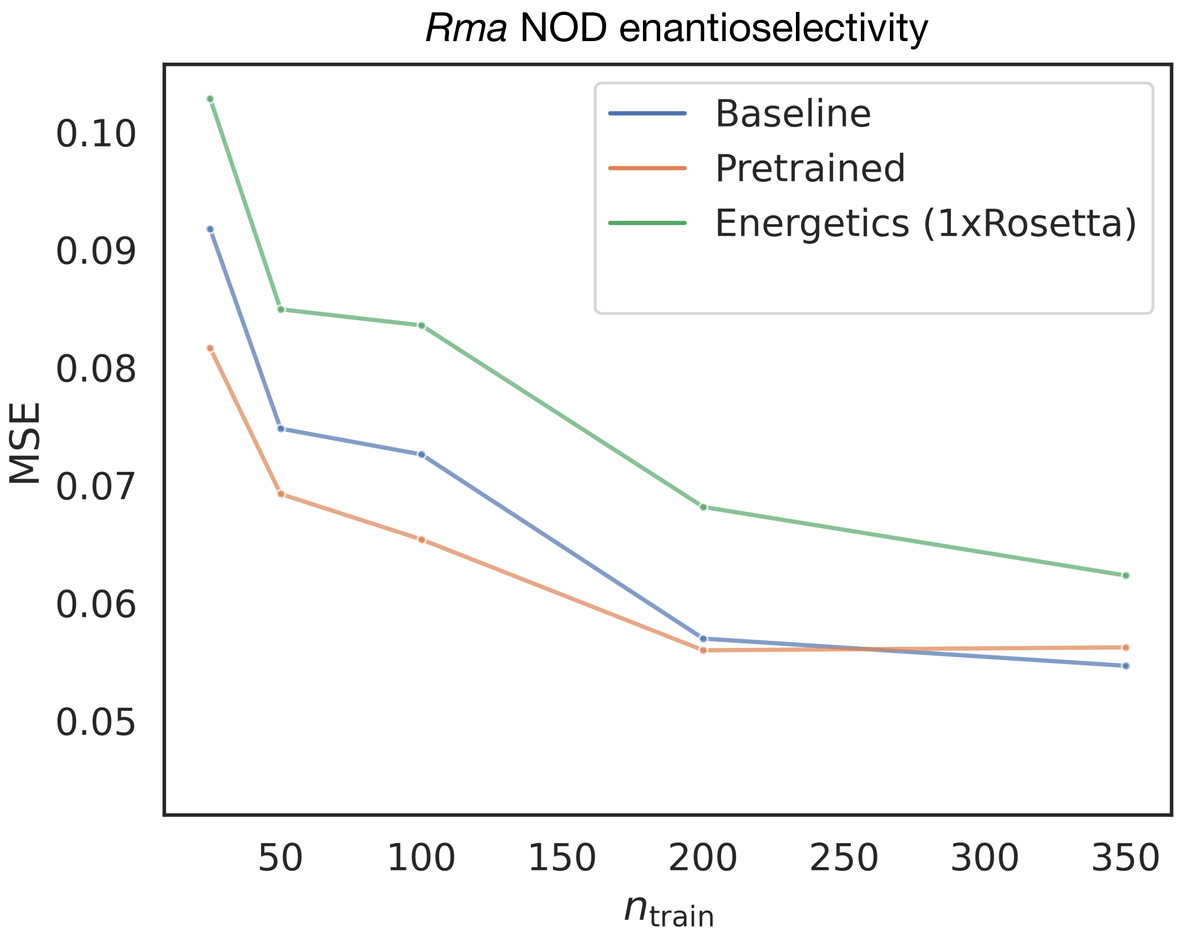

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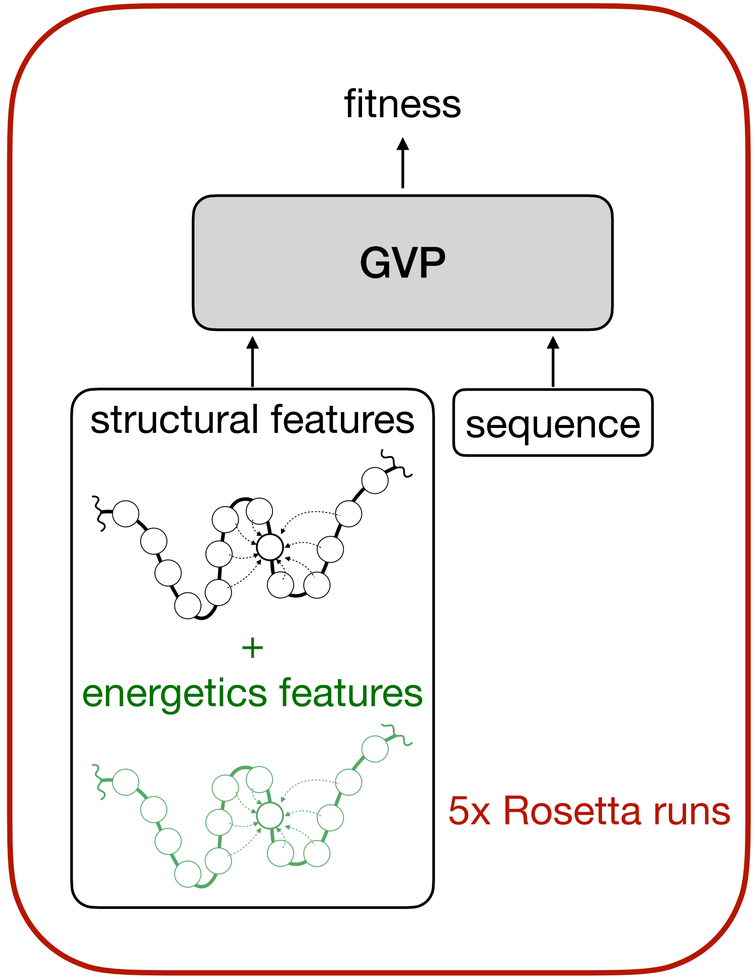

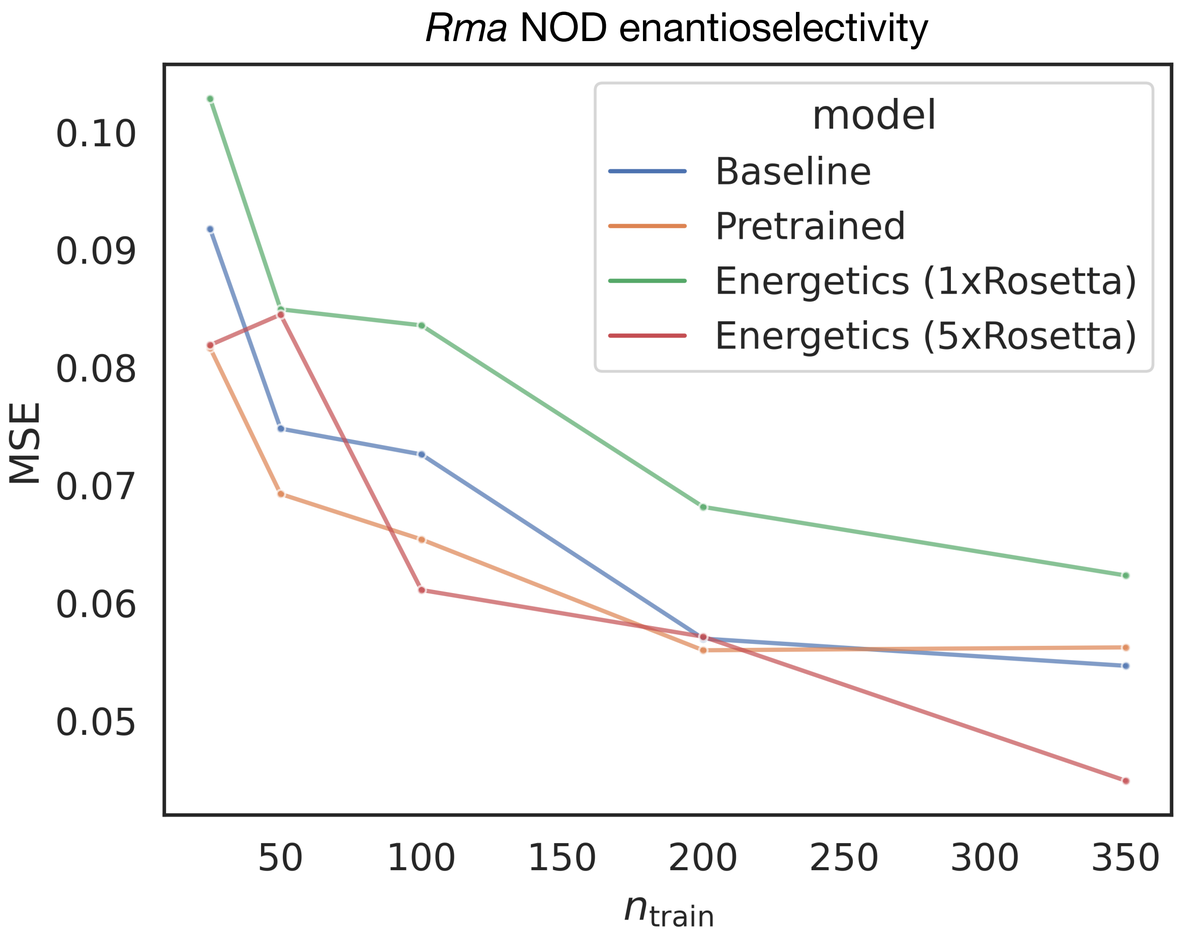

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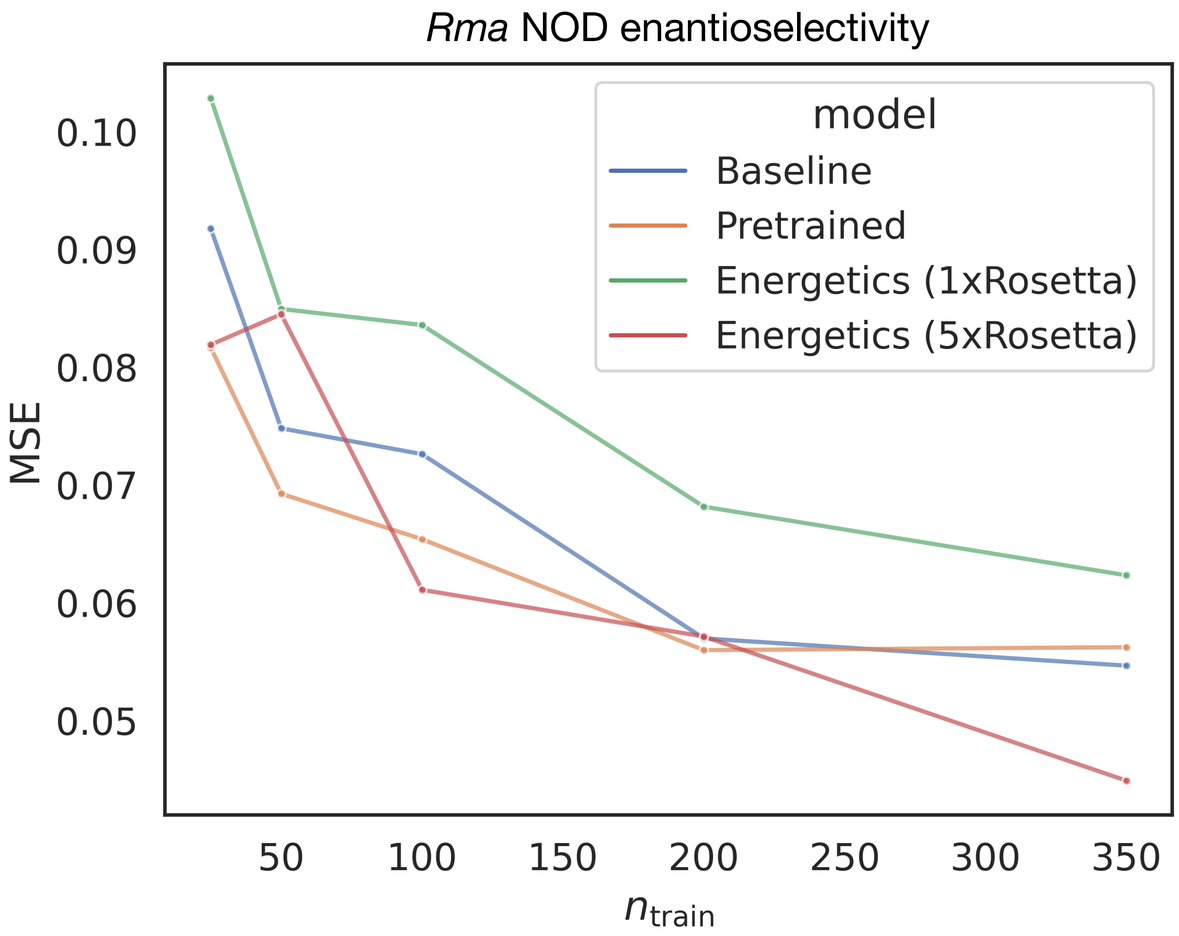

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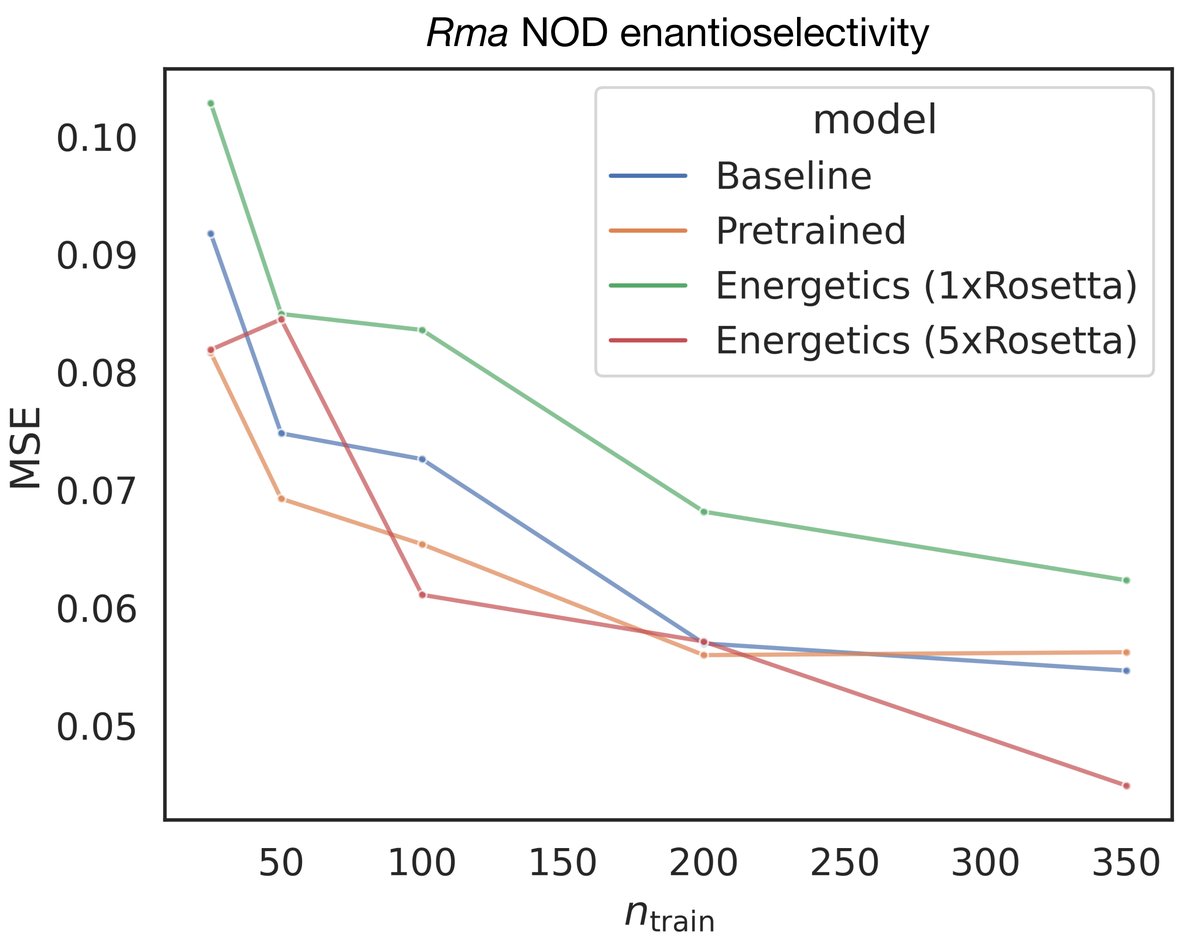
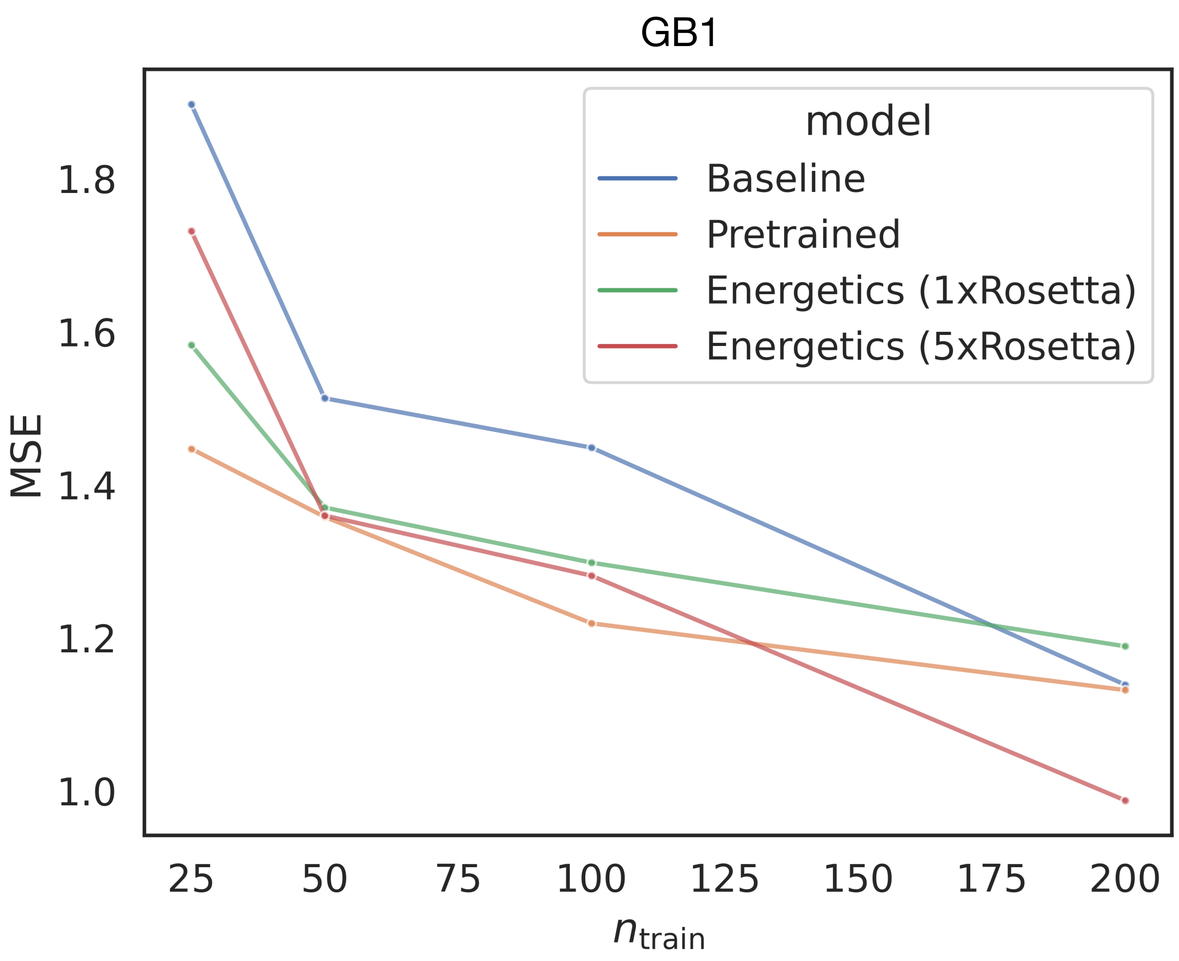
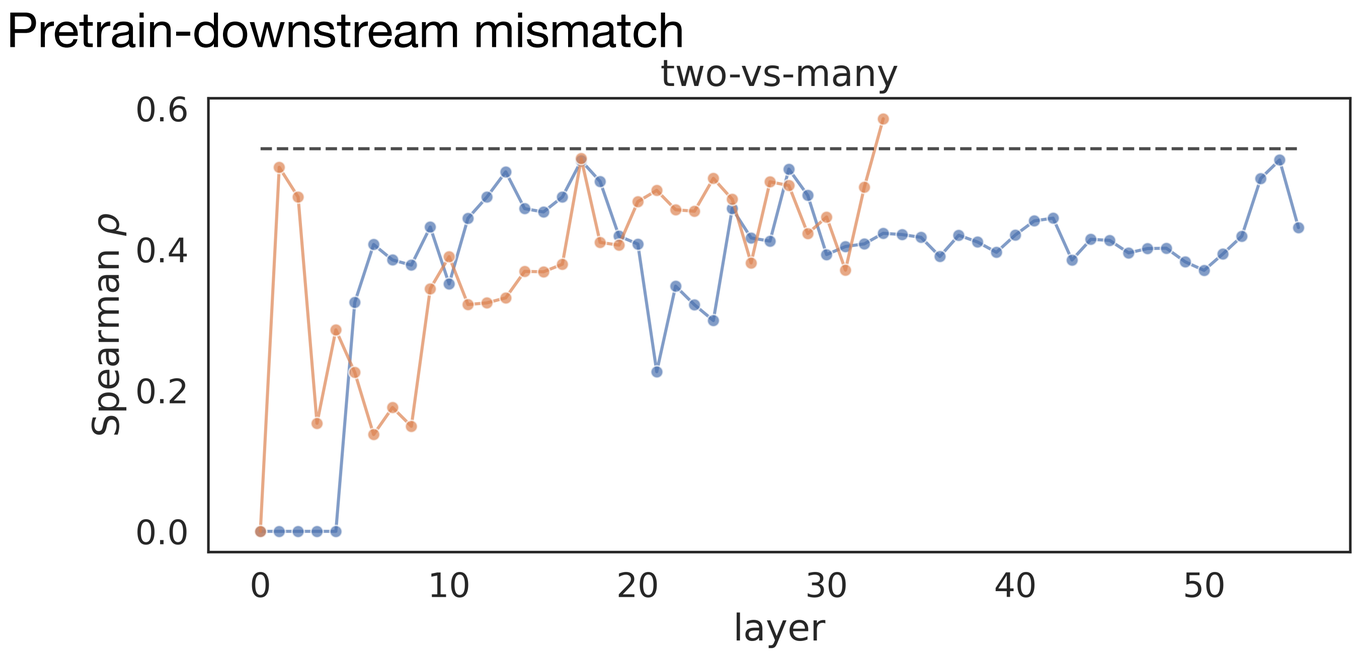
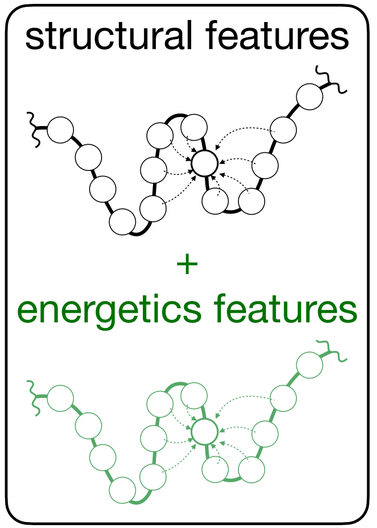




Use energetics and structure to reduce pretrain-downstream mismatch





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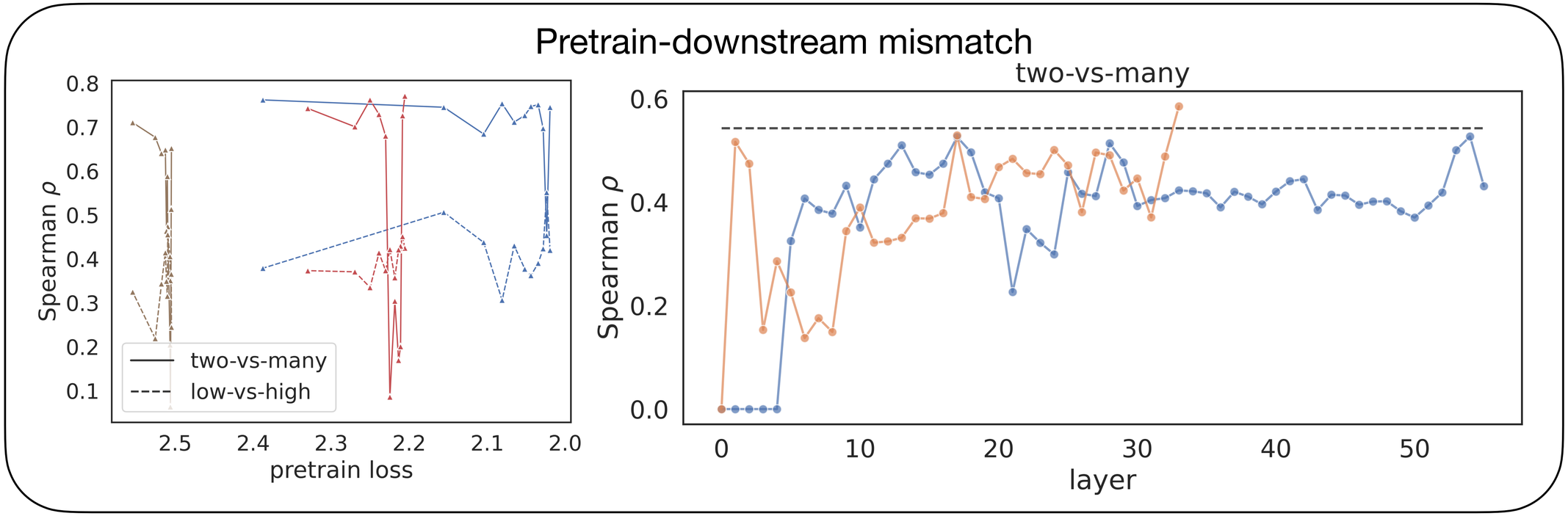
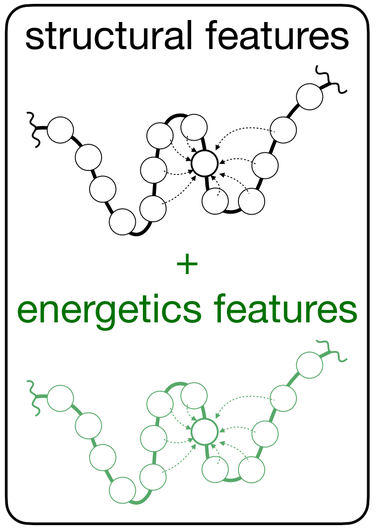
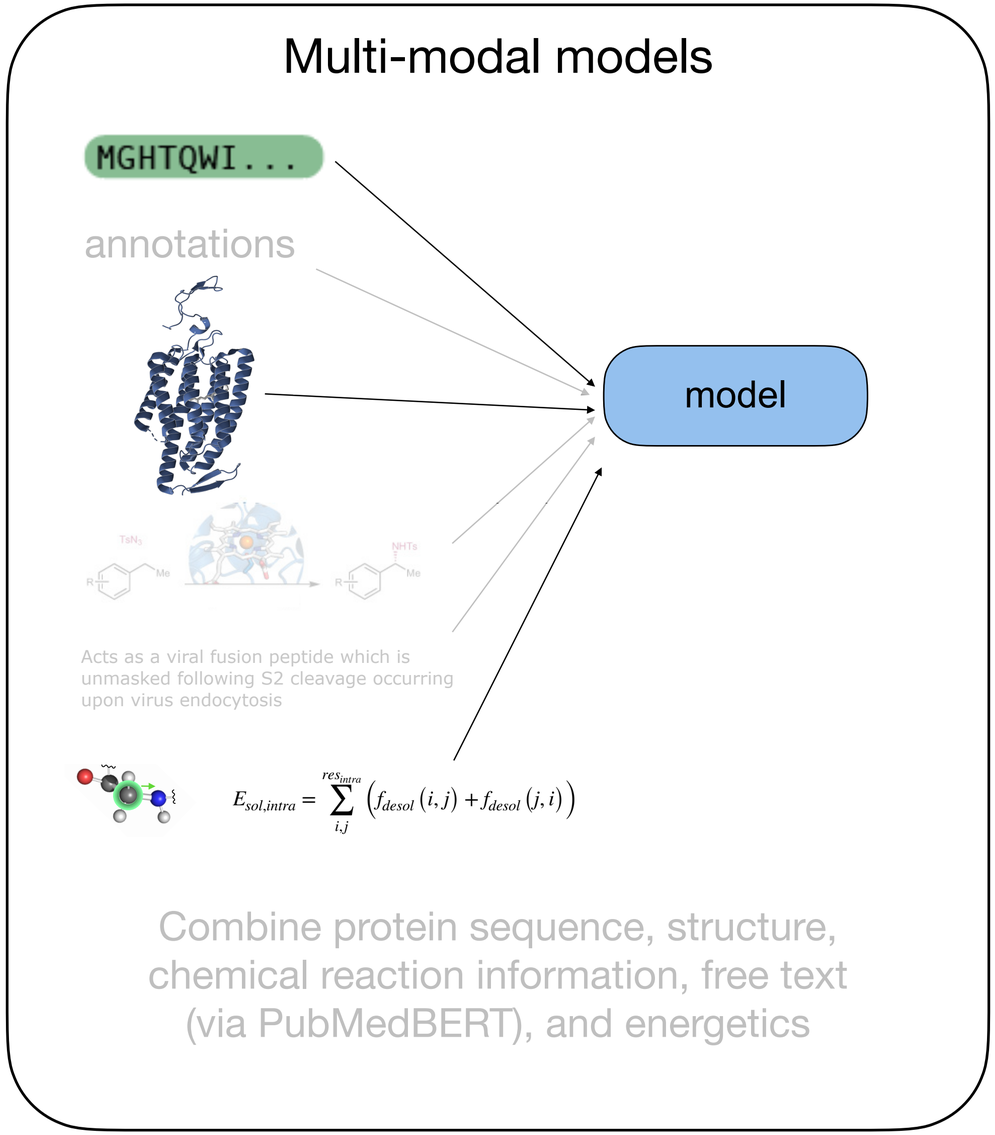




Can different modalities and pretraining tasks do better?



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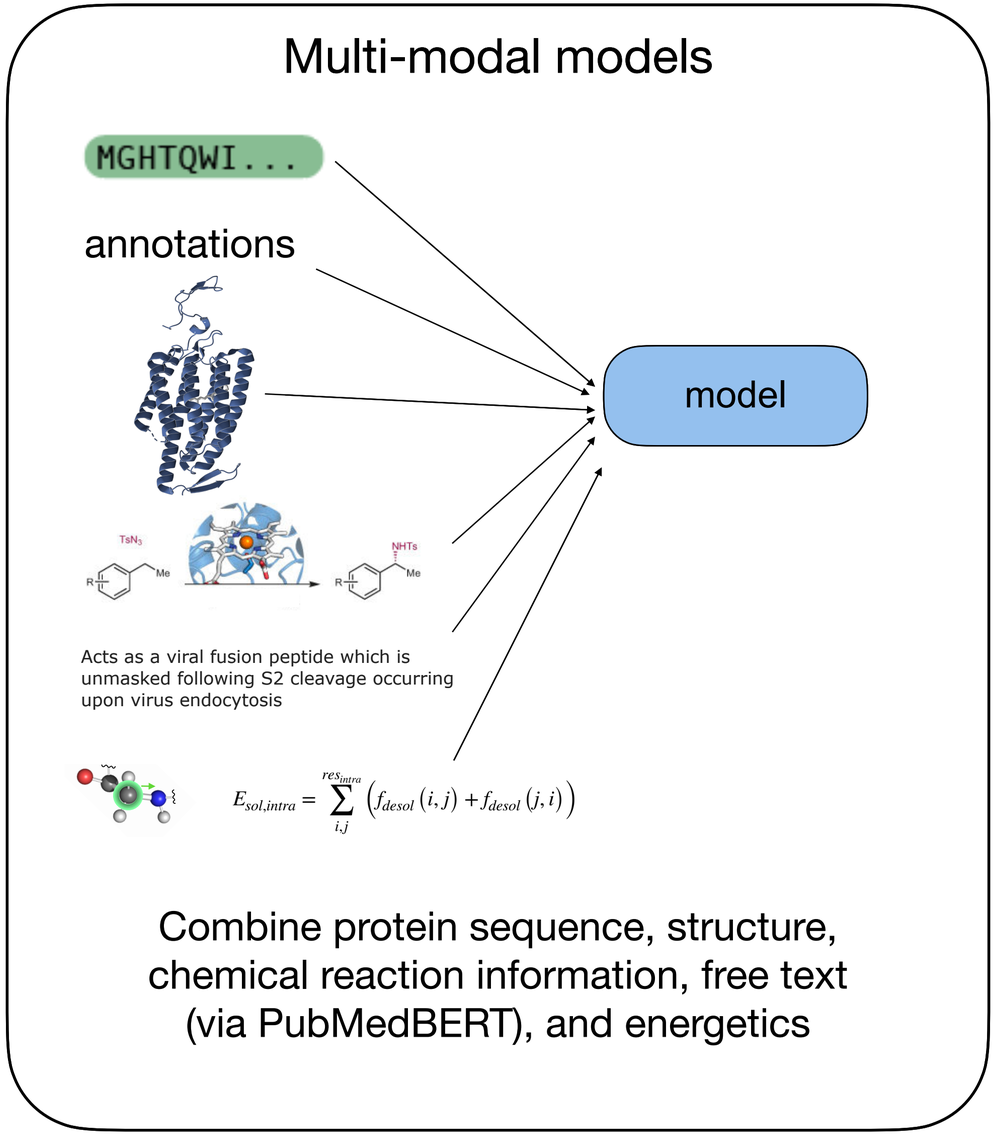
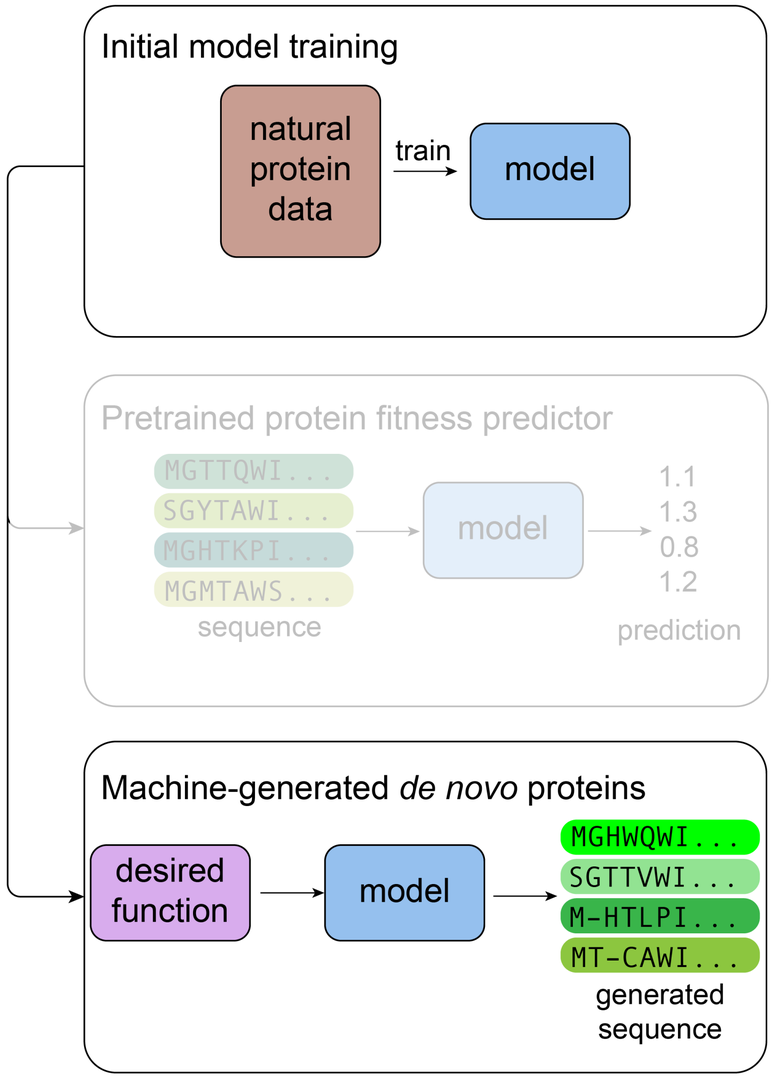
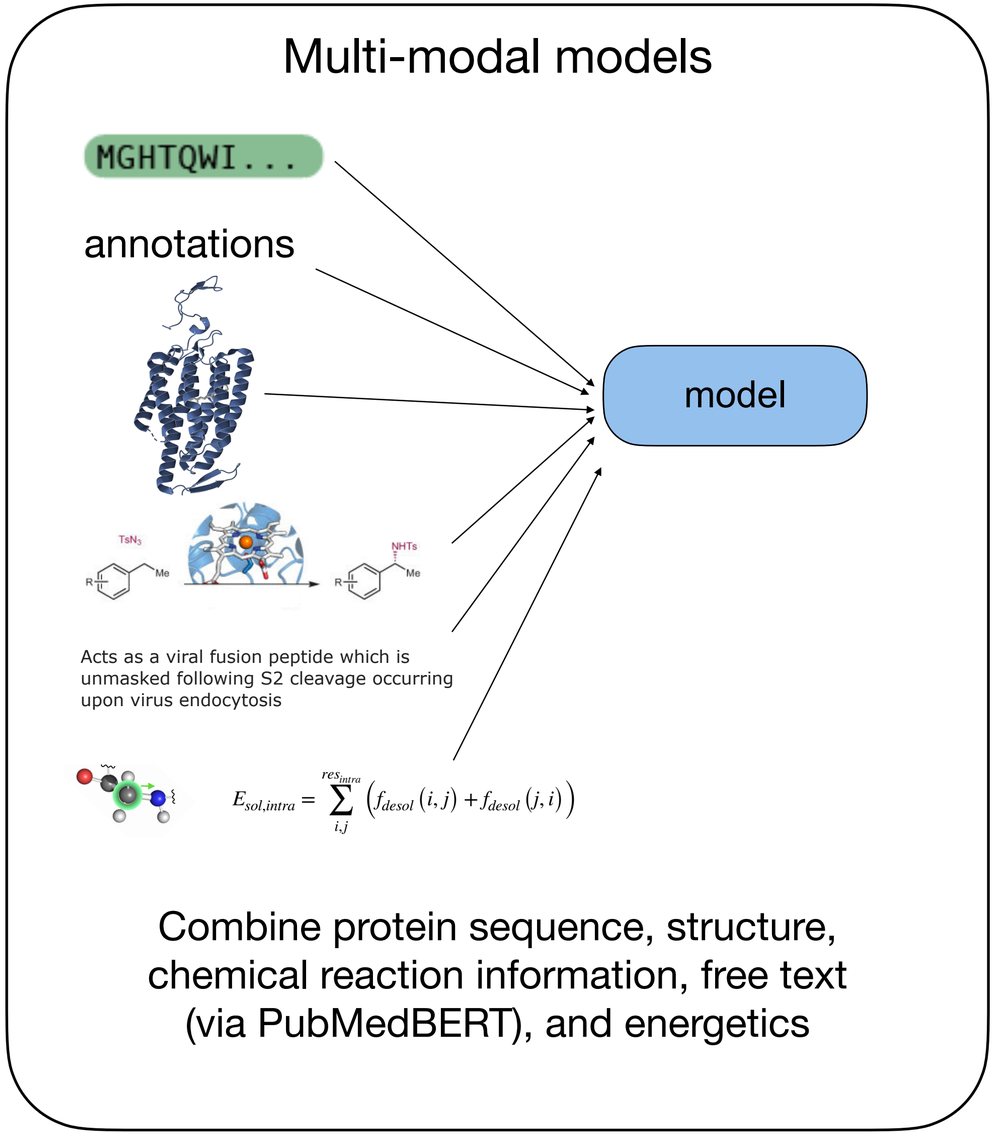


Use multiple data modalities to evaluate proteins





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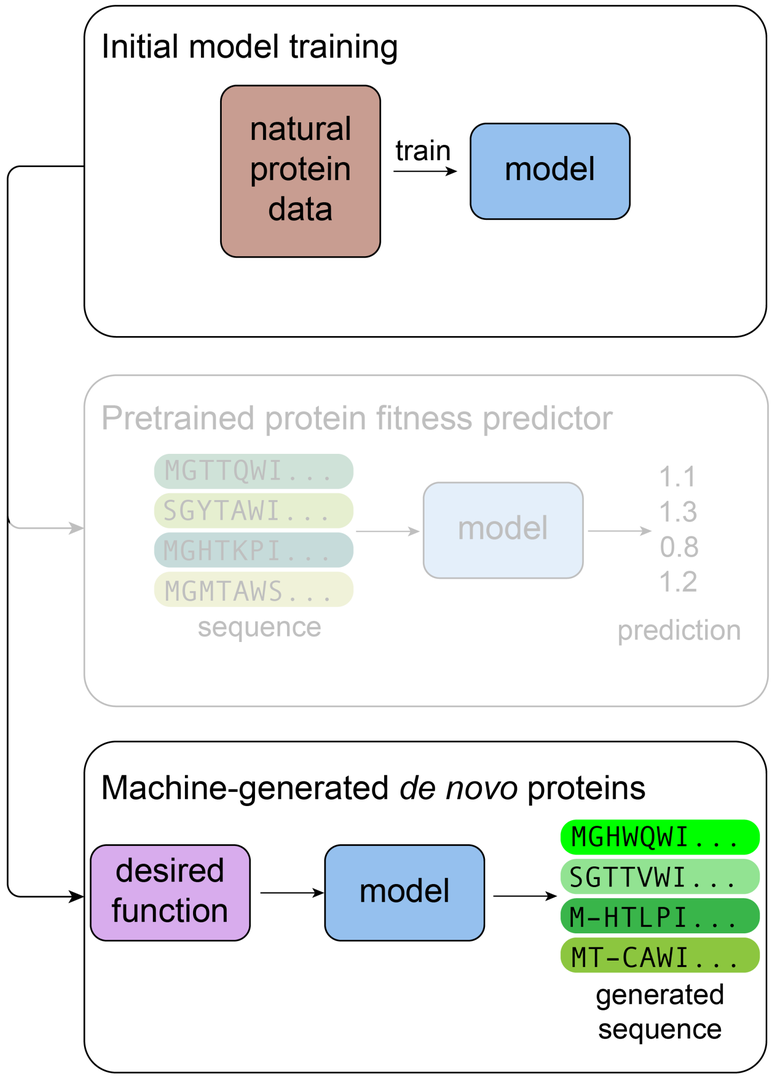

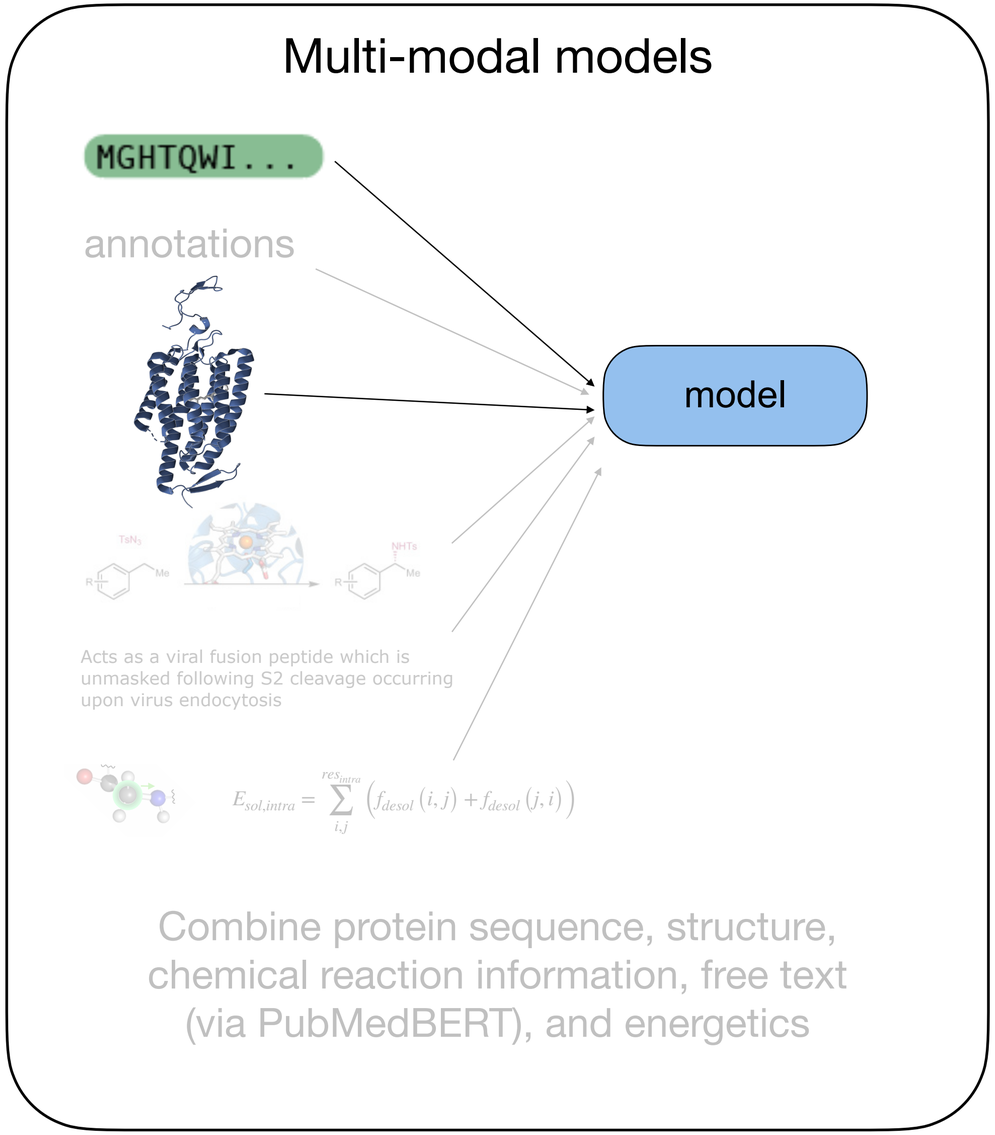

Generative models can expand functional space

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MGTGDHDD...

Generative models can expand functional space

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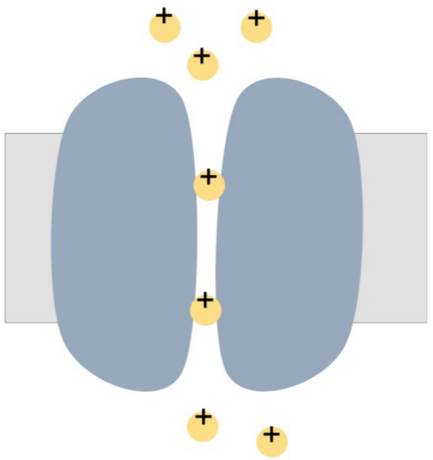

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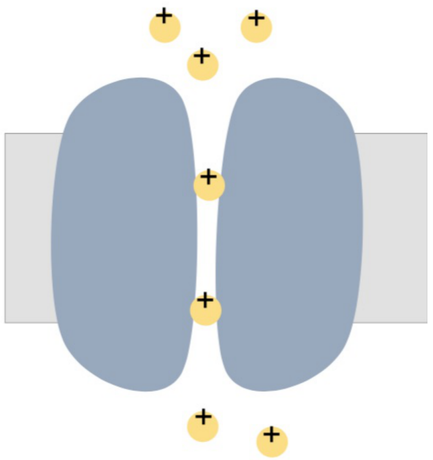
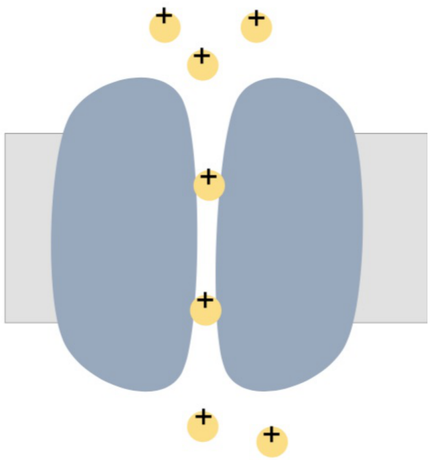


All natural proteins

Members of a protein family

Generative models can expand functional space

MGTGDHDD...



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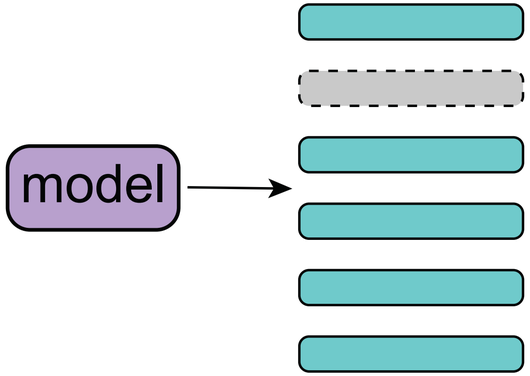

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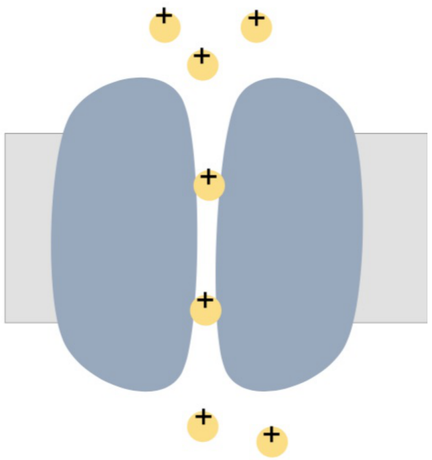
MGTGDHDD...



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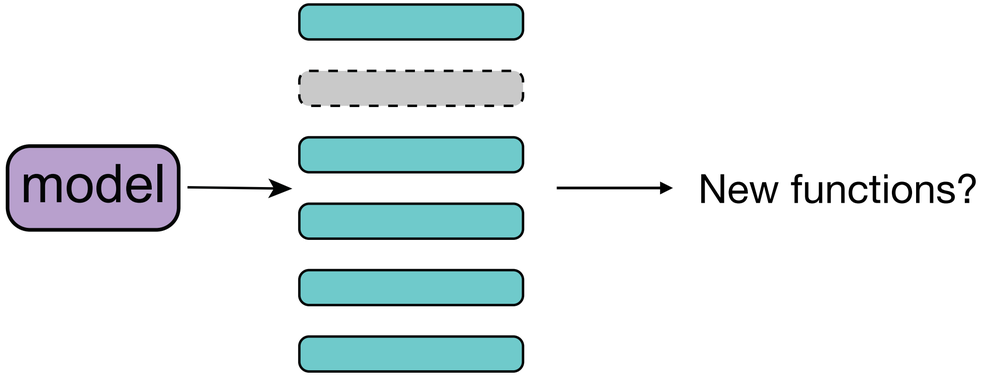

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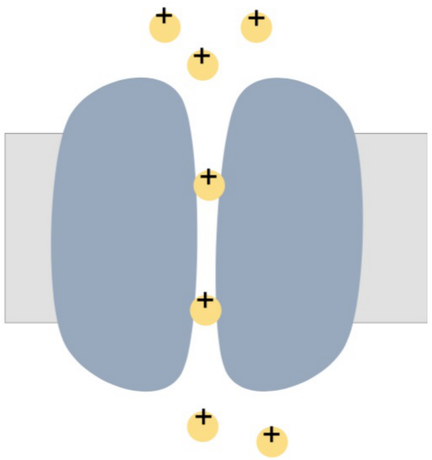

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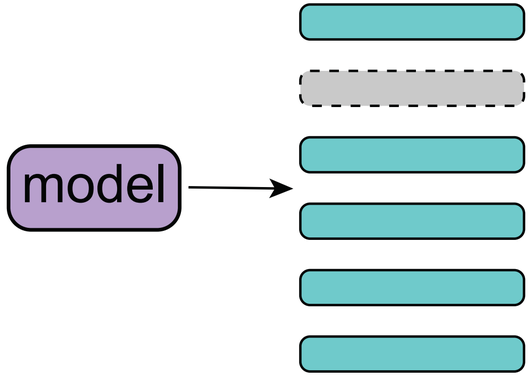
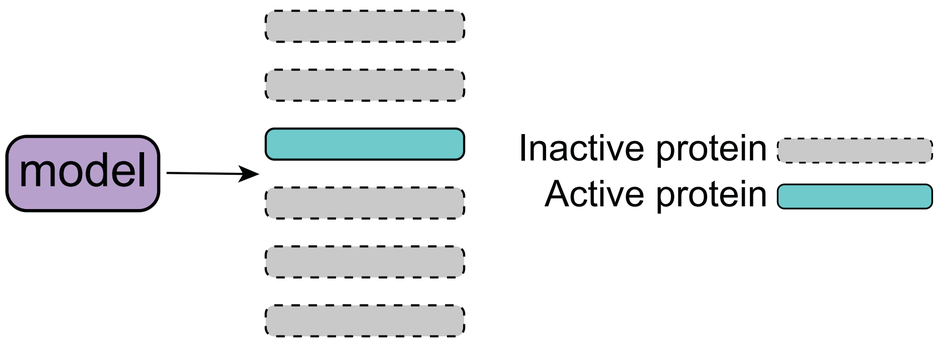


New functions?

Most generated sequences are inactive



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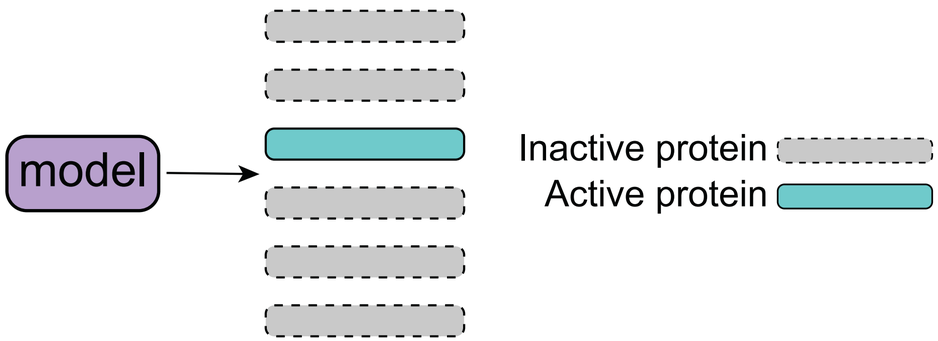
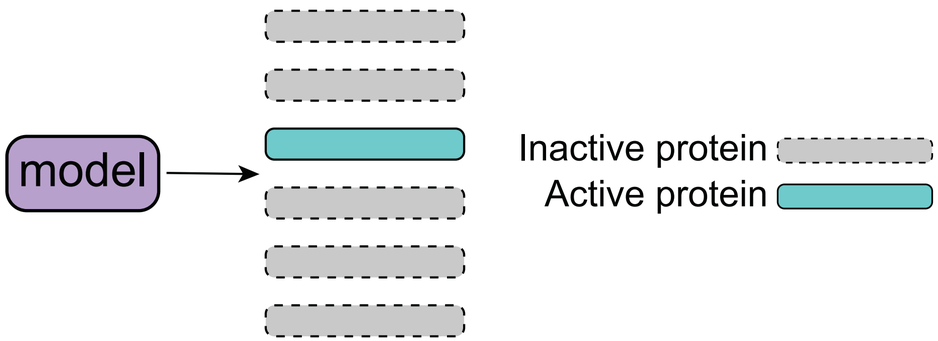


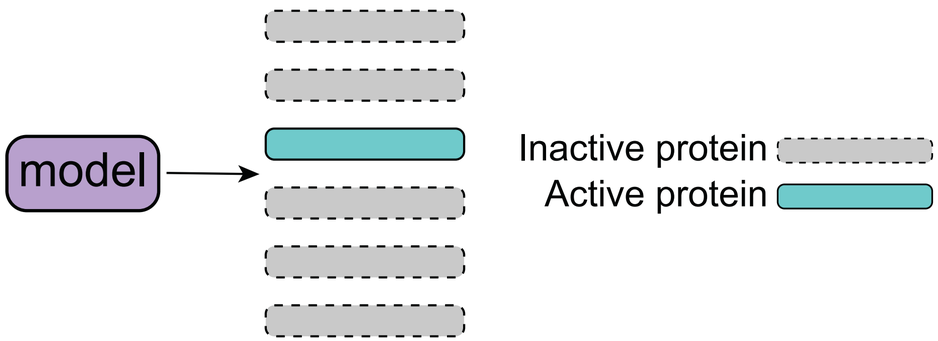
Model
GAN
ESM-MSA
Total

Most generated sequences are inactive



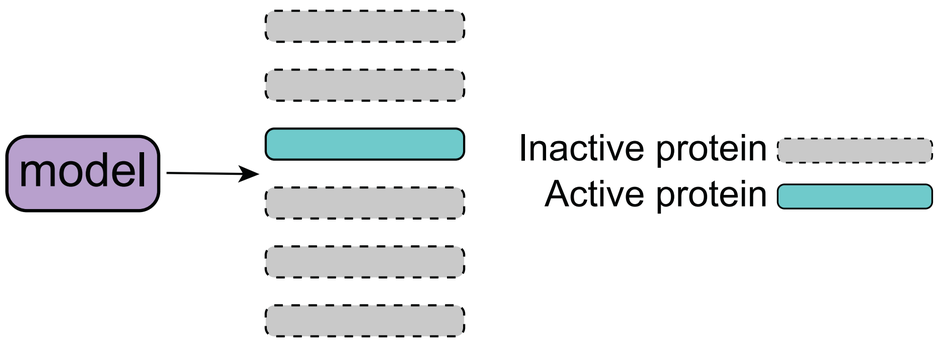
Model	Enzyme
GAN	MDH
	CuSOD
ESM-MSA	MDH
	CuSOD
Total	

Most generated sequences are inactive



Model	Enzyme	Naive
GAN	MDH	0 / 18
	CuSOD	2 / 18
ESM-MSA	MDH	0 / 17
	CuSOD	0 / 18
Total		2 / 71

Most generated sequences are inactive



- Destabilized

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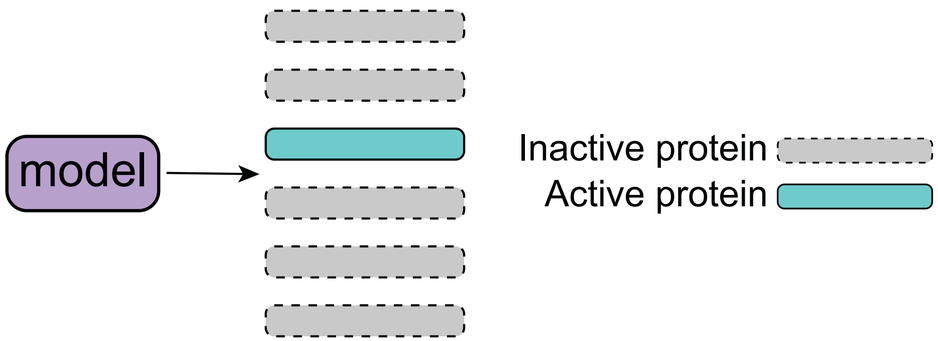

- Destabilized
- Mismatched signal peptide

Model	Enzyme	Naive
GAN	MDH	0 / 18
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ESM-MSA	MDH	0 / 17
	CuSOD	0 / 18
Total		2 / 71

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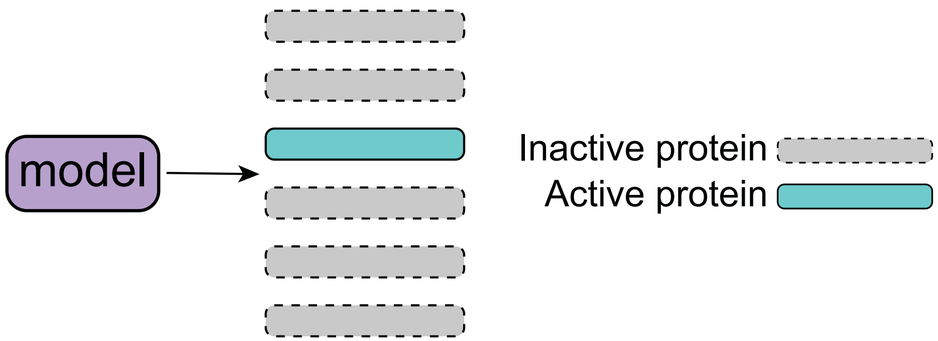
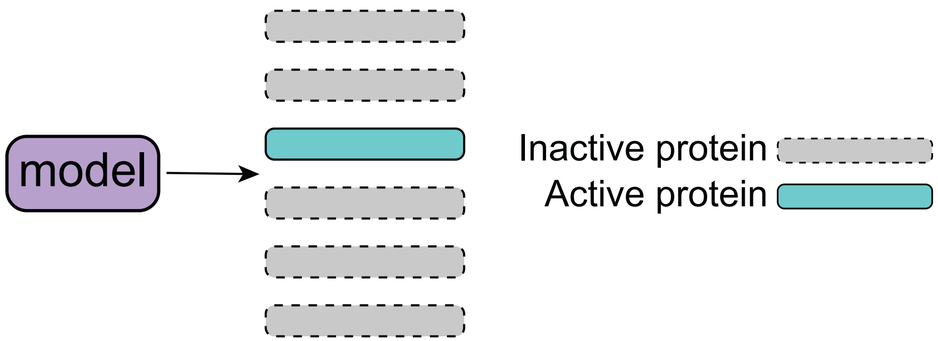


Model	Enzyme	Naive
GAN	MDH	0 / 18
	CuSOD	2 / 18
ESM-MSA	MDH	0 / 17
	CuSOD	0 / 18
Total		2 / 71

- Destabilized
- Mismatched signal peptide
- Transmembrane domain

Most generated sequences are inactive



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ESM-MSA	MDH	0 / 17
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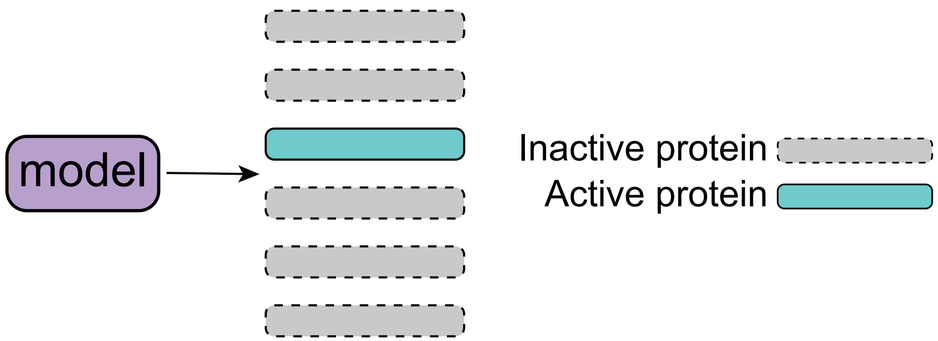
Total		2 / 71

- Destabilized
- Mismatched signal peptide
- Transmembrane domain
- Long repeats

Most generated sequences are inactive



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ESM-MSA	MDH	0 / 17
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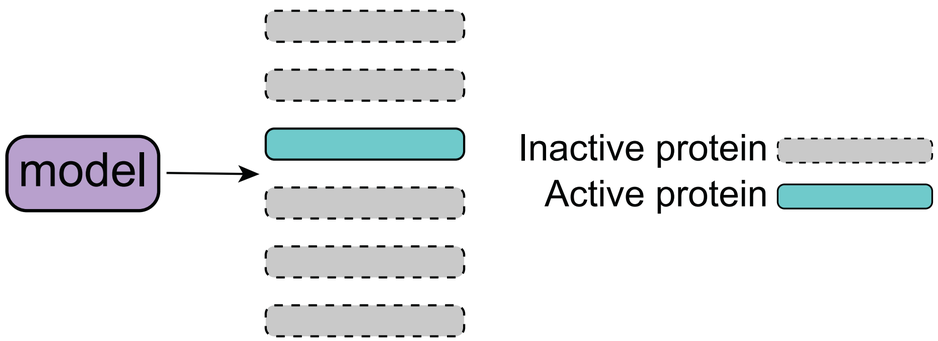
Total		2 / 71

- Destabilized
- Mismatched signal peptide
- Transmembrane domain
- Long repeats
- No catalytic residue

Most generated sequences are inactive



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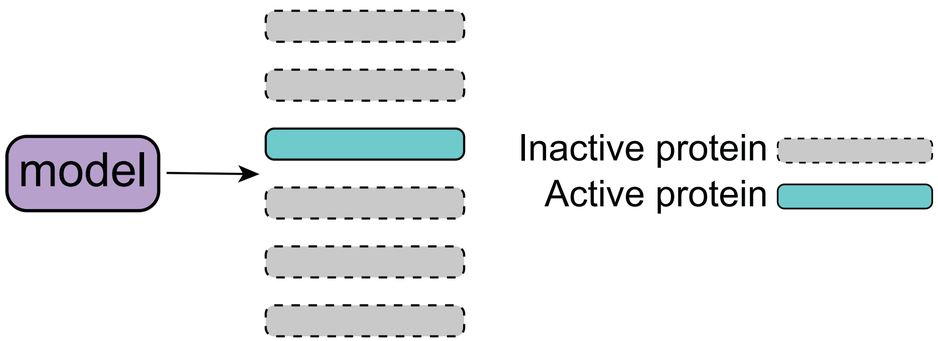

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ESM-MSA	MDH	0 / 17
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Total		2 / 71

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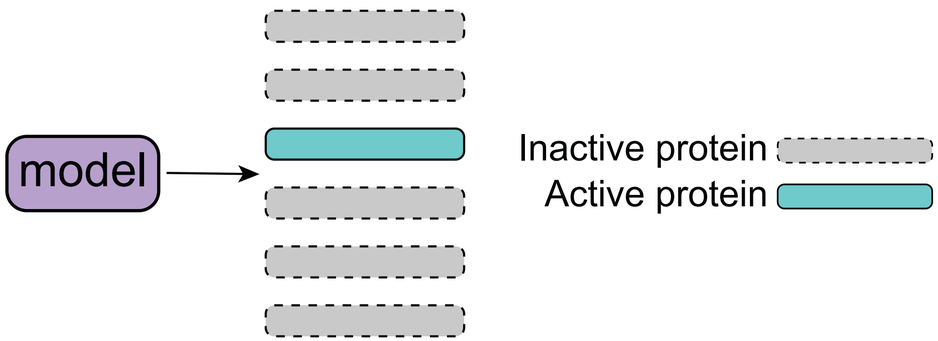
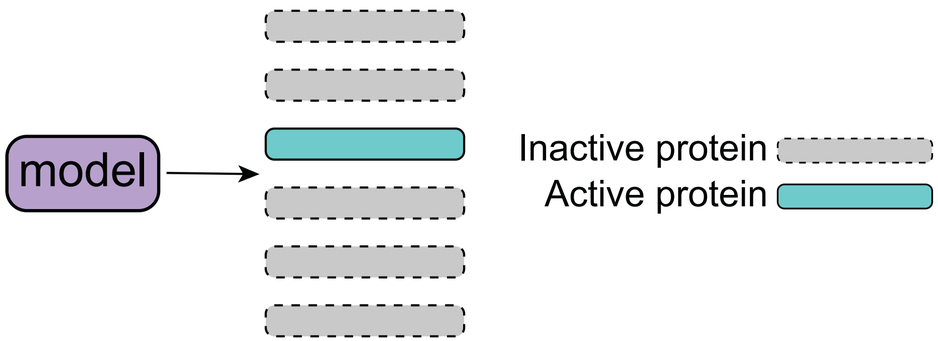
Most generated sequences are inactive



Model	Enzyme	Naive	Checks
GAN	MDH	0 / 18	2 / 18
	CuSOD	2 / 18	12 / 18
ESM-MSA	MDH	0 / 17	9 / 18
	CuSOD	0 / 18	12 / 18
Total		2 / 71	35 / 72

- Destabilized
- Mismatched signal peptide
- Transmembrane domain
- Long repeats
- No catalytic residue
- …

Most generated sequences are inactive



Model	Enzyme	Naive	Checks
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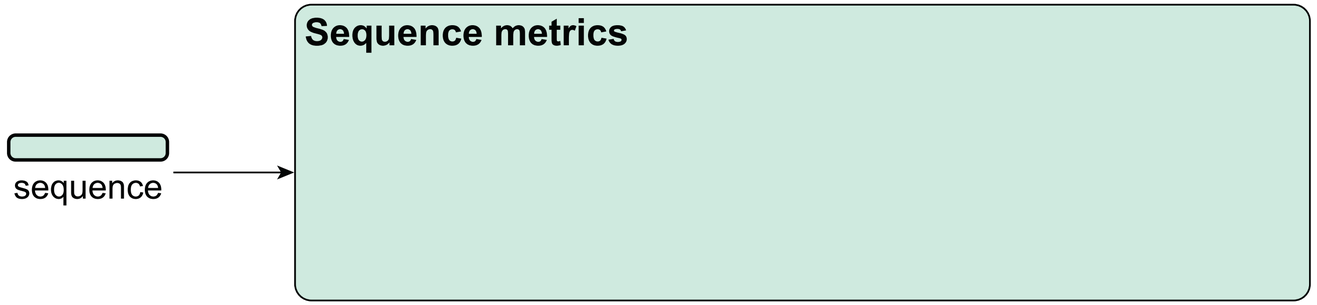
	CuSOD	0 / 18	12 / 18
Total		2 / 71	35 / 72

- Destabilized
- Mismatched signal peptide
- Transmembrane domain
- Long repeats
- No catalytic residue
- …

How can we do a better job selecting sequences?

Many possible metrics for selection



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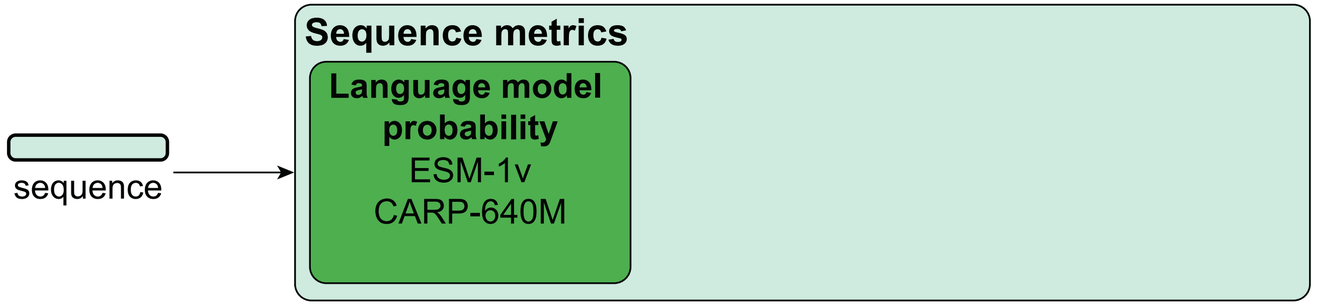

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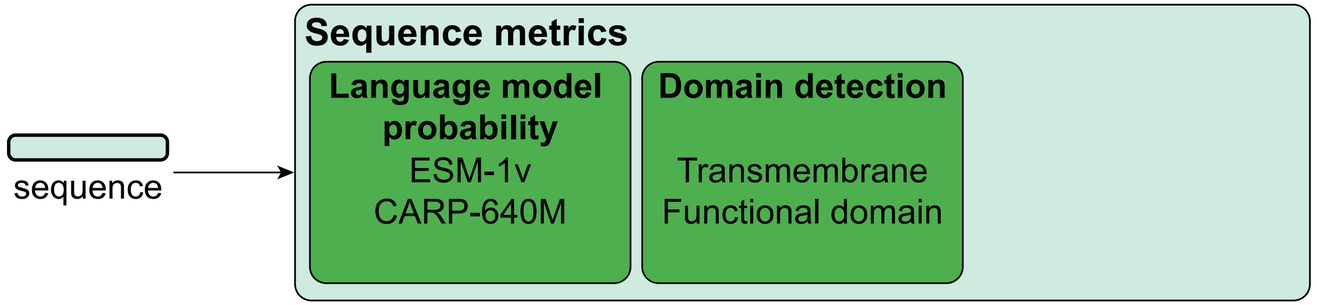

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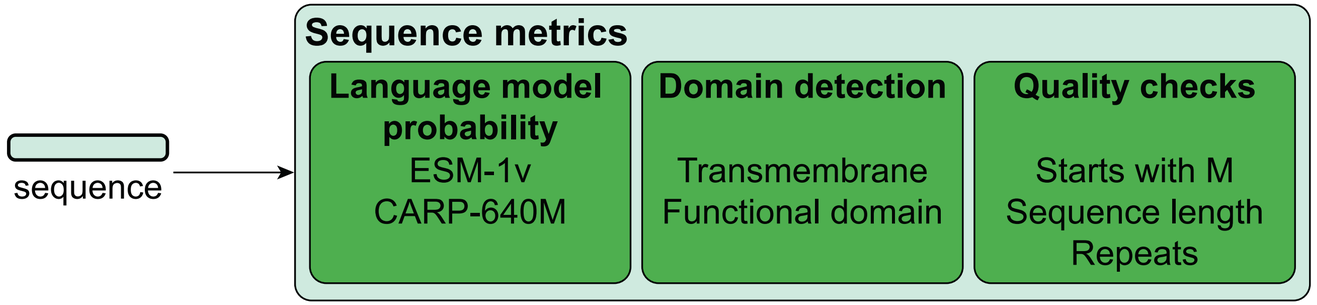

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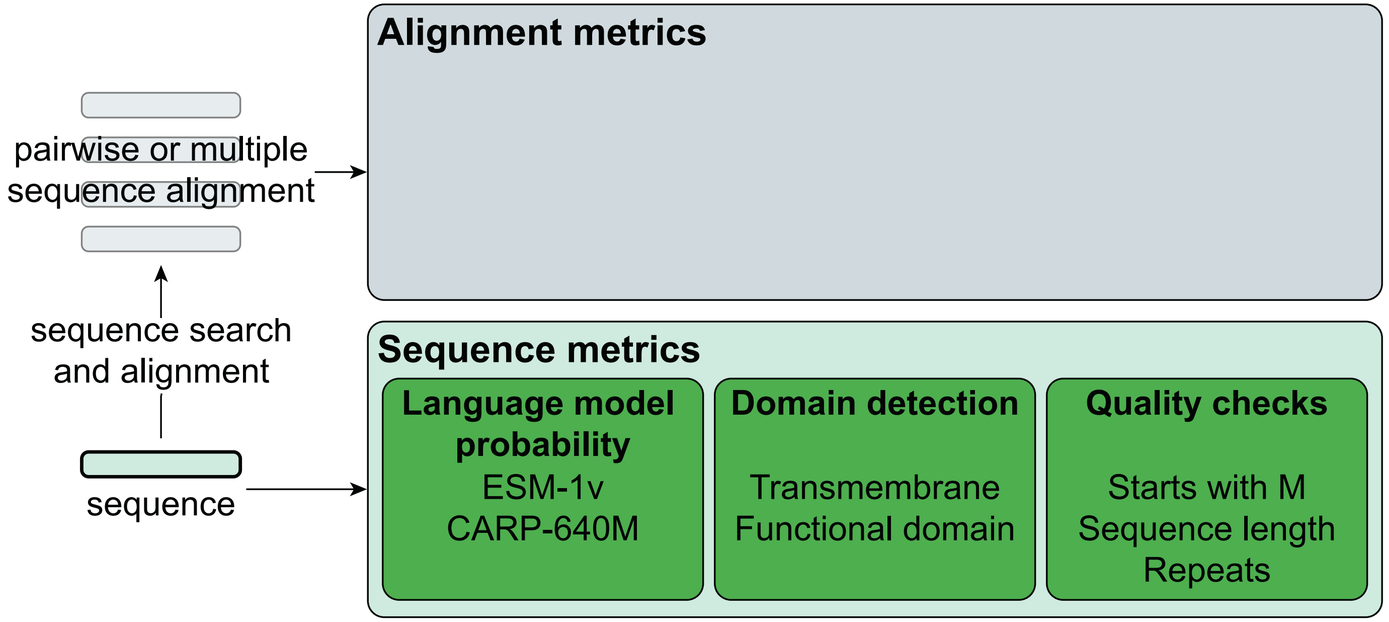

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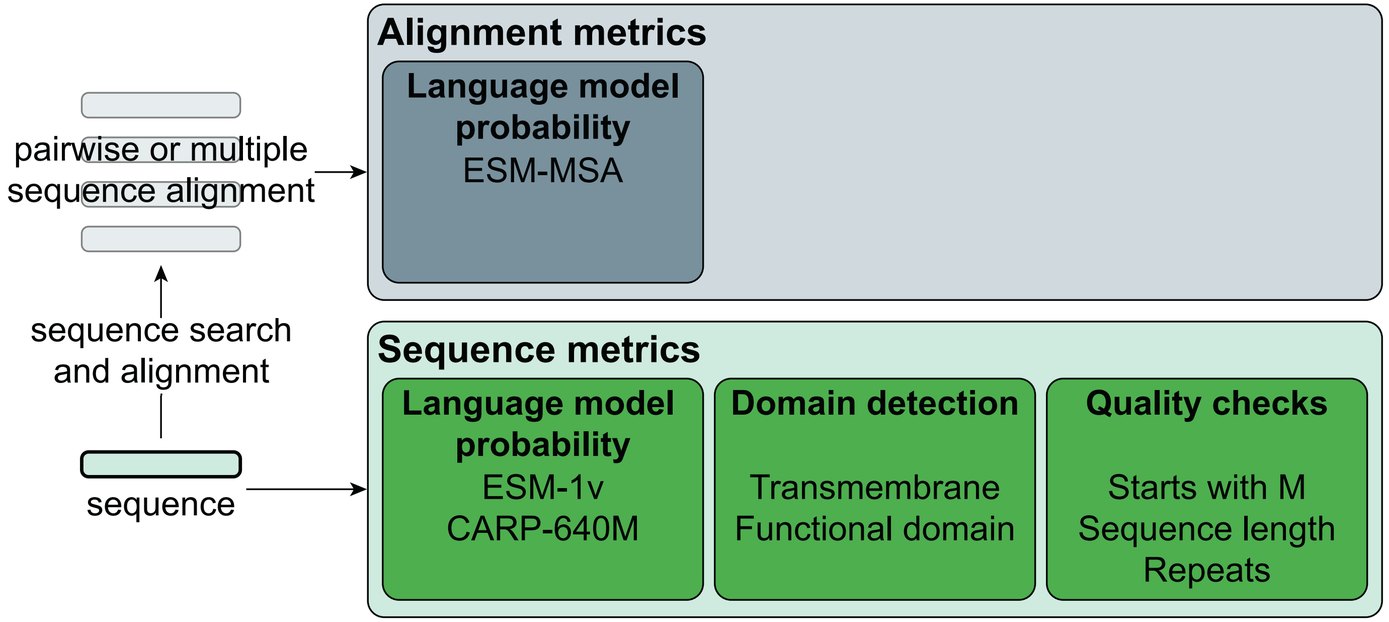

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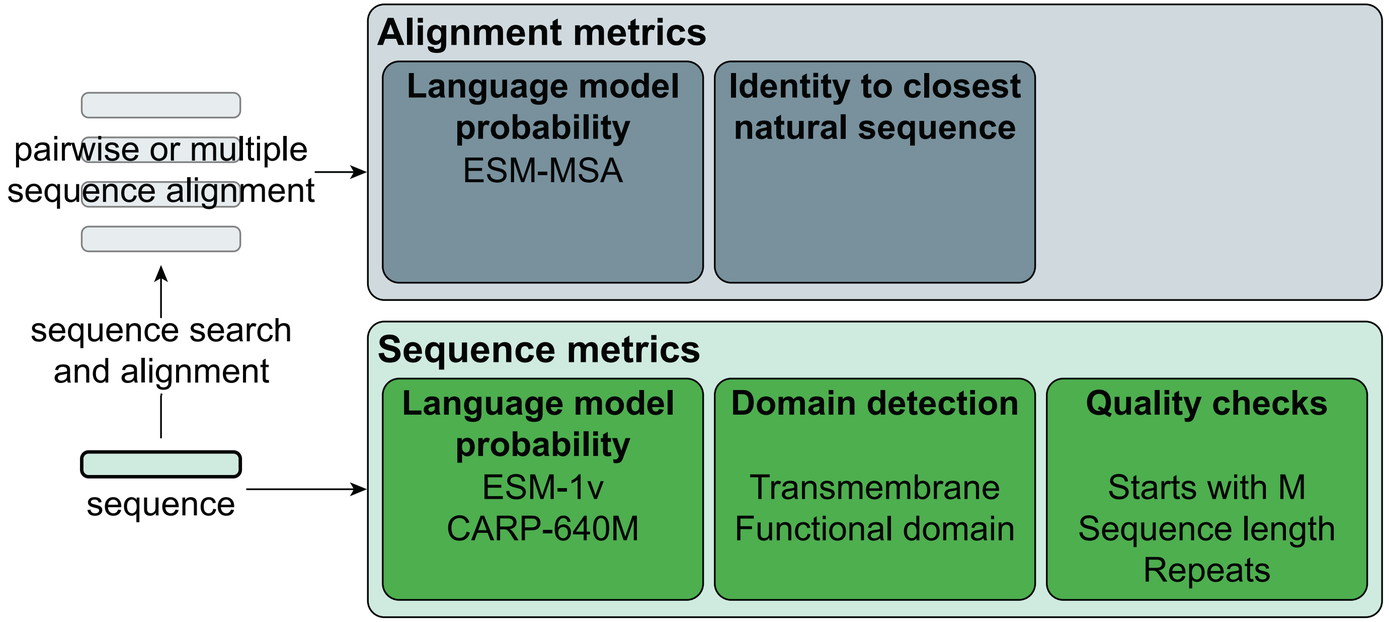

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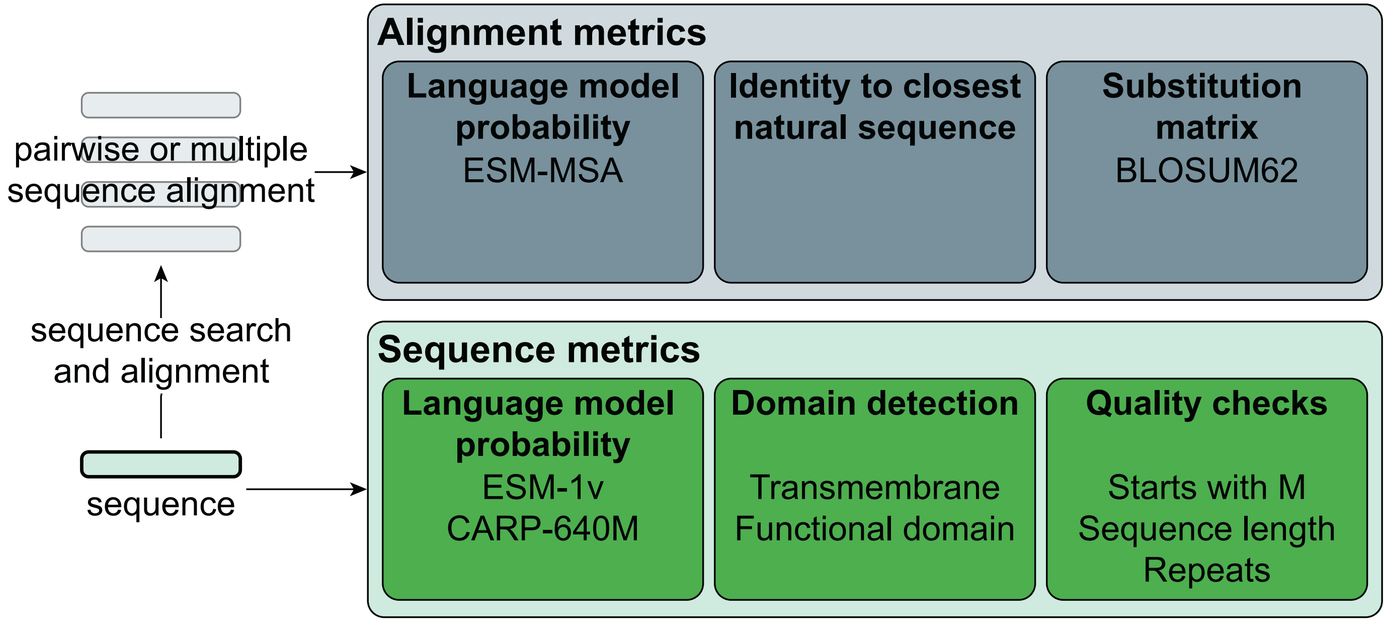

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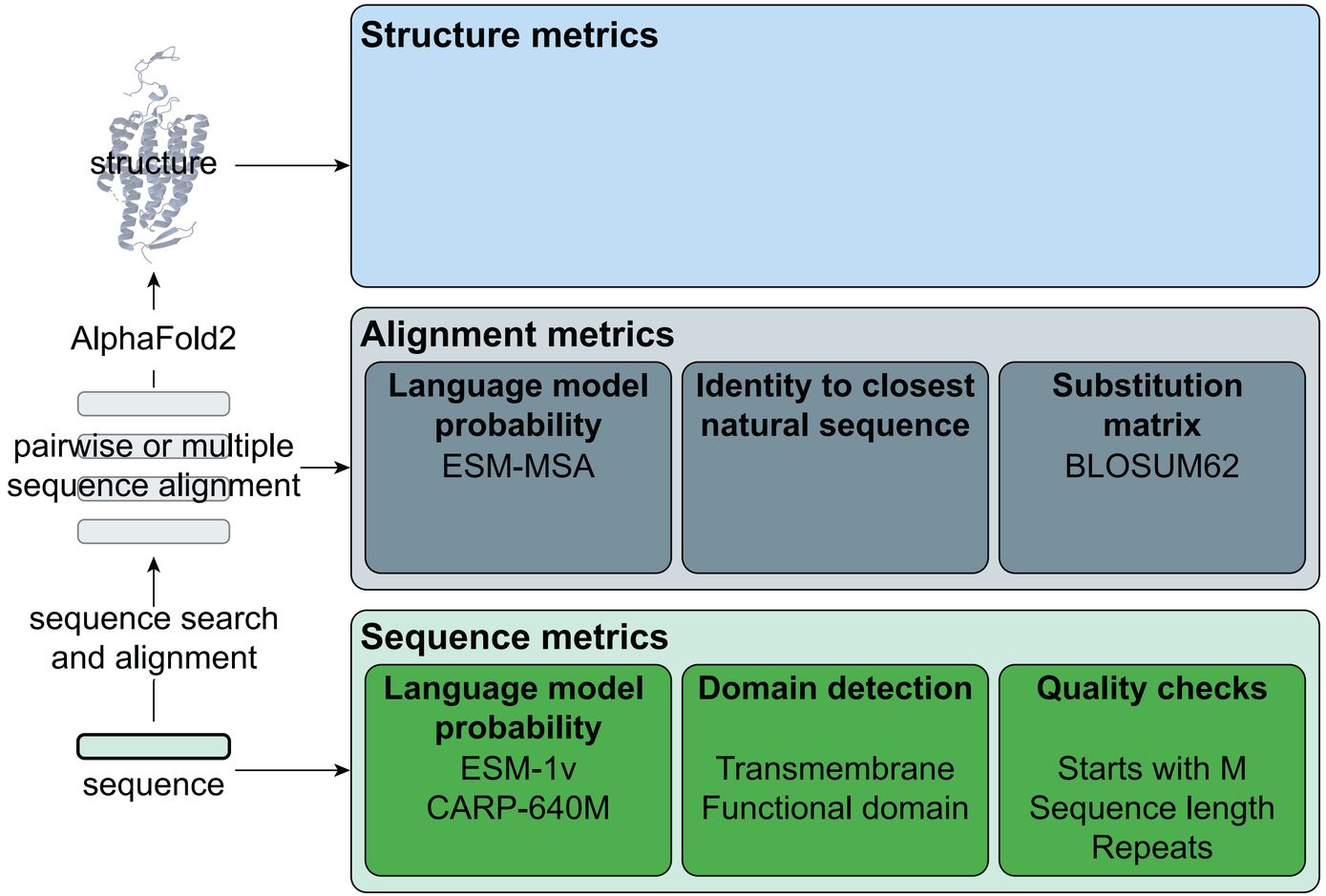

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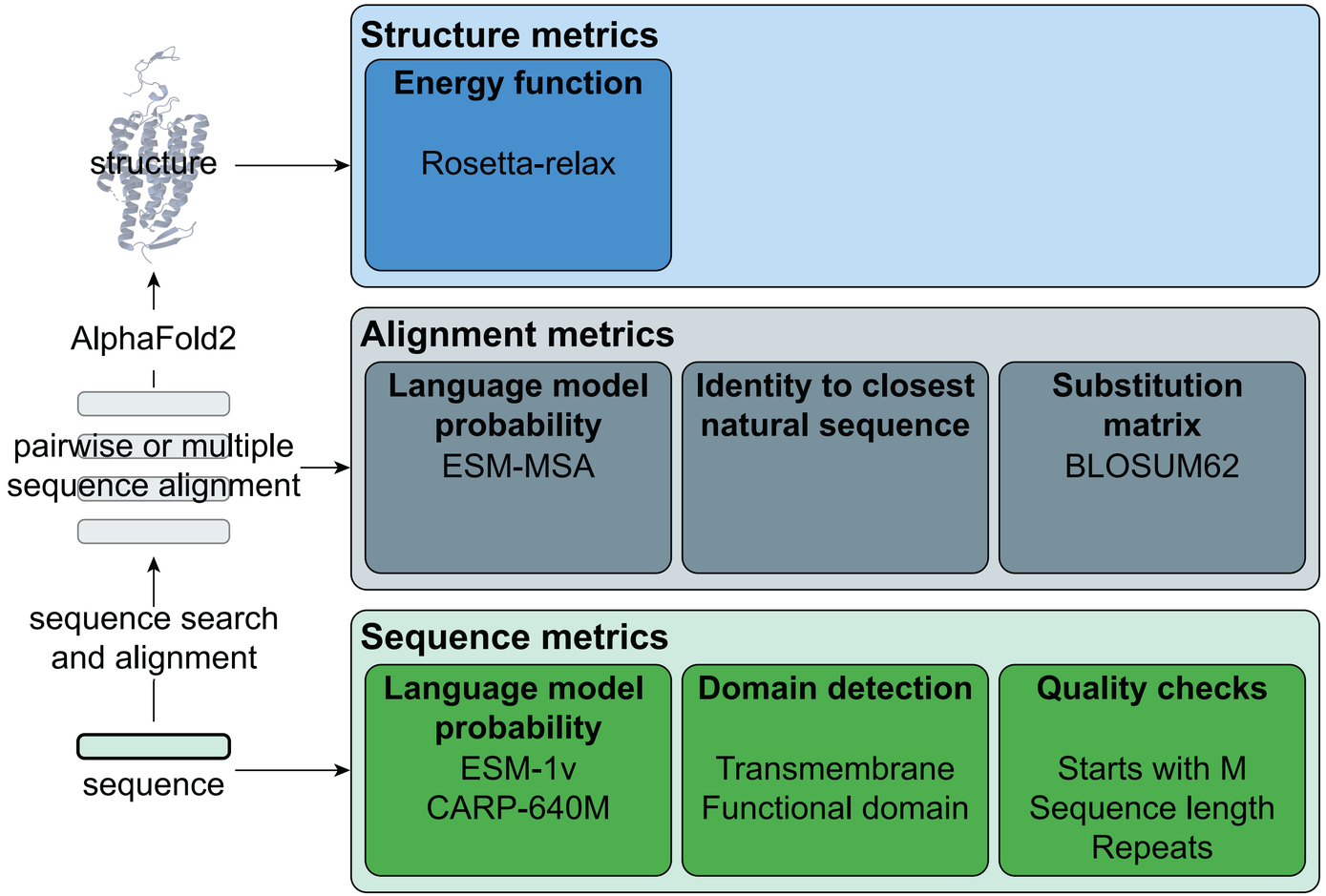

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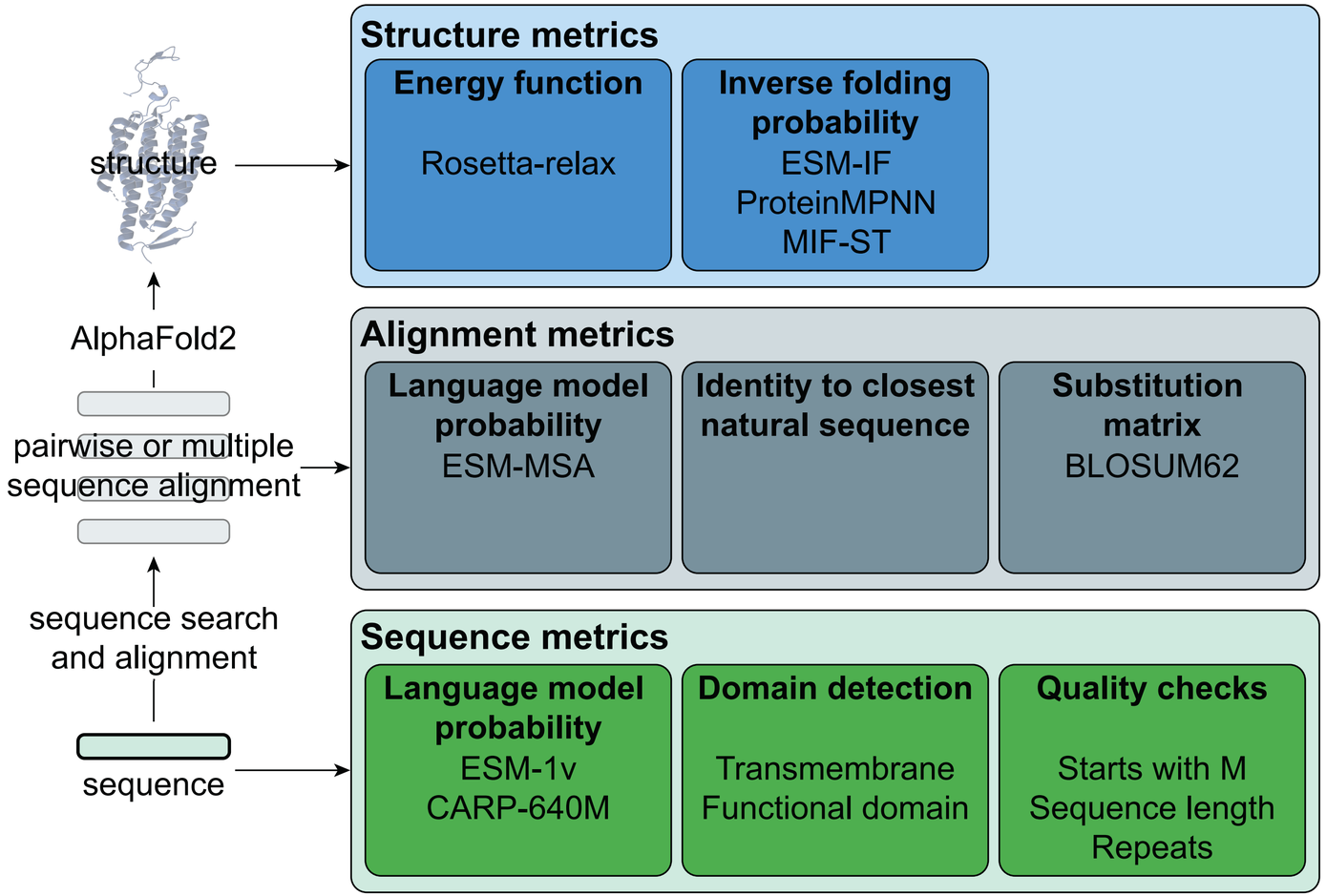

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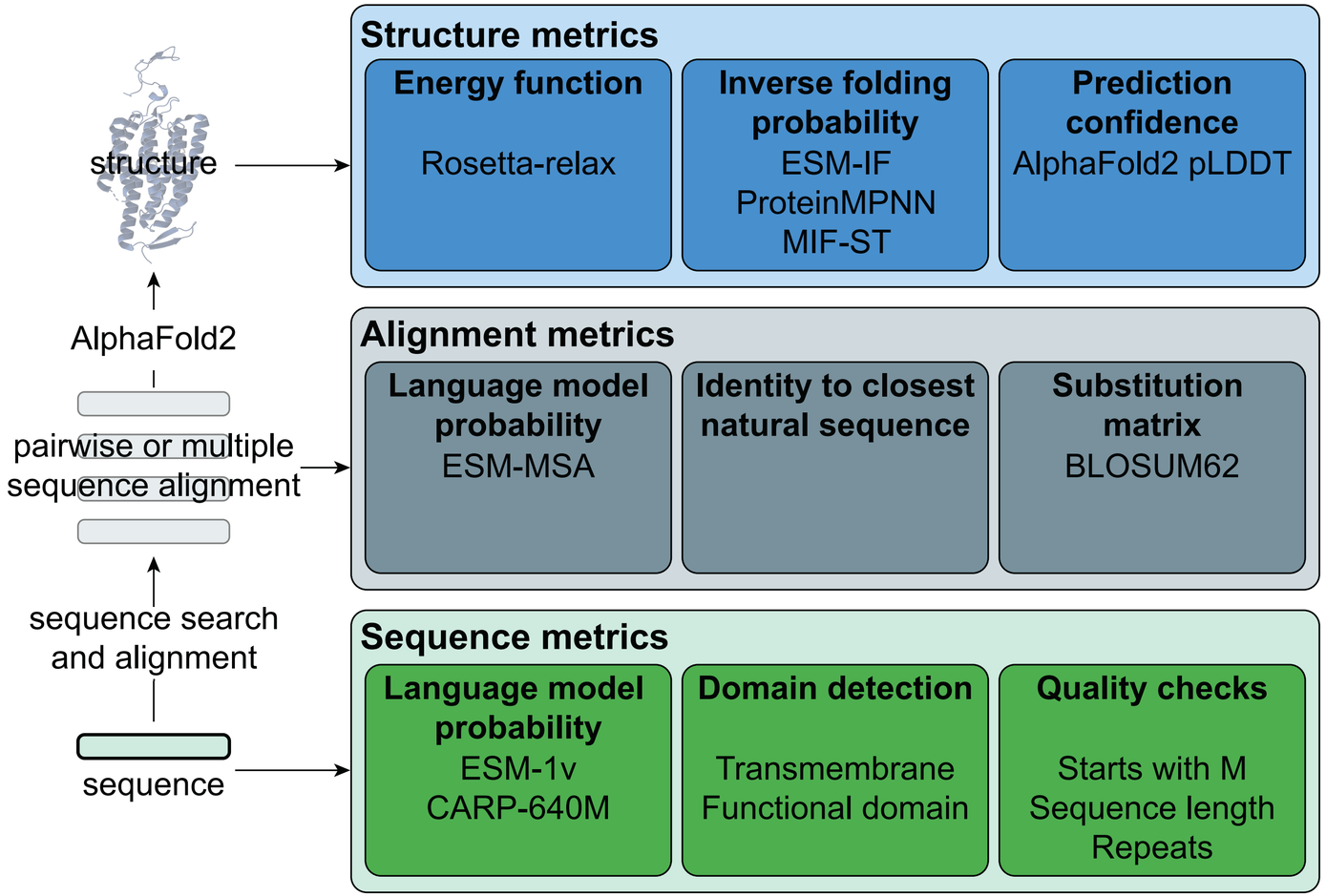
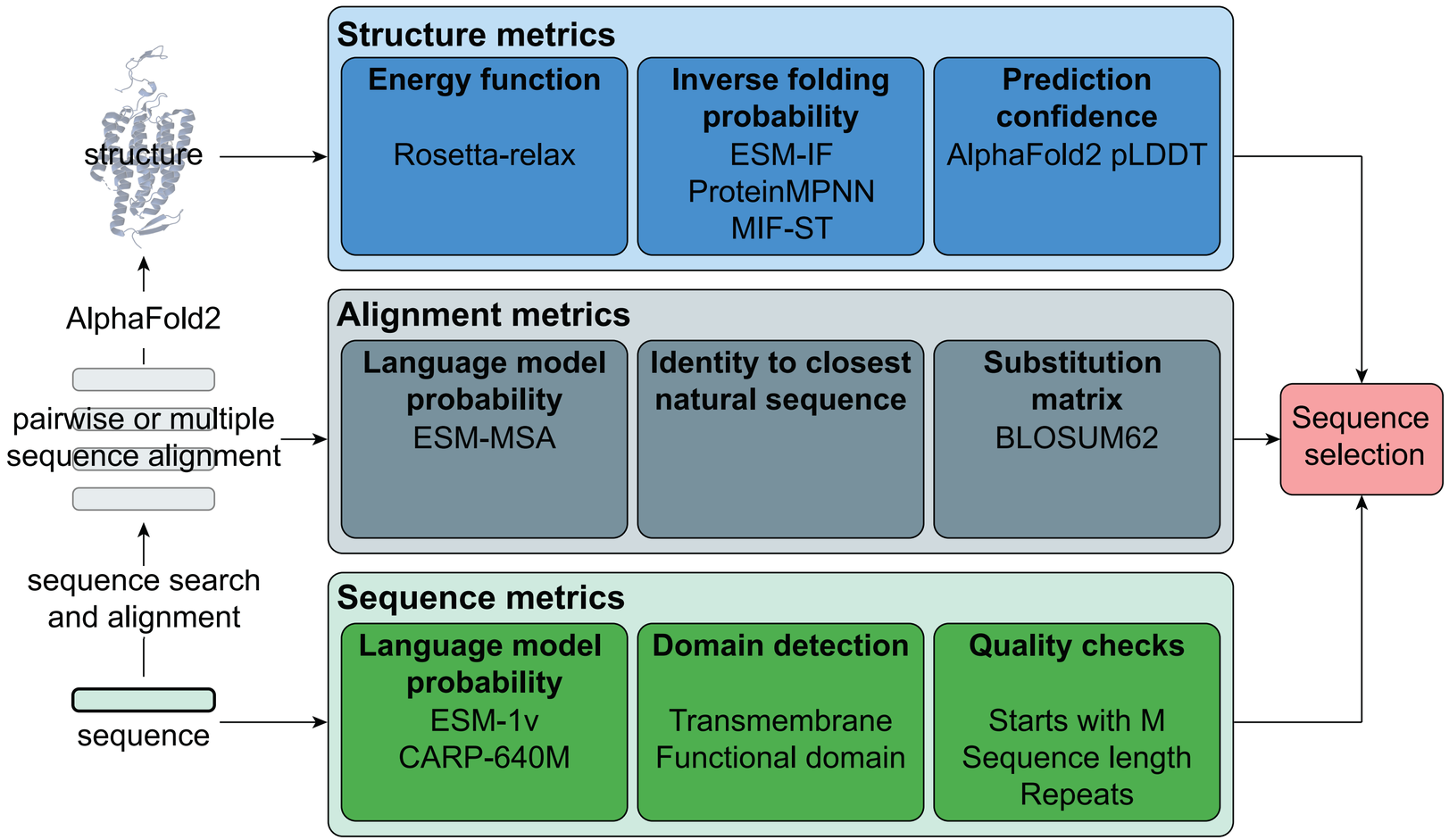
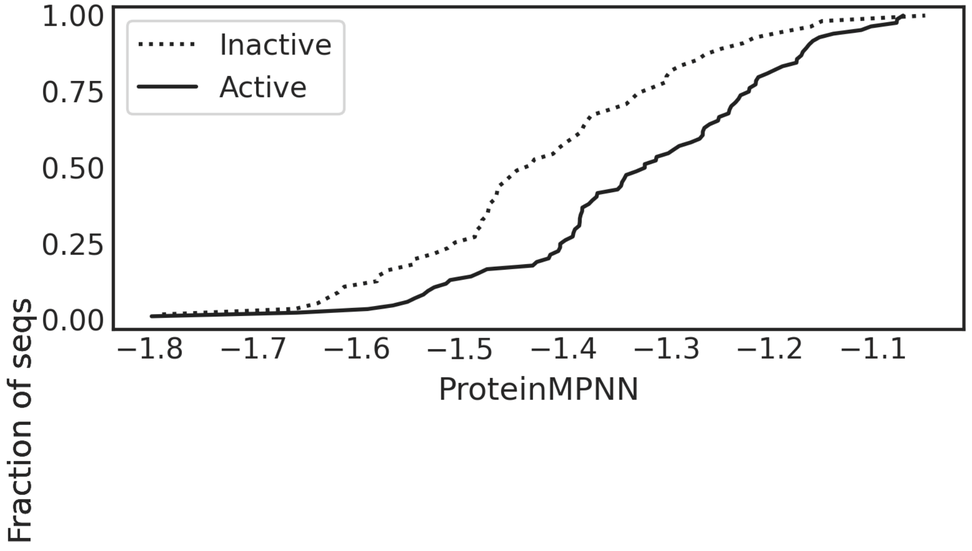


Many possible metrics for selection



Choose metrics that are predictive, fast, and uncorrelated



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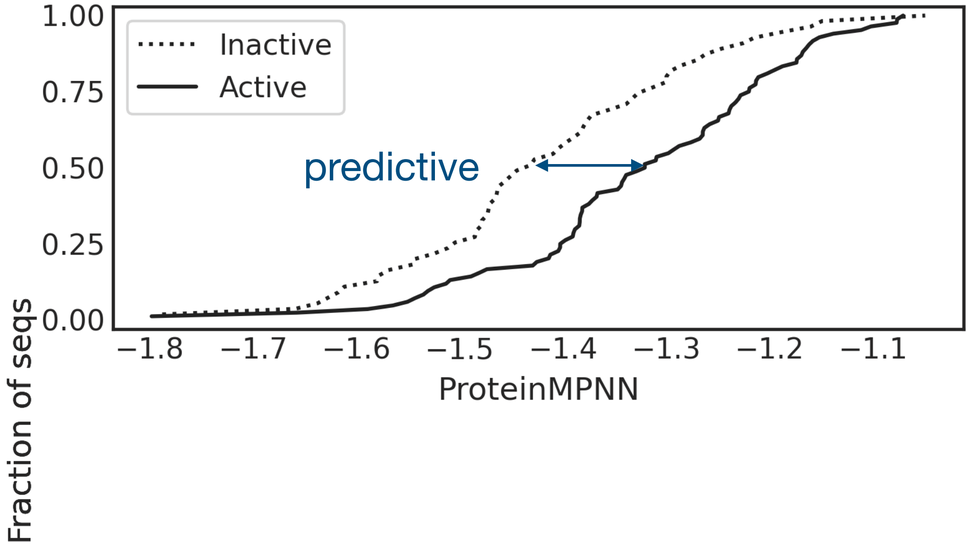

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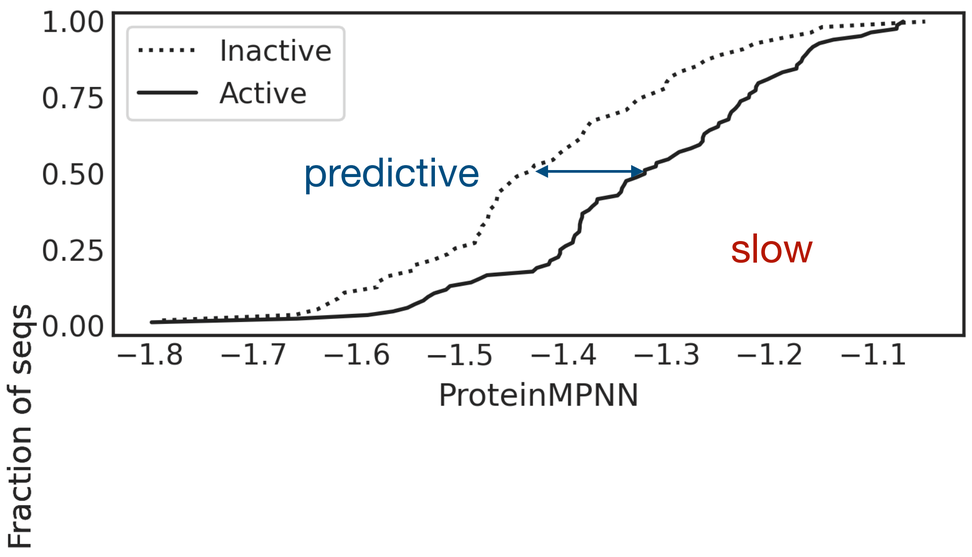

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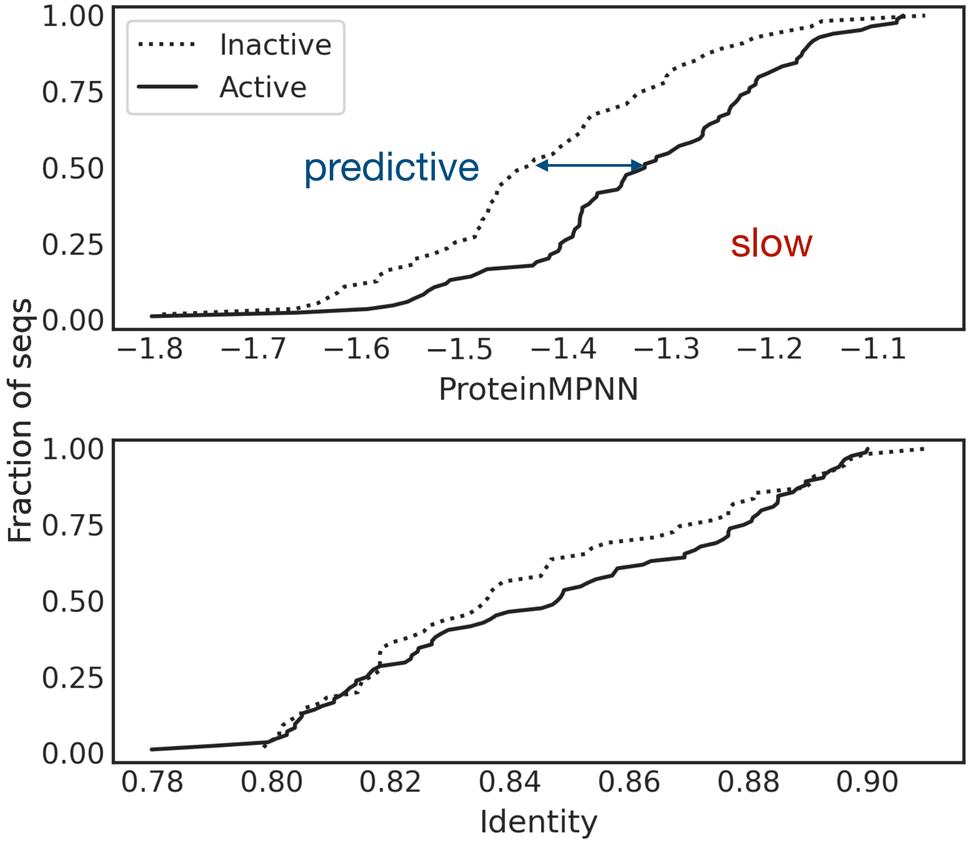

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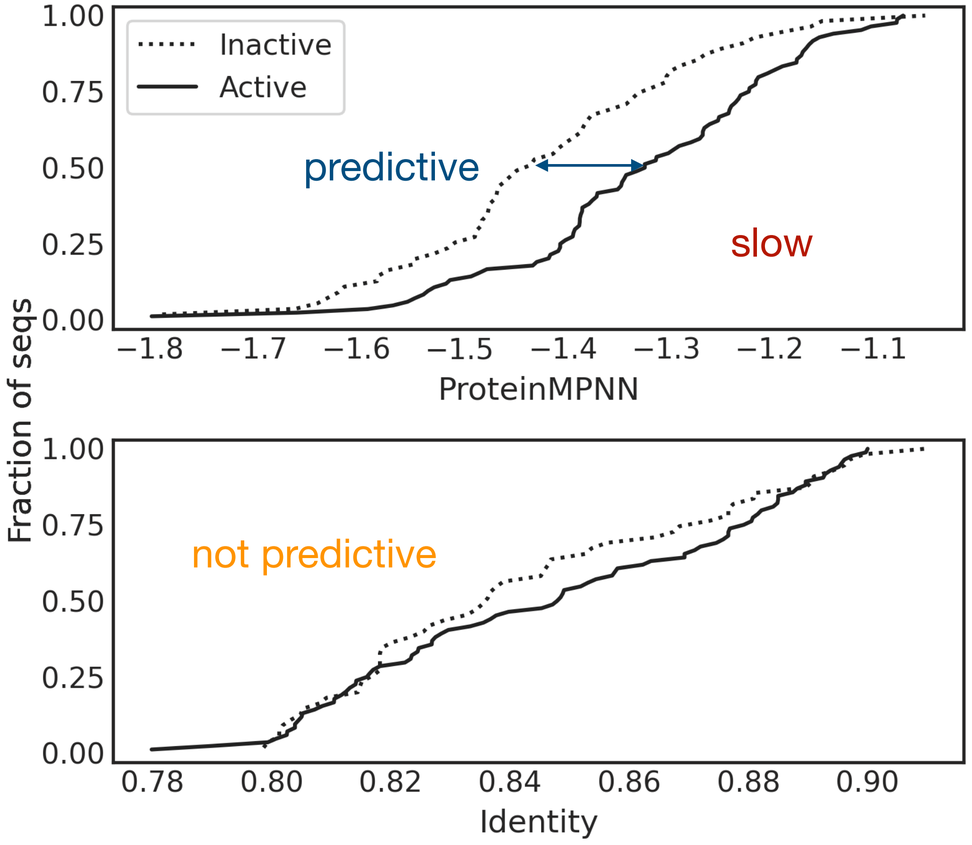

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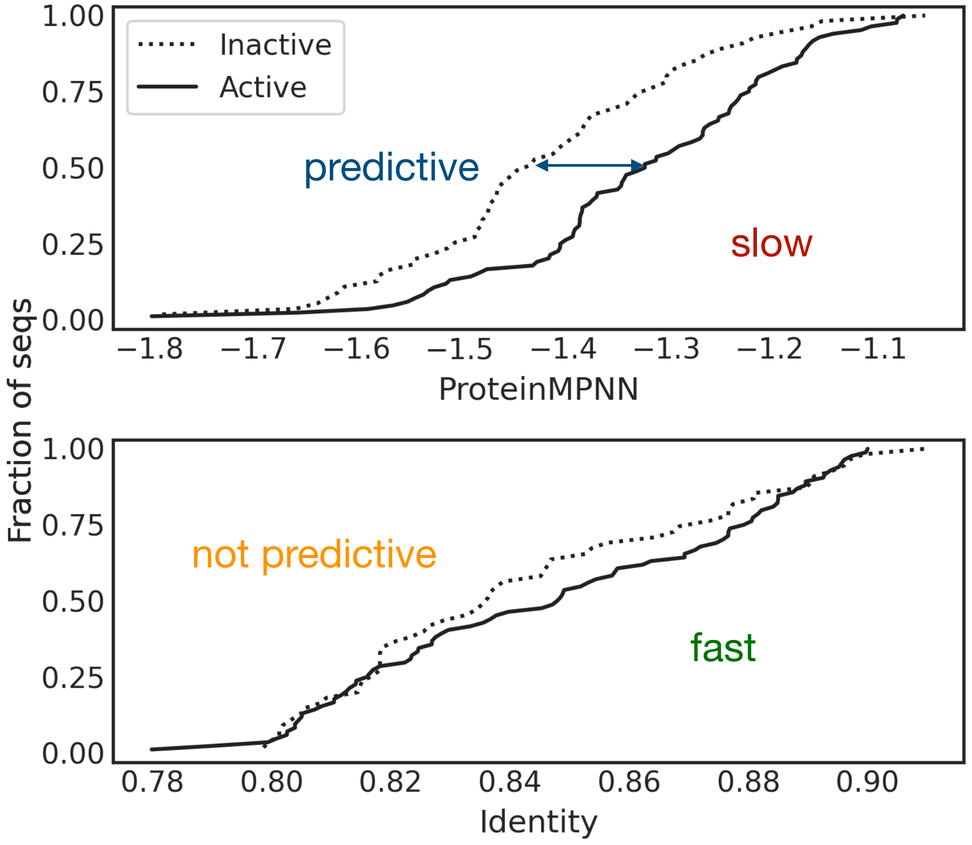

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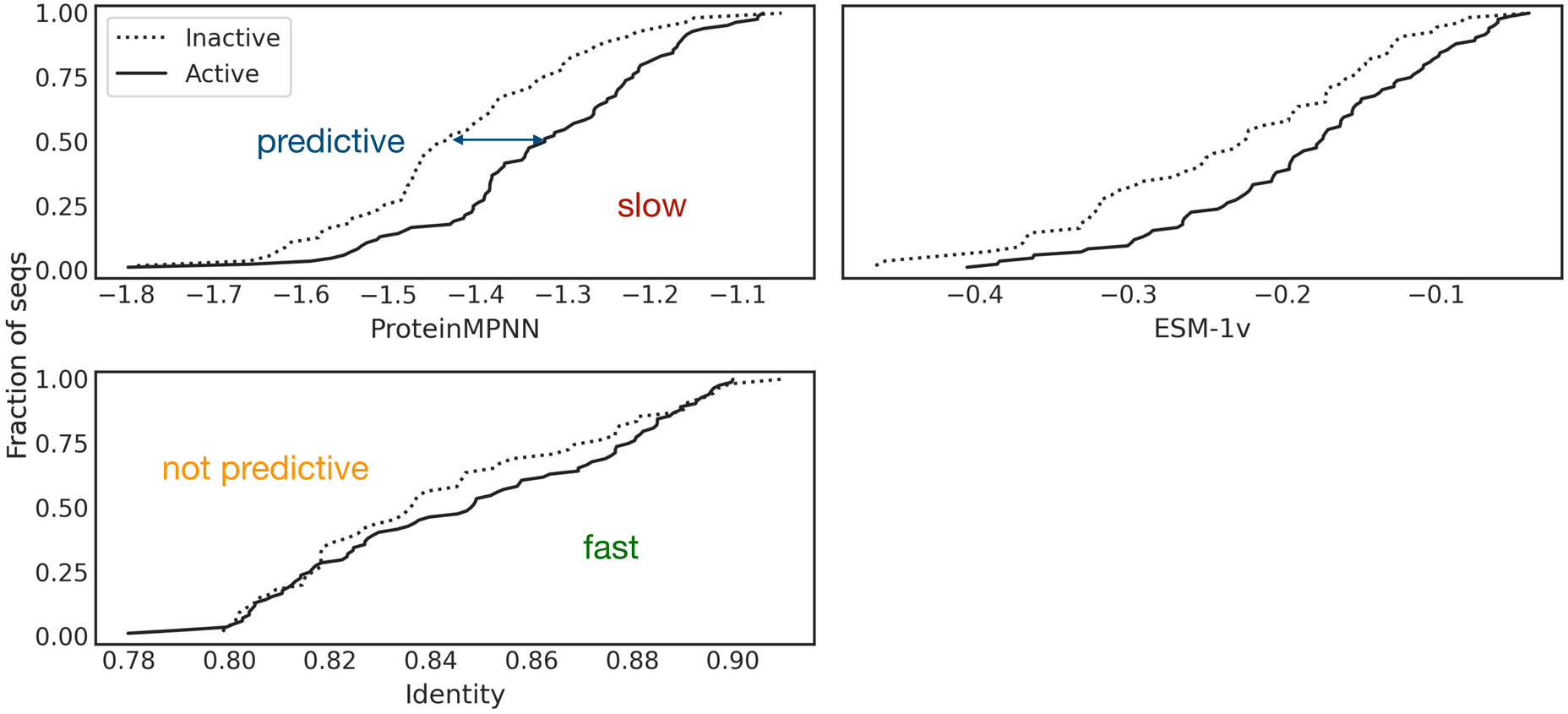

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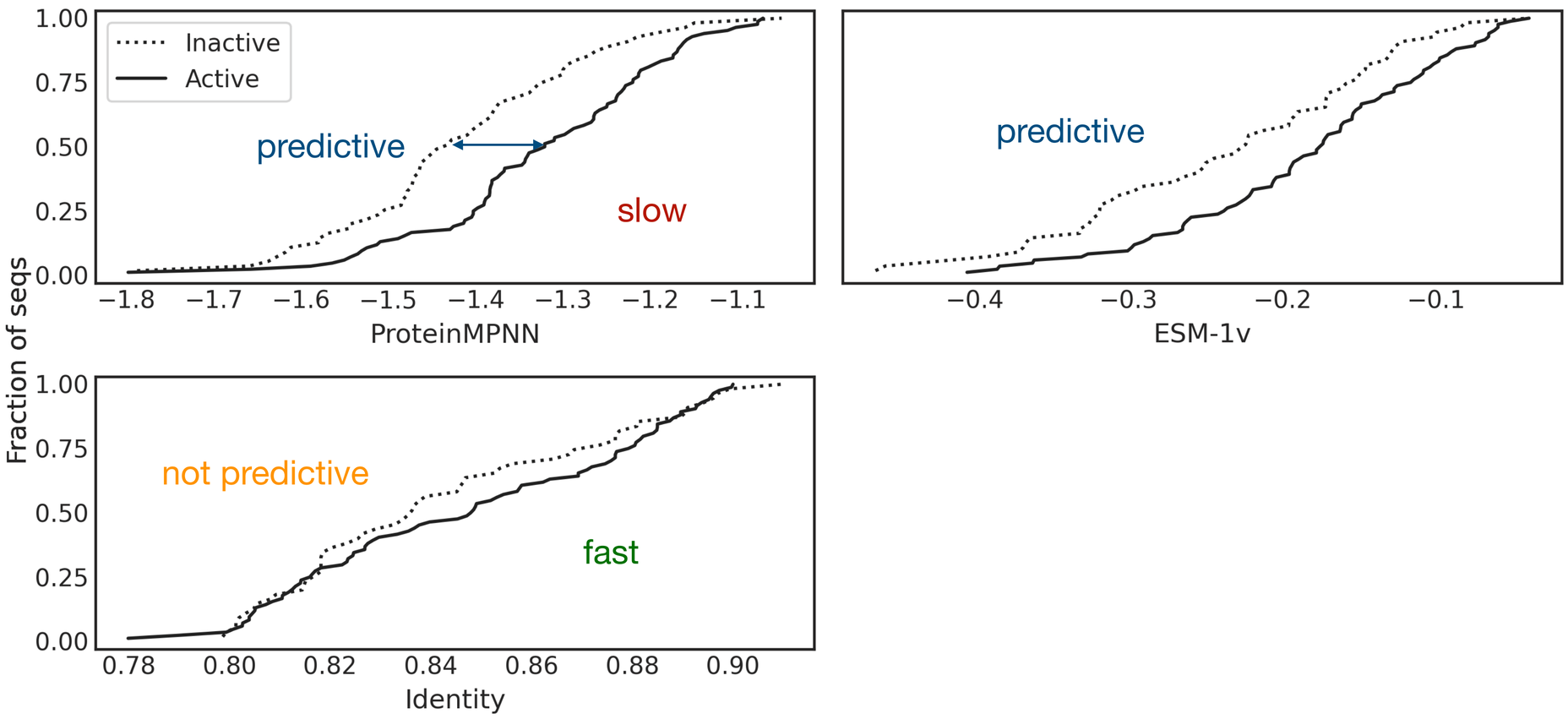

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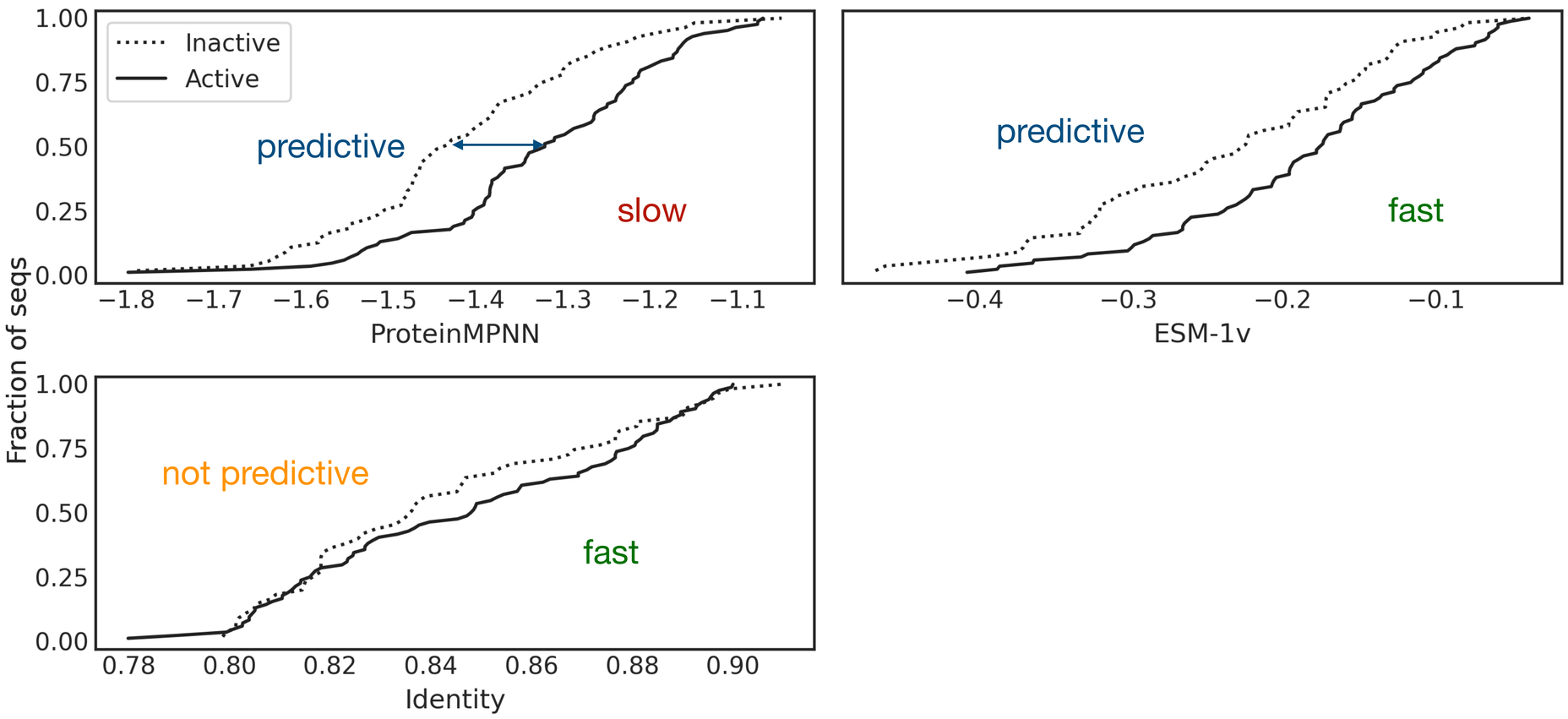

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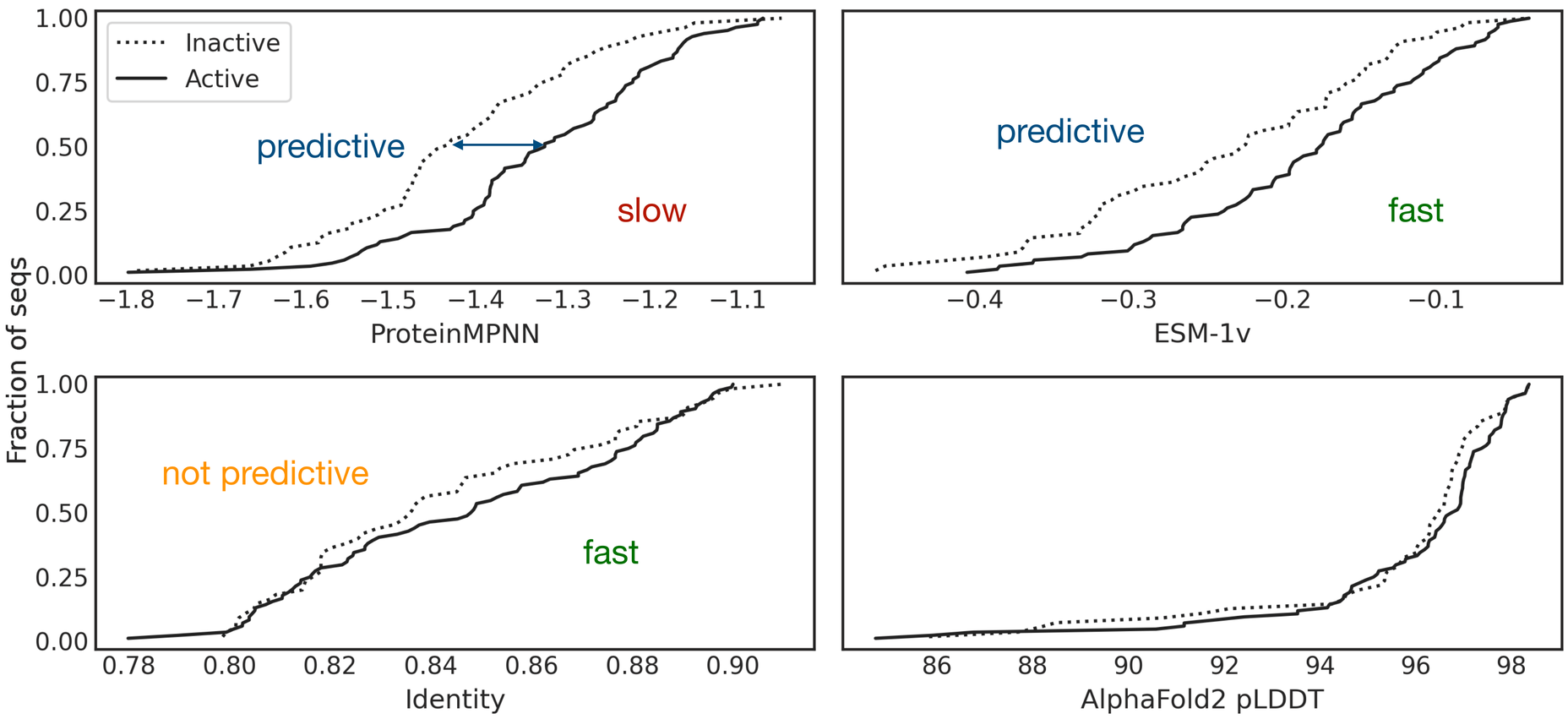

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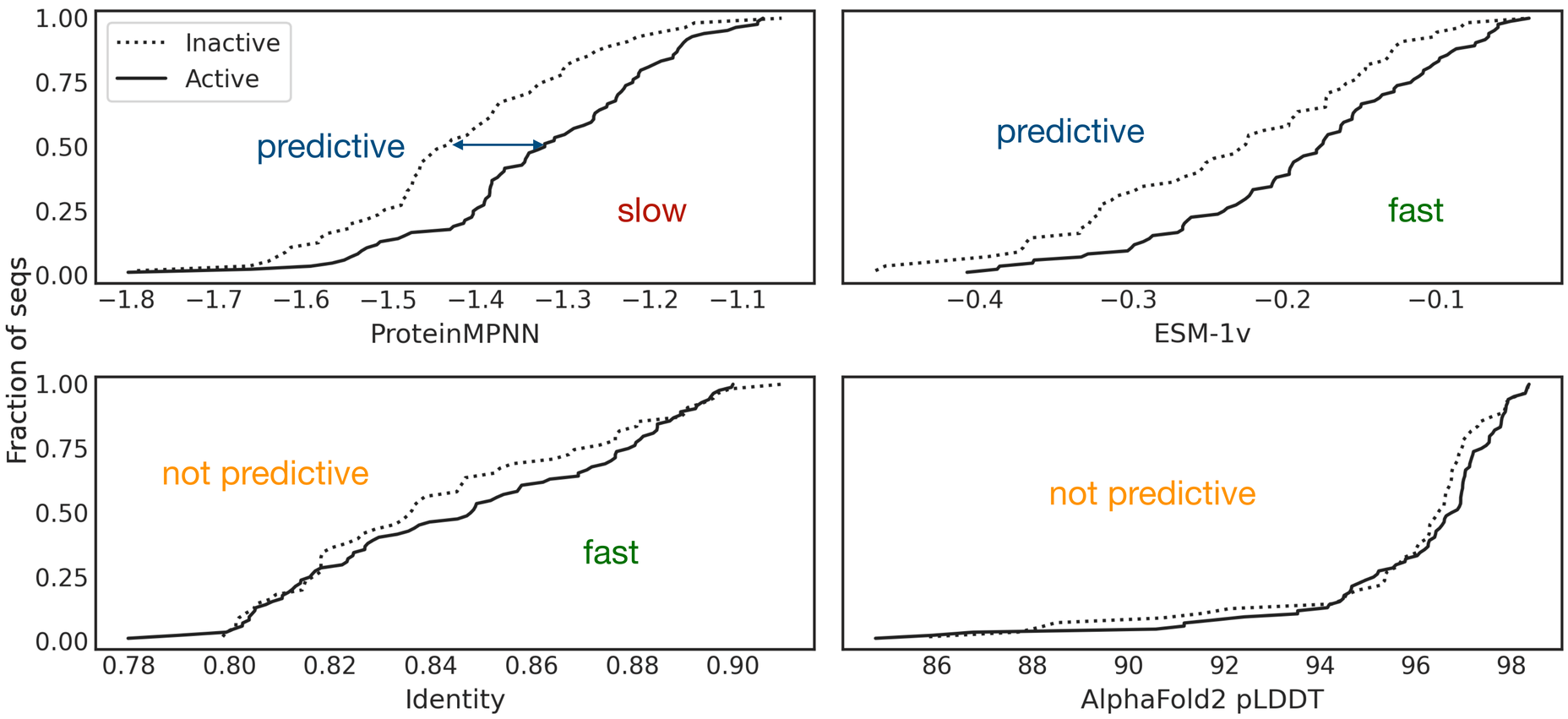

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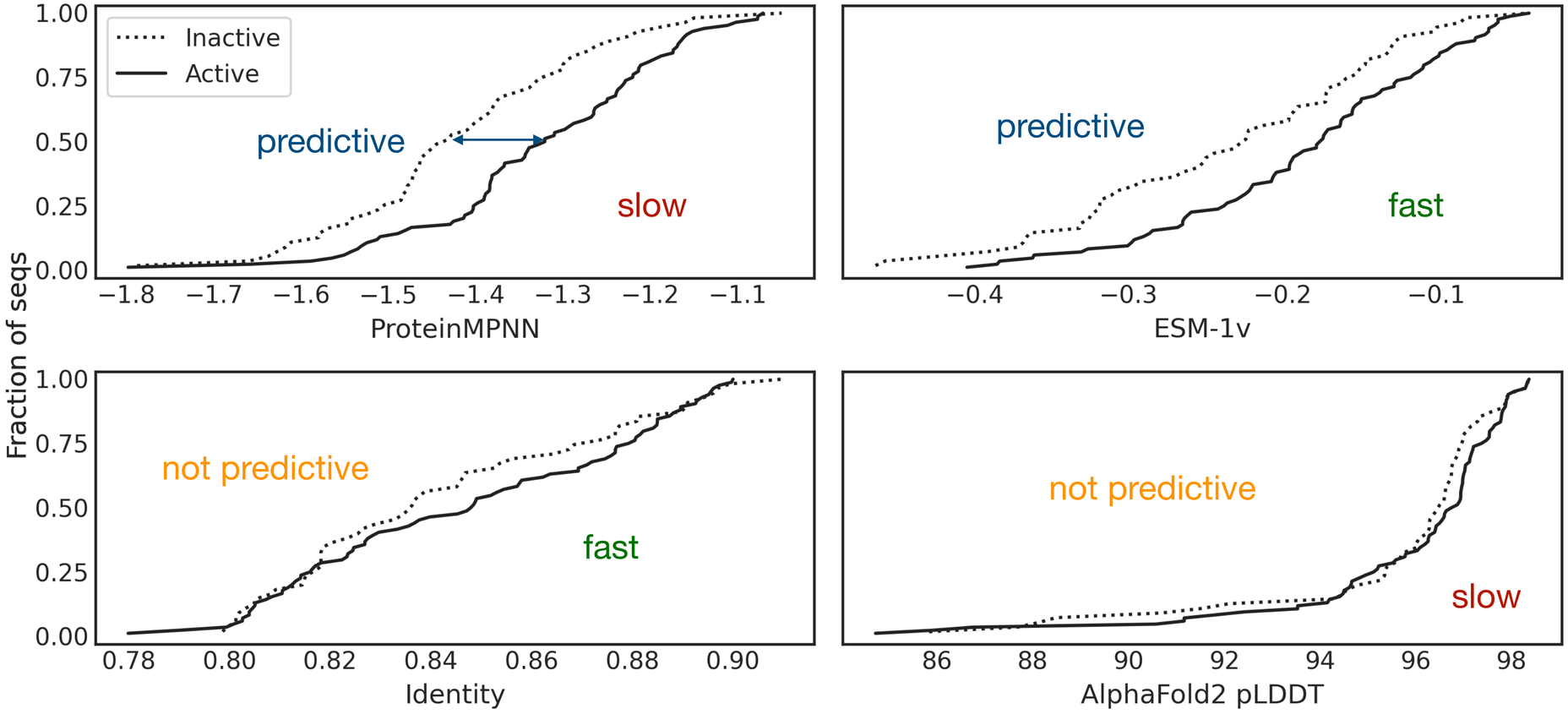

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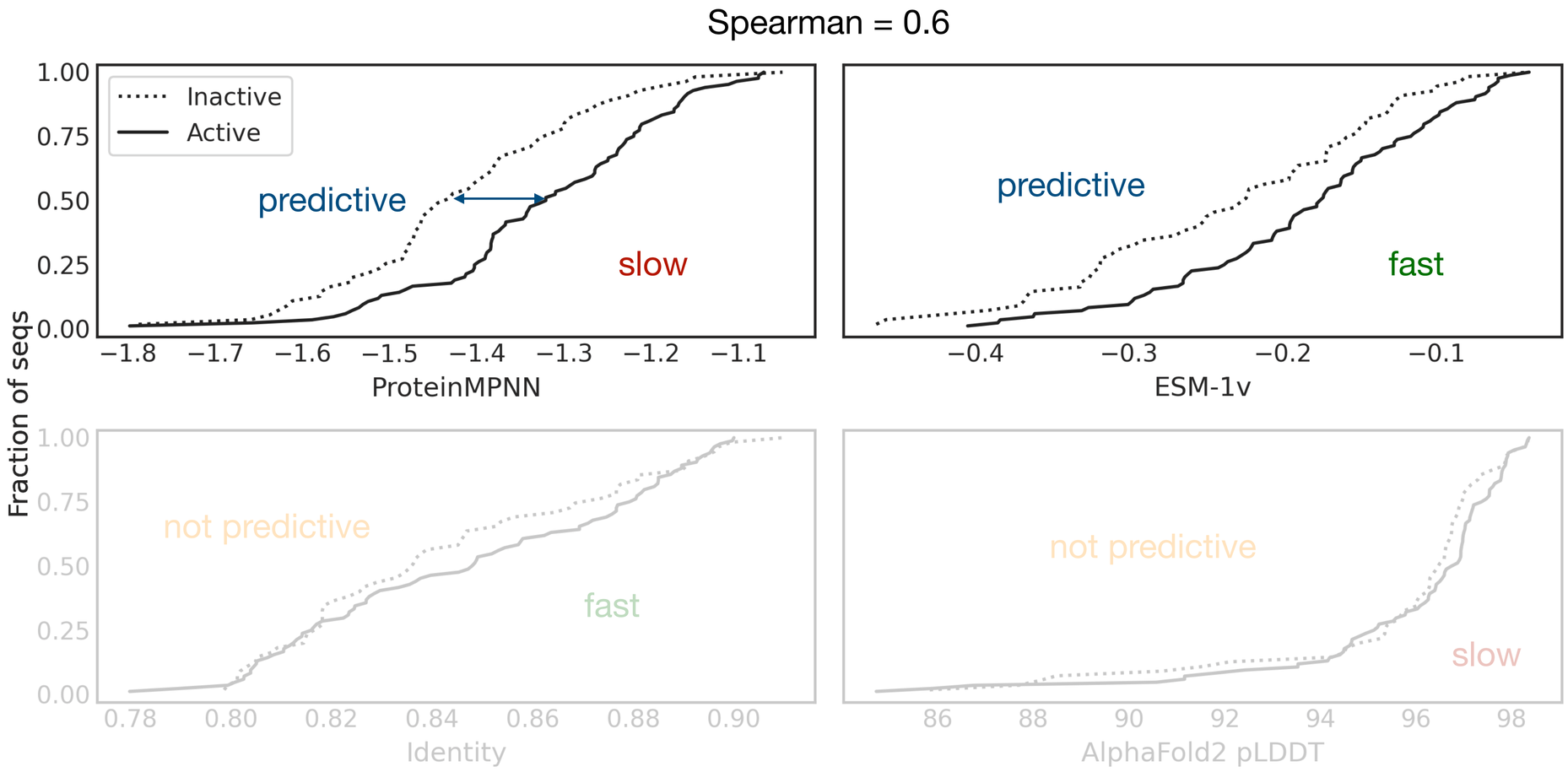
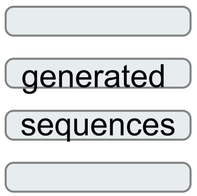


Combine many models into a filtering pipeline



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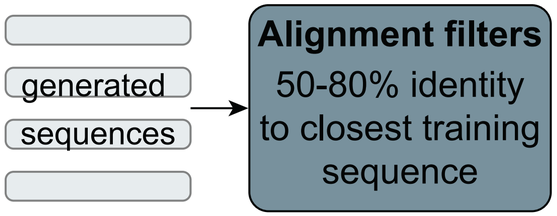

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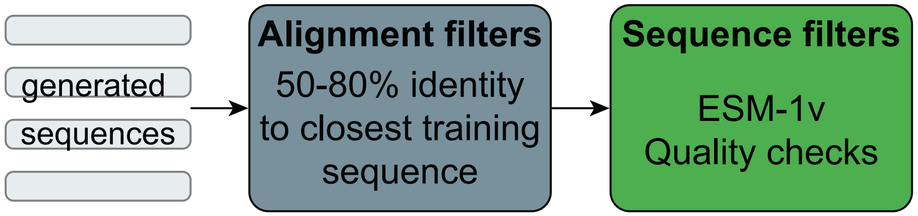

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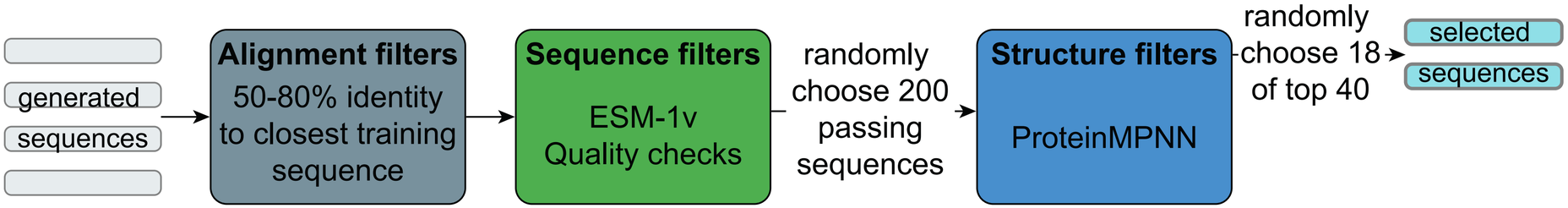

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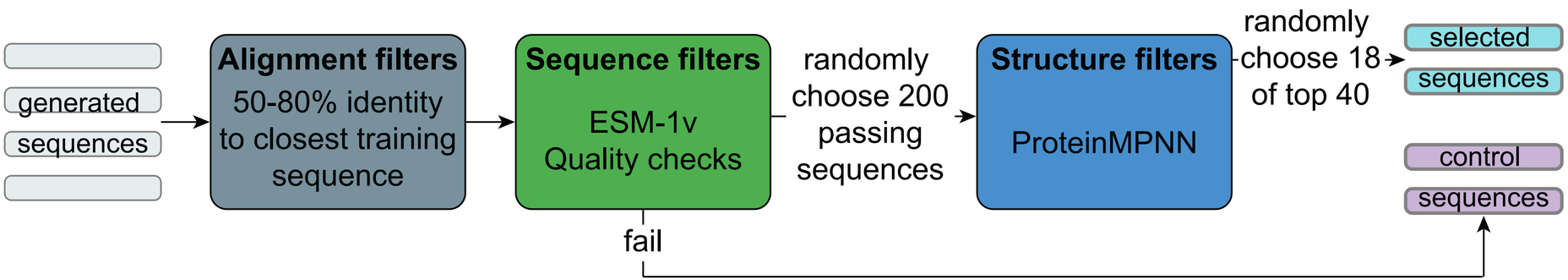
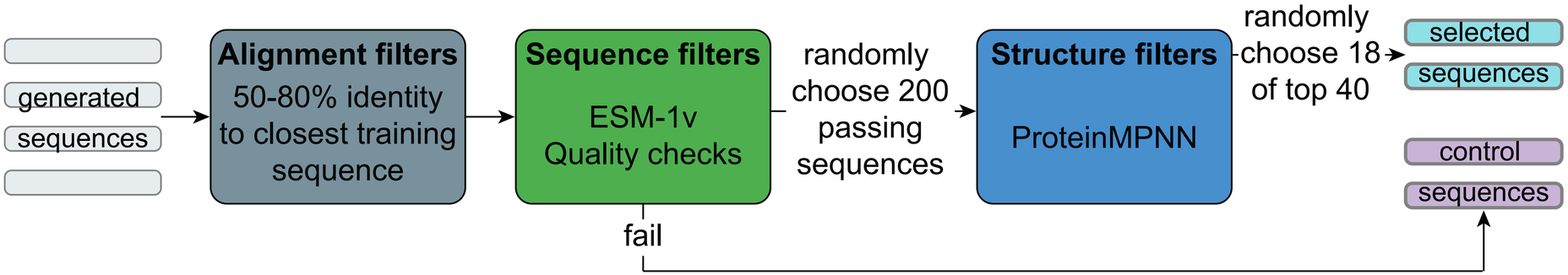
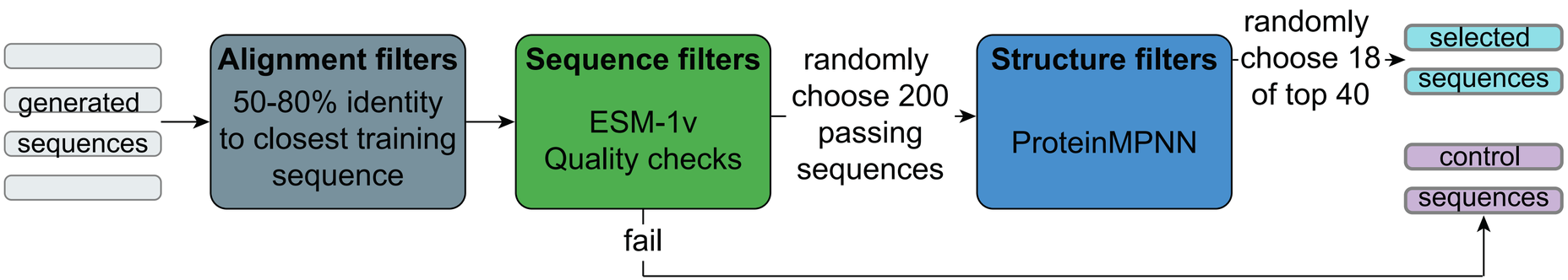


Pipeline increases number of active variants found



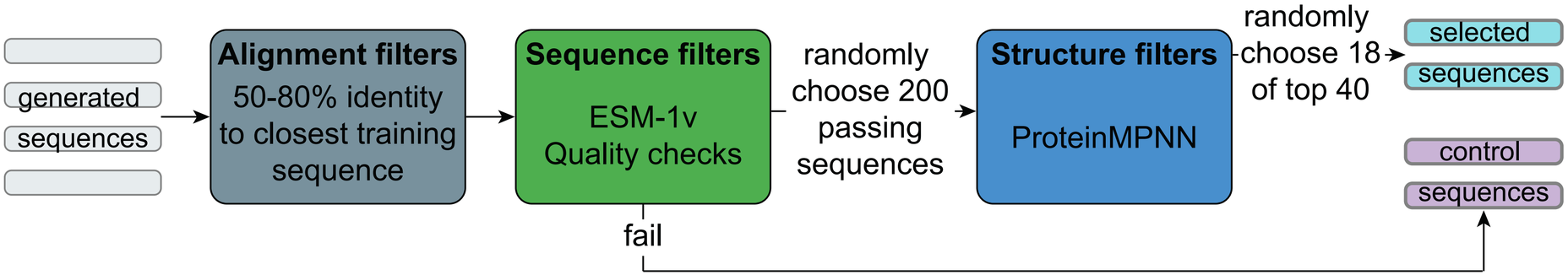
	Naive	Checks
Active	2 / 71	35 / 72

Pipeline increases number of active variants found



	Naive	Checks	Control
Active	2 / 71	35 / 72	32 / 72

Pipeline increases number of active variants found



	Naive	Checks	Control
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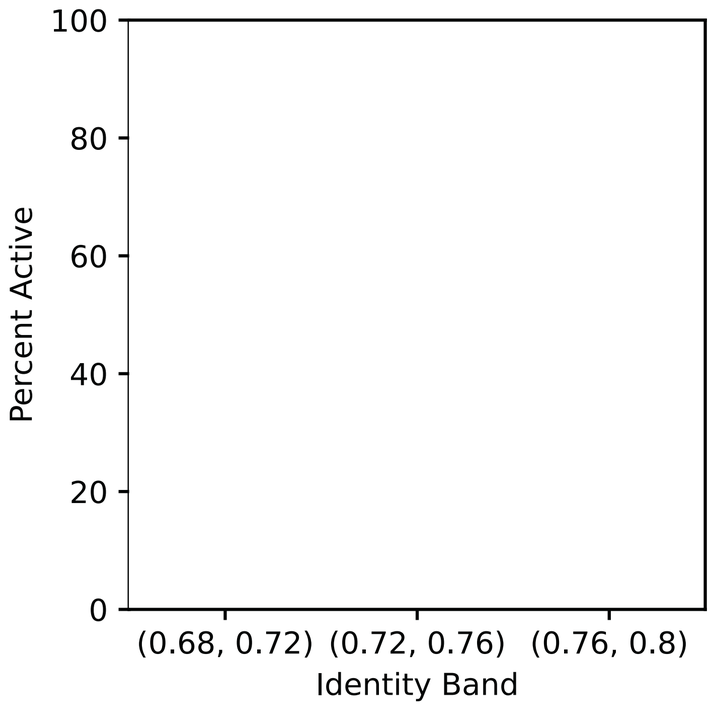

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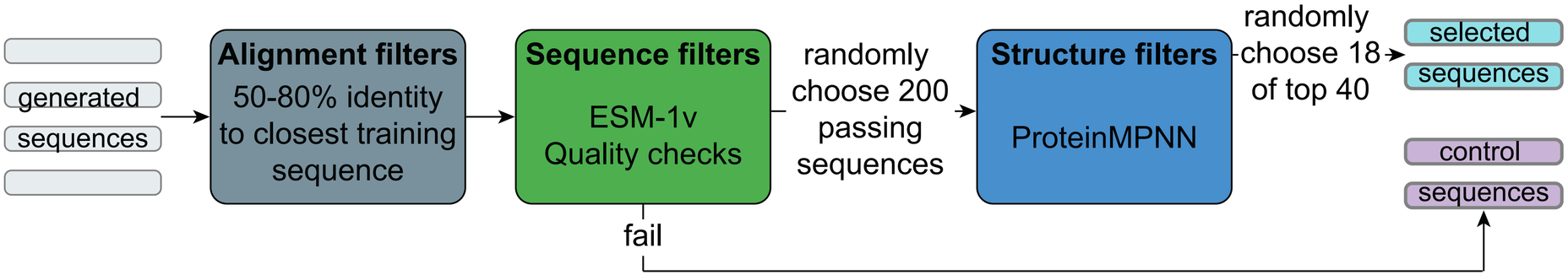
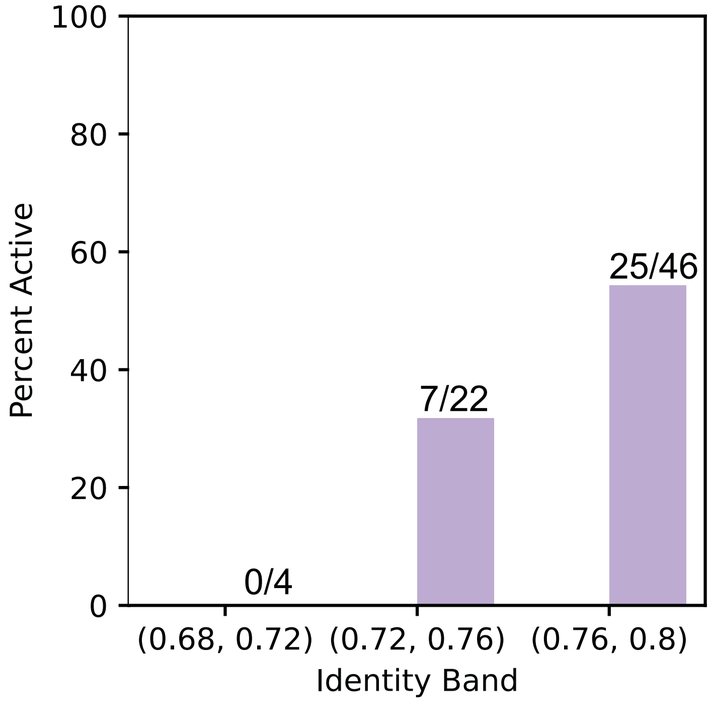


	Naive	Checks	Control
Active	2 / 71	35 / 72	32 / 72



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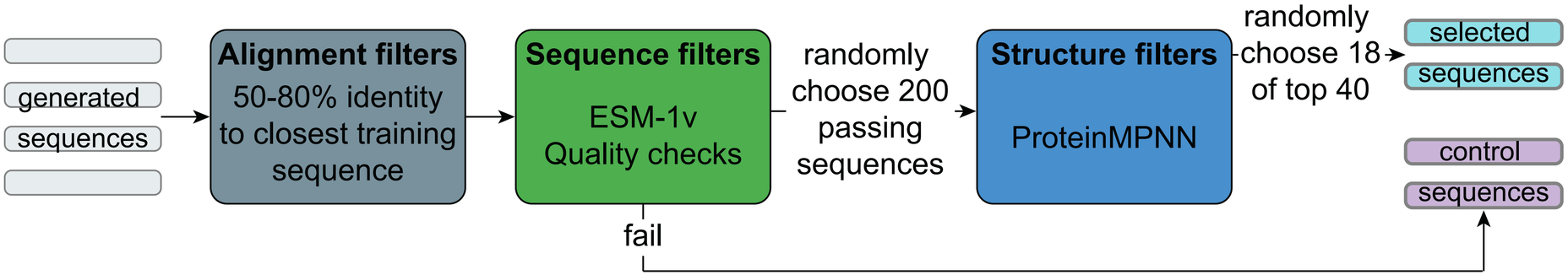
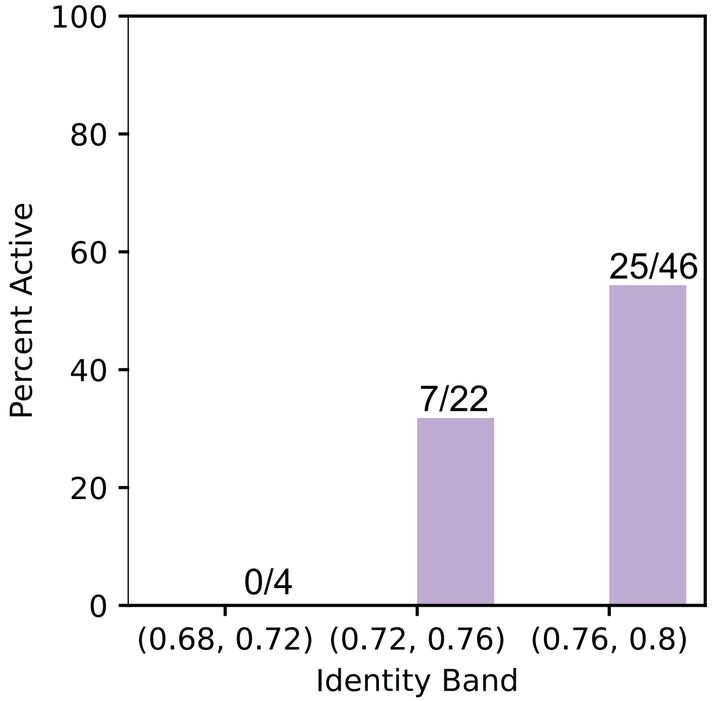
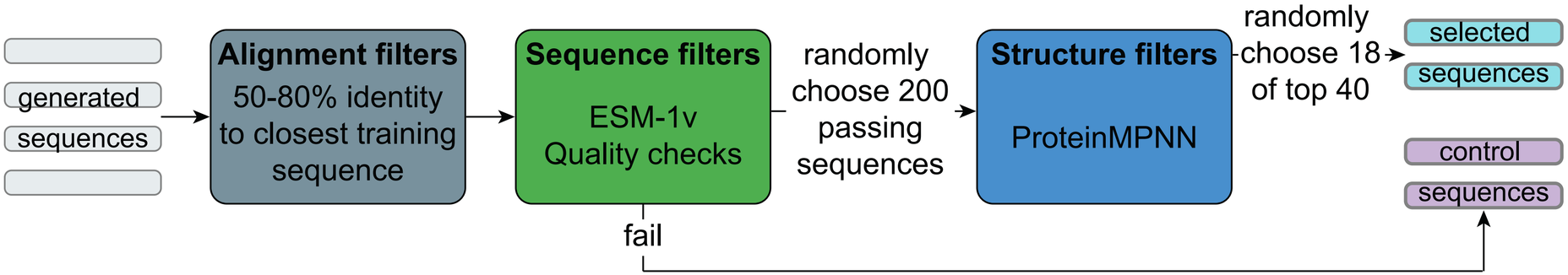


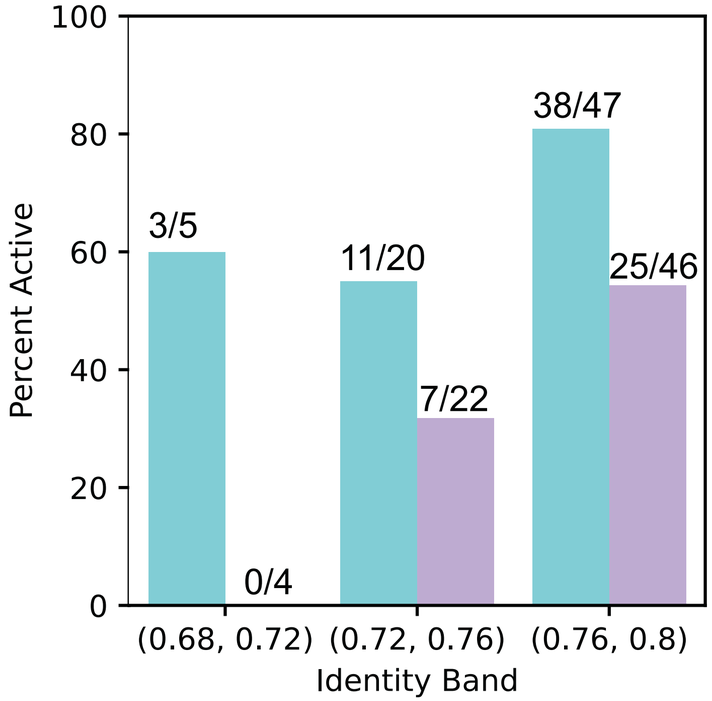
	Naive	Checks	Control	Selected
Active	2 / 71	35 / 72	32 / 72	52 / 72



Pipeline increases number of active variants found



	Naive	Checks	Control	Selected
Active	2 / 71	35 / 72	32 / 72	52 / 72



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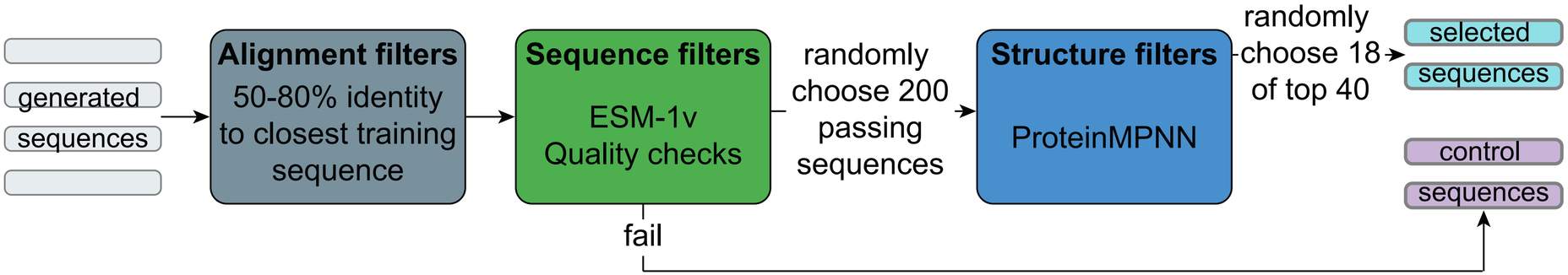
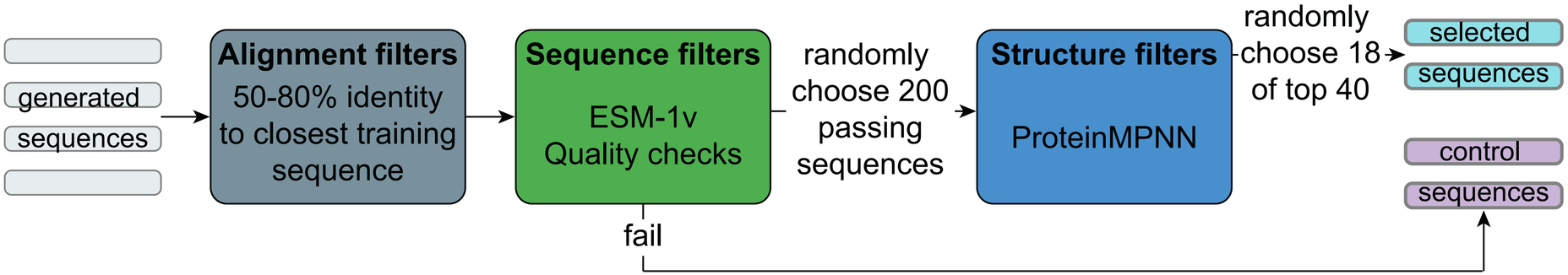


Model	Enzyme	Naive	Checks	Control	Selected
GAN	MDH	0 / 18	2 / 18		
	CuSOD	2 / 18	12 / 18		
ESM-MSA	MDH	0 / 17	9 / 18		
	CuSOD	0 / 18	12 / 18		
Total		2 / 71	35 / 72	32 / 72	52 / 72

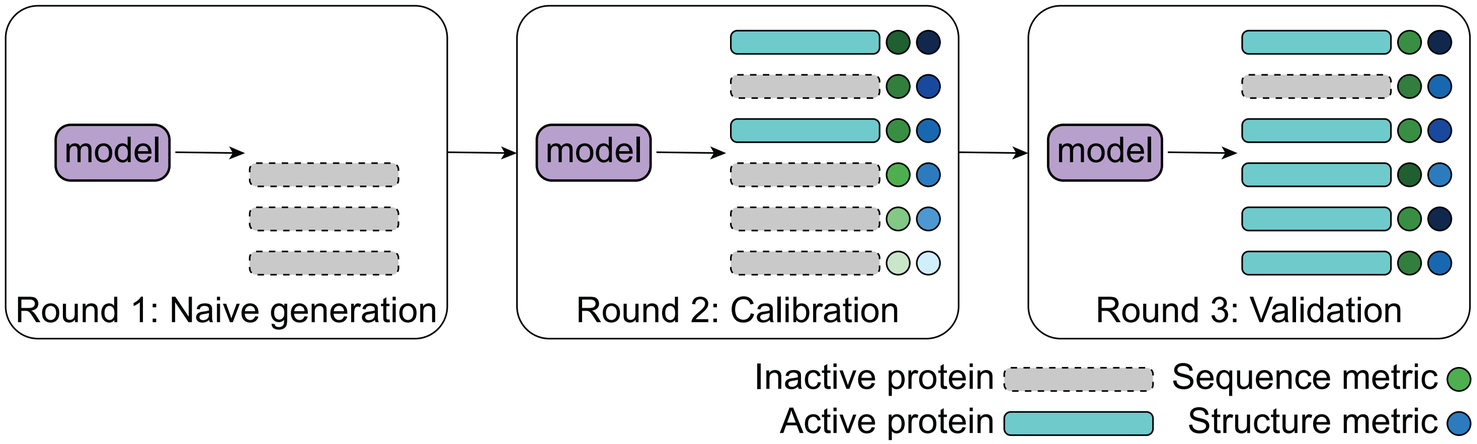
Pipeline increases number of active variants found



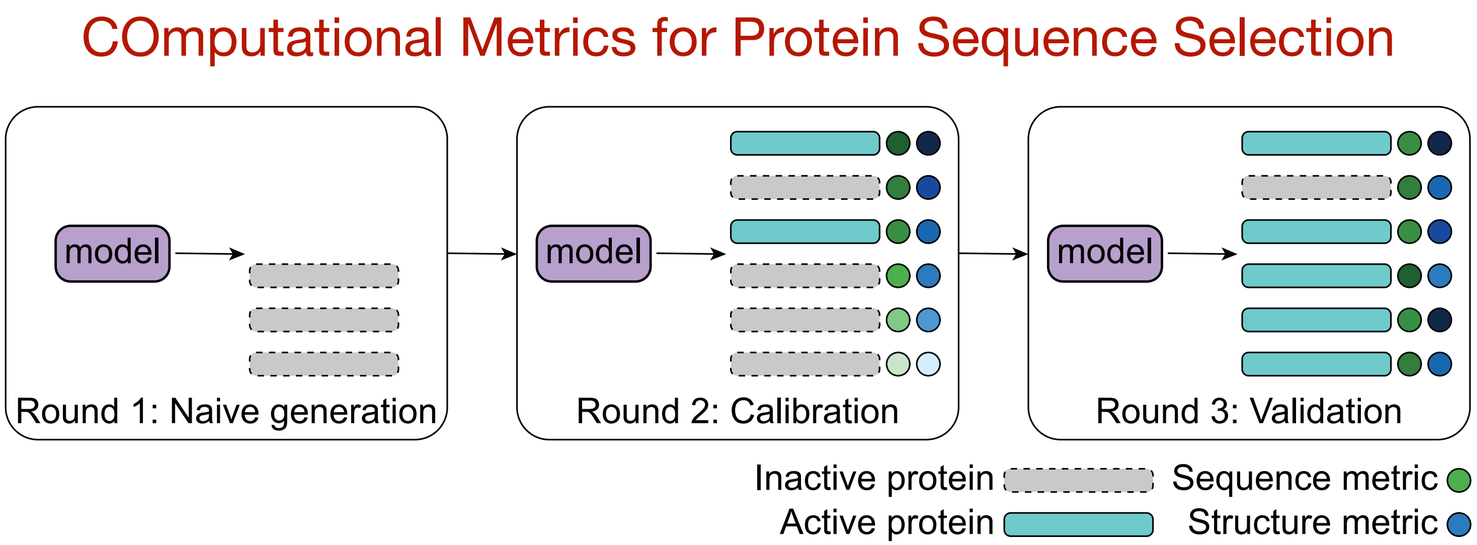
Model	Enzyme	Naive	Checks	Control	Selected
GAN	MDH	0 / 18	2 / 18	2 / 18	4 / 18
	CuSOD	2 / 18	12 / 18	9 / 18	13 / 18
ESM-MSA	MDH	0 / 17	9 / 18	12 / 18	18 / 18
	CuSOD	0 / 18	12 / 18	9 / 18	17 / 18
Total		2 / 71	35 / 72	32 / 72	52 / 72

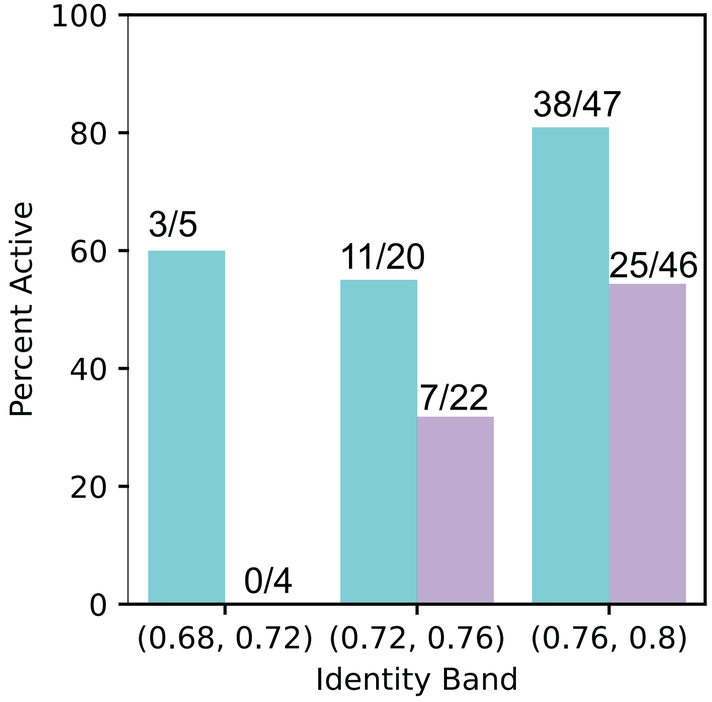
COMPSS is a tool for selecting generated proteins

COmputational Metrics for Protein Sequence Selection



COMPSS is a tool for selecting generated proteins





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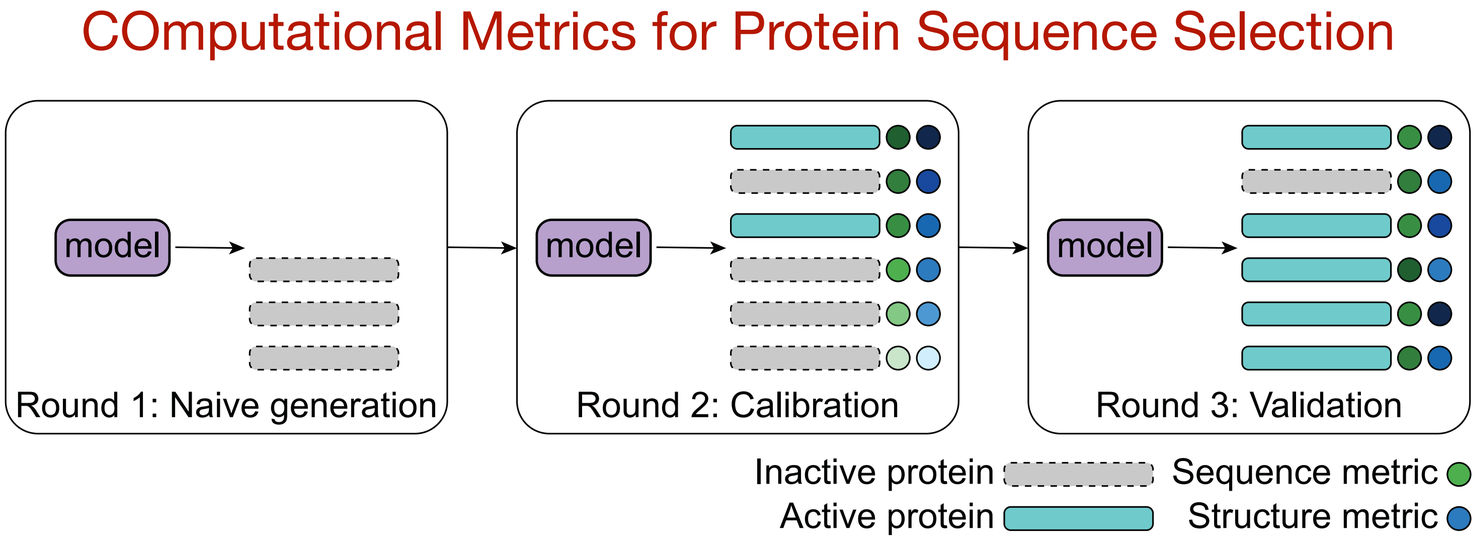
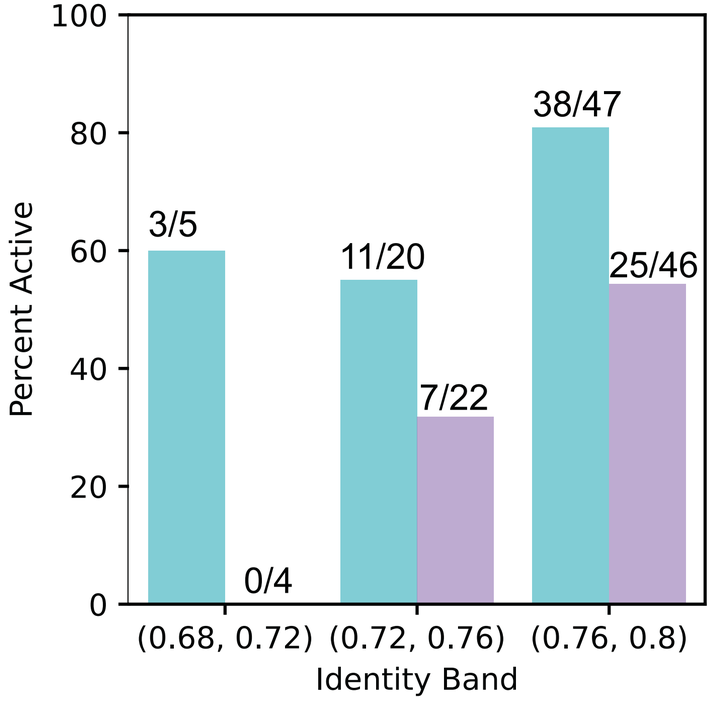
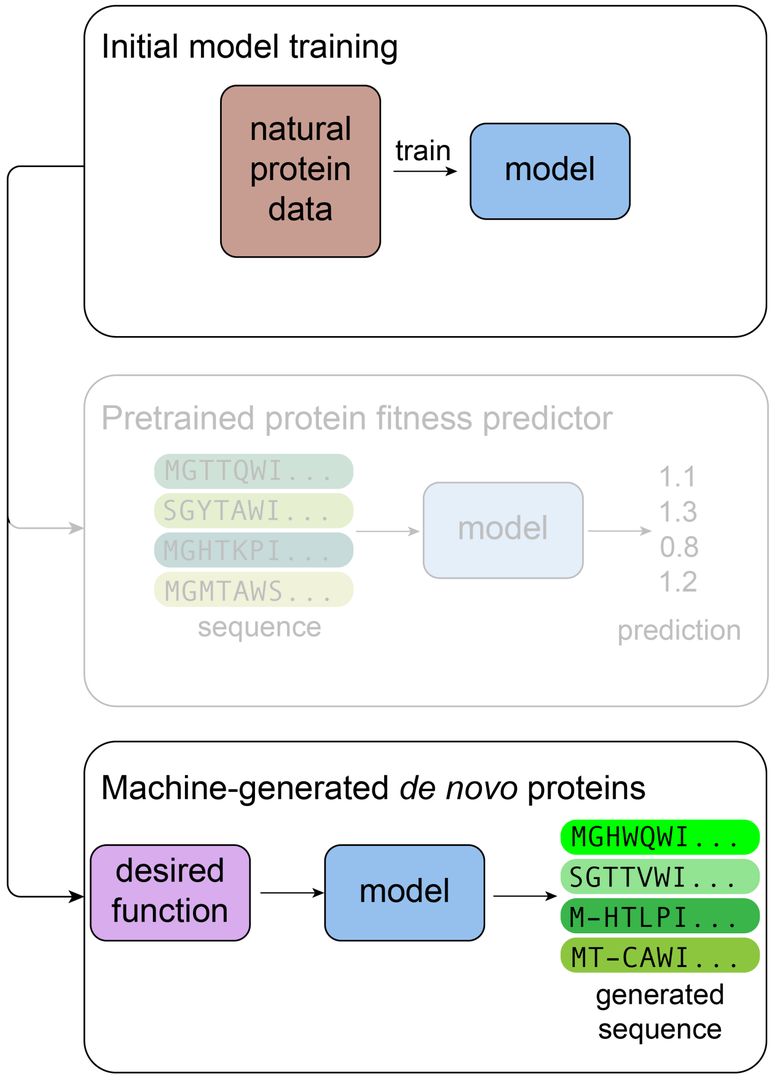
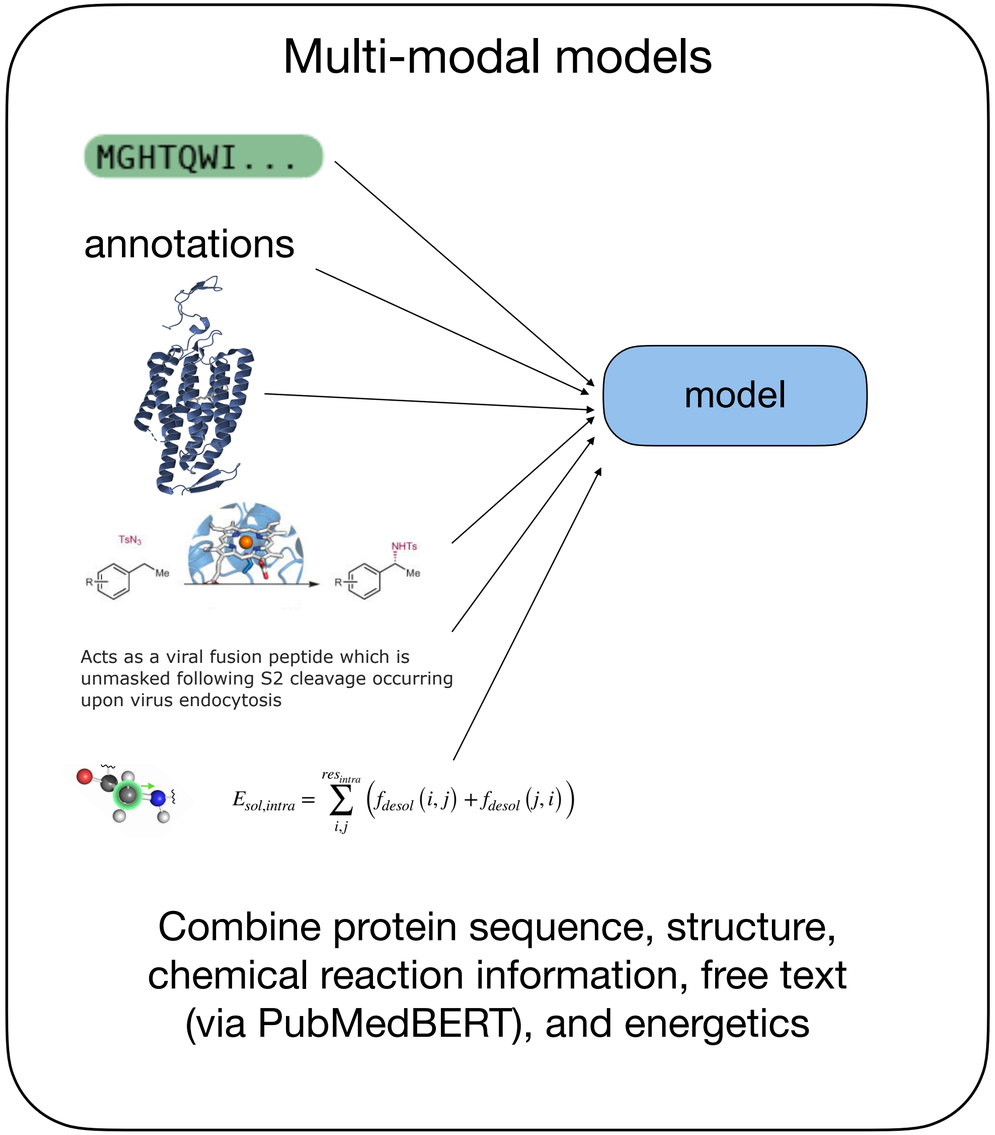




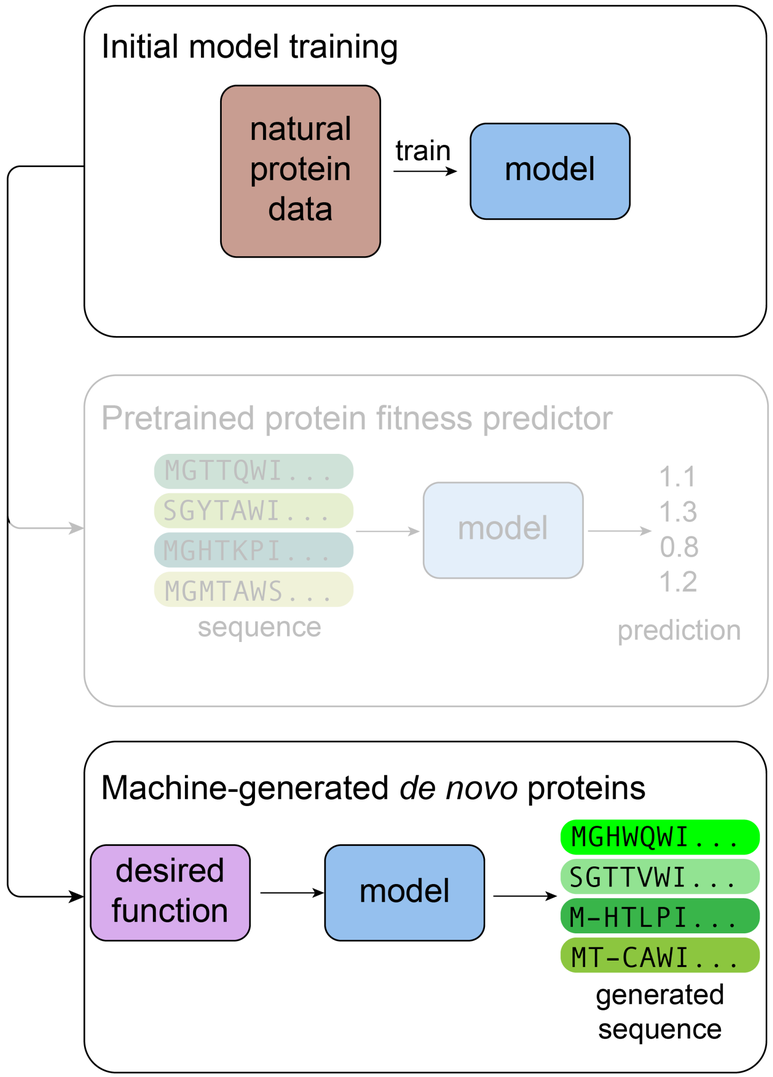
https://github.com/seanrjohnson/protein_scoring

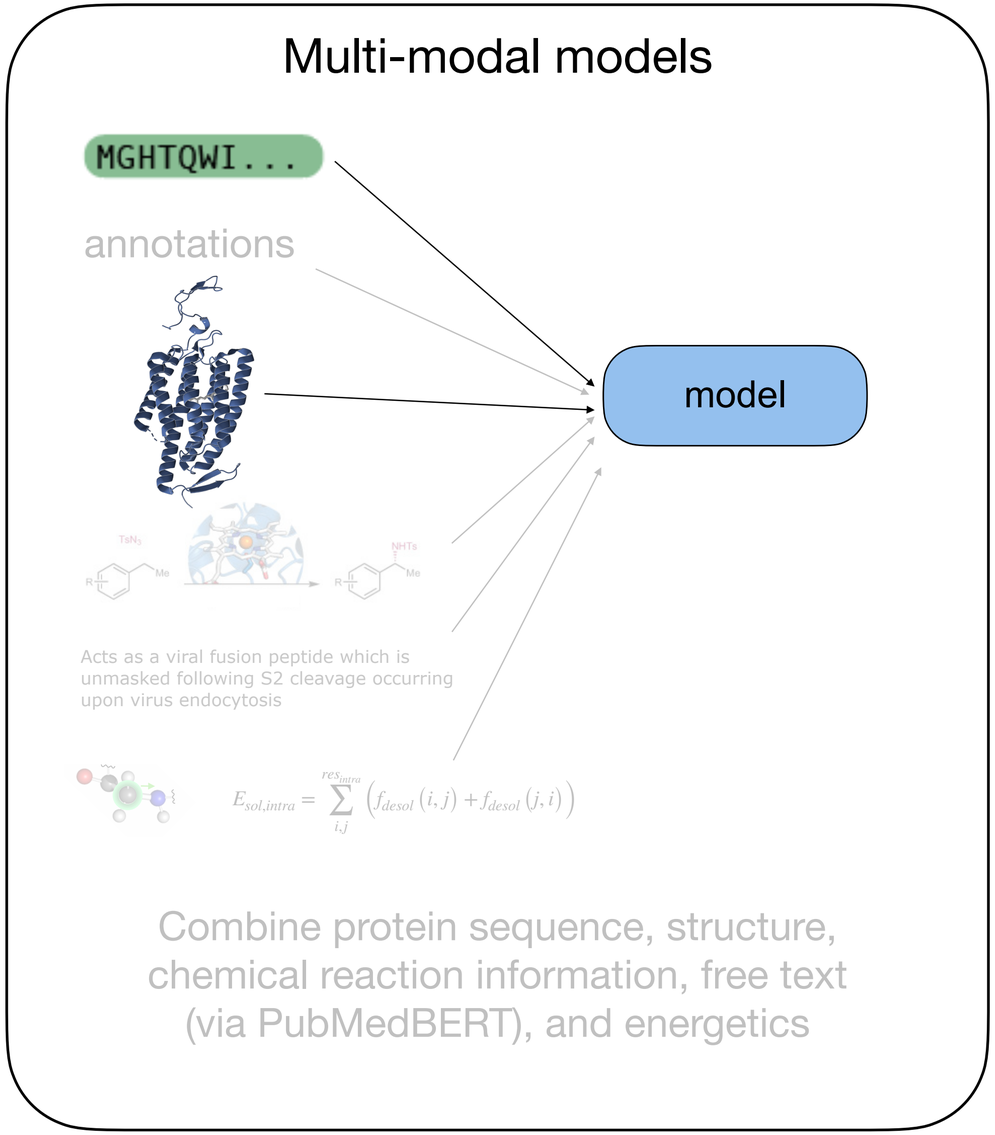
Use multiple data modalities to discover proteins





Use multiple data modalities to discover proteins





Sequence determines structure determines function

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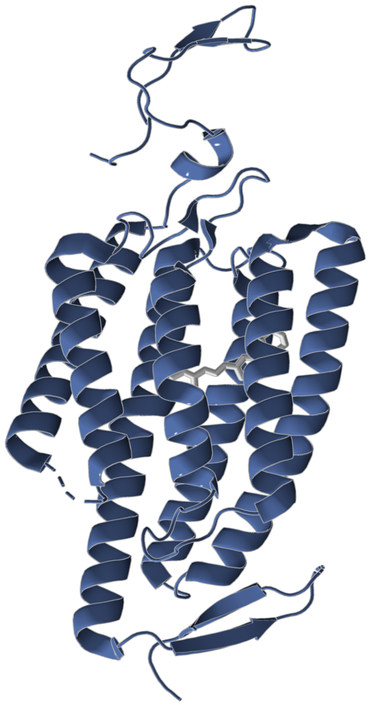
MGTGDHDD...

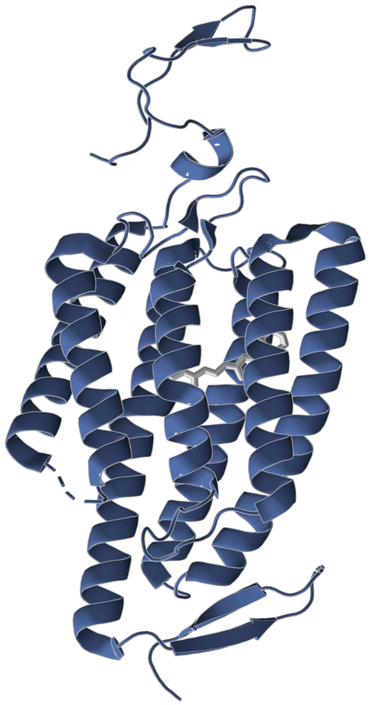
Sequence determines structure determines function

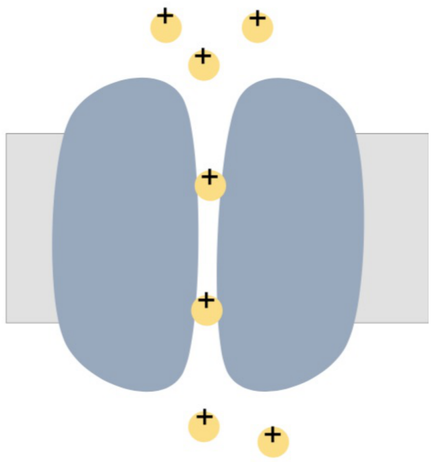
MGTGDHDD... →



Sequence determines structure determines function

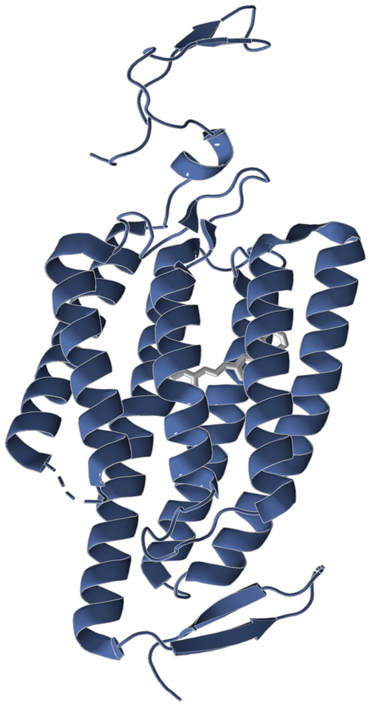
MGTGDHDD...

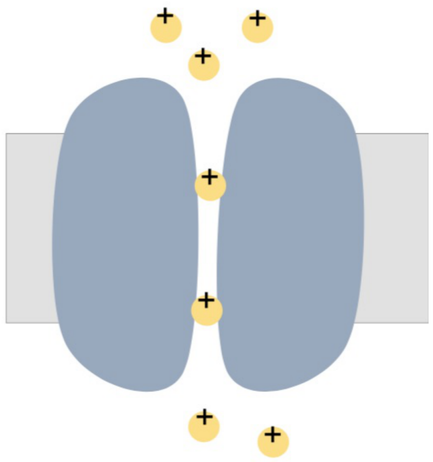




Generating new, designable structures expands functional space

MGTGDHDD...





Generating new, designable structures expands functional space

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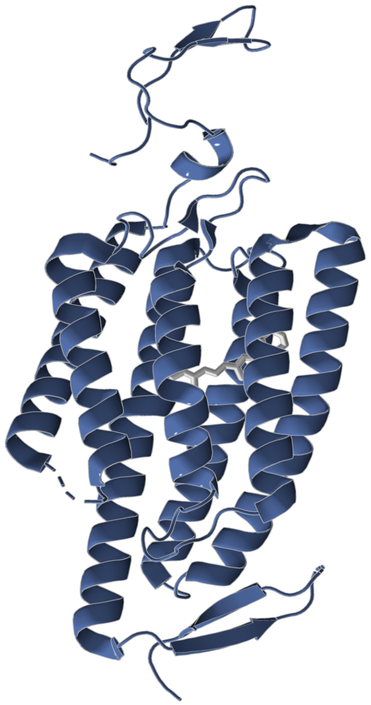

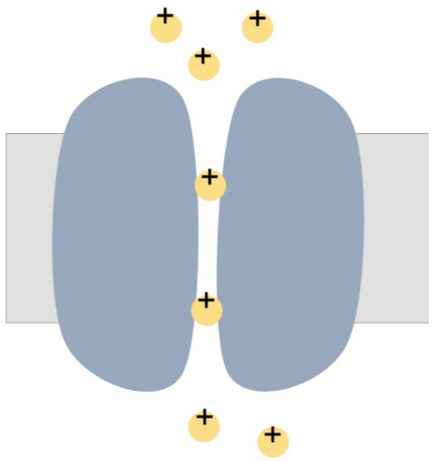

Generating new, designable structures expands functional space

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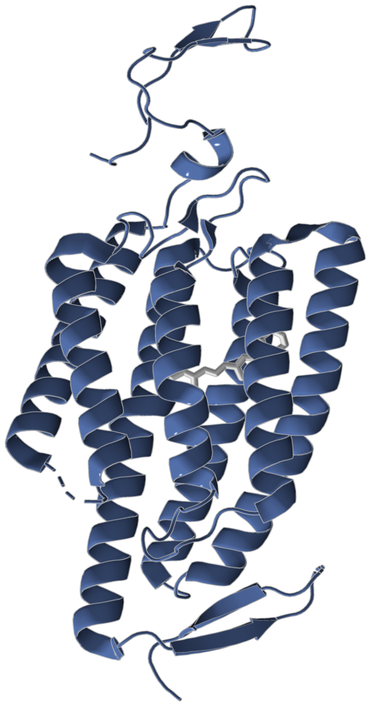
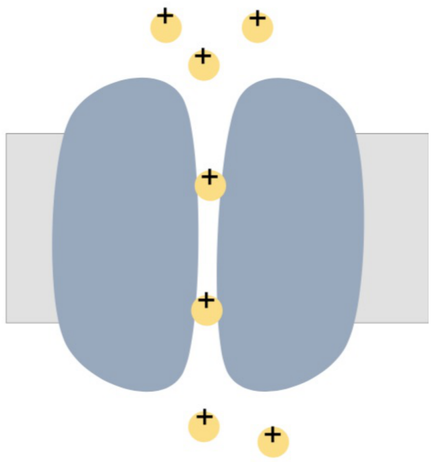
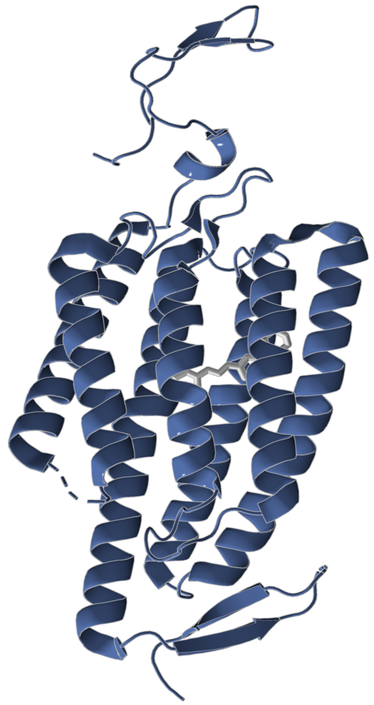


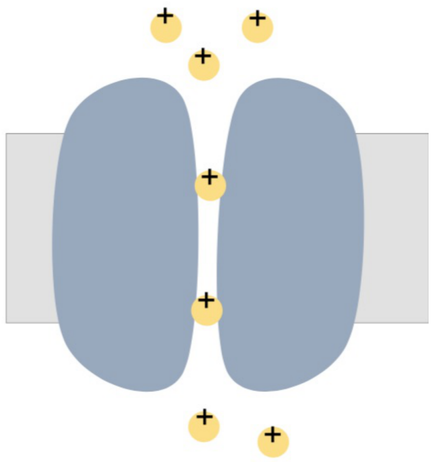


Challenge: Generate diverse and designable structures

Generating new, designable structures expands functional space

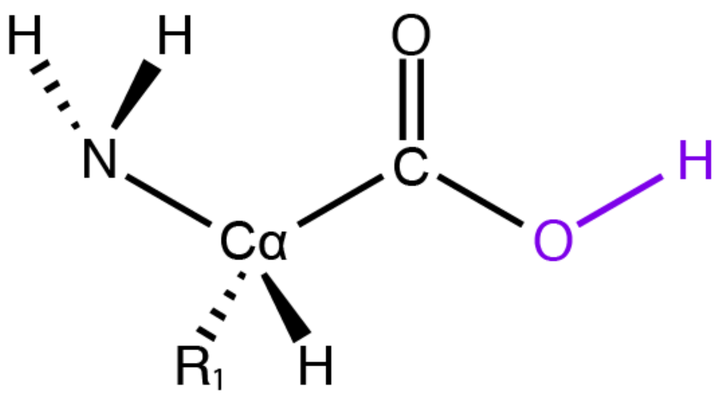
MGTGDHDD...





Challenge: Generate diverse and designable structures

Proteins are polypeptide chains



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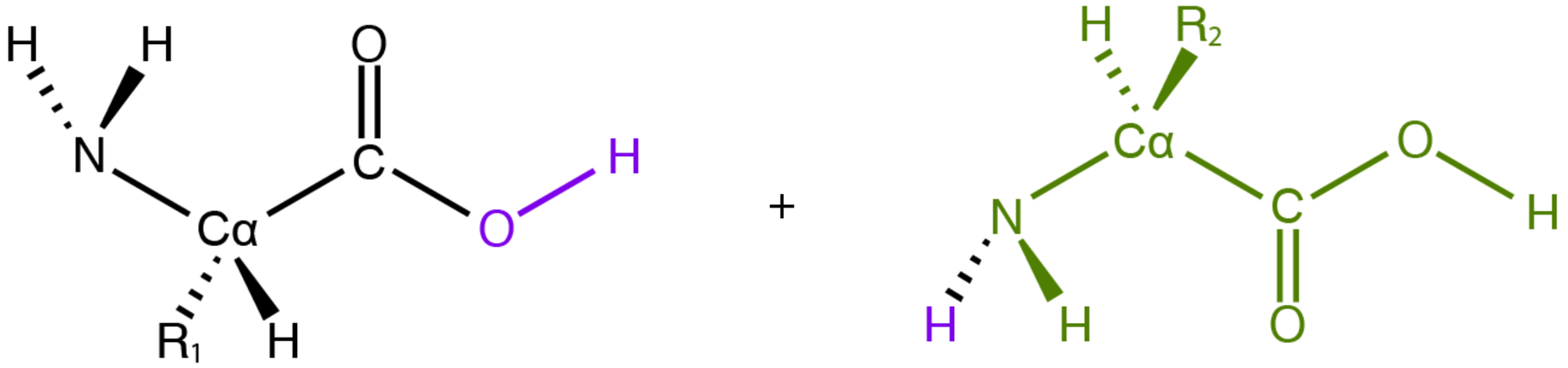

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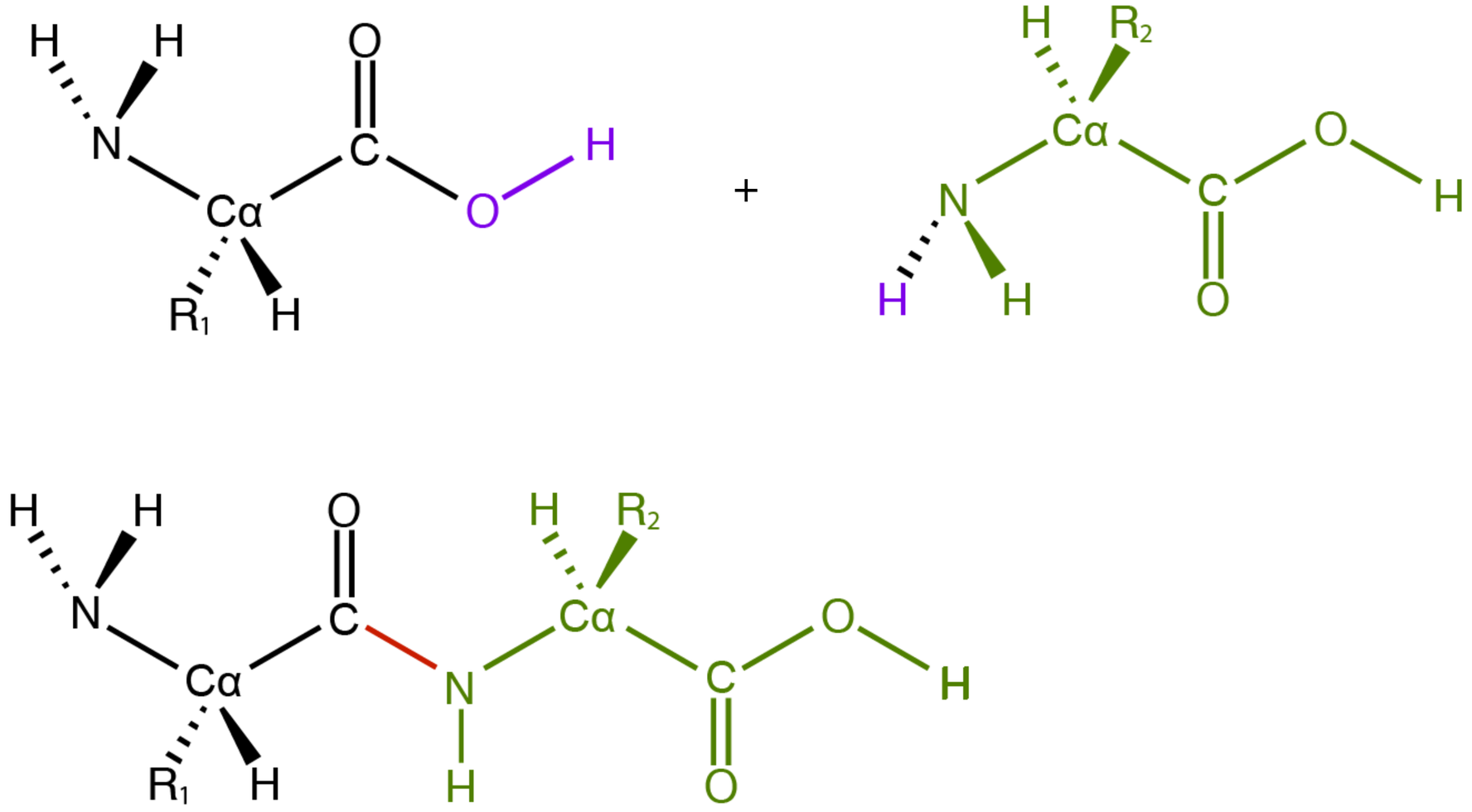

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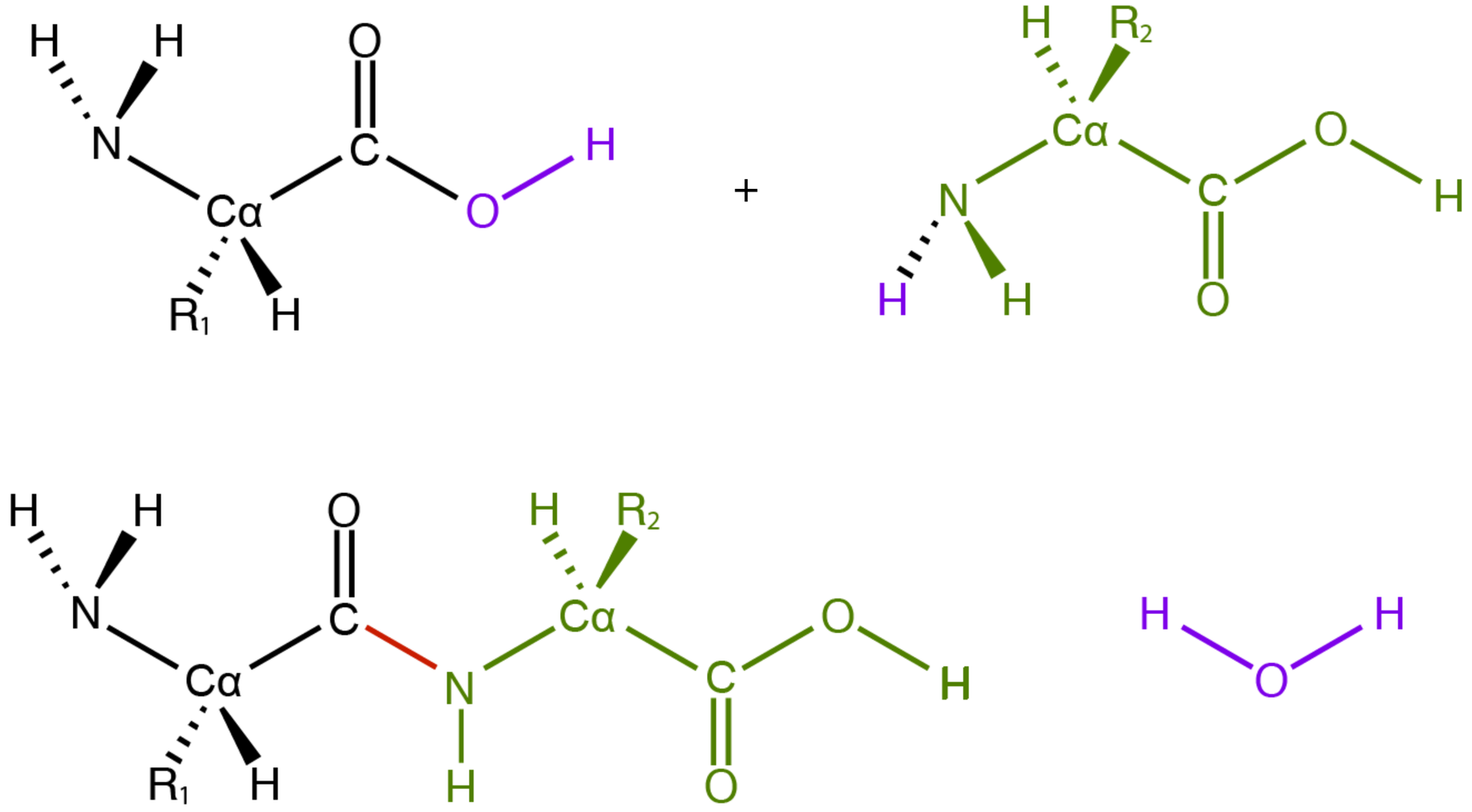
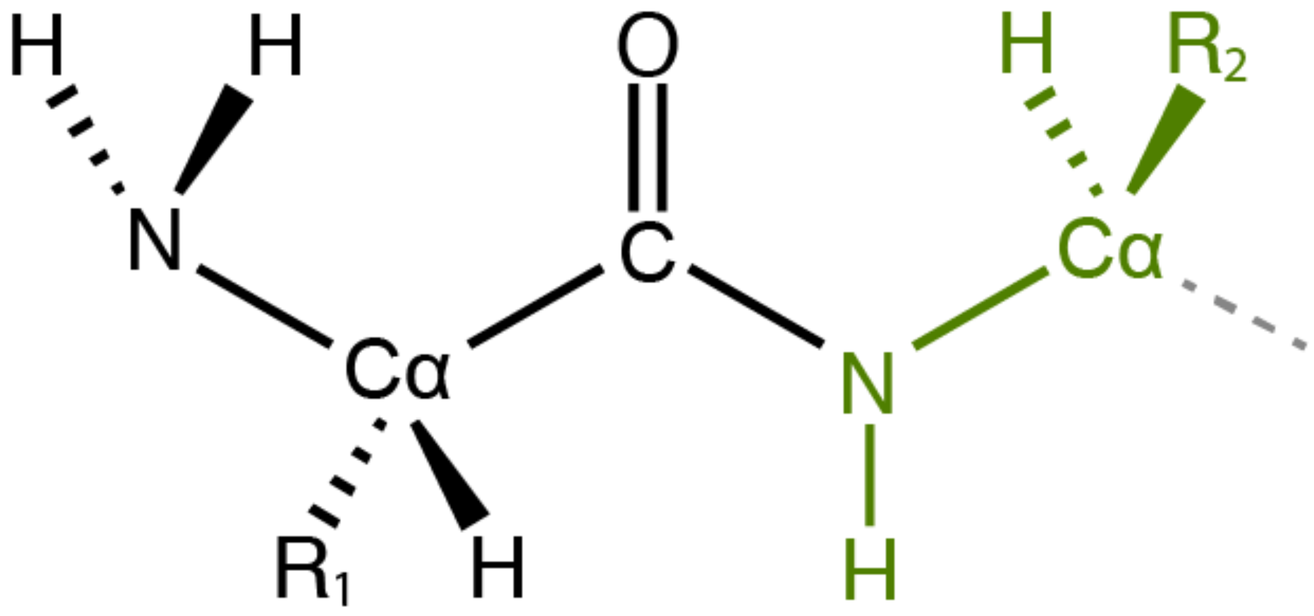


Protein structure is determined by bond angles



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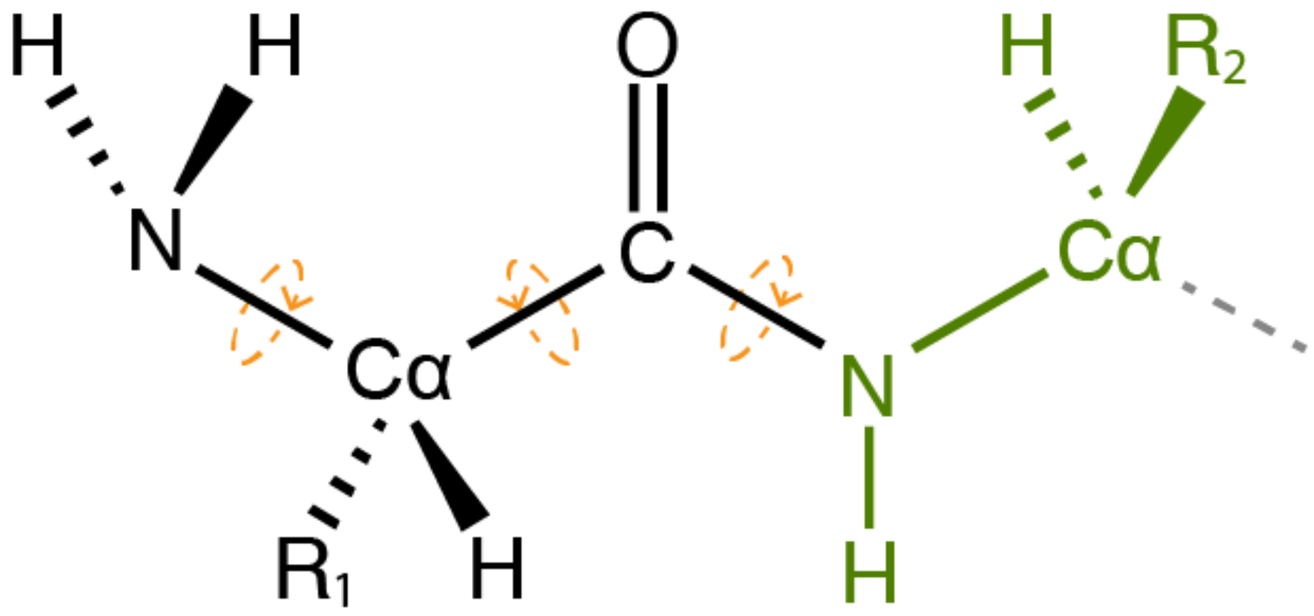

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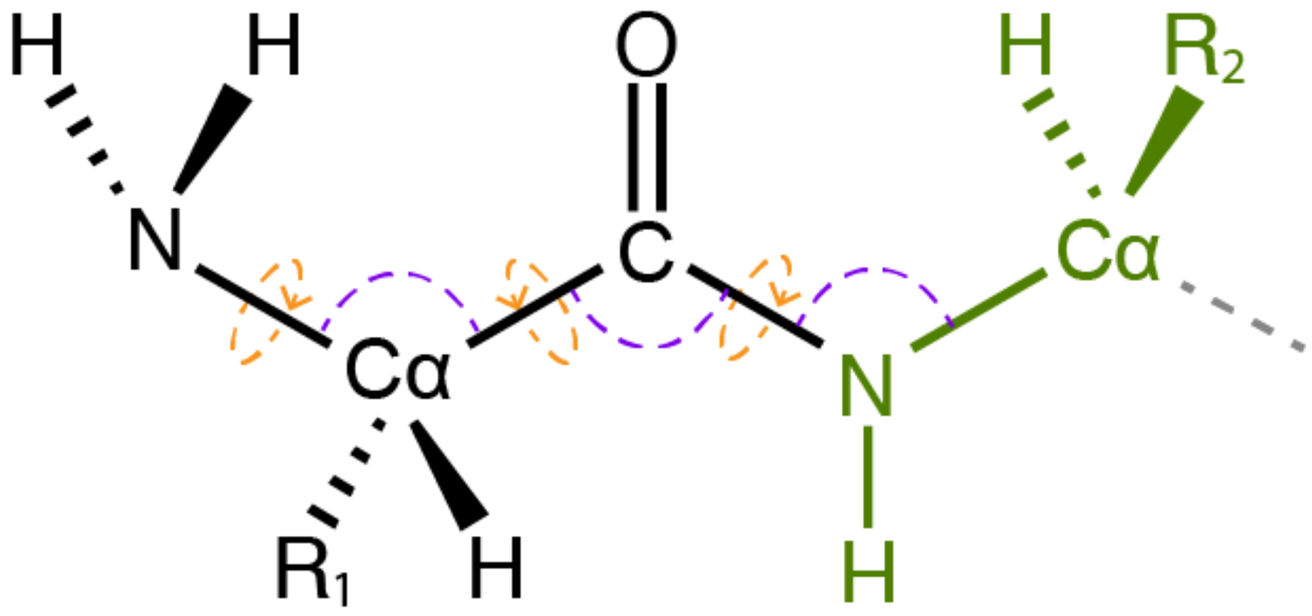

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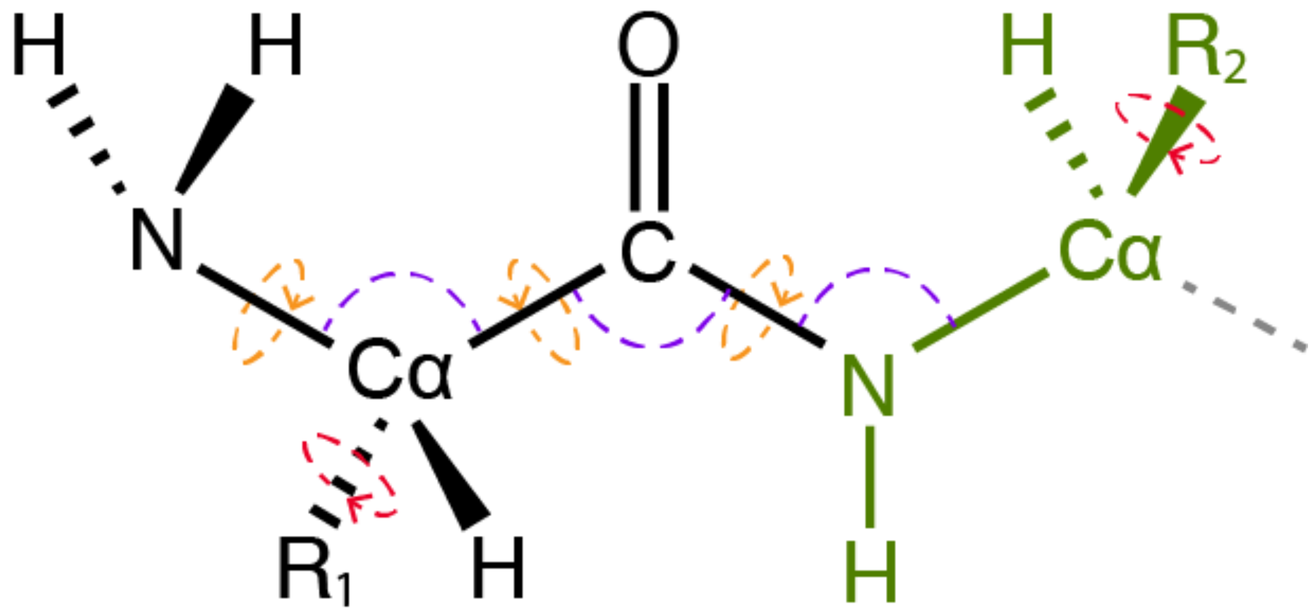
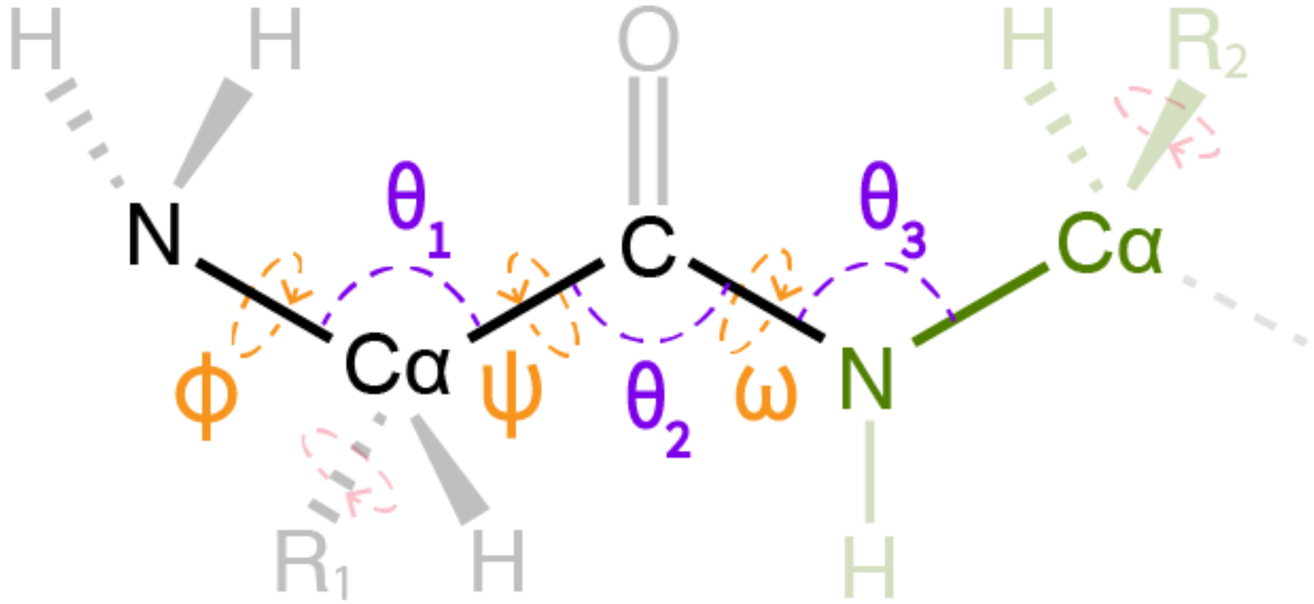


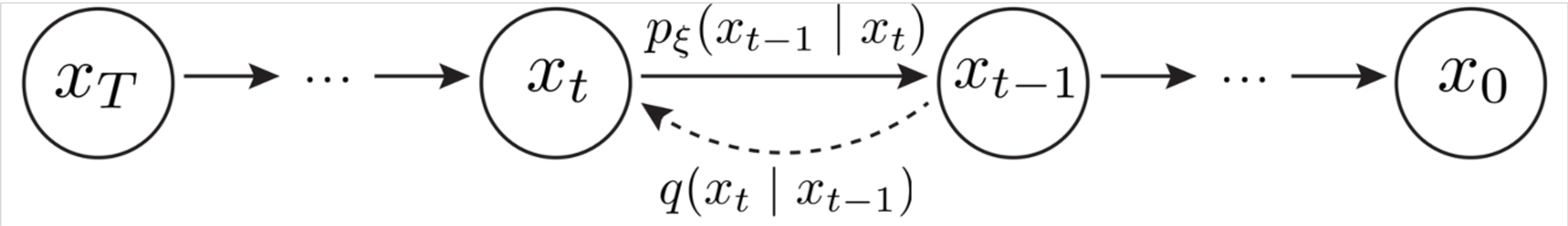
These six angles (for every consecutive pair of amino acids) fully determine the structure

We generate backbone structures represented by dihedral and bond angles



These six angles (for every consecutive pair of amino acids) fully determine the backbone structure

FoldingDiff uses diffusion to generate angles



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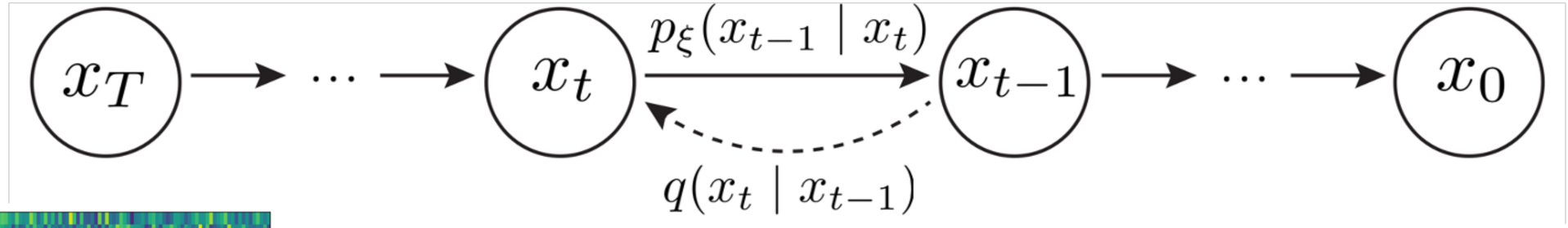
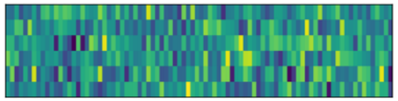
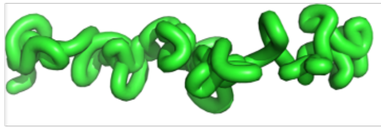




random angles



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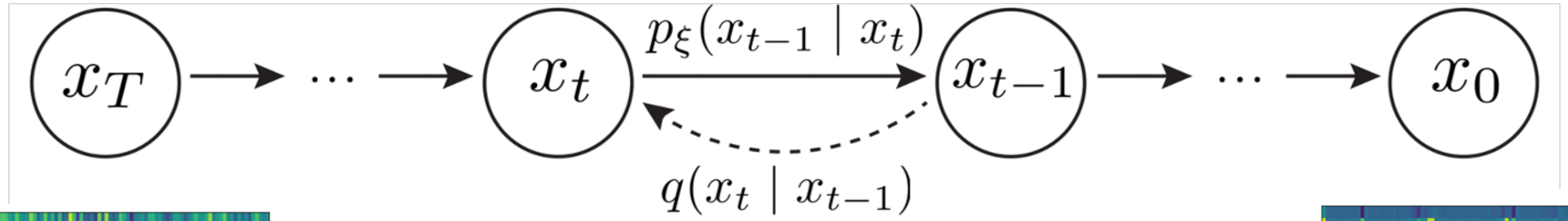

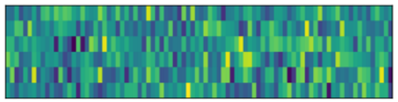

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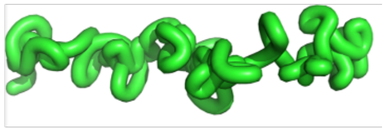

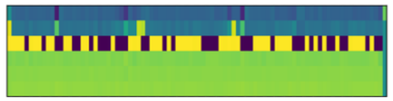

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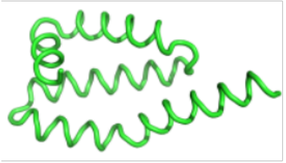
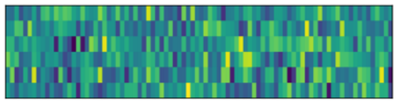


FoldingDiff uses diffusion to generate angles

Vanilla transformer

$$x_T \rightarrow \cdots \rightarrow x_t \xrightarrow{p_\xi(x_{t-1} \mid x_t)} x_{t-1} \rightarrow \cdots \rightarrow x_0$$

$$q(x_t \mid x_{t-1})$$



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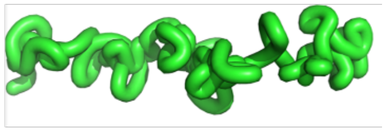

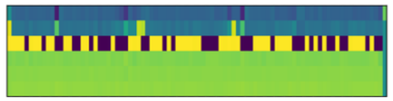

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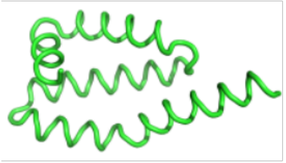

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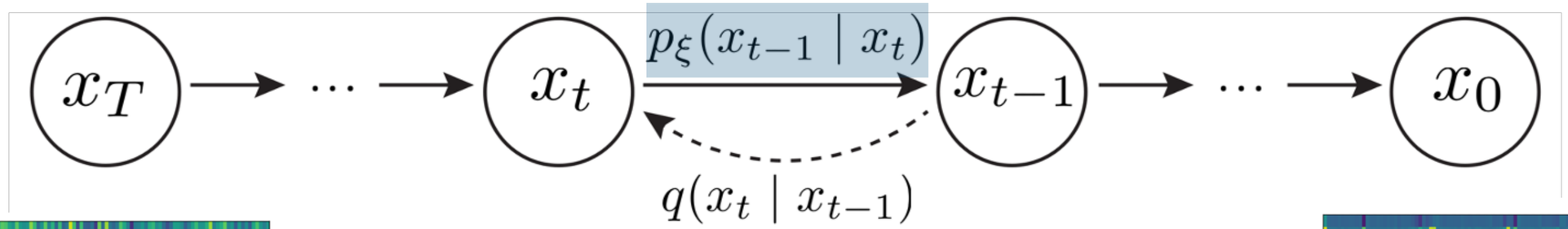

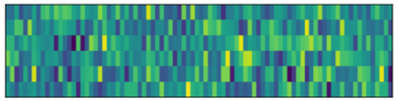

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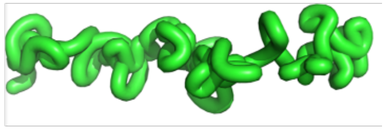
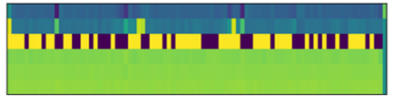


30k structures from CATH

40 - 128 residues



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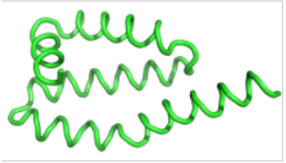
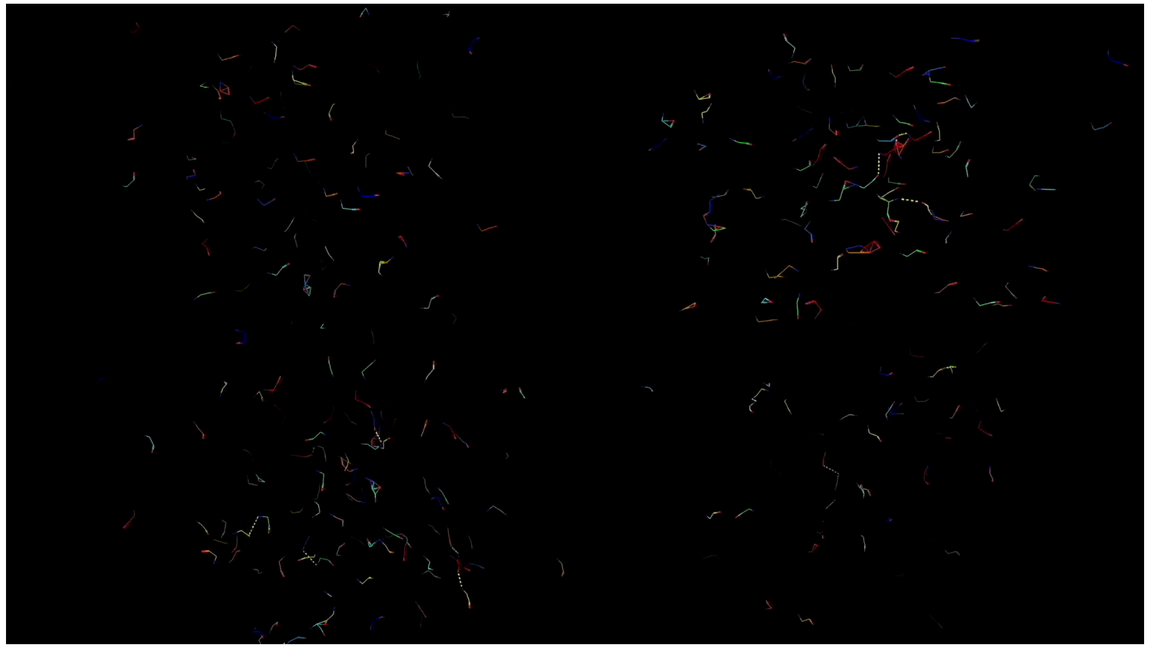


Diffusion on 3D coordinates requires equivariances



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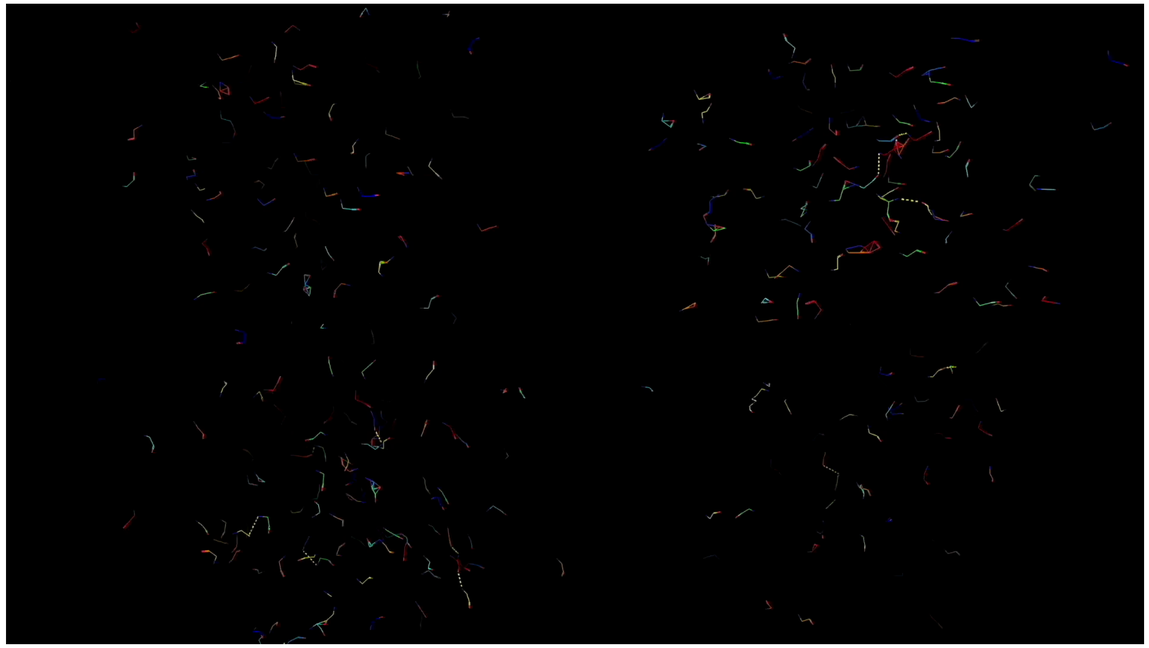

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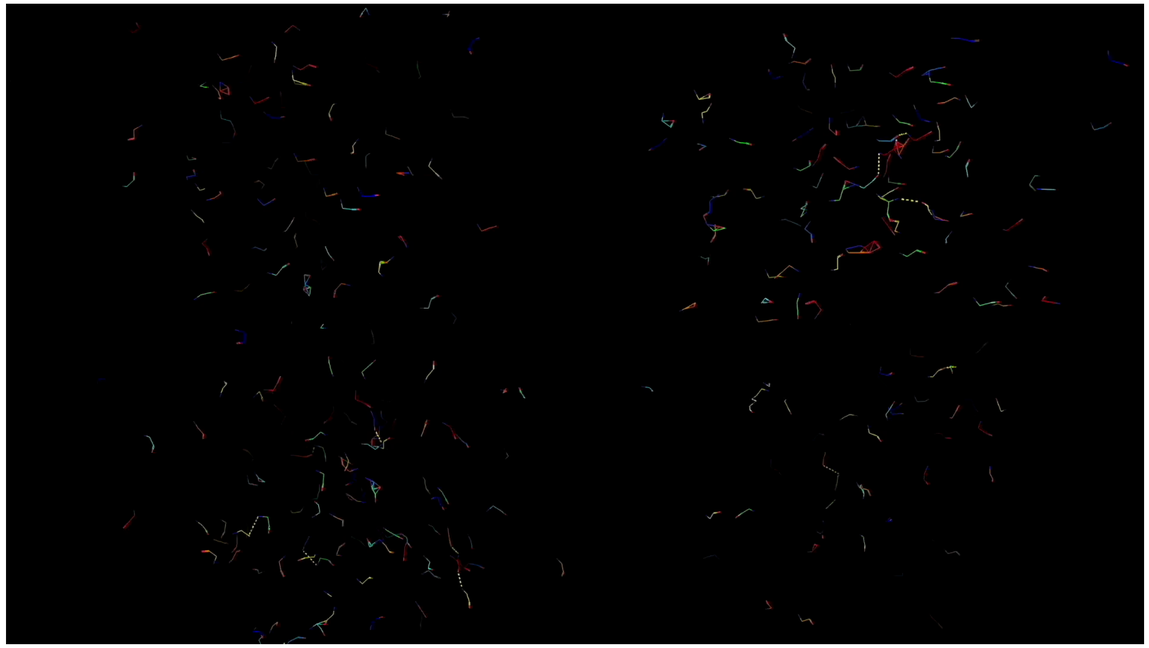
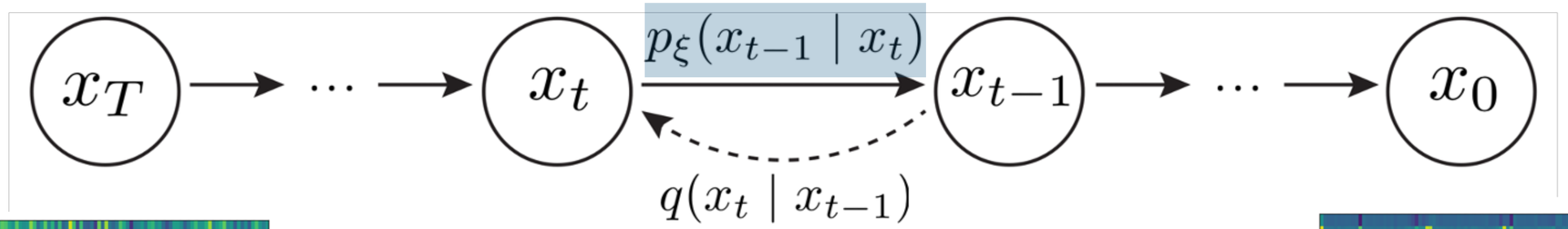
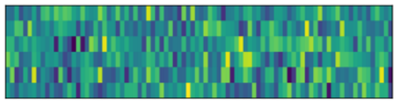


Evaluate generations at 3 levels

Vanilla transformer





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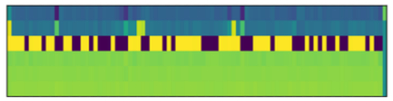

generated angles

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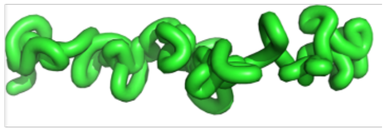

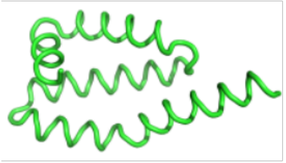

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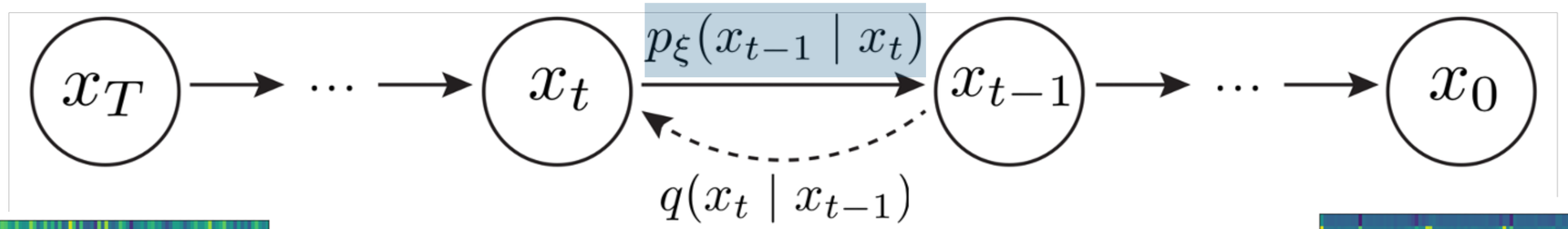

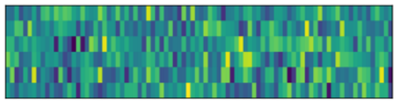

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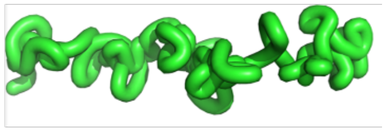

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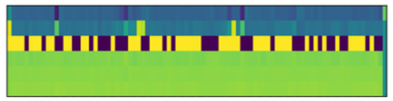

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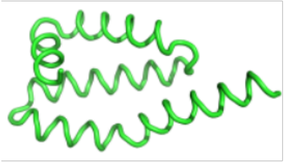

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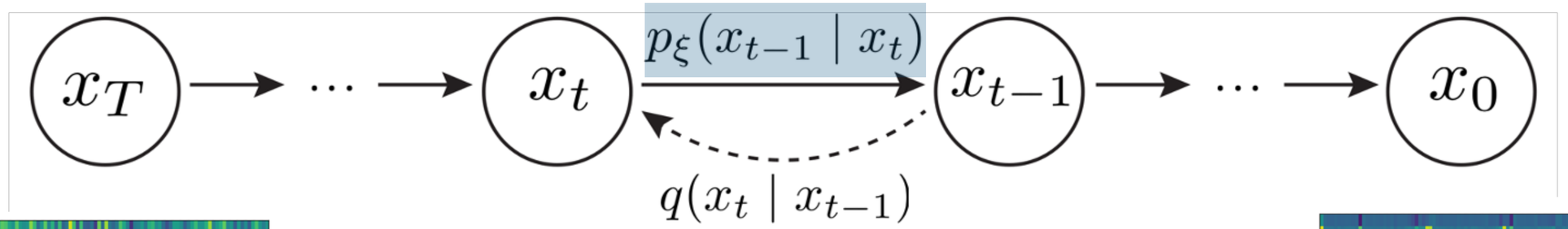

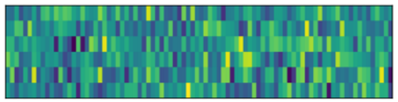

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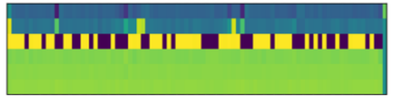
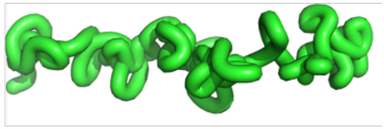
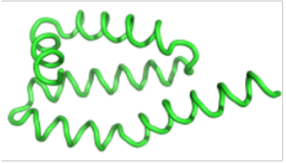


generated angles

30k structures from CATH

40 - 128 residues



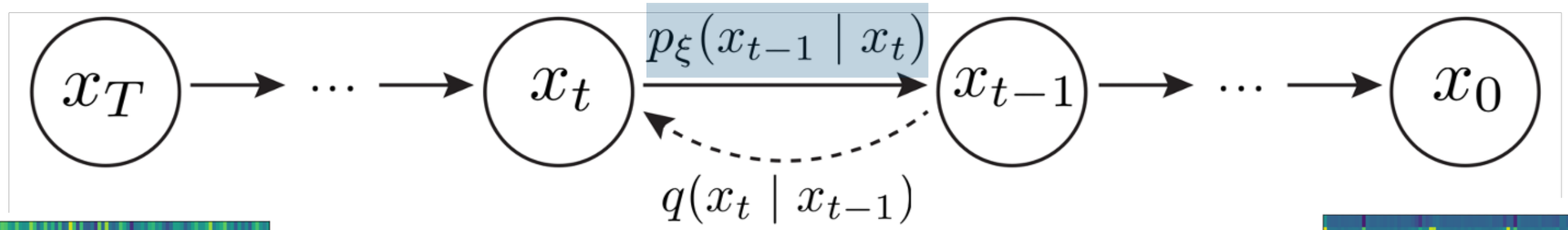


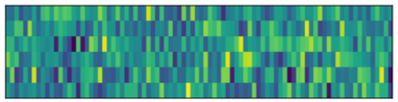
generated angles

structural motifs

Evaluate generations at 3 levels

Vanilla transformer





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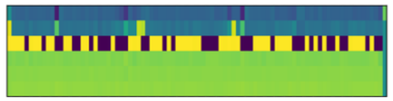
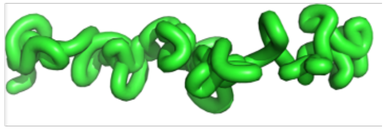
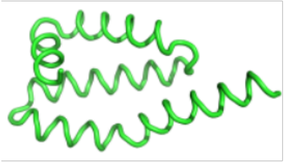


generated angles

30k structures from CATH

40 - 128 residues





generated angles

structural motifs

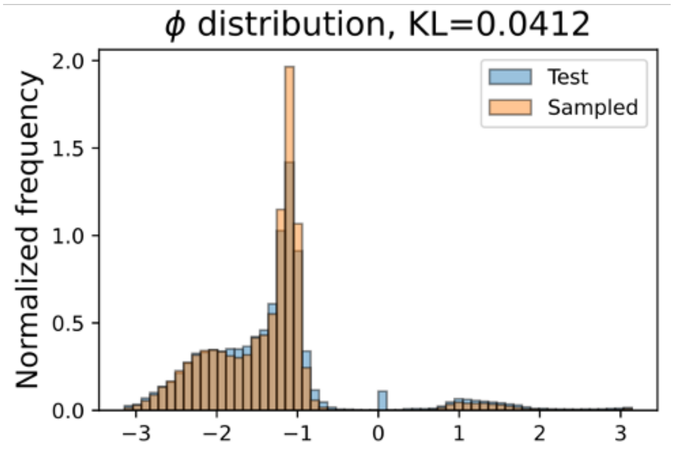
overall structures

Generated angles match test distribution

noise → sample → compare to true distribution

Generated angles match test distribution

noise → sample → compare to true distribution



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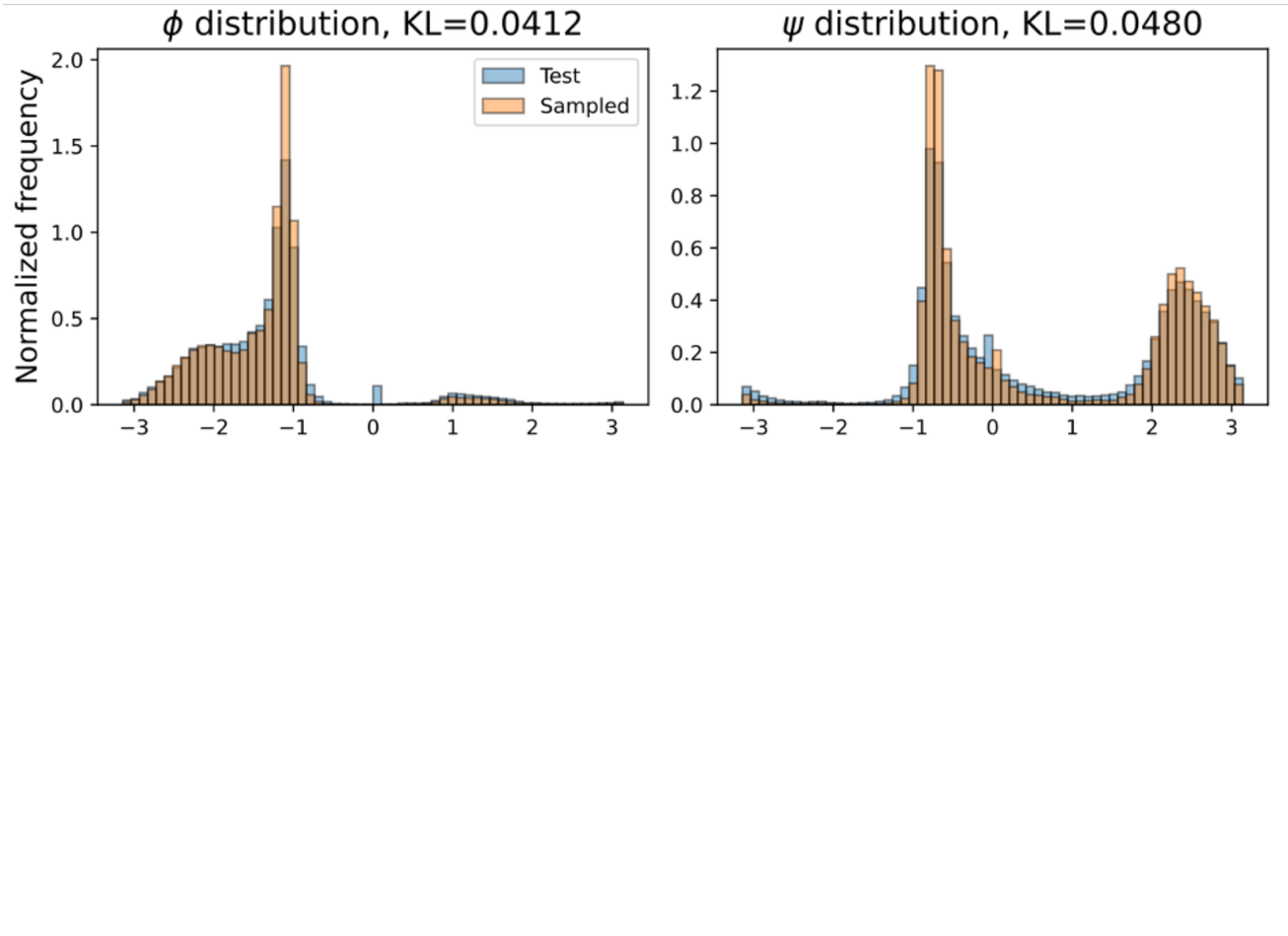

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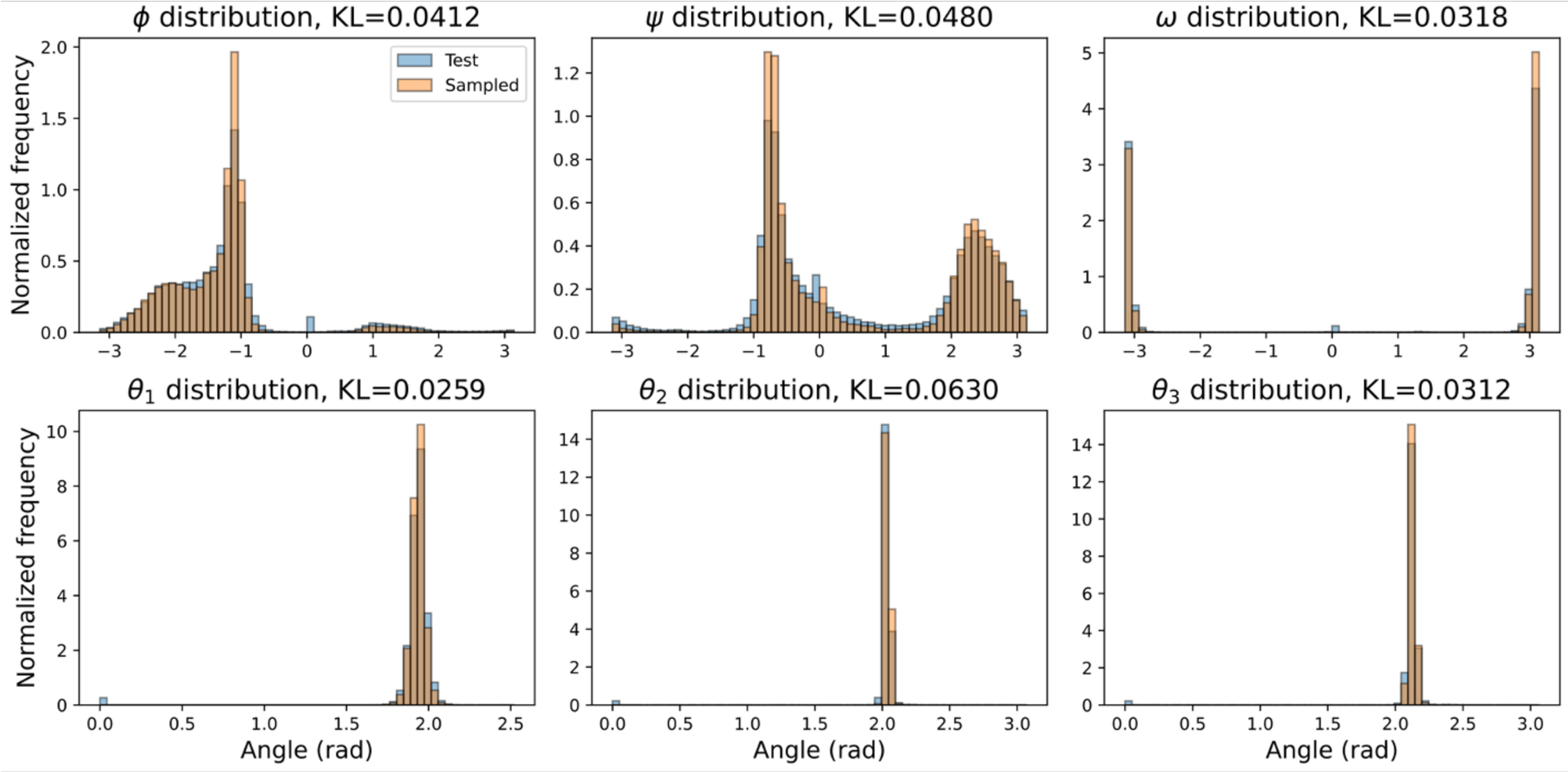

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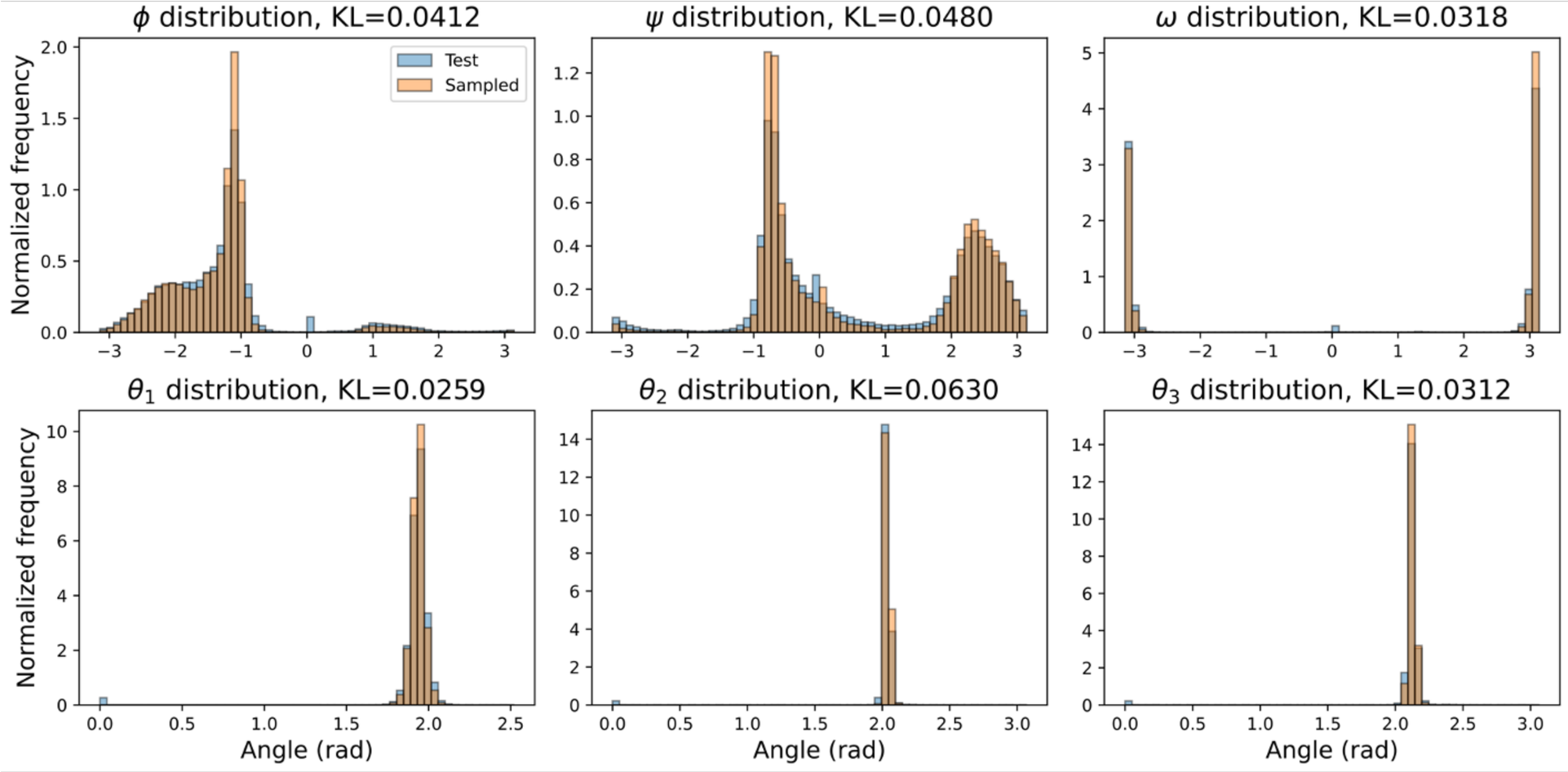

Generated distributions match natural distribution of individual angles

FoldingDiff captures correlations between angles

noise → sample → compare (ϕ, ψ) co-occurence

FoldingDiff generates correlations that define common structural motifs

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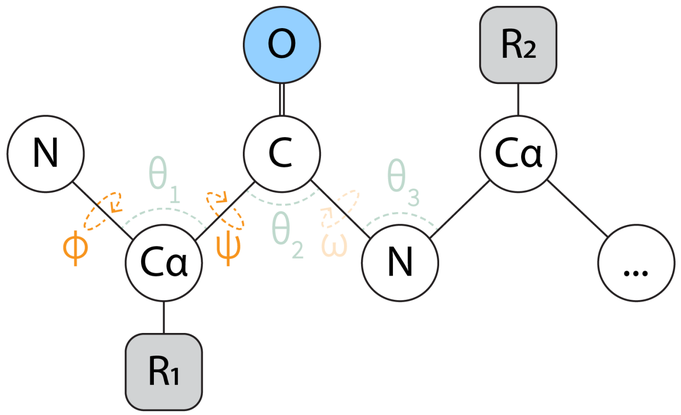

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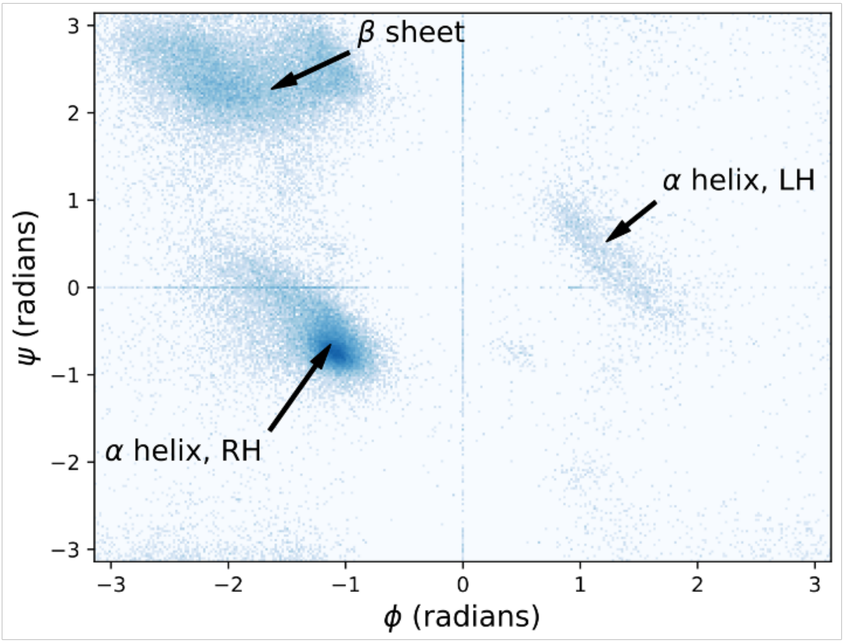
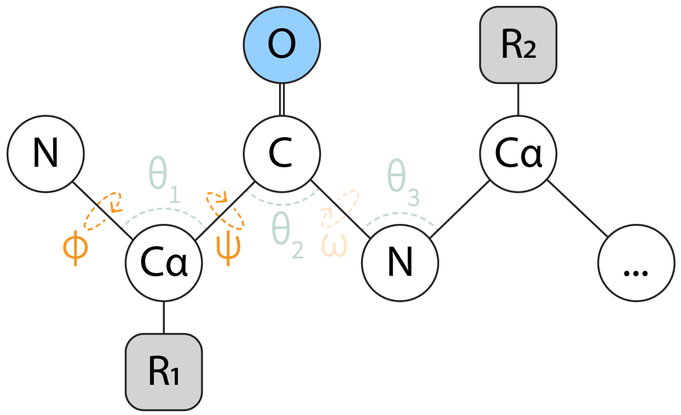
True





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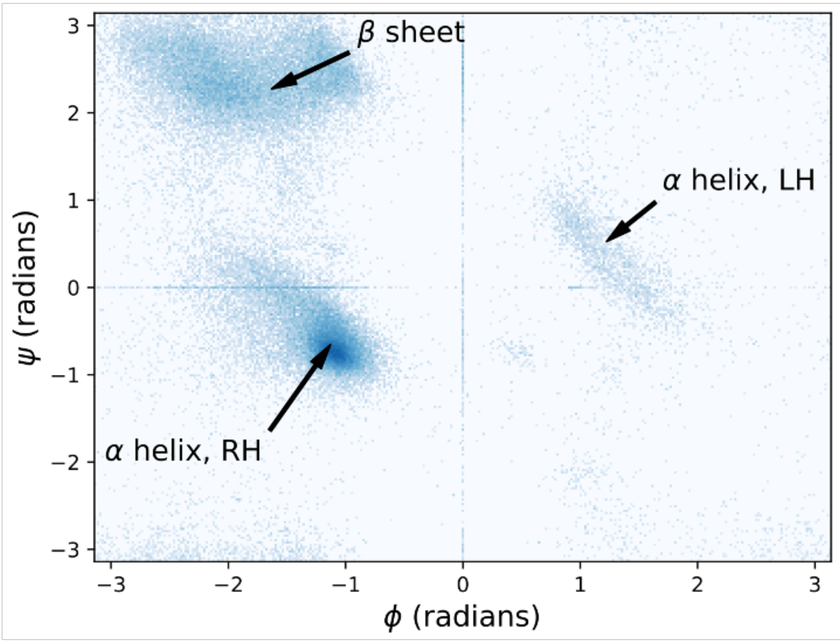
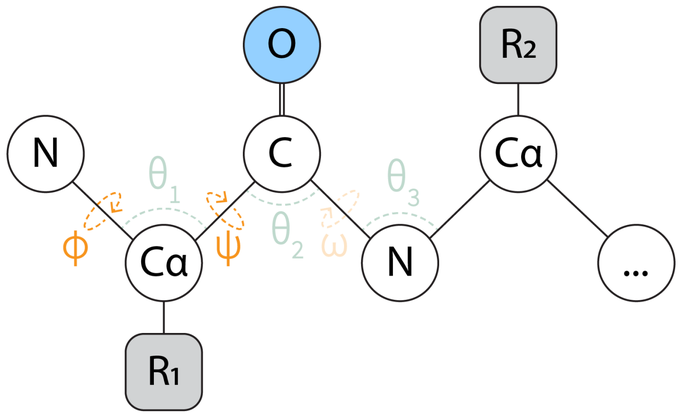
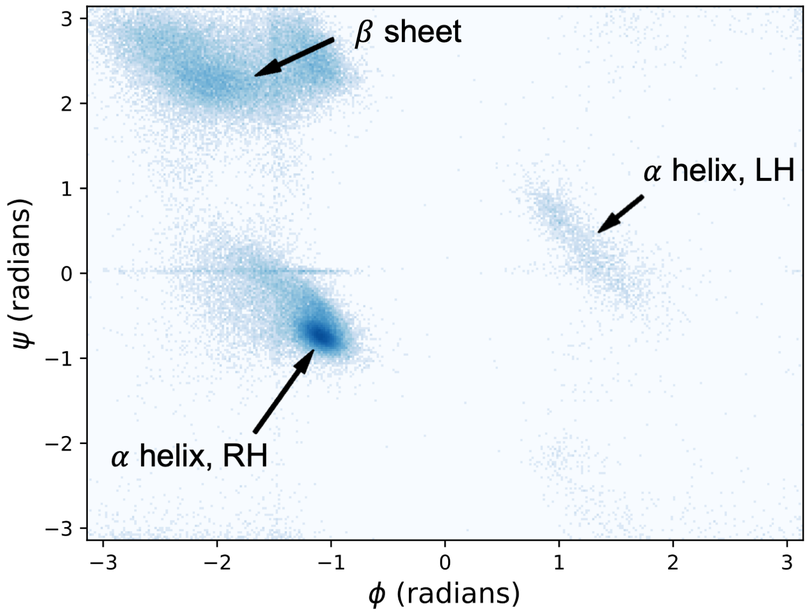




Generated

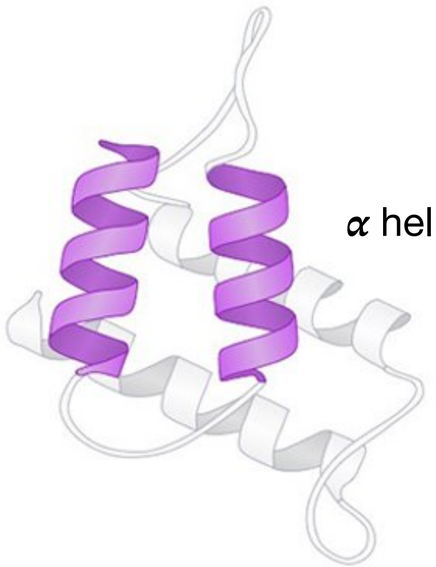


FoldingDiff generates correlations that define common structural motifs

Generated secondary structures match test structures

noise → sample → measure helix, sheet structures

Generated secondary structures match test structures



α helix

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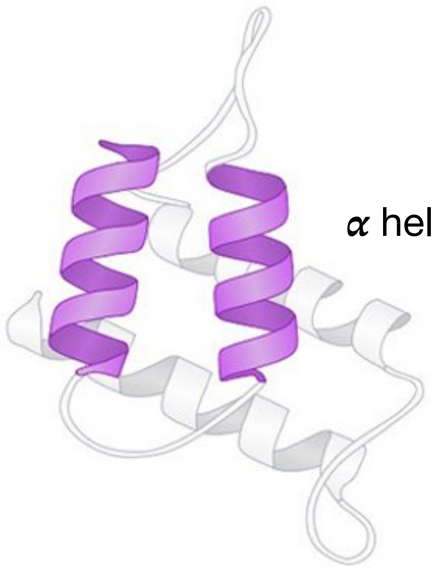

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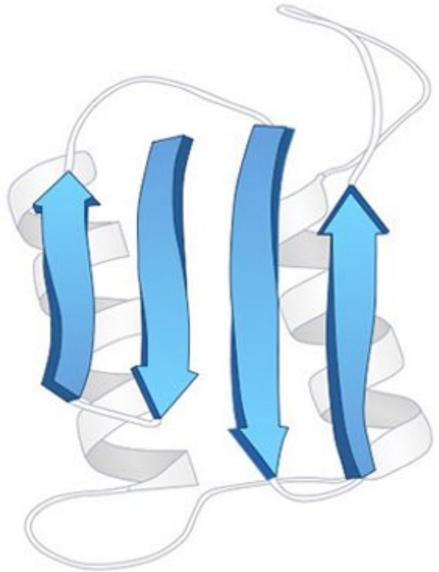

β sheet

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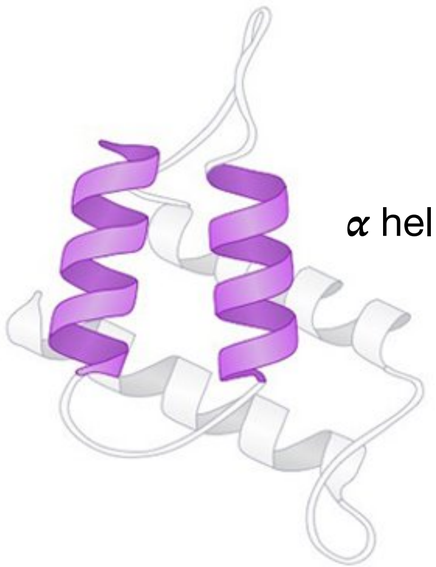

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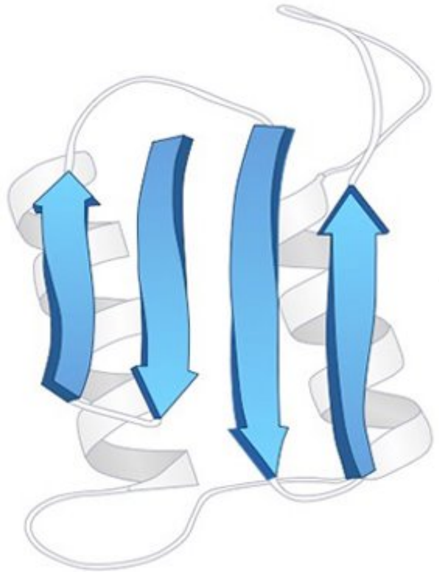
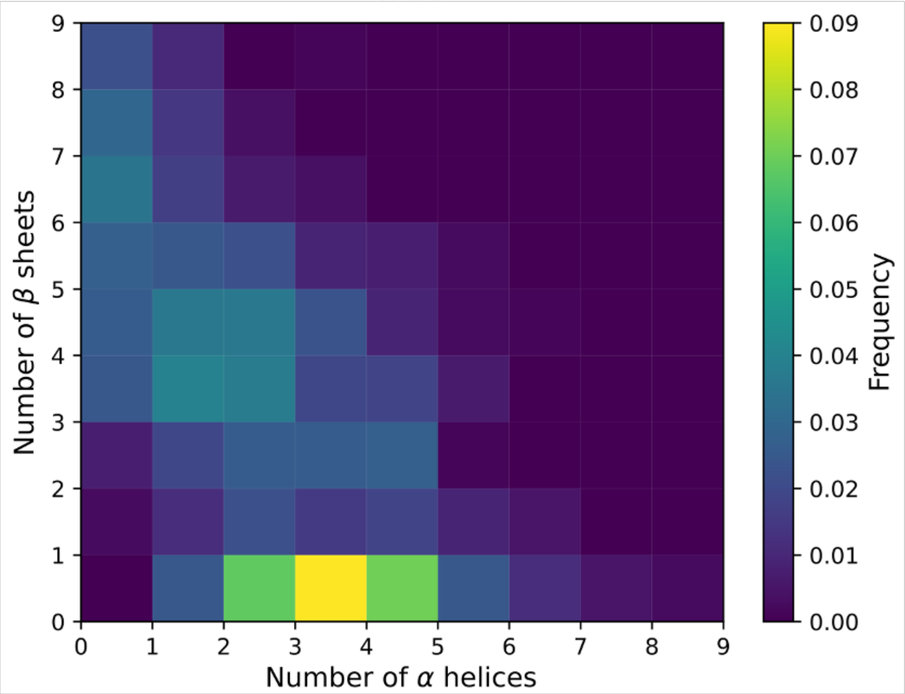


β sheet

True



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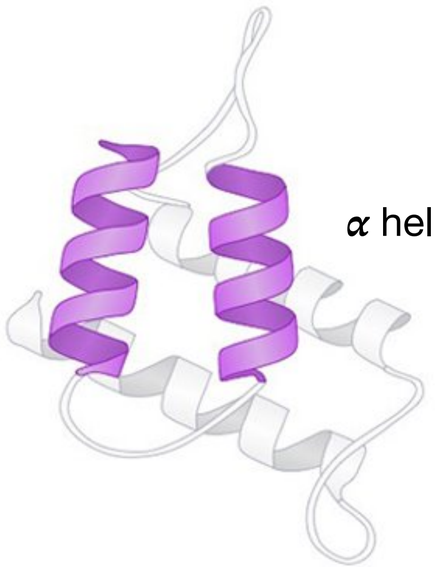

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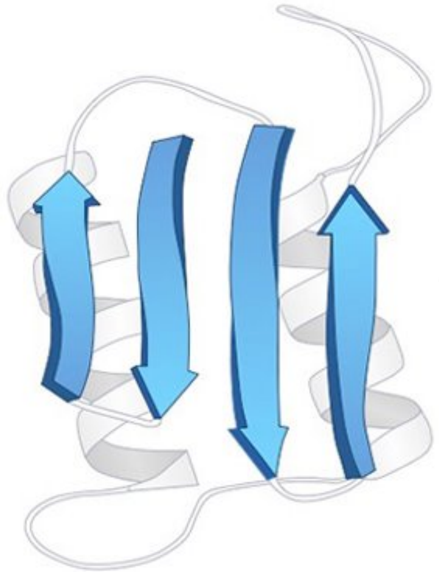

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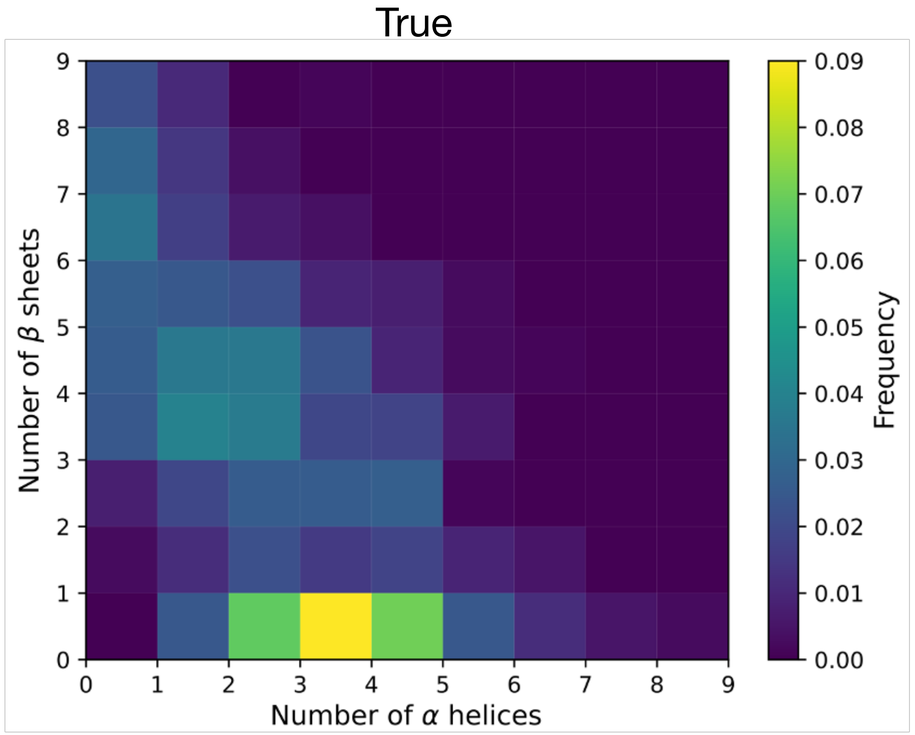
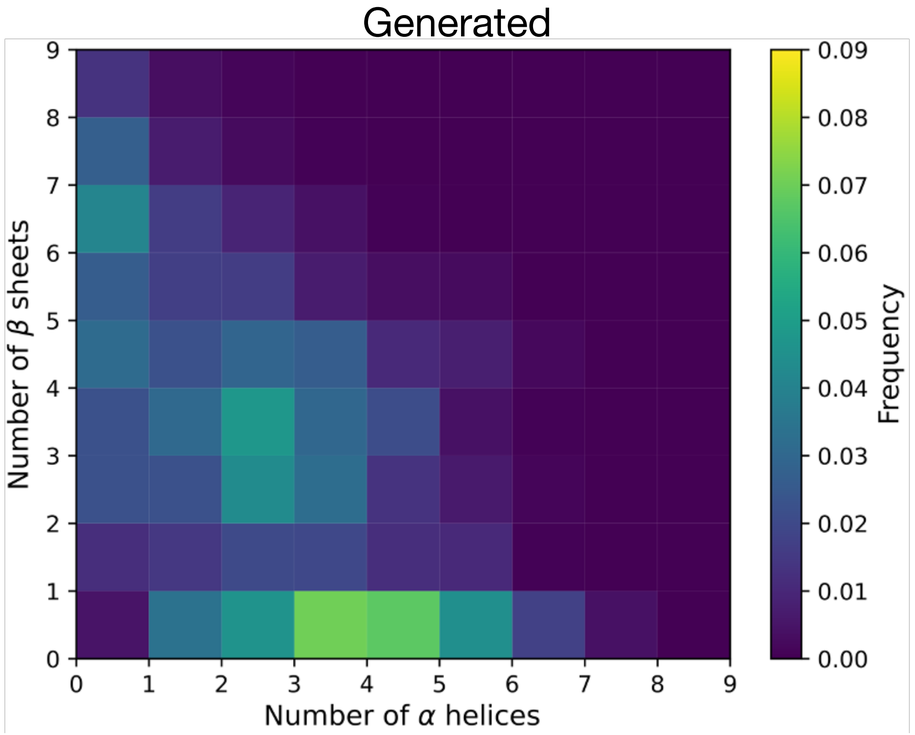
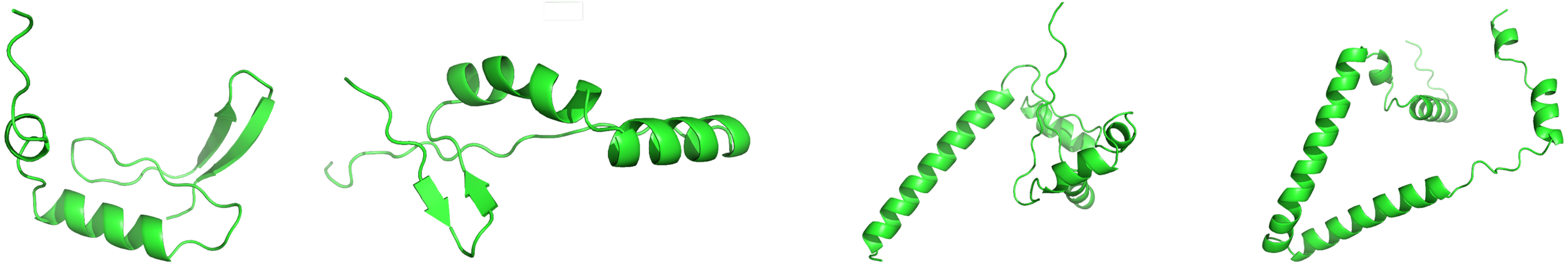


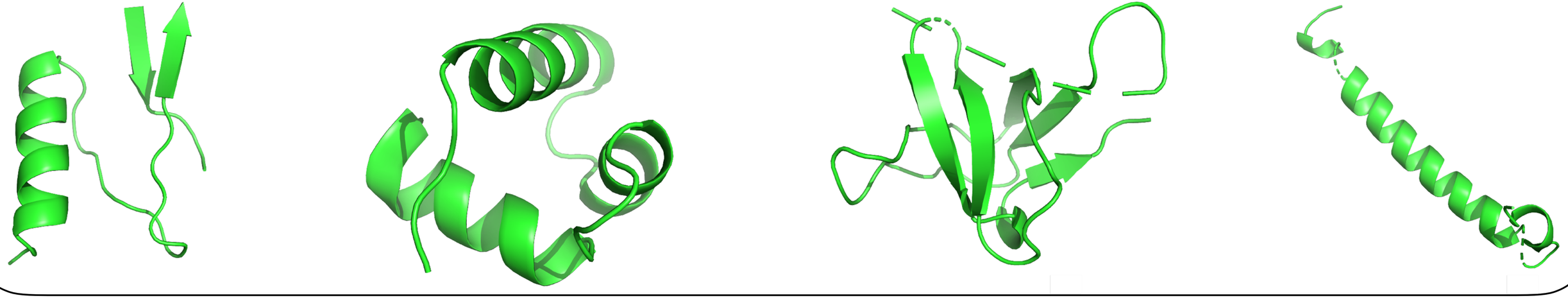


Generated structures look reasonable

Generated structures



Training set structures



Measure designability of structures with self-consistency TMscore

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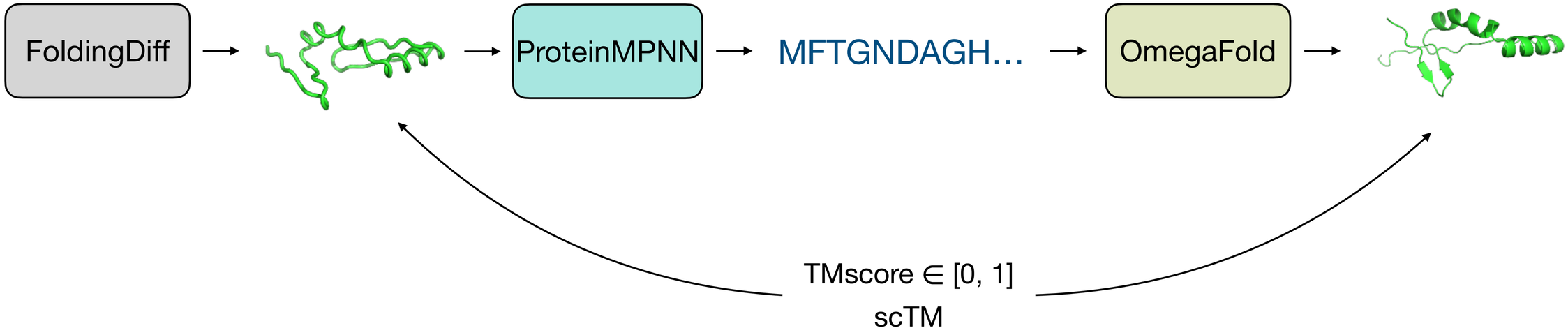
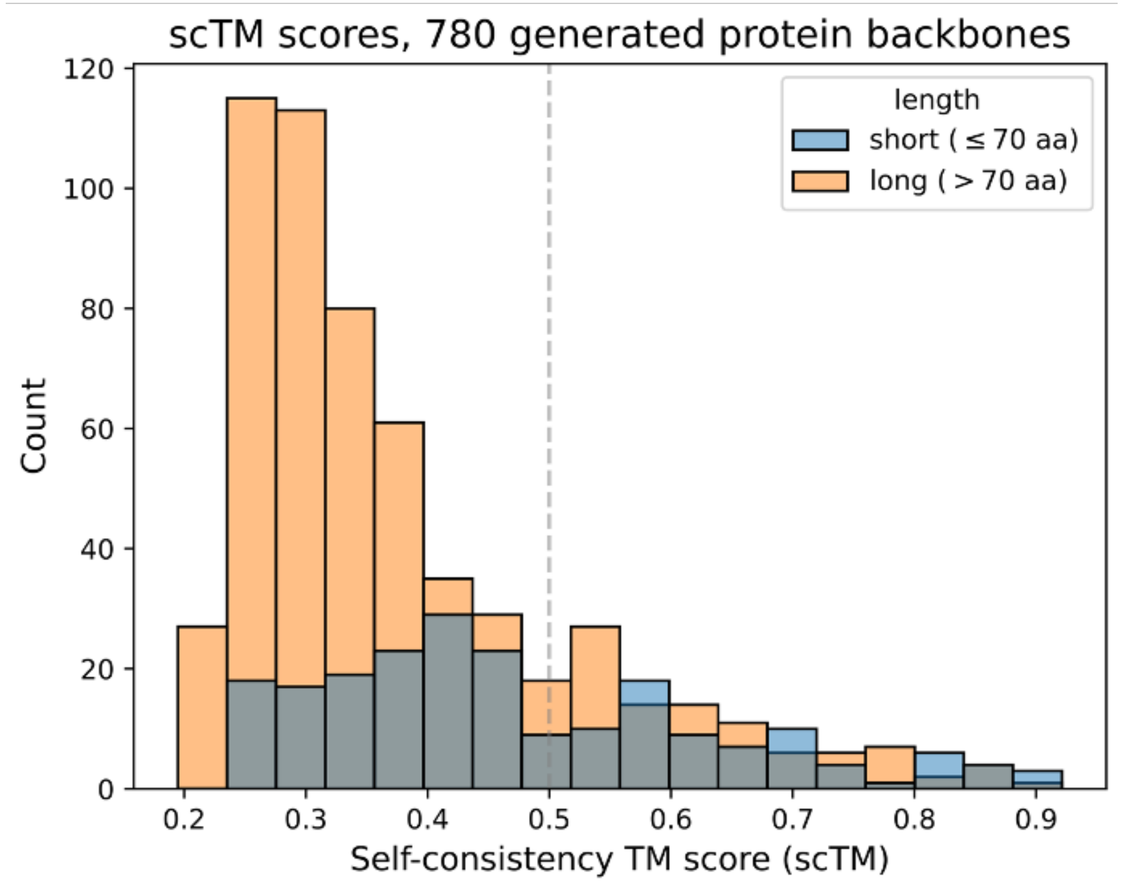


Many generated structures are designable



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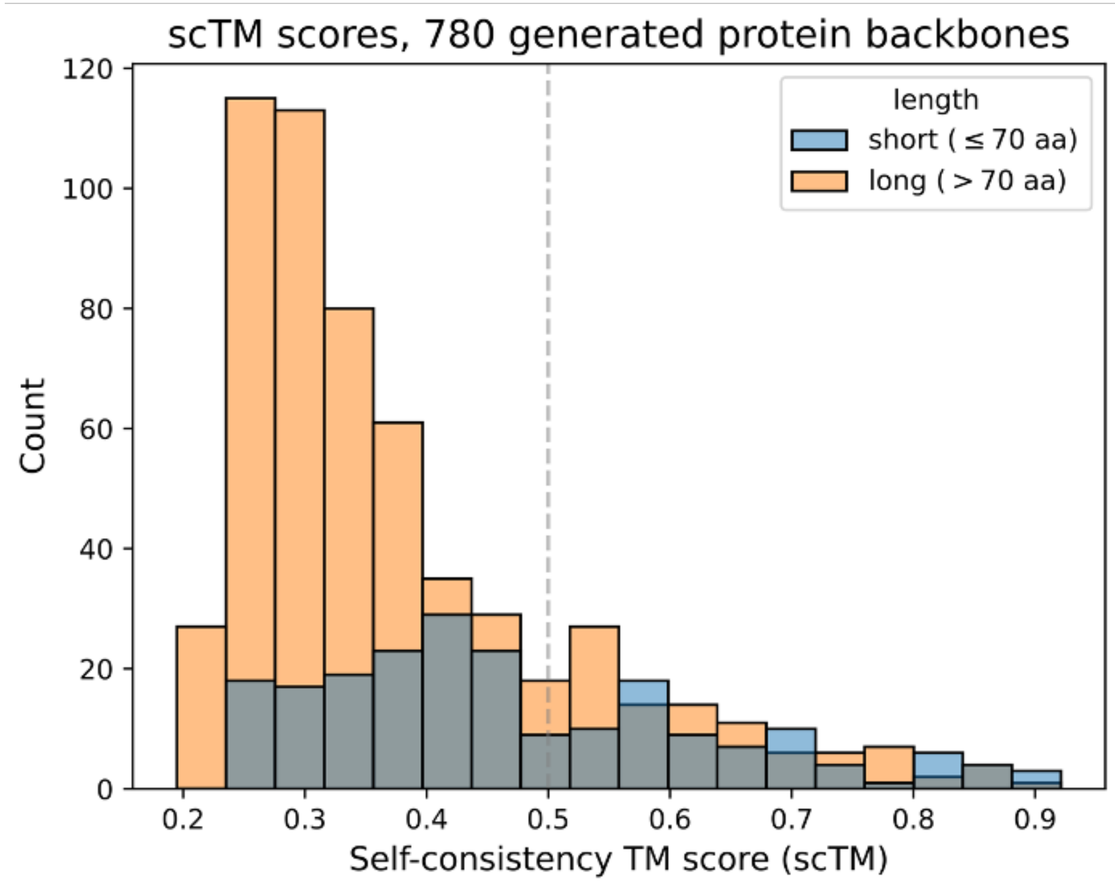

scTM > 0.5	≤ 70 aa	> 70 aa
FoldingDiff	76/210	87/570
ProtDiff (Trippe *et al.*)	36/210	56/570

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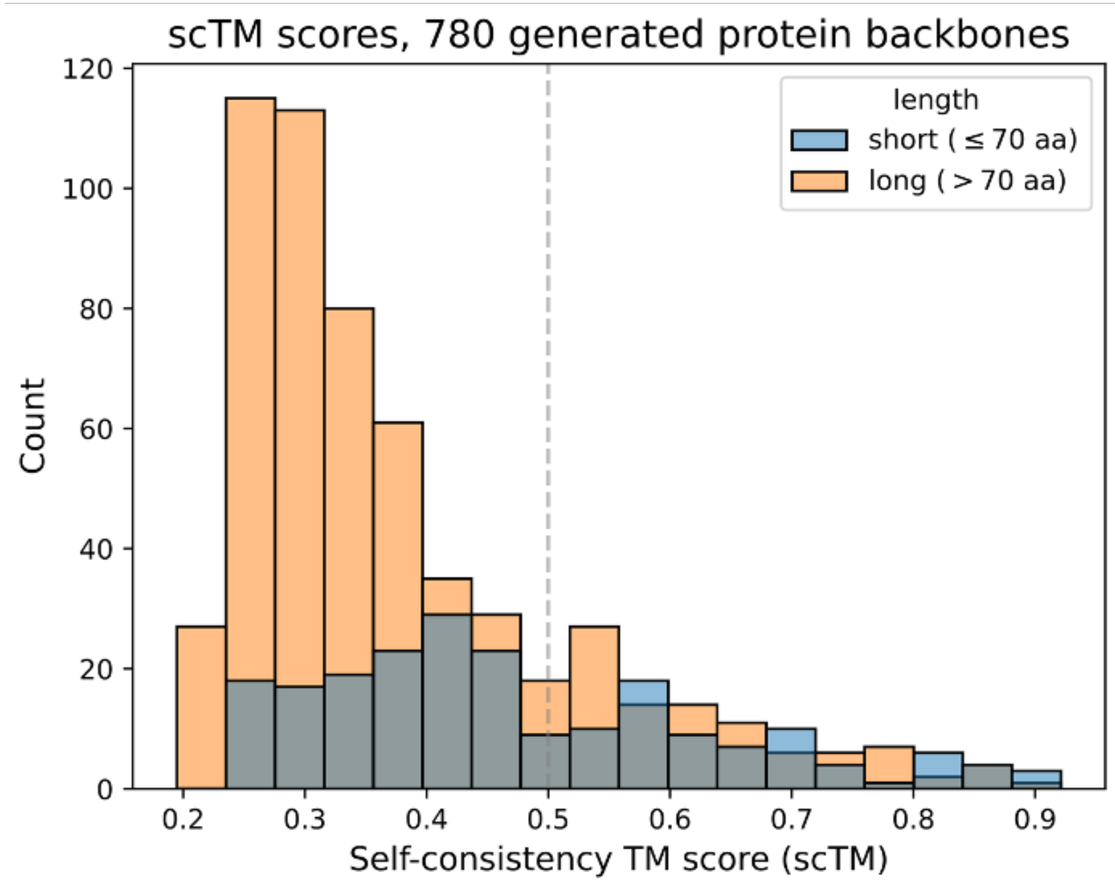

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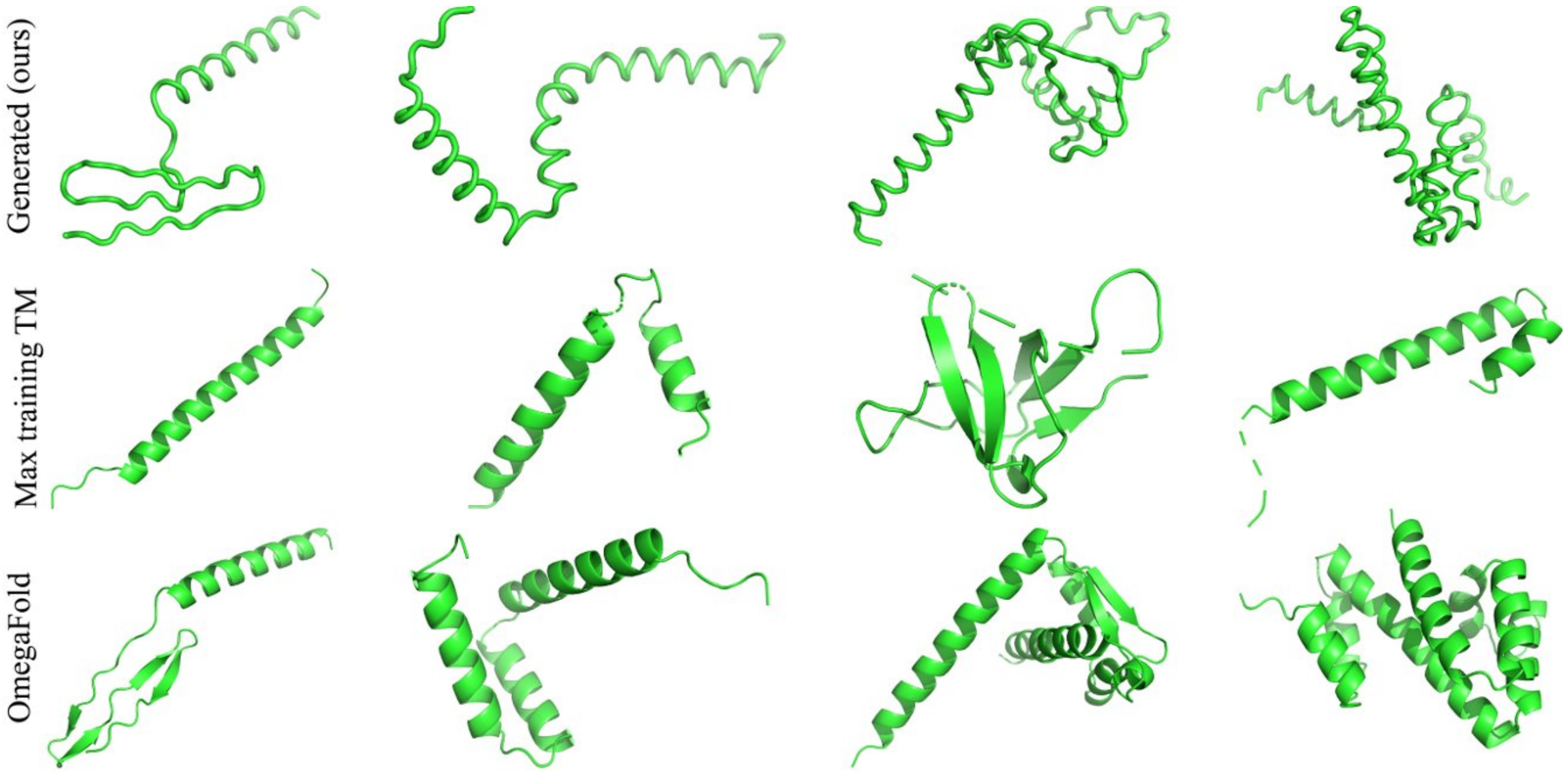
Significant improvements over point cloud diffusion model

Generated structures are diverse



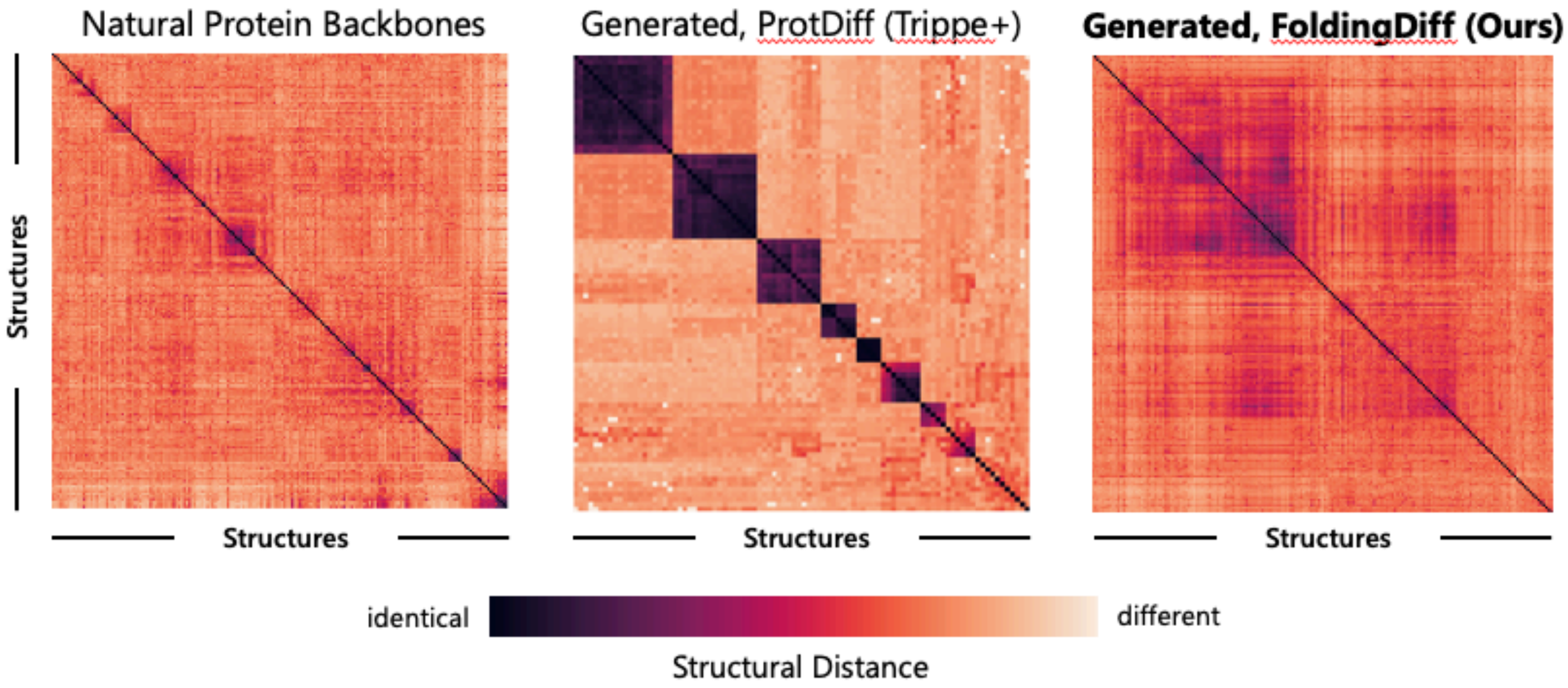
59 residues
scTM = 0.46
max training TM = 0.63

68 residues
scTM = 0.54
max training TM = 0.60

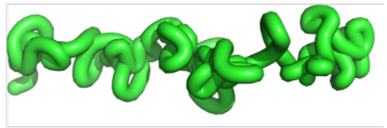
107 residues
scTM = 0.46
max training TM = 0.71

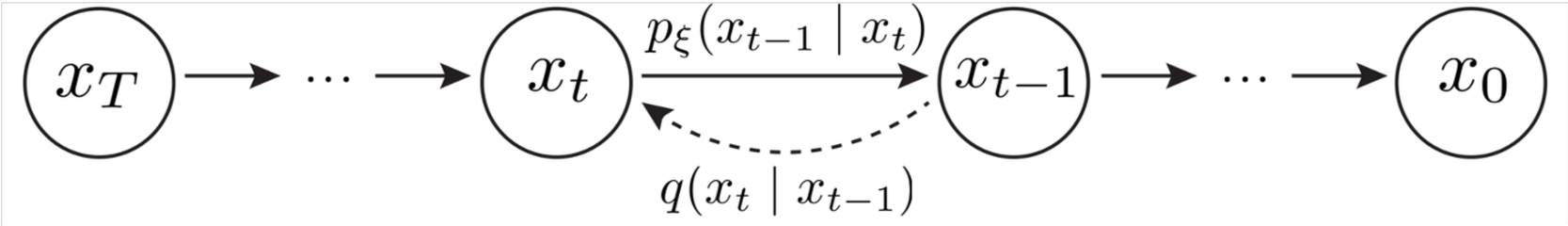
126 residues
scTM = 0.46
max training TM = 0.69

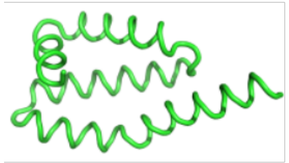
Generated structures are diverse



FoldingDiff is first step towards generating new functions

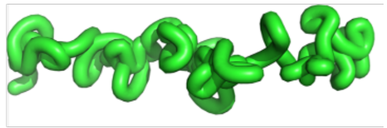


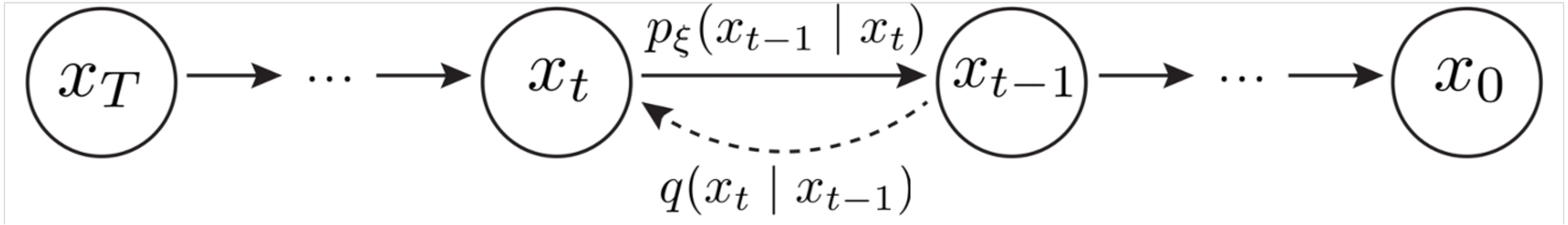


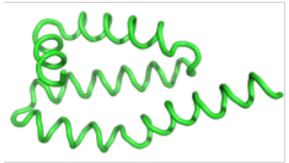


Generate protein backbones by mirroring the folding process

FoldingDiff is first step towards generating new functions

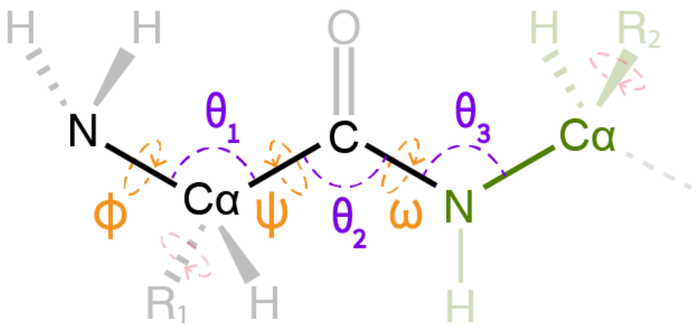






Generate protein backbones by mirroring the folding process

Internal coordinates



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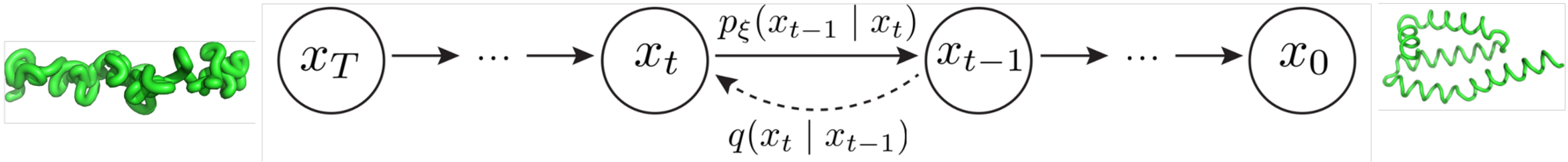

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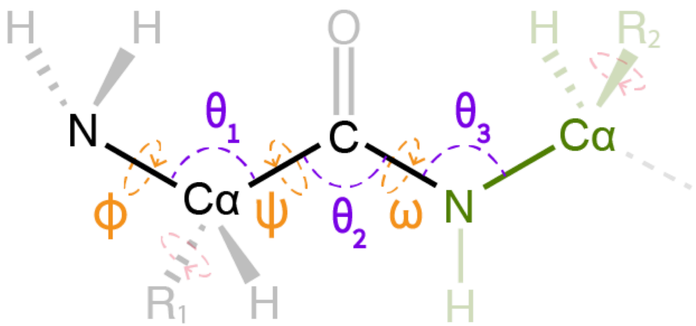
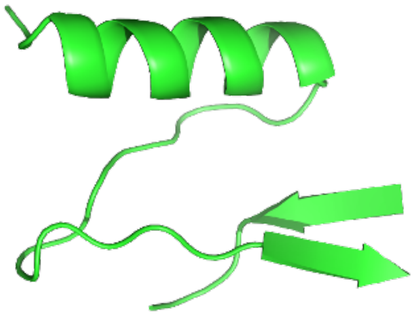


Structural motifs



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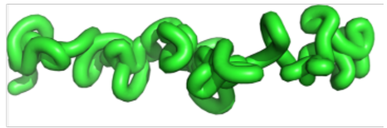
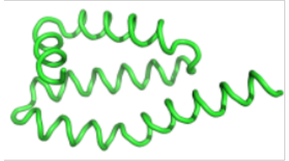


$$x_T \rightarrow \cdots \rightarrow x_t \underset{q(x_t \mid x_{t-1})}{\overset{p_\xi(x_{t-1} \mid x_t)}{\rightleftarrows}} x_{t-1} \rightarrow \cdots \rightarrow x_0$$



Generate protein backbones by mirroring the folding process

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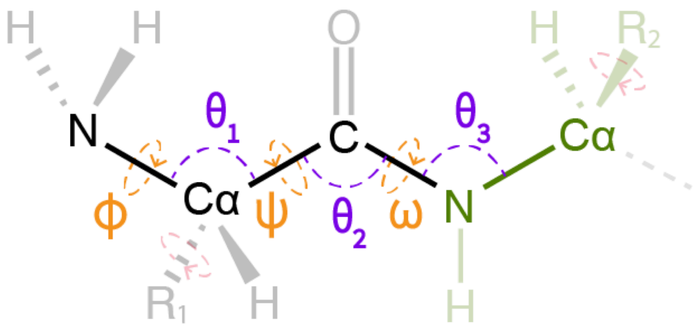

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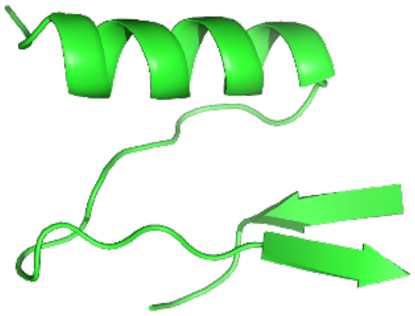
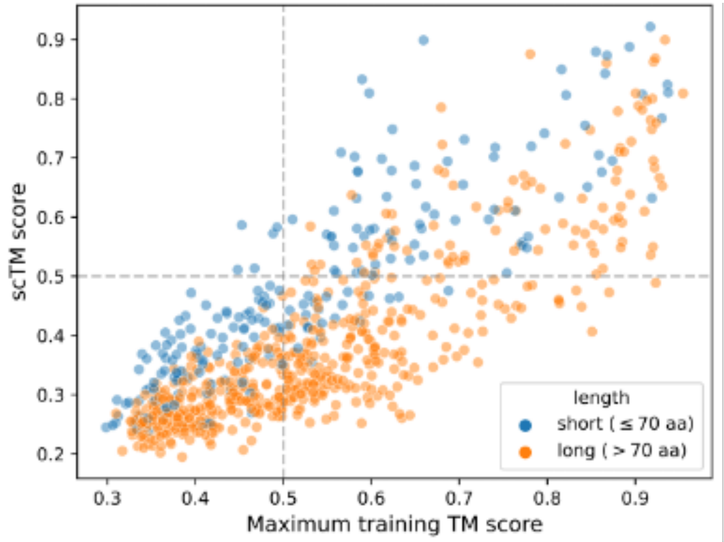


Realistic, diverse samples



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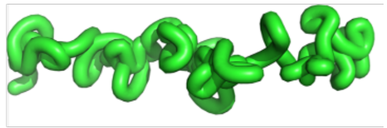

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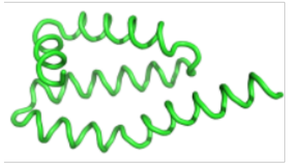

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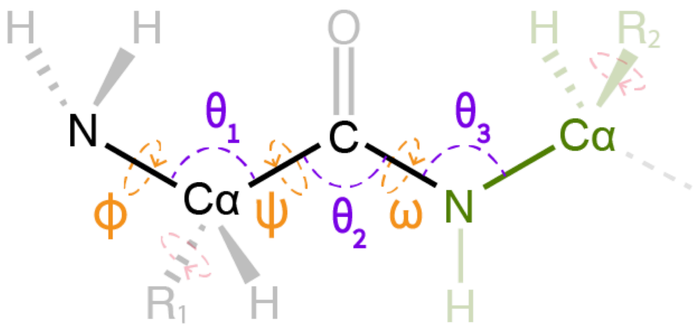

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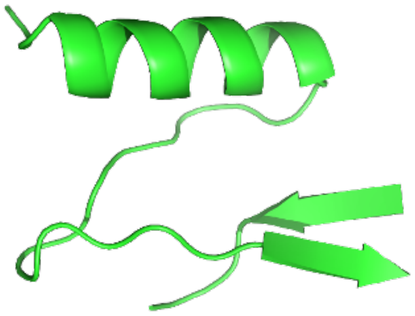

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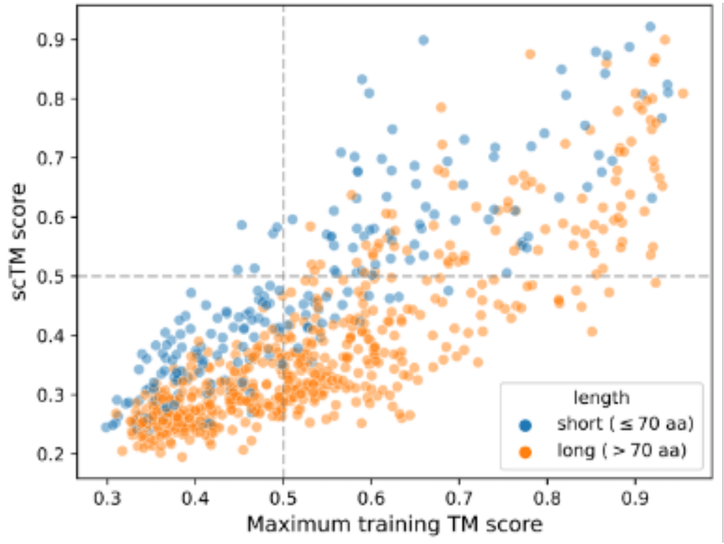
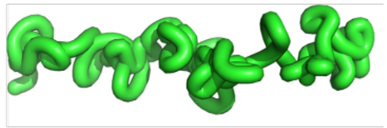


github.com/microsoft/foldingdiff

FoldingDiff is first step towards generating new functions



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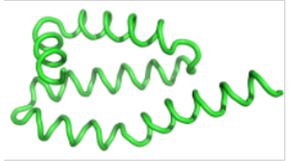

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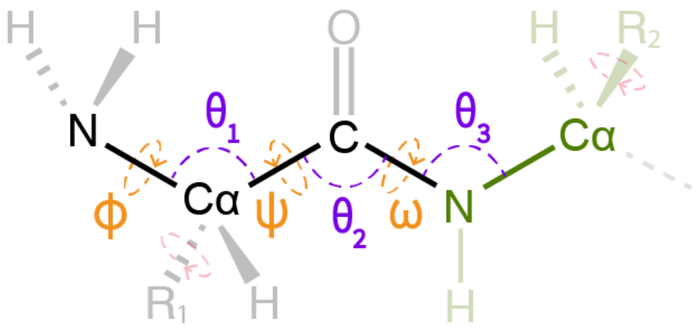

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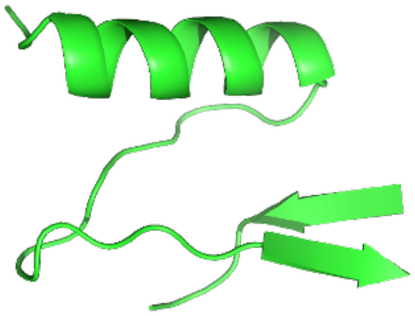

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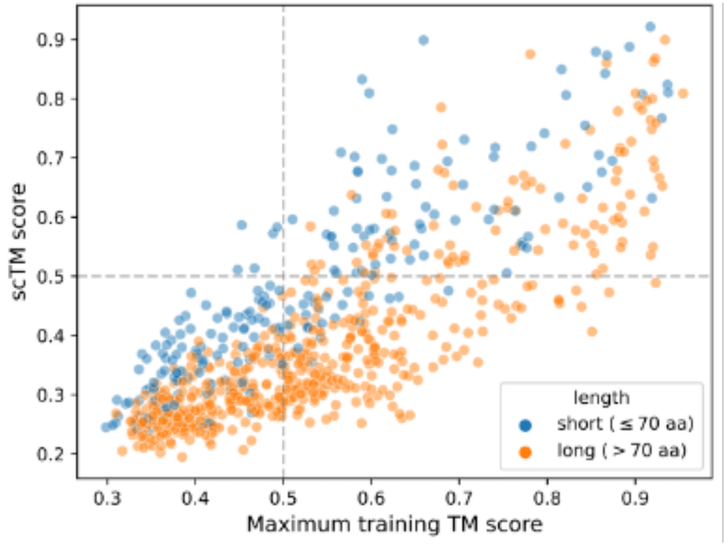

github.com/microsoft/foldingdiff

huggingface.co/spaces/wukevin/foldingdiff

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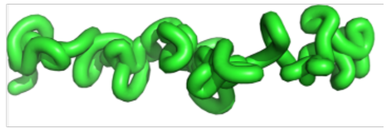
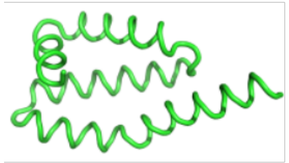
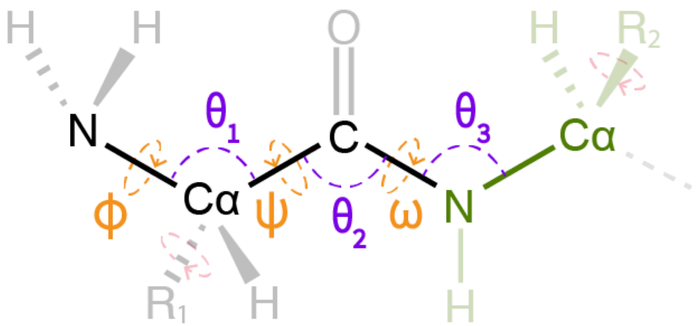


$$x_T \rightarrow \cdots \rightarrow x_t \underset{q(x_t \mid x_{t-1})}{\overset{p_\xi(x_{t-1} \mid x_t)}{\rightleftarrows}} x_{t-1} \rightarrow \cdots \rightarrow x_0$$

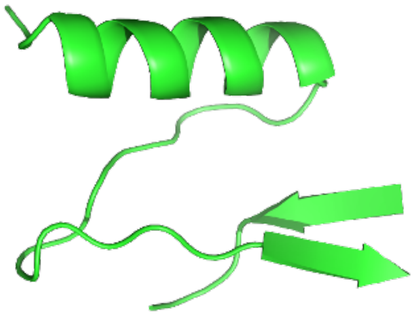


Generate protein backbones by mirroring the folding process

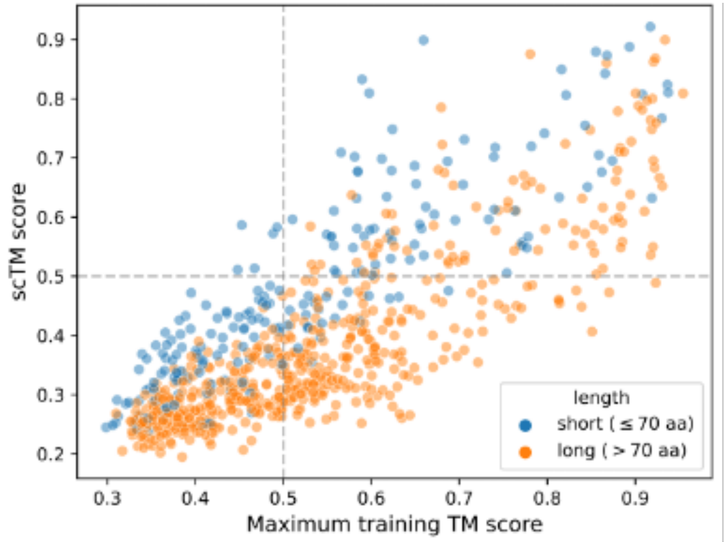
Internal coordinates



Structural motifs



Realistic, diverse samples

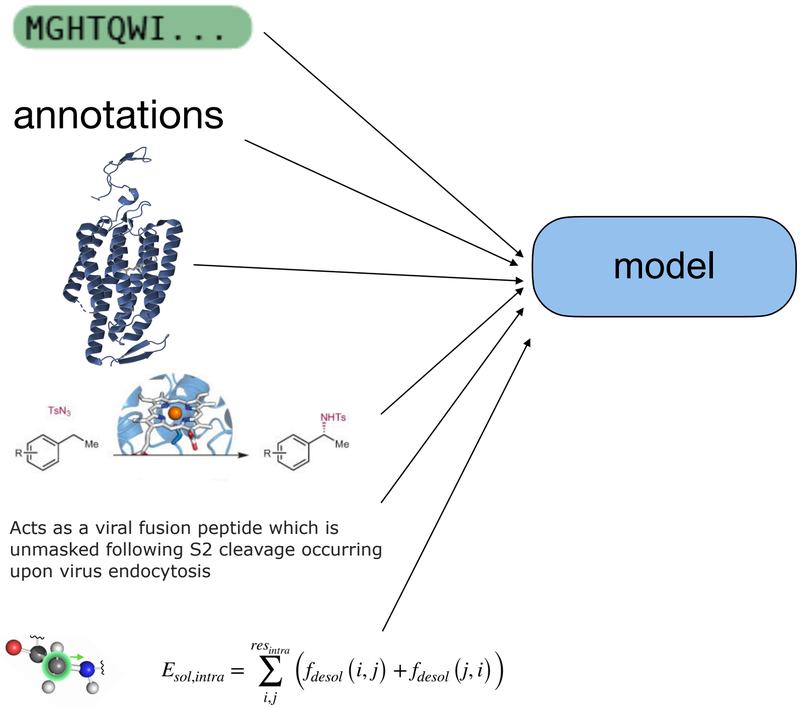


github.com/microsoft/foldingdiff

huggingface.co/spaces/wukevin/foldingdiff

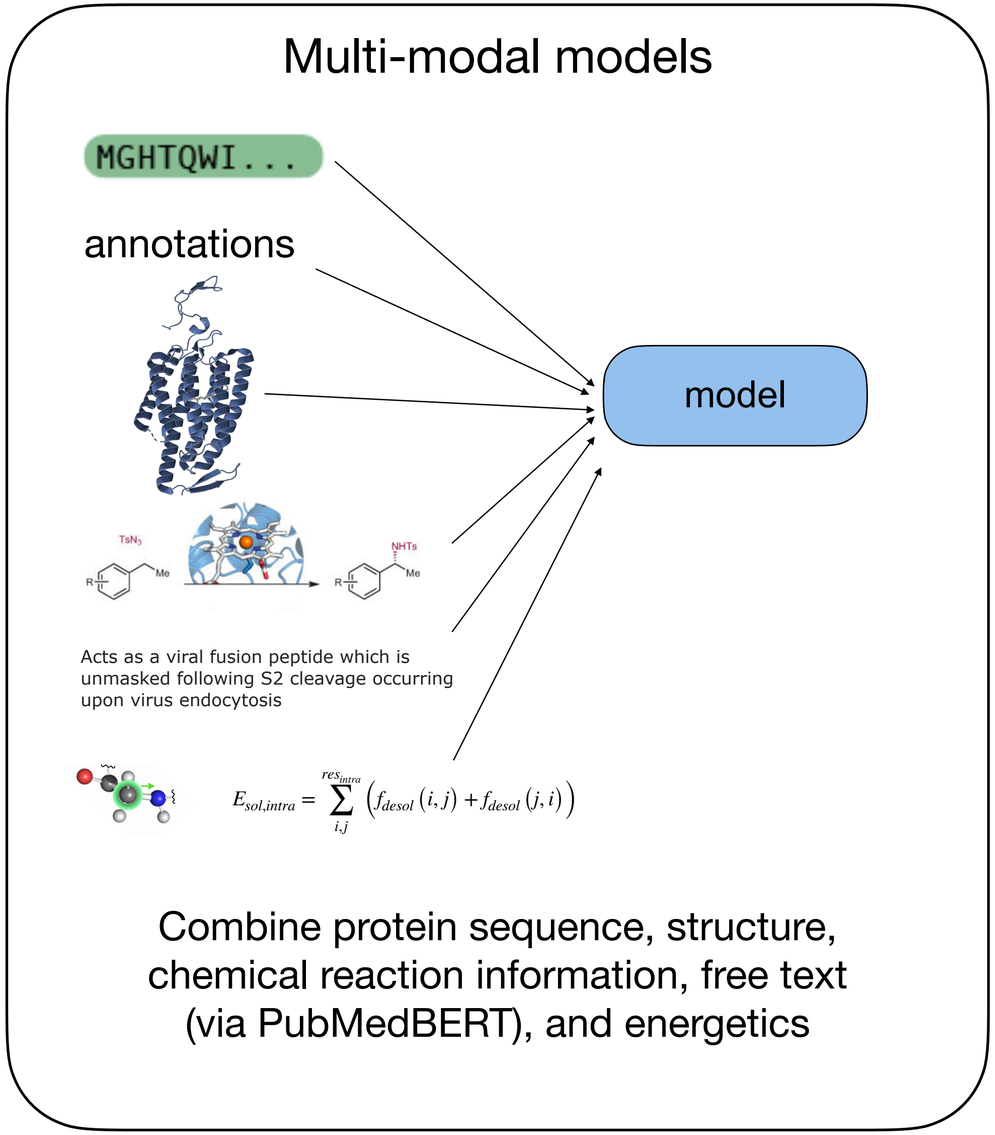
BioNeMo?

Multi-modal models

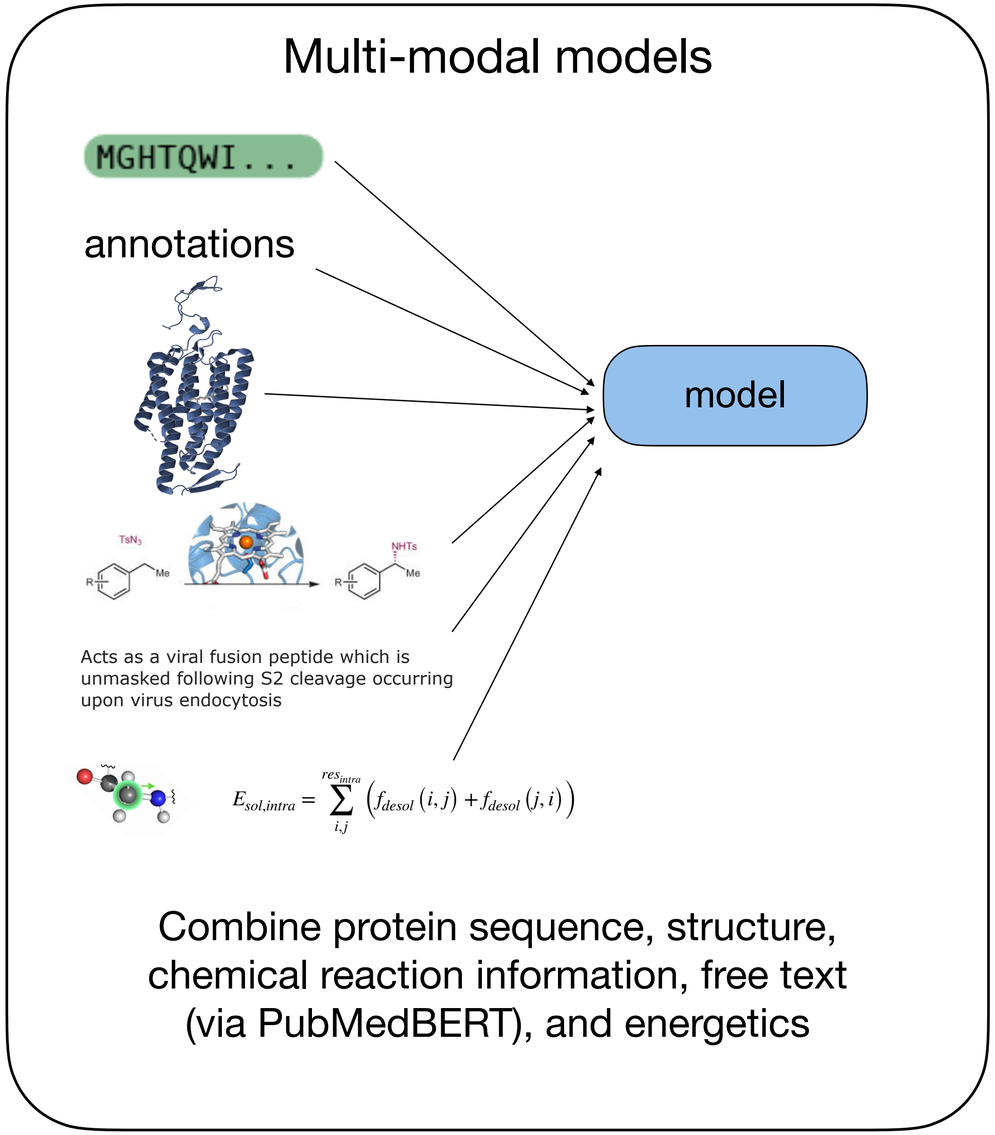


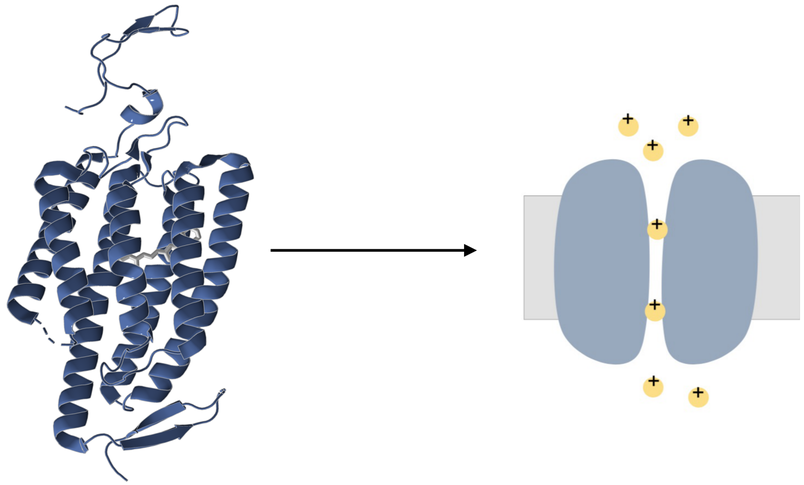
Combine protein sequence, structure, chemical reaction information, free text (via PubMedBERT), and energetics

Can we predict and generate proteins with new functions?



Can we predict and generate proteins with new functions?





Acknowledgments

BioML at MSR New England