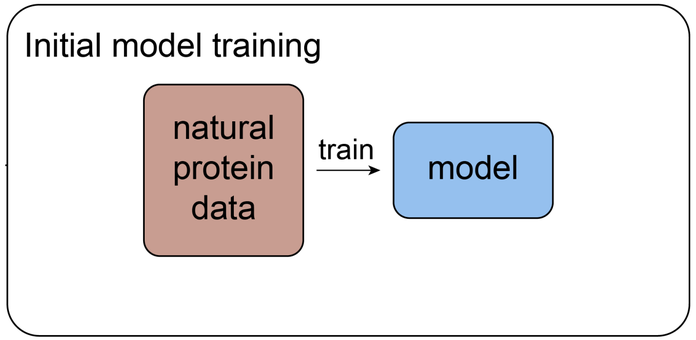
Multimodal deep learning for protein engineering

Kevin Kaichuang Yang
Microsoft Research New England
@KevinKaichuang

Use multiple data modalities to discover and design proteins



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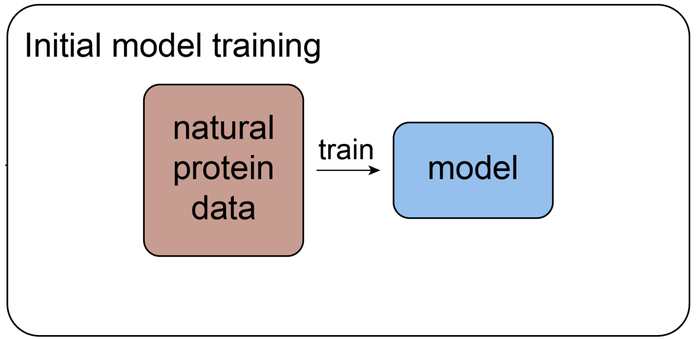

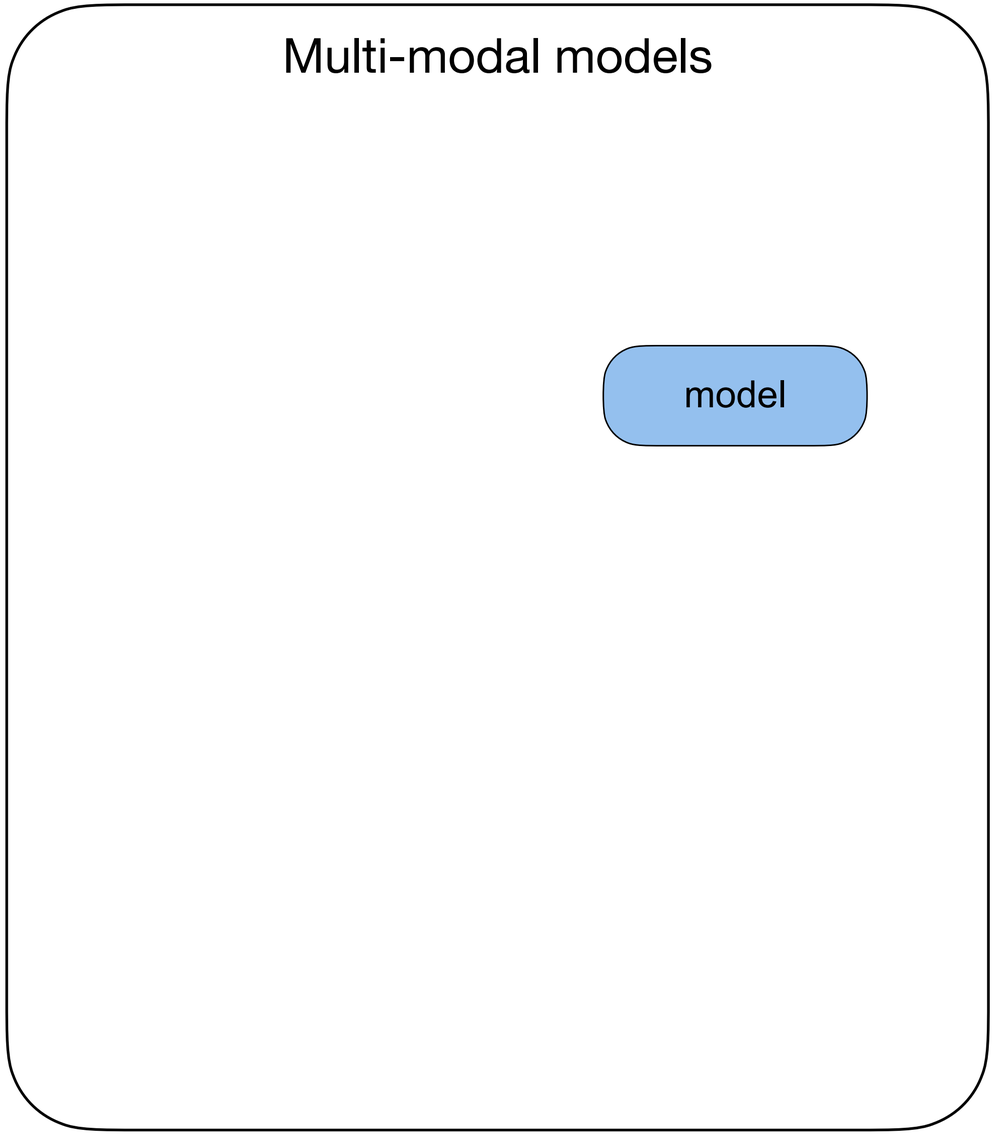

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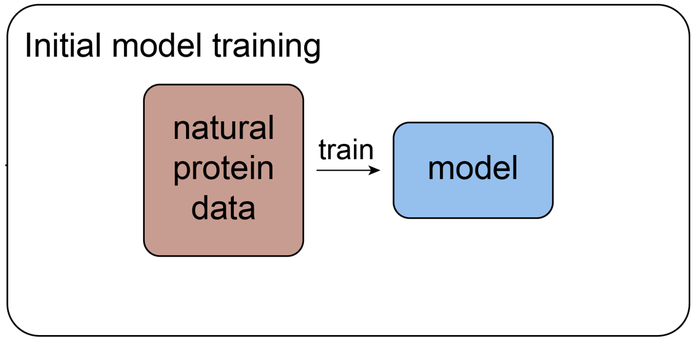

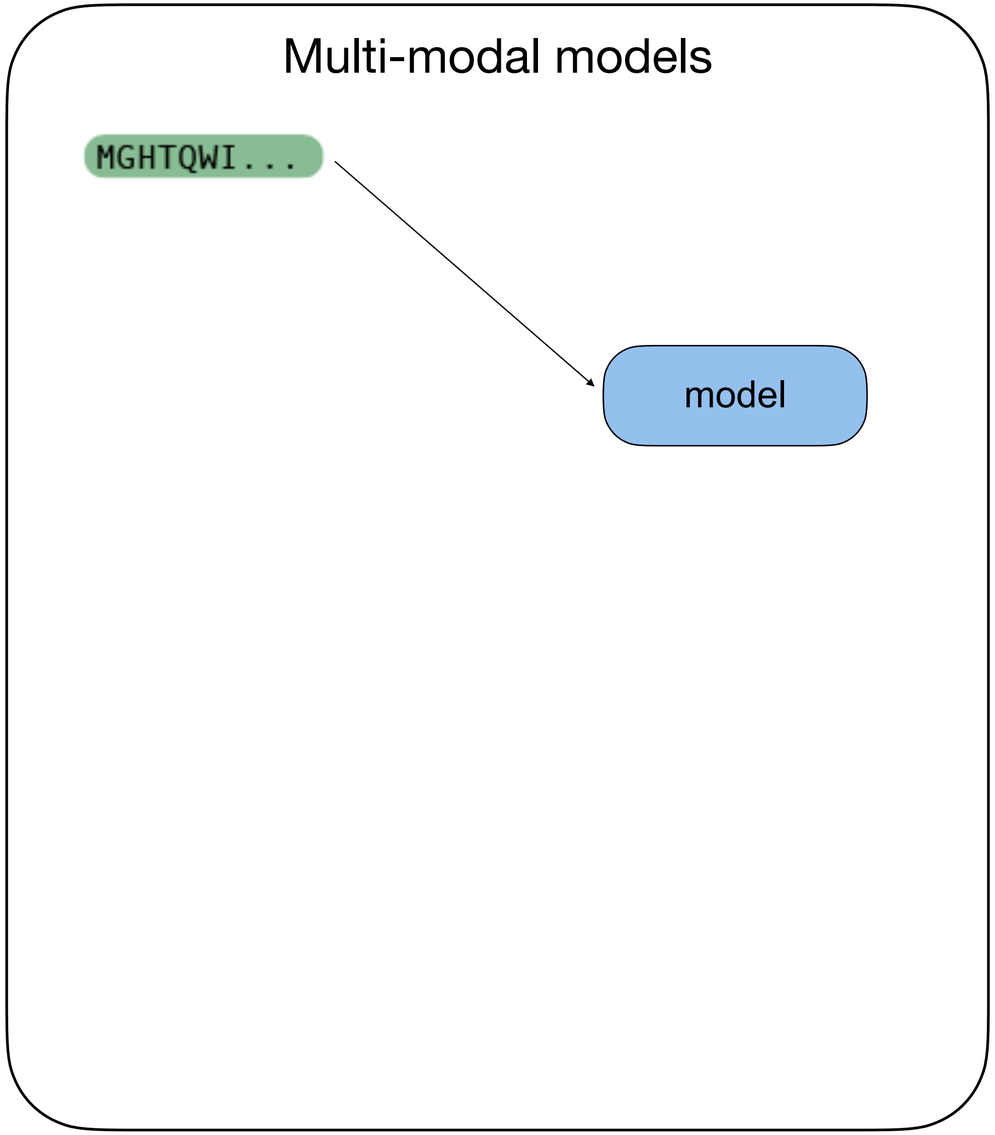

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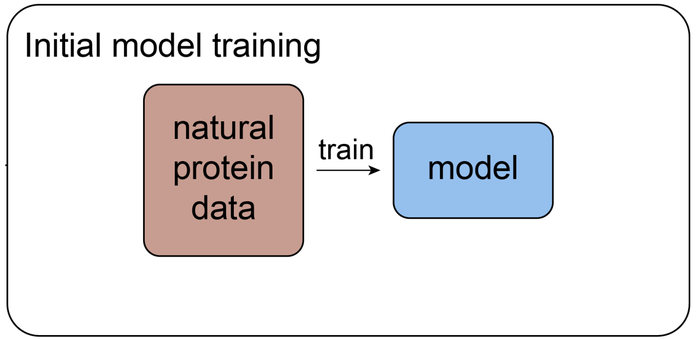

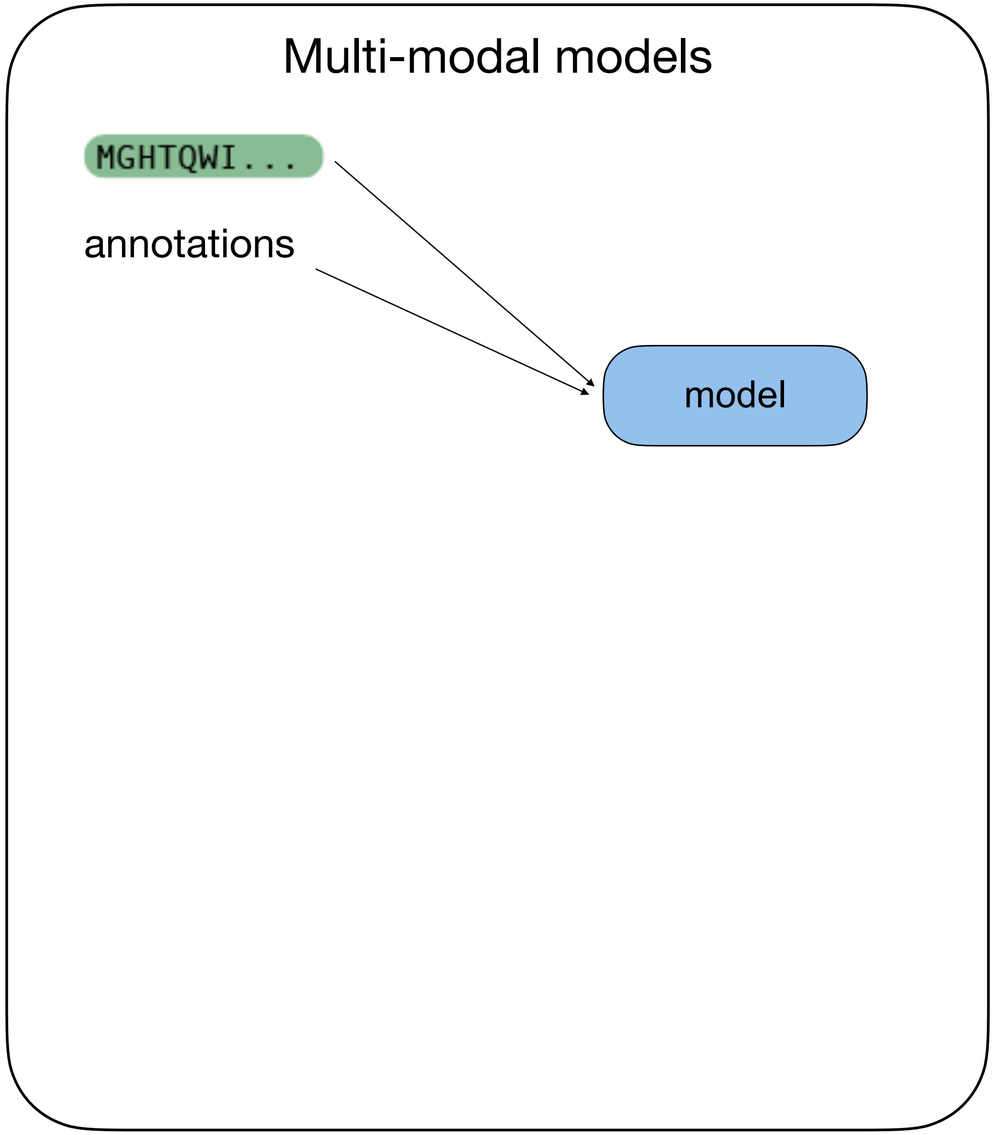

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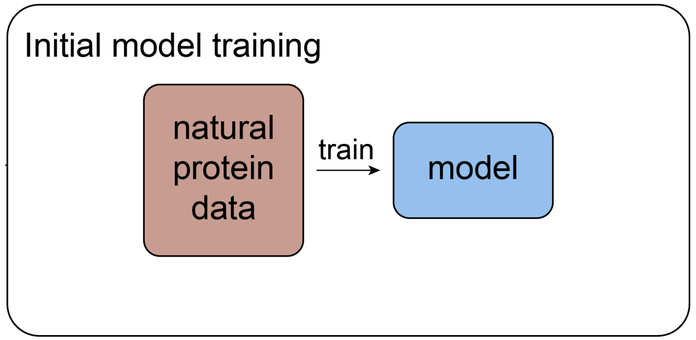

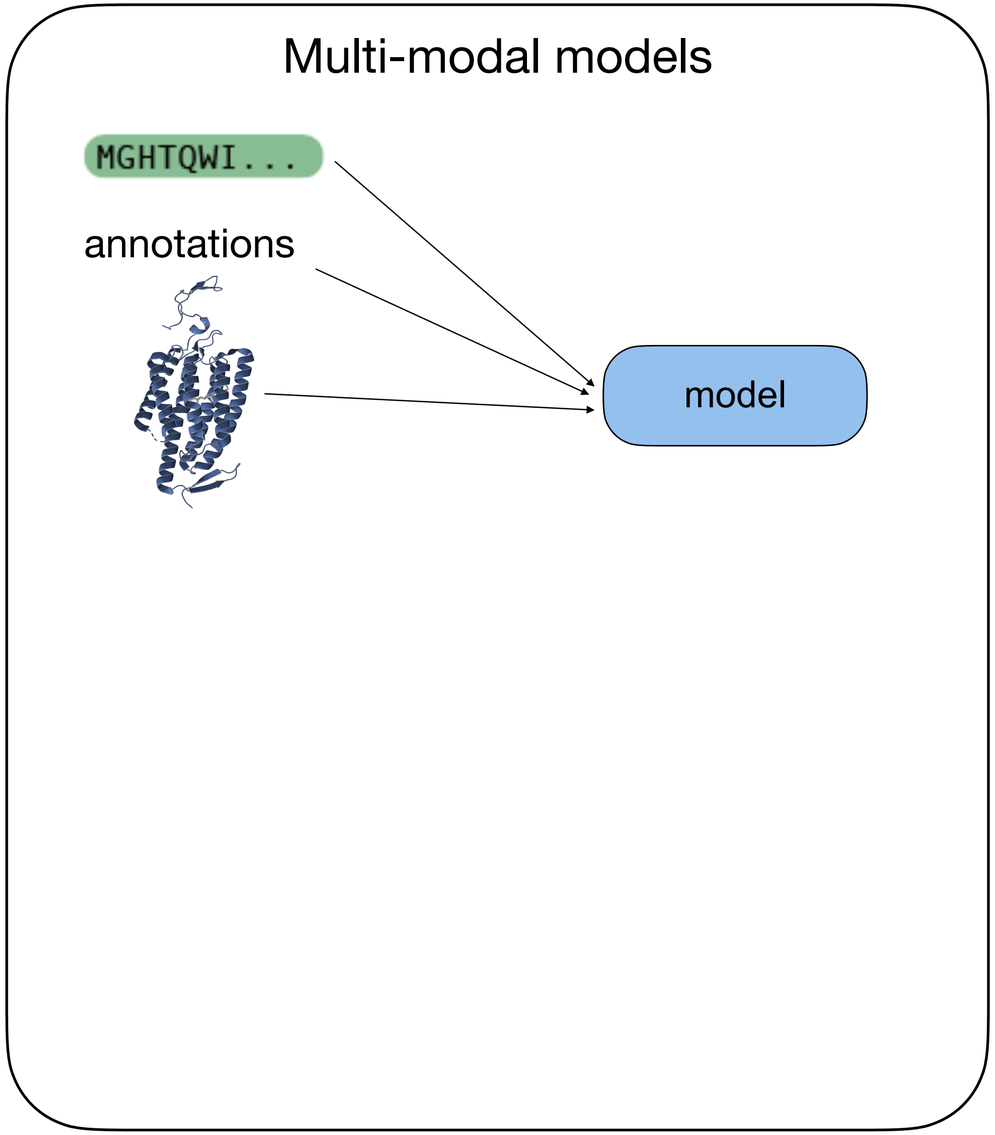

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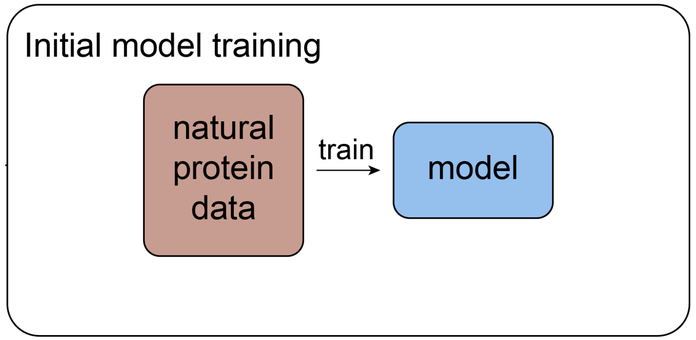

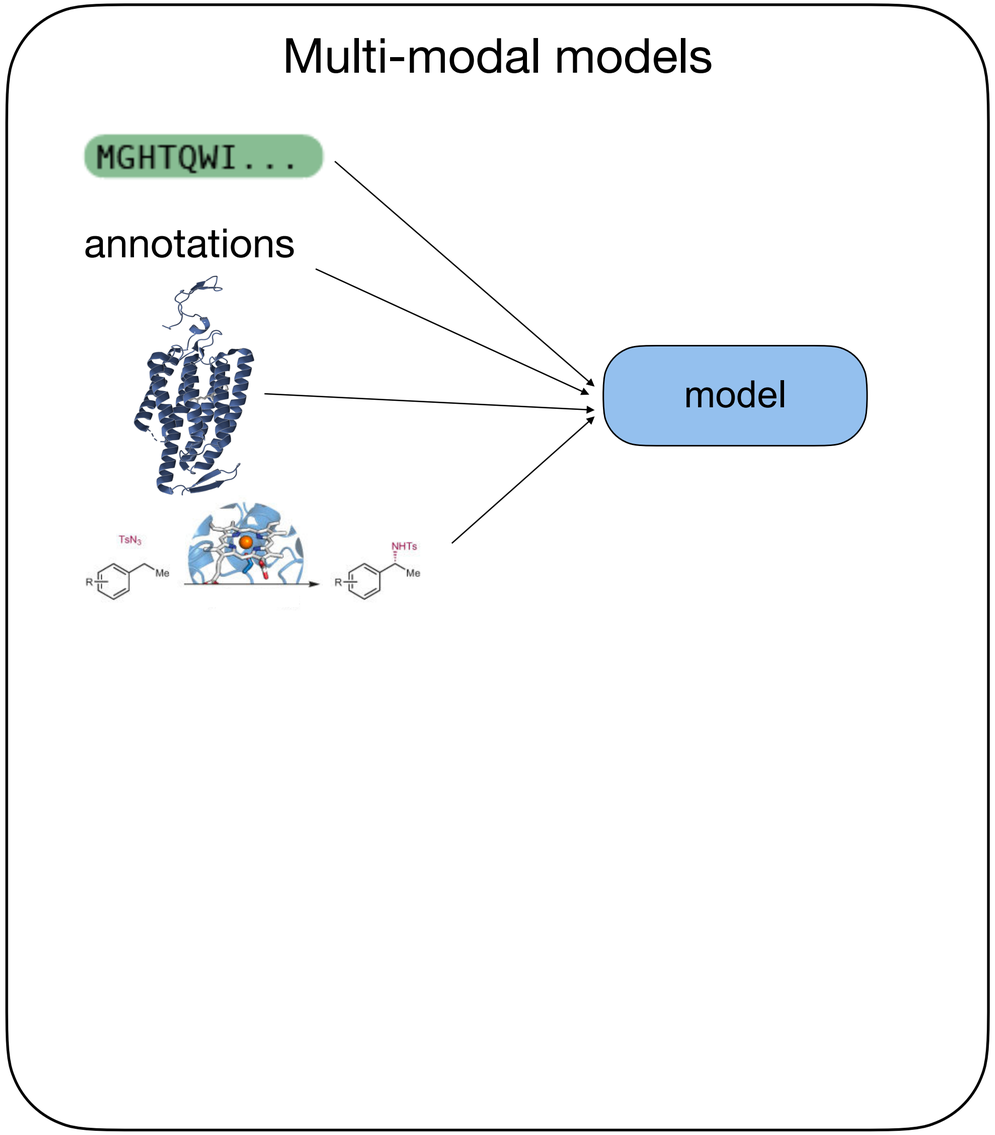

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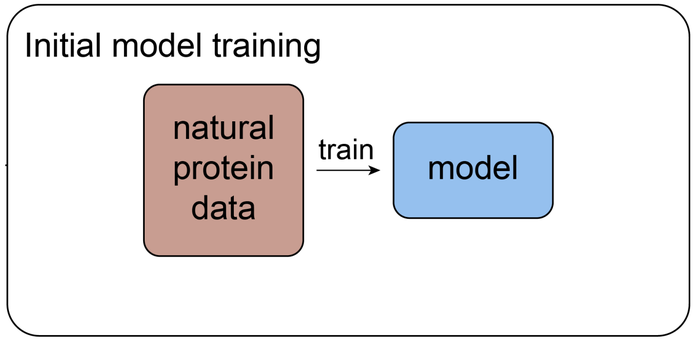

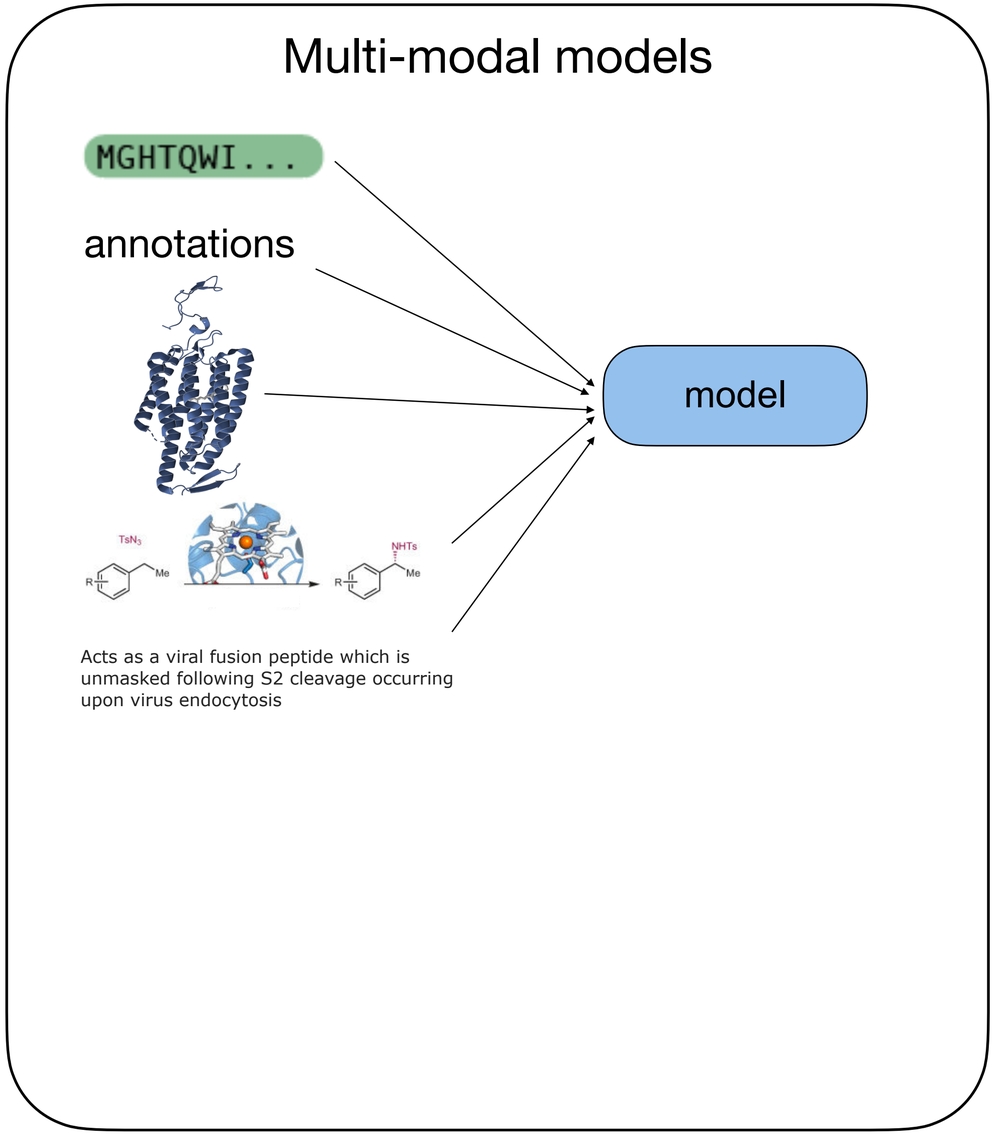

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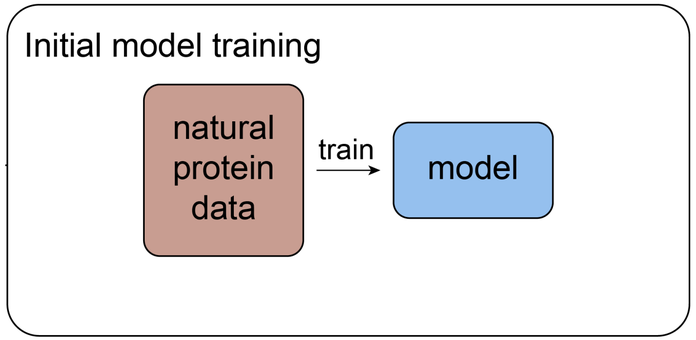

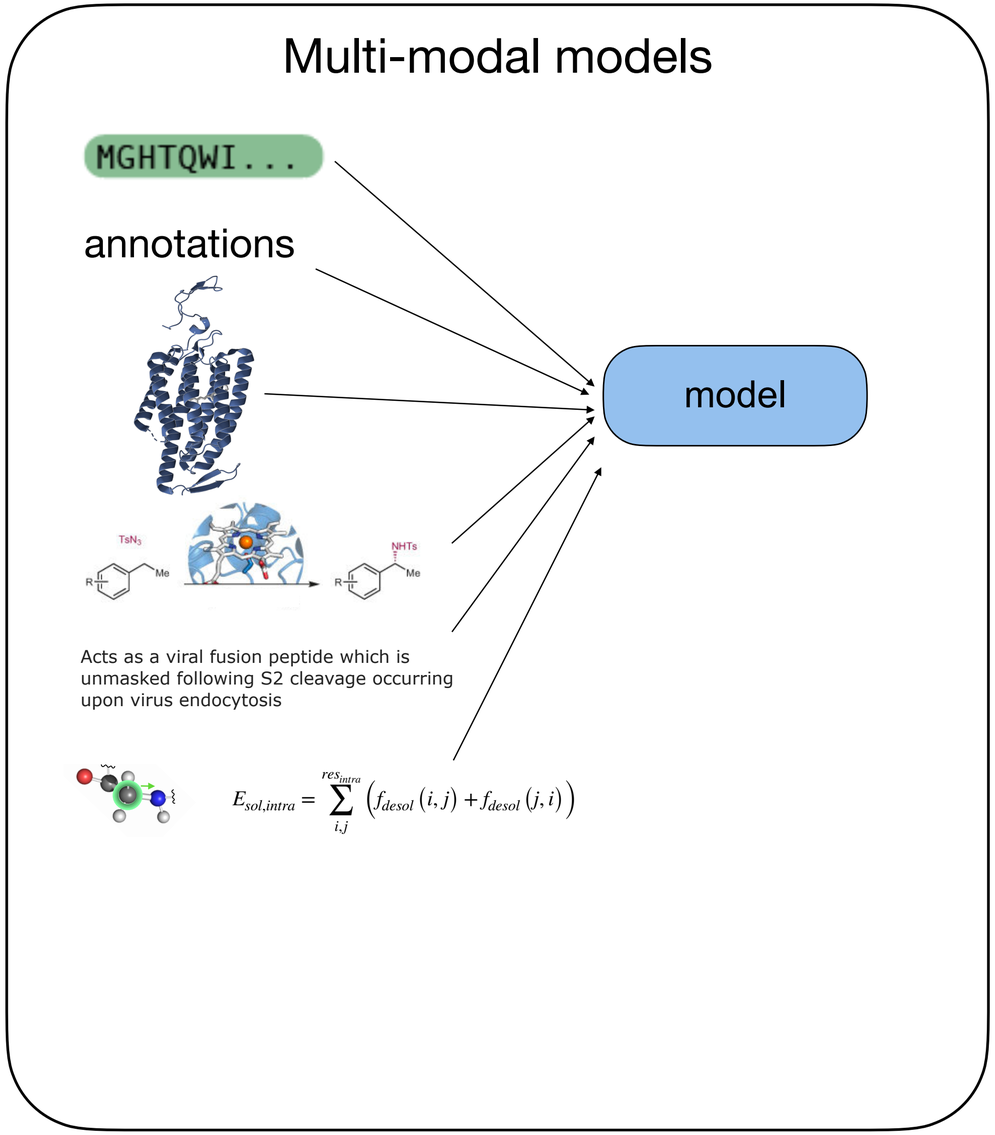

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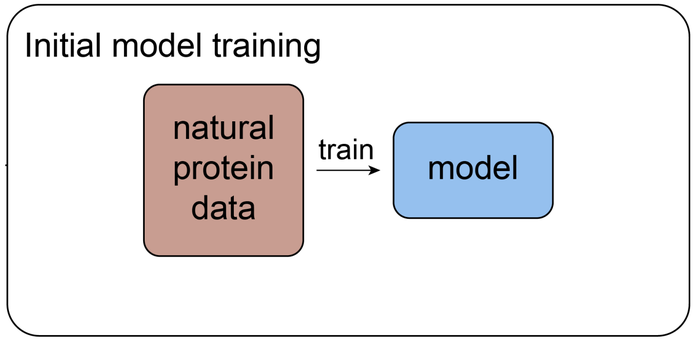

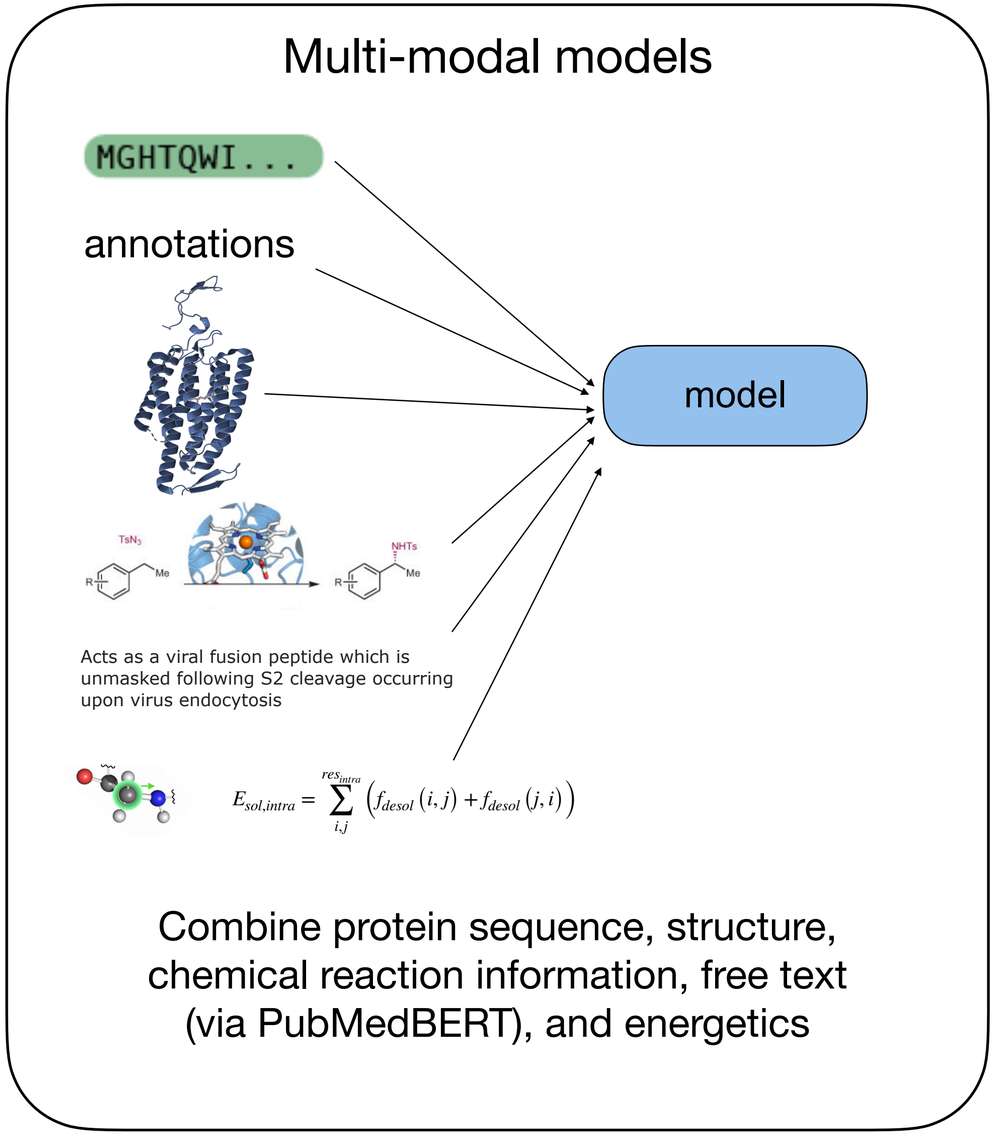

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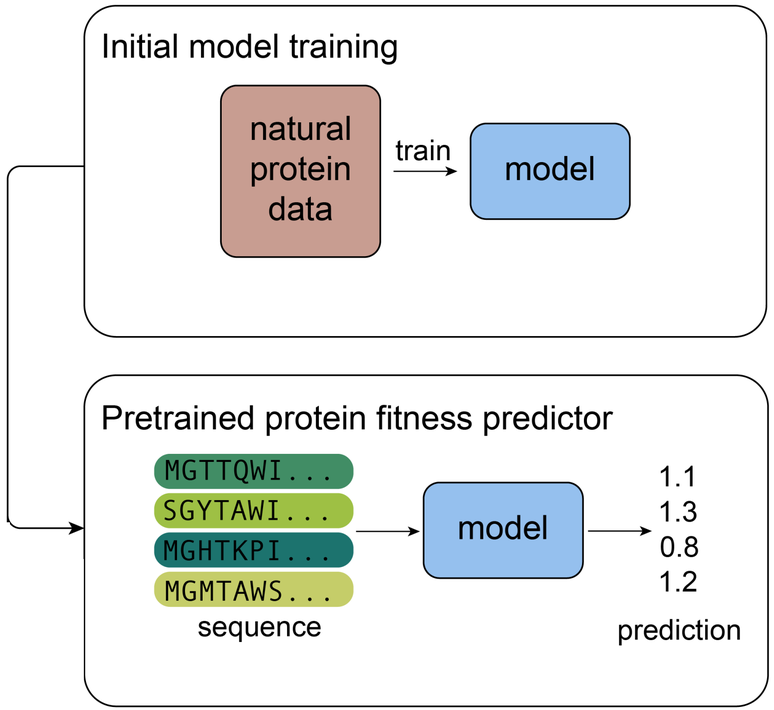

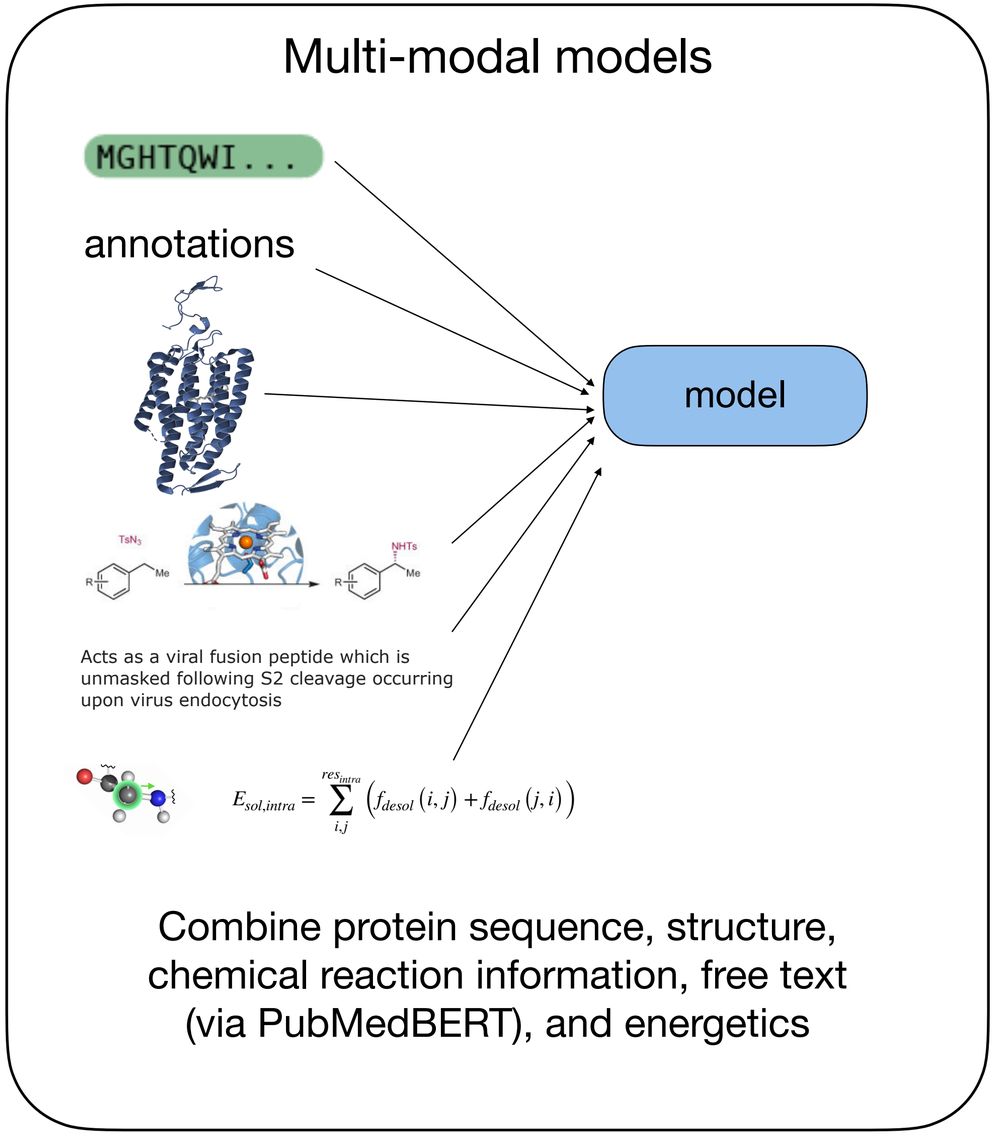

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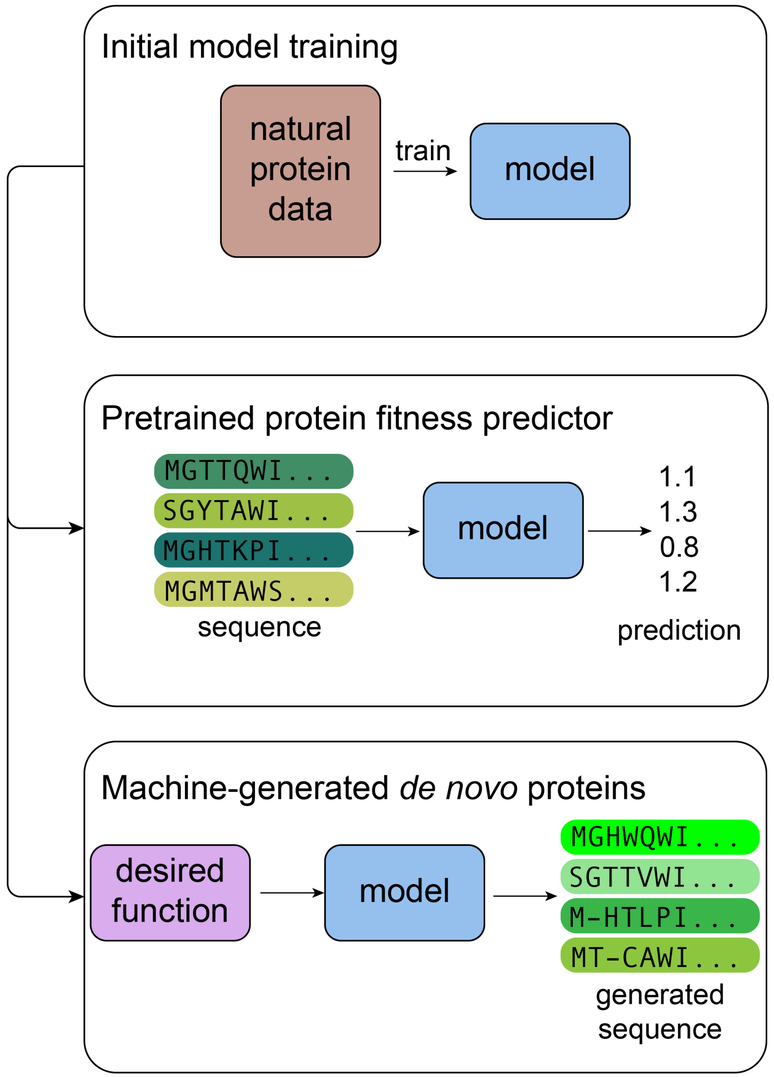

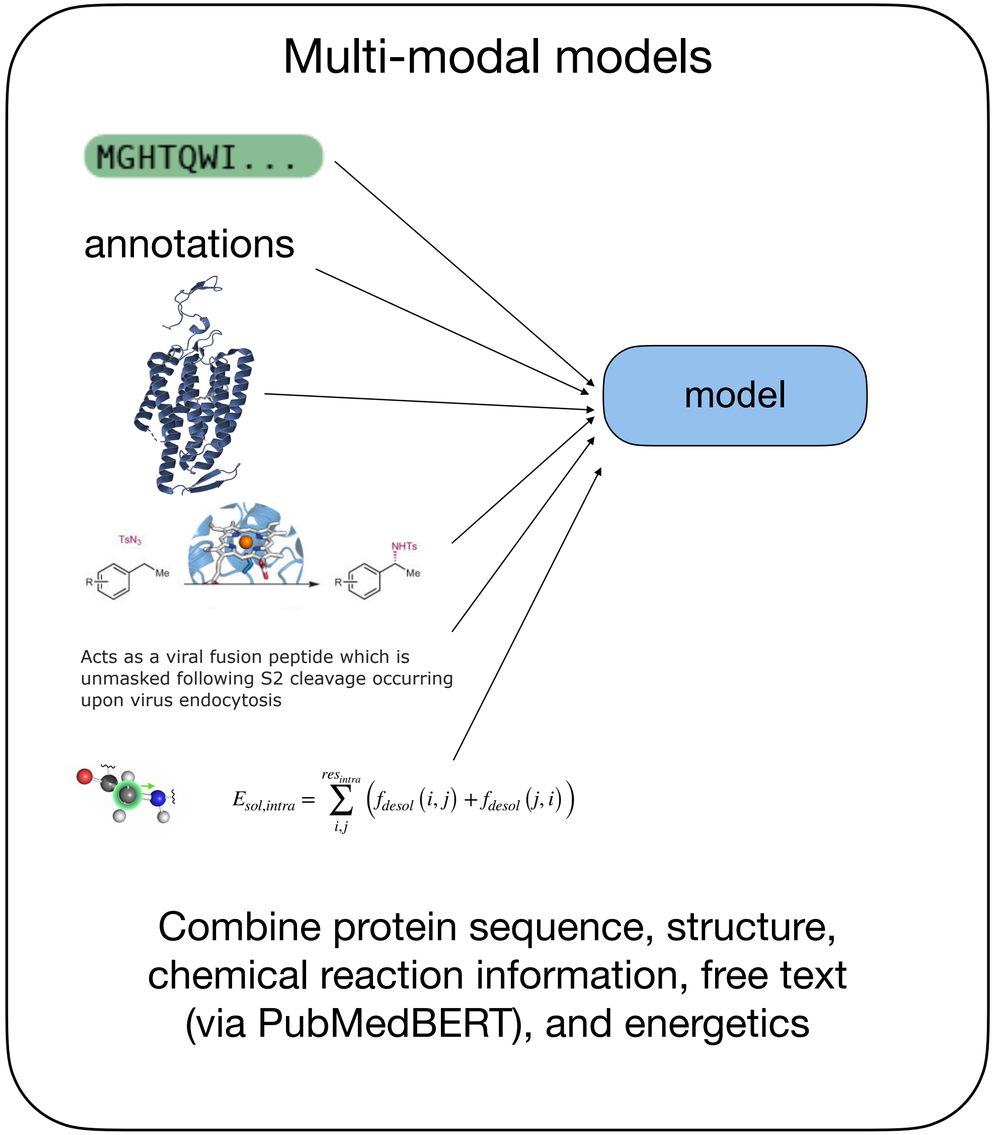

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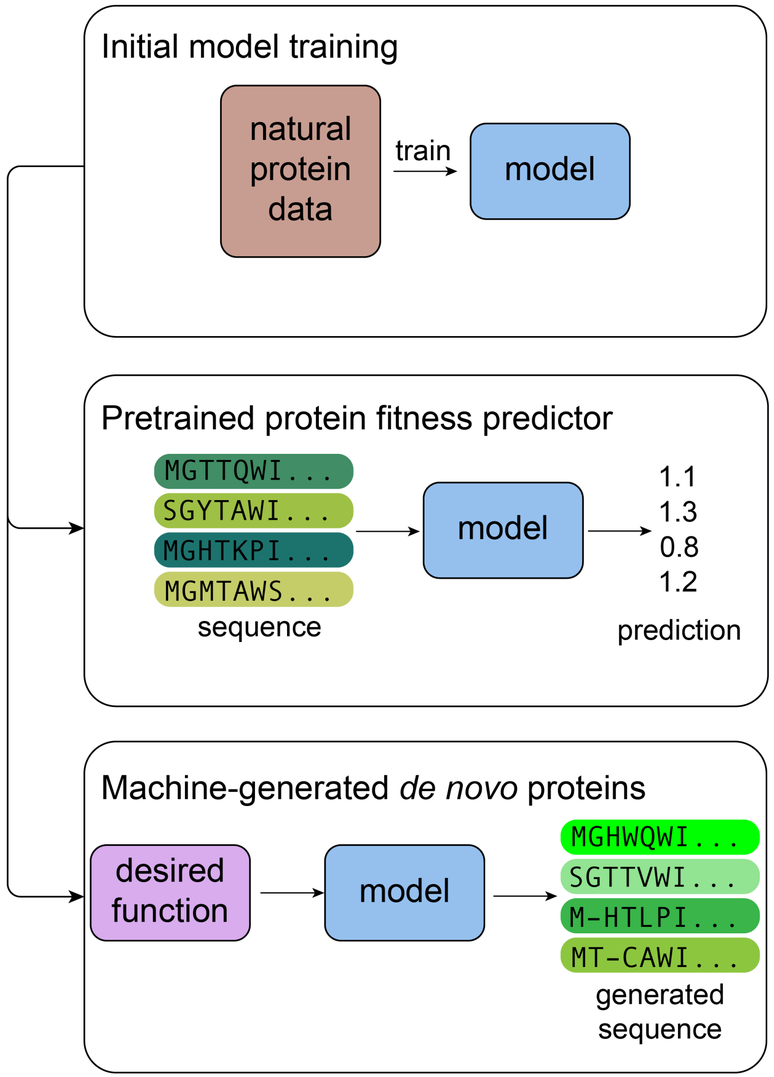

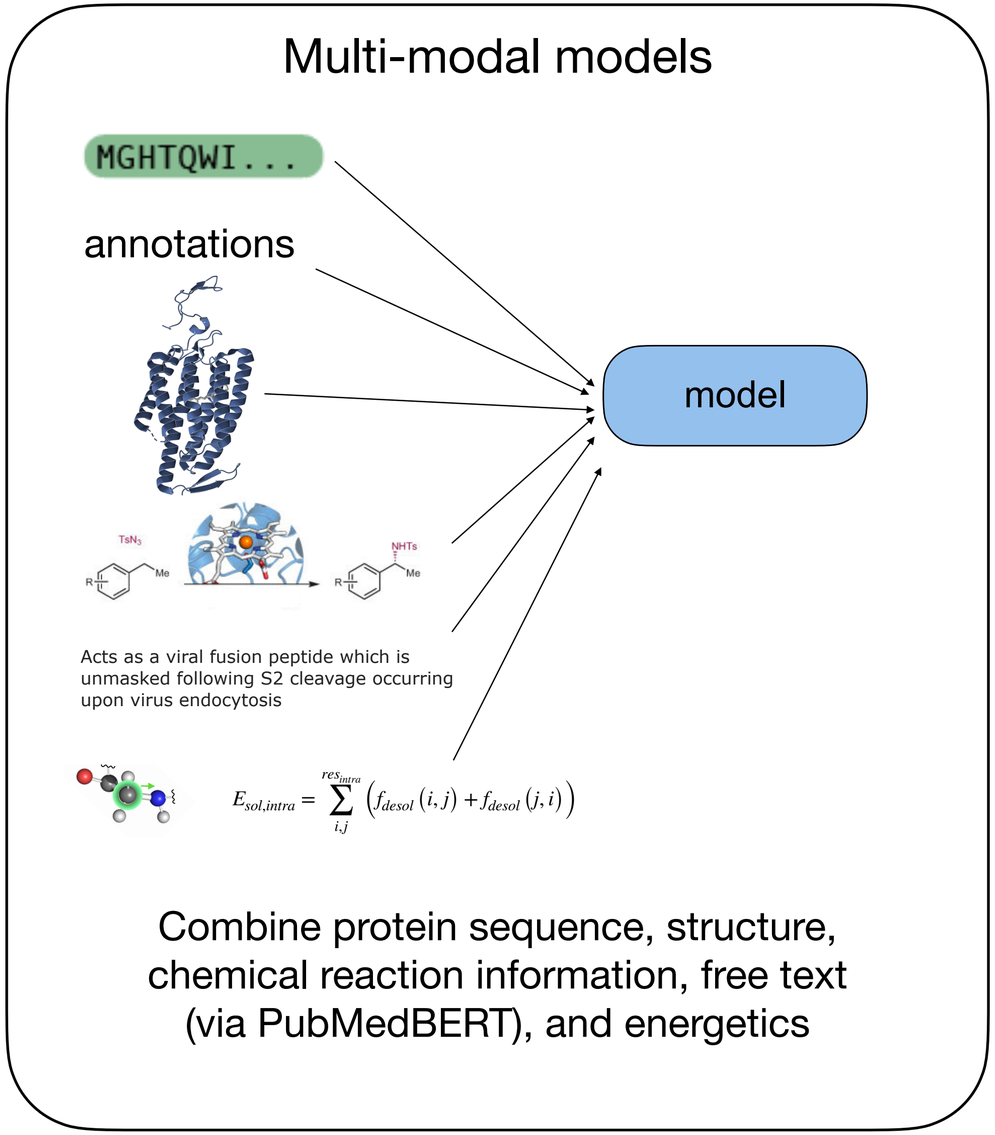

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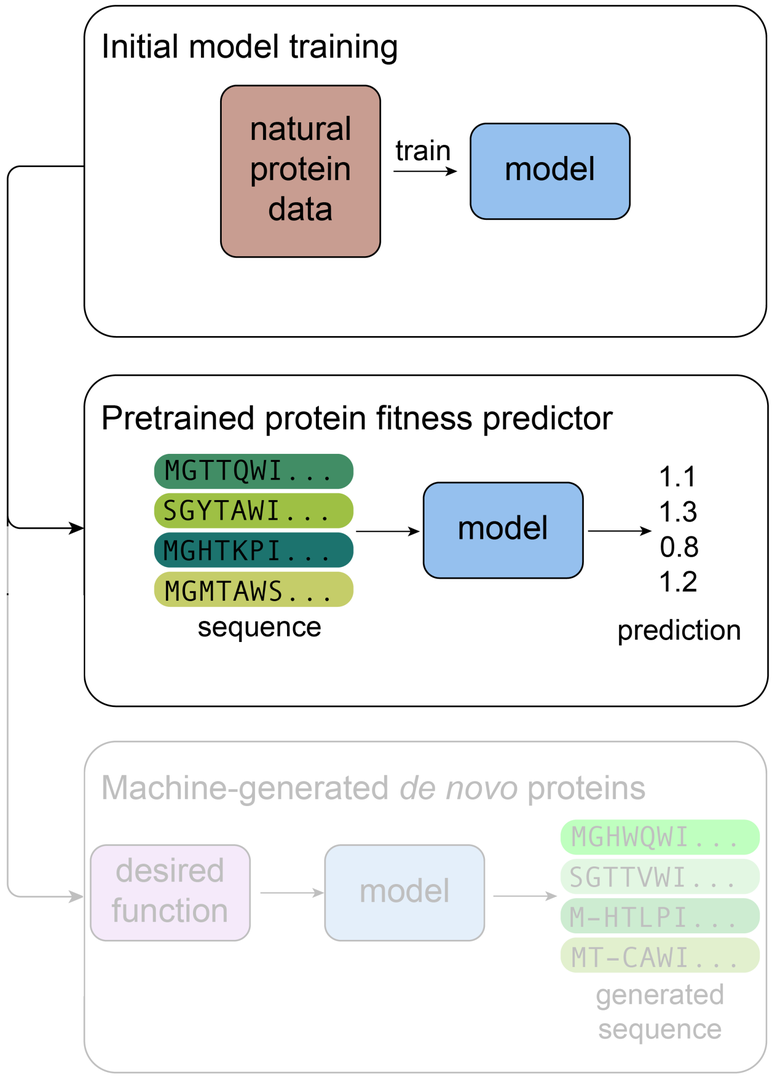
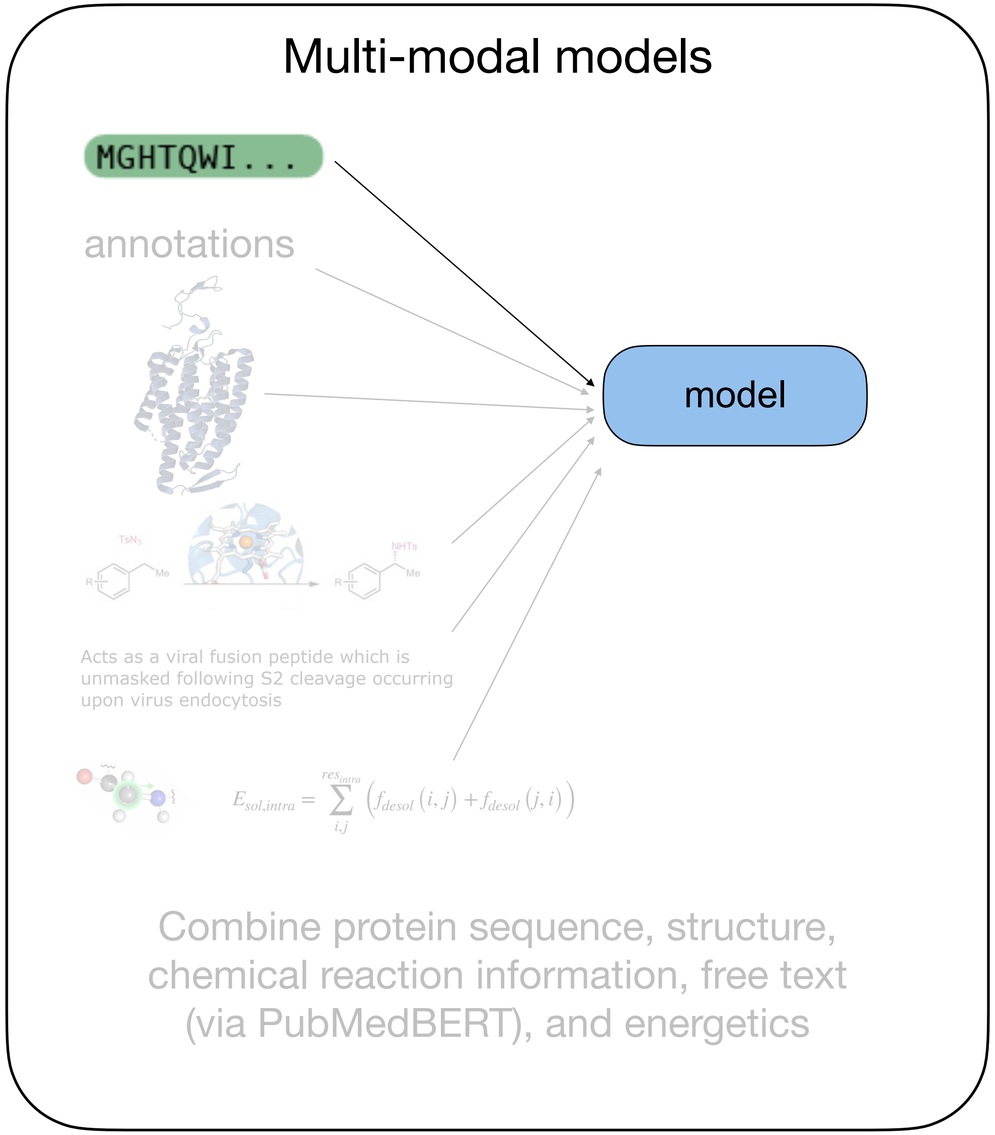
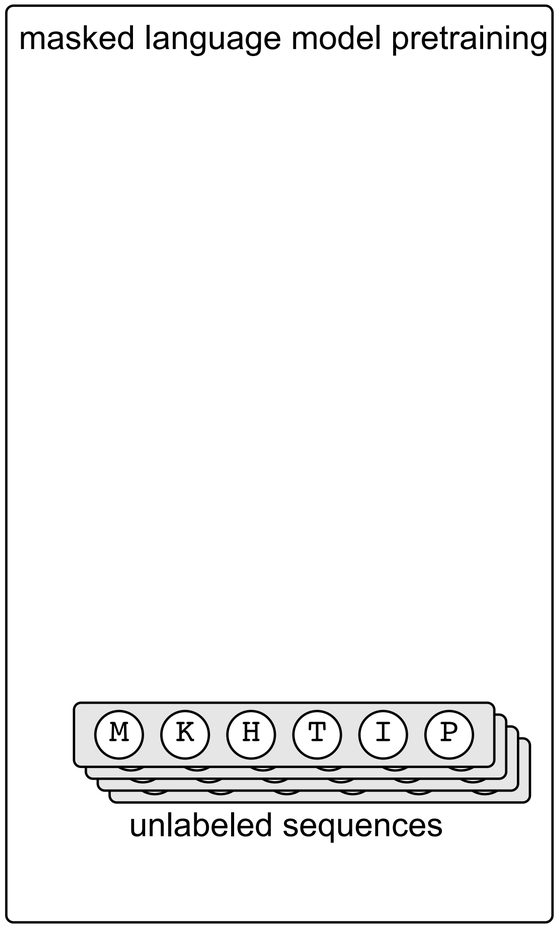




Use pretraining to leverage unlabeled sequences



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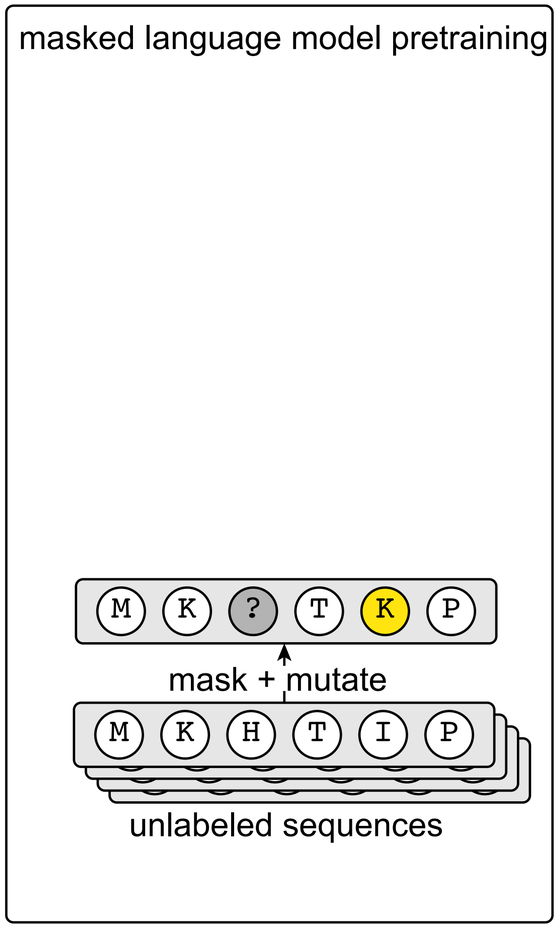

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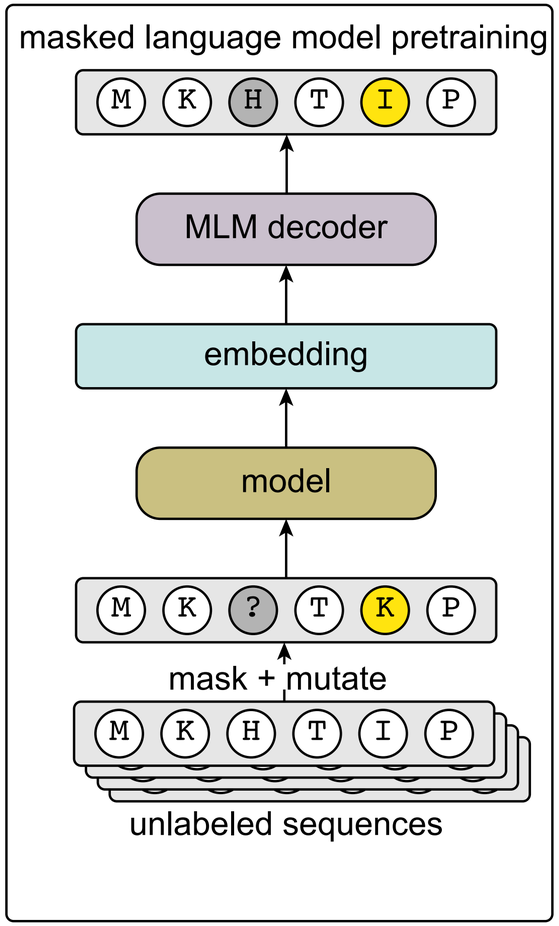

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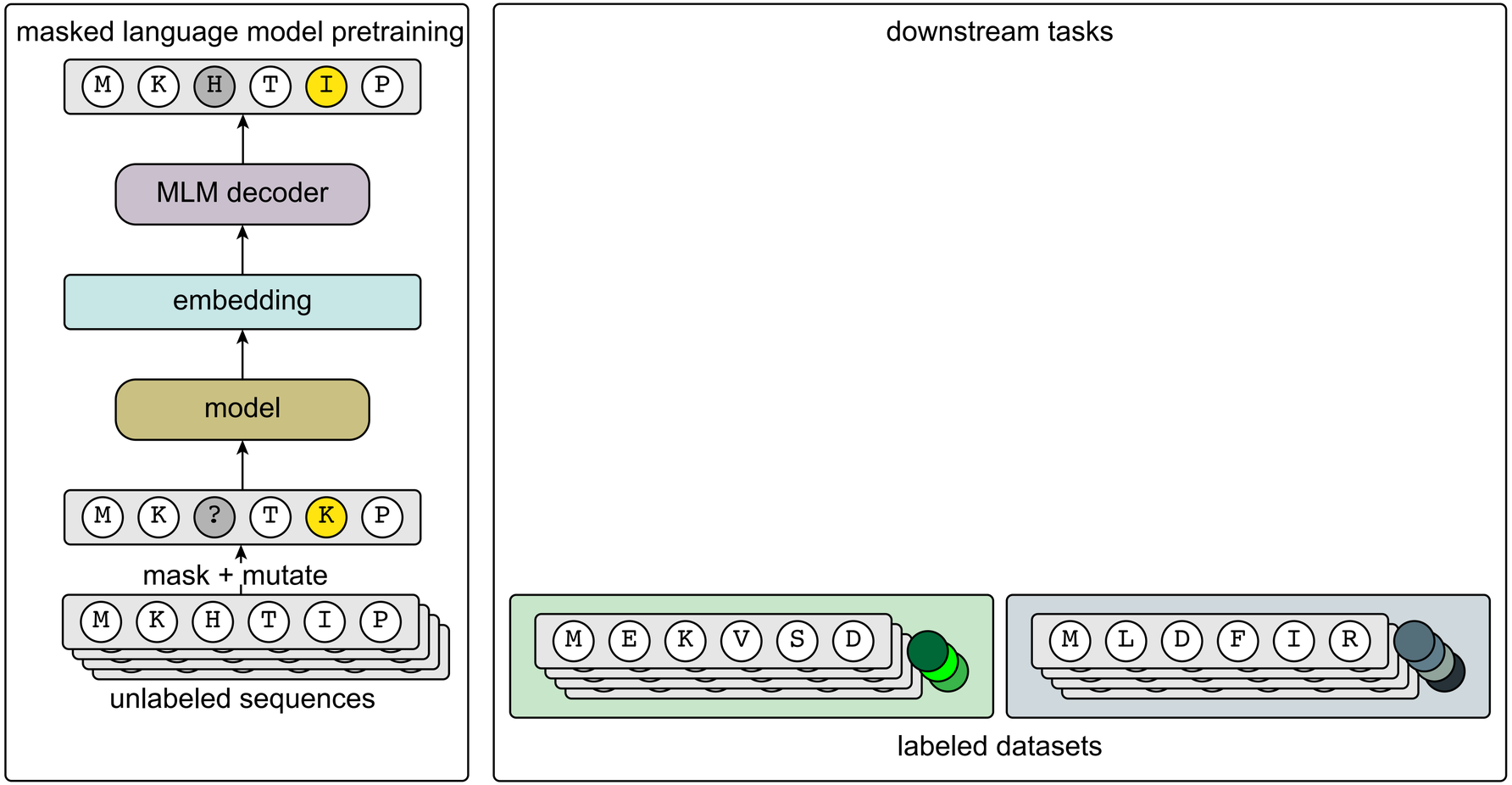

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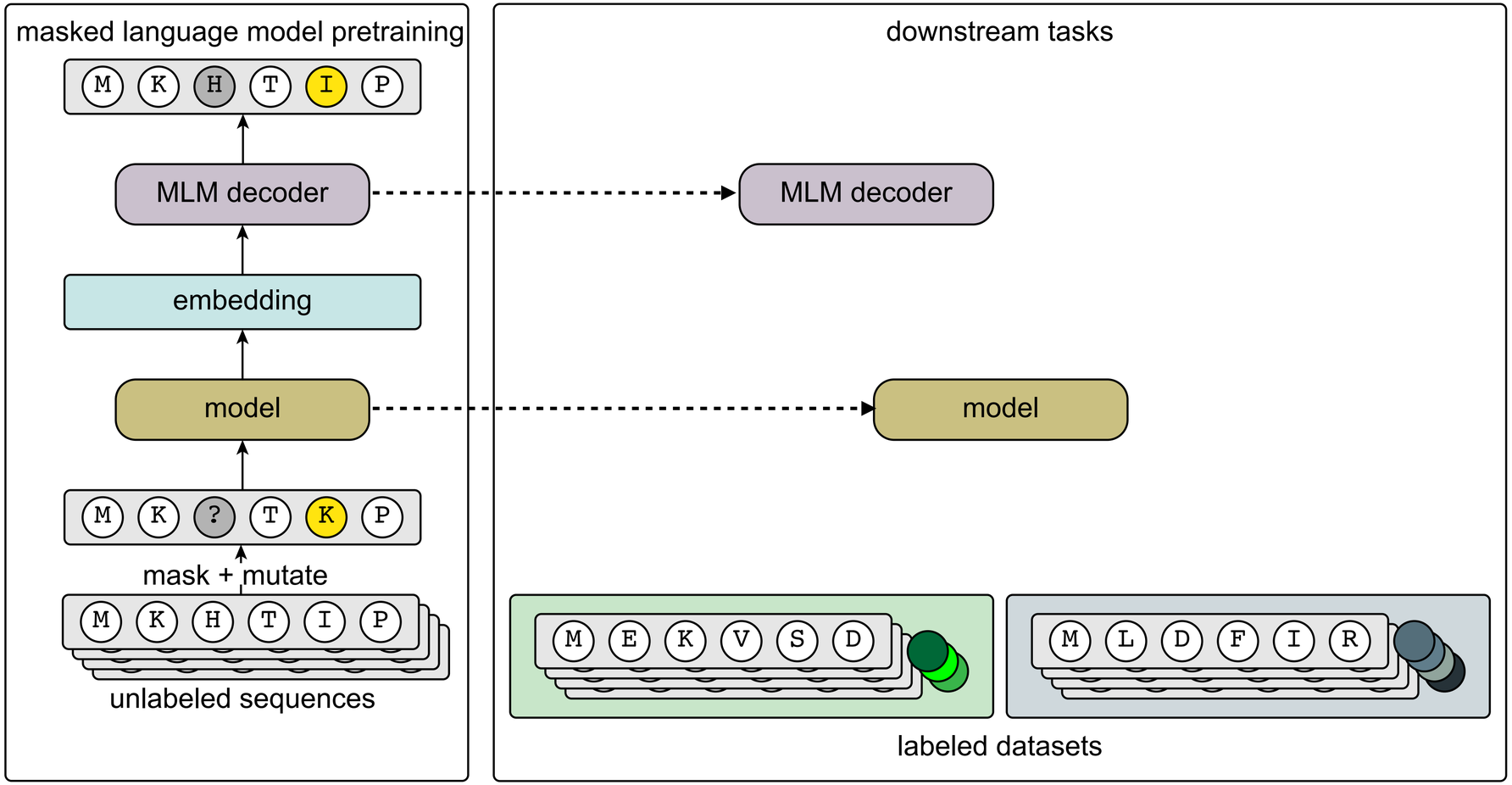

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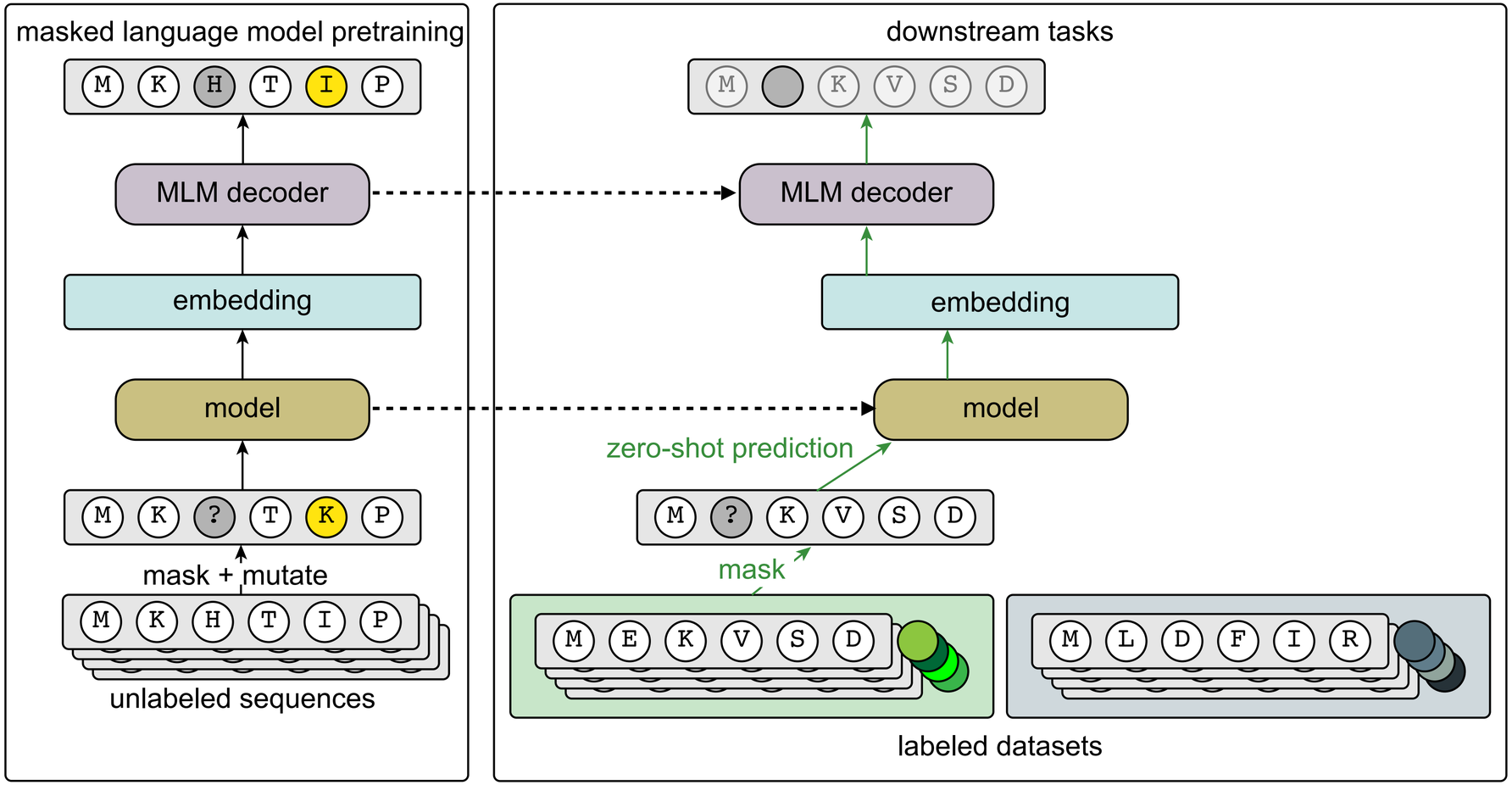

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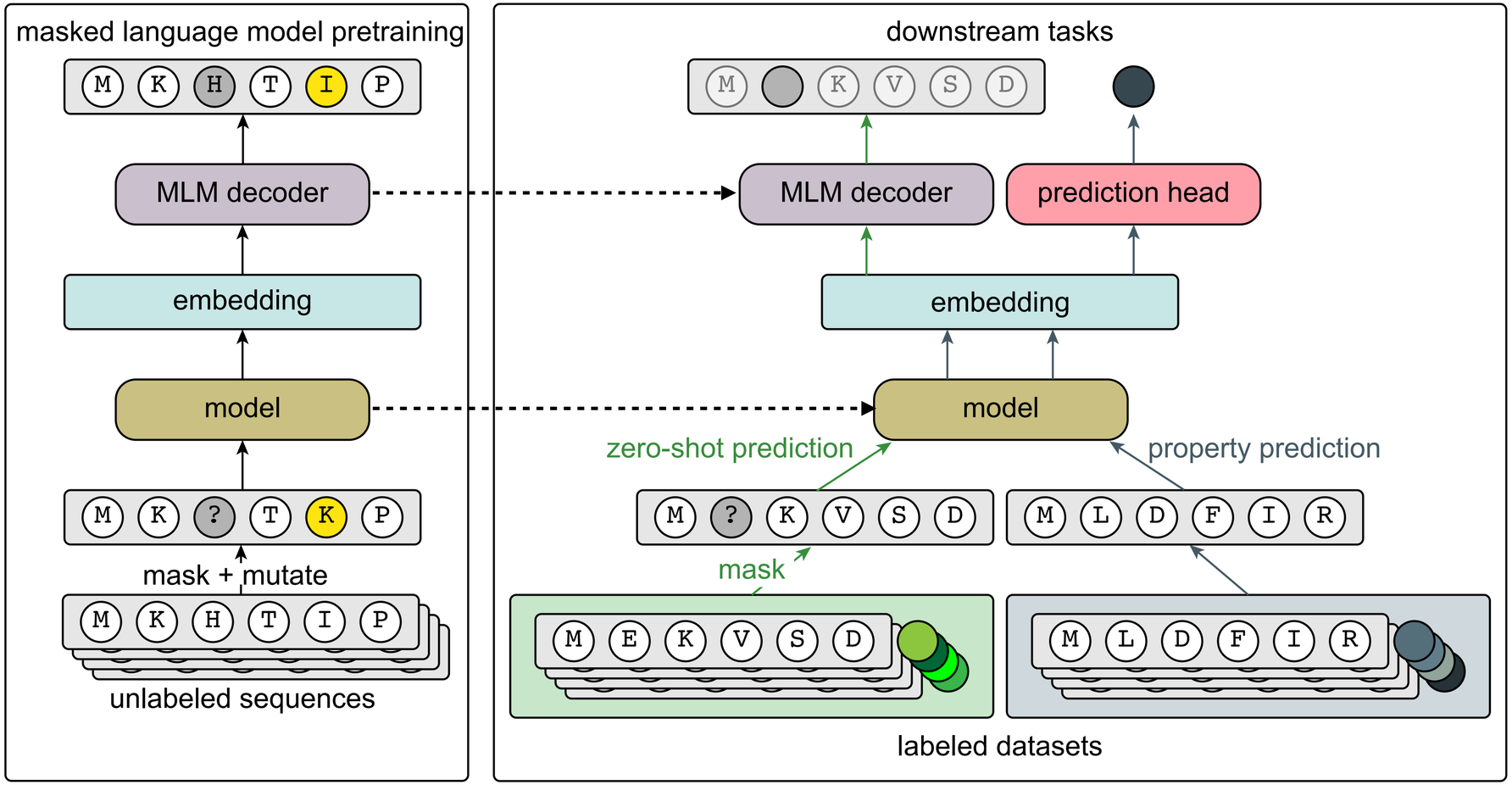

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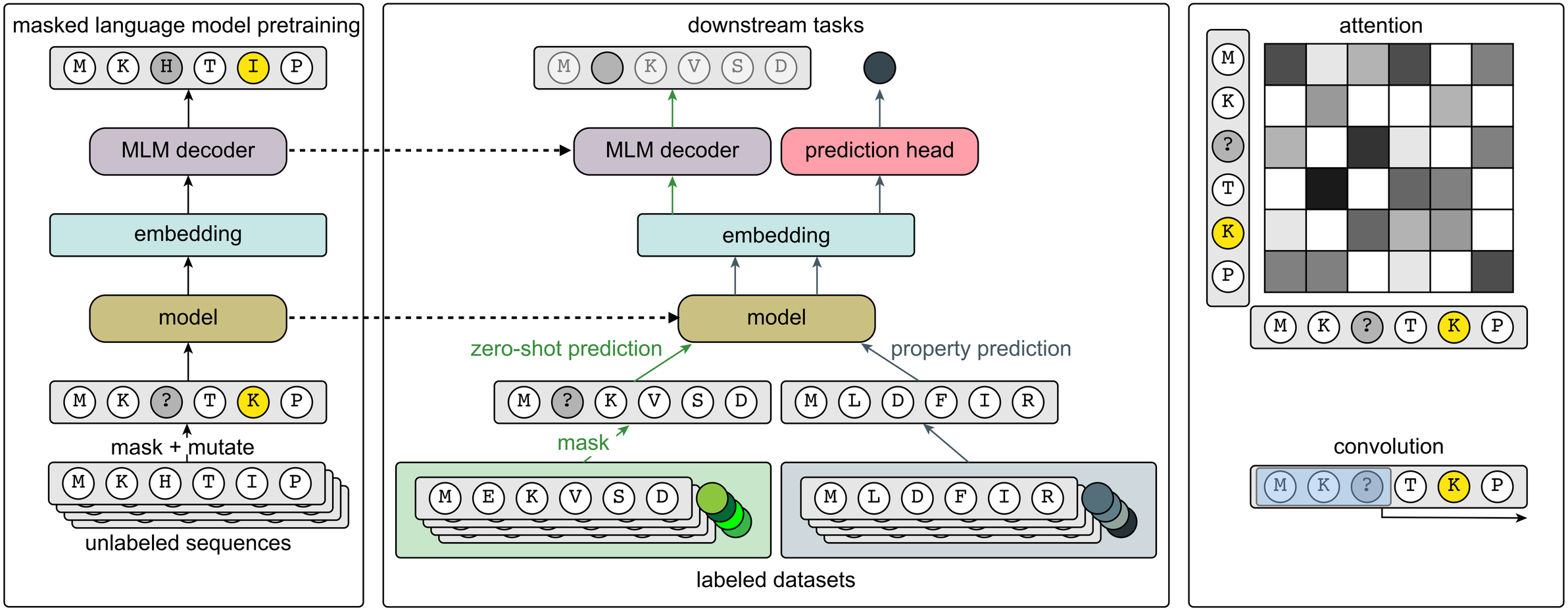

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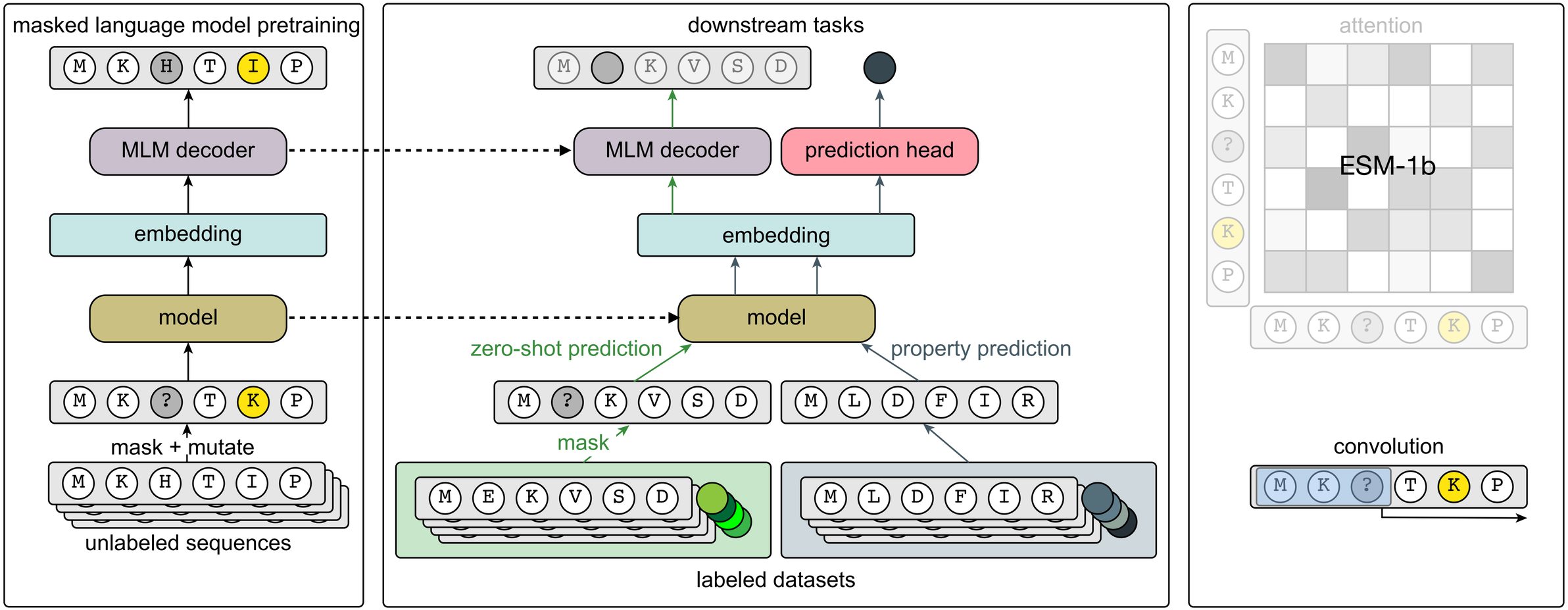

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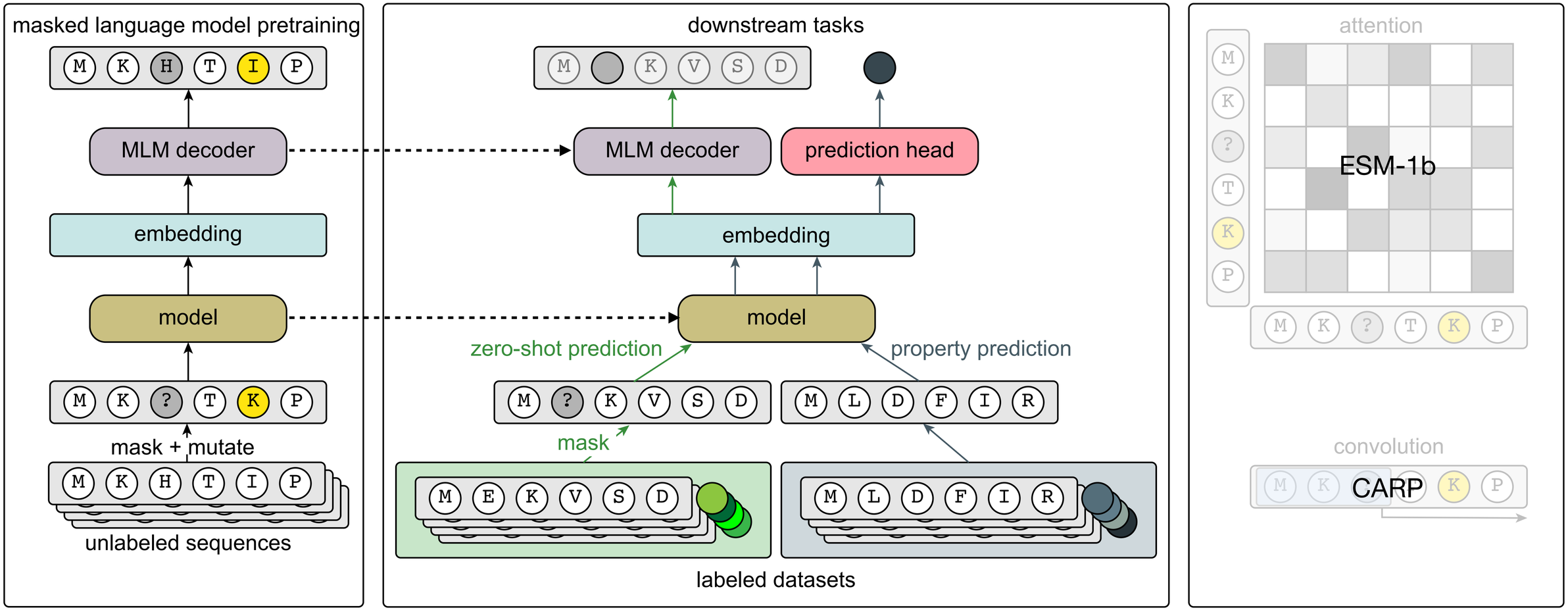

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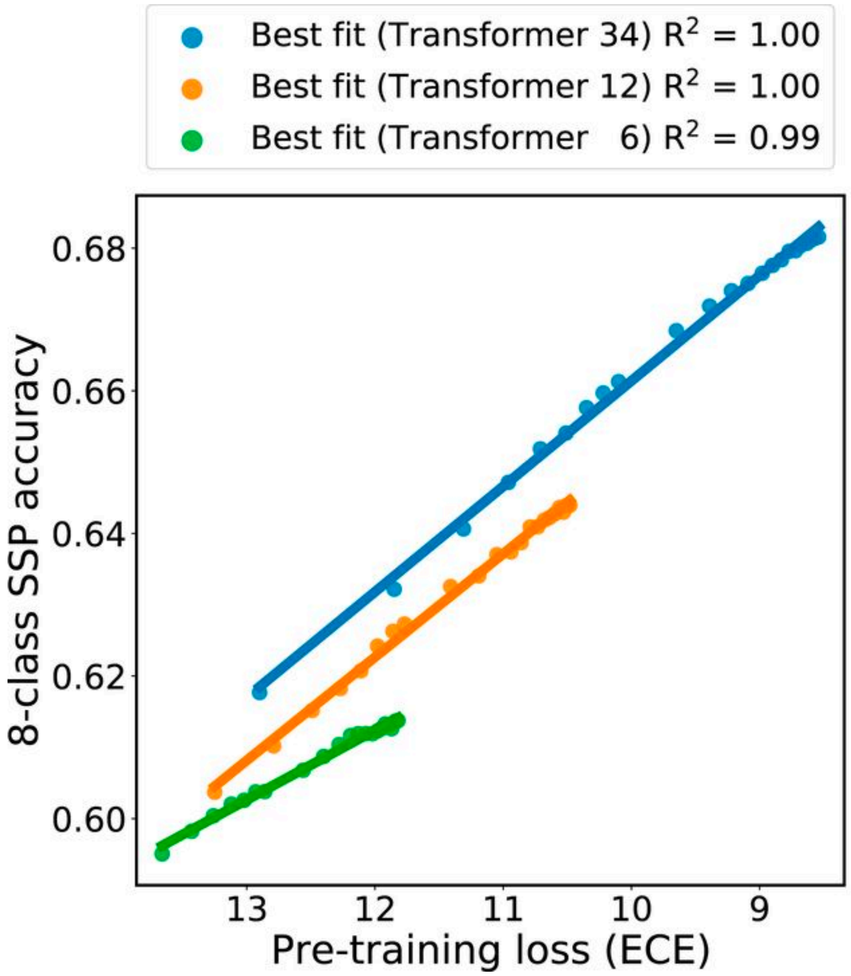

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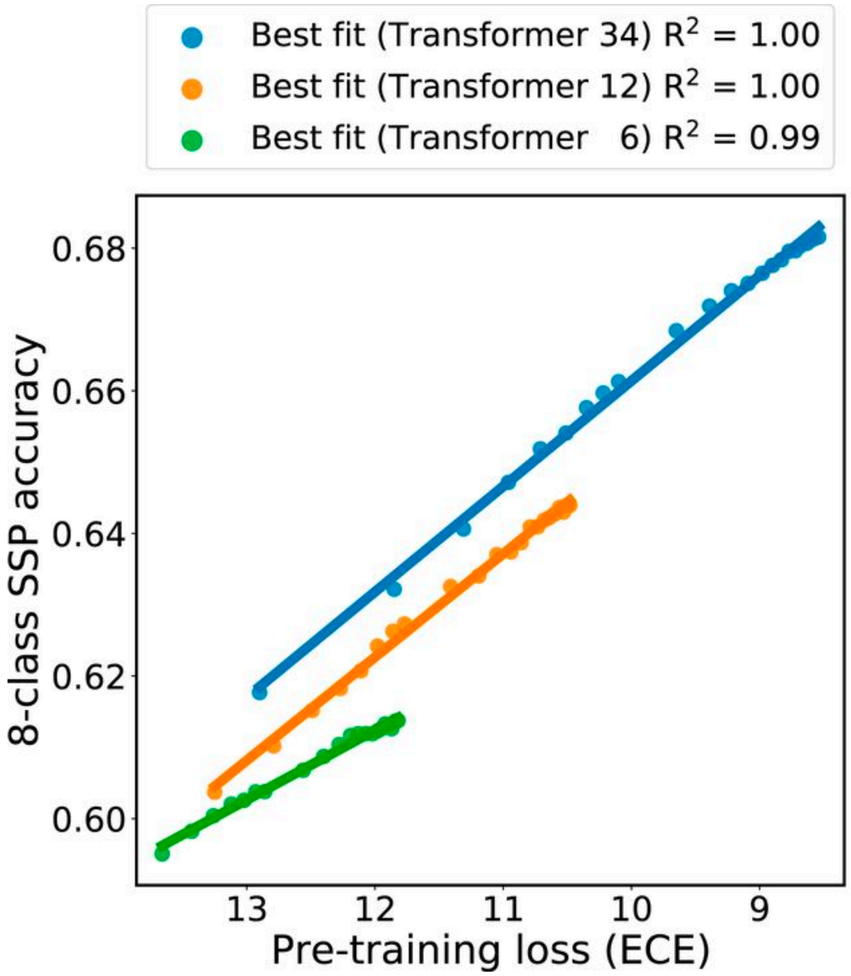

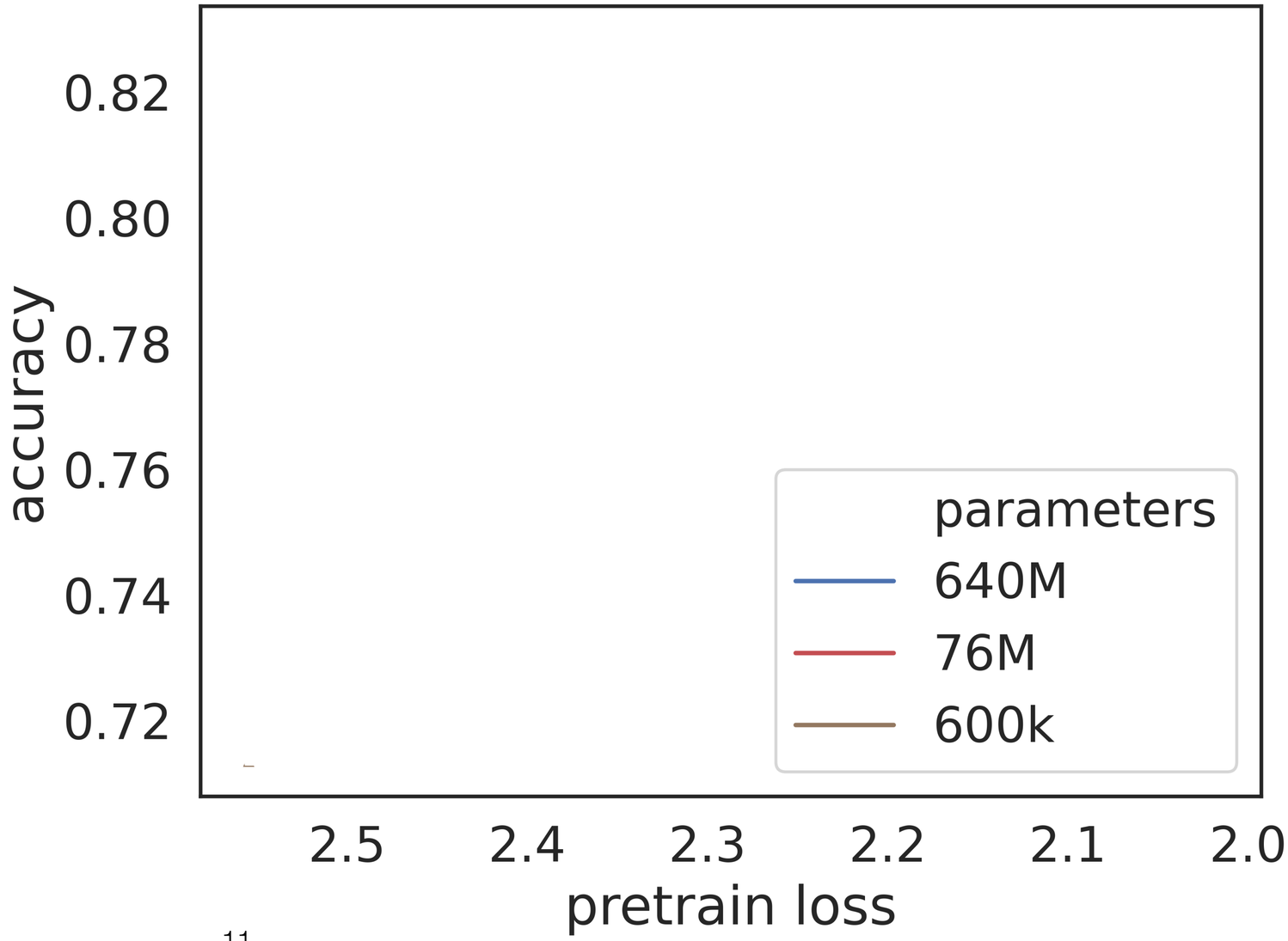

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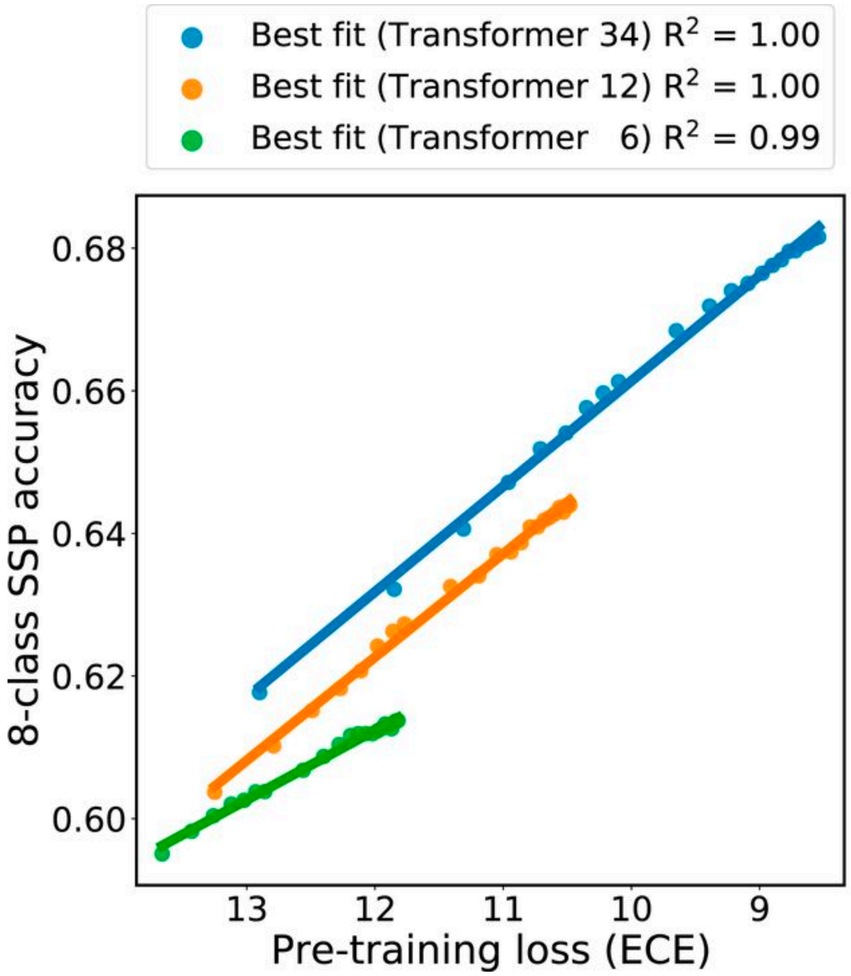

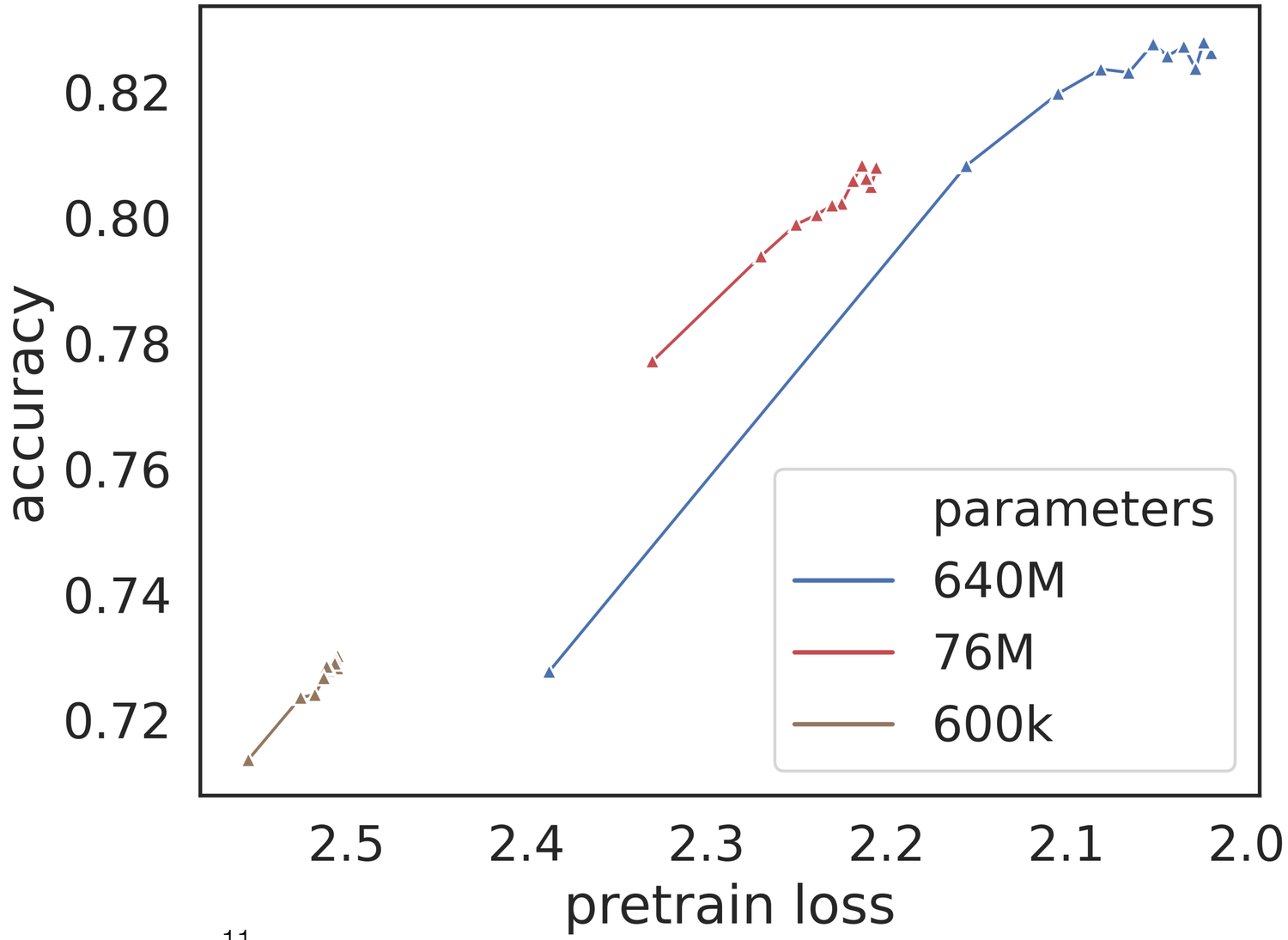

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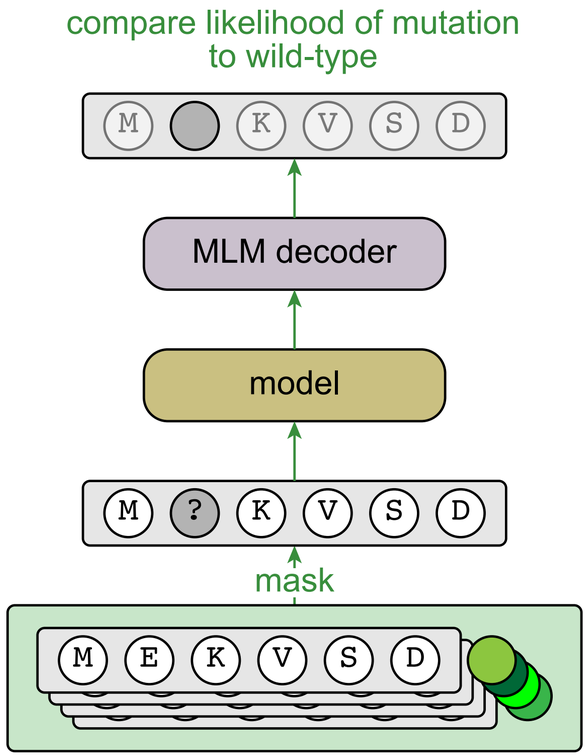

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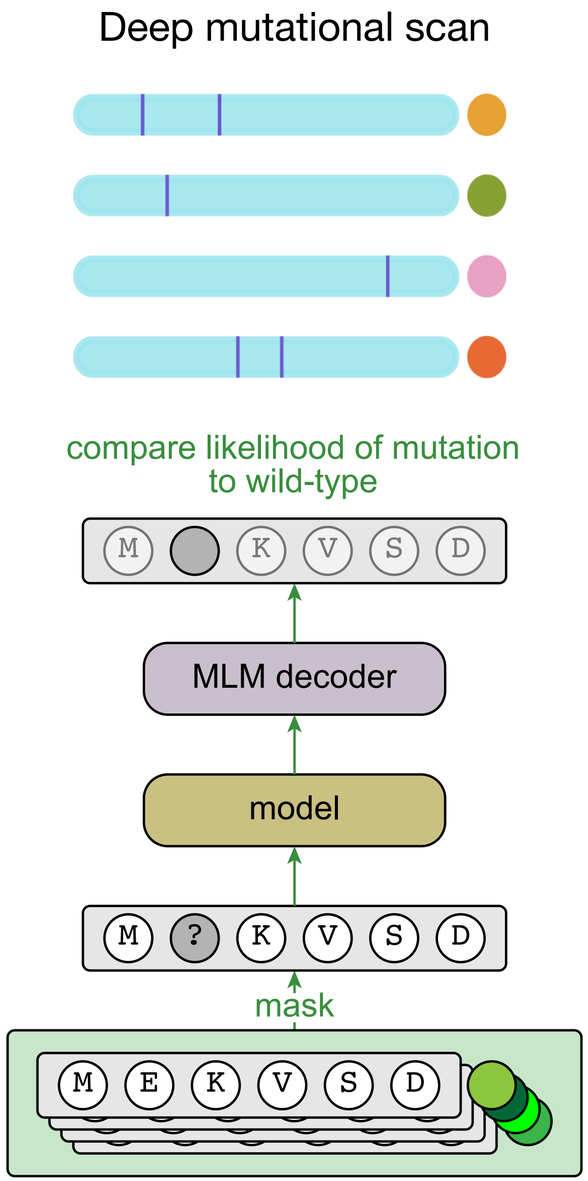

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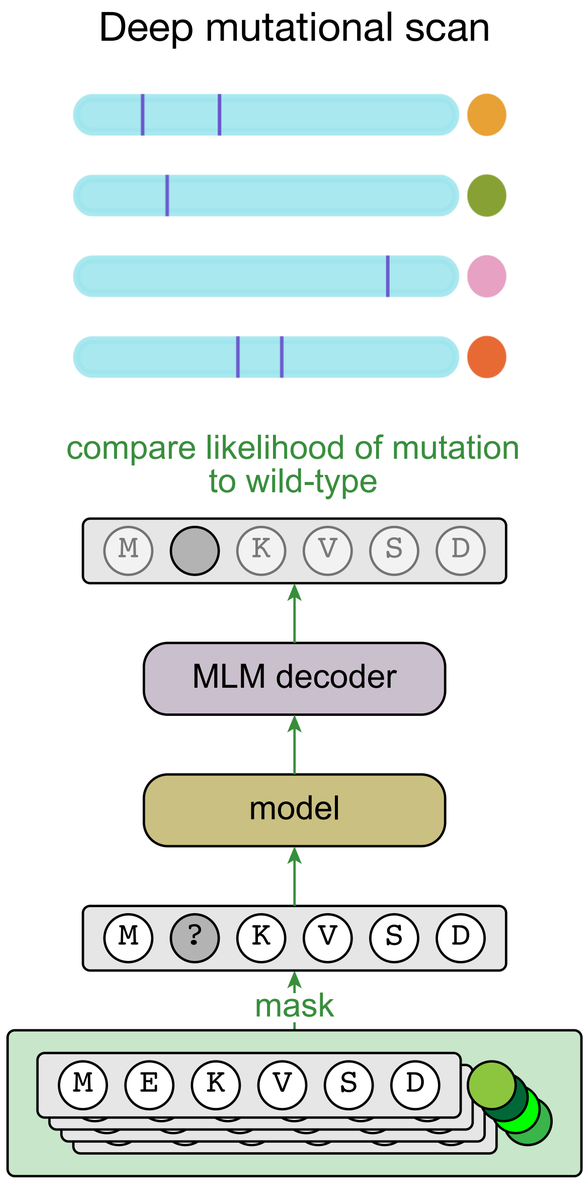

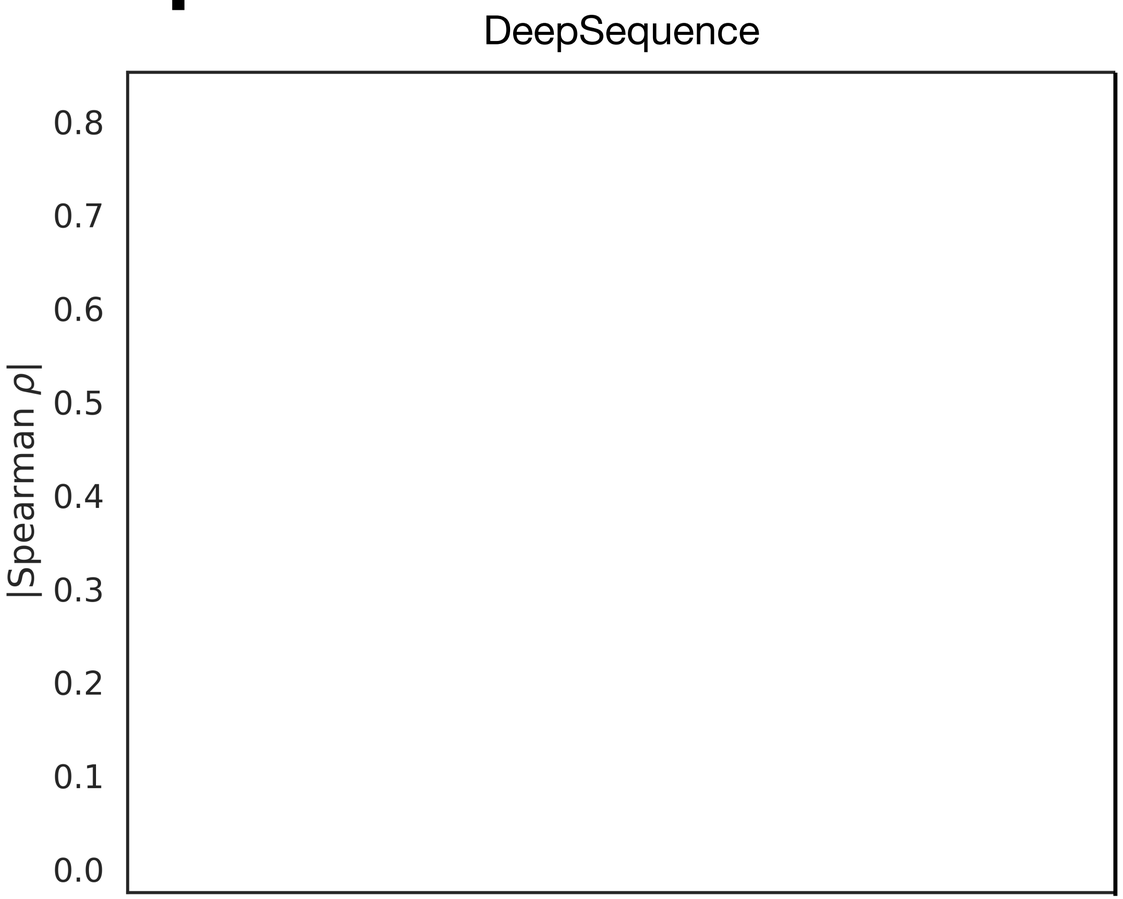

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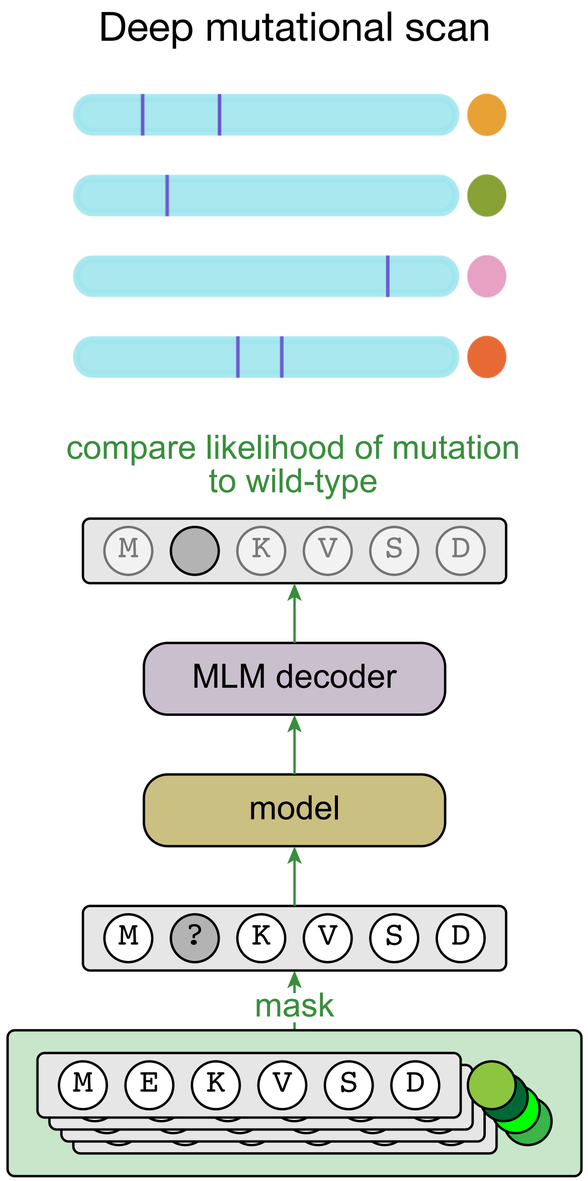

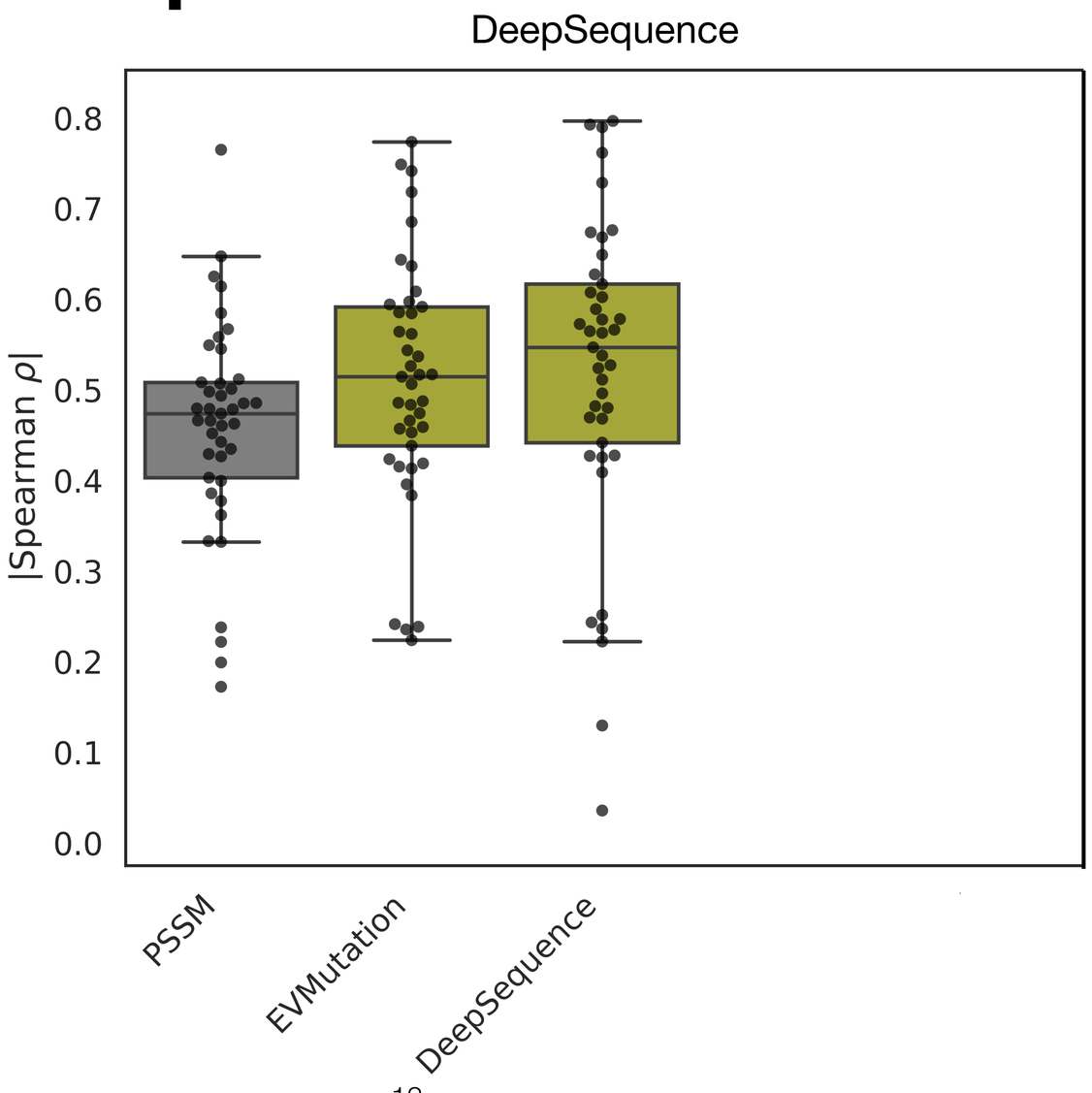

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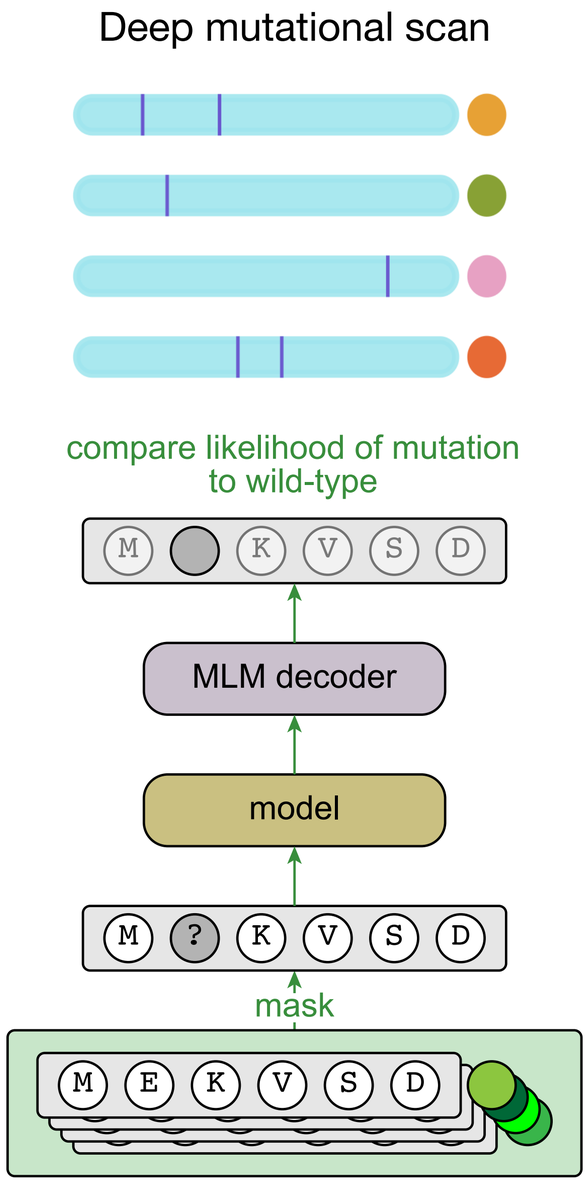

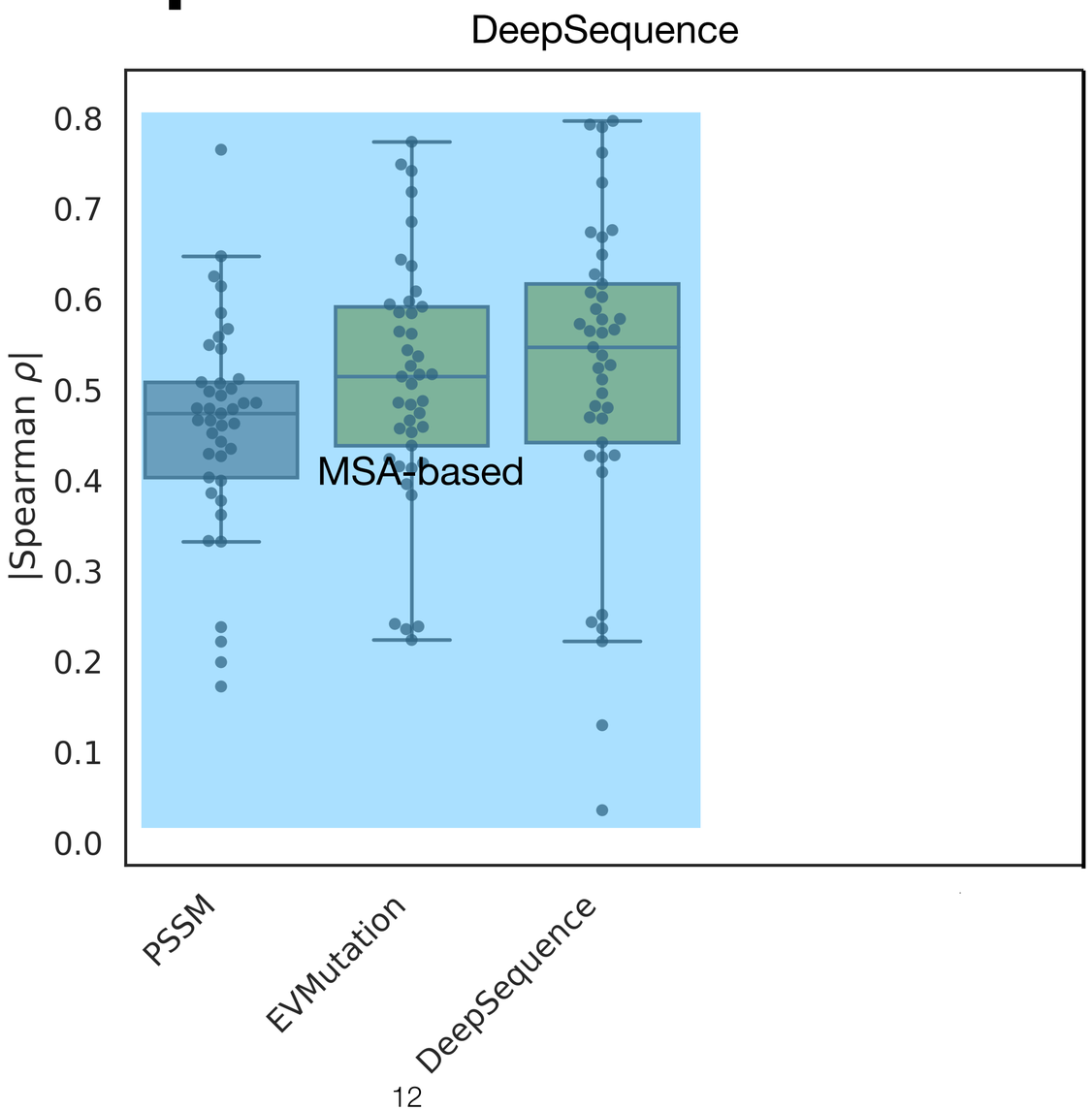

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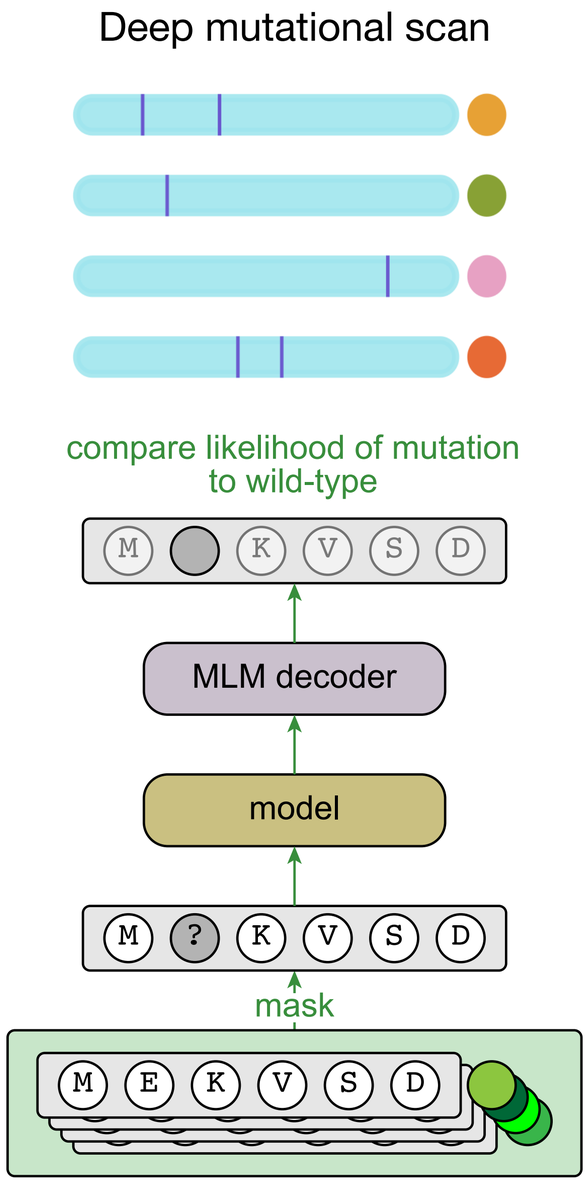

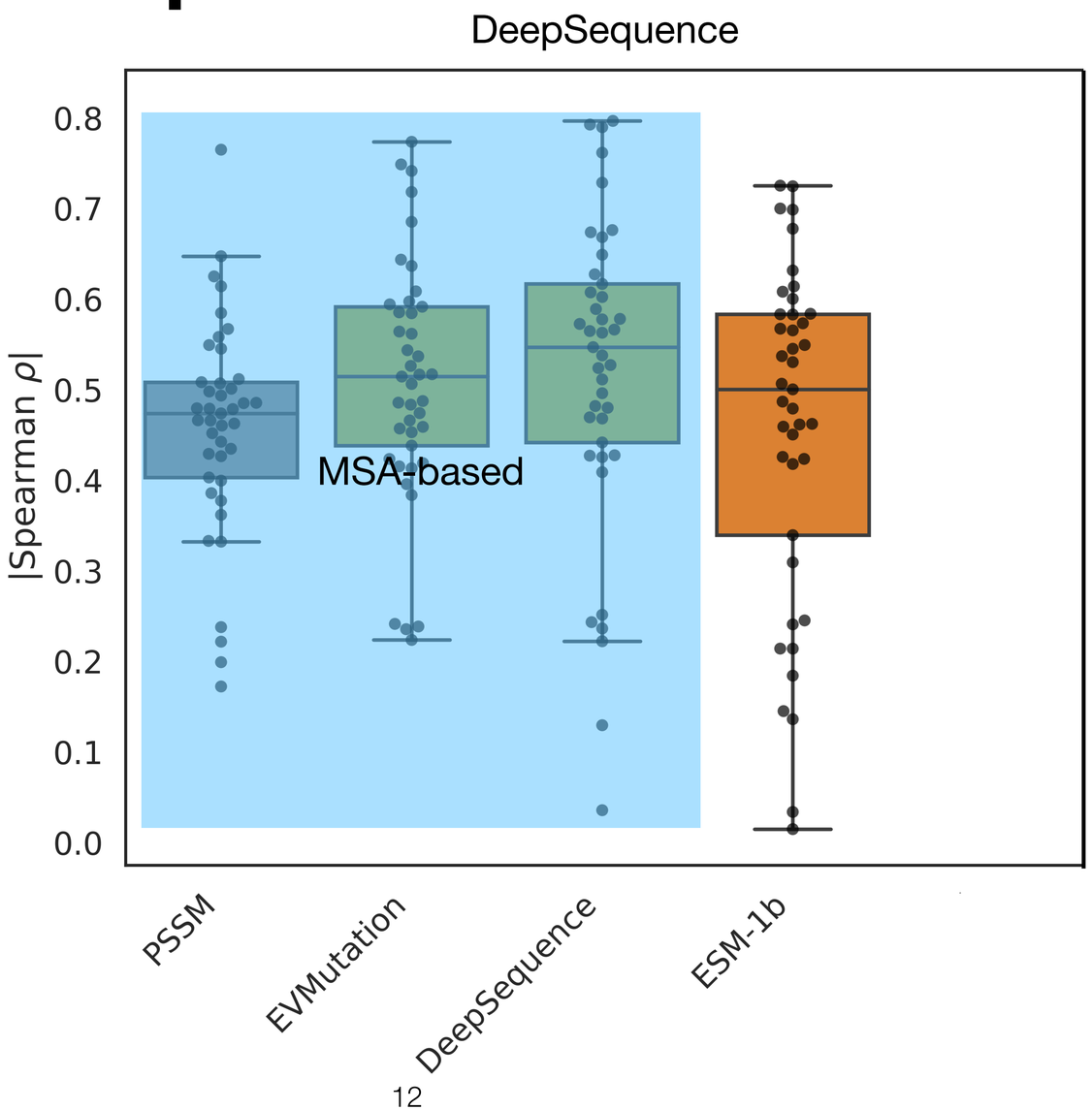

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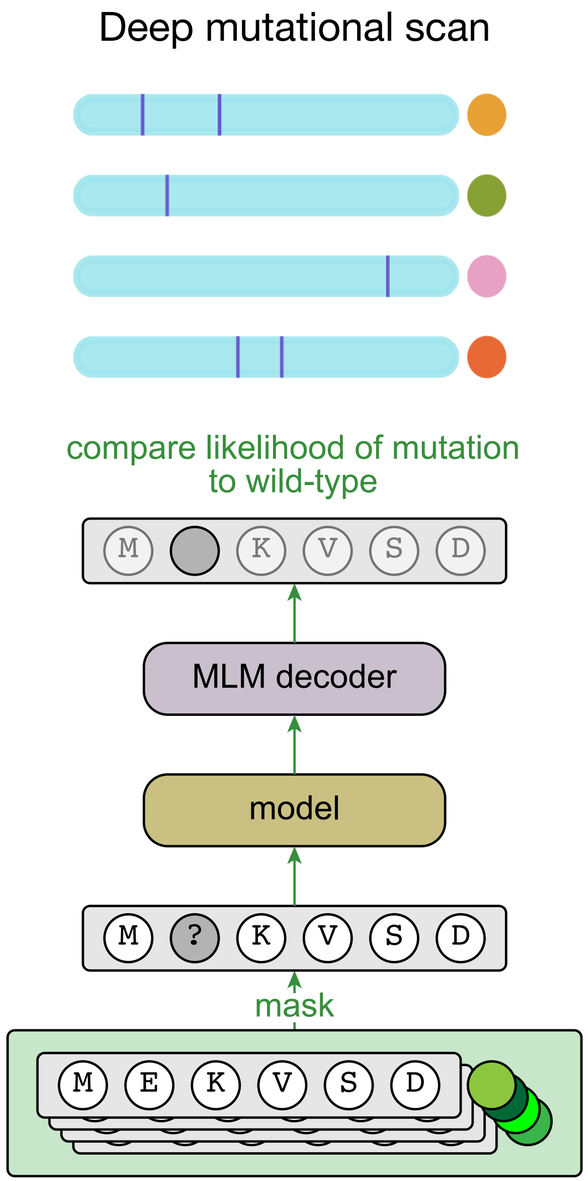
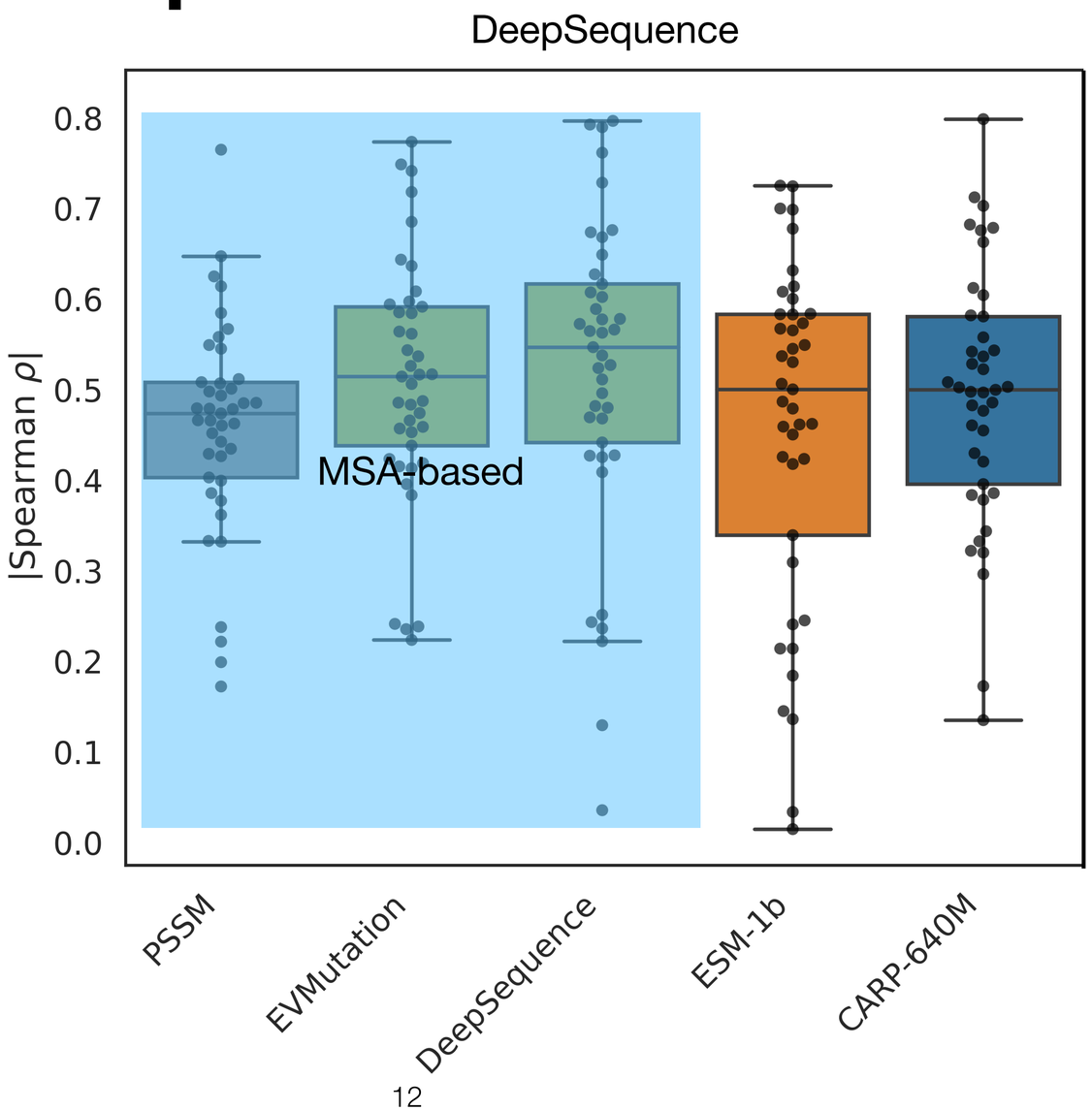
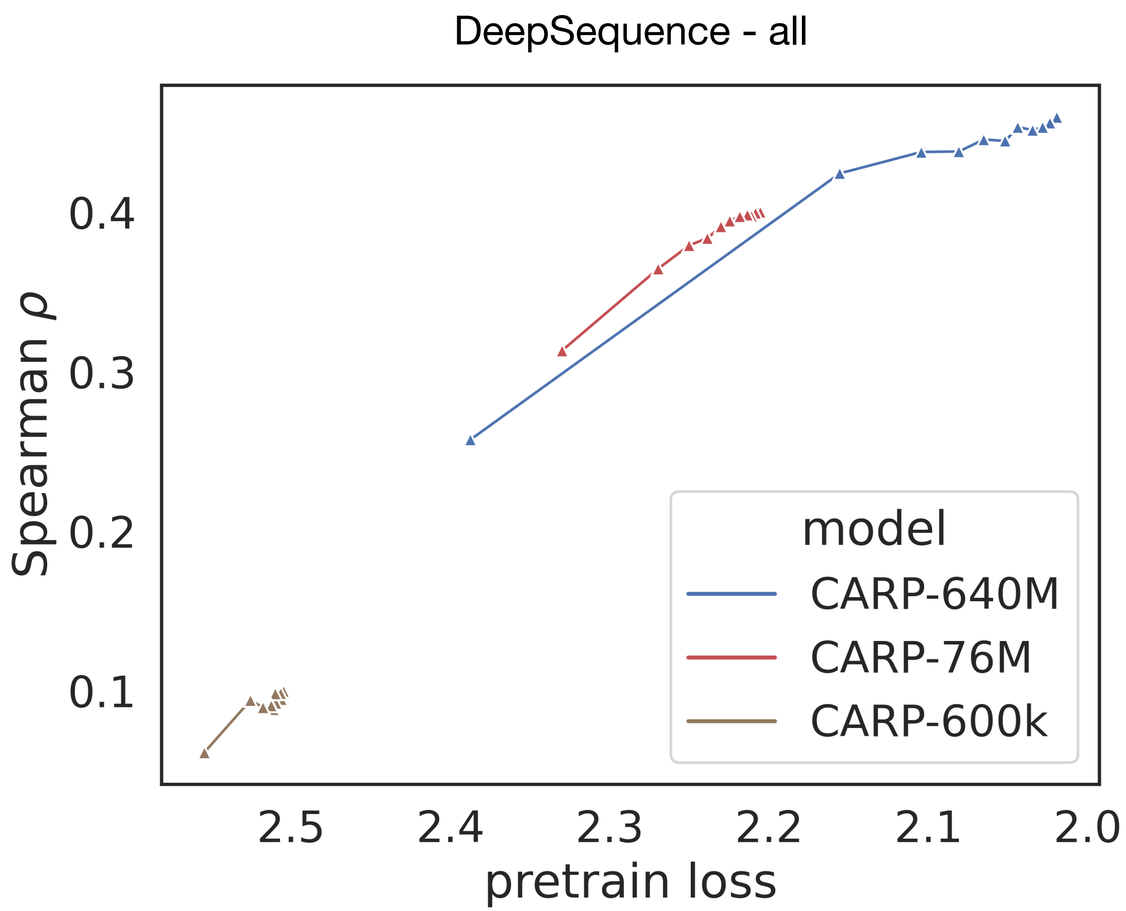




Zero-shot performance mostly improves with pretraining



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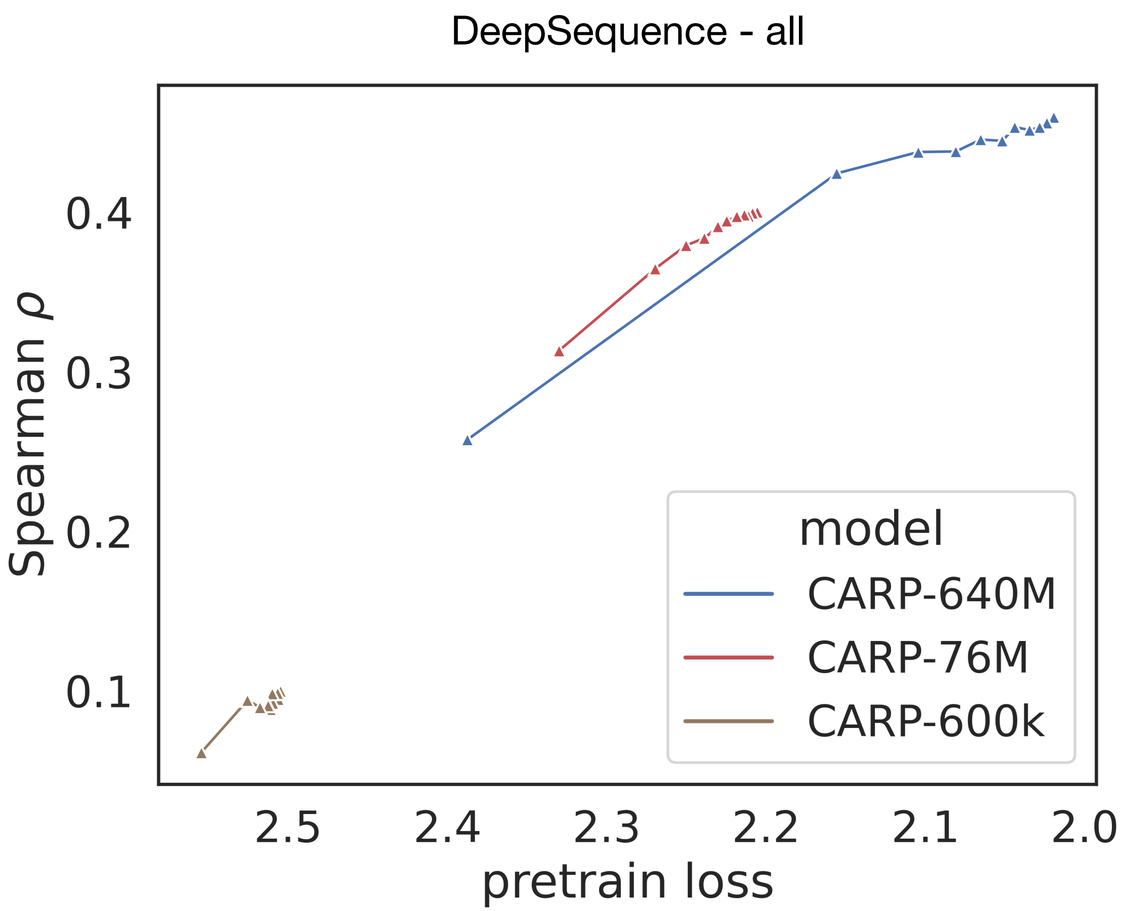

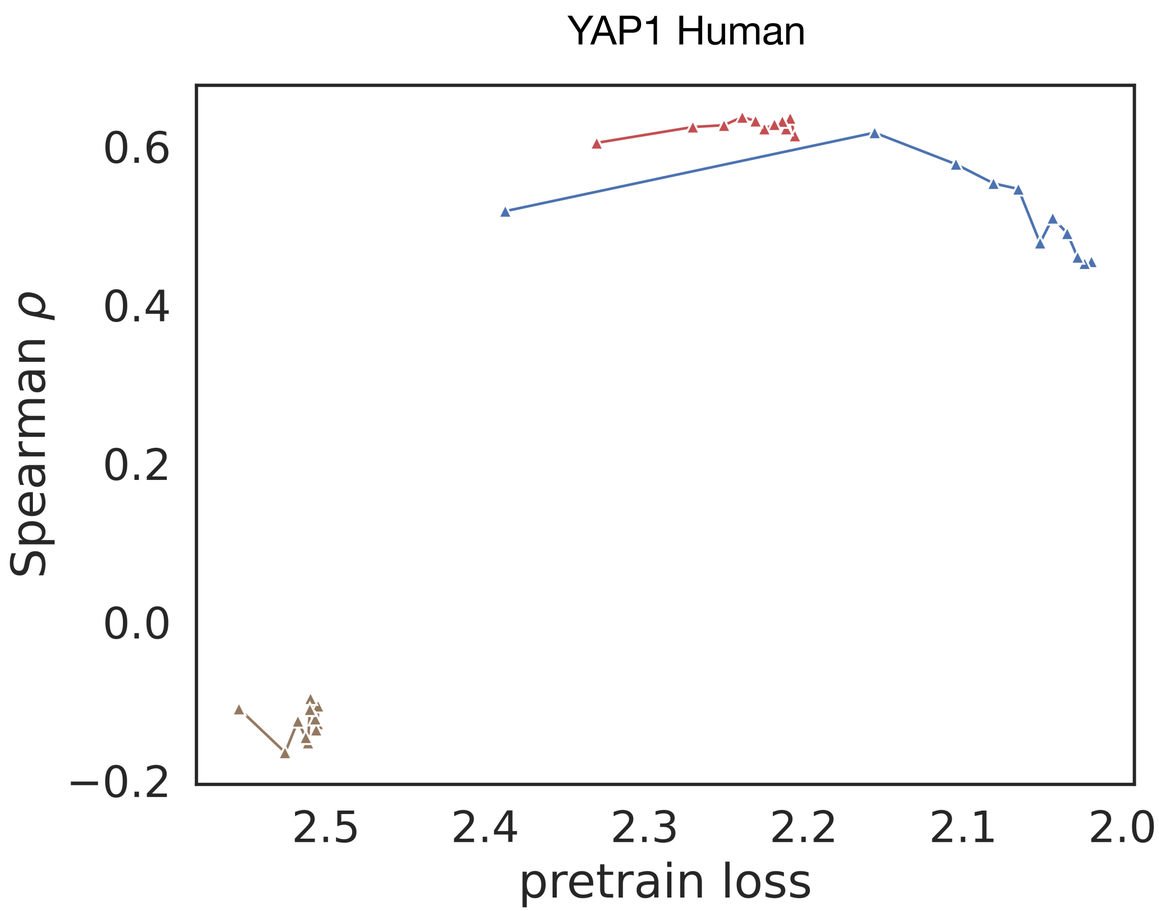

Protein engineering campaigns require out-of-domain generalization

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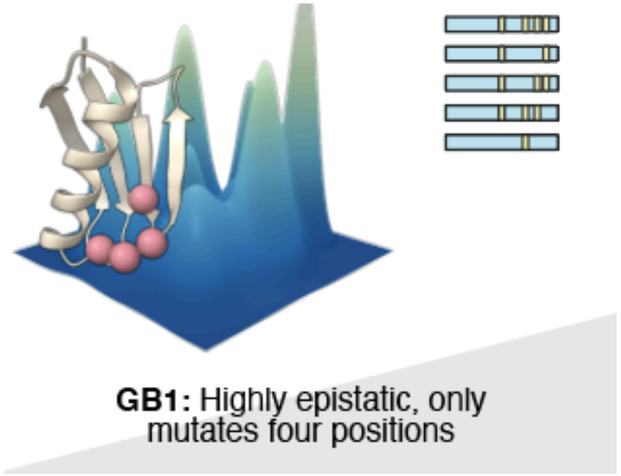

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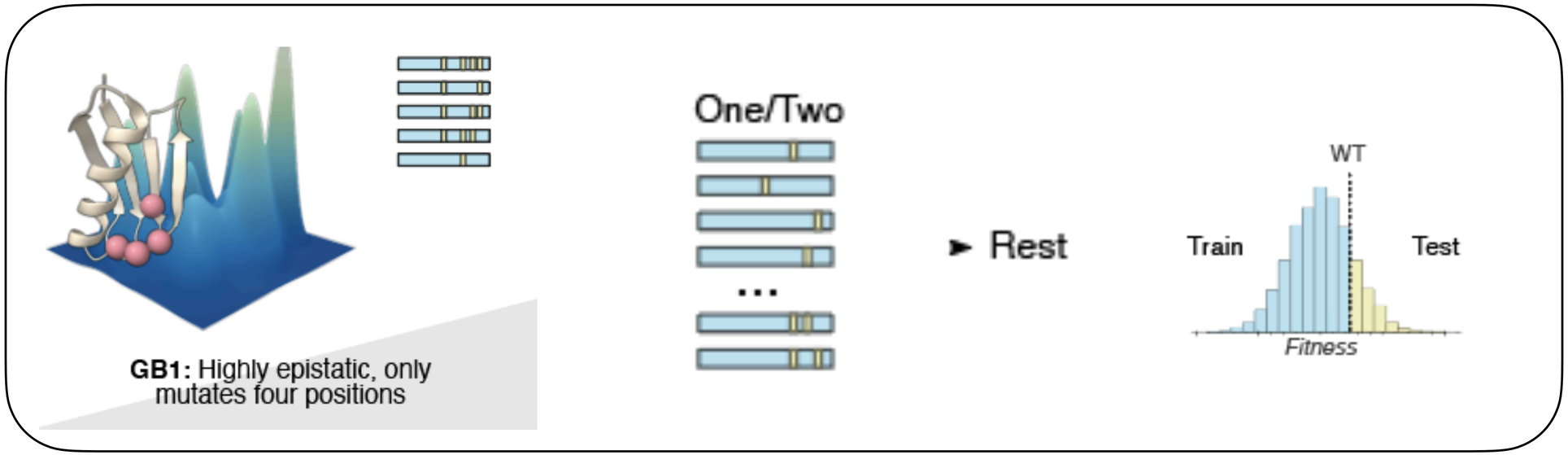
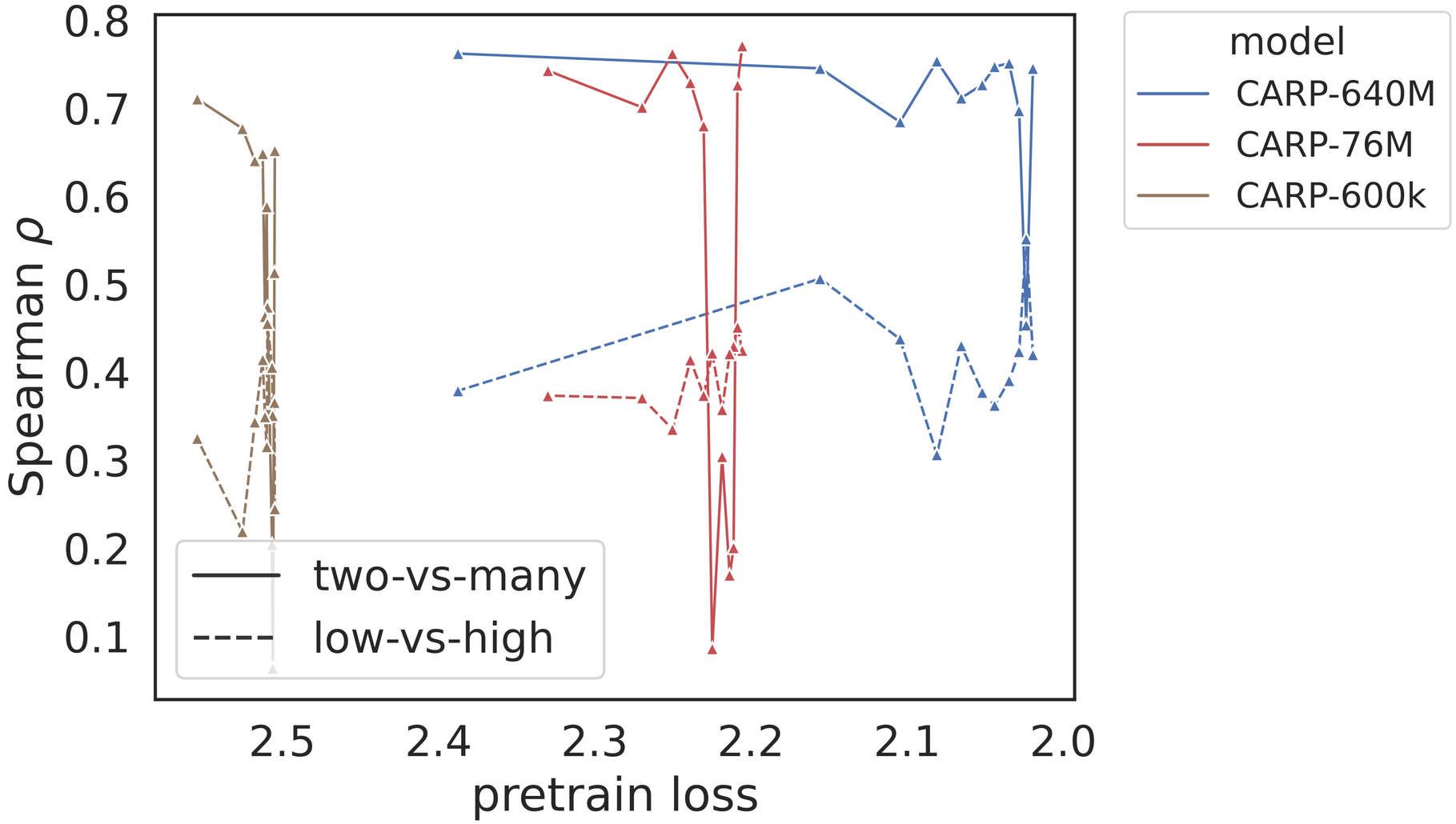


OOD performance does not improve with more pretraining



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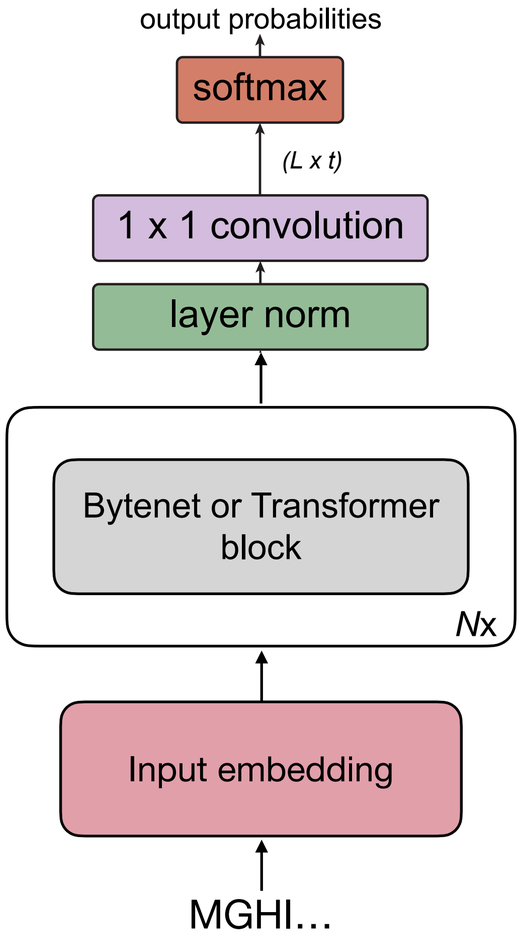

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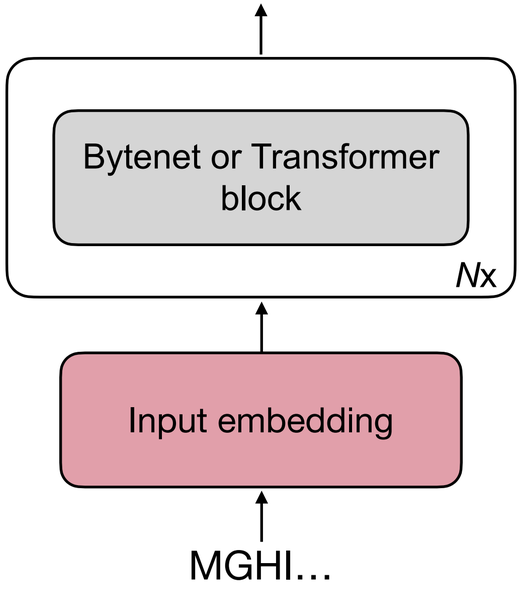

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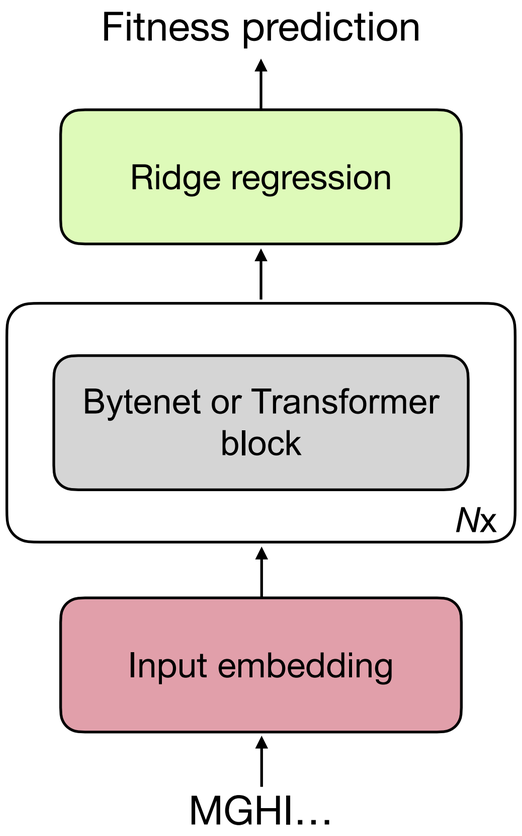

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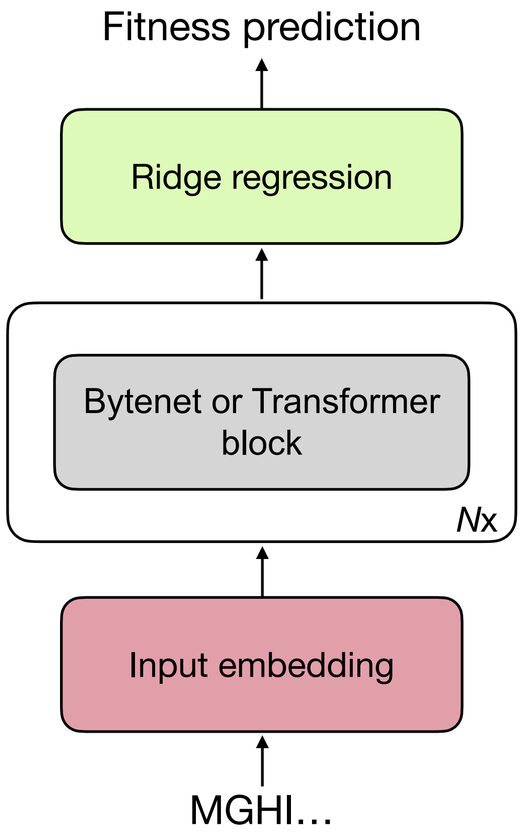

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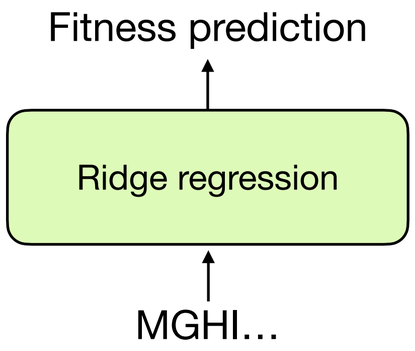

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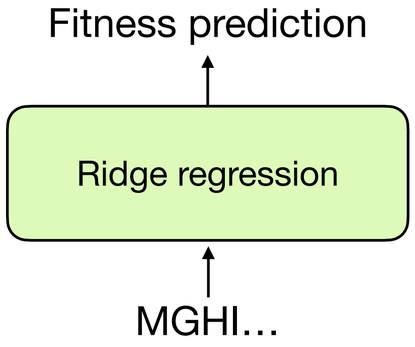

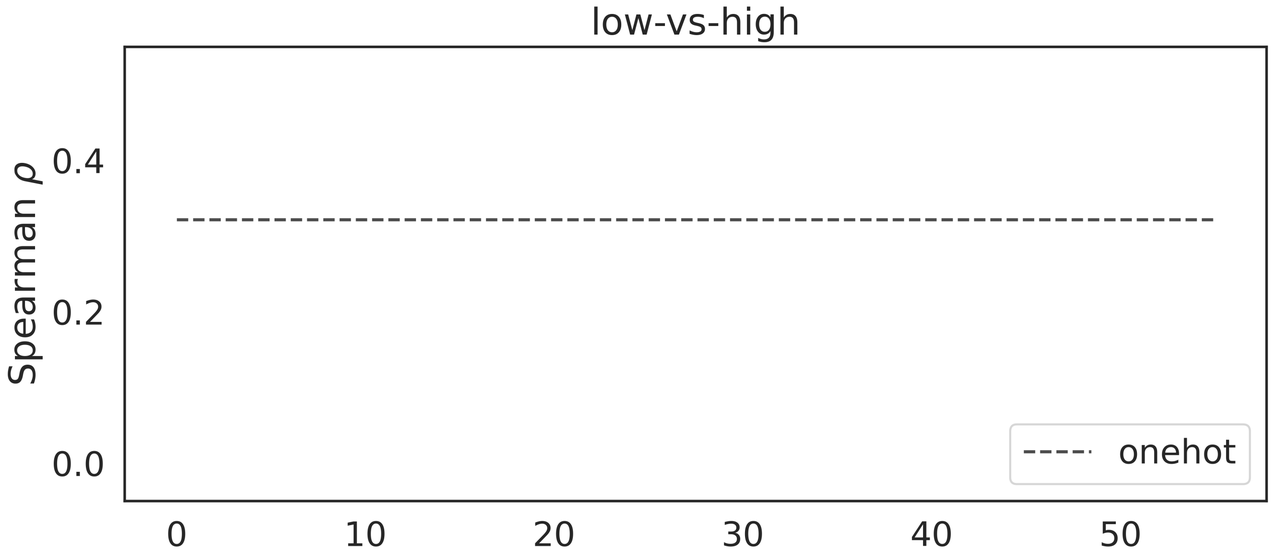

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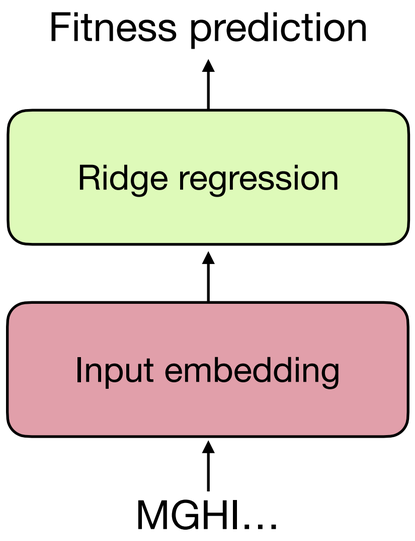

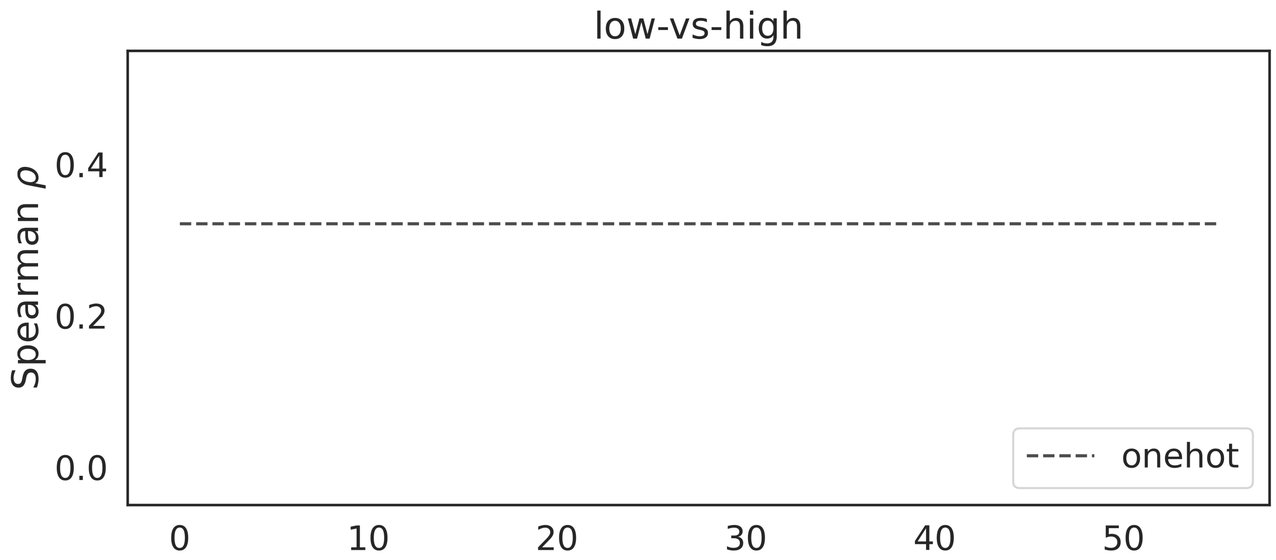

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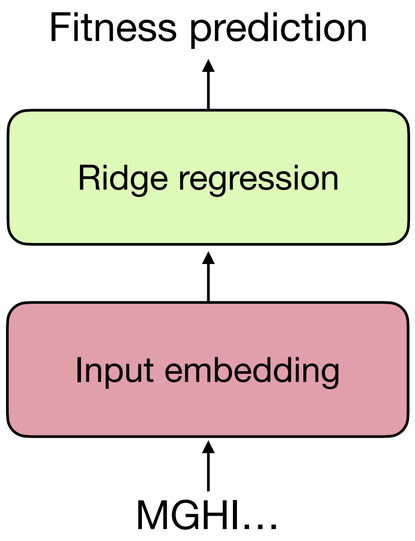

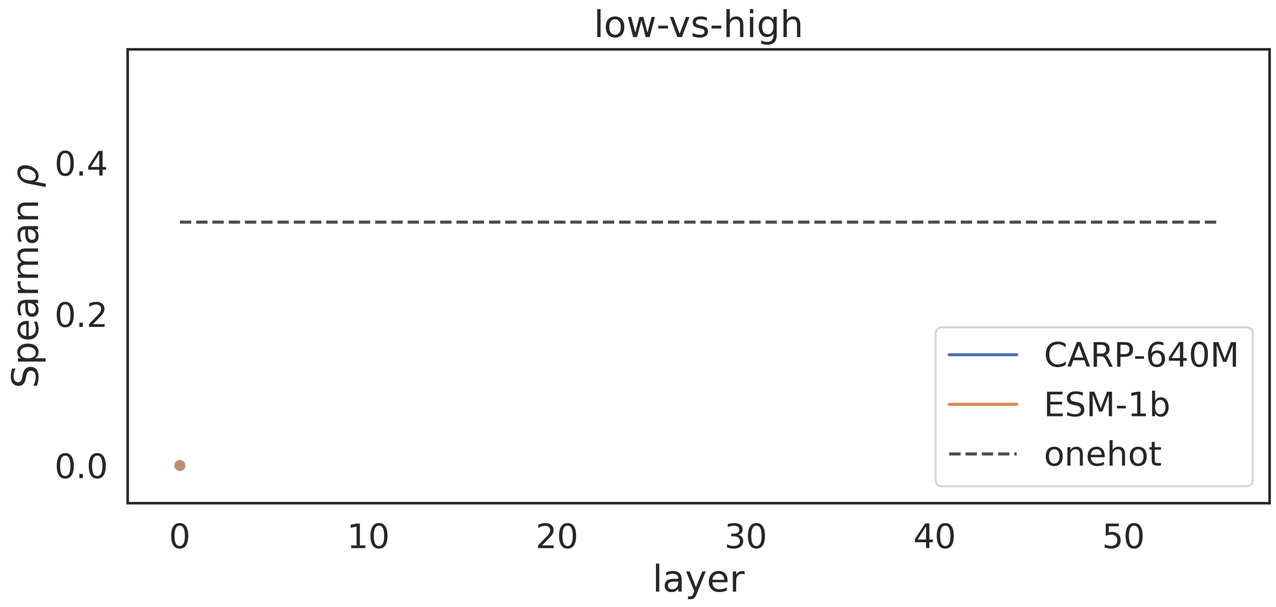

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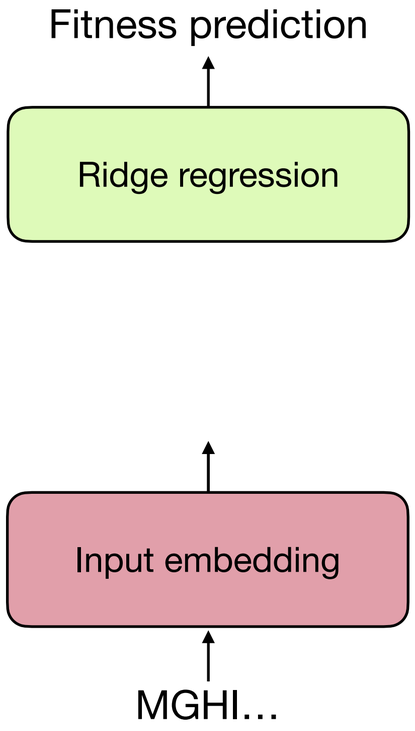

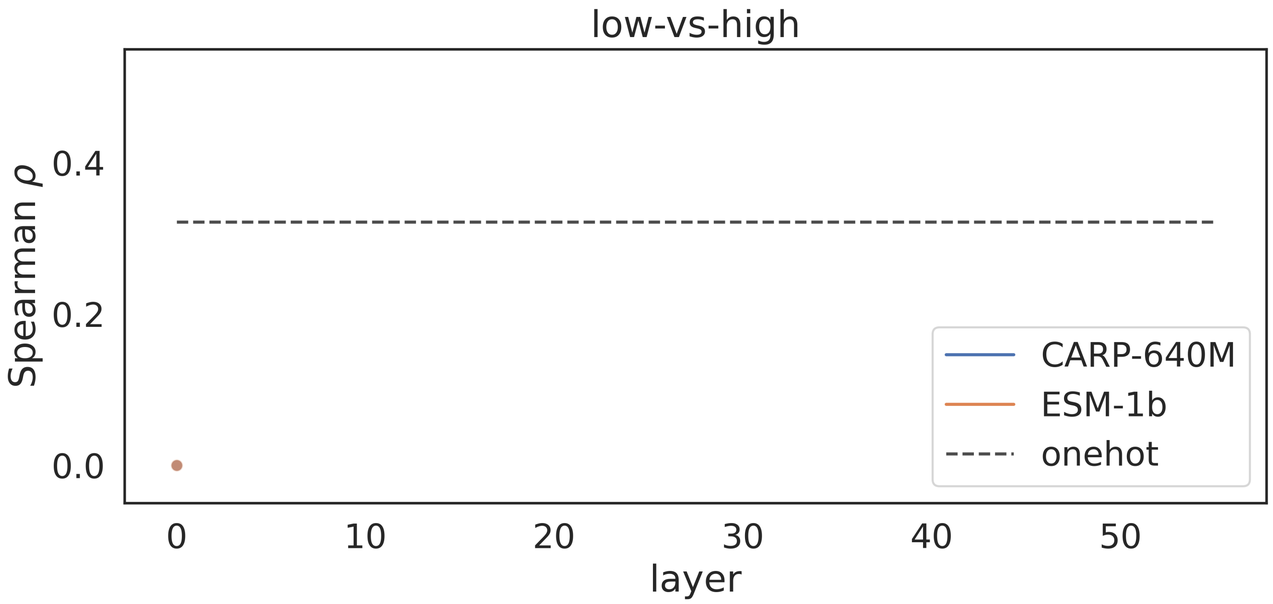

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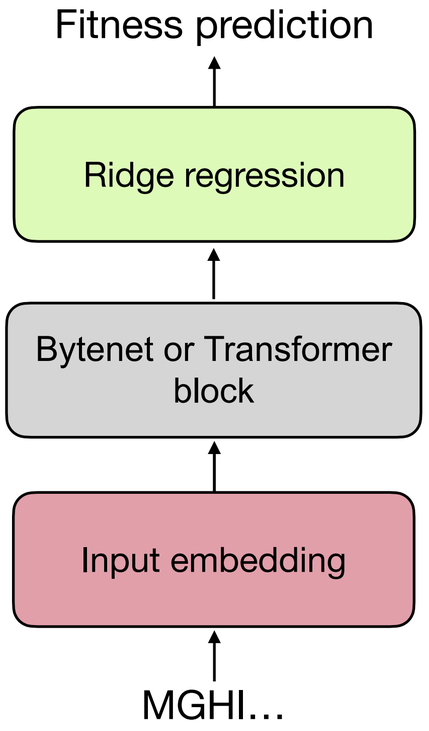

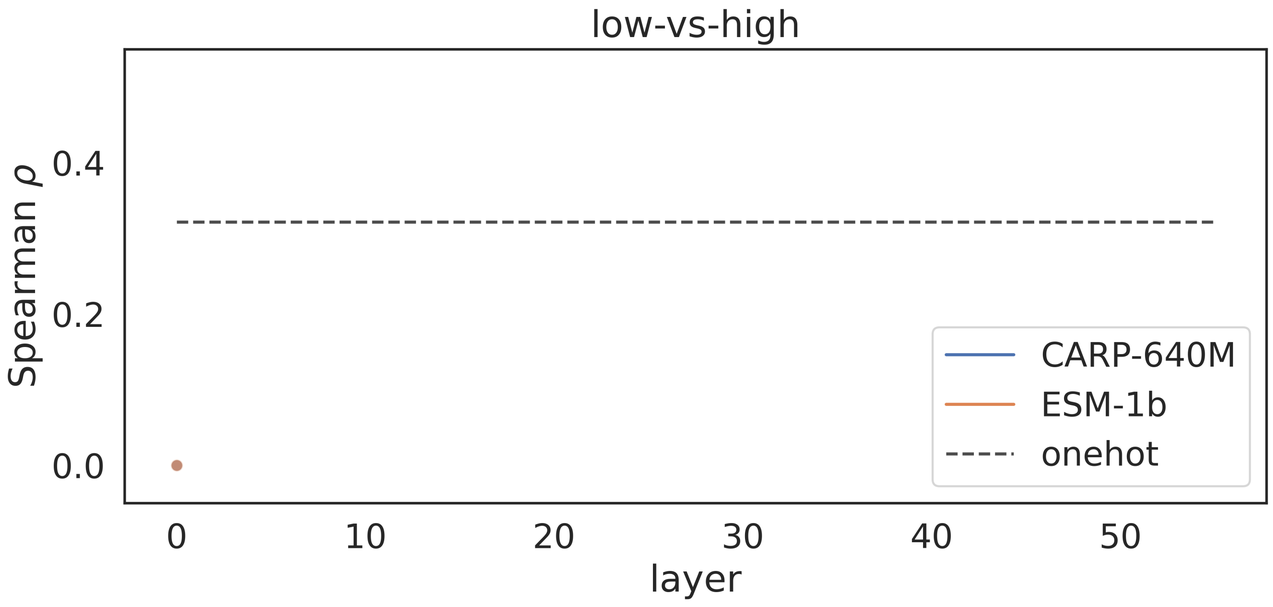

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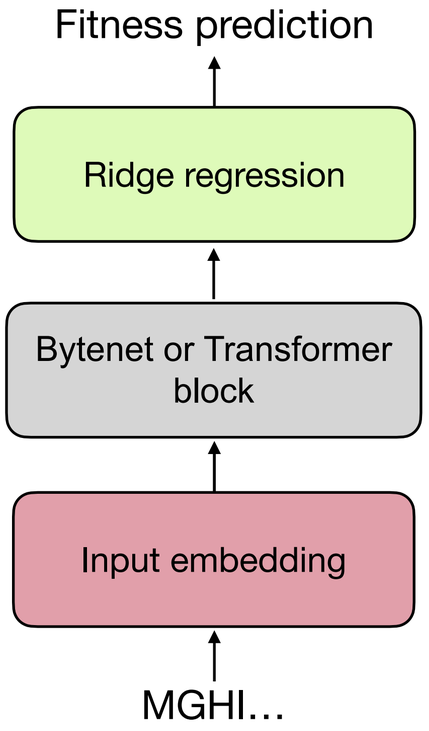

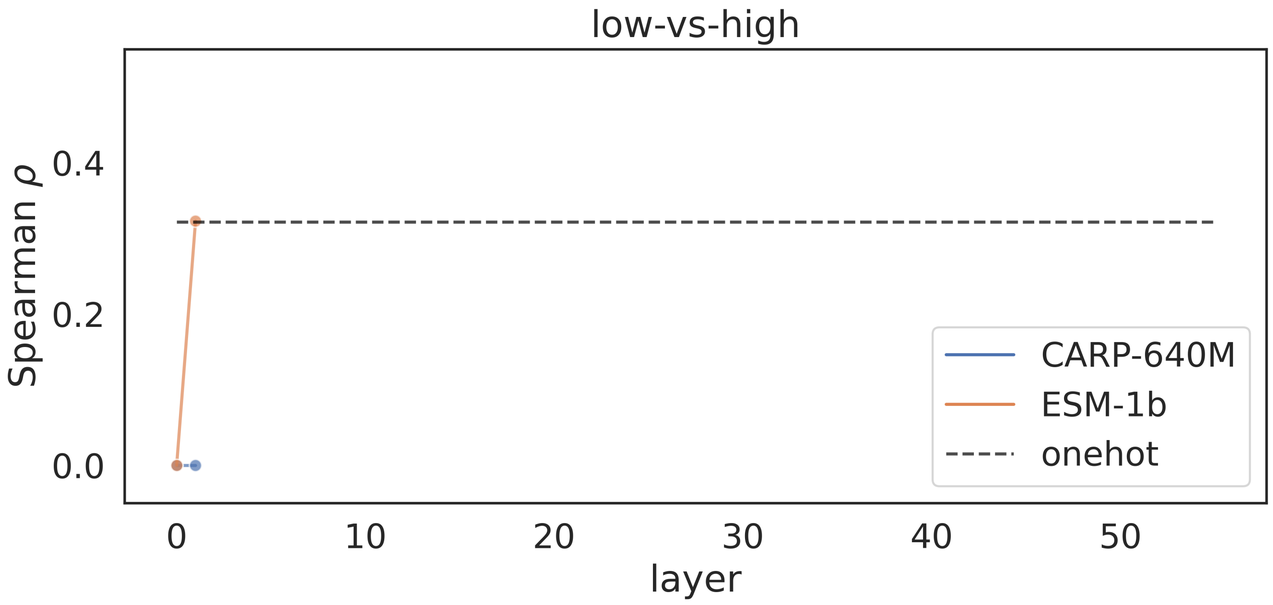

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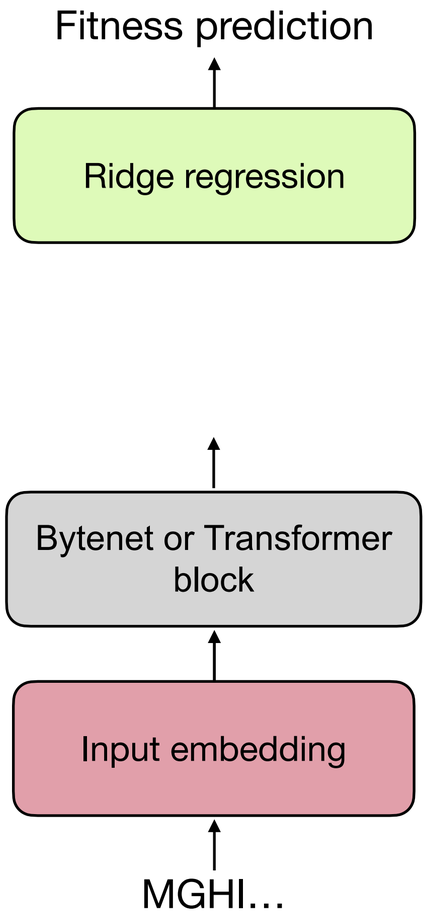

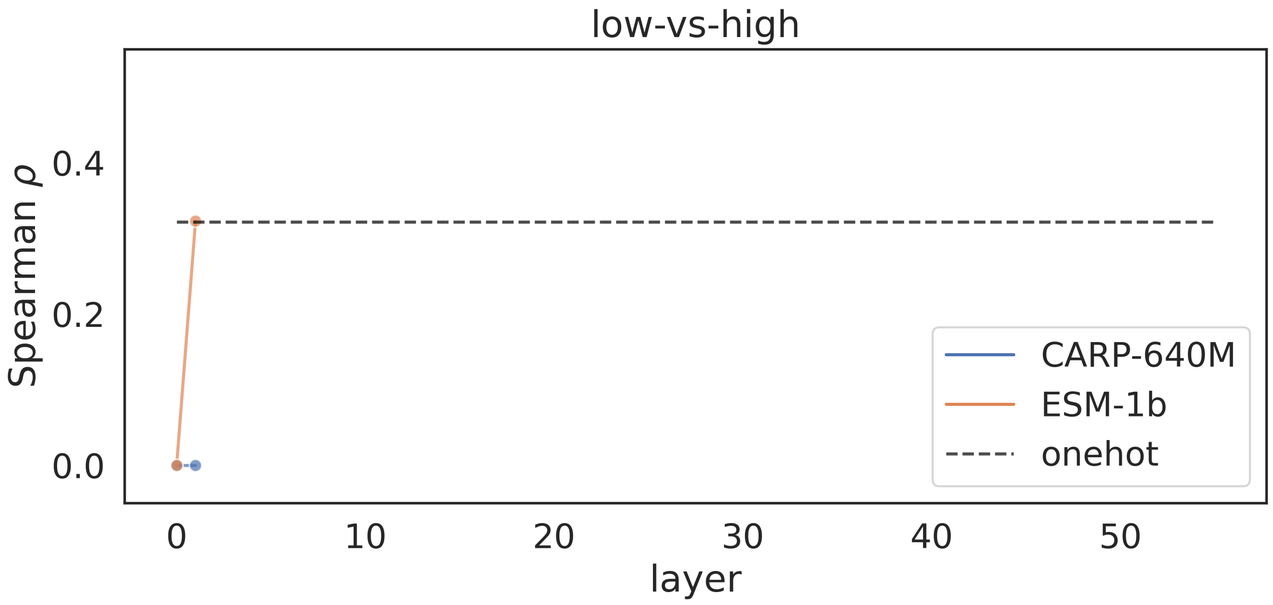

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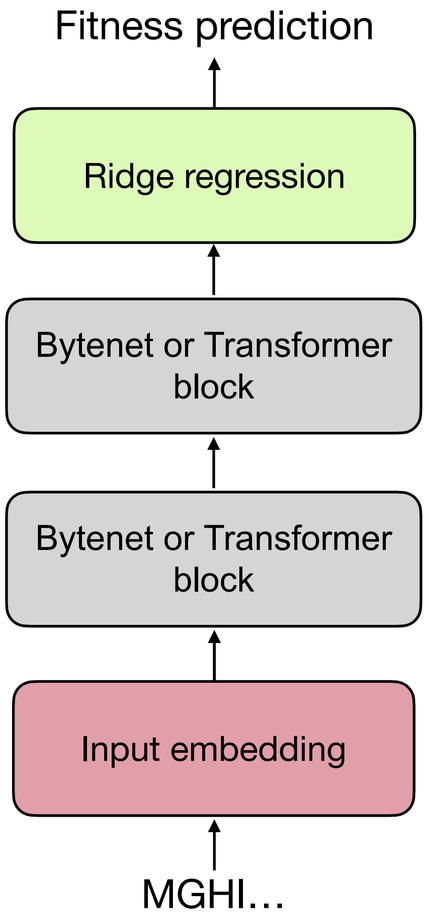

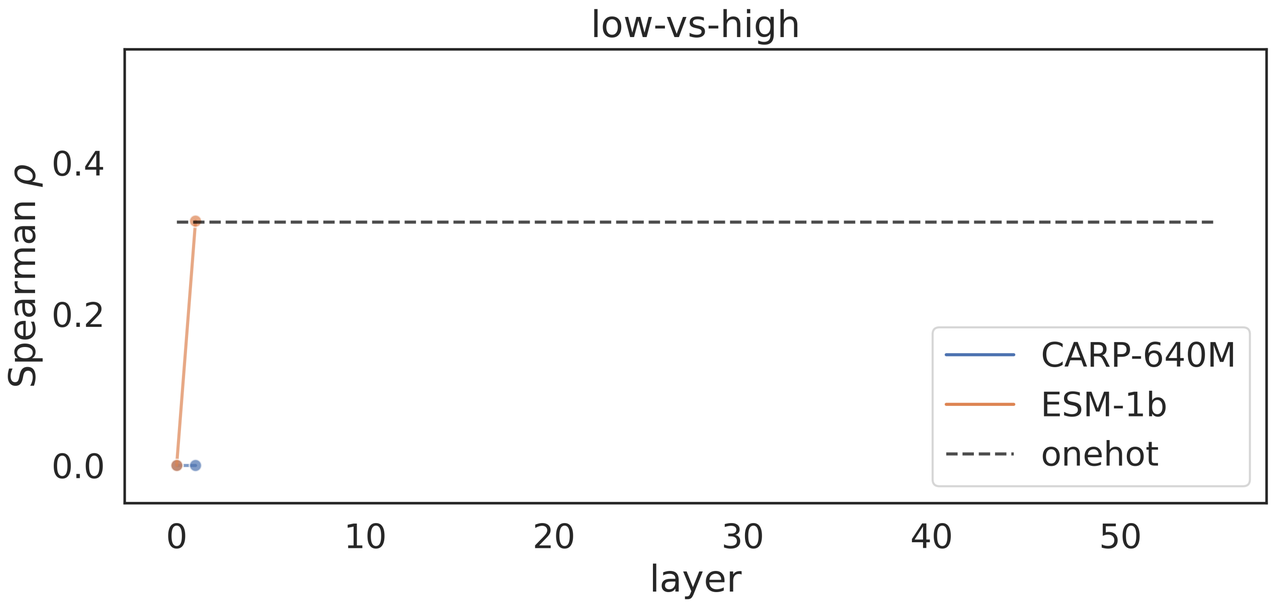

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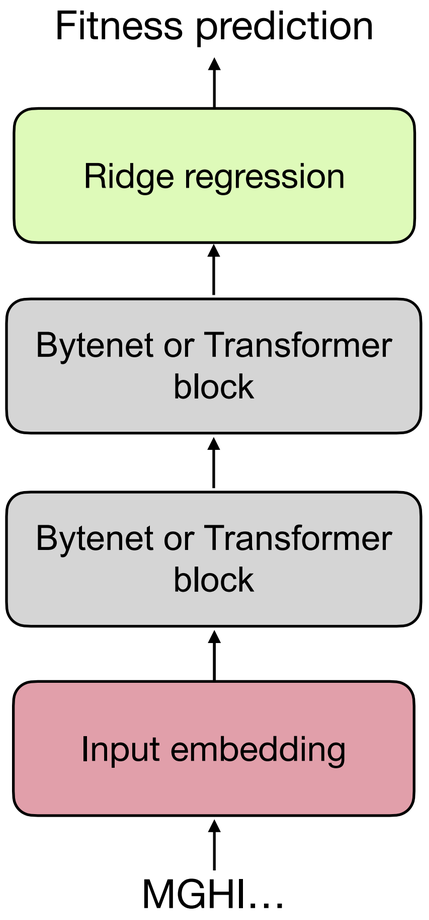

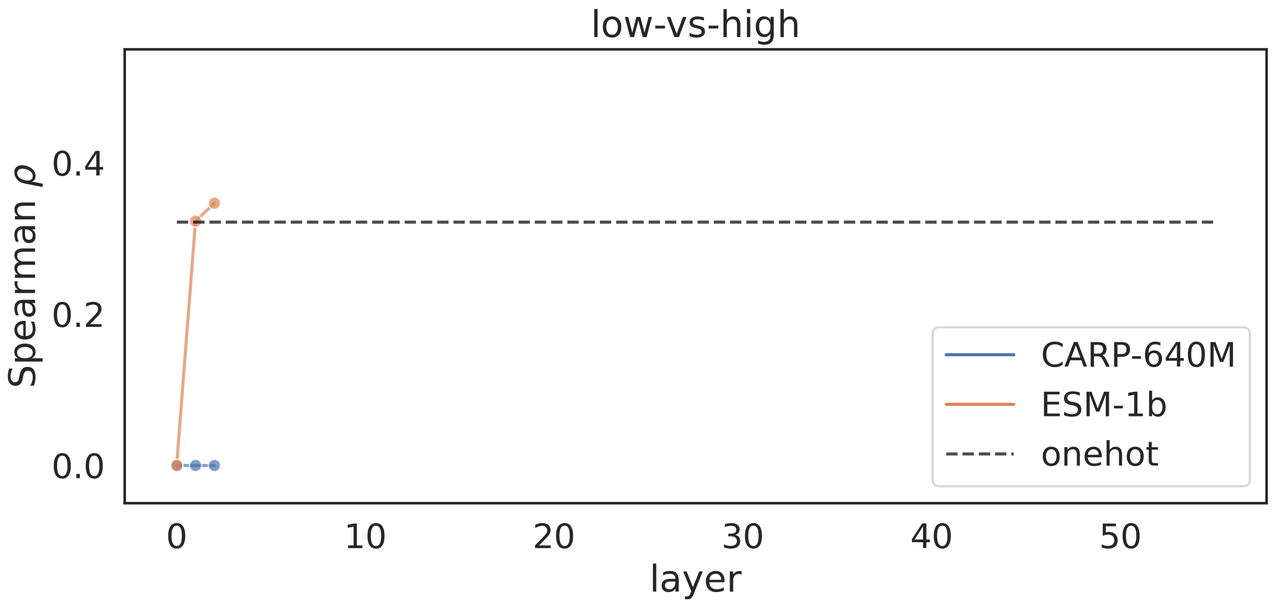

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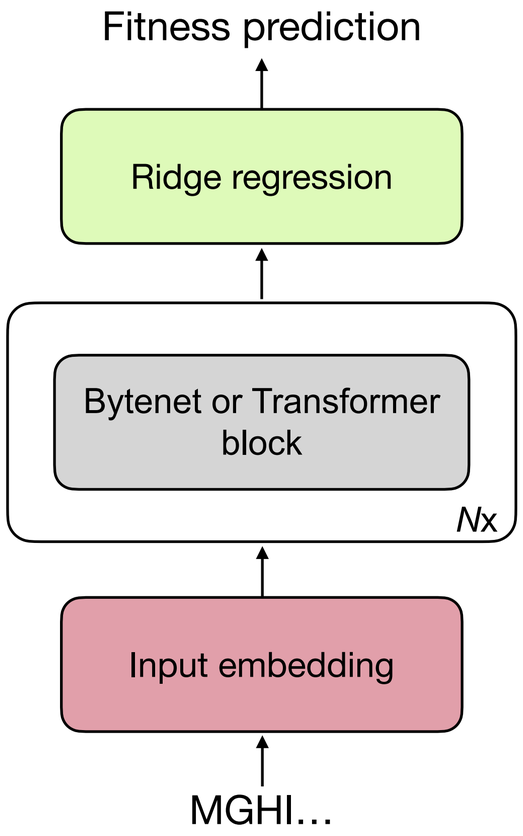
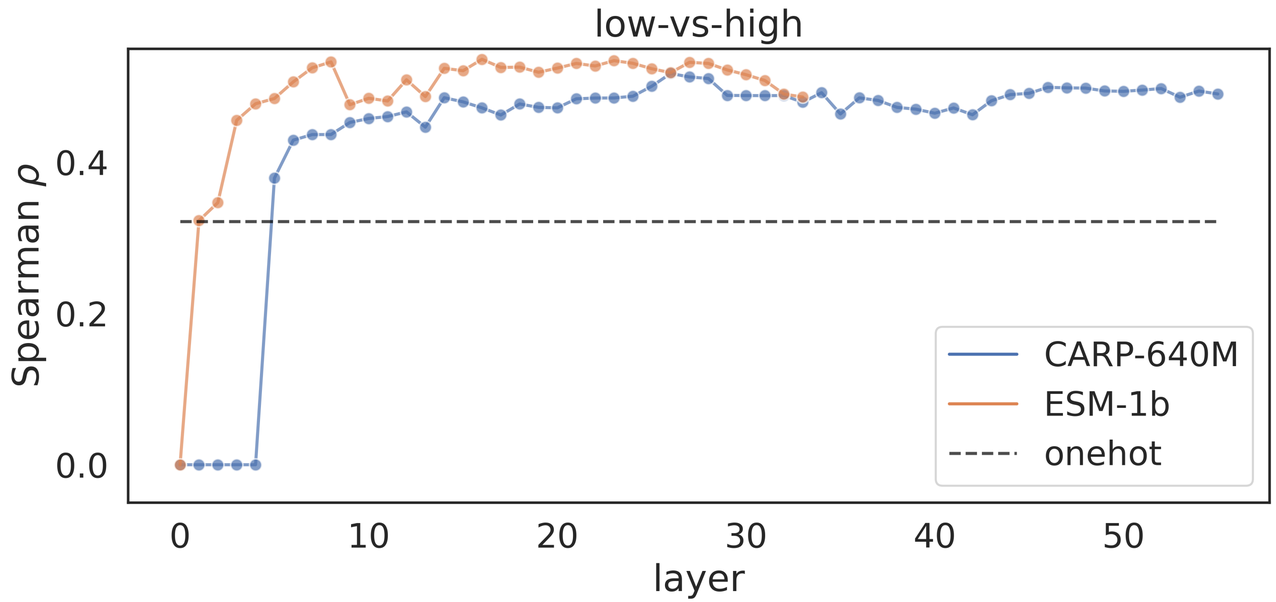
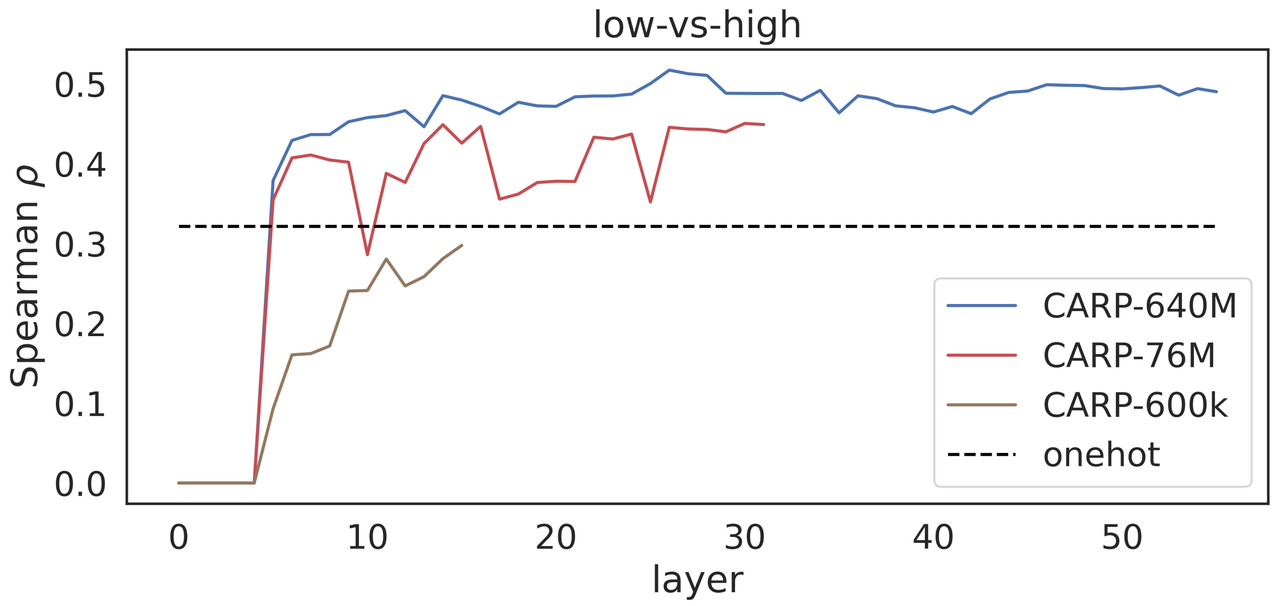




Bigger models do not always help



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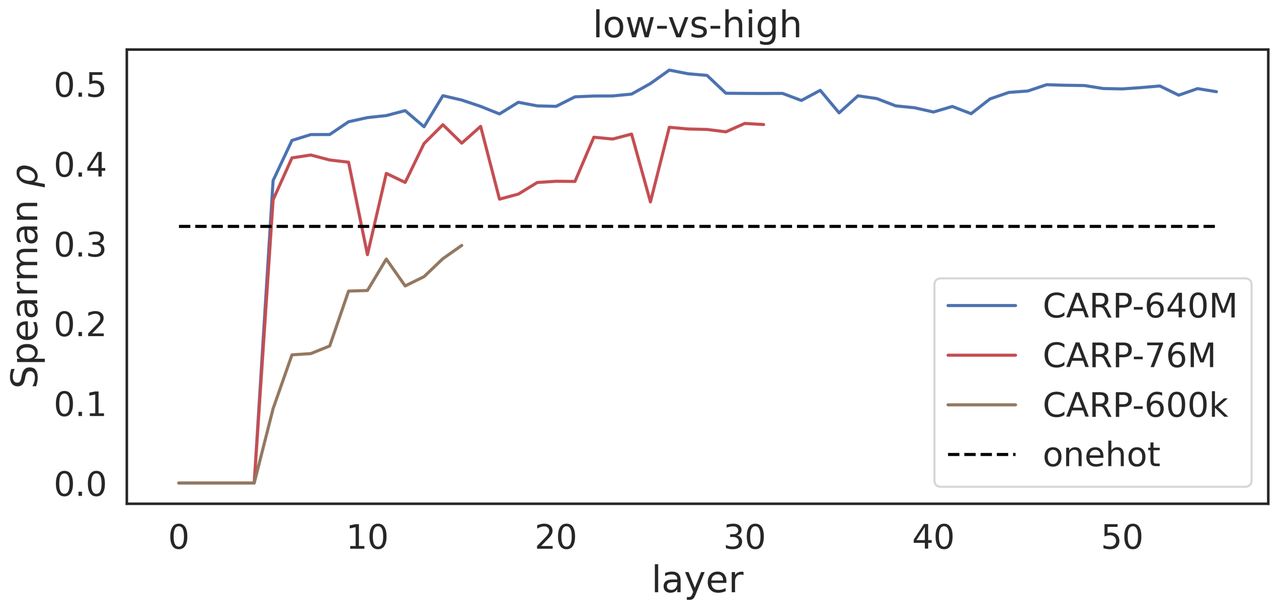
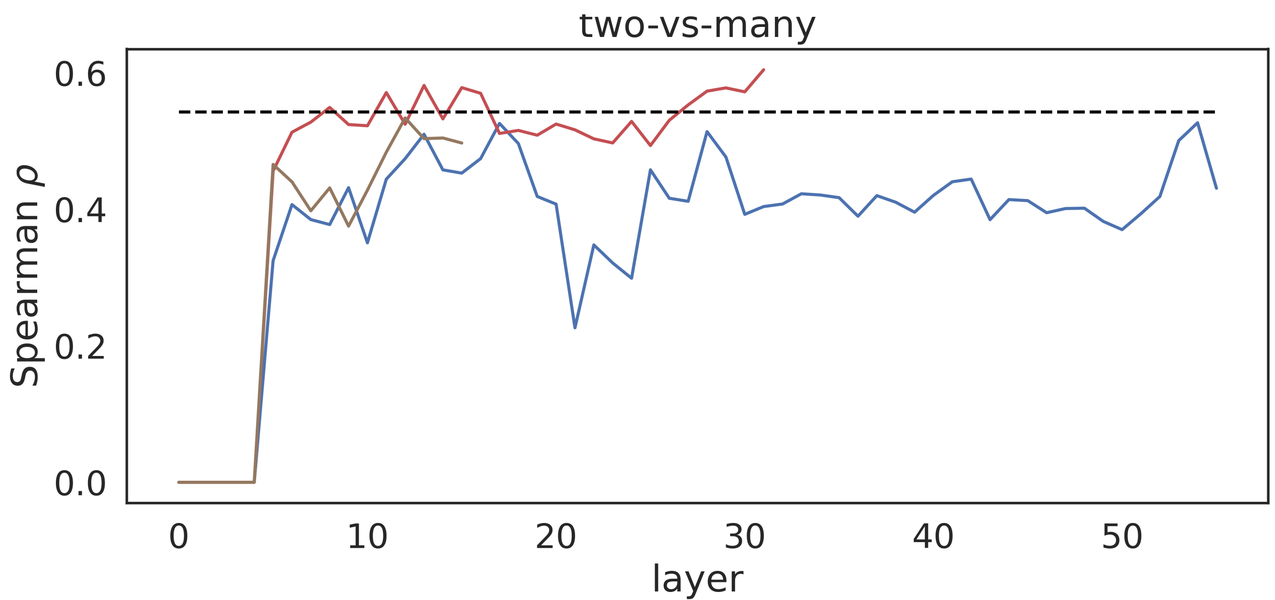
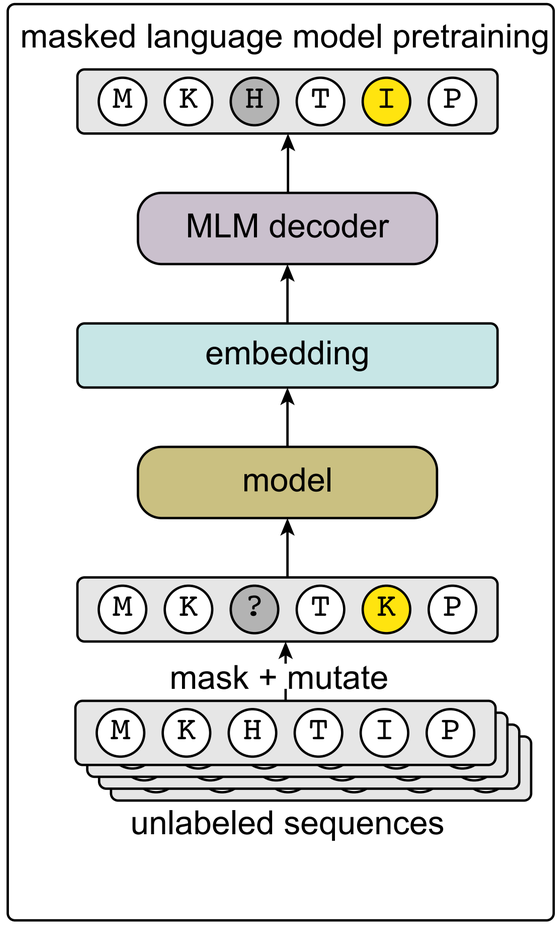
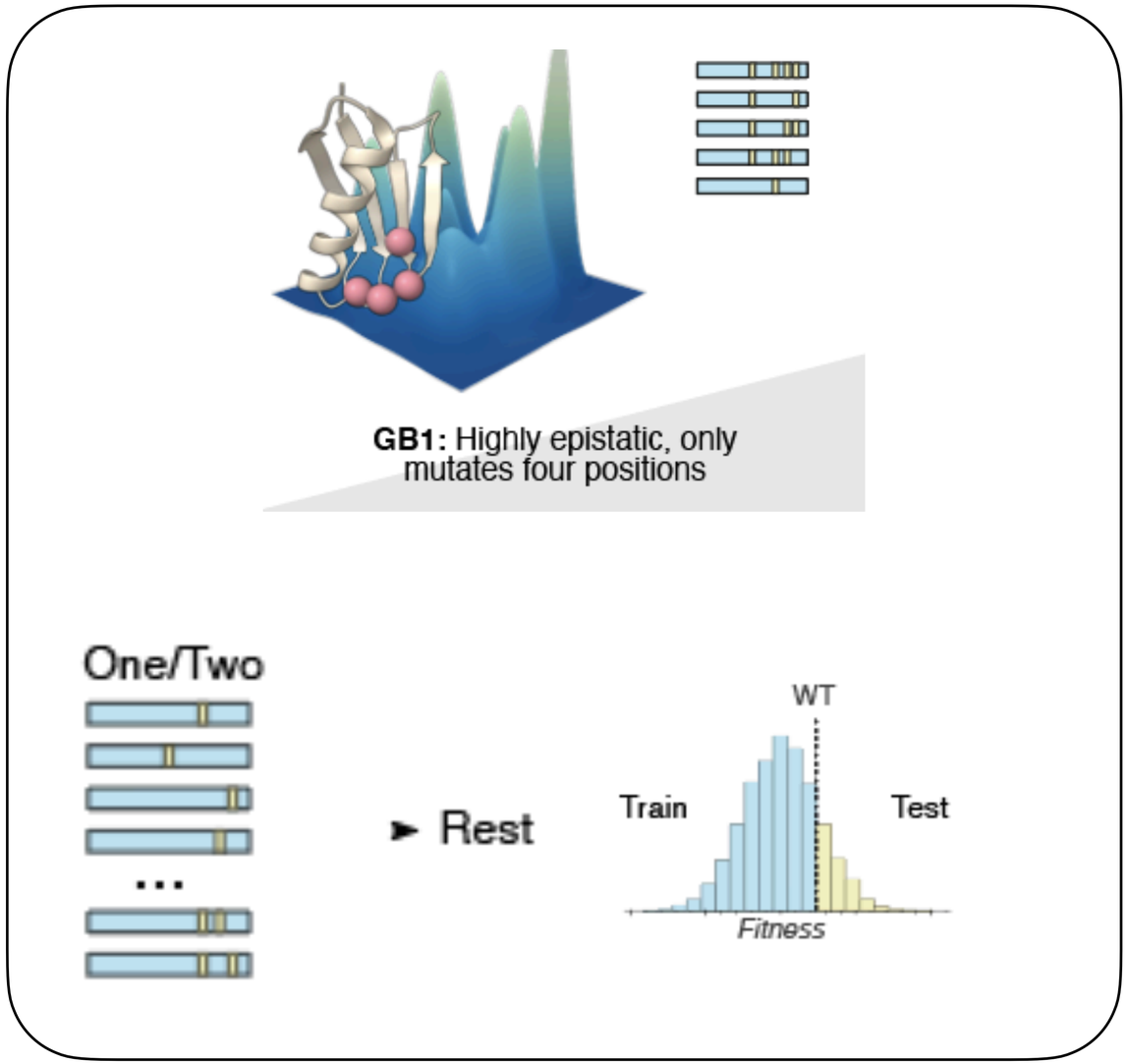


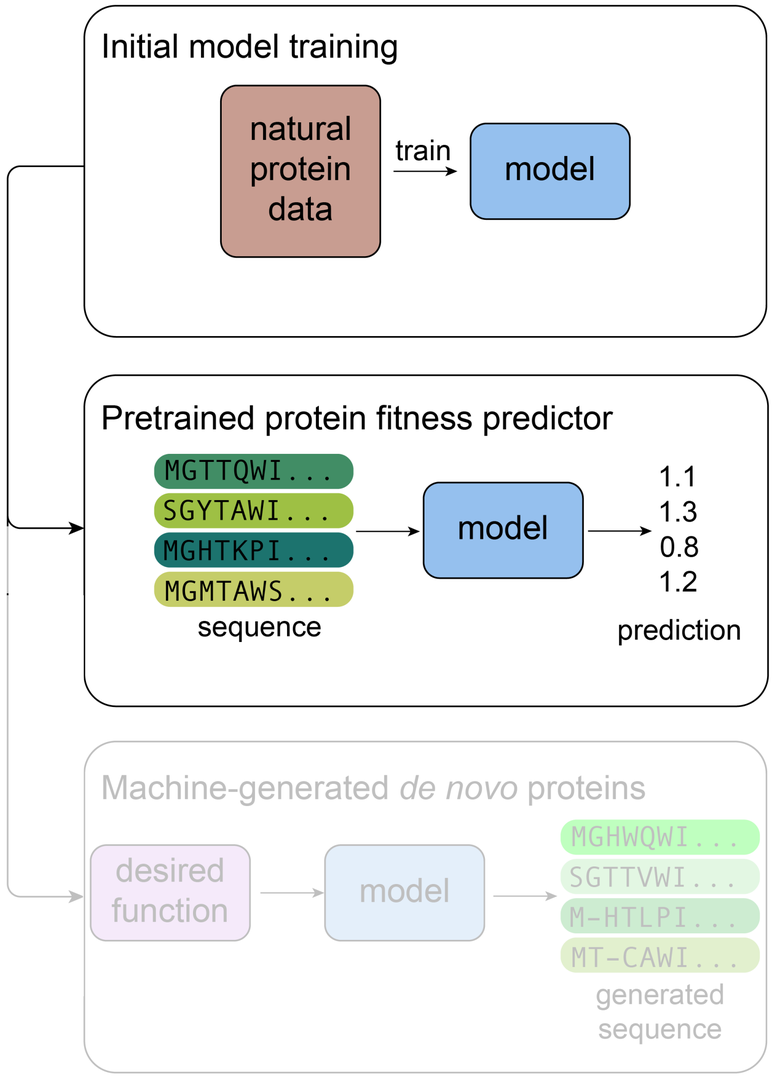


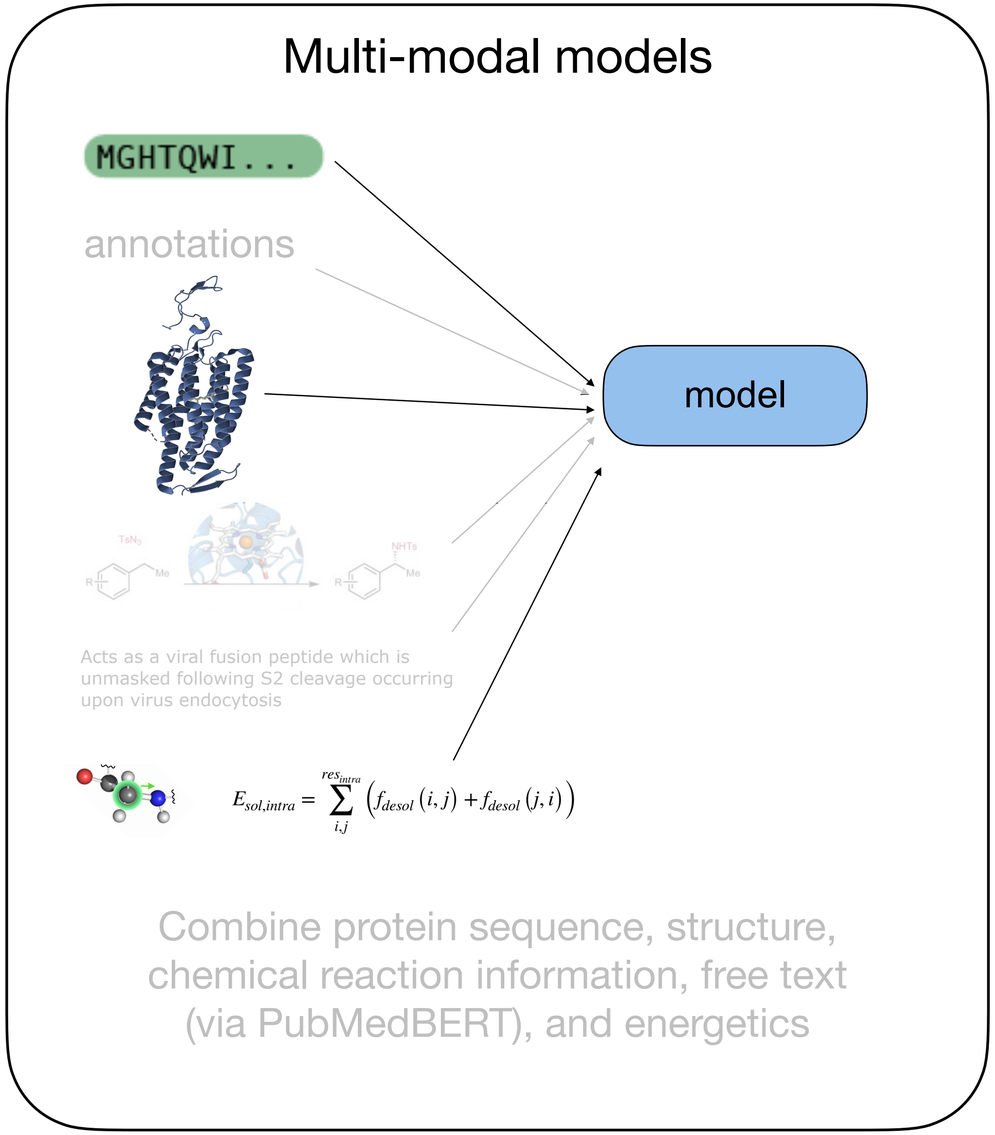
Pretrain and downstream tasks are mismatched





Use structure and energetic features as inputs





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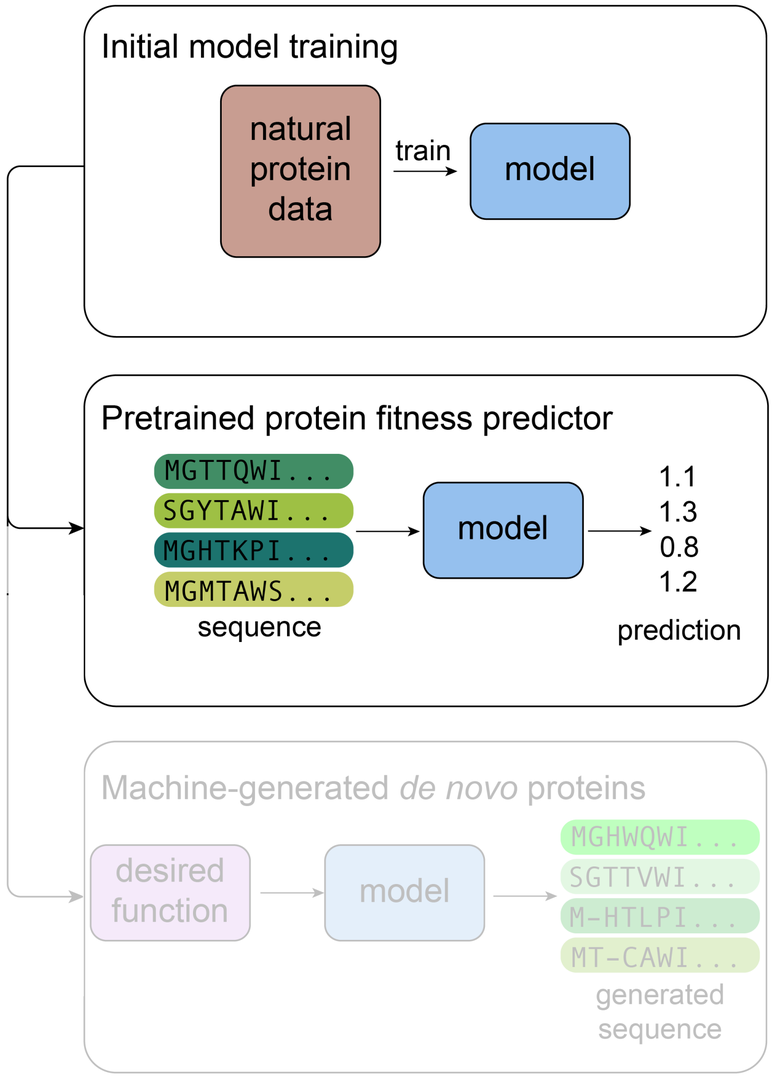
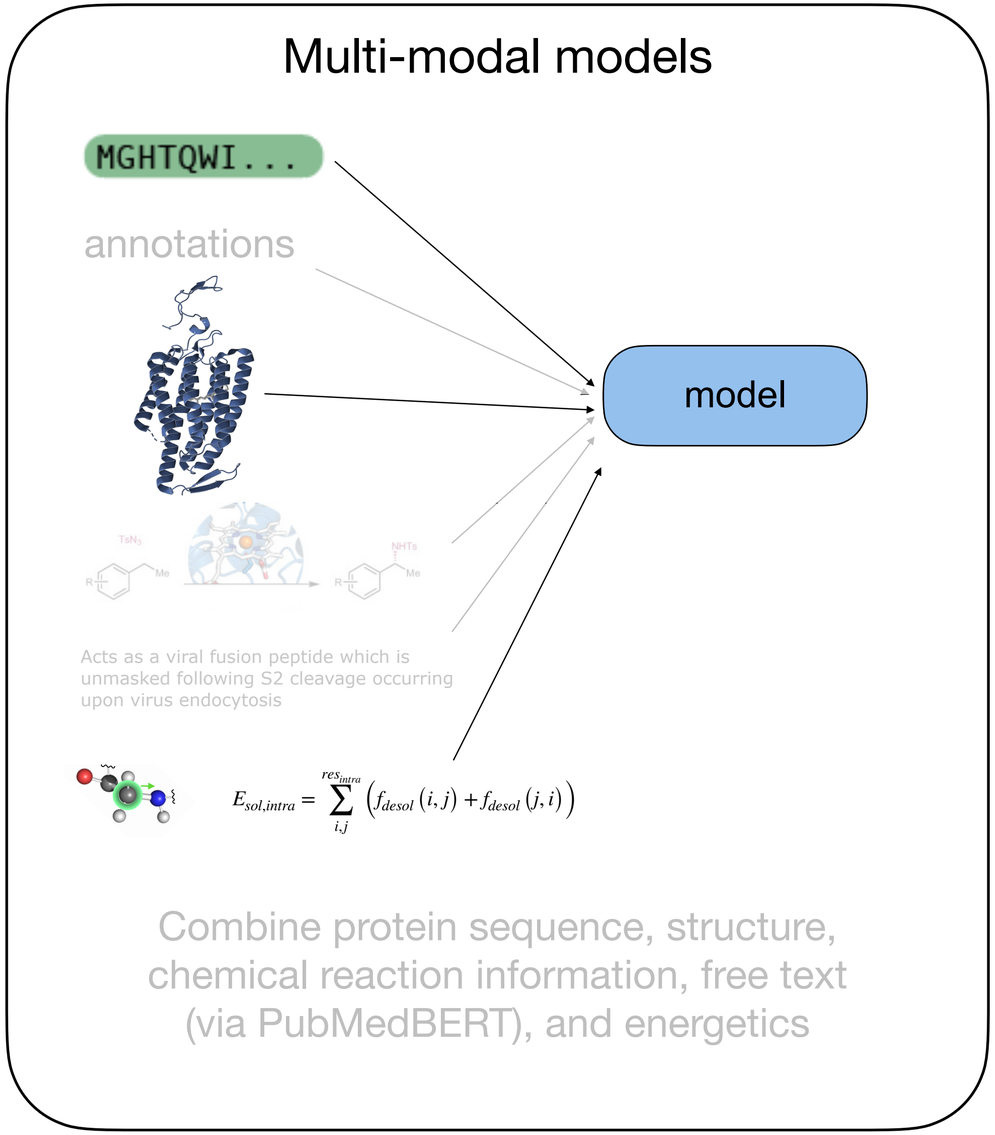
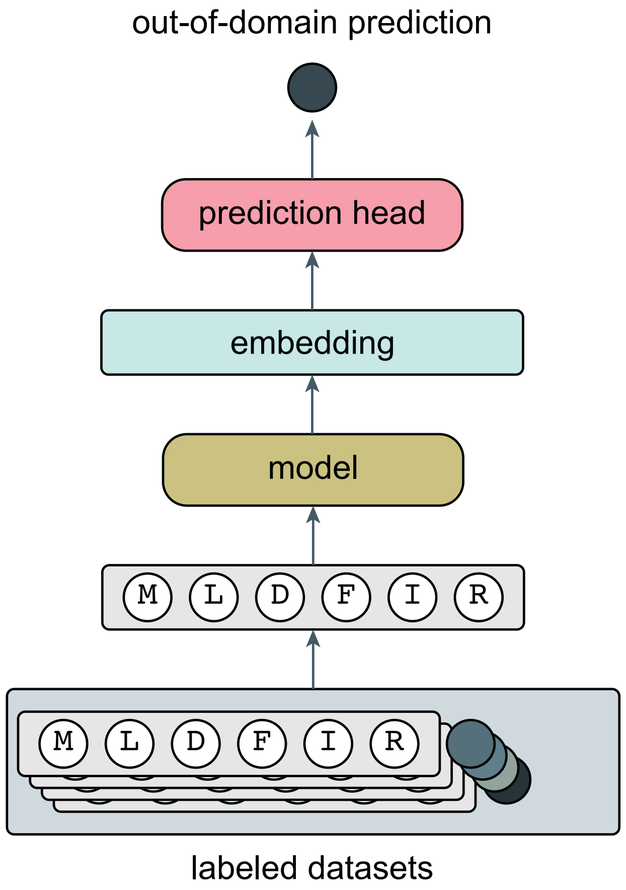




Structure-conditioned pretraining improve performance in low-data regimes



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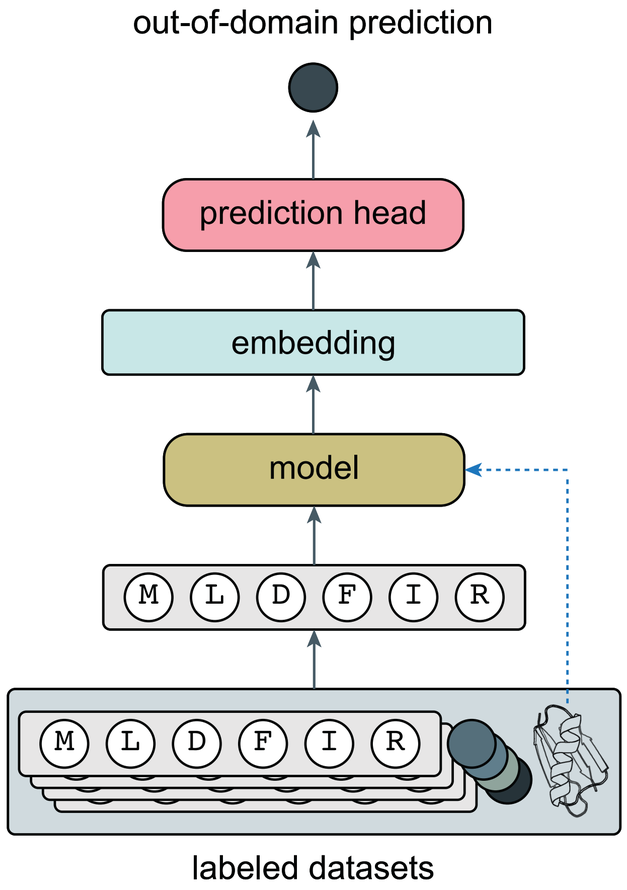

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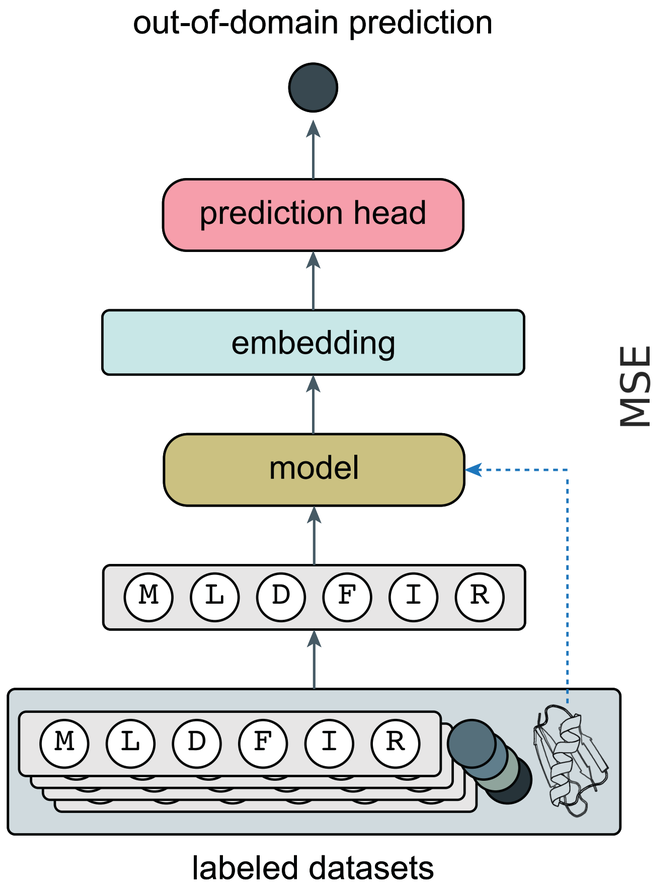

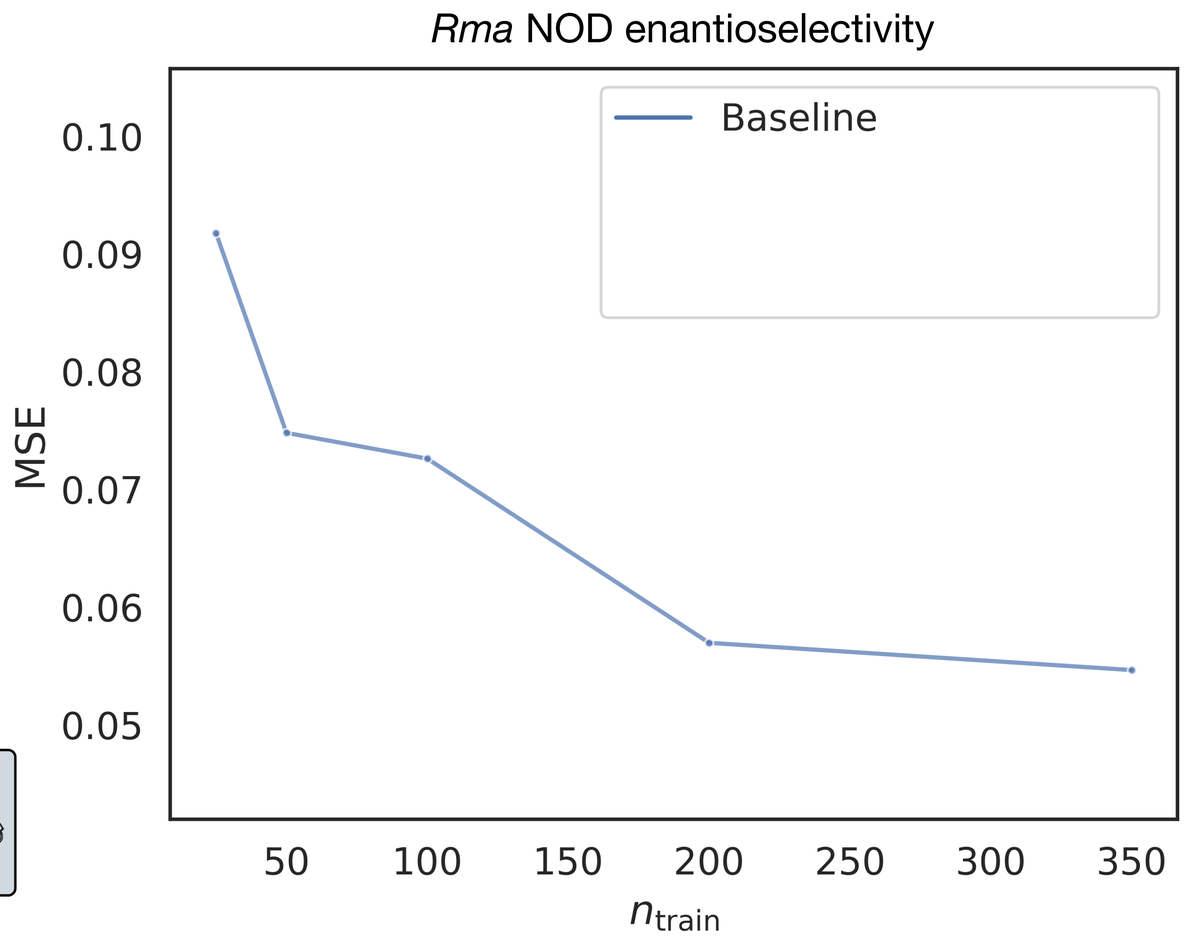

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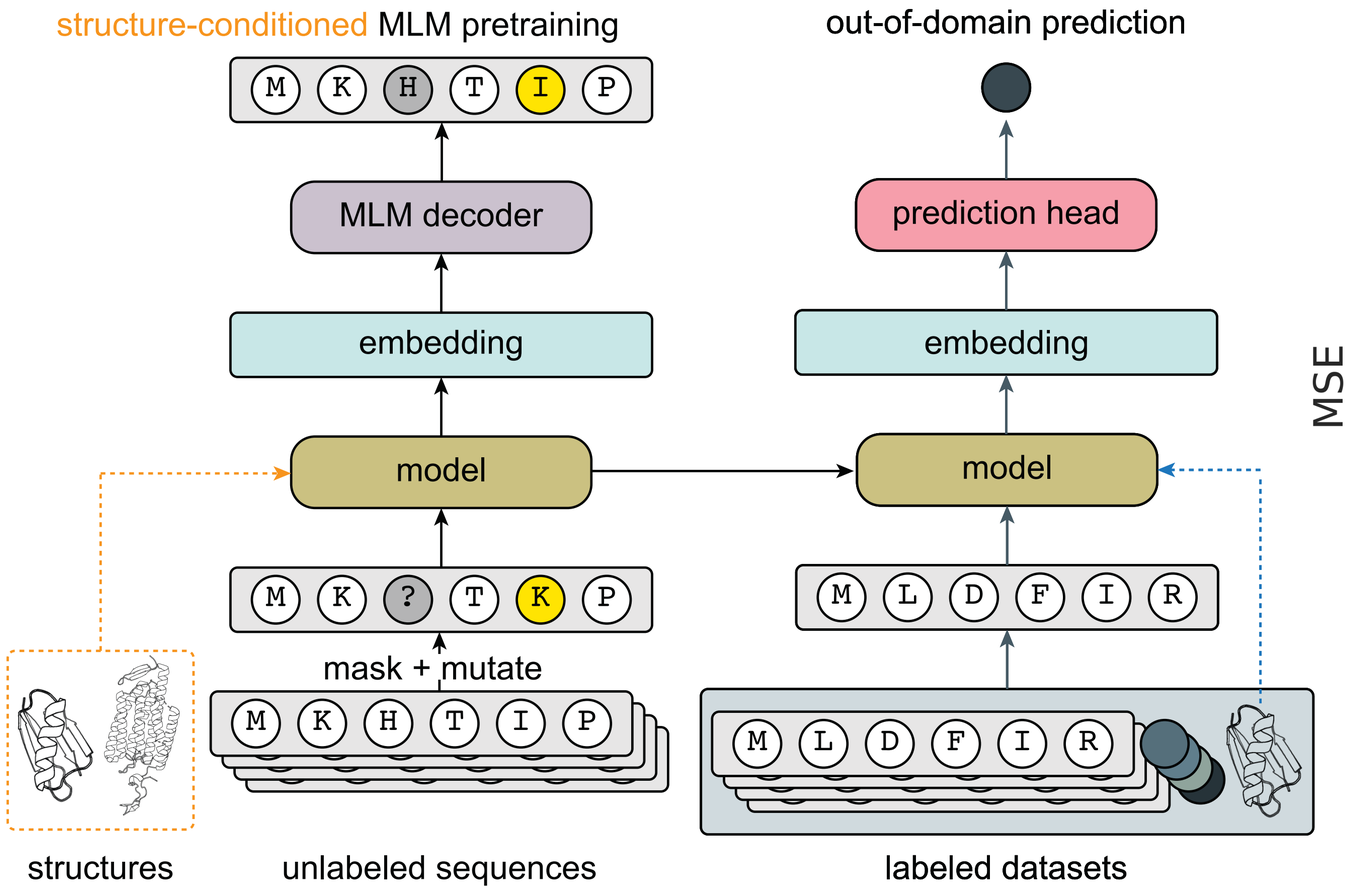

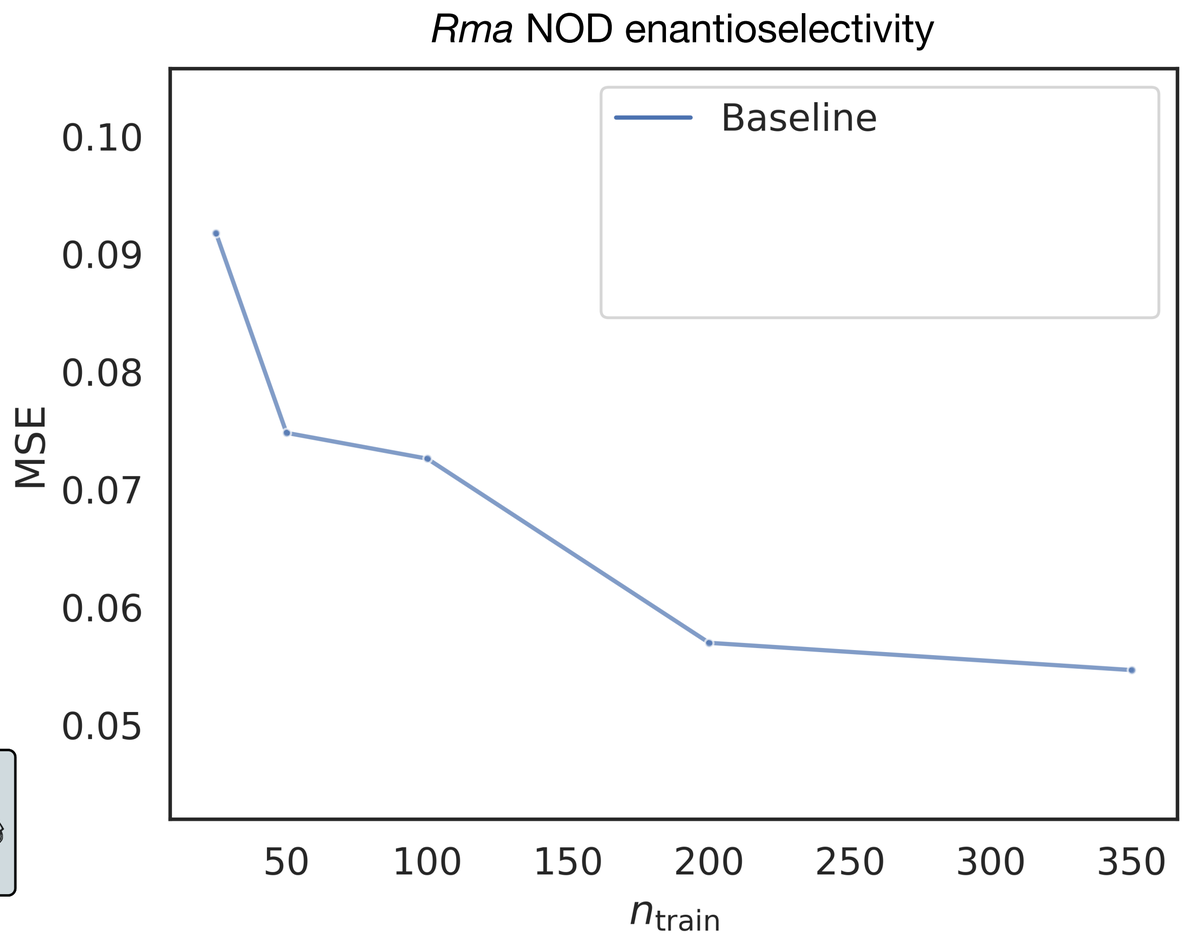

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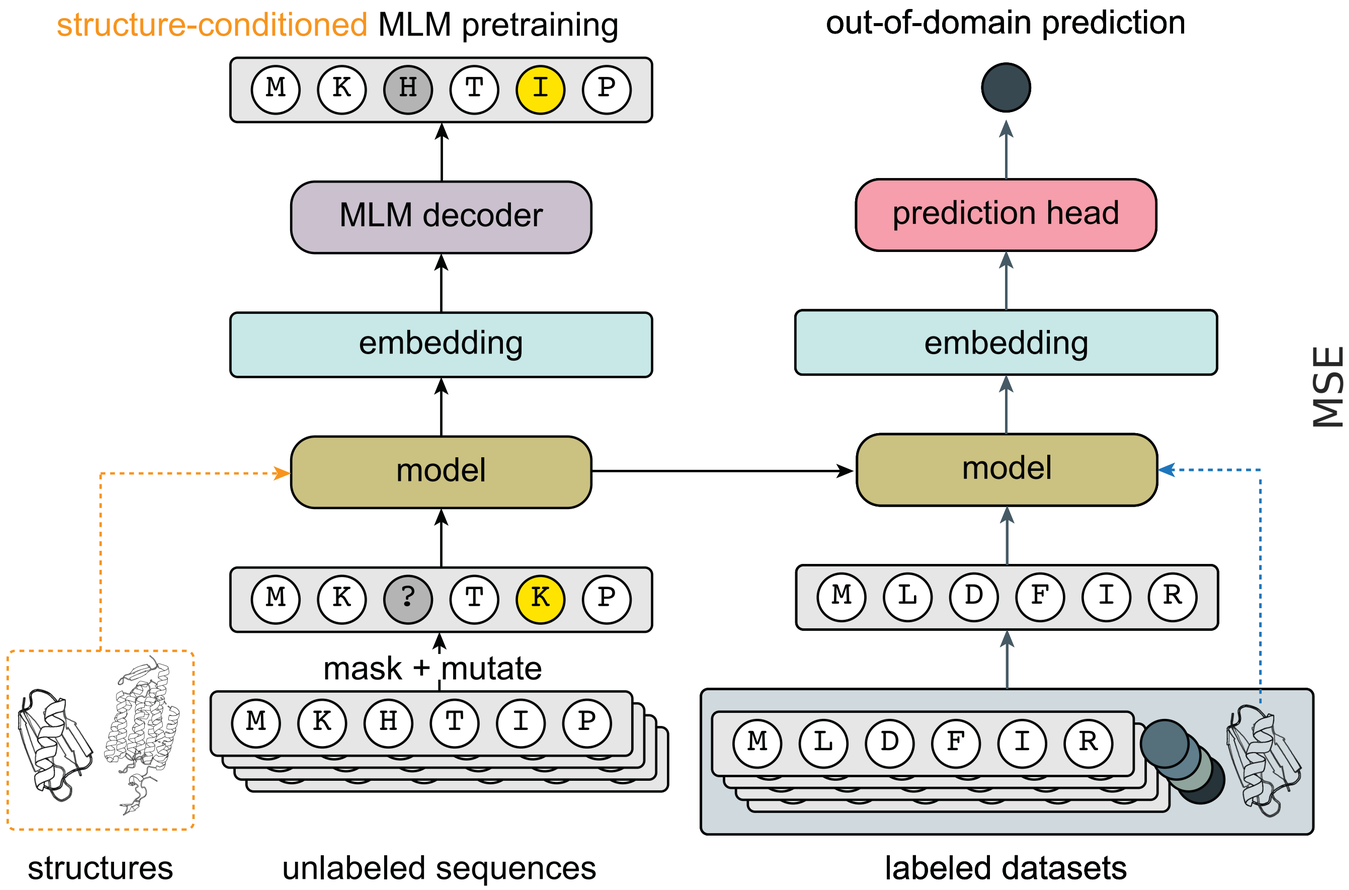

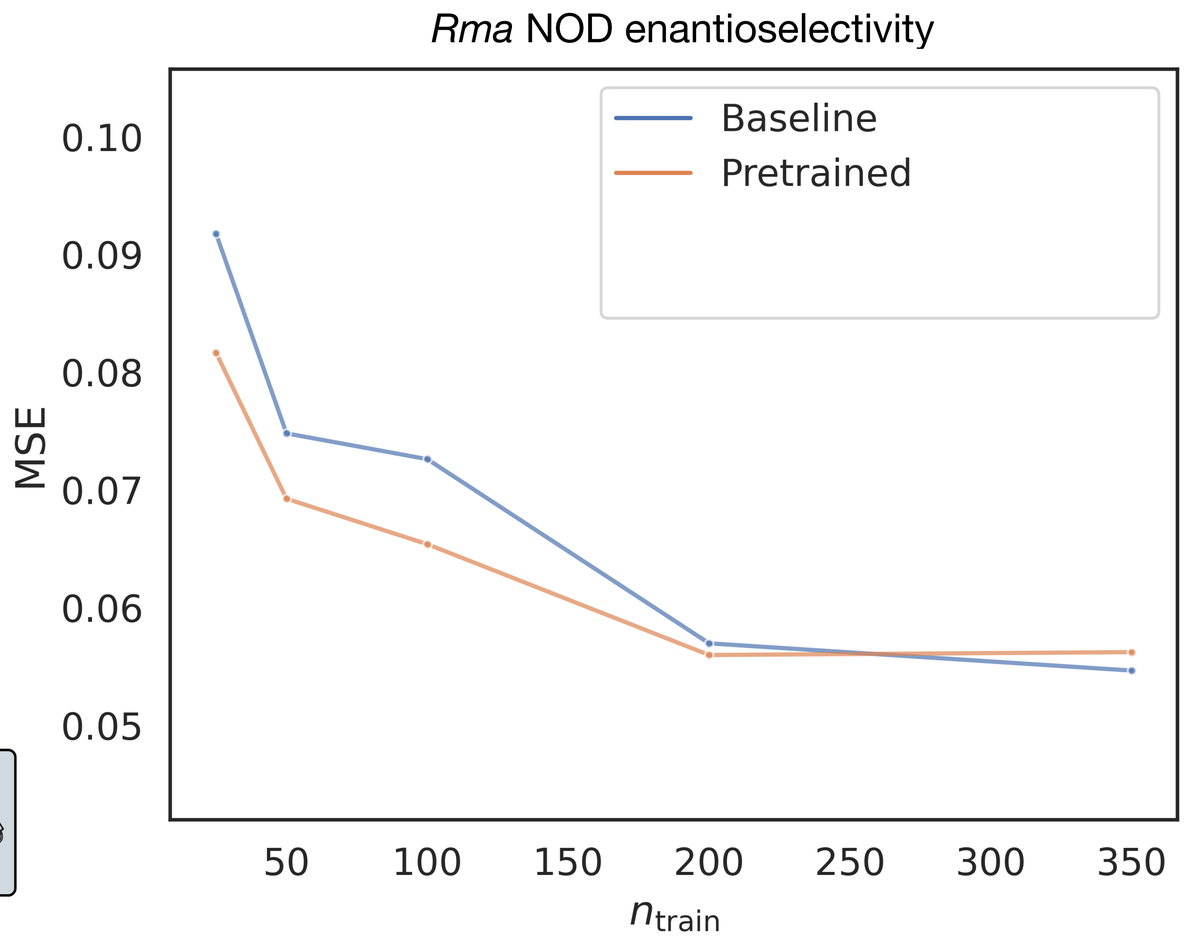

Use precomputed physics-based energies as input features

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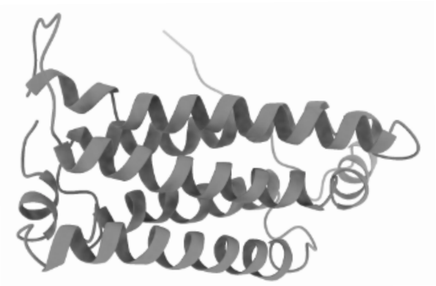

Reference protein

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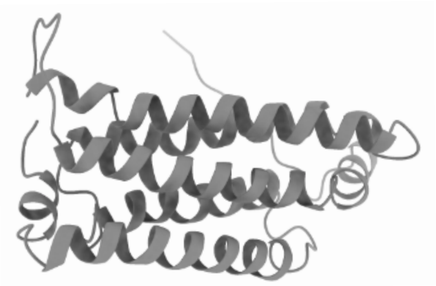

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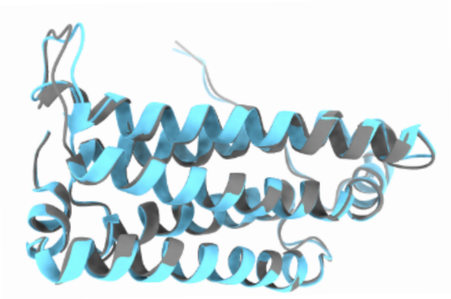

Protein variant: L10E

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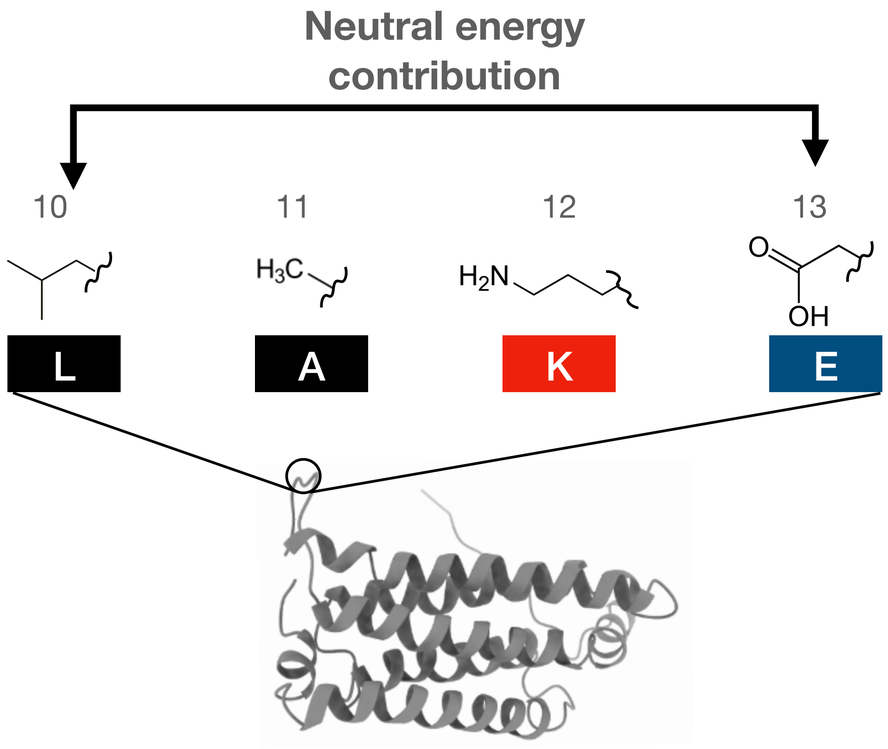

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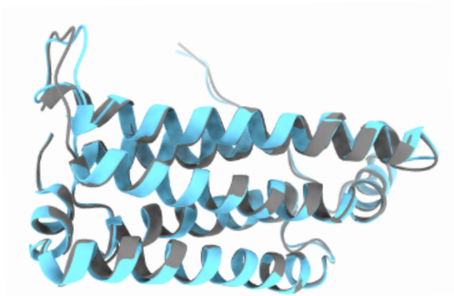

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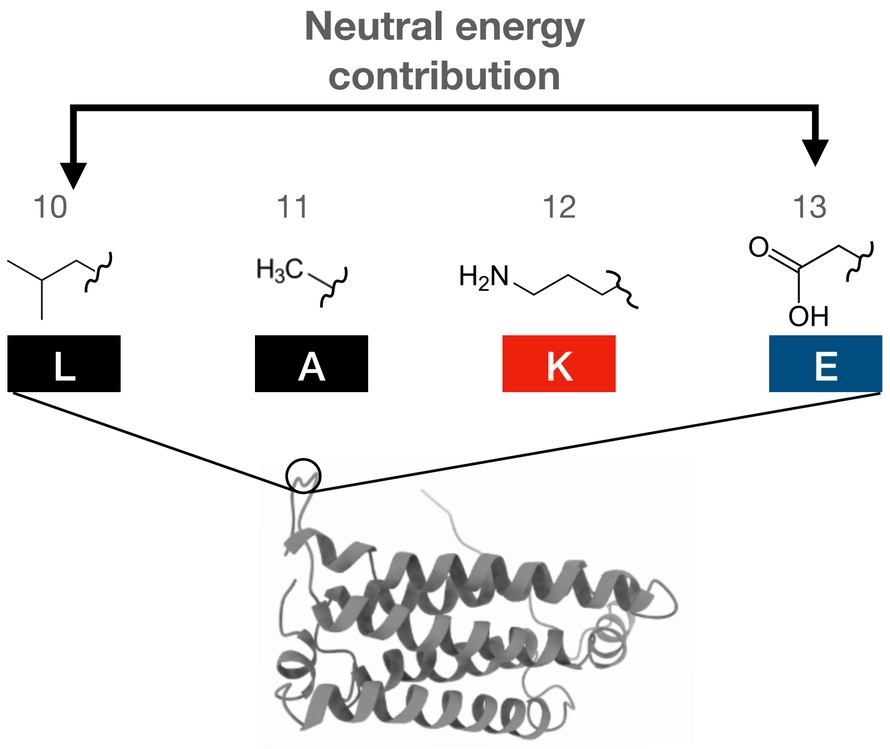
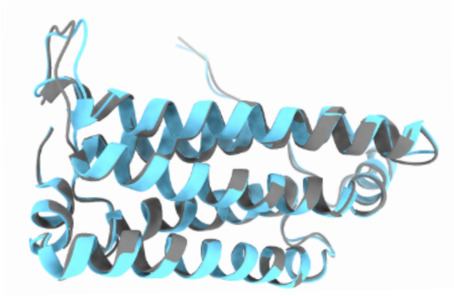


Reference protein

Mutate and relax

Rosetta Commons



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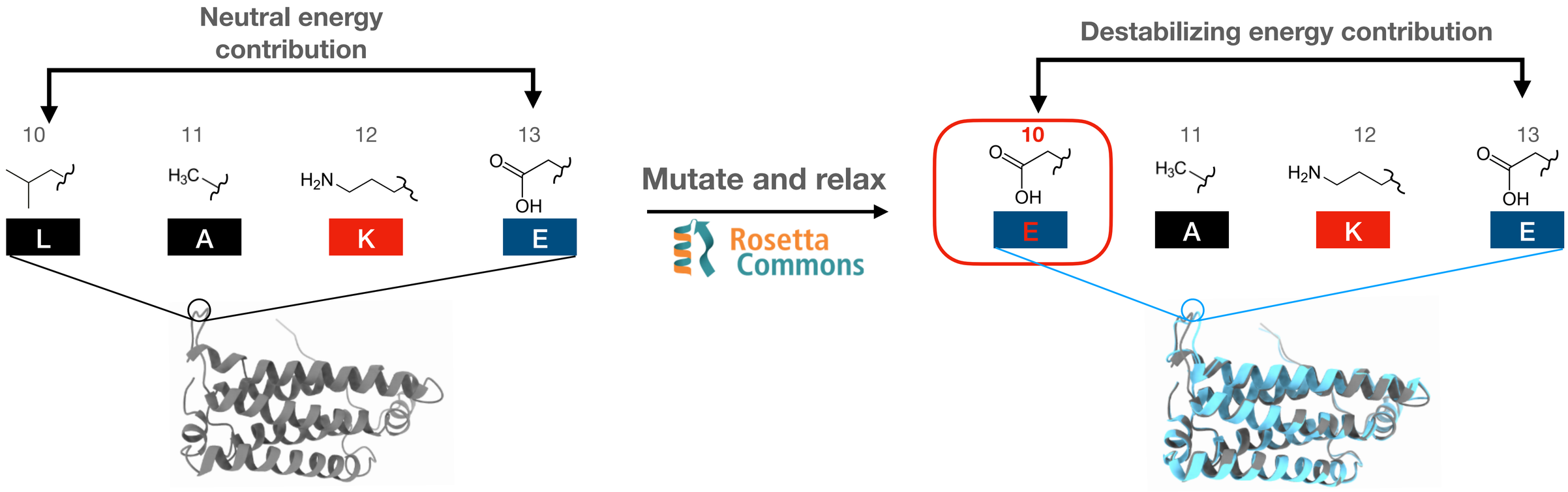

Reference protein

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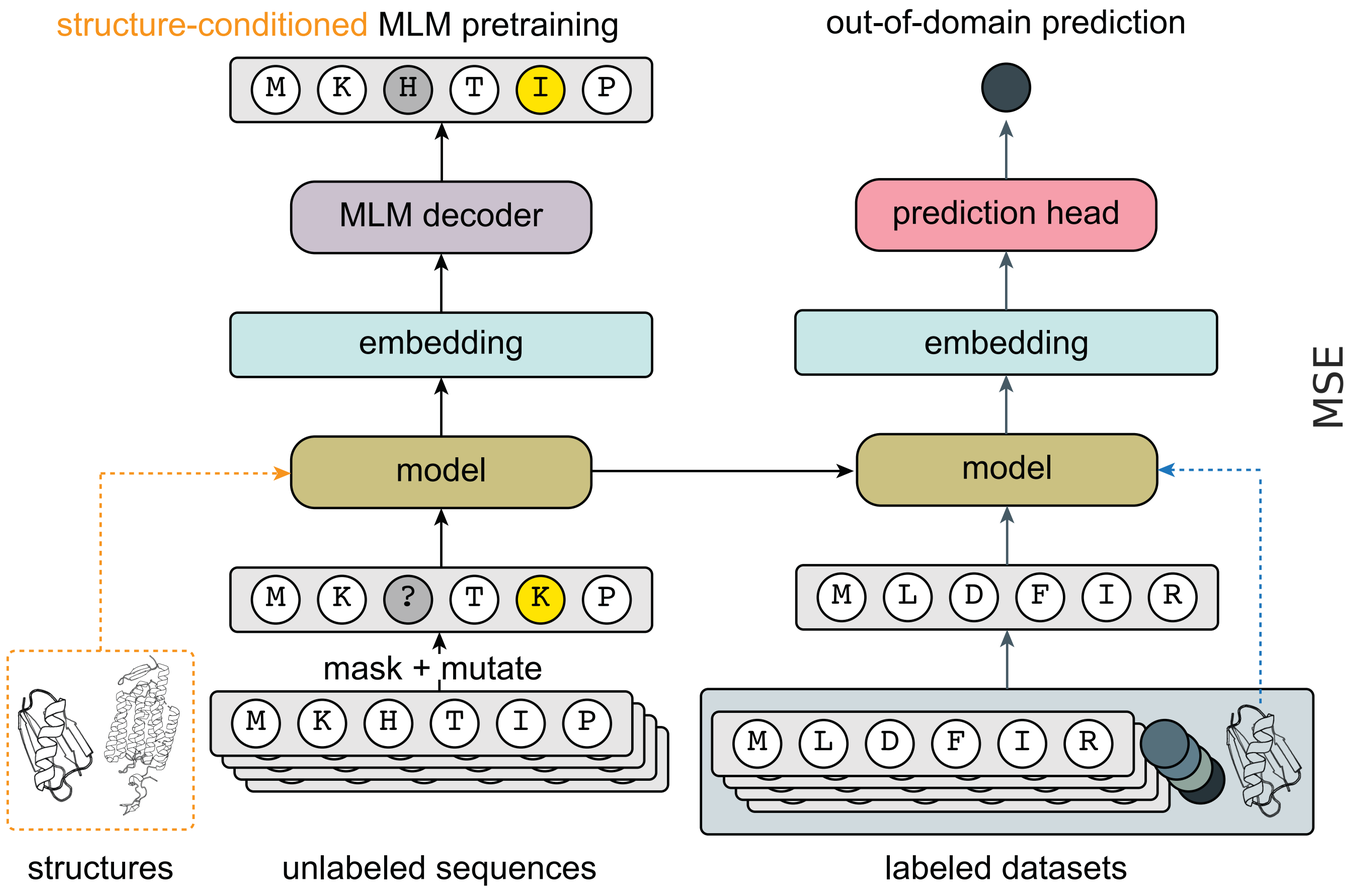
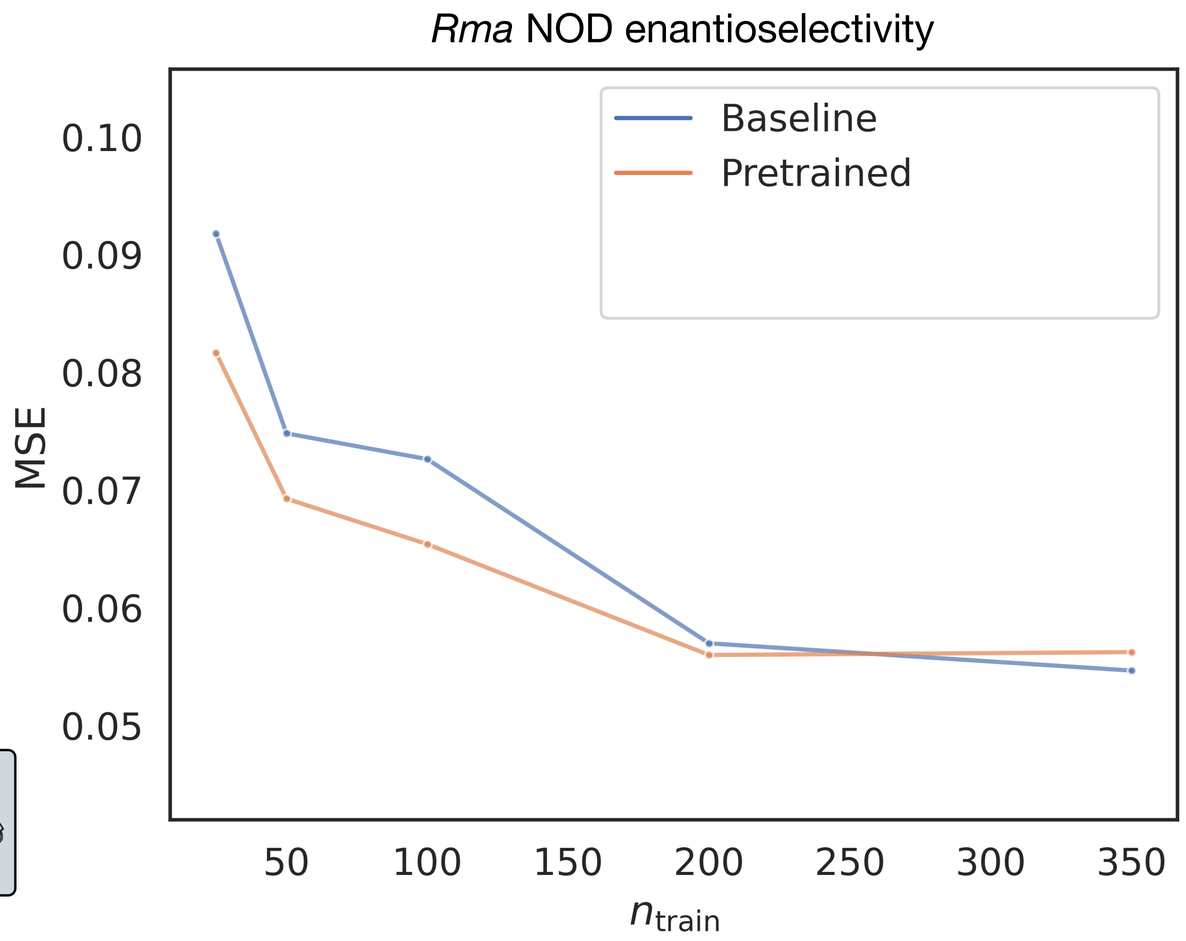
Energetics features improve performance in low-data regimes





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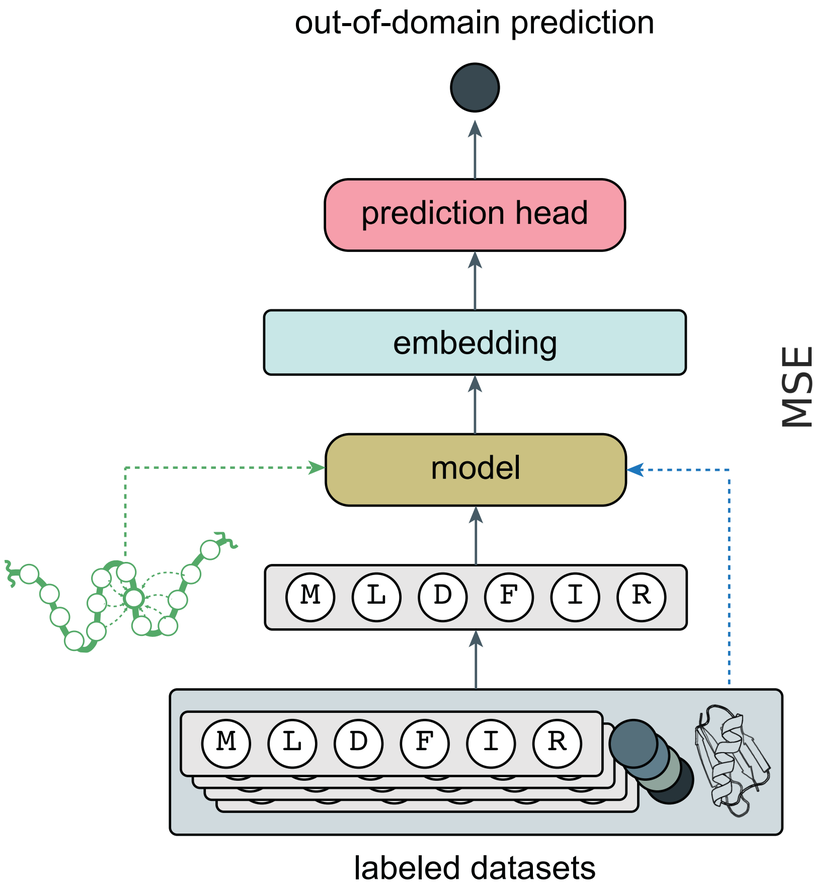

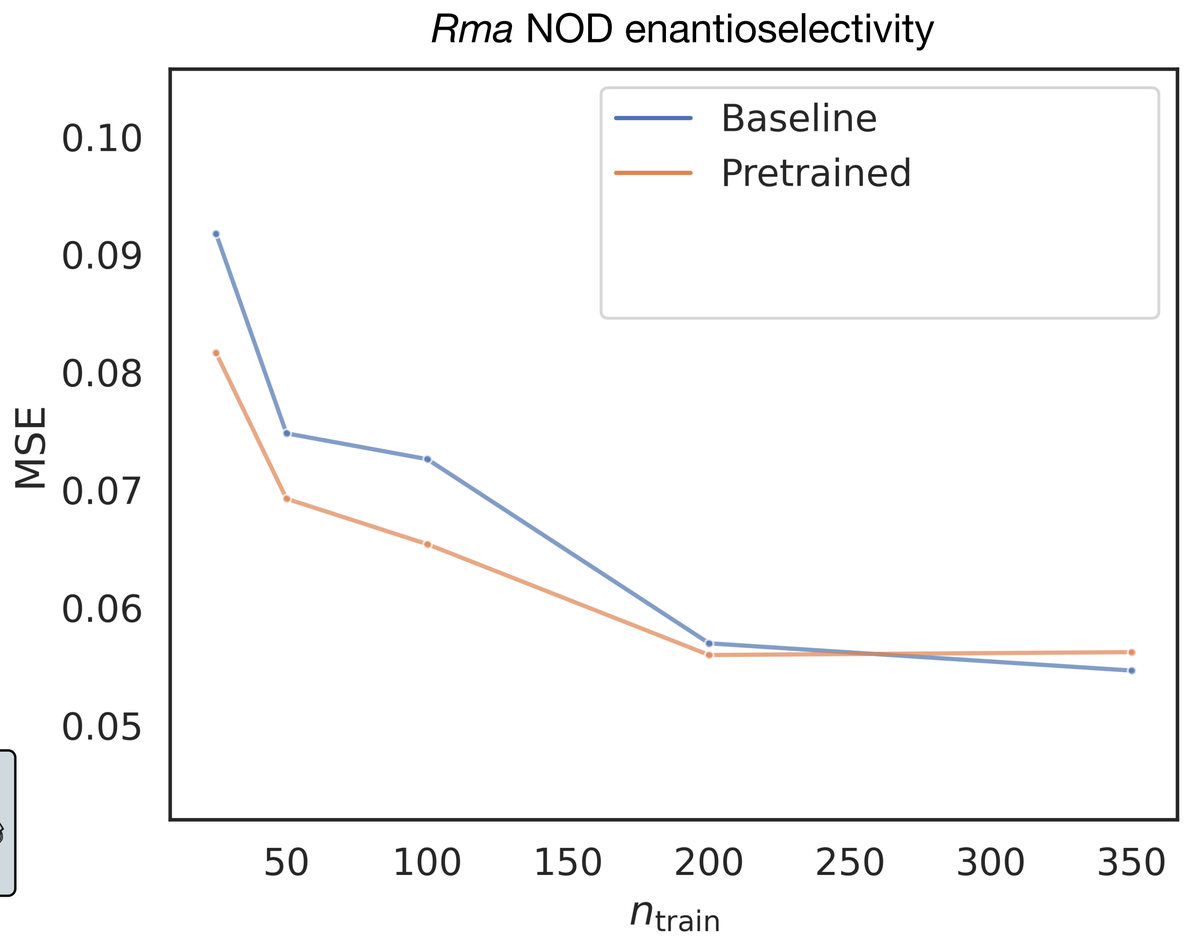

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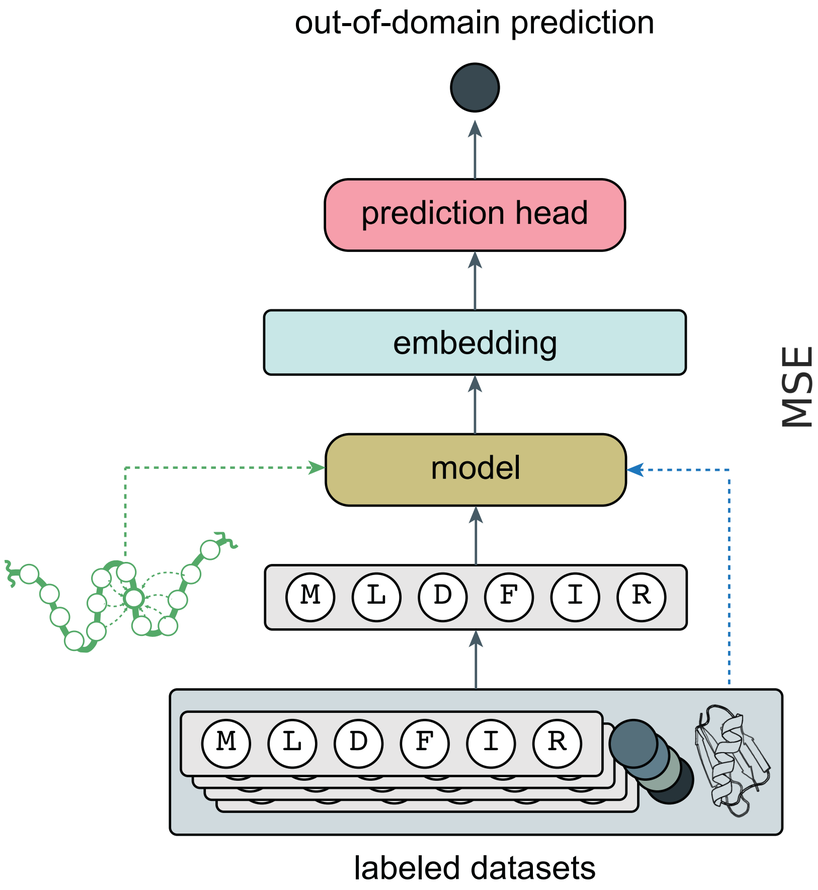
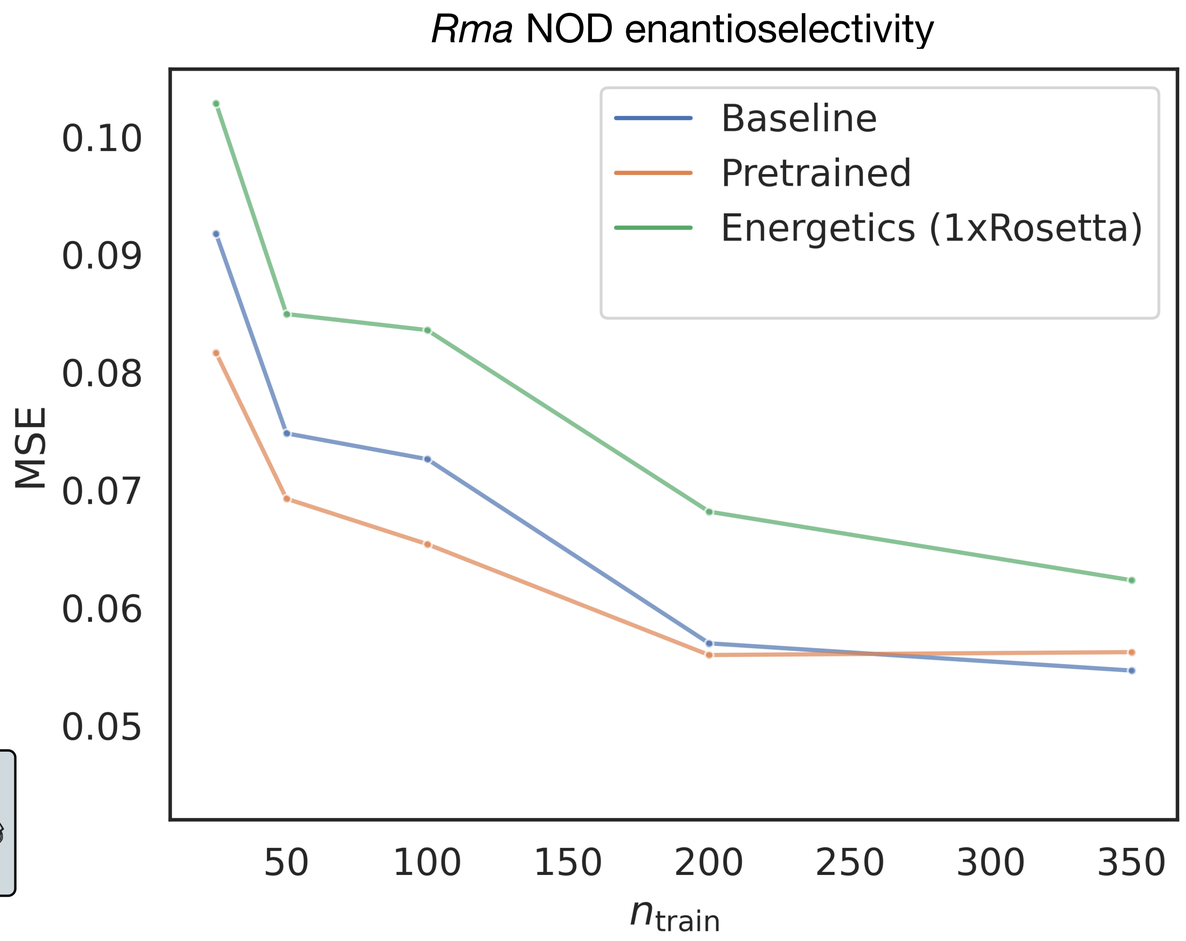
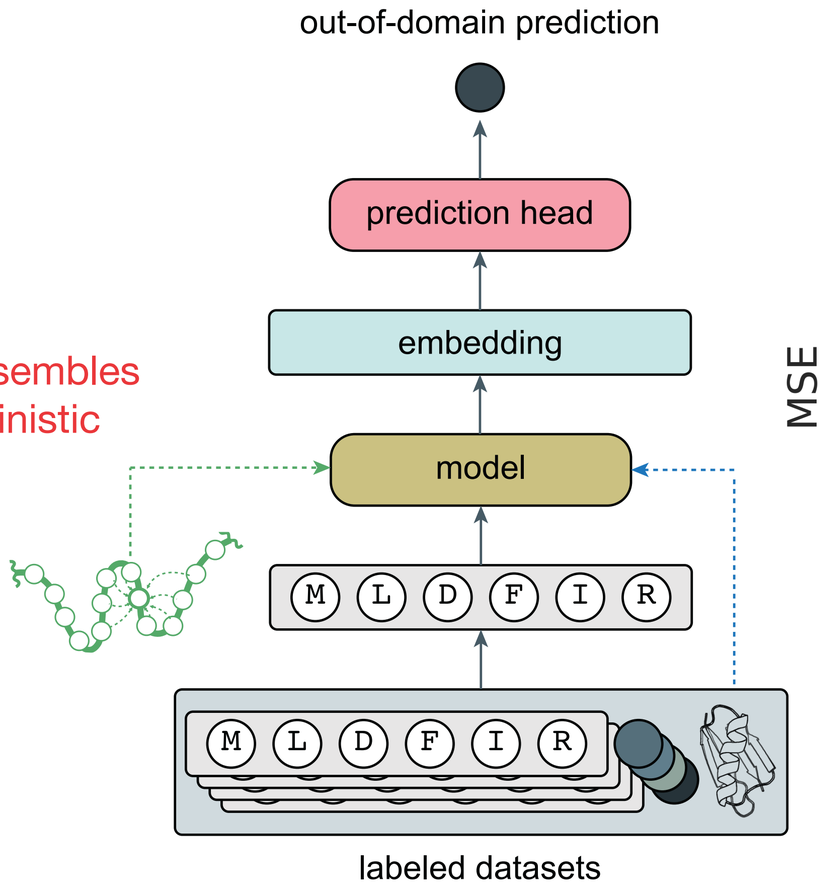
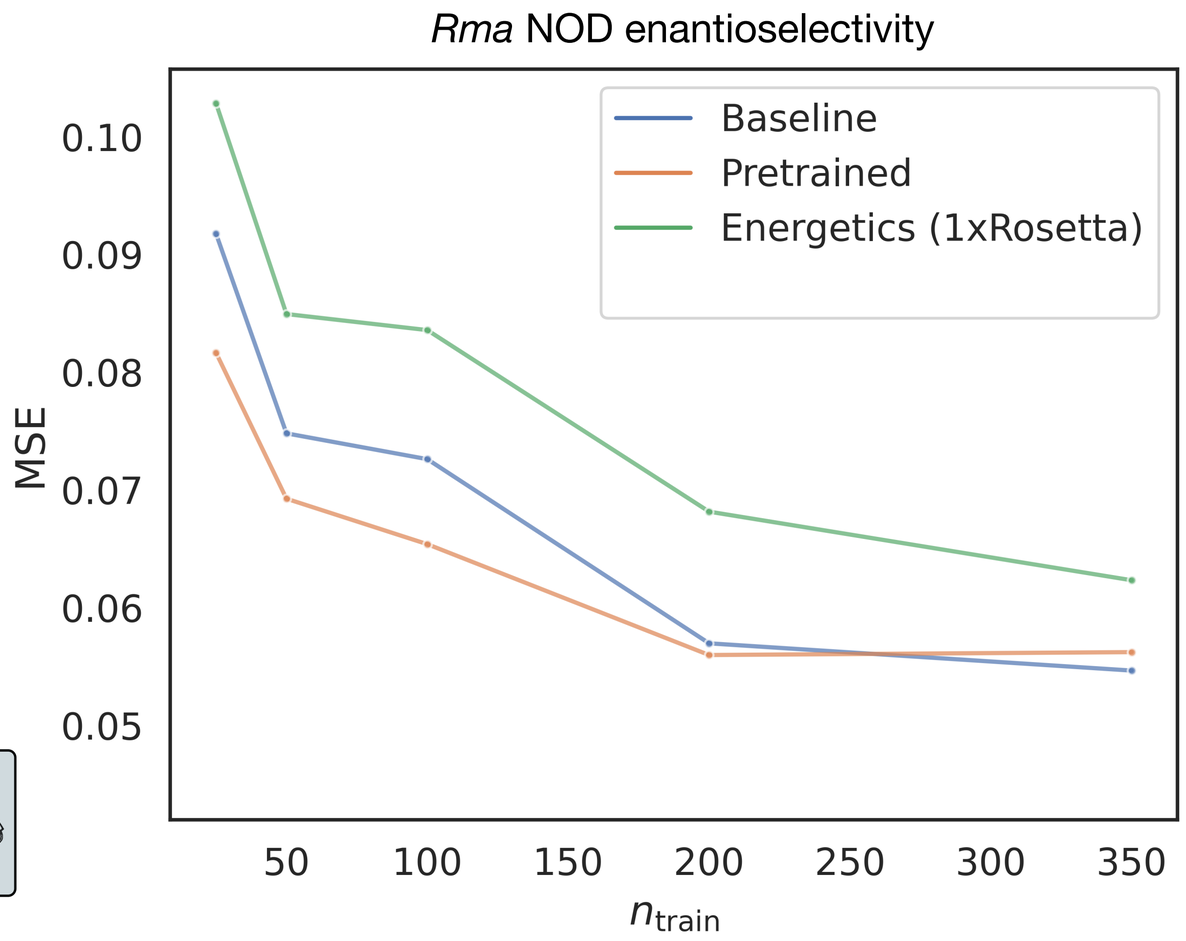




Energetics features improve performance in low-data regimes

Proteins exist in structural ensembles
Rosetta-relax is not deterministic





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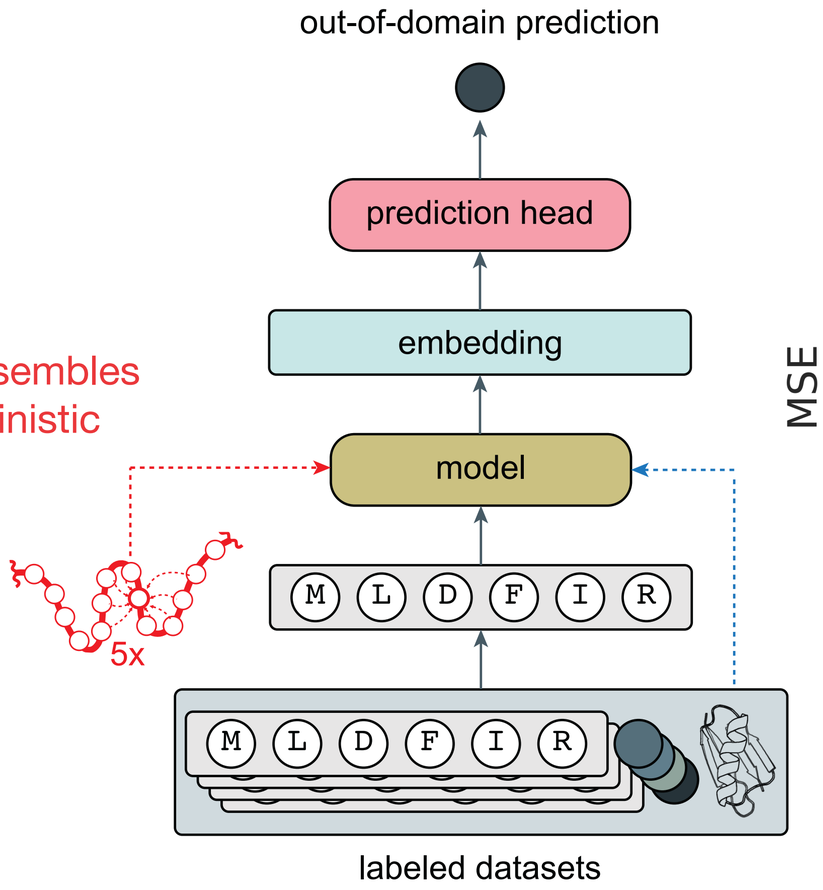

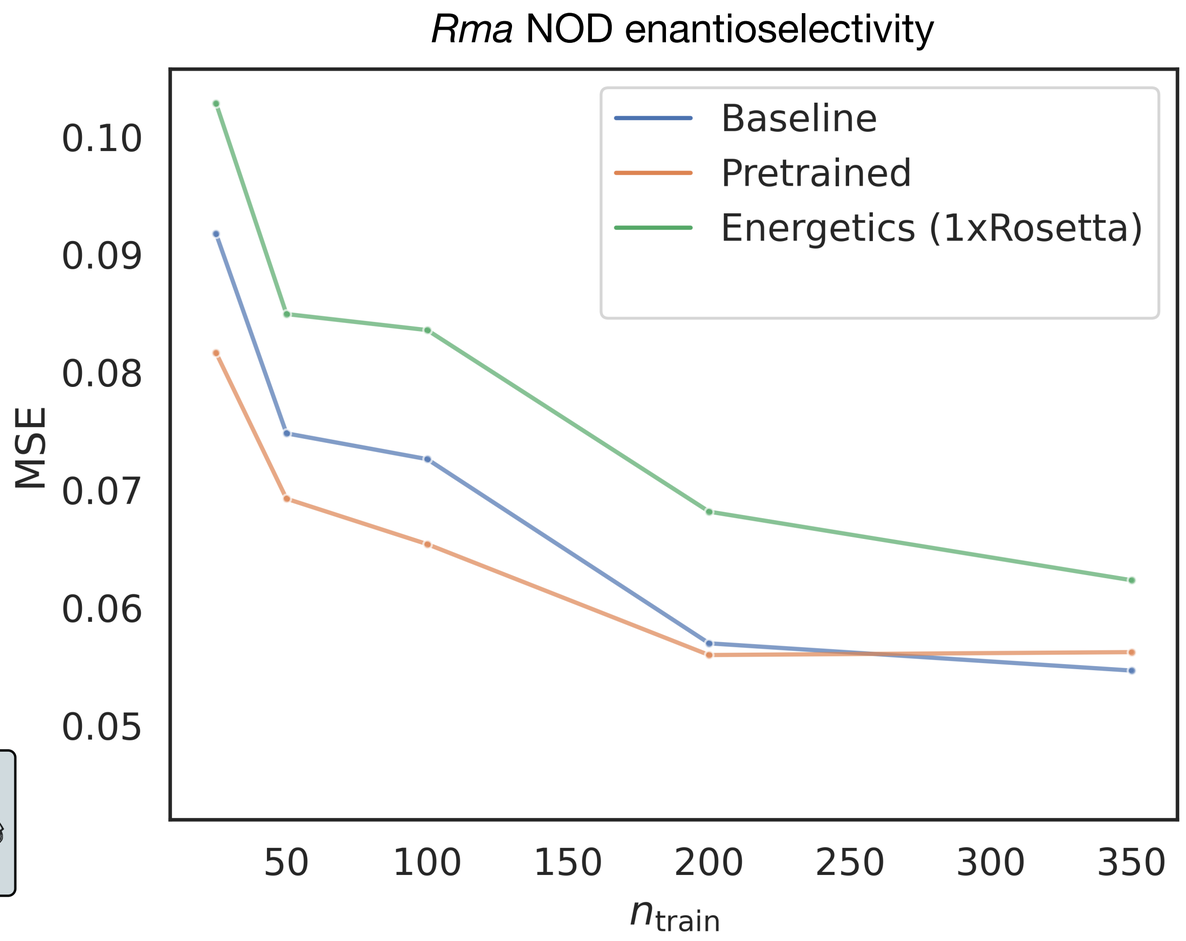

Energetics features improve performance in low-data regimes

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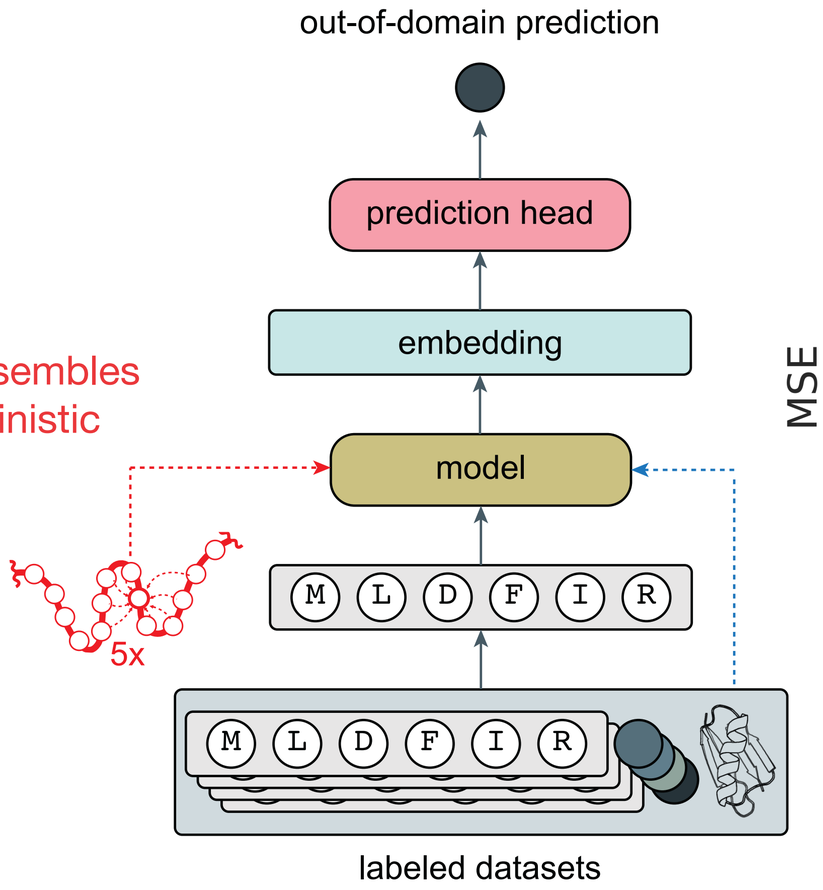
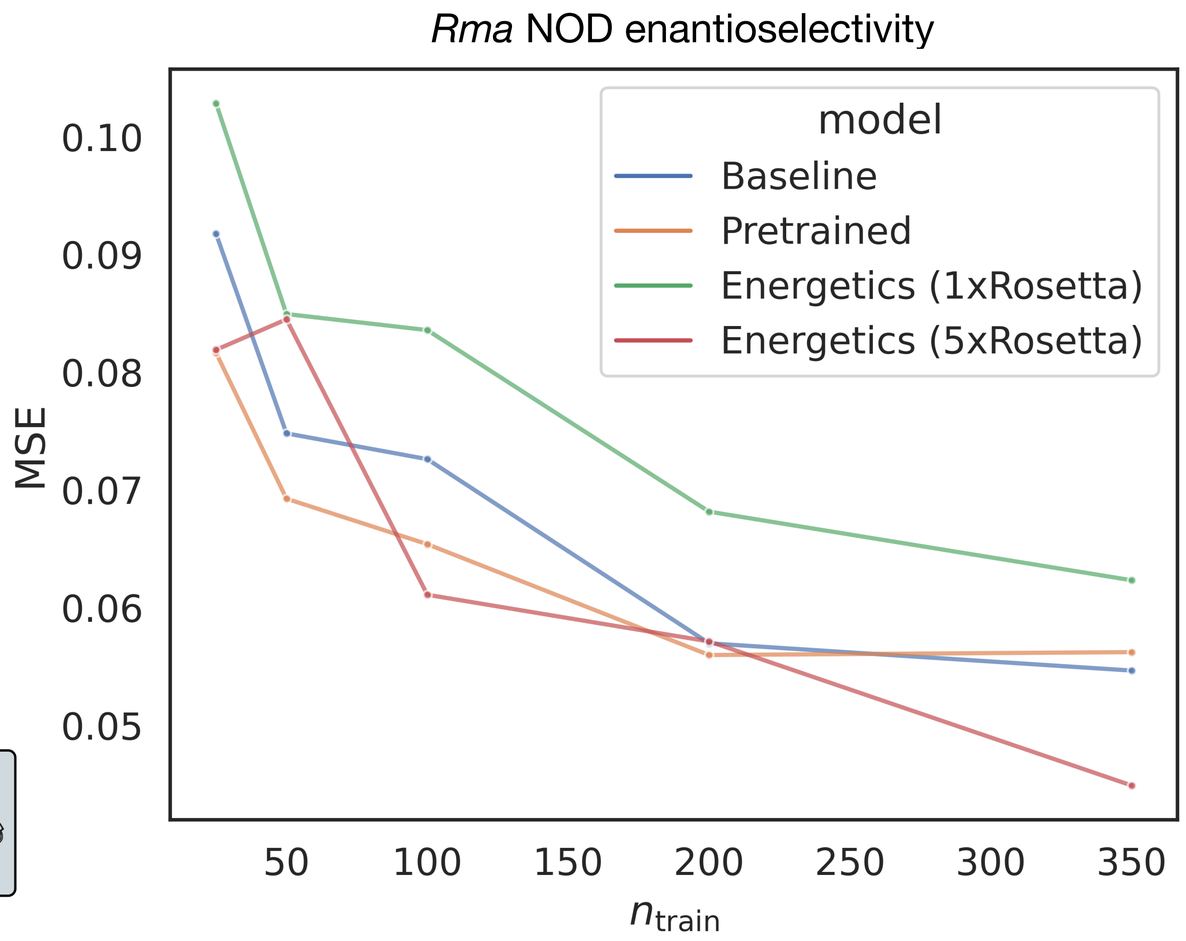
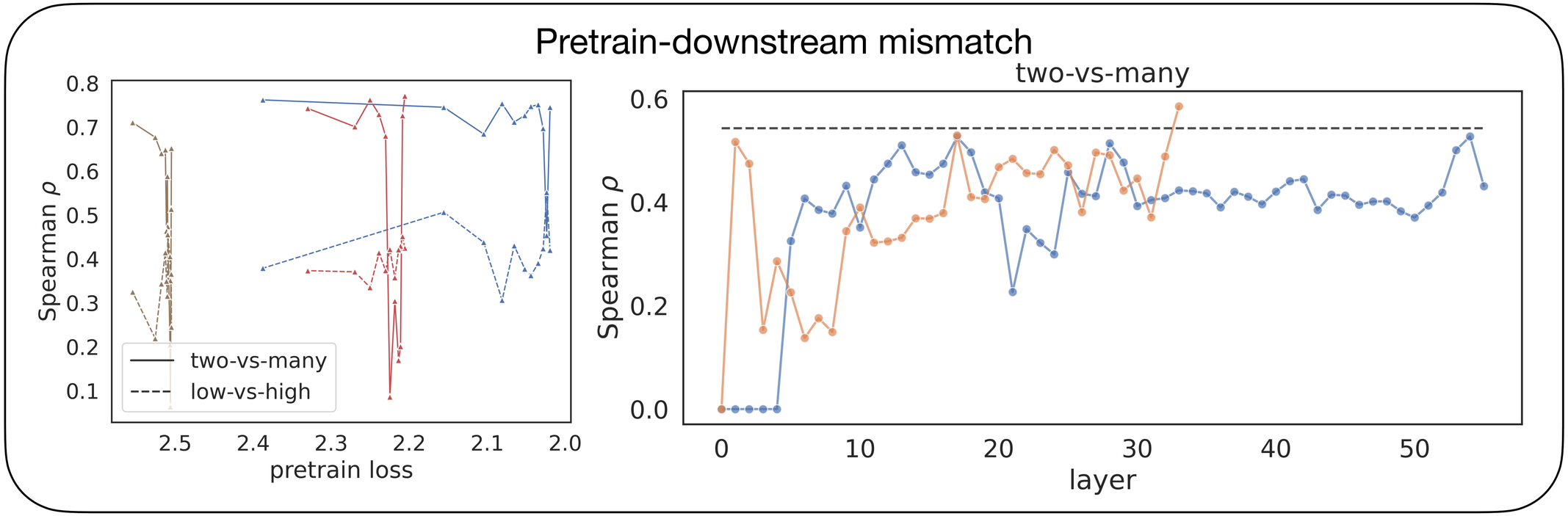
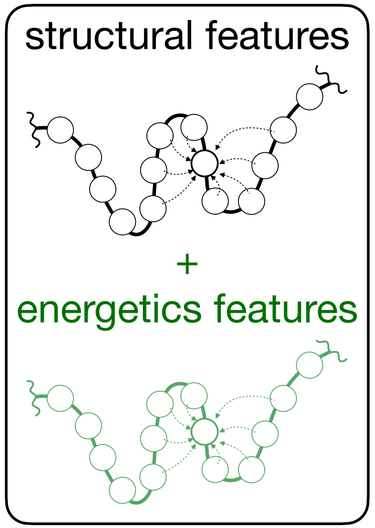


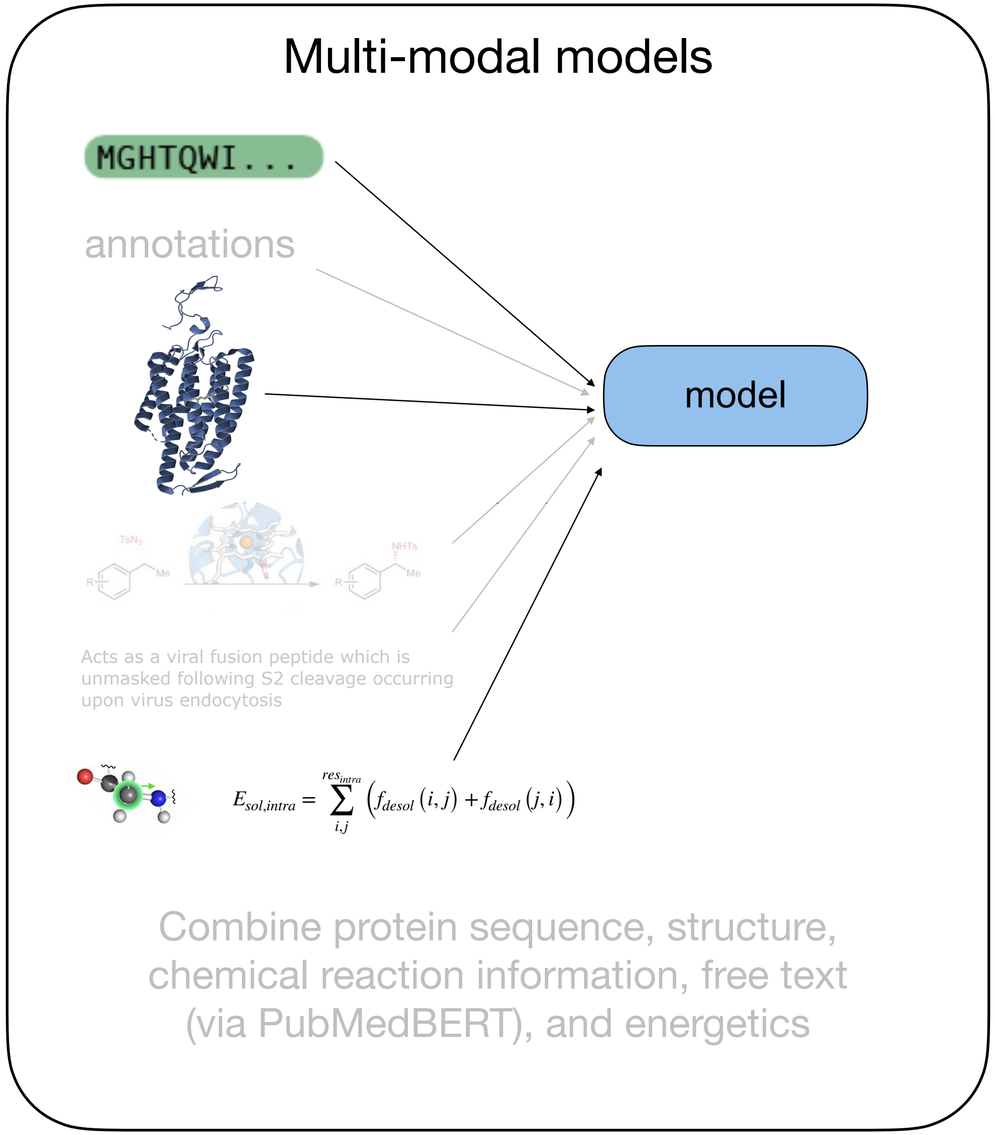


Use energetics and structure to reduce pretrain-downstream mismatch





Can different modalities and pretraining tasks do better?



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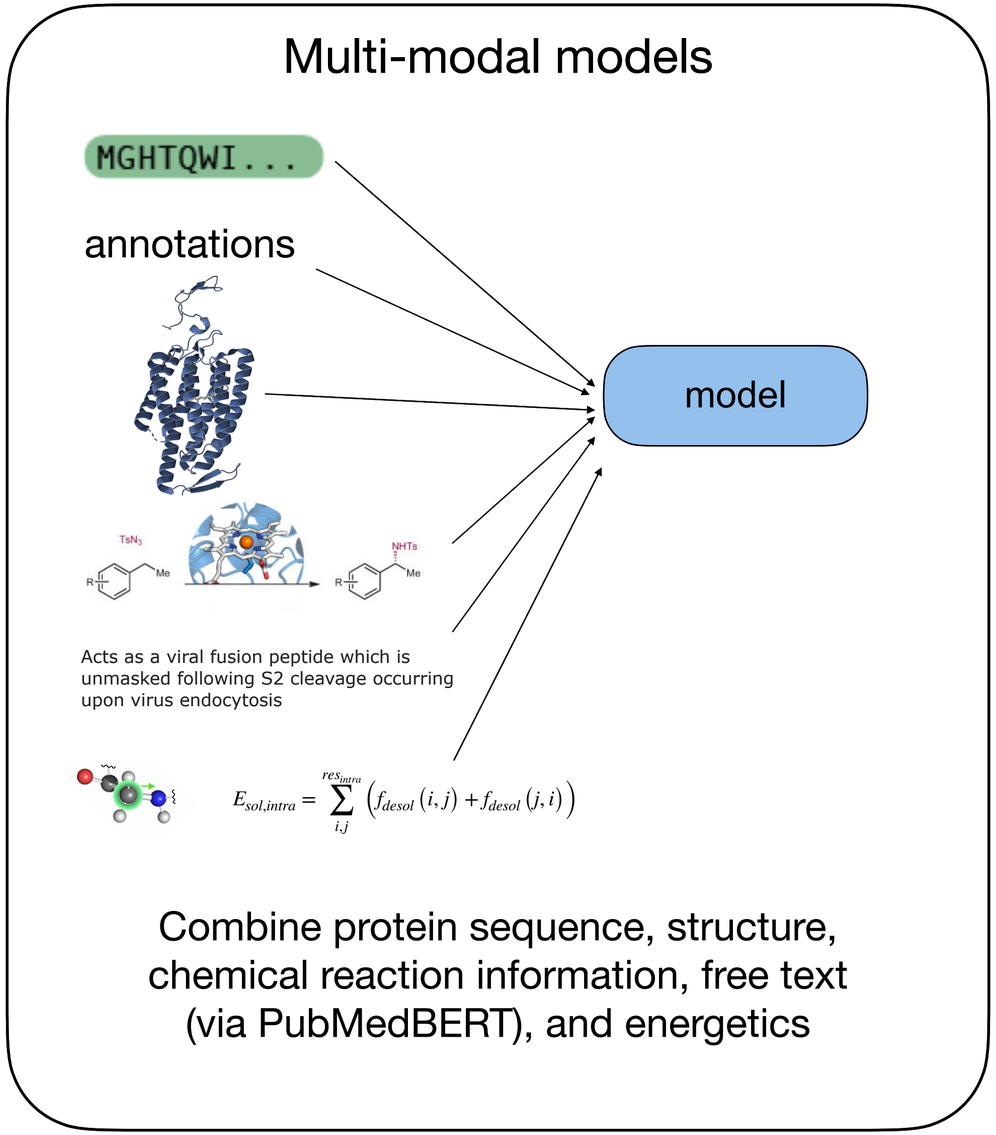
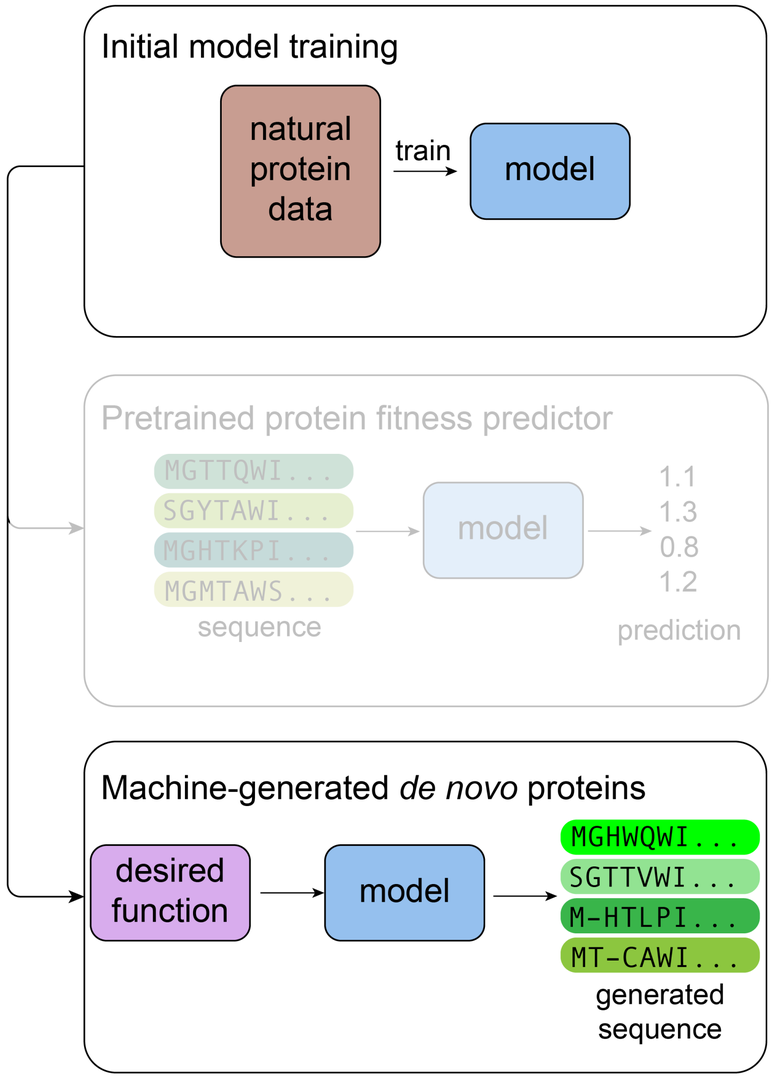
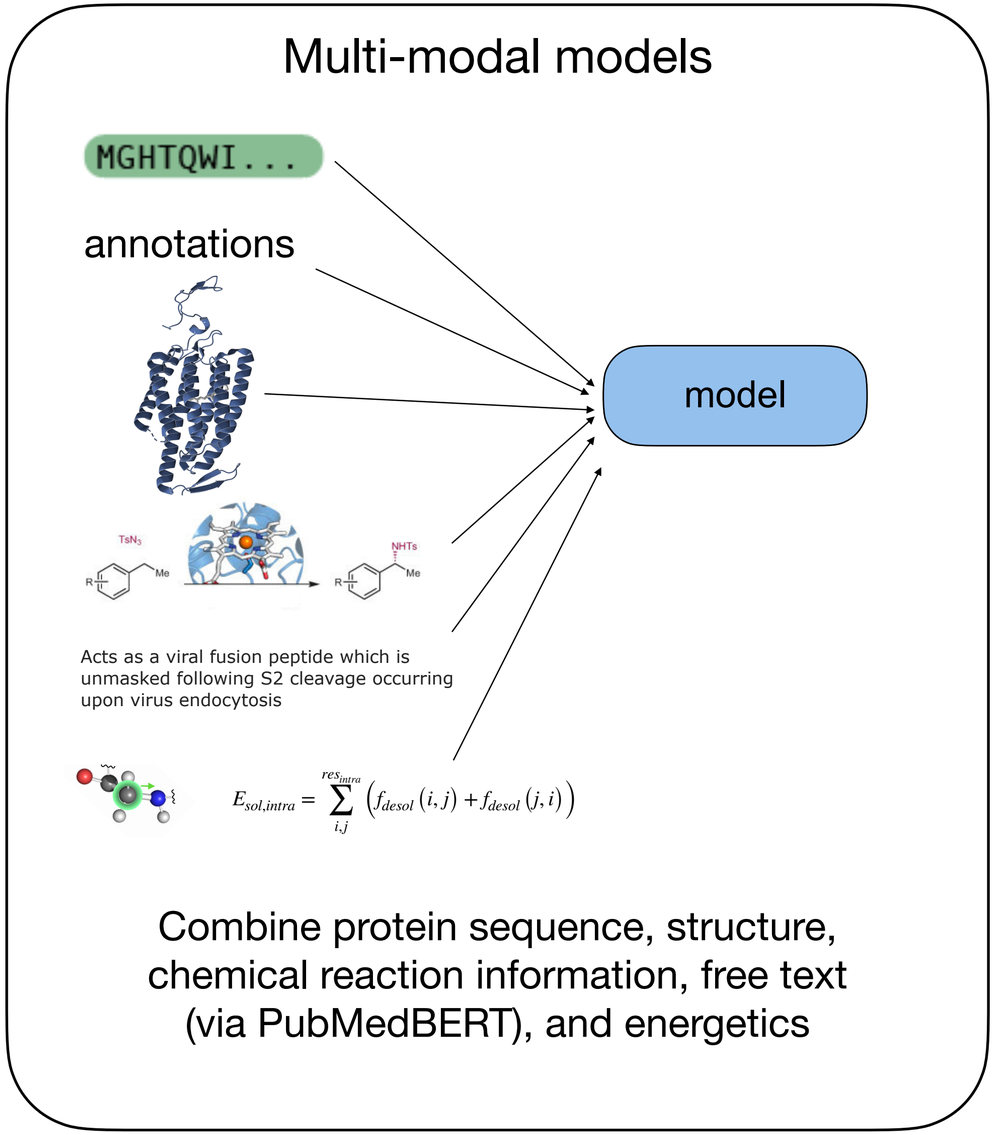


Use multiple data modalities to evaluate proteins





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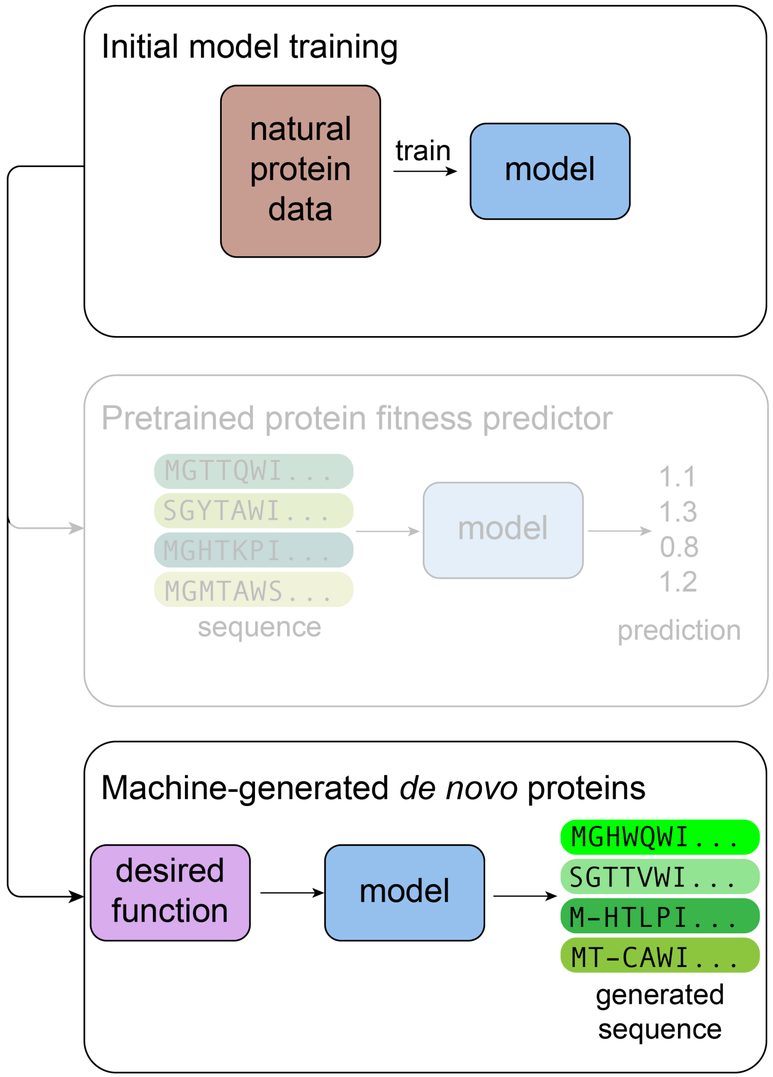

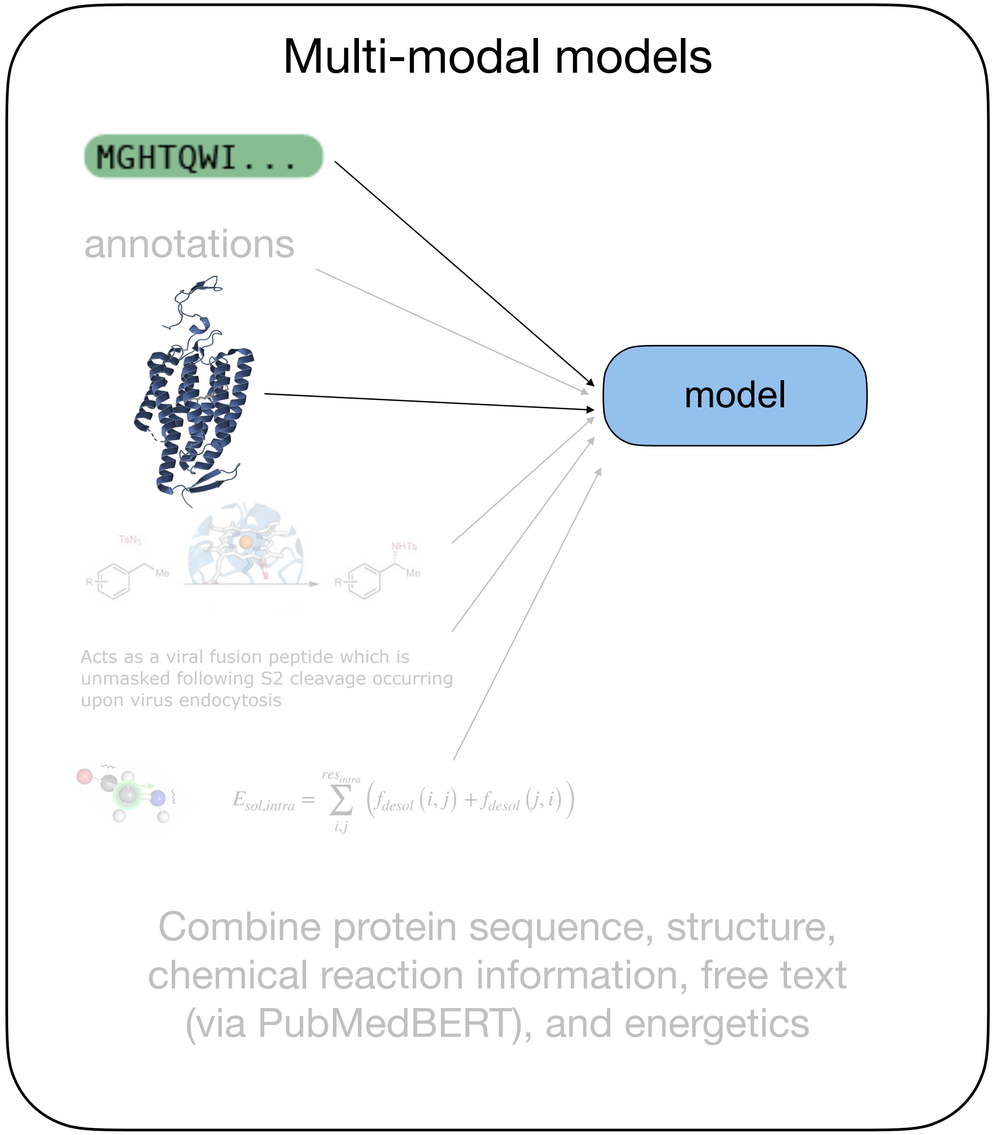

Generative models can expand functional space

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MGTGDHDD...

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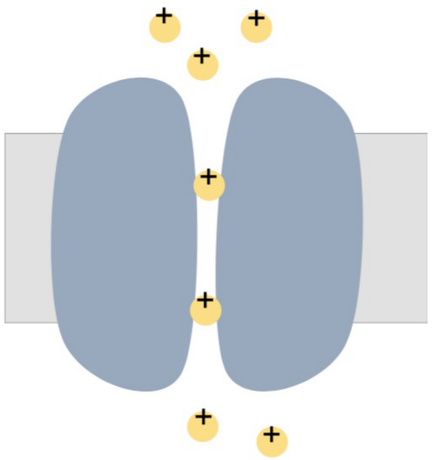

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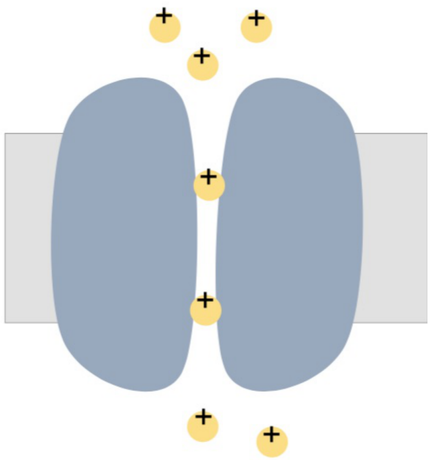

All natural proteins

Members of a protein family

Generative models can expand functional space

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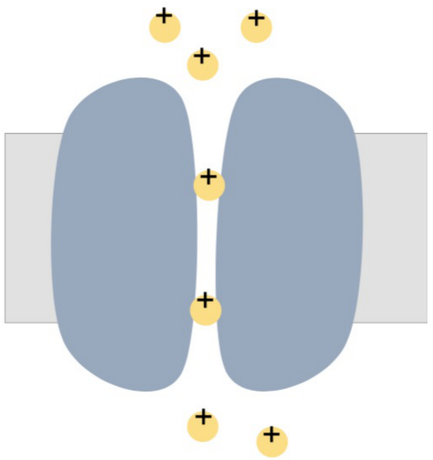

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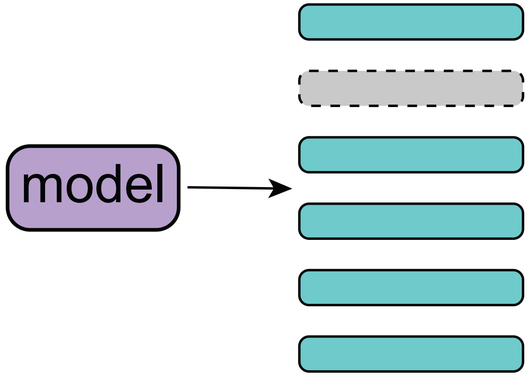

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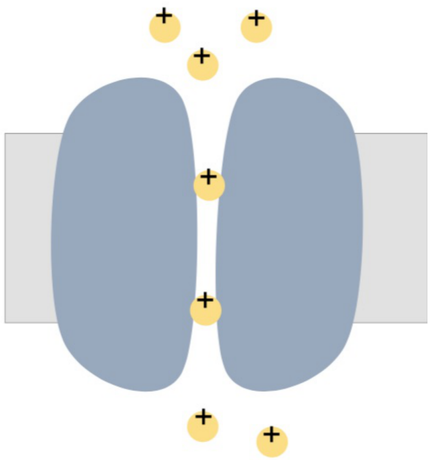

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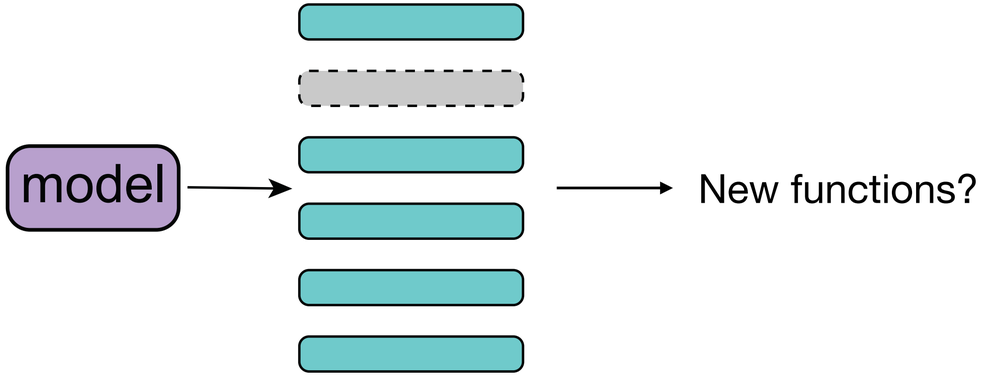

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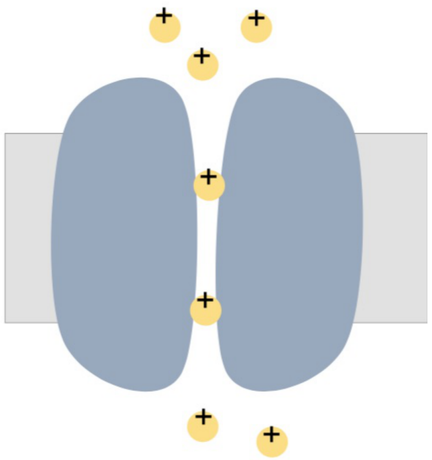

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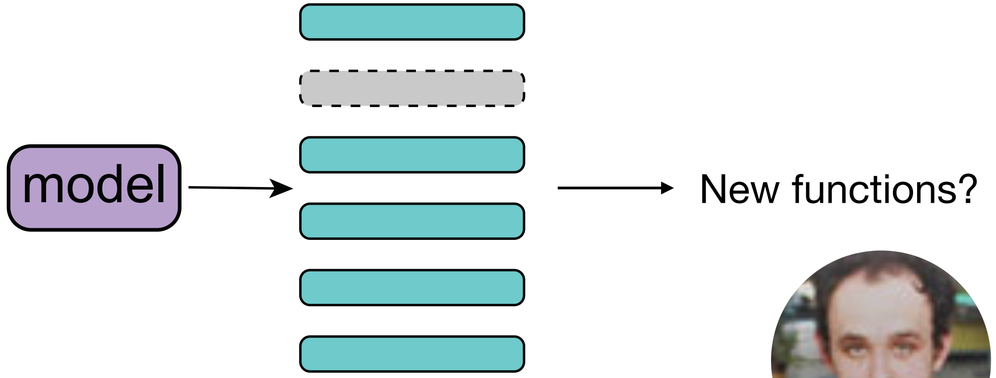
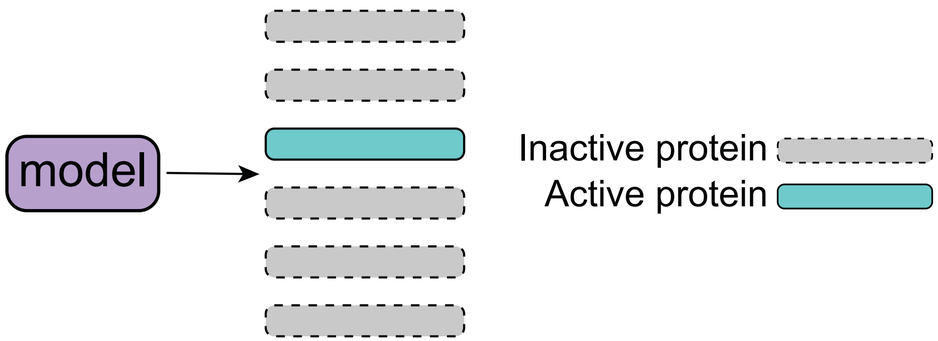


Most generated sequences are inactive



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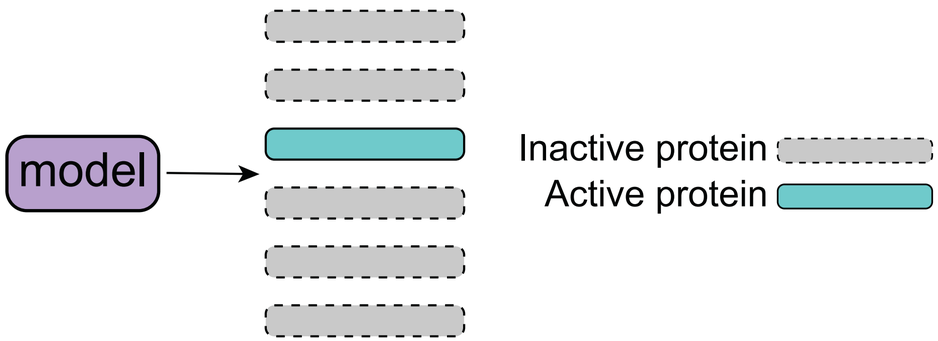
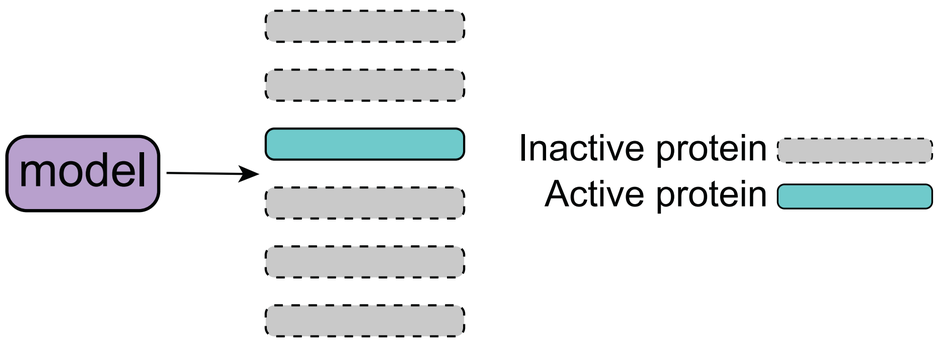


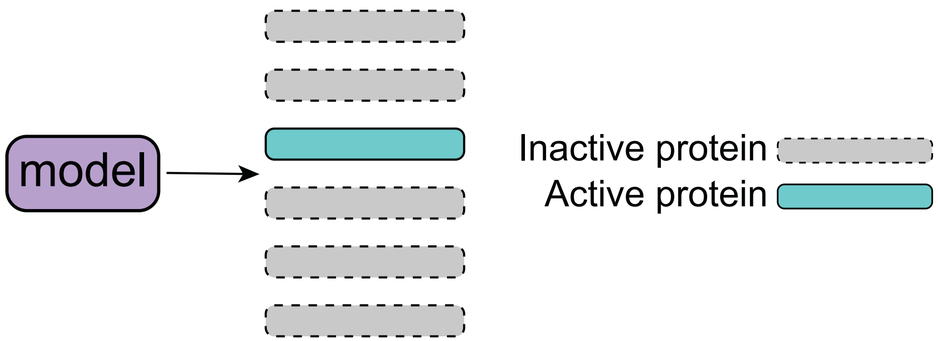
Model
GAN
ESM-MSA
Total

Most generated sequences are inactive



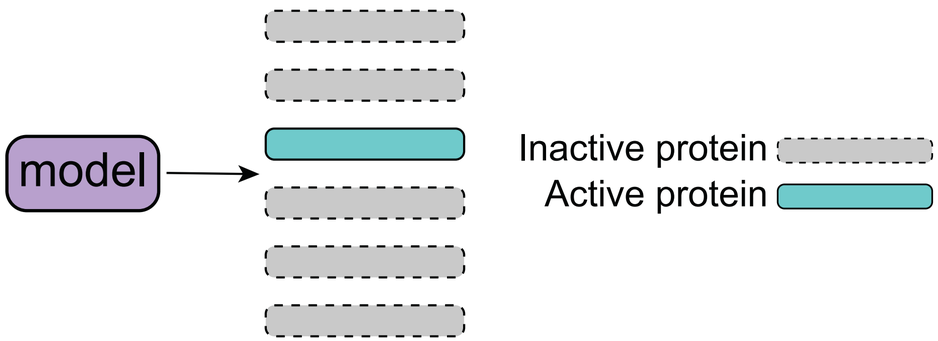
Model	Enzyme
GAN	MDH
	CuSOD
ESM-MSA	MDH
	CuSOD
Total	

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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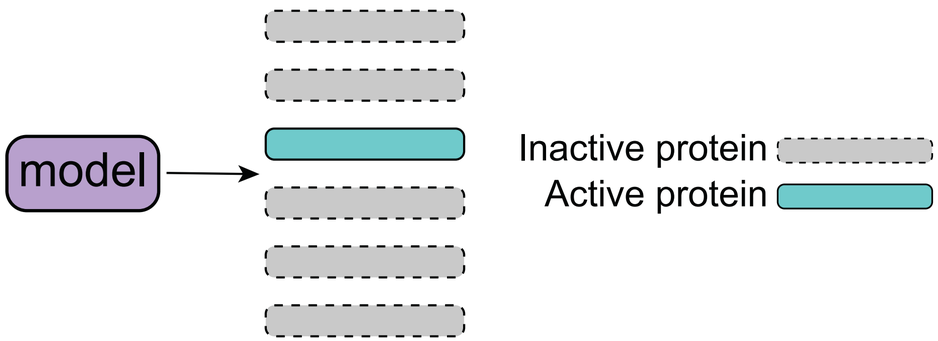

- Destabilized
- Mismatched signal peptide

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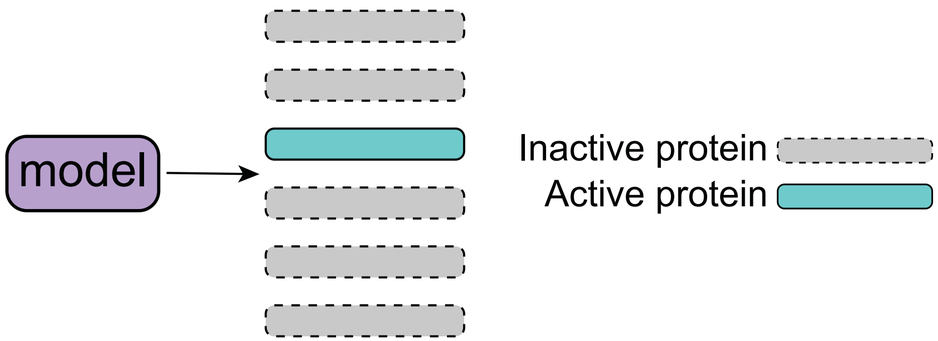
ESM-MSA	MDH	0 / 17
	CuSOD	0 / 18
Total		2 / 71

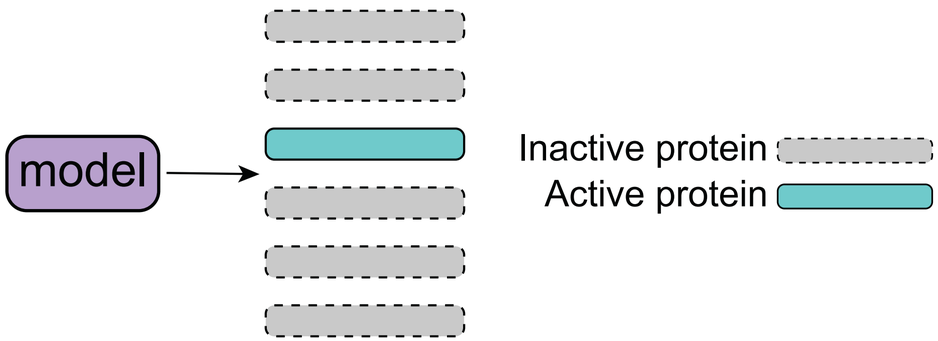
Most generated sequences are inactive



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

- Destabilized
- Mismatched signal peptide
- Transmembrane domain

Most generated sequences are inactive



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ESM-MSA	MDH	0 / 17
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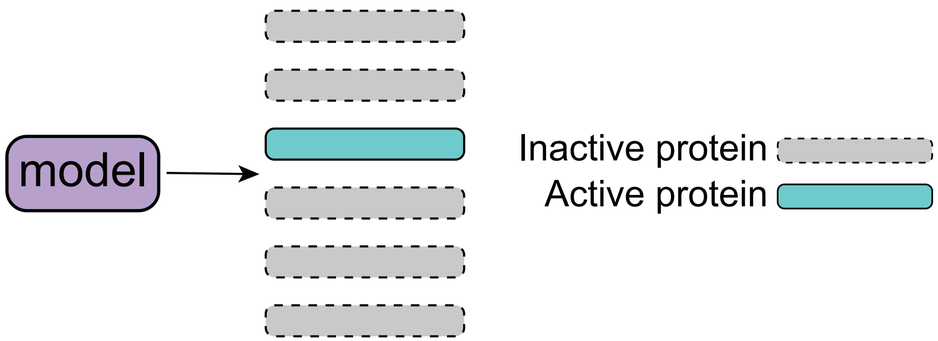
Total		2 / 71

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

Most generated sequences are inactive



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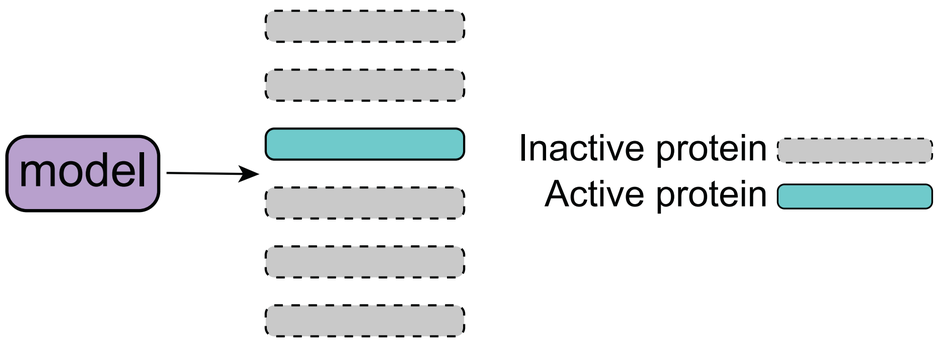
Total		2 / 71

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

Most generated sequences are inactive



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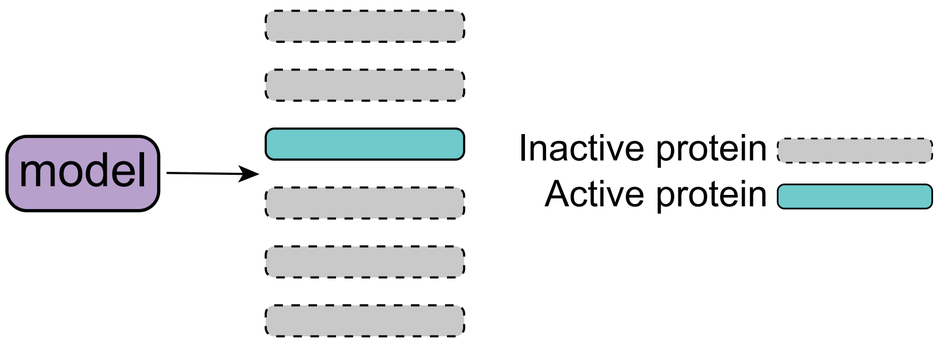

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ESM-MSA	MDH	0 / 17
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Total		2 / 71

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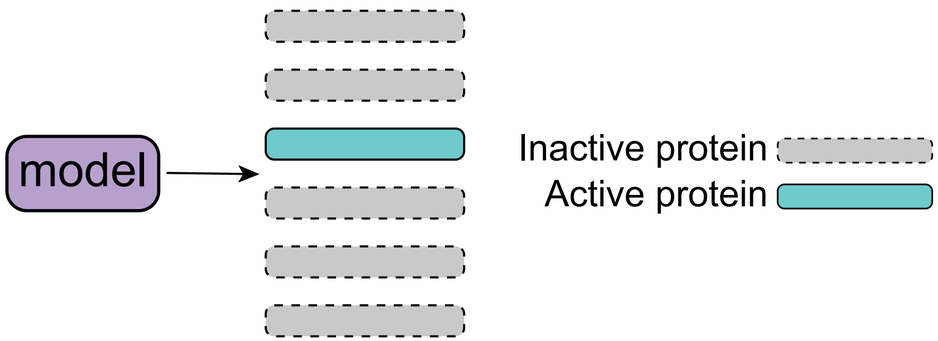
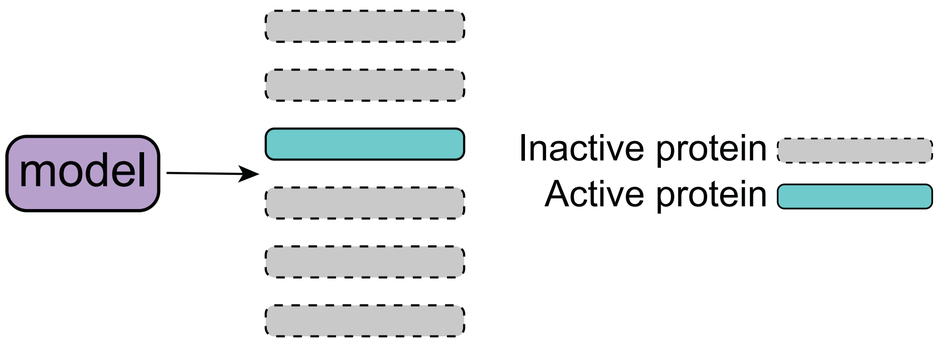


Model	Enzyme	Naive	Checks
GAN	MDH	0 / 18	2 / 18
	CuSOD	2 / 18	12 / 18
ESM-MSA	MDH	0 / 17	9 / 18
	CuSOD	0 / 18	12 / 18
Total		2 / 71	35 / 72

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

Most generated sequences are inactive



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

- Destabilized
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- Transmembrane domain
- Long repeats
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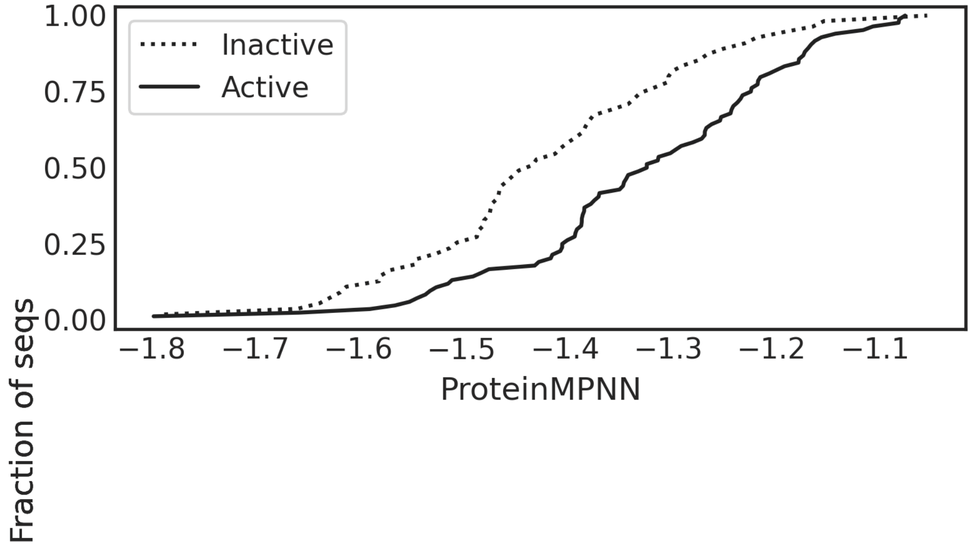
- …

How can we do a better job selecting sequences?

Choose metrics that are predictive, fast, and uncorrelated



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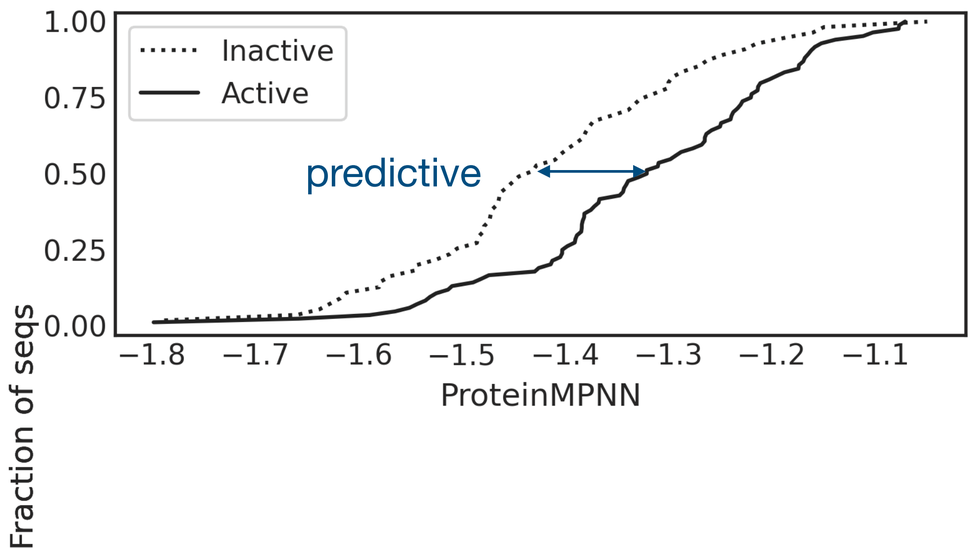

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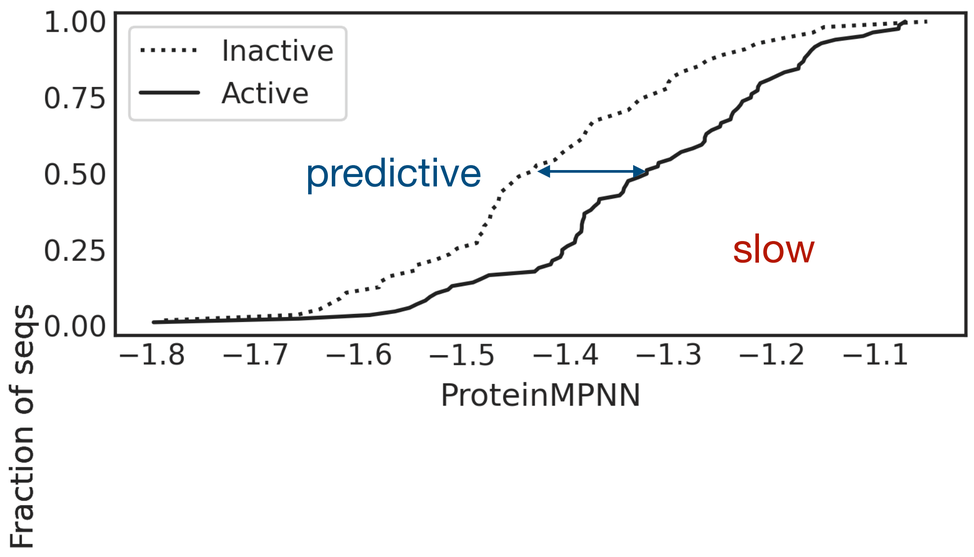

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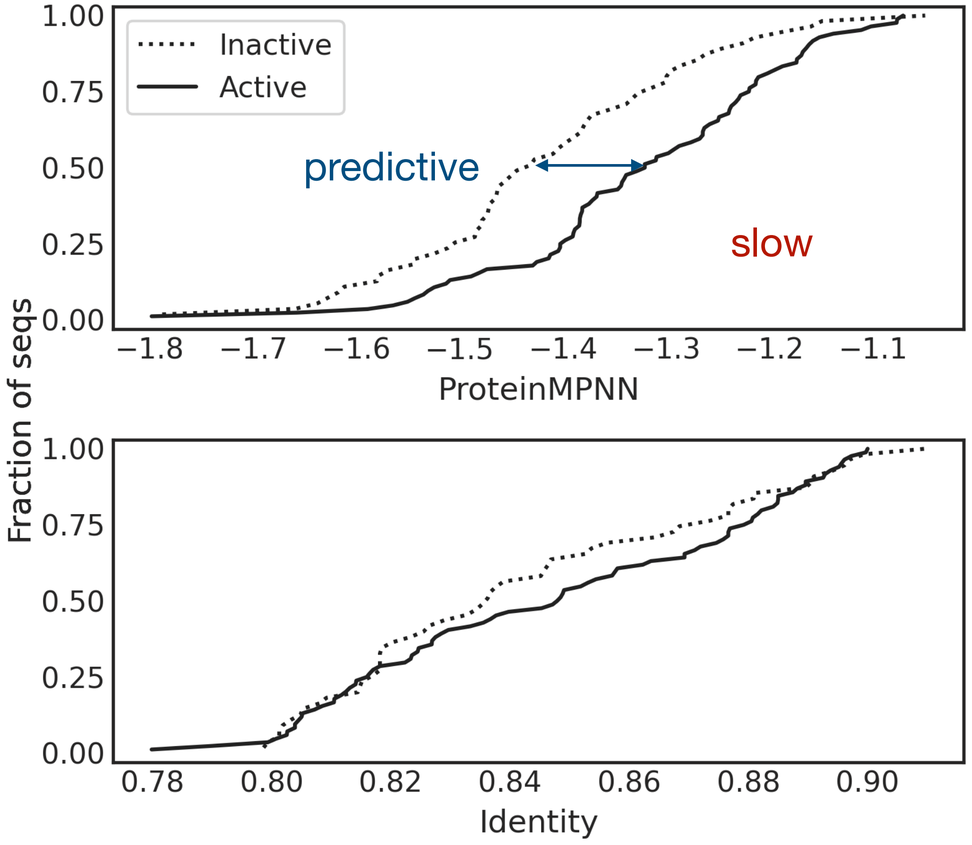

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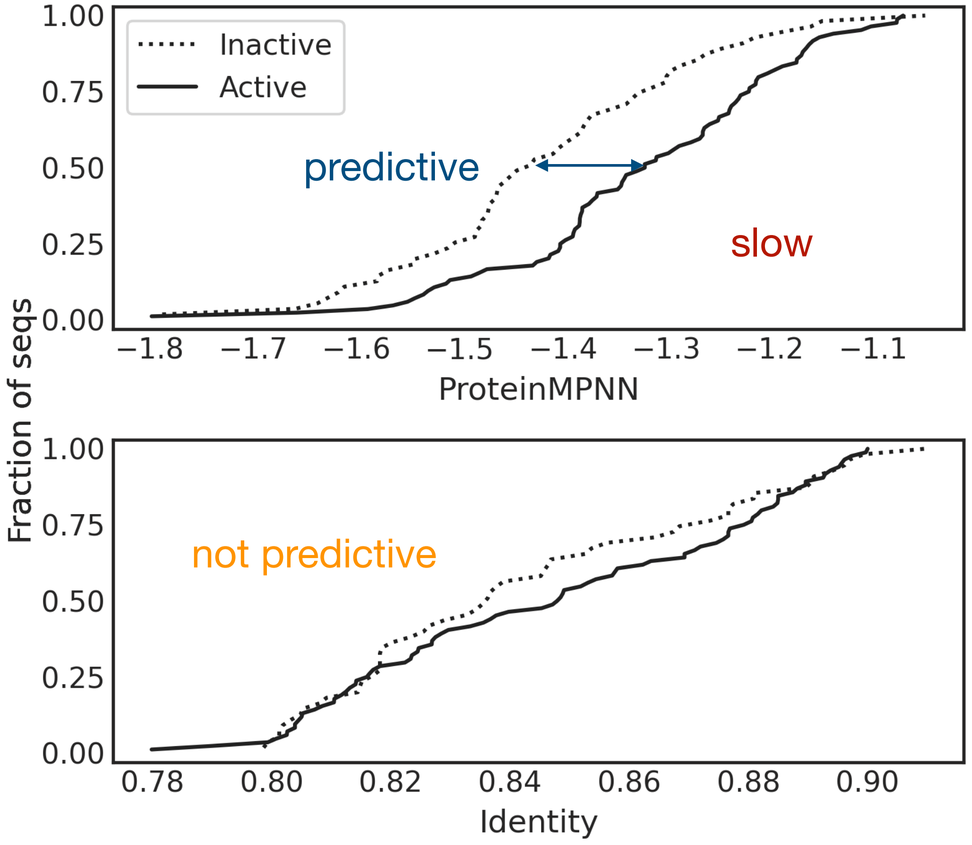

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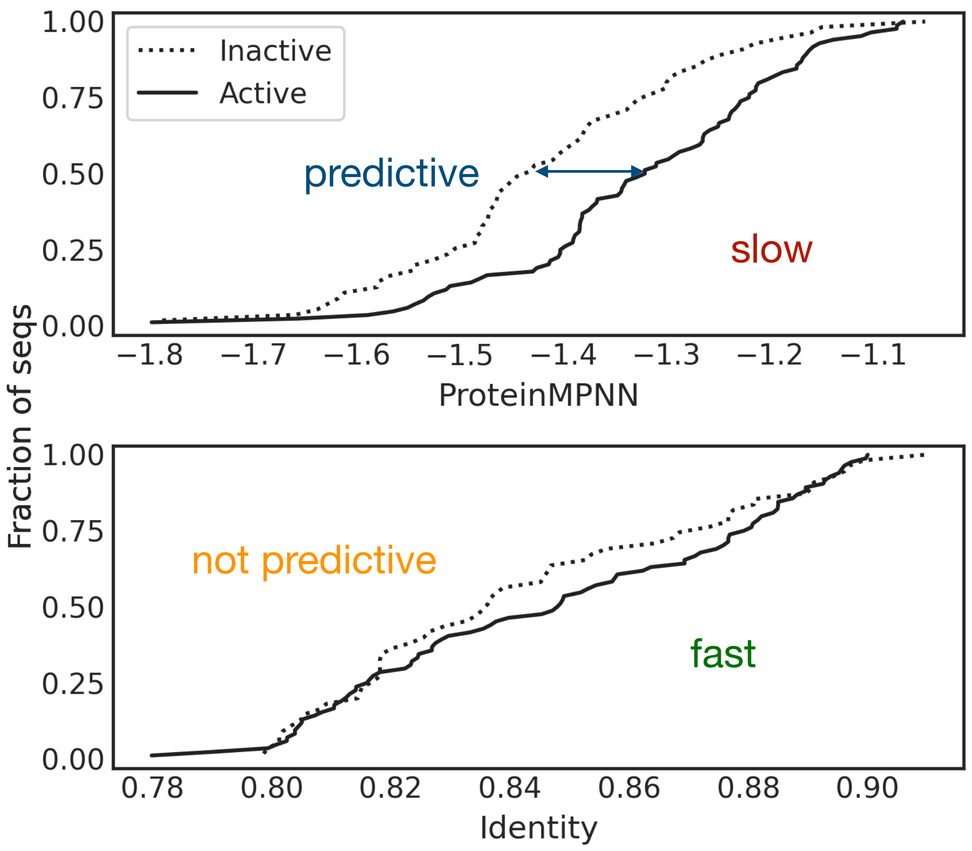
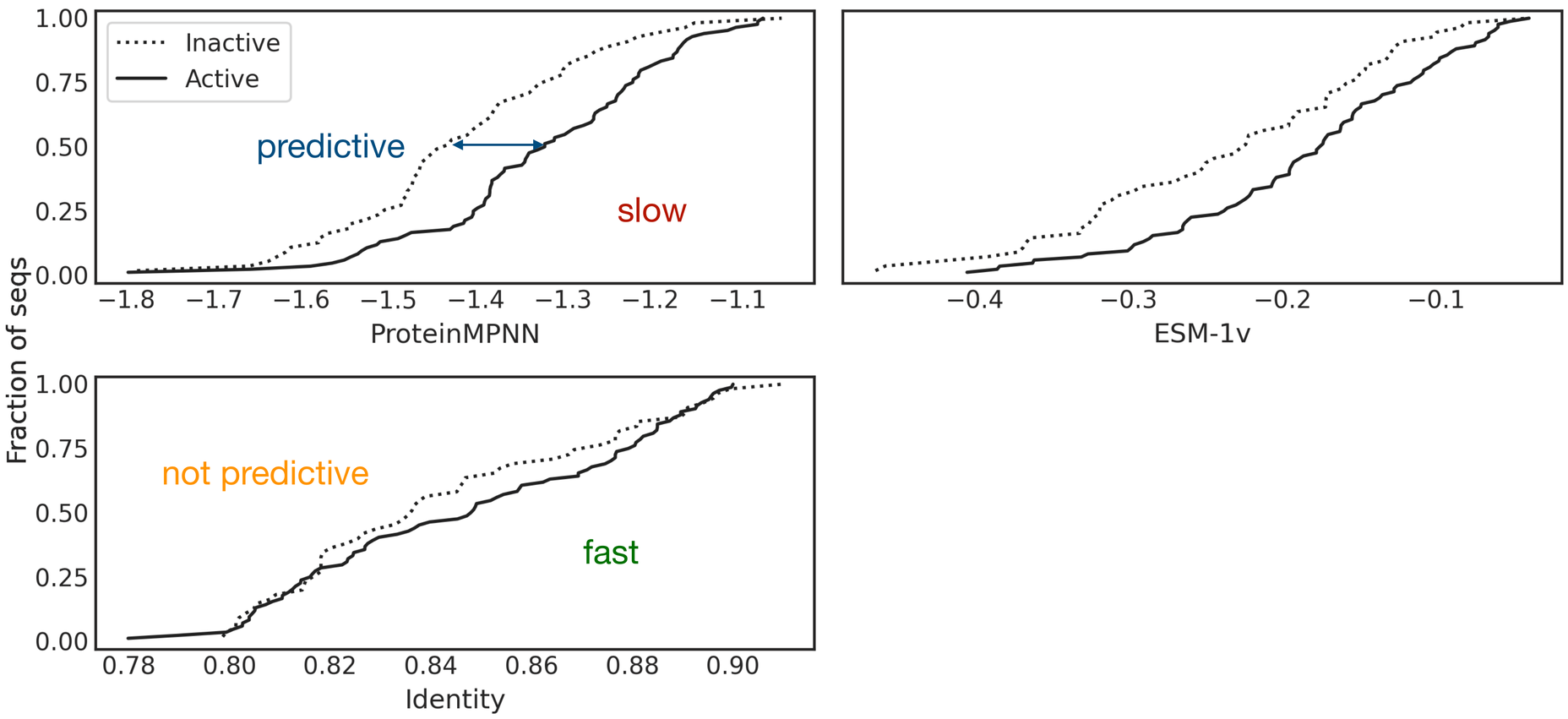


Choose metrics that are predictive, fast, and uncorrelated



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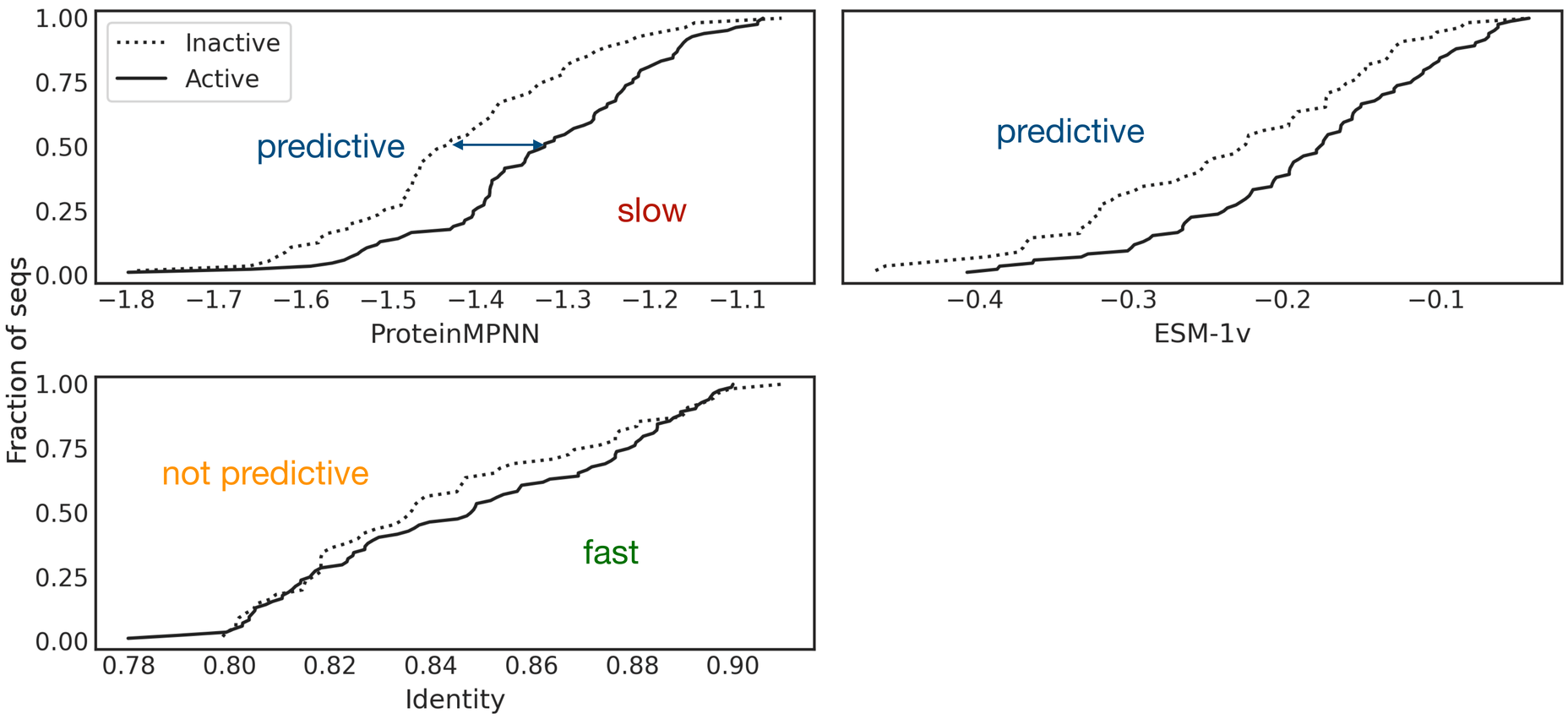

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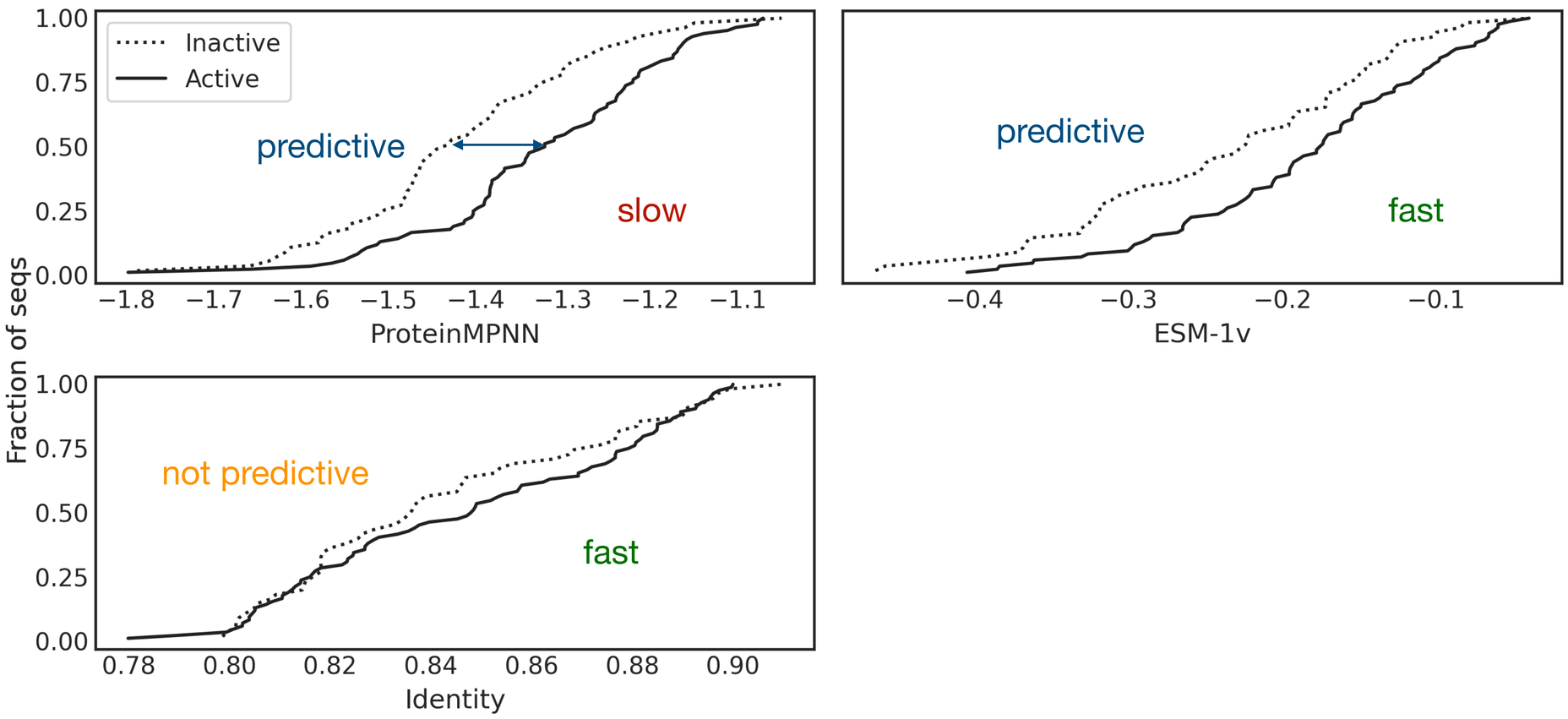

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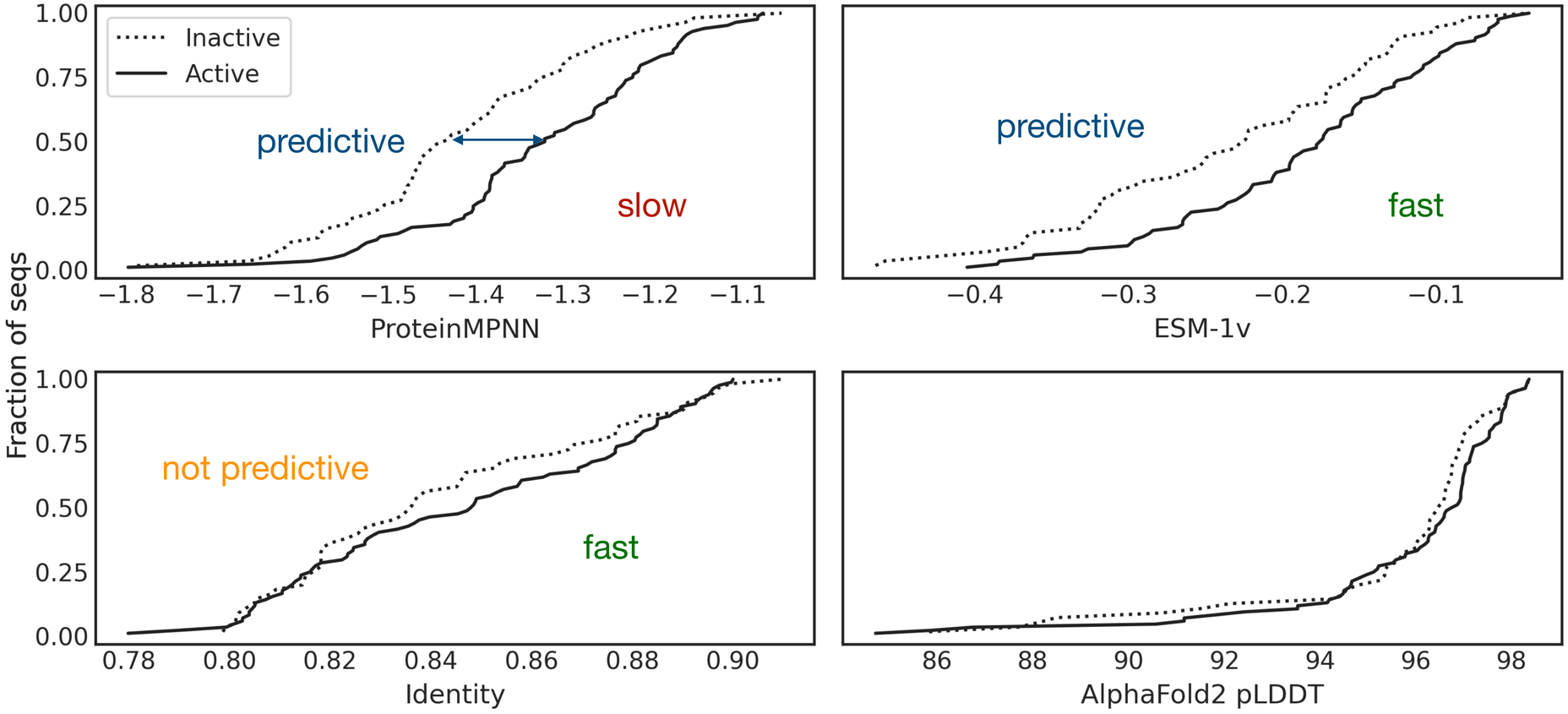

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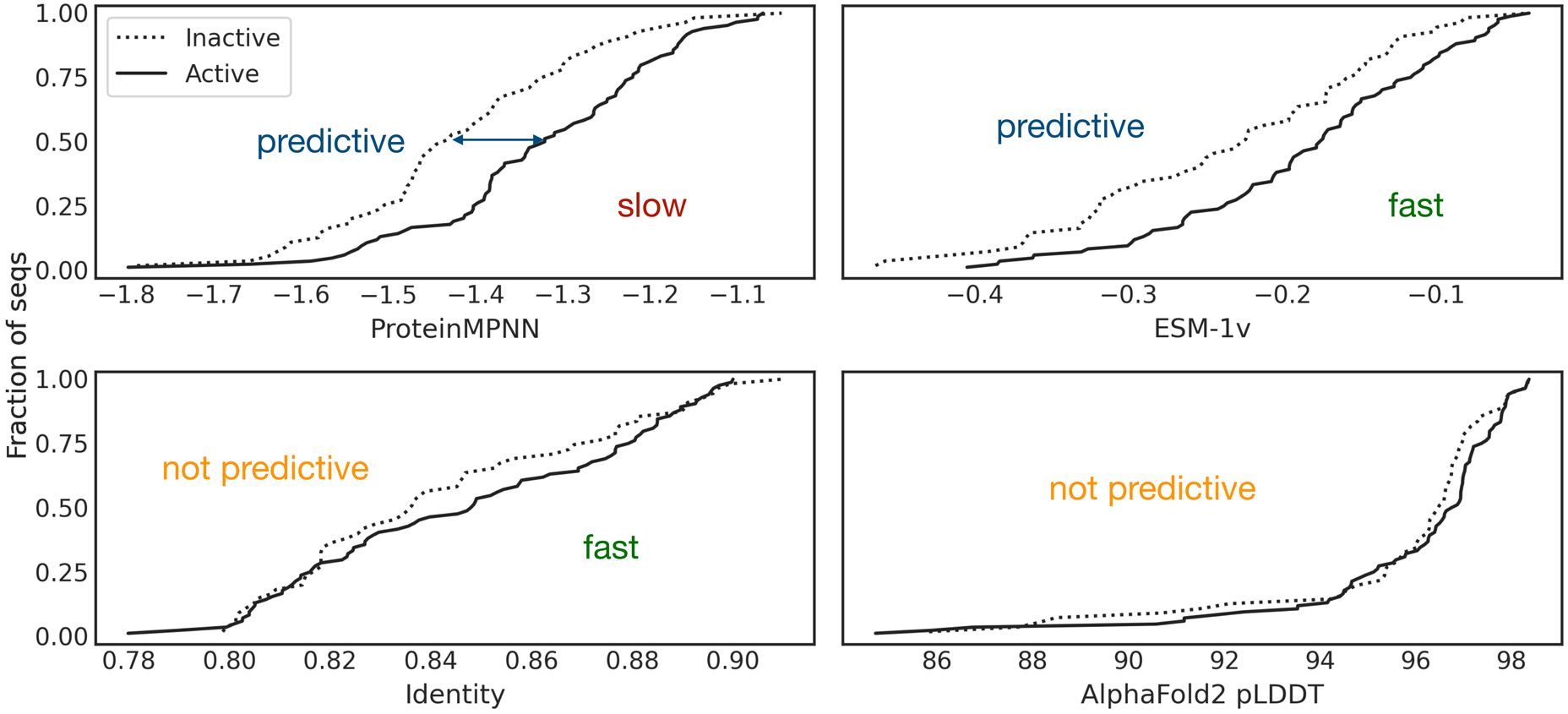

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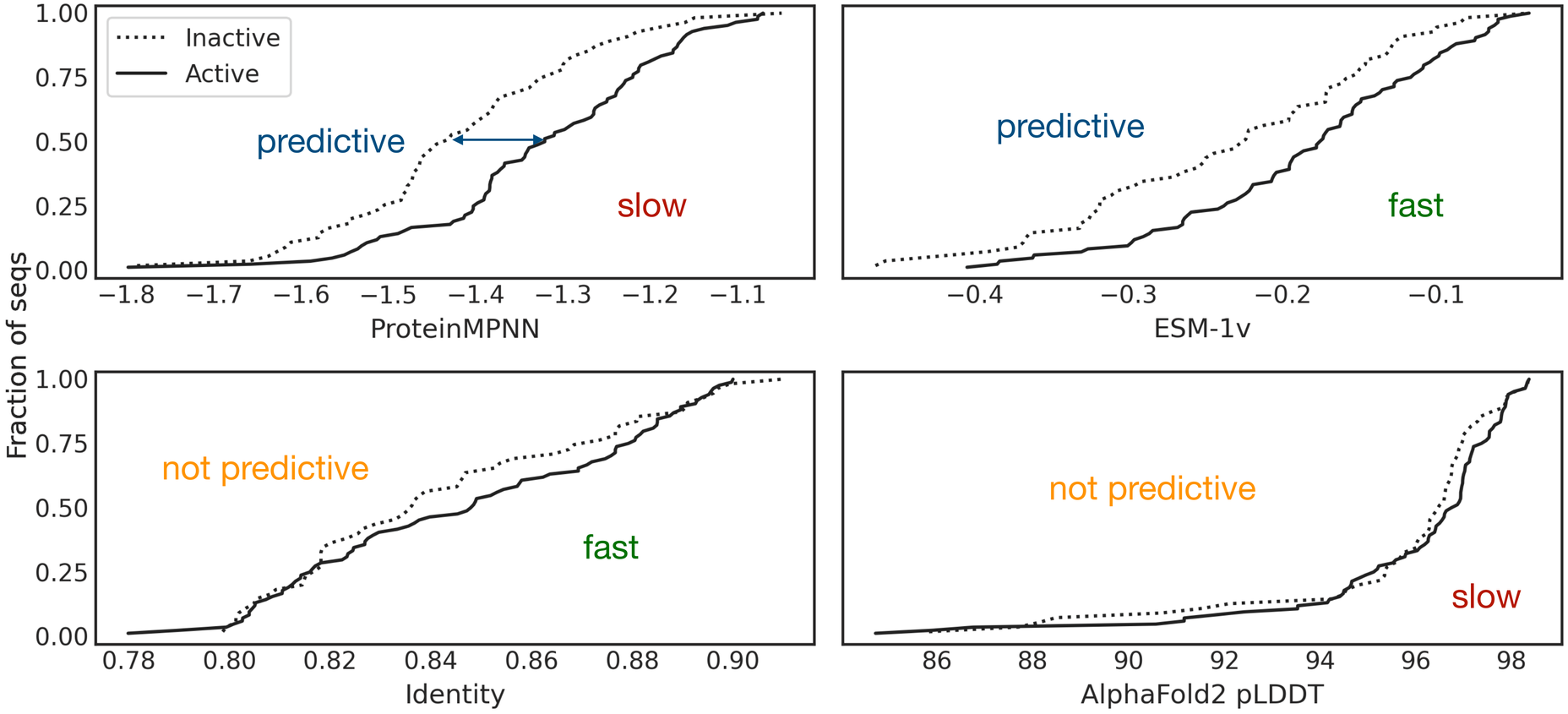

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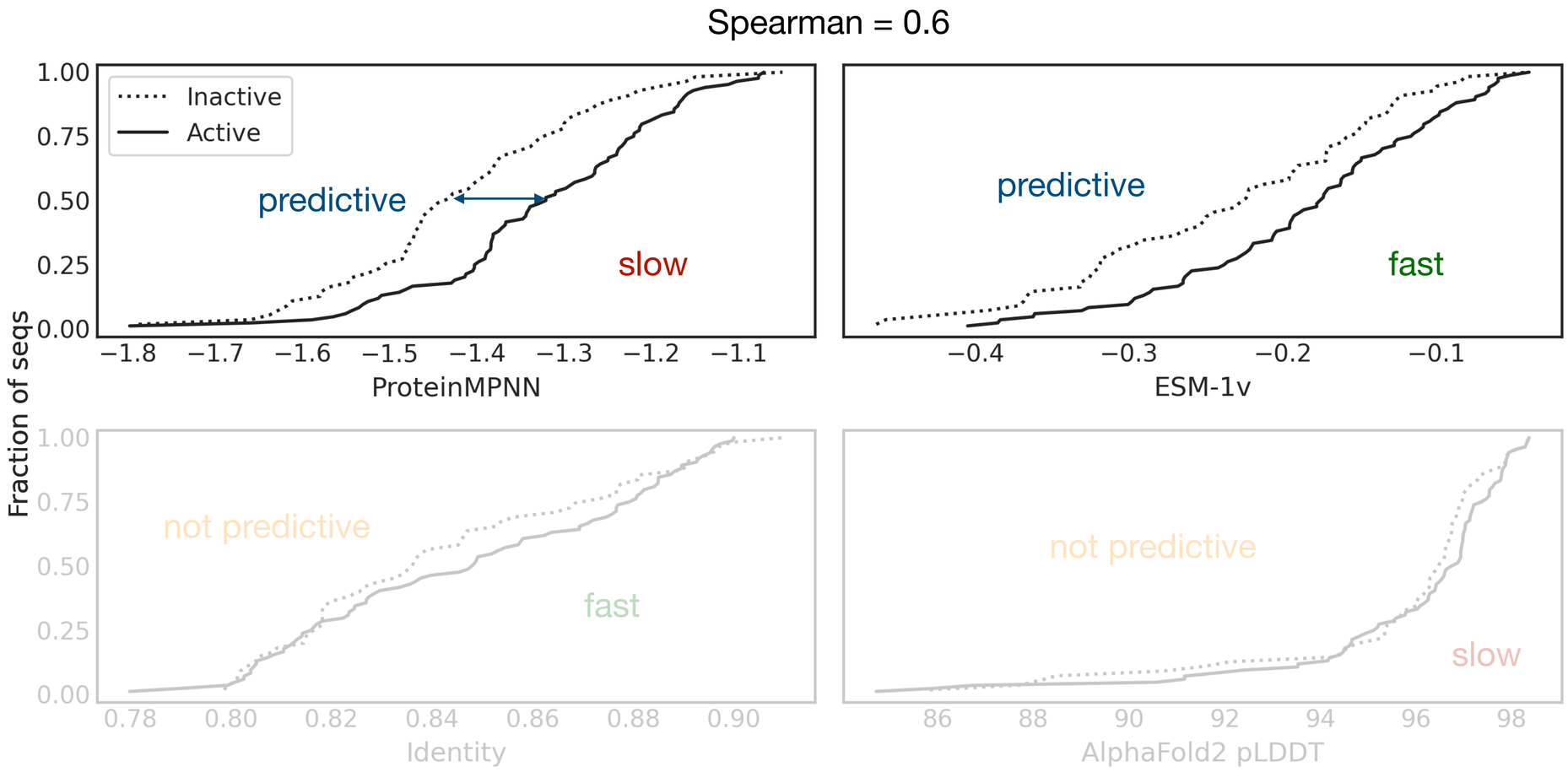
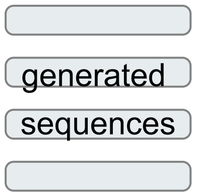


Combine many models into a filtering pipeline



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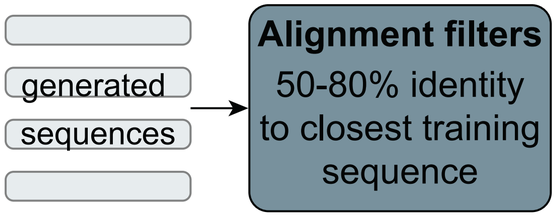

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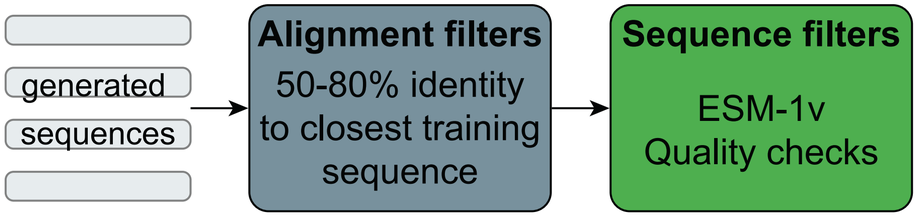

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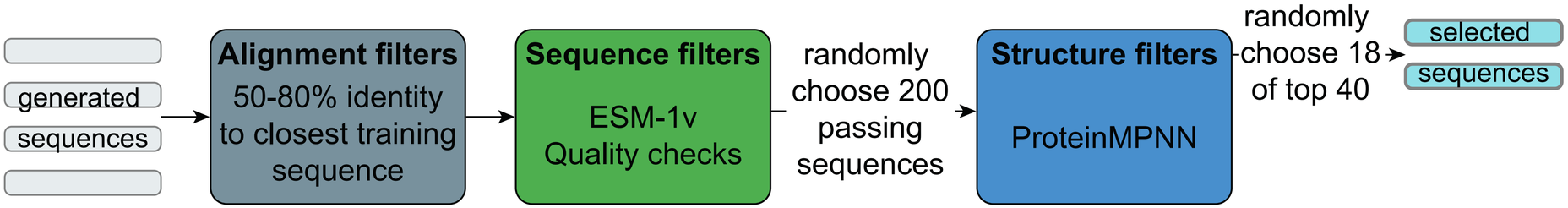

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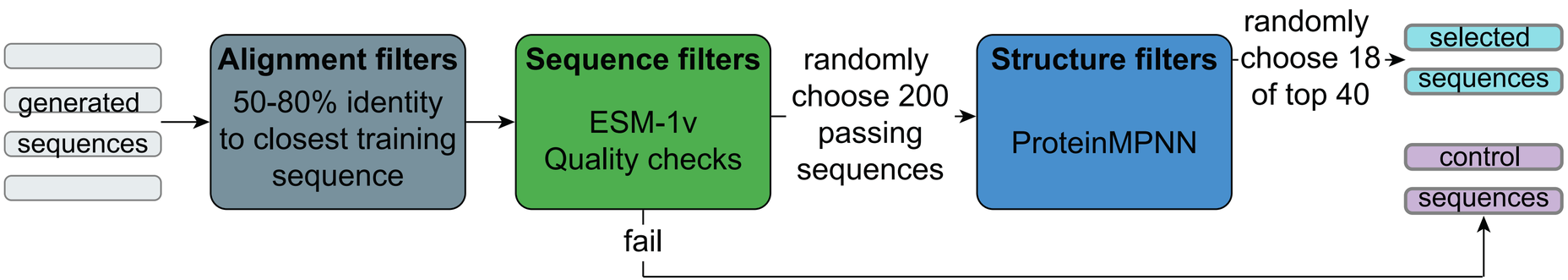
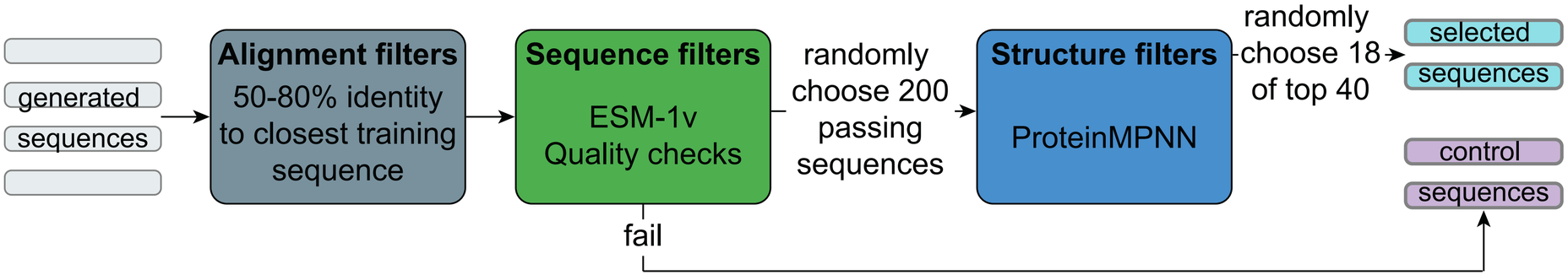
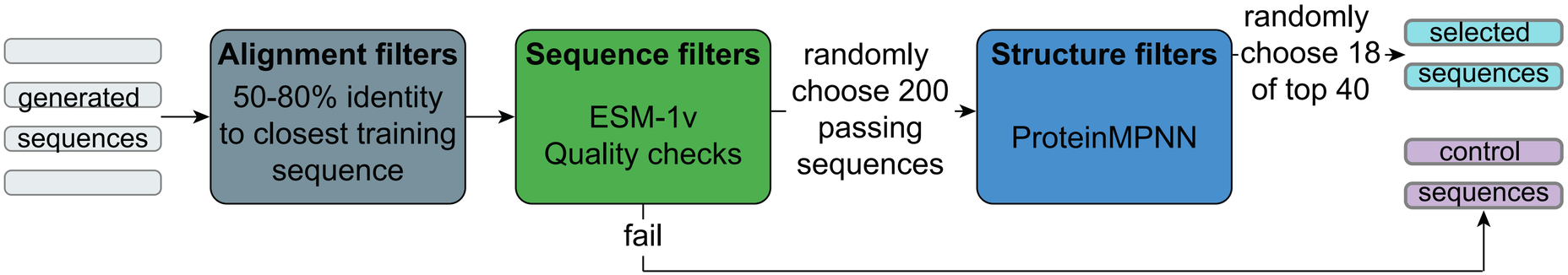


Pipeline increases number of active variants found



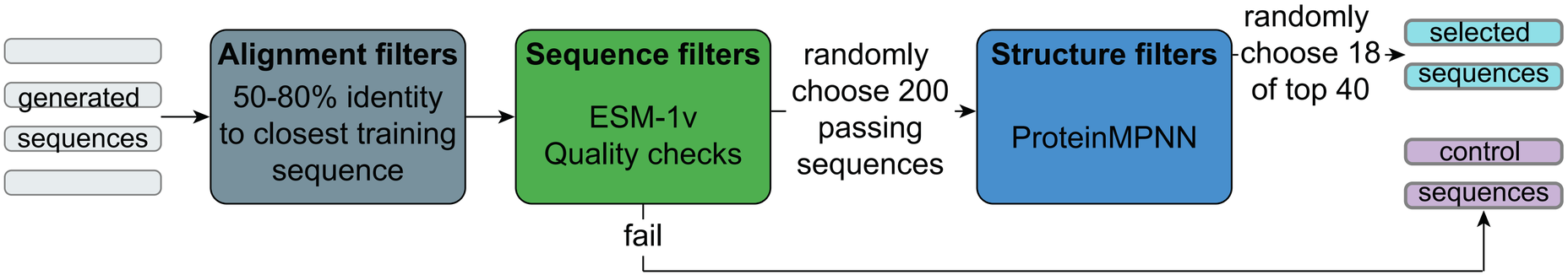
	Naive	Checks
Active	2 / 71	35 / 72

Pipeline increases number of active variants found



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

Pipeline increases number of active variants found



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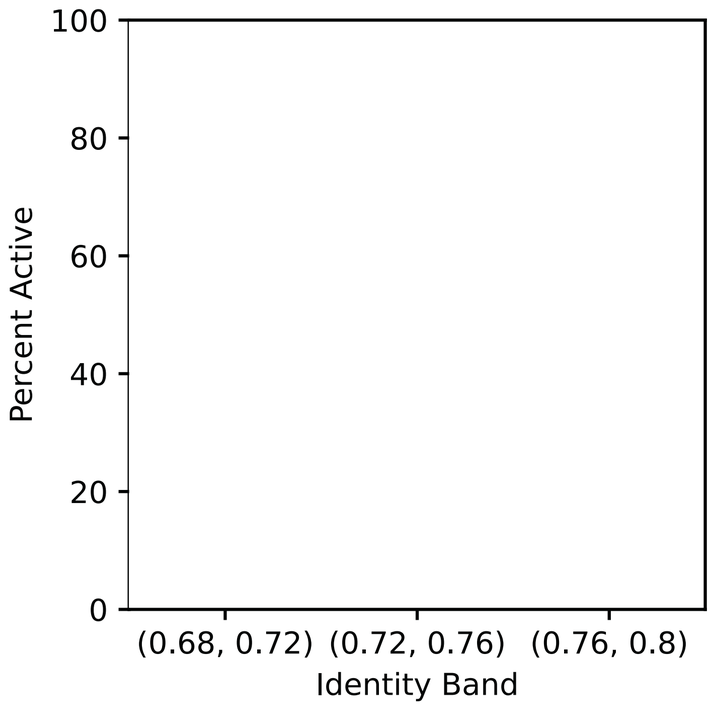

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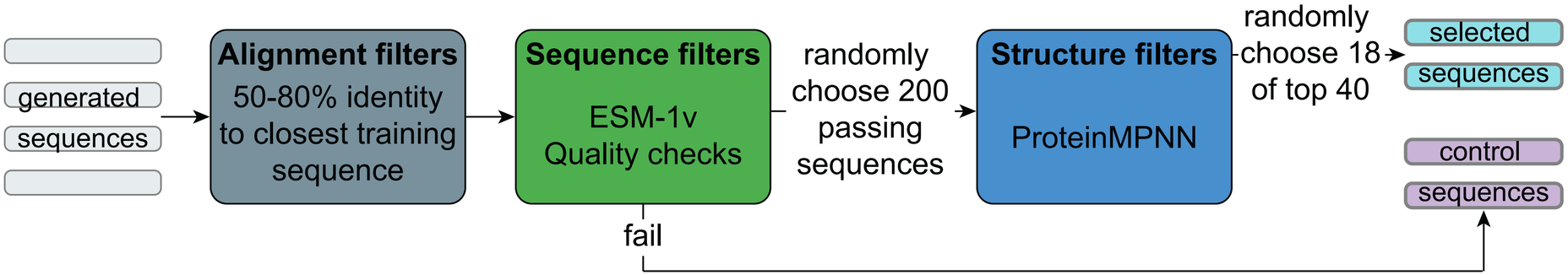

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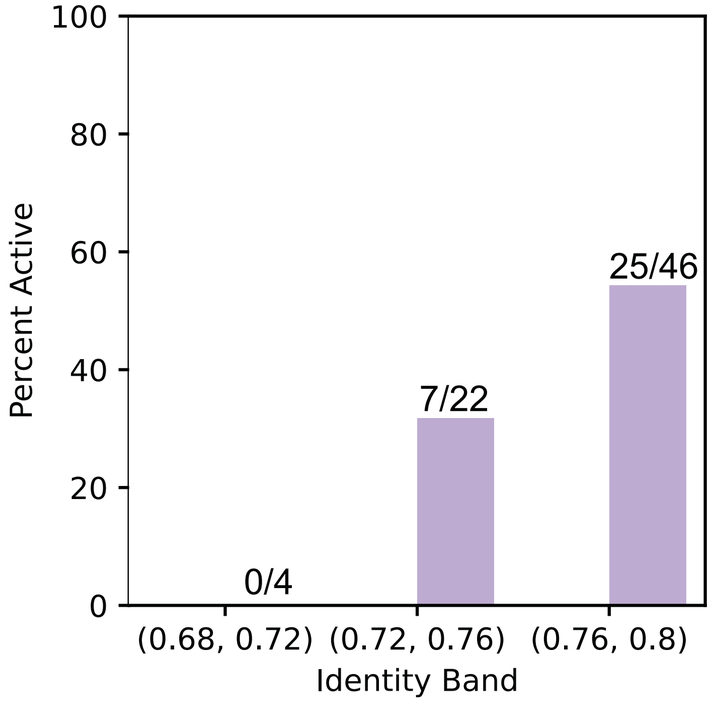

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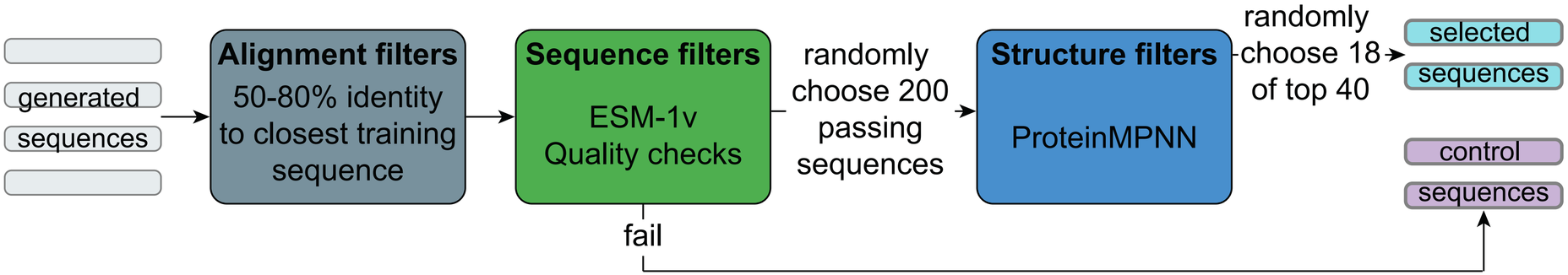
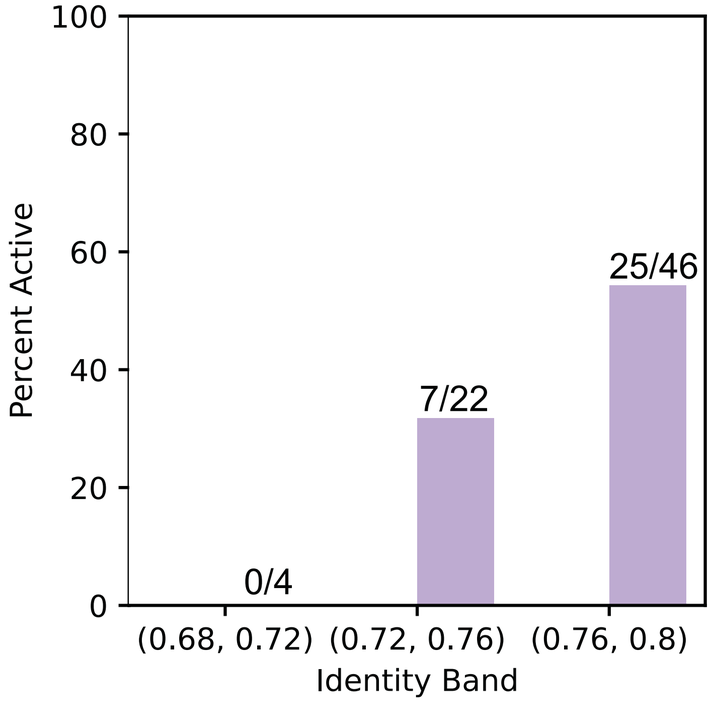


	Naive	Checks	Control	Selected
Active	2 / 71	35 / 72	32 / 72	52 / 72



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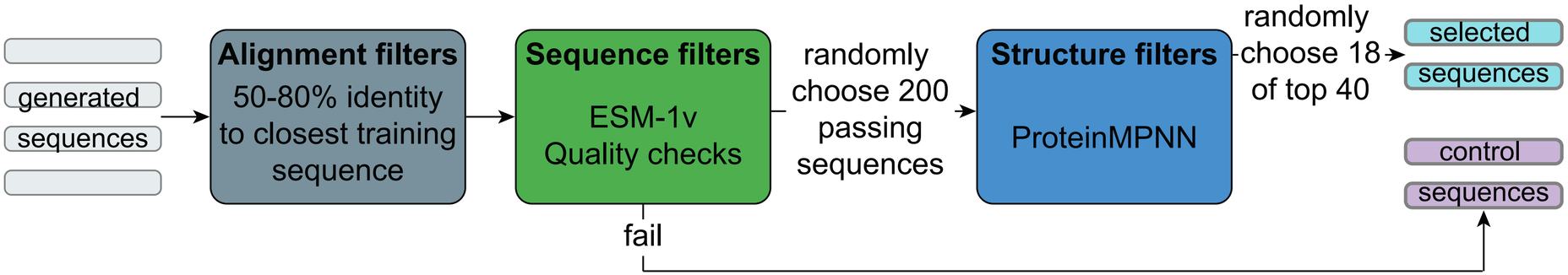

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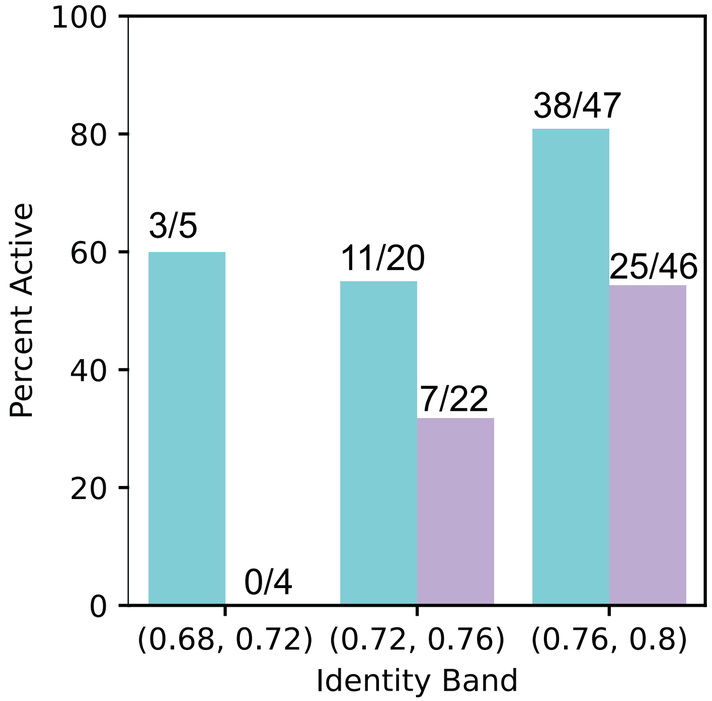
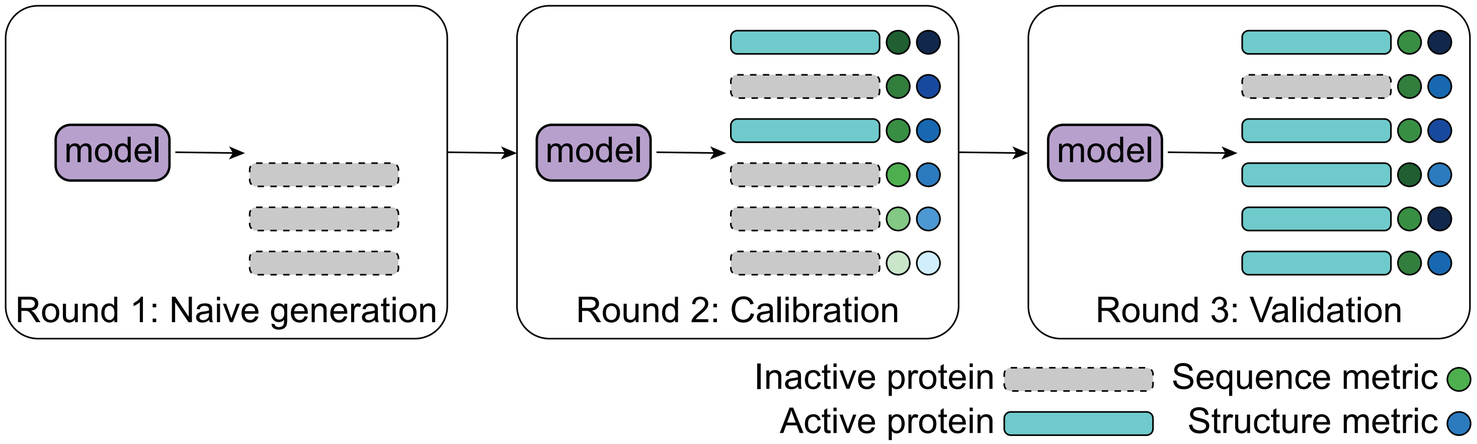
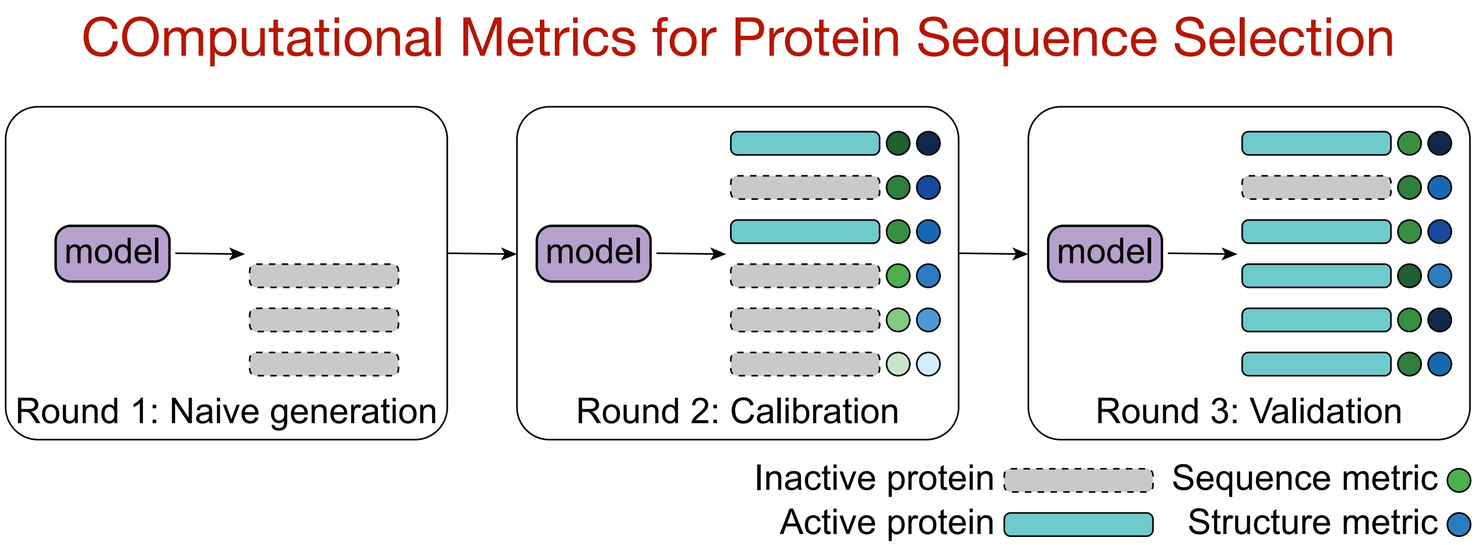


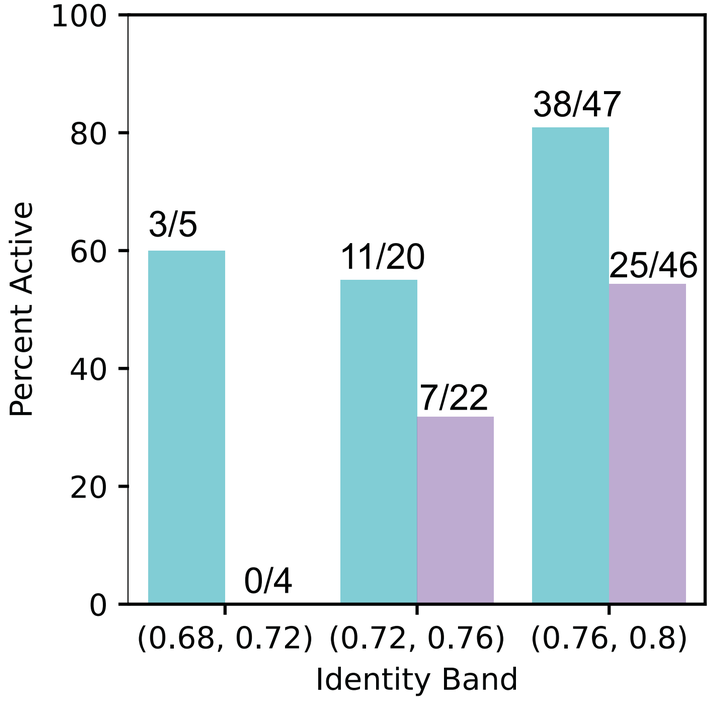
COMPSS is a tool for selecting generated proteins

COmputational Metrics for Protein Sequence Selection



COMPSS is a tool for selecting generated proteins





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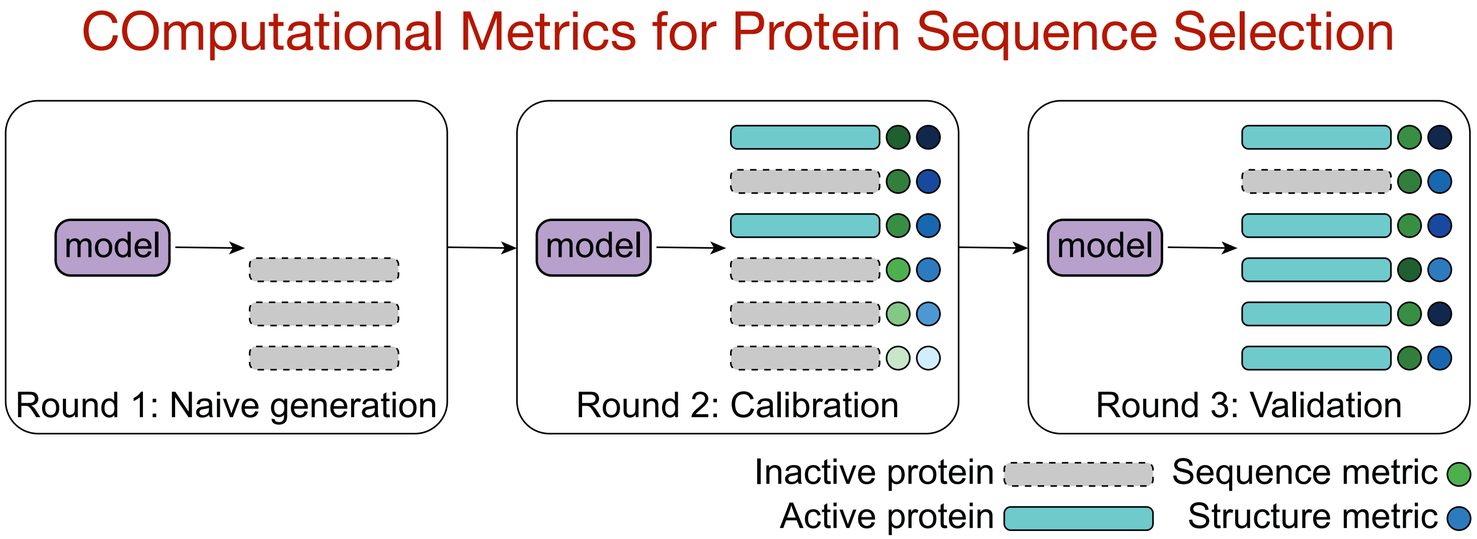
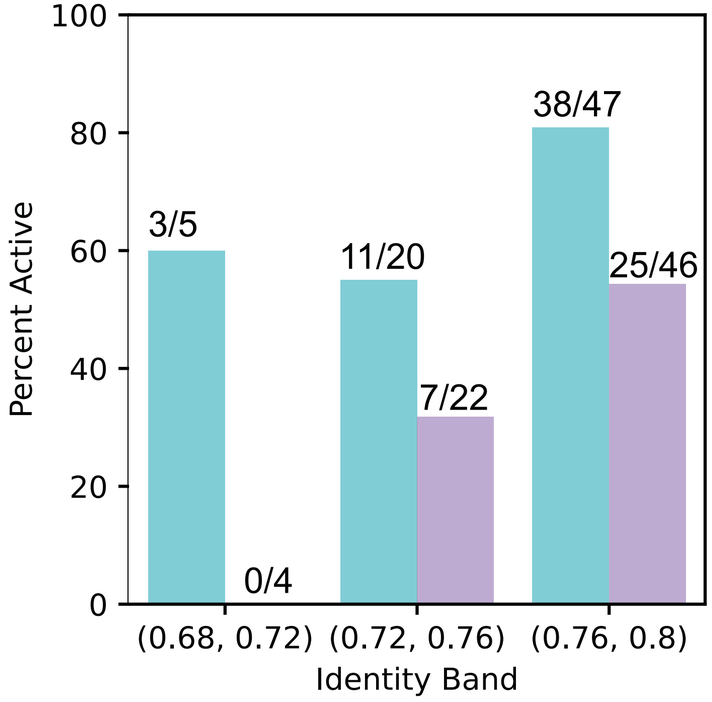
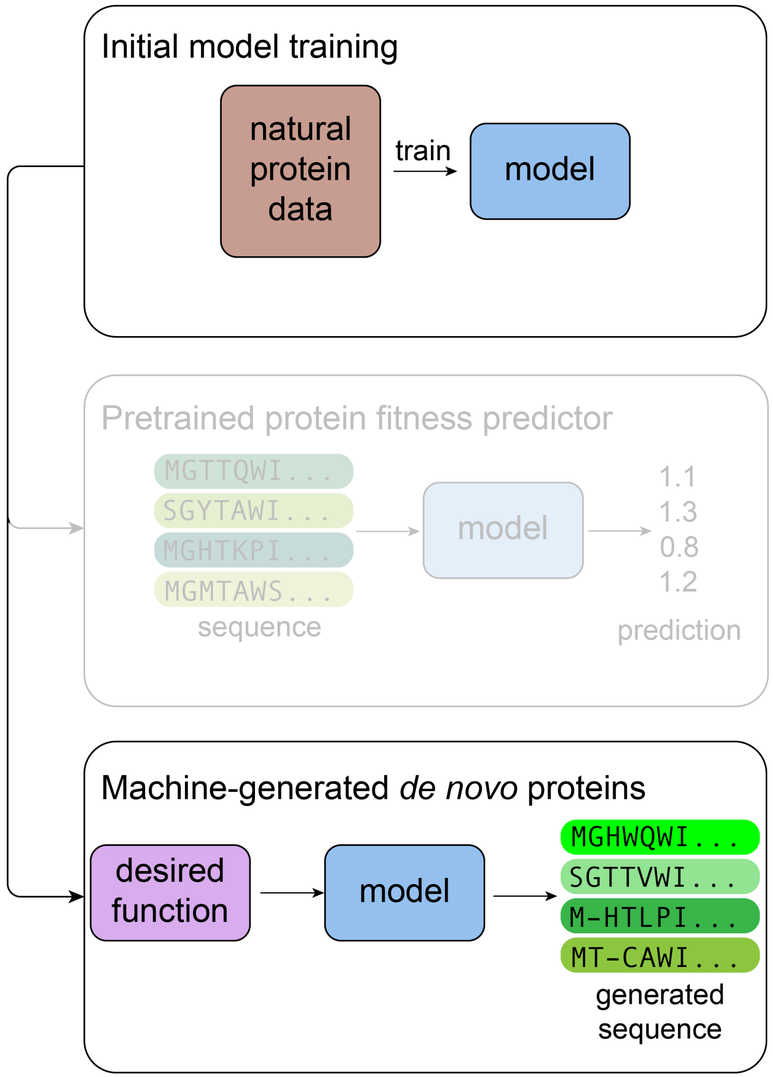
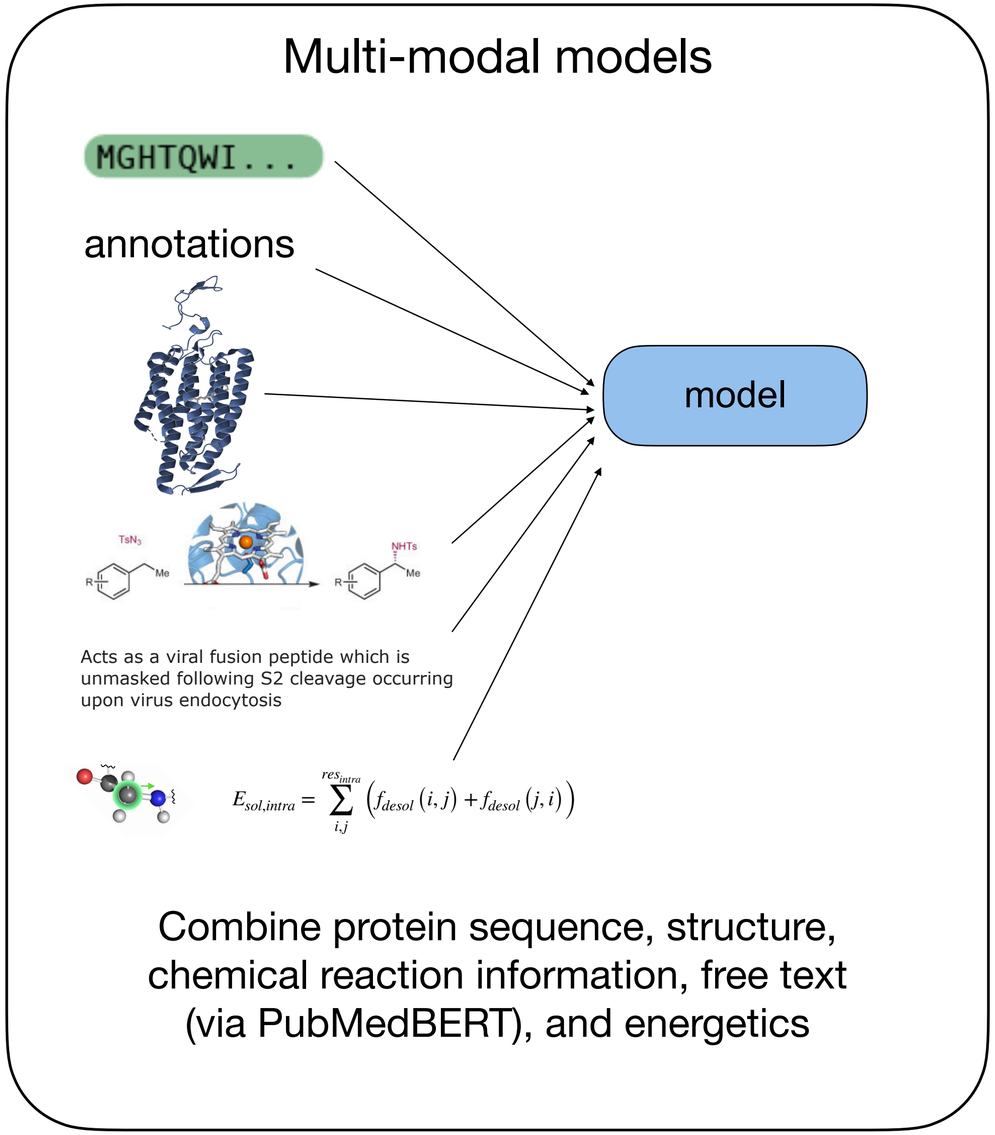




https://github.com/seanrjohnson/protein_scoring

Use multiple data modalities to discover proteins





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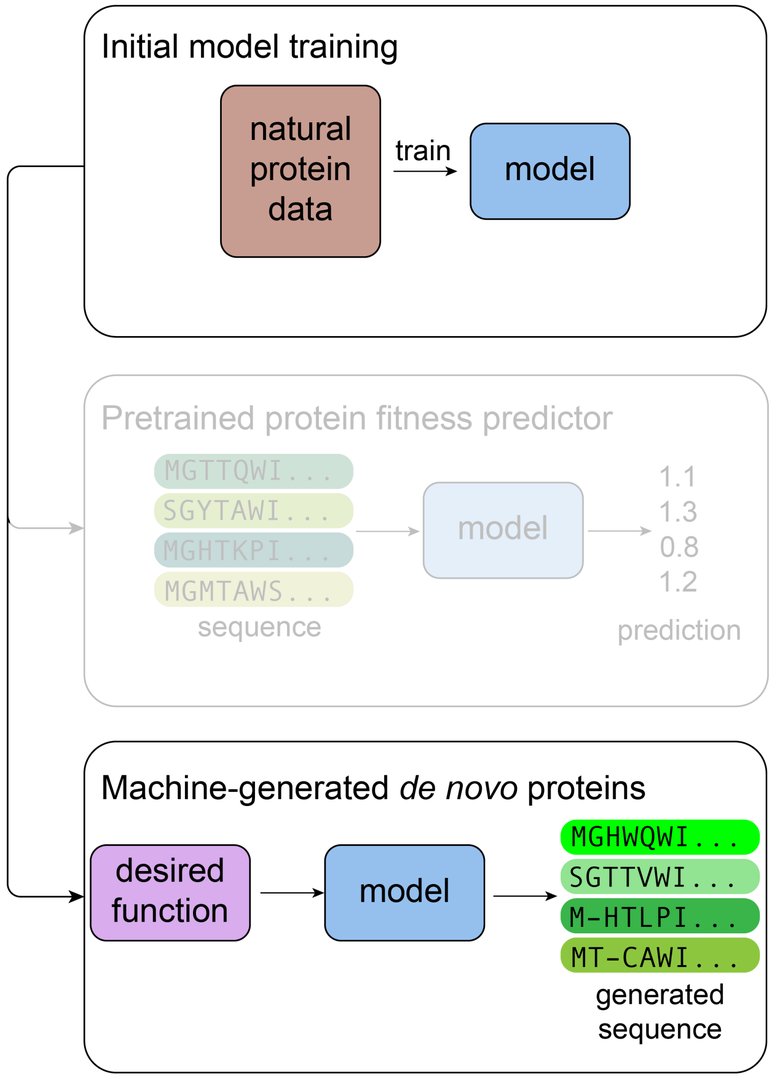
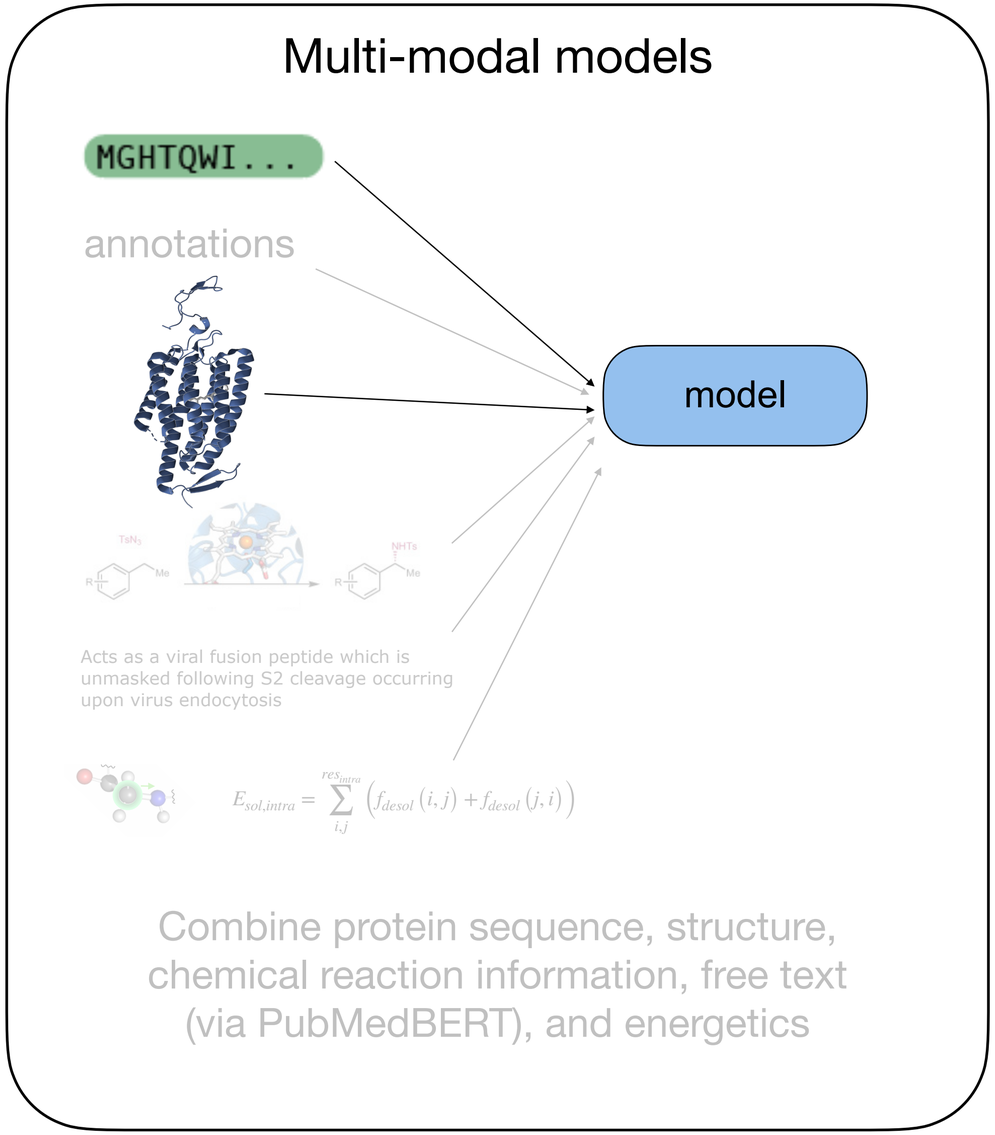
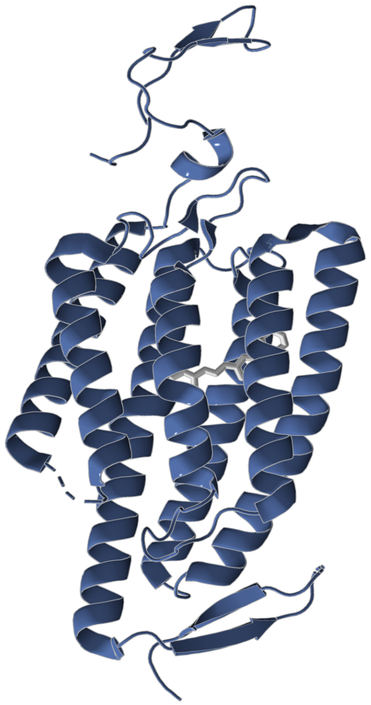
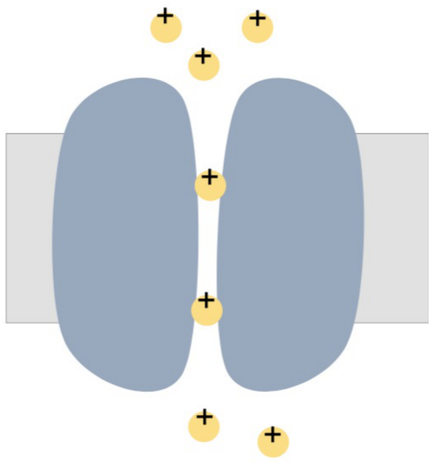




Generating new, designable structures expands functional space

MGTGDHDD...





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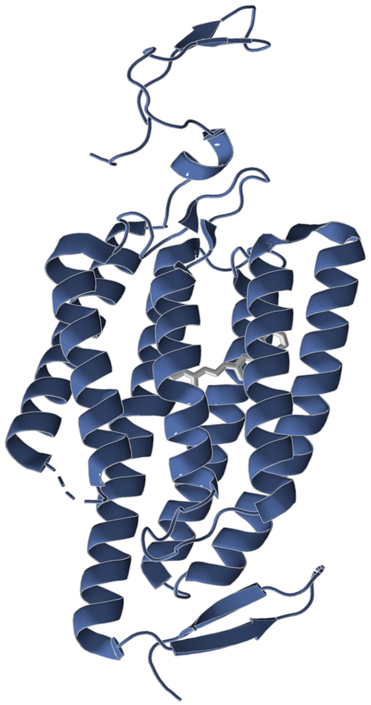

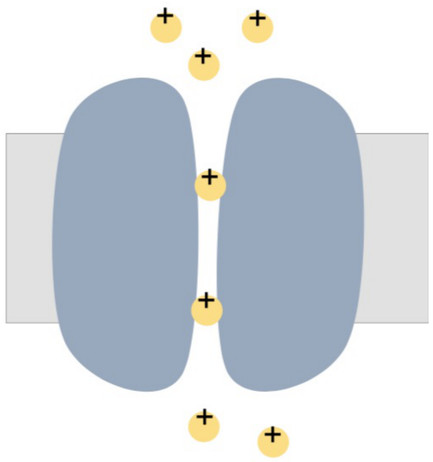

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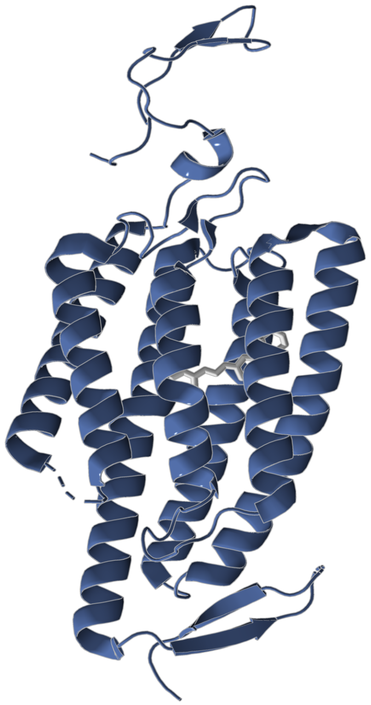
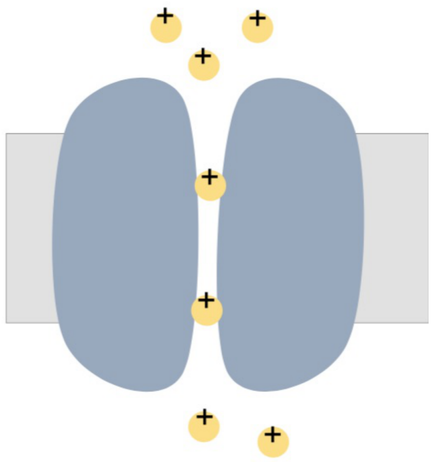
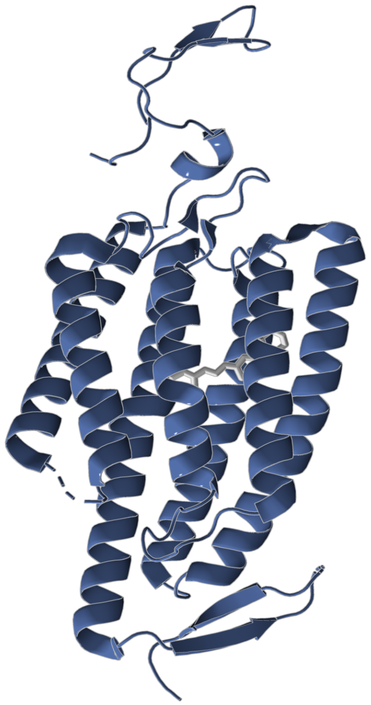


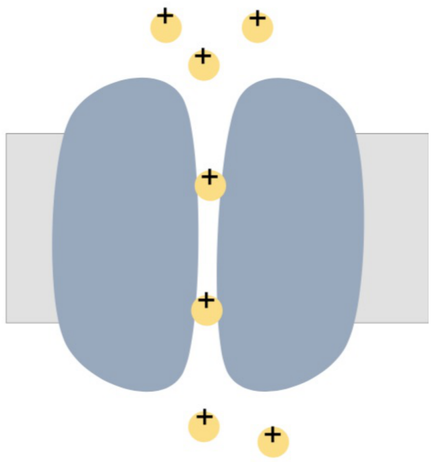


Challenge: Generate diverse and designable structures

Generating new, designable structures expands functional space

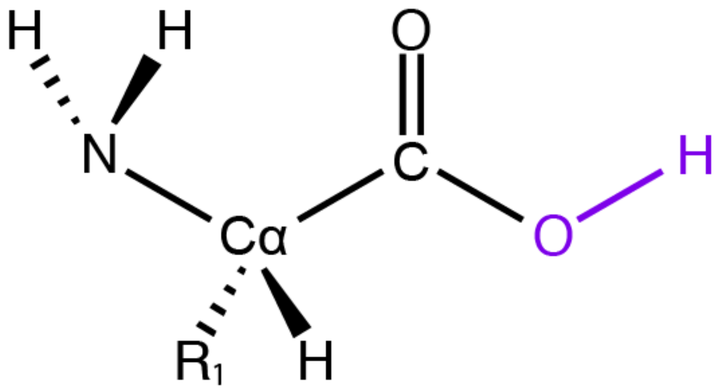
MGTGDHDD...





Challenge: Generate diverse and designable structures

Proteins are polypeptide chains



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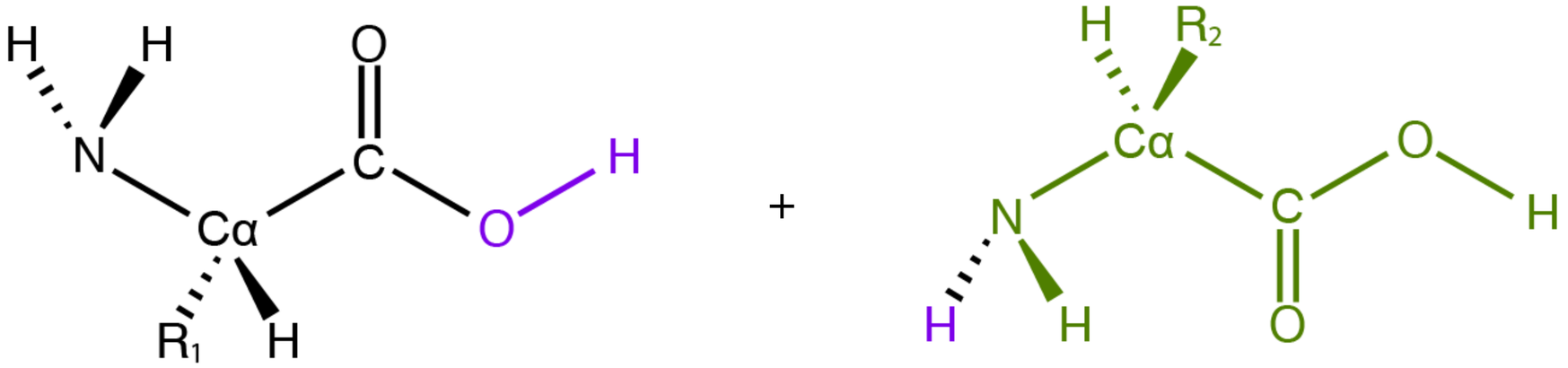

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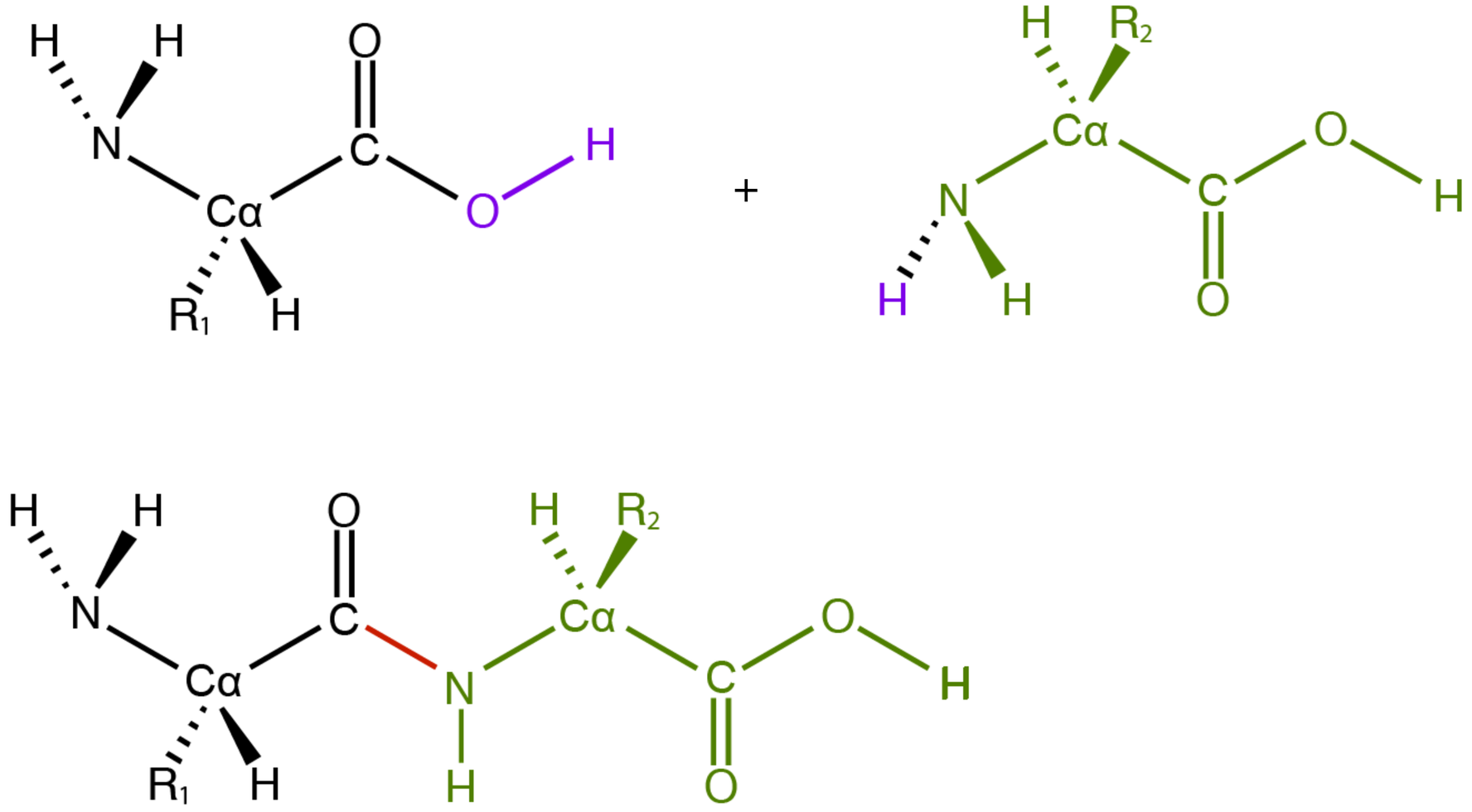

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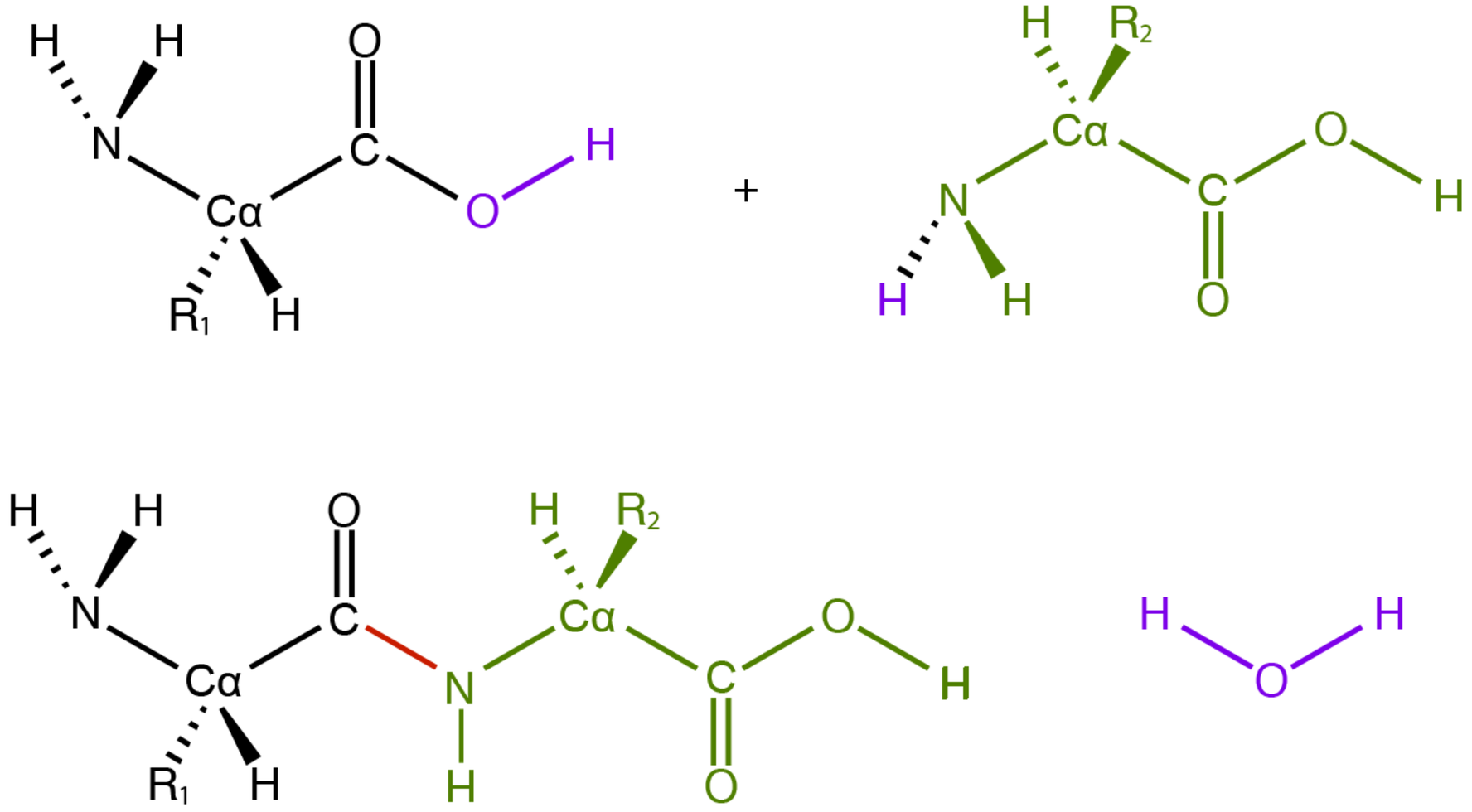
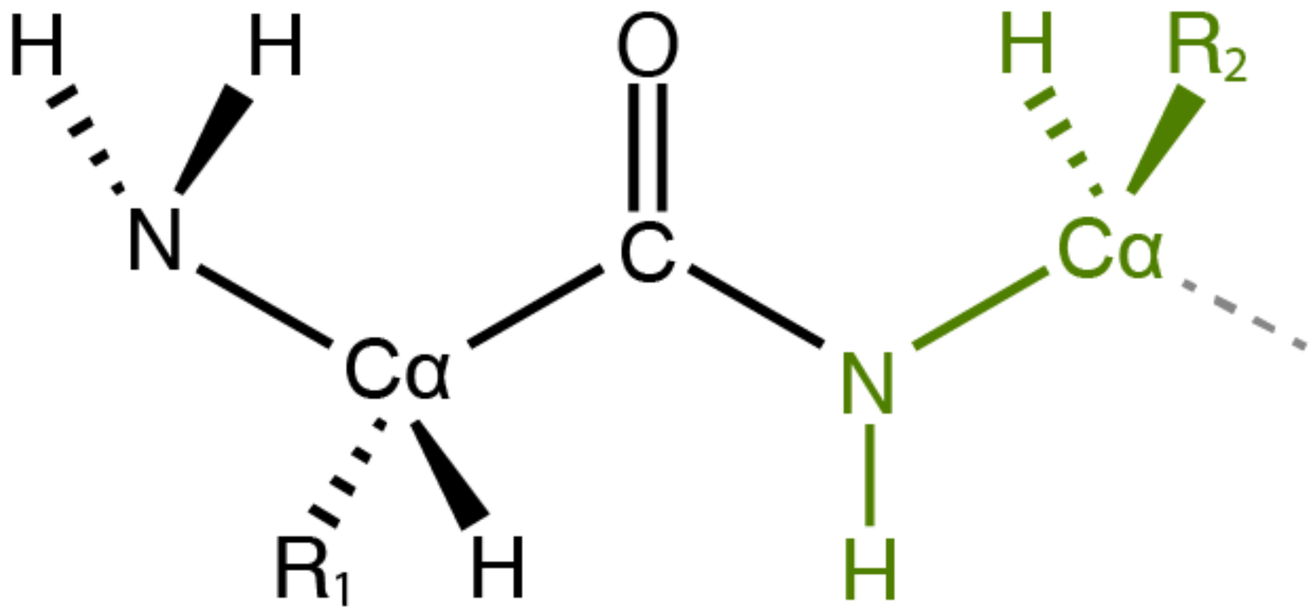


Protein structure is determined by bond angles



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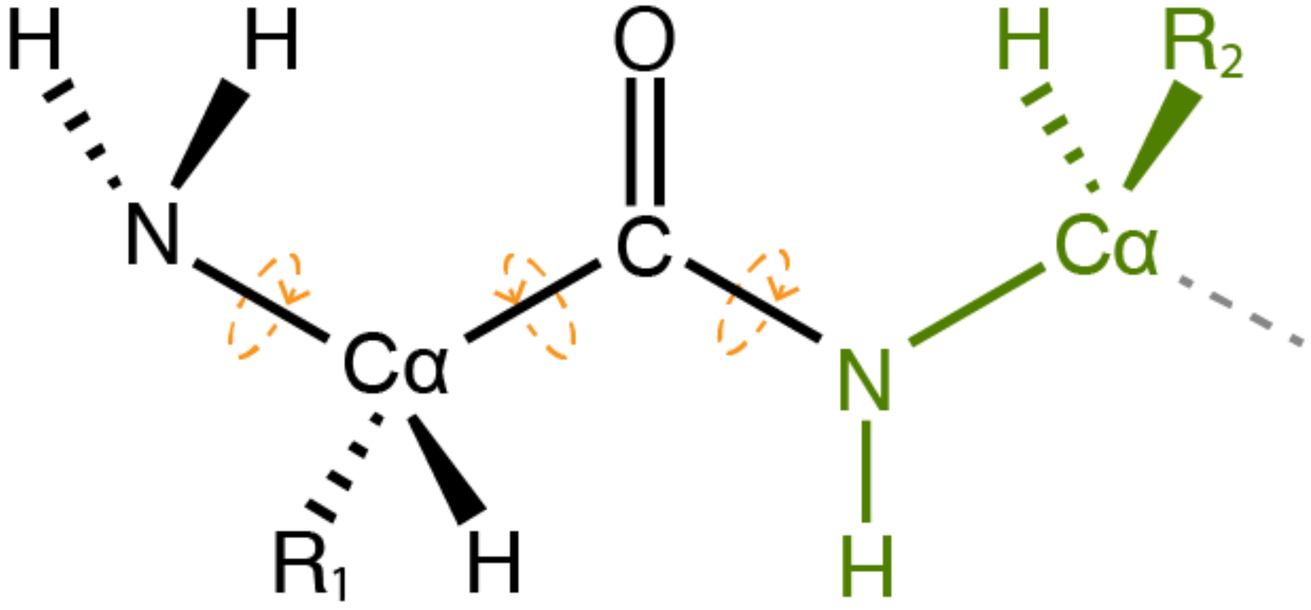

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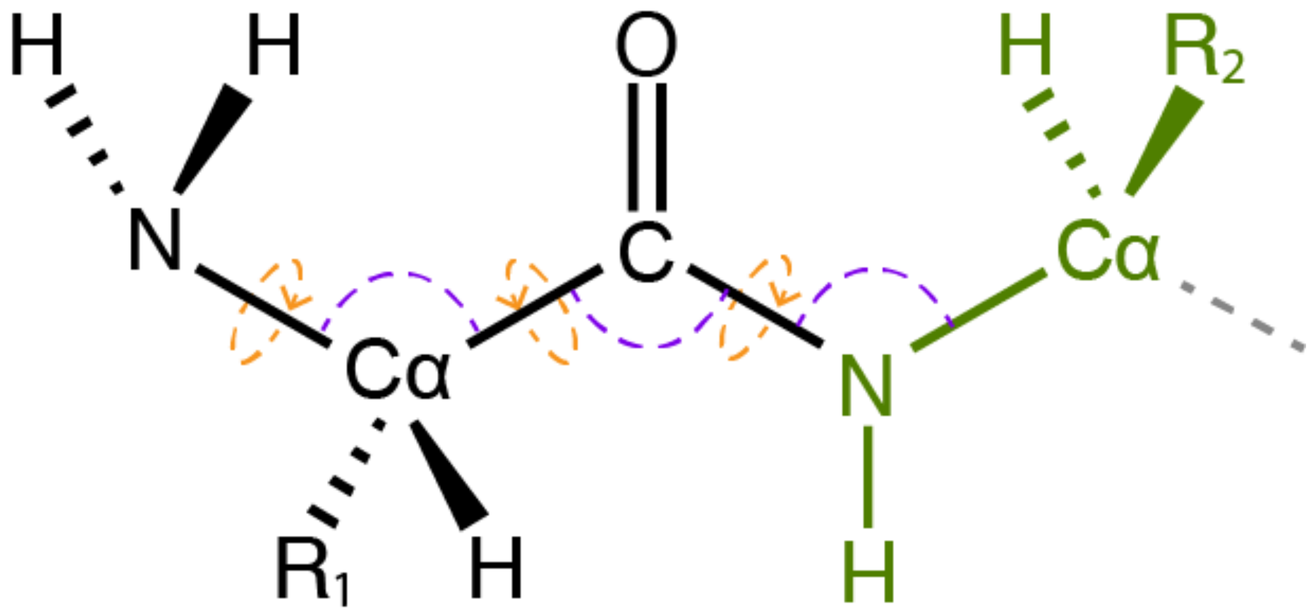

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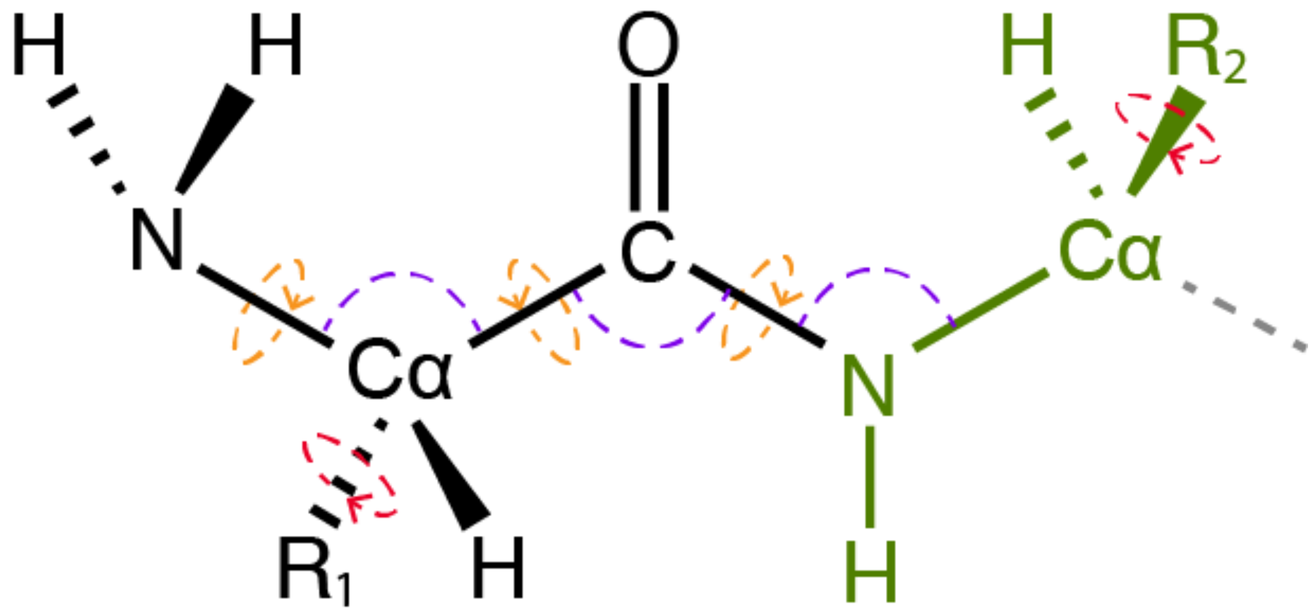
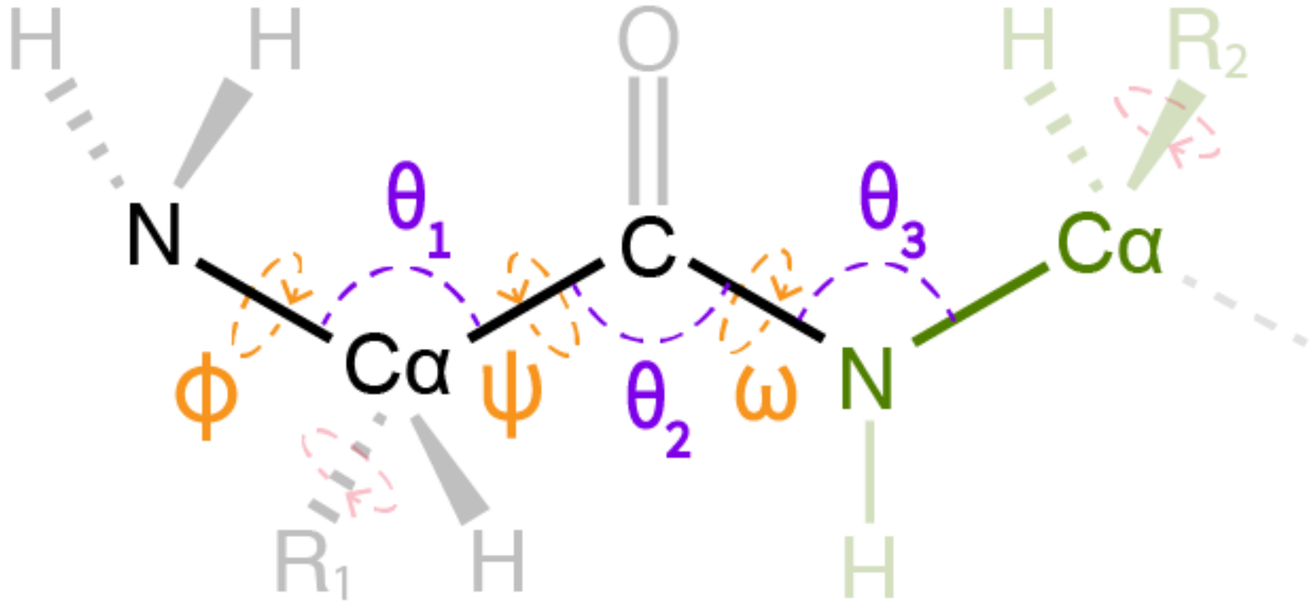


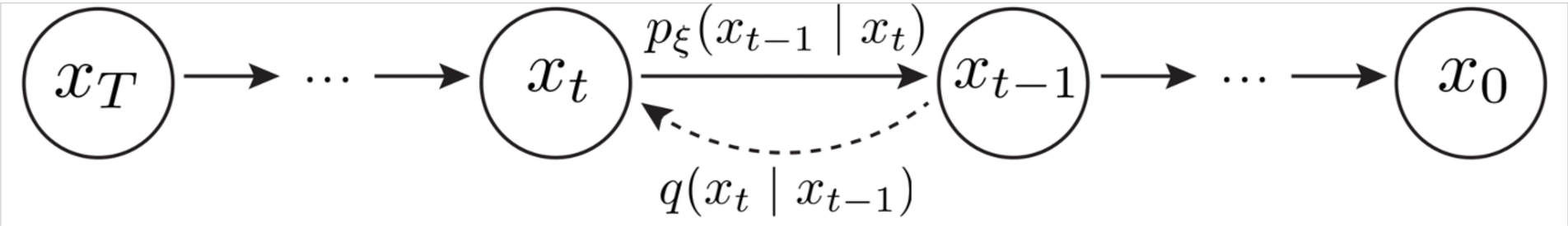
These six angles (for every consecutive pair of amino acids) fully determine the structure

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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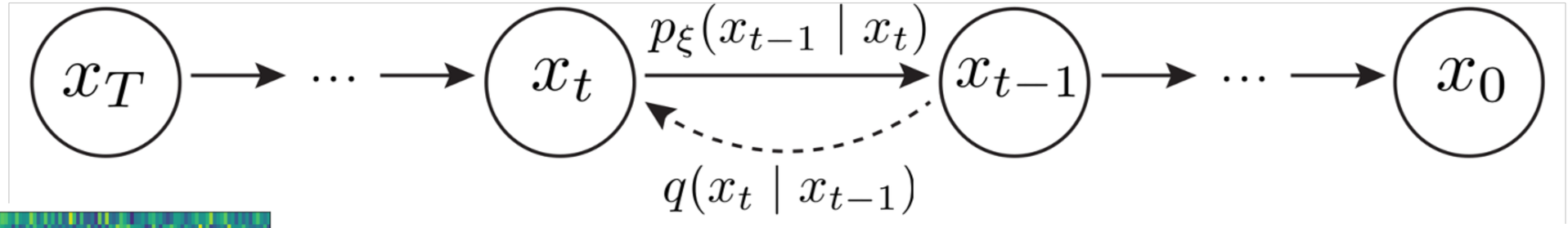
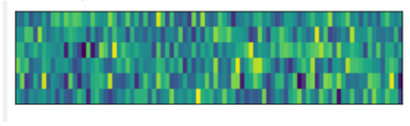
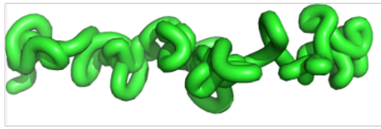
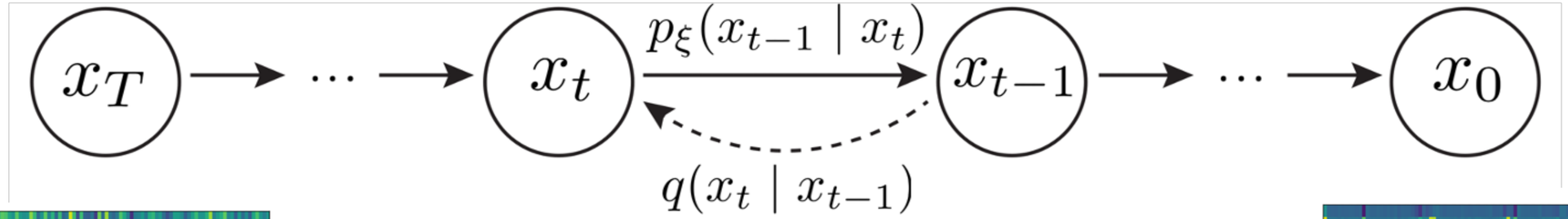


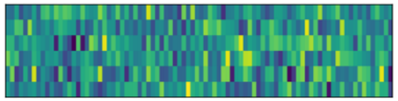


random angles

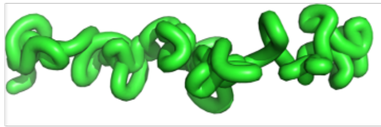


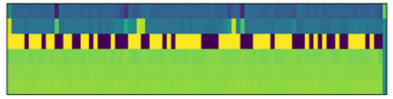
FoldingDiff uses diffusion to generate angles



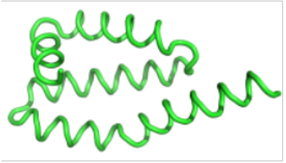


random angles





generated angles

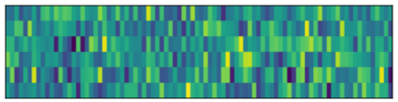


FoldingDiff uses diffusion to generate angles

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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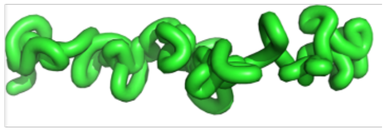

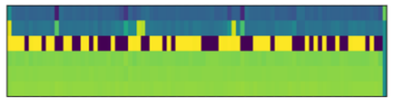

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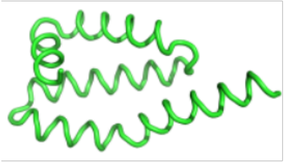

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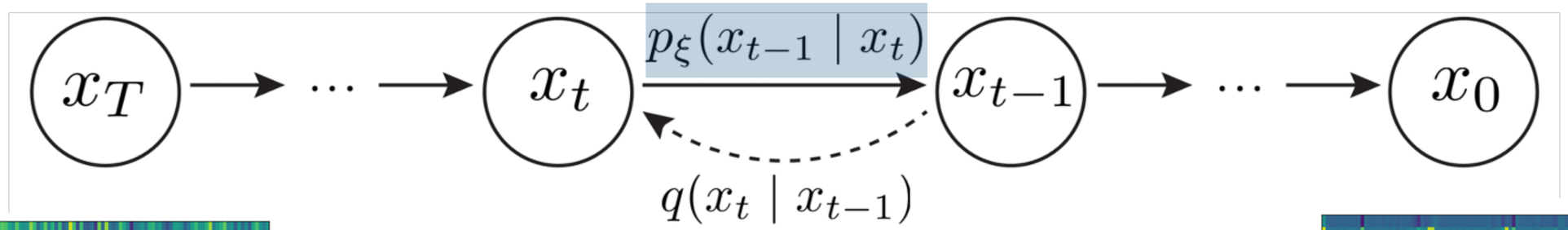

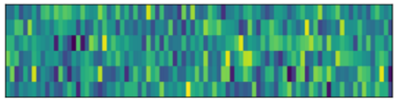

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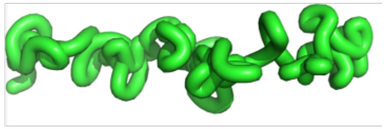
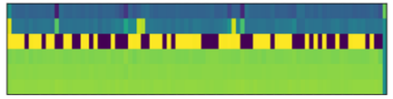


30k structures from CATH

40 - 128 residues



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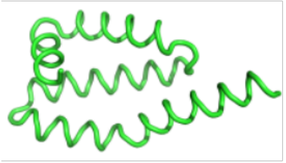
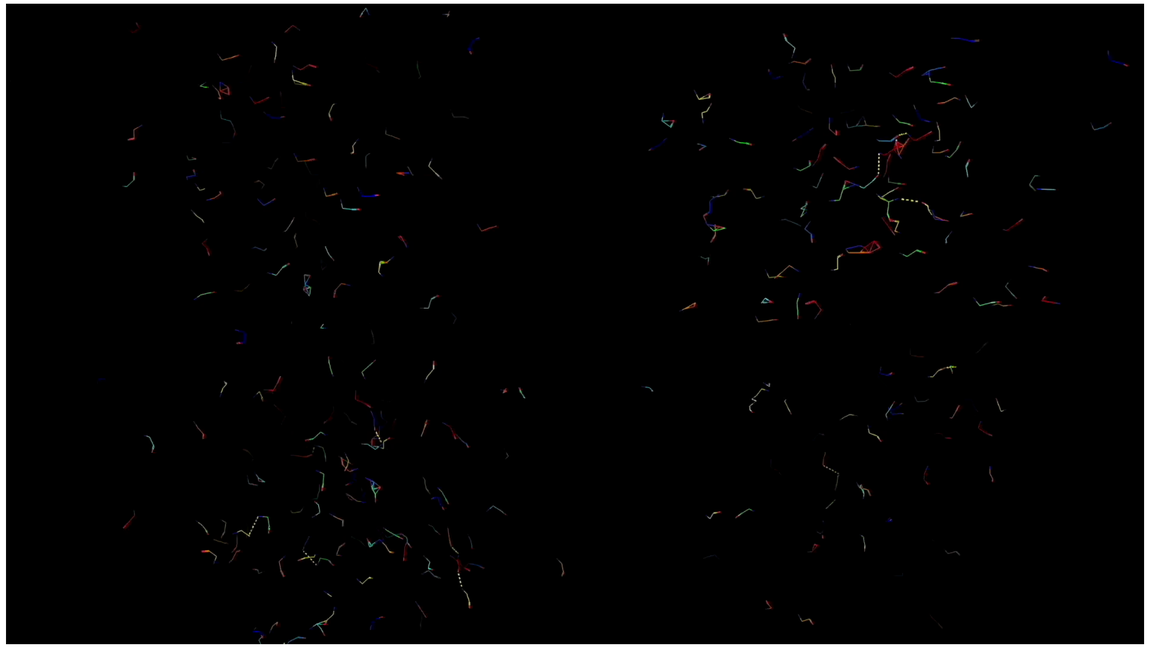


Diffusion on 3D coordinates requires equivariances



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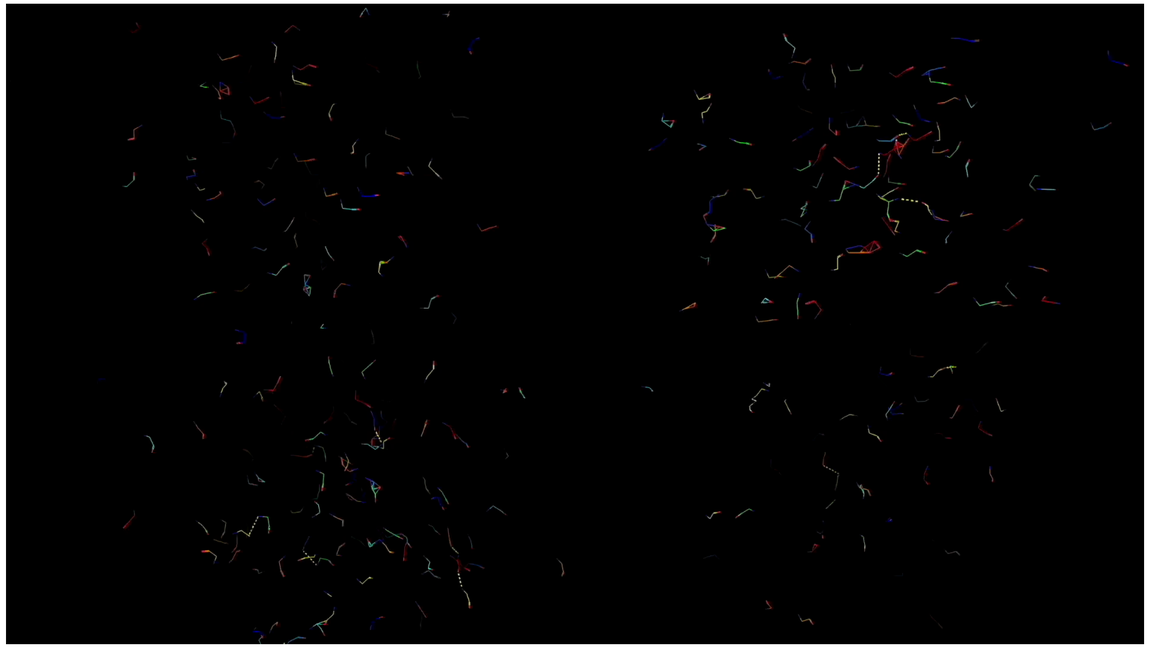

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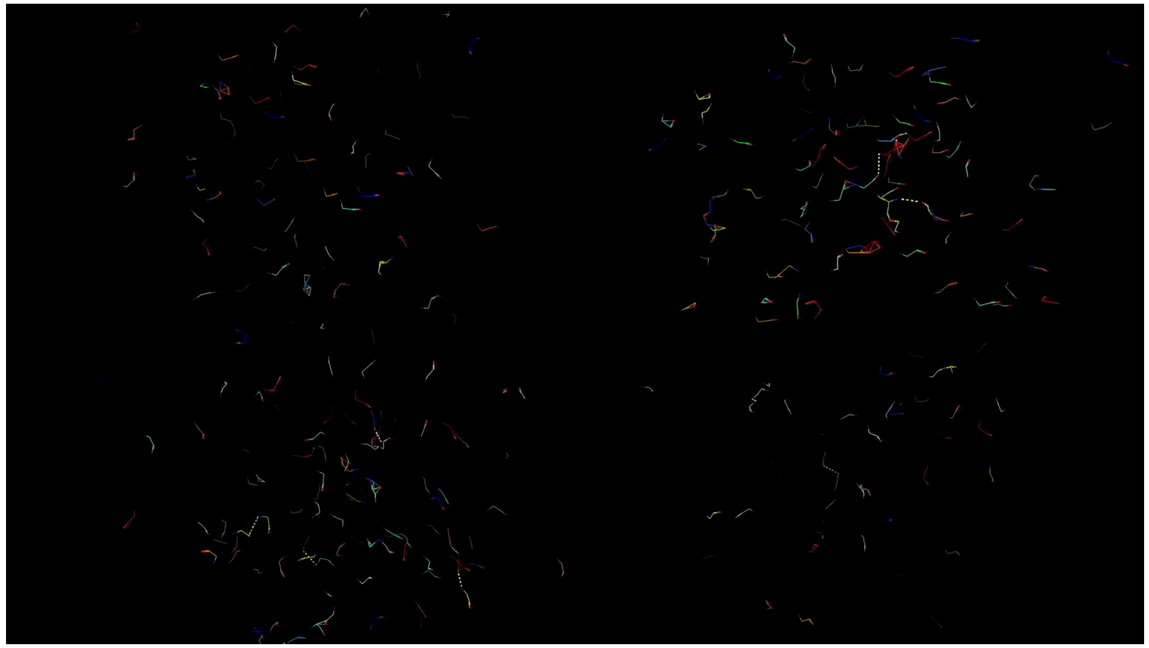
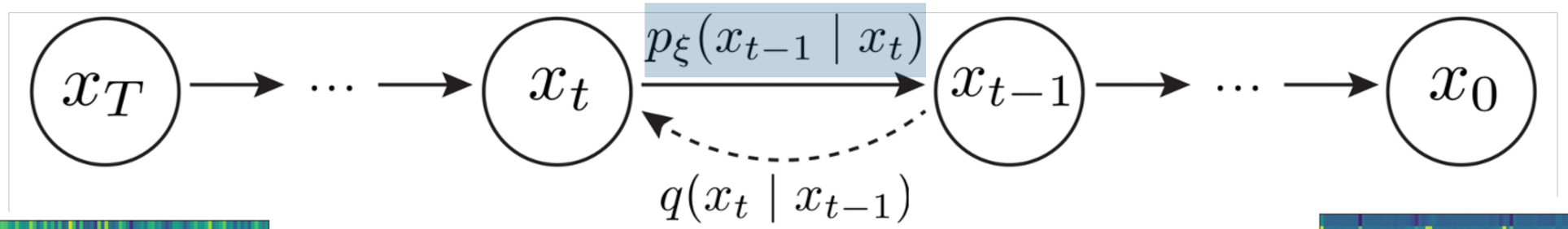
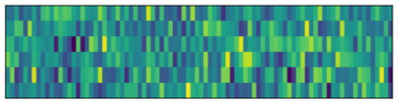


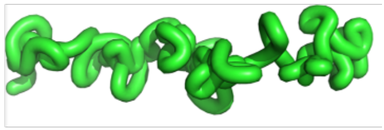
Evaluate generations at 3 levels

Vanilla transformer





random angles



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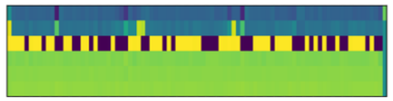

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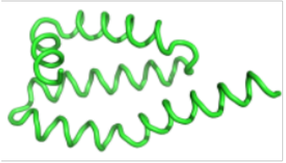

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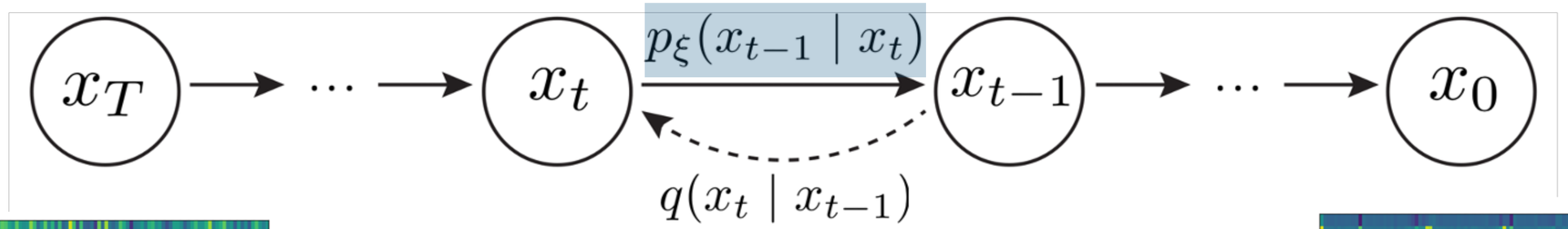

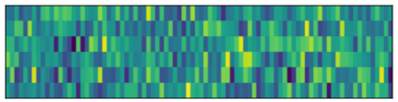

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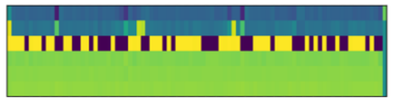

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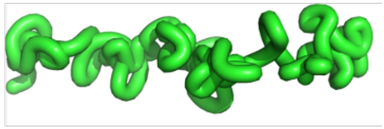

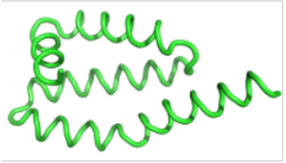

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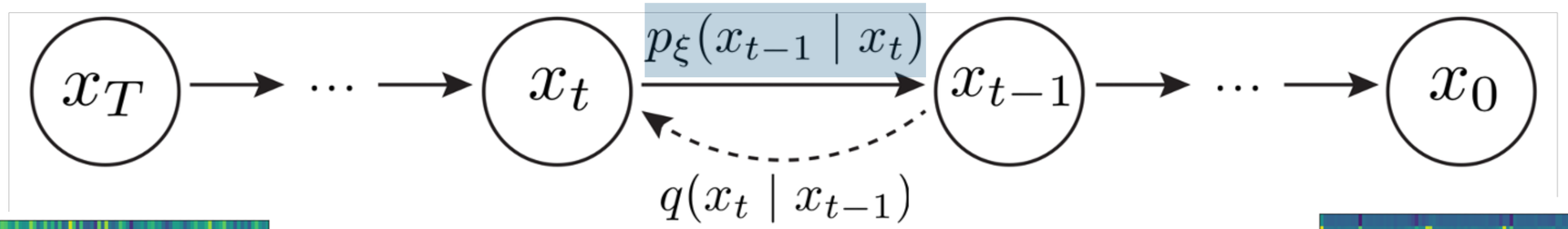

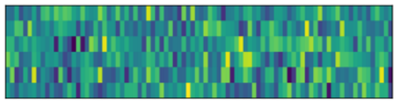

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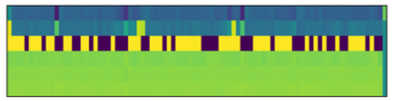

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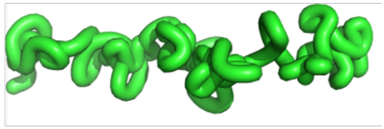
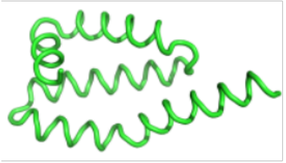


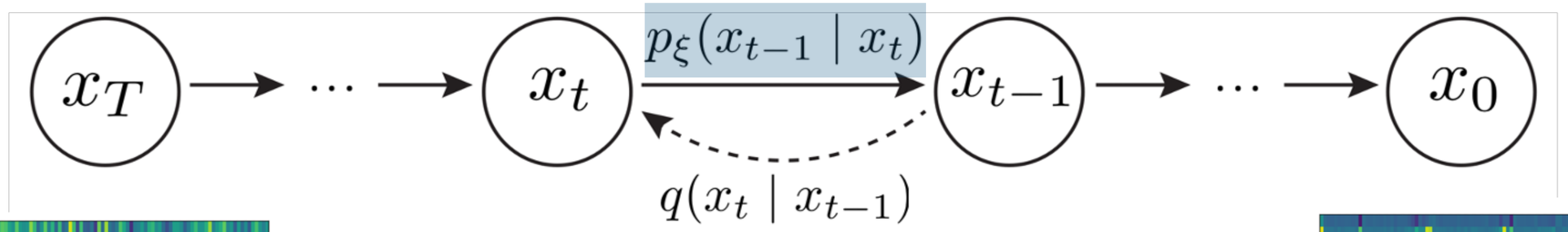


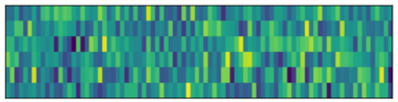
generated angles

structural motifs

Evaluate generations at 3 levels

Vanilla transformer





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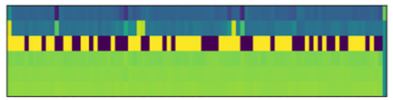

generated angles

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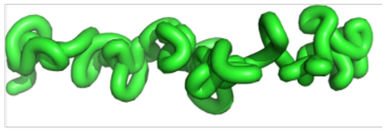
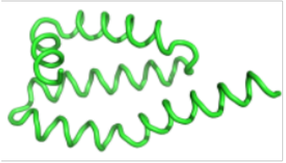
40 - 128 residues





generated angles

structural motifs

overall structures

Sample noised angles from a wrapped normal

$$q(x_t \mid x_{t-1}) = \mathcal{N}_{\text{wrapped}}(x_t; \sqrt{1-\beta_t} x_{t-1}, \beta_t I)$$

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Normalize angles to be zero mean

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Normalize angles to be zero mean

$$\beta_t = \text{clip}\left(1 - \frac{\bar{\alpha}_t}{\bar{\alpha}_{t-1}}, 0.999\right) \quad \bar{\alpha}_t = \frac{f(t)}{f(0)} \quad f(t) = \cos\left(\frac{t/T + s}{1+s} \cdot \frac{\pi}{2}\right)$$

1000 timesteps, cosine variance schedule

Train by predicting the noise at each step

timestep as random Fourier embedding

actual noise

noised angle

angle wrapping

$$d_w = w\left(\epsilon - \mathrm{nn}_\xi\left(w\left(\sqrt{\bar{\alpha}_t}x_0 + \sqrt{1-\bar{\alpha}_t}\epsilon\right), t\right)\right)$$

$$[-\pi, \pi):\ w(x) = ((x+\pi) \bmod 2\pi) - \pi$$

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$$L_w = \begin{cases} 0.5\frac{d_w^2}{\beta_L} & \text{if } |d_w| < \beta_L \\ |d_w| - 0.5\beta_L & \text{otherwise} \end{cases}$$

L2, B_L = 0.1pi

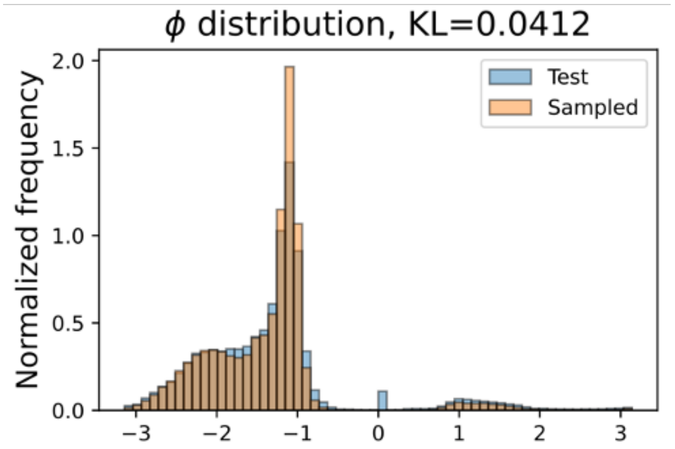
L1

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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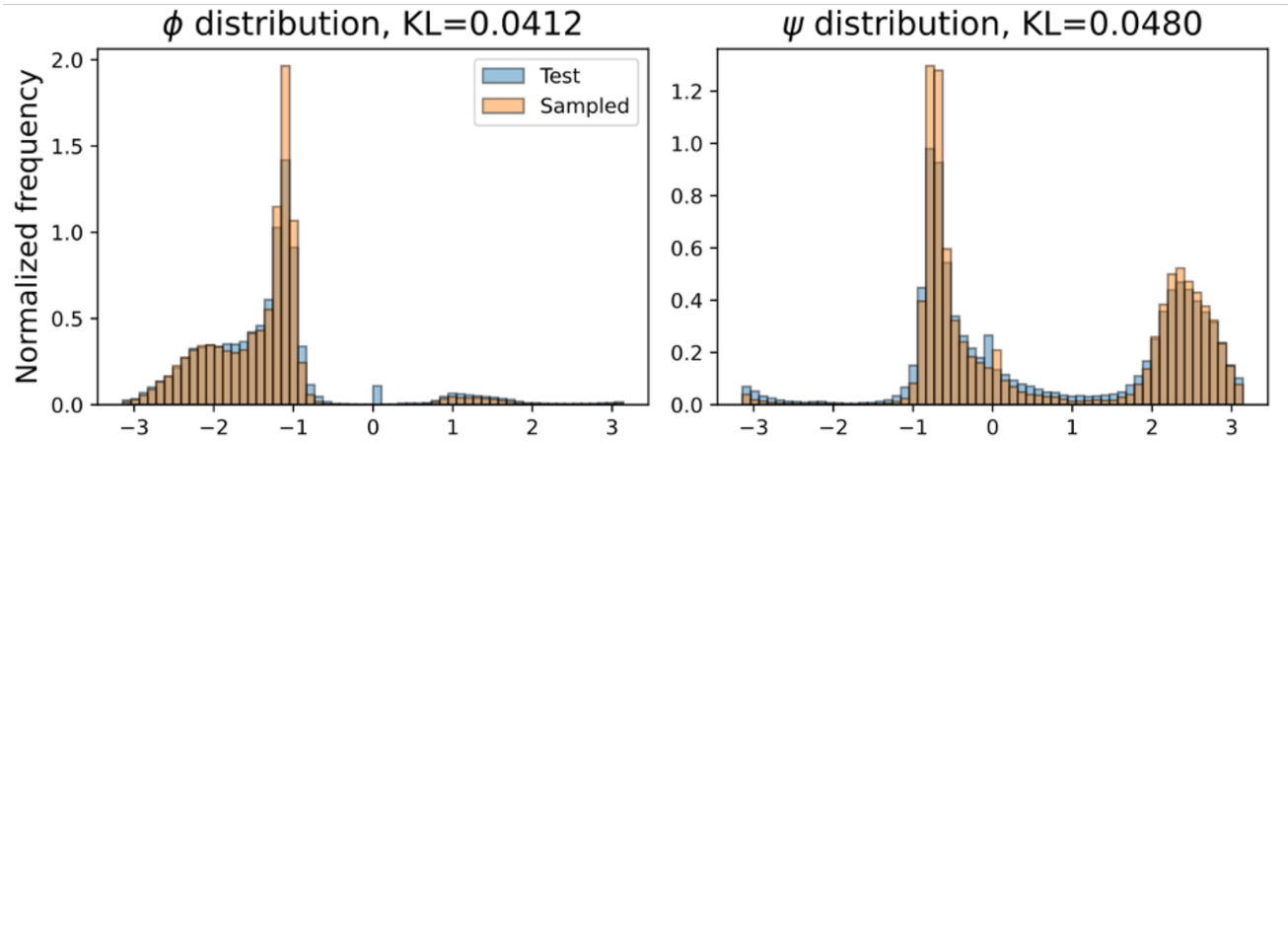

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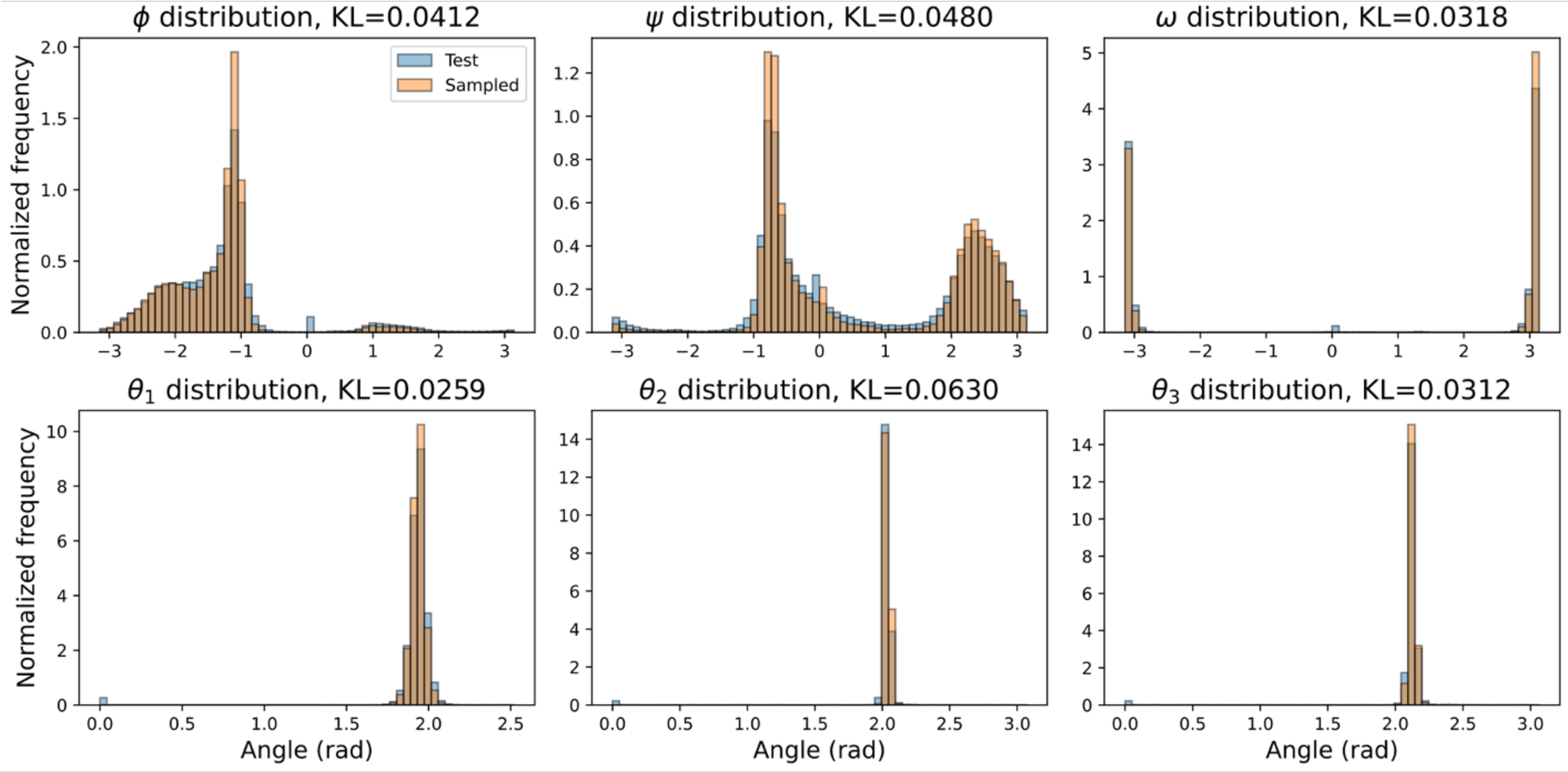

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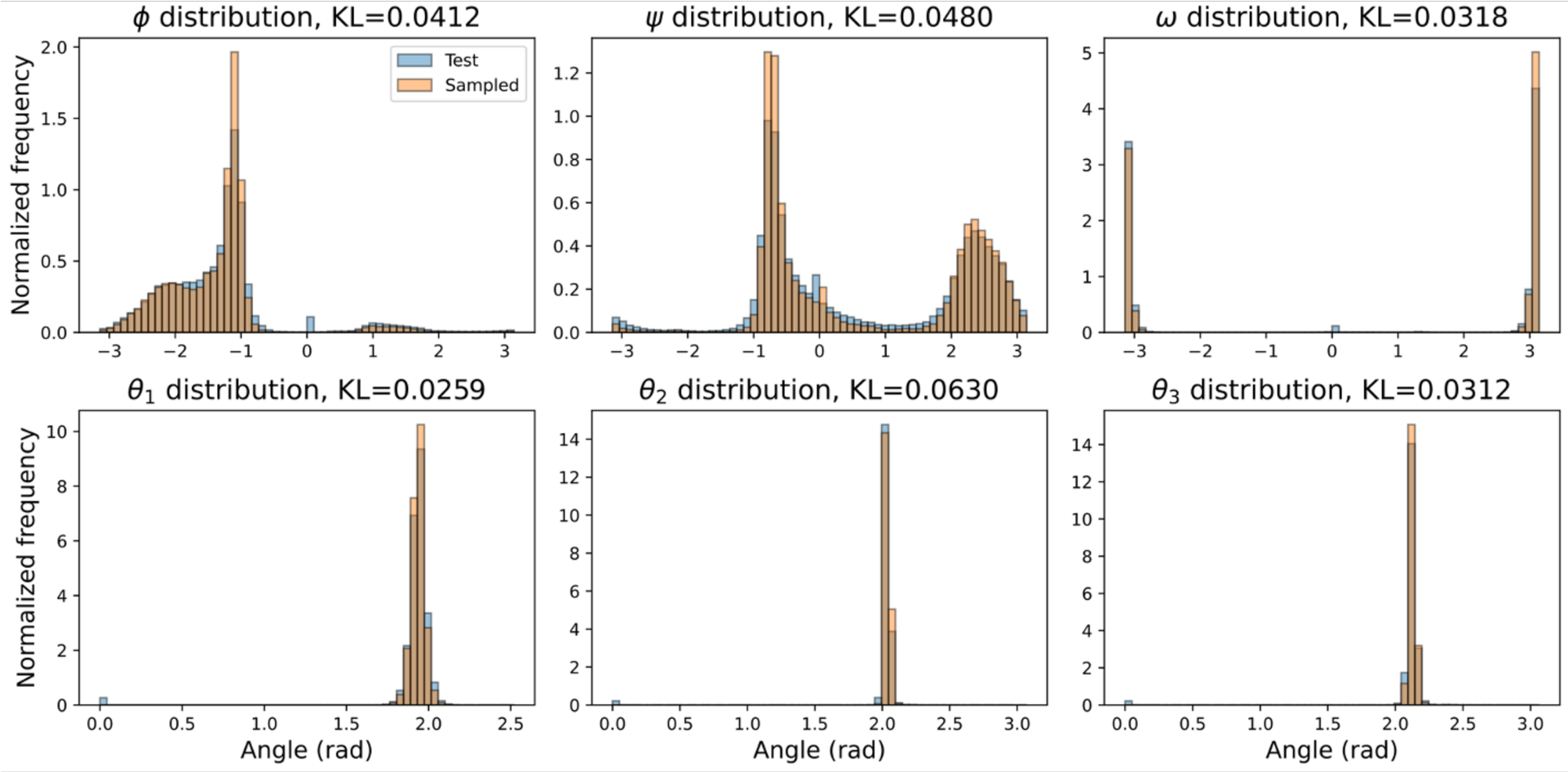


Generated distributions match natural distribution of individual angles

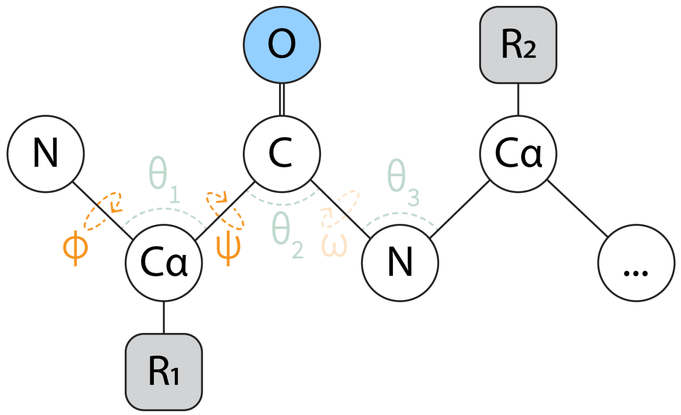
FoldingDiff captures correlations between angles

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

FoldingDiff generates correlations that define common structural motifs

FoldingDiff captures correlations between angles

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



FoldingDiff generates correlations that define common structural motifs

FoldingDiff captures correlations between angles

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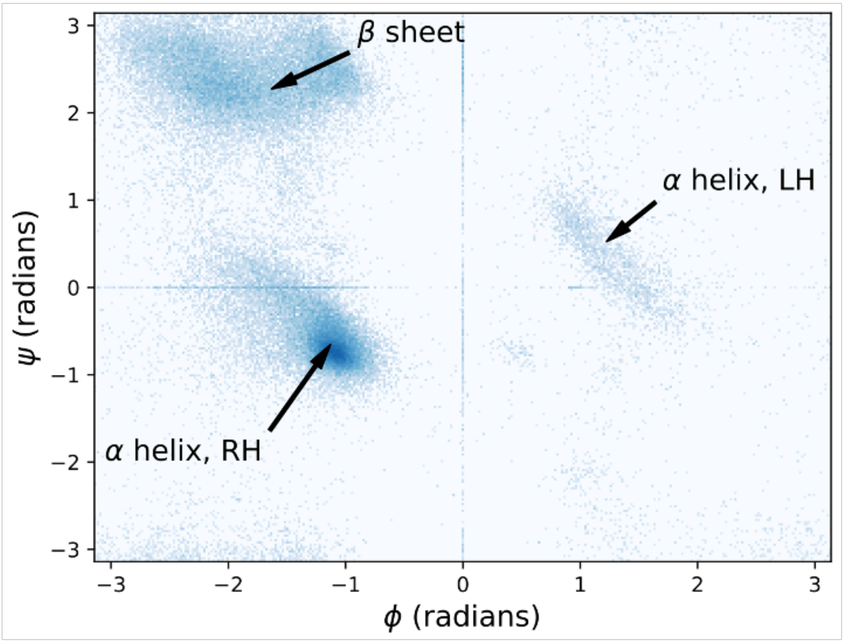
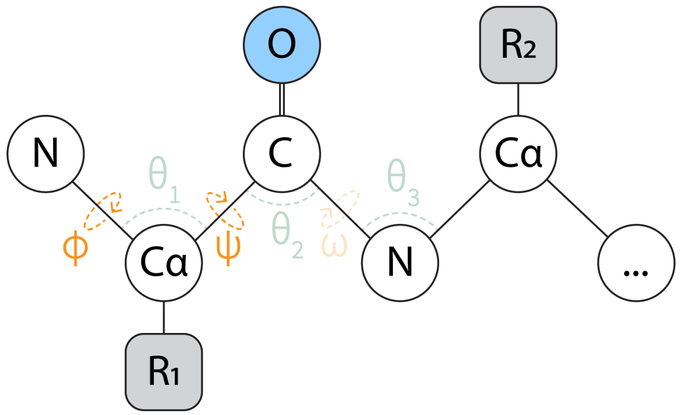
True





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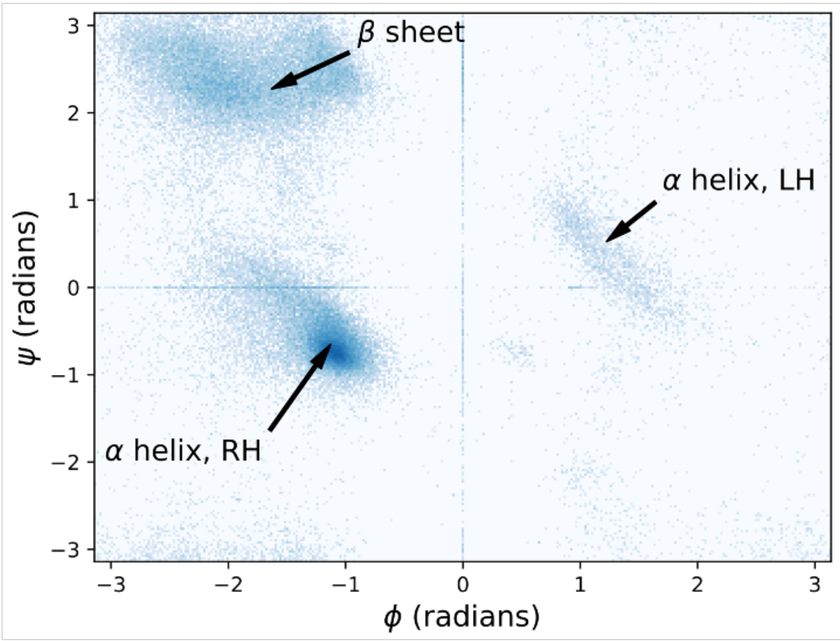
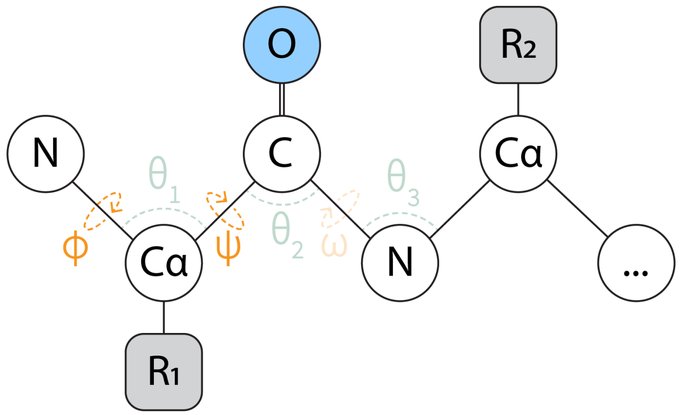
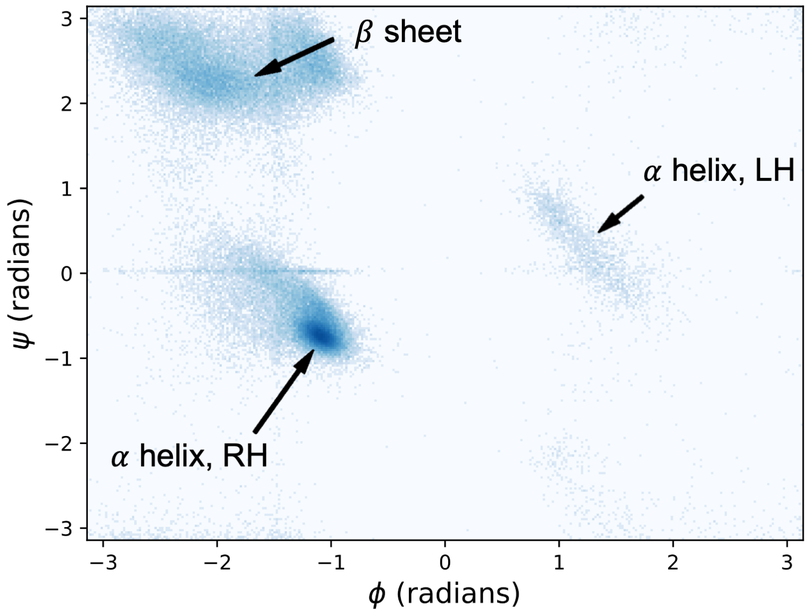




Generated

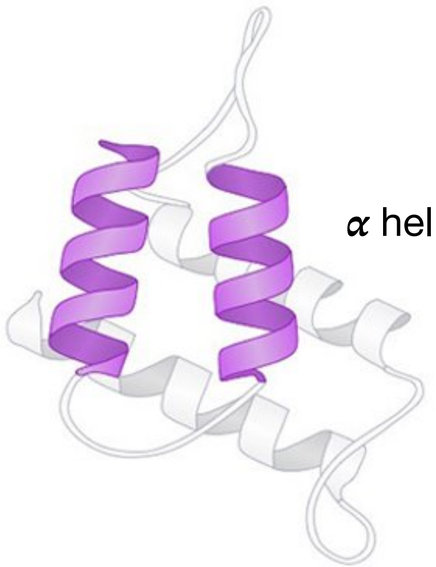


FoldingDiff generates correlations that define common structural motifs

Generated secondary structures match test structures

noise → sample → measure helix, sheet structures

Generated secondary structures match test structures

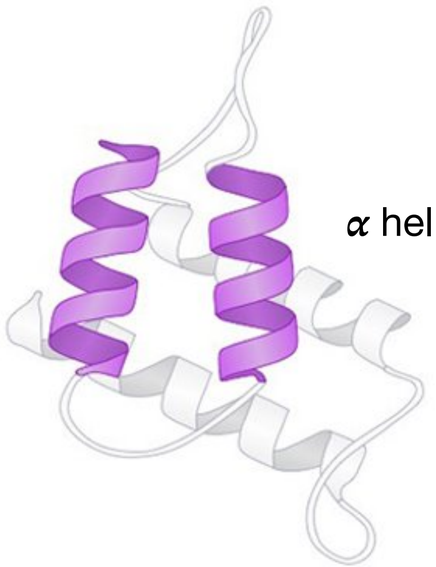


α helix

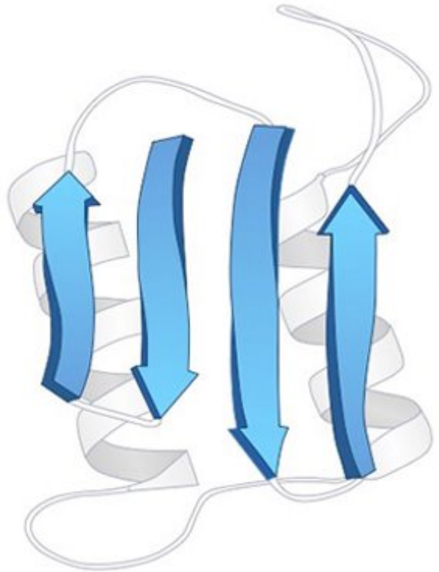
noise → sample → measure helix, sheet structures

Generated secondary structures match test structures

noise → sample → measure helix, sheet structures



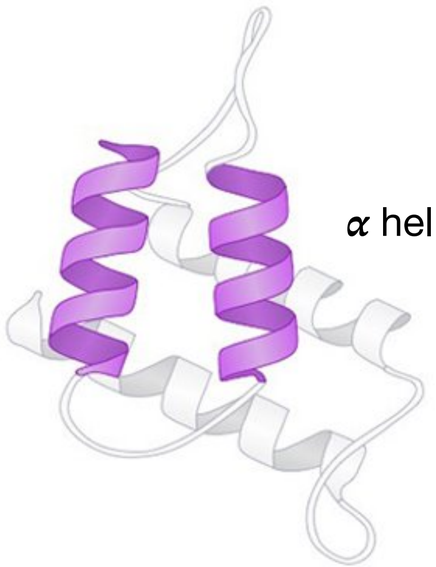
α helix



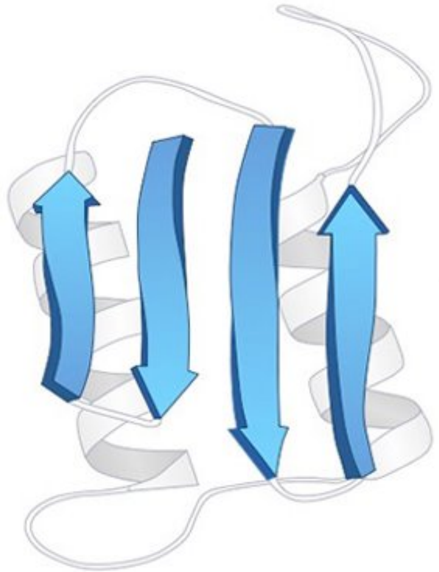
β sheet

Generated secondary structures match test structures

noise → sample → measure helix, sheet structures

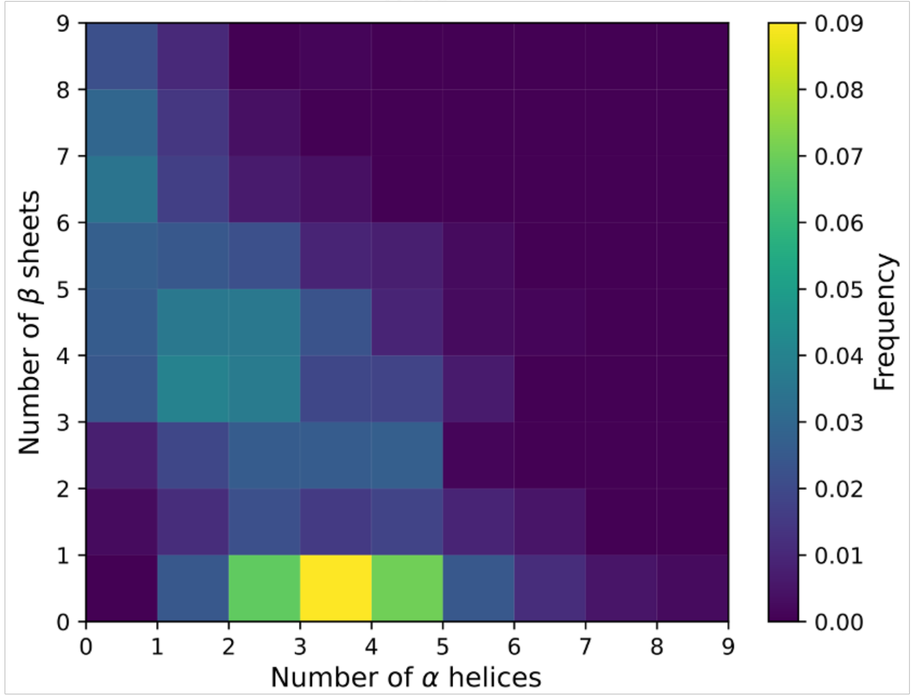


α helix



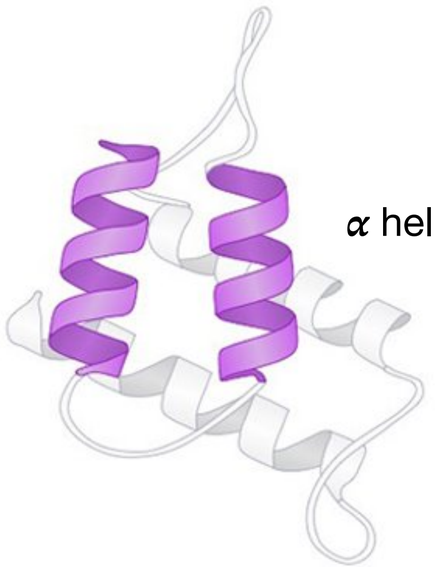
β sheet

True

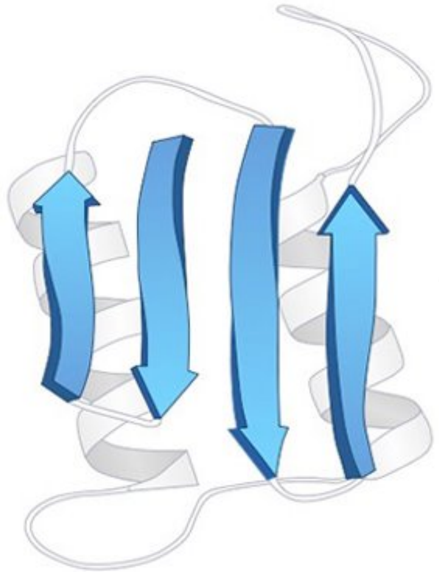


Generated secondary structures match test structures

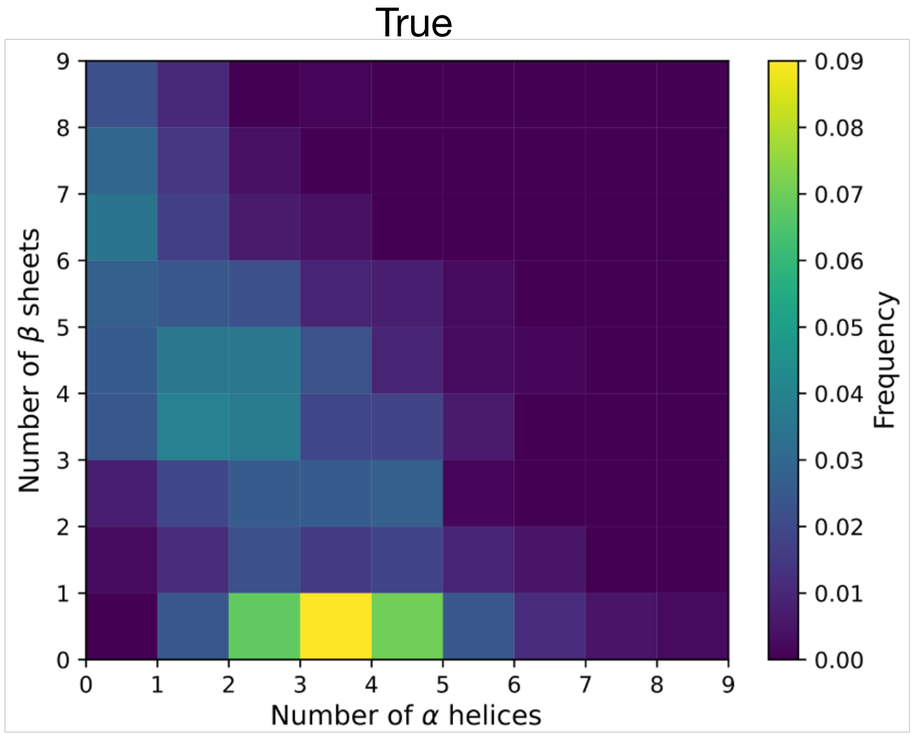
noise → sample → measure helix, sheet structures

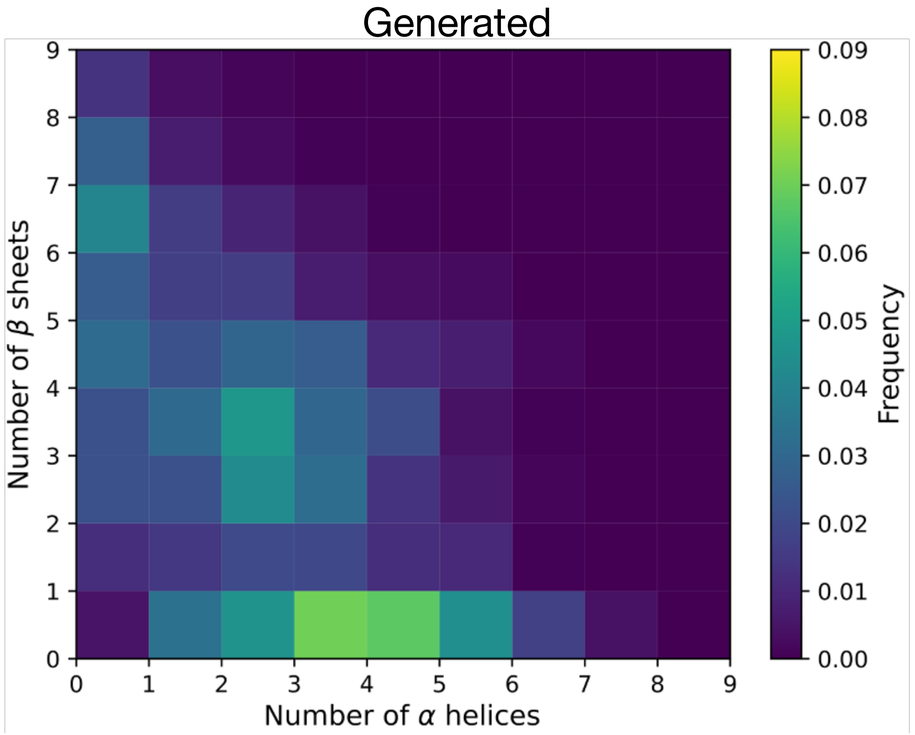


α helix



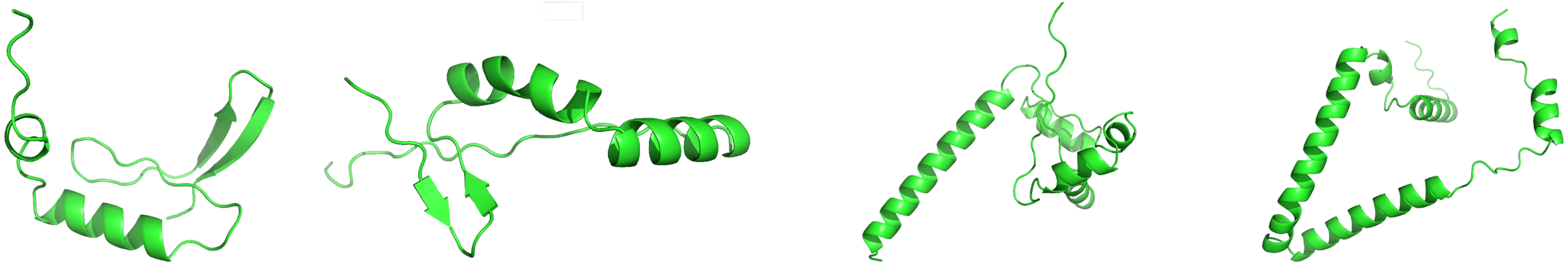
β sheet



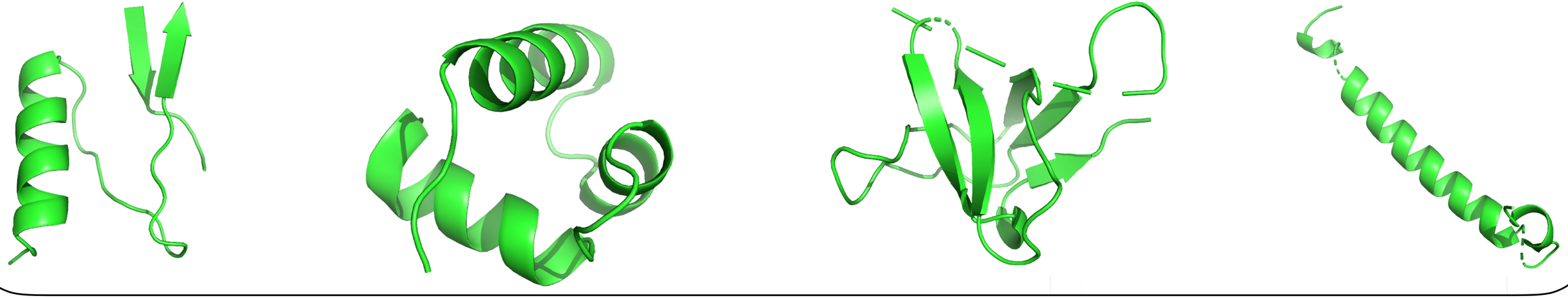


Generated structures look reasonable

Generated structures

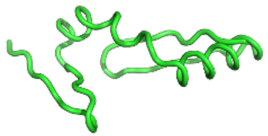


Training set structures

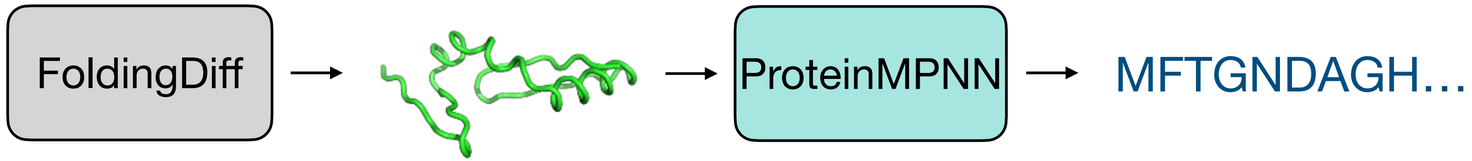


Measure designability of structures with self-consistency TMscore

FoldingDiff →



Measure designability of structures with self-consistency TMscore



Measure designability of structures with self-consistency TMscore

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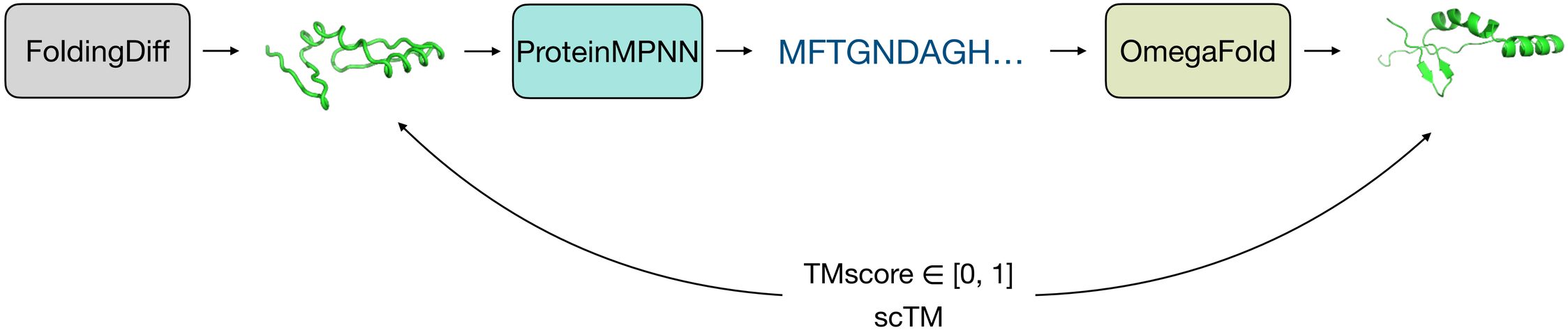
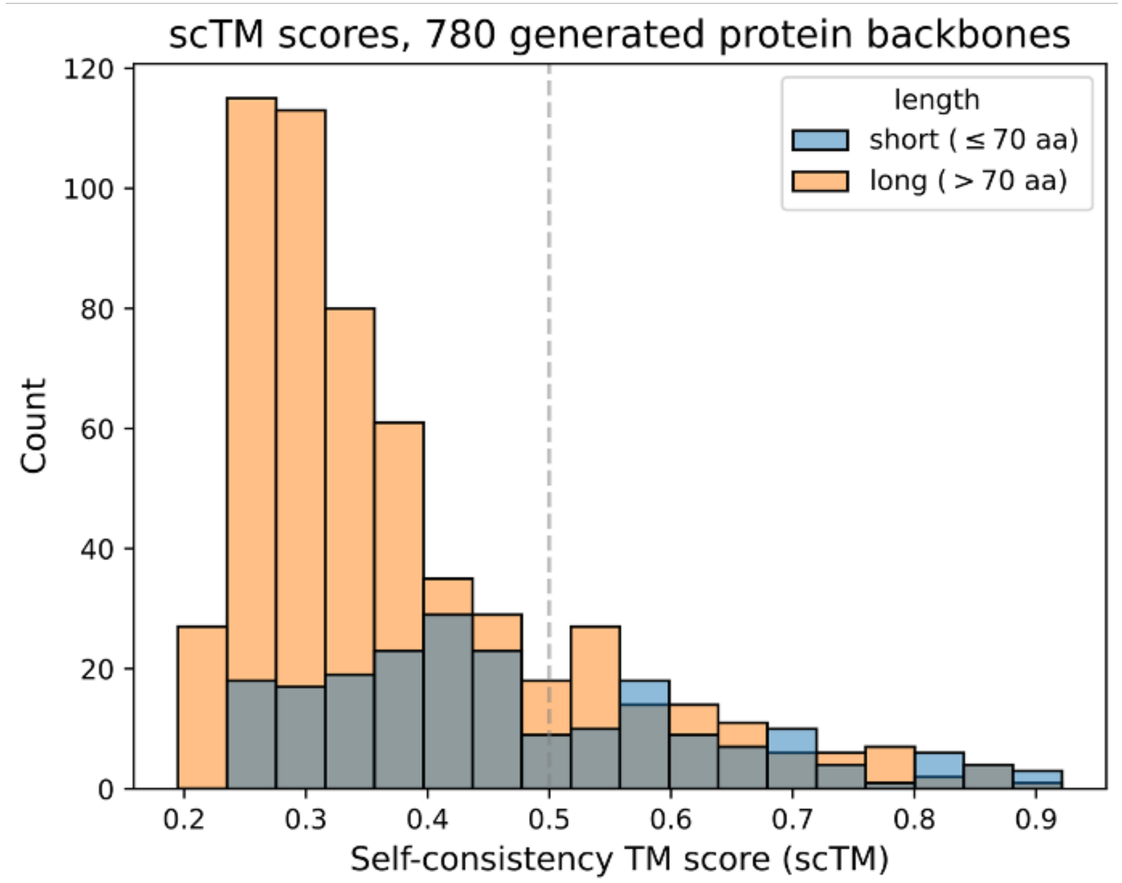


Many generated structures are designable



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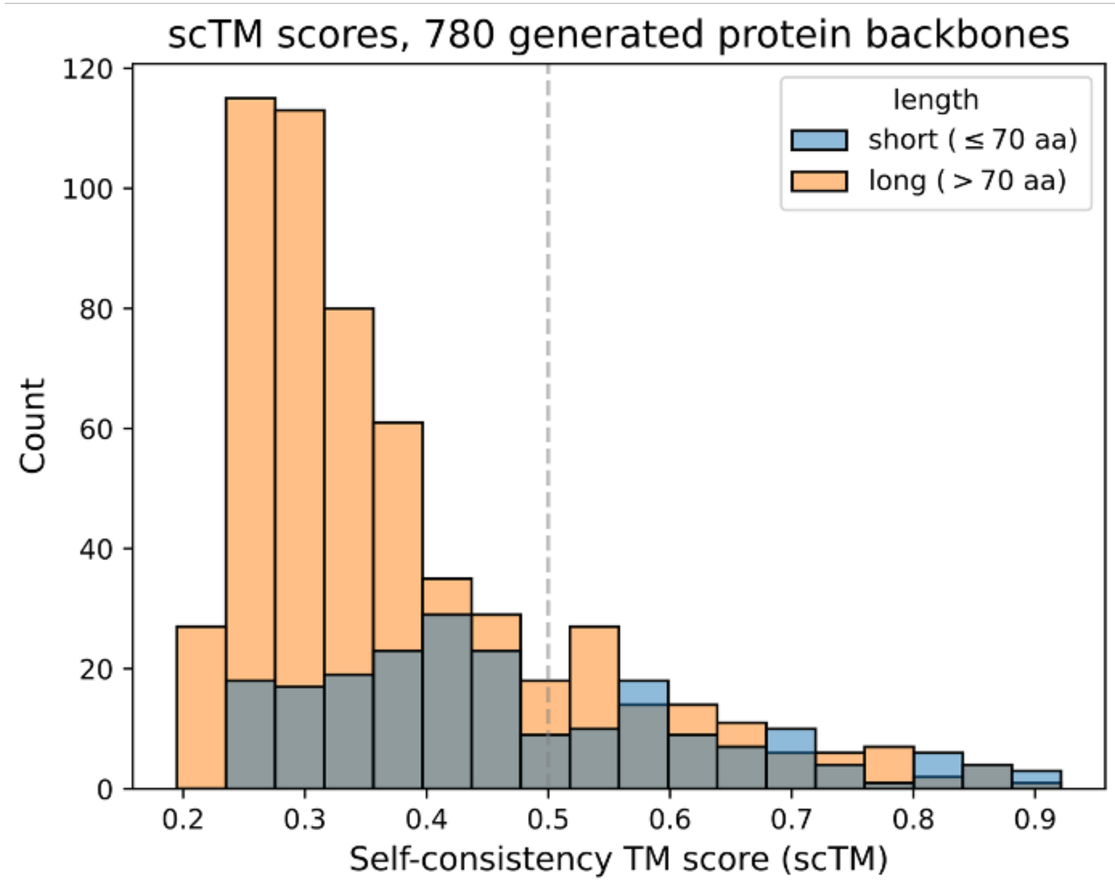
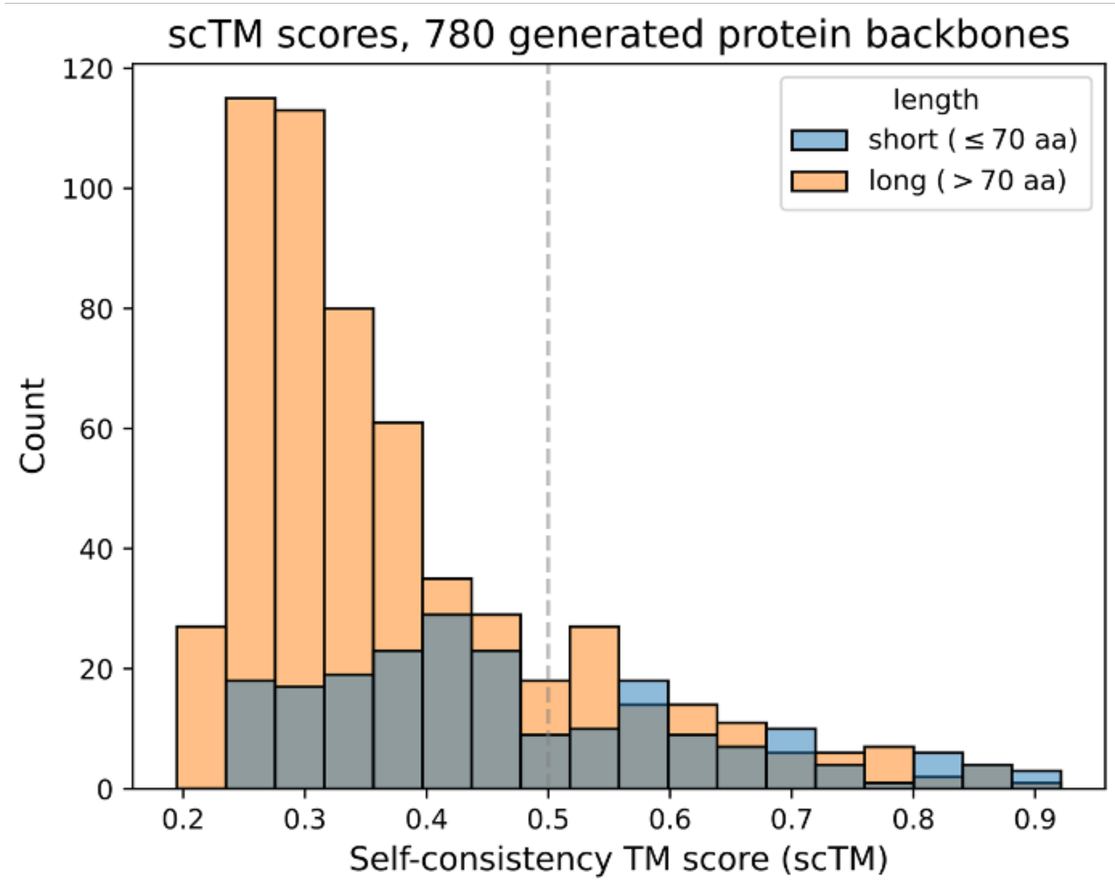


scTM > 0.5	≤ 70 aa	> 70 aa
FoldingDiff	76/210	87/570
ProtDiff (Trippe *et al.*)	36/210	56/570

Many generated structures are designable



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

Significant improvements over point cloud diffusion model

Generated structures are diverse

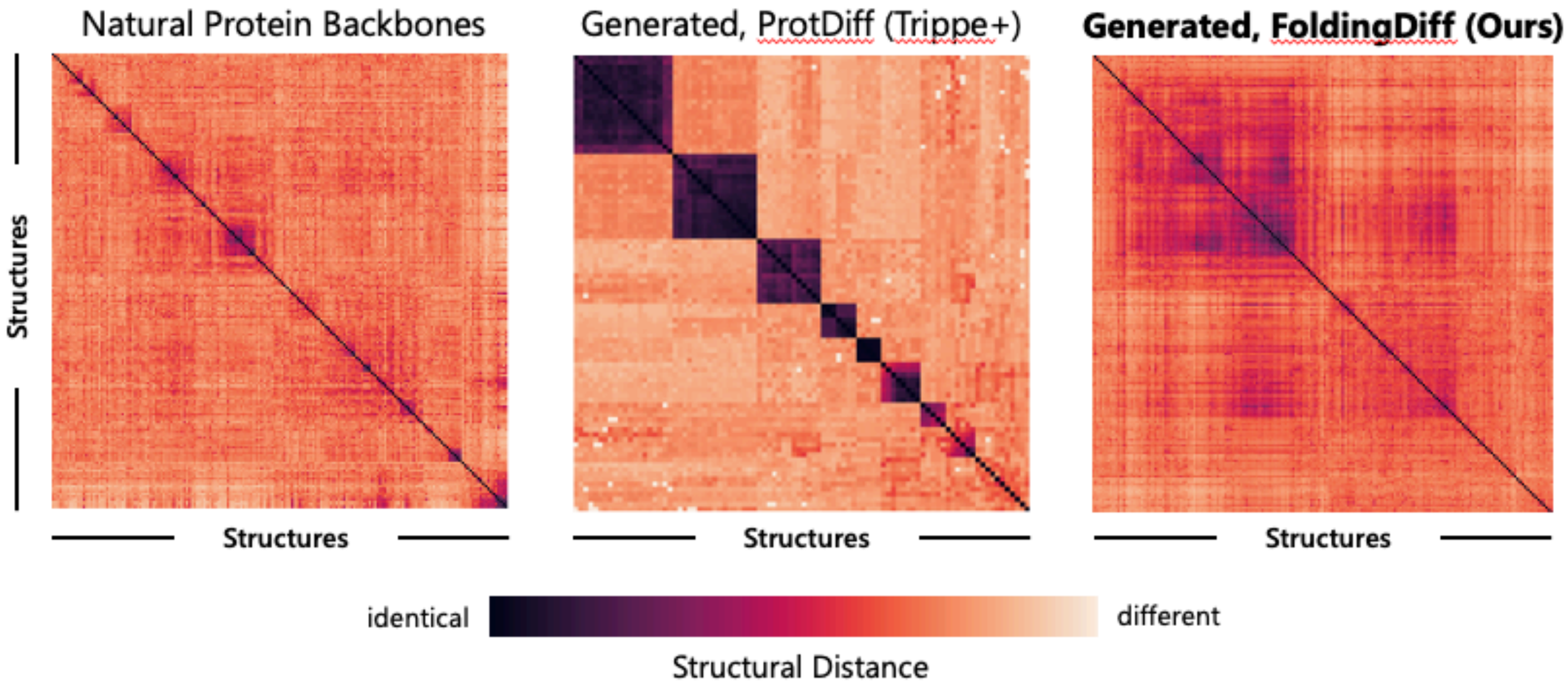
59 residues
scTM = 0.46
max training TM = 0.63

68 residues
scTM = 0.54
max training TM = 0.60

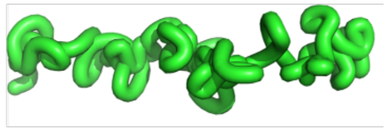
107 residues
scTM = 0.46
max training TM = 0.71

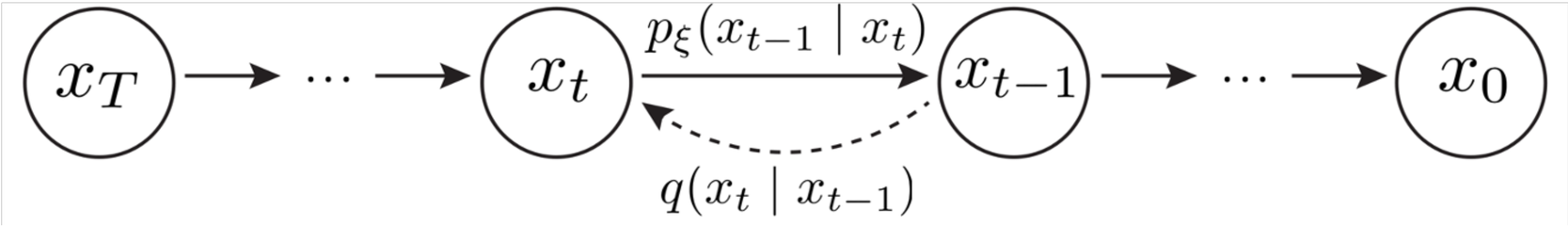
126 residues
scTM = 0.46
max training TM = 0.69

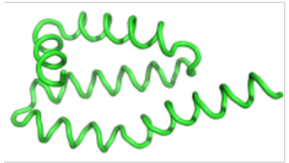
Generated structures are diverse



FoldingDiff is first step towards generating new functions

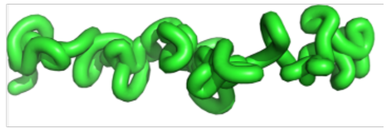




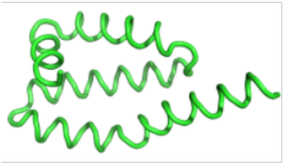


Generate protein backbones by mirroring the folding process

FoldingDiff is first step towards generating new functions

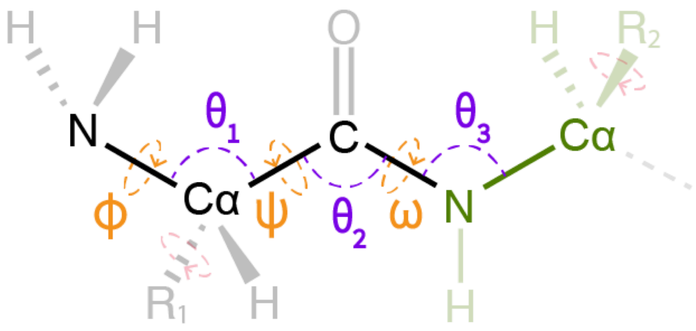


$$x_T \rightarrow \cdots \rightarrow x_t \underset{q(x_t \mid x_{t-1})}{\overset{p_\xi(x_{t-1} \mid x_t)}{\rightleftarrows}} x_{t-1} \rightarrow \cdots \rightarrow x_0$$



Generate protein backbones by mirroring the folding process

Internal coordinates



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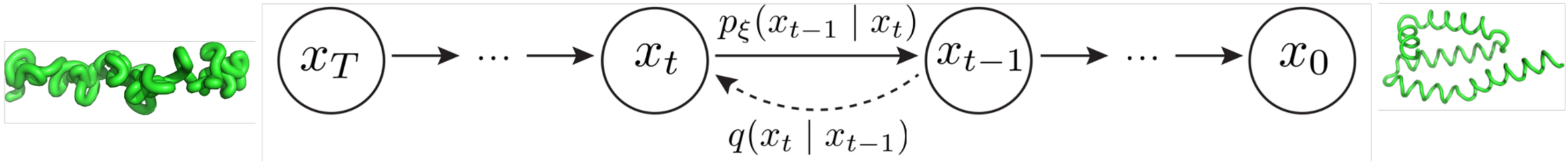
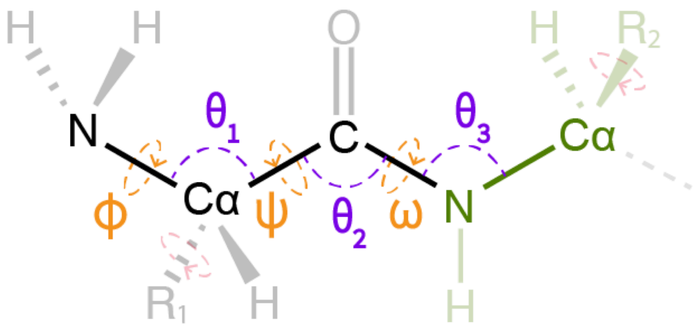
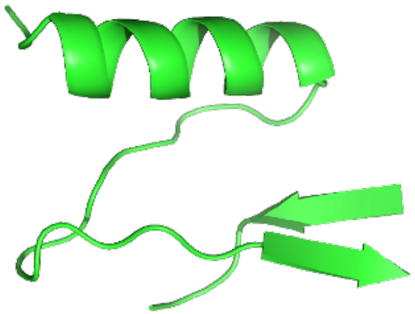


Generate protein backbones by mirroring the folding process

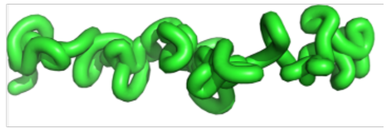
Internal coordinates



Structural motifs



FoldingDiff is first step towards generating new functions



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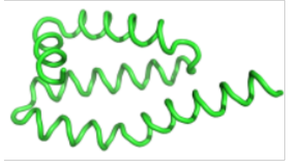
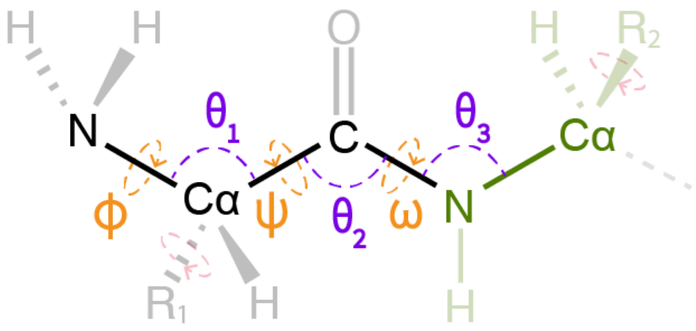
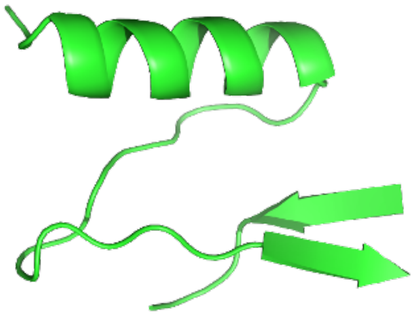


Generate protein backbones by mirroring the folding process

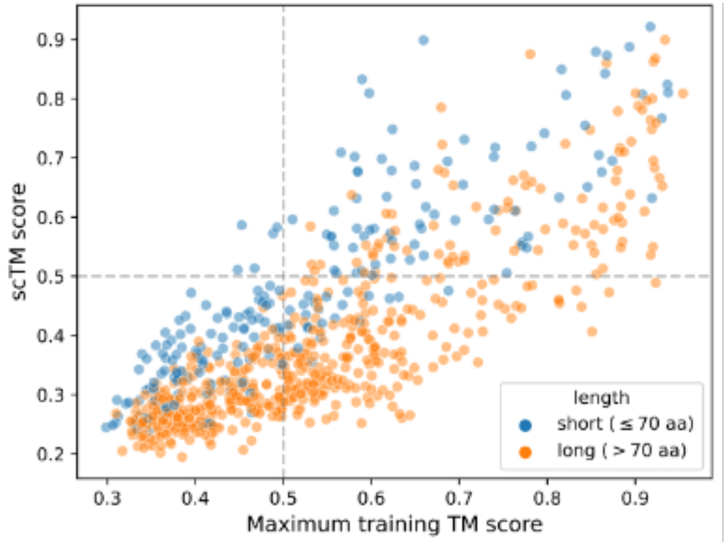
Internal coordinates



Structural motifs



Realistic, diverse samples



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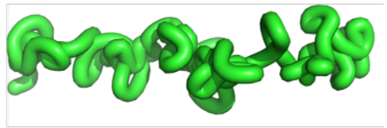
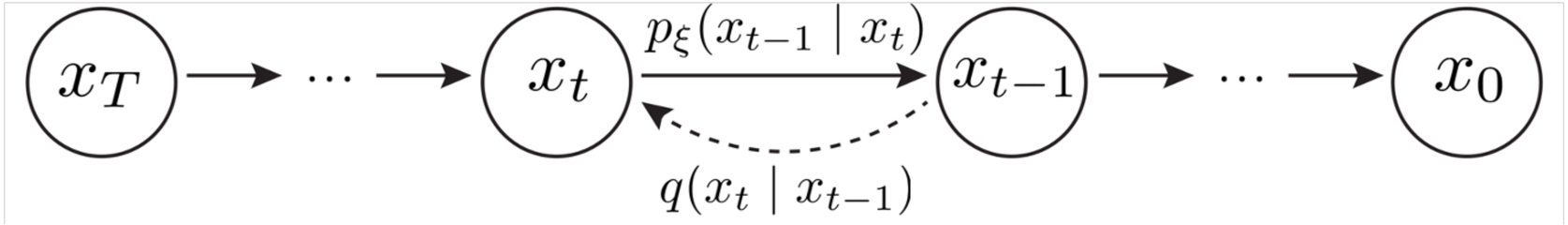
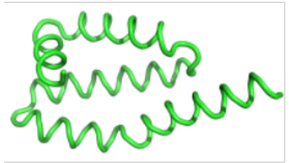
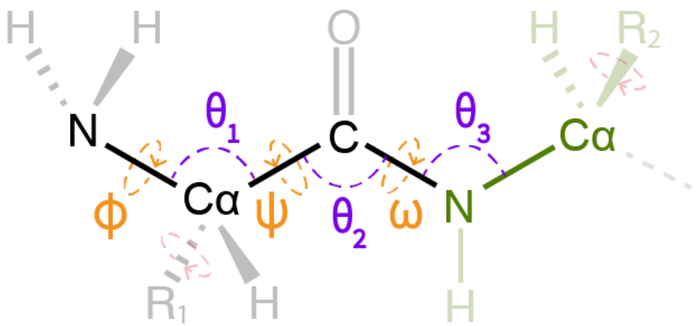




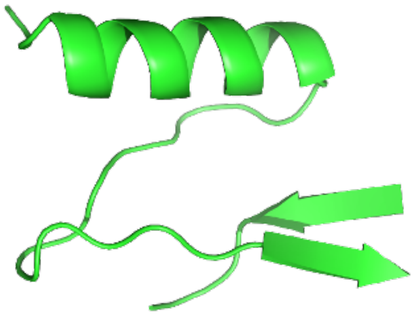


Generate protein backbones by mirroring the folding process

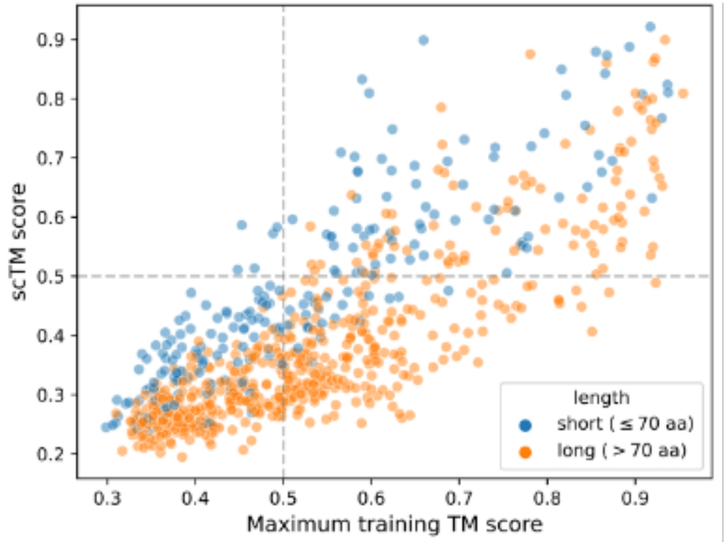
Internal coordinates



Structural motifs

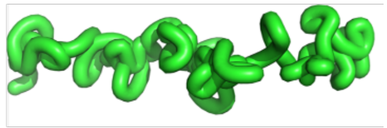


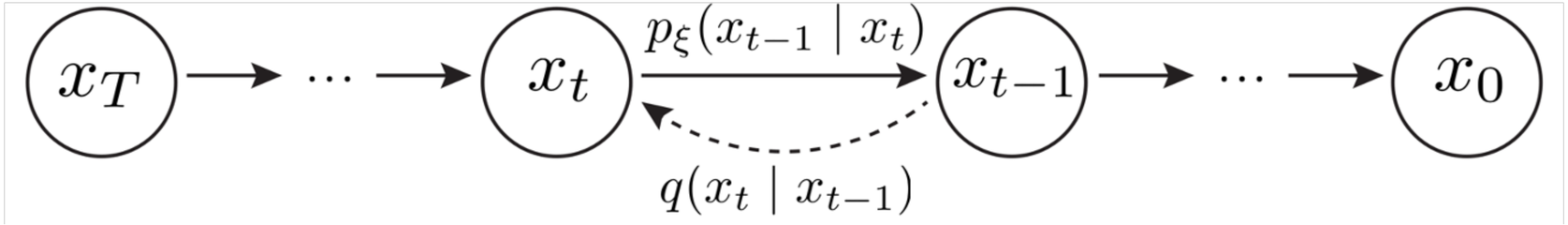
Realistic, diverse samples

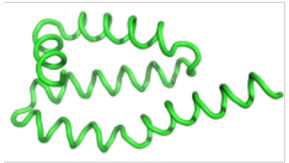


github.com/microsoft/foldingdiff

FoldingDiff is first step towards generating new functions

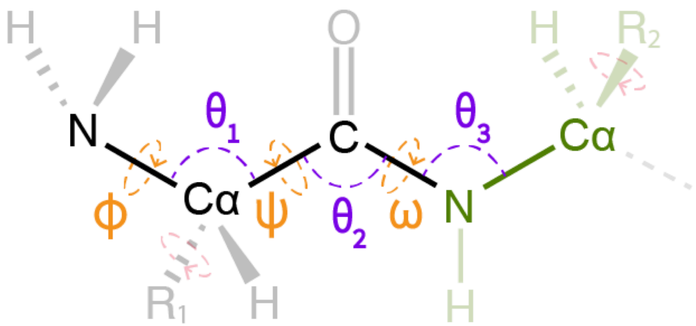




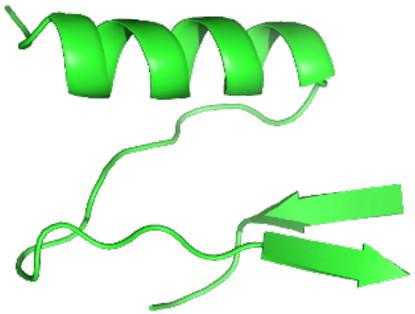


Generate protein backbones by mirroring the folding process

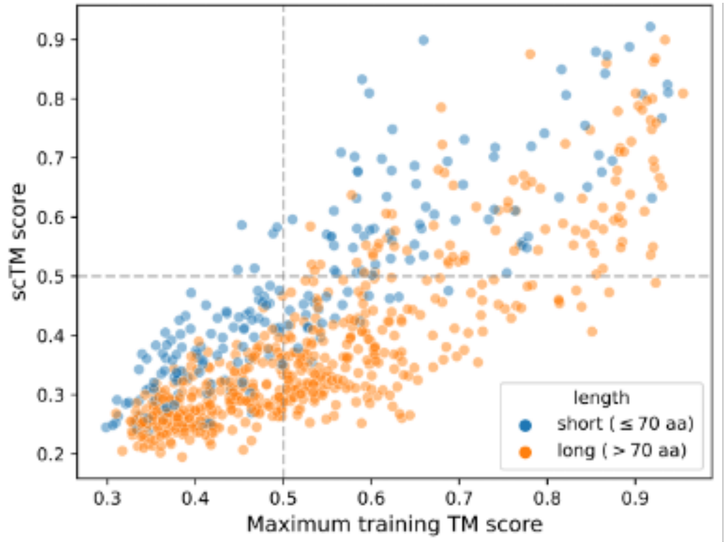
Internal coordinates



Structural motifs



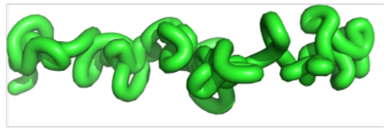
Realistic, diverse samples



github.com/microsoft/foldingdiff

huggingface.co/spaces/wukevin/foldingdiff

FoldingDiff is first step towards generating new functions



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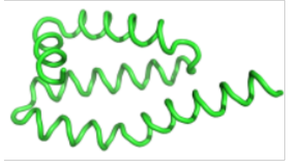
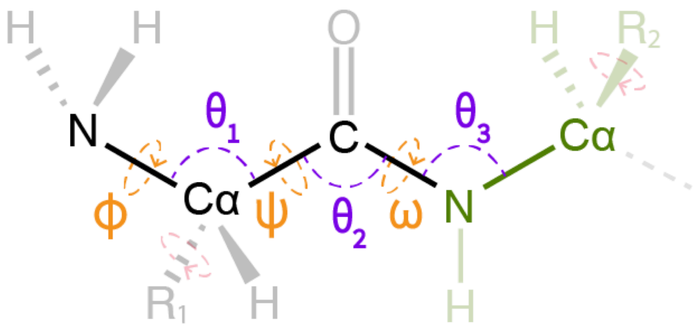
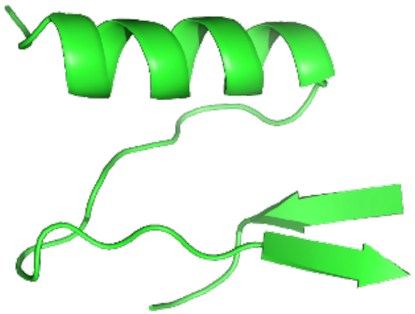


Generate protein backbones by mirroring the folding process

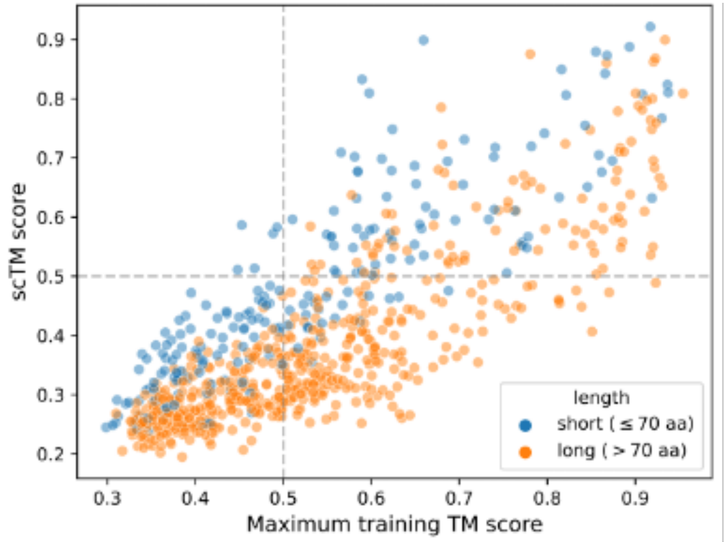
Internal coordinates



Structural motifs



Realistic, diverse samples

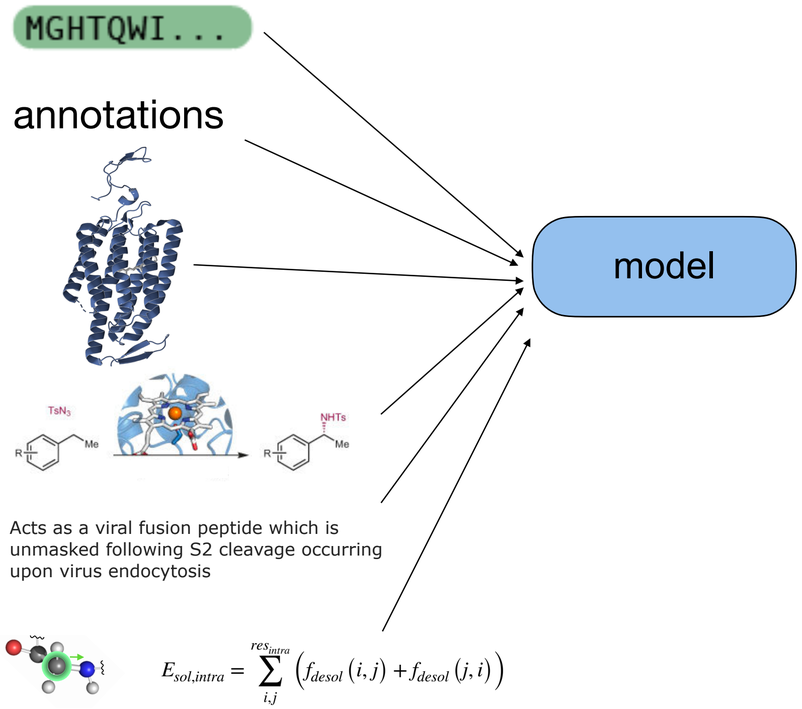


github.com/microsoft/foldingdiff

huggingface.co/spaces/wukevin/foldingdiff

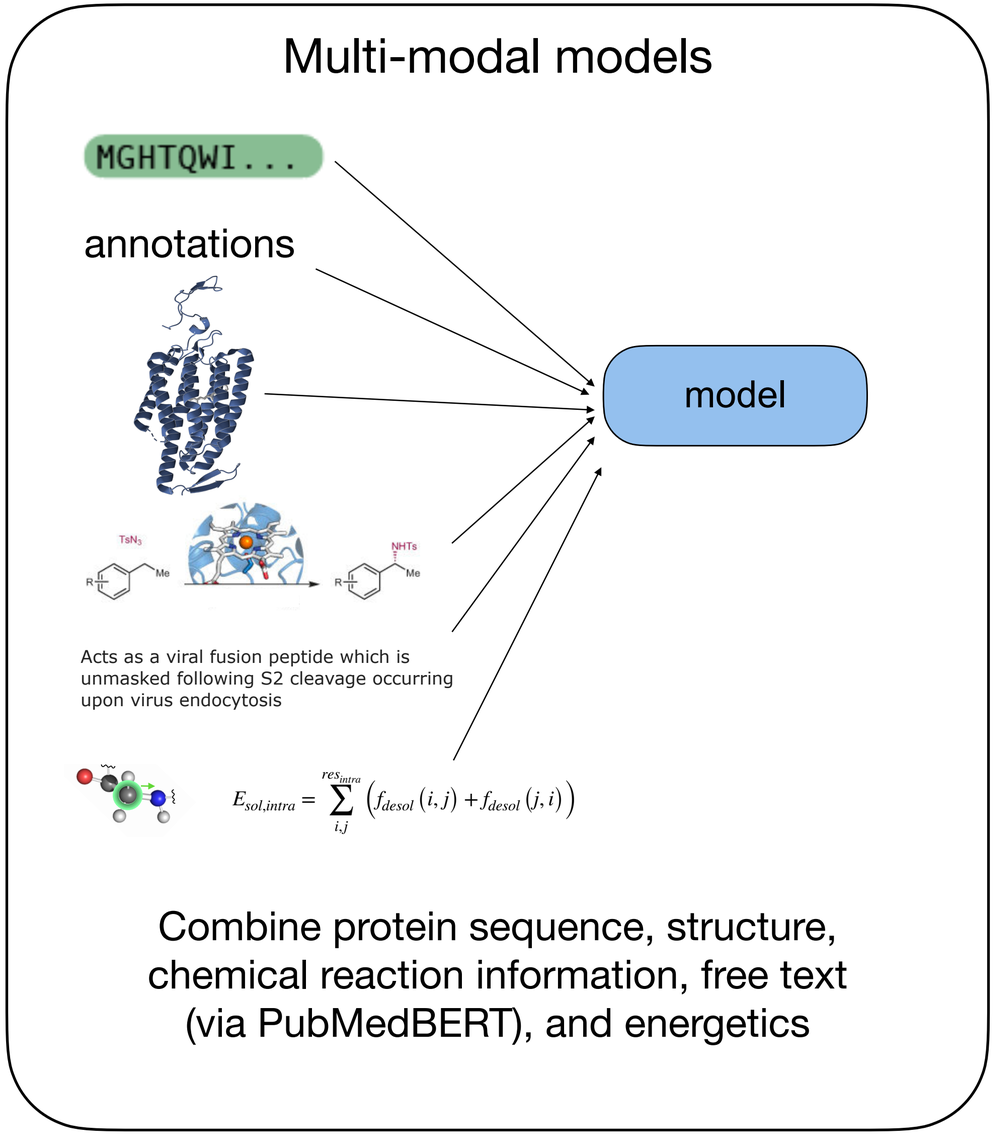
BioNeMo?

Multi-modal models

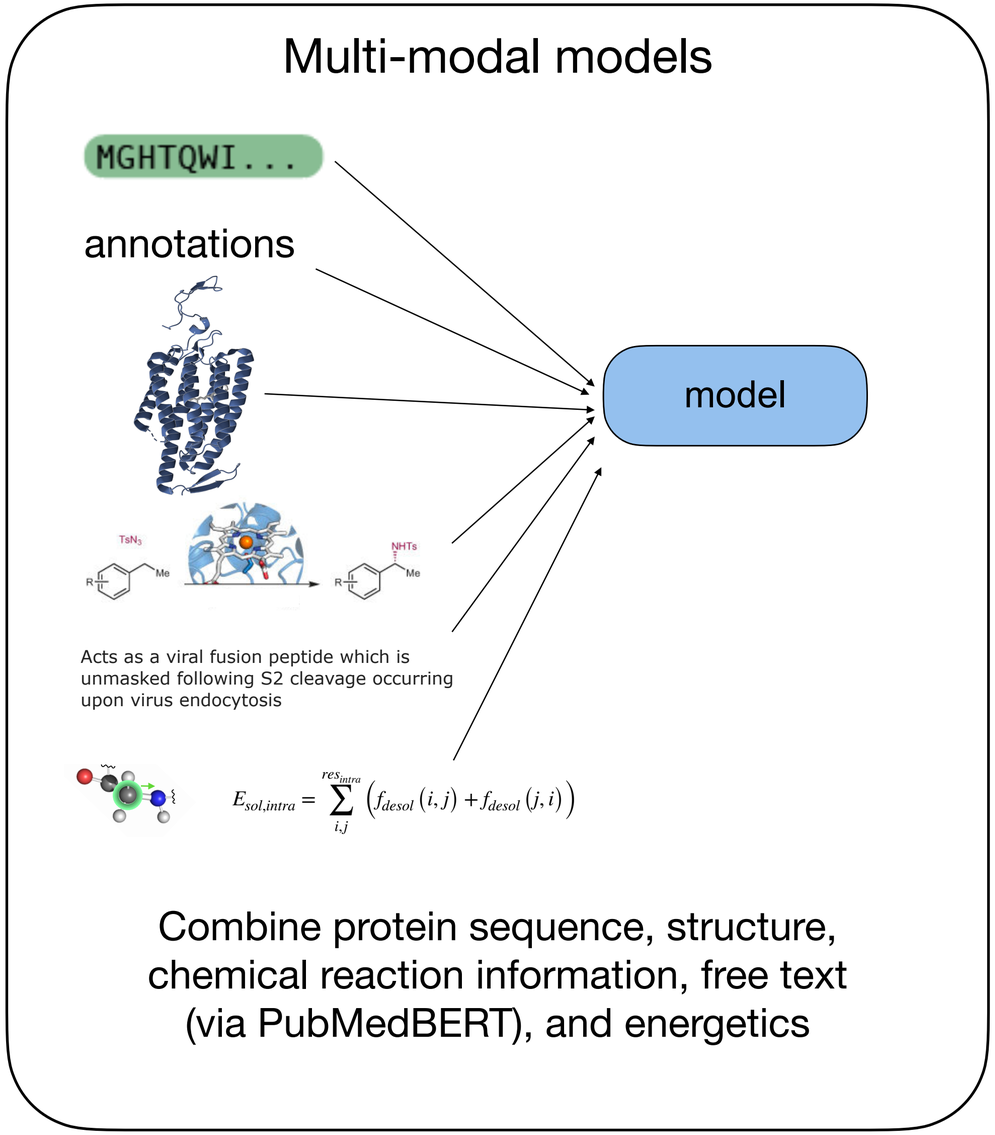


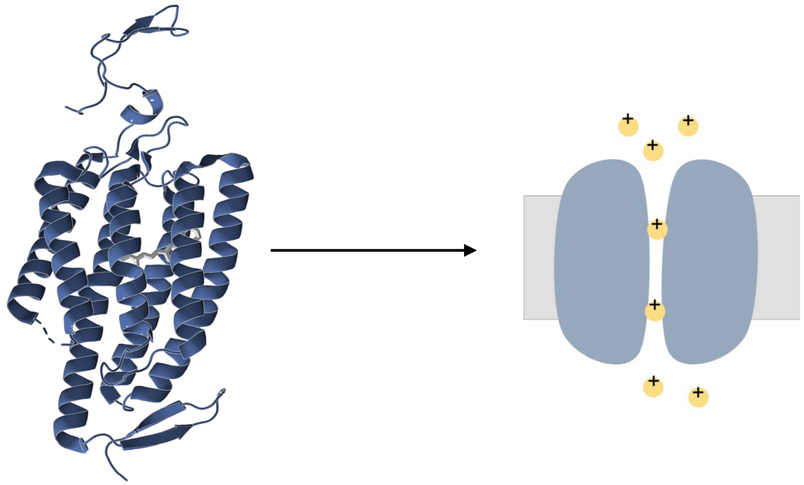
Combine protein sequence, structure, chemical reaction information, free text (via PubMedBERT), and energetics

Can we predict and generate proteins with new functions?



Can we predict and generate proteins with new functions?





Acknowledgments

BioML at MSR New England