Pretraining and Representation Learning on Proteins

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Proteins are biology’s actuators

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

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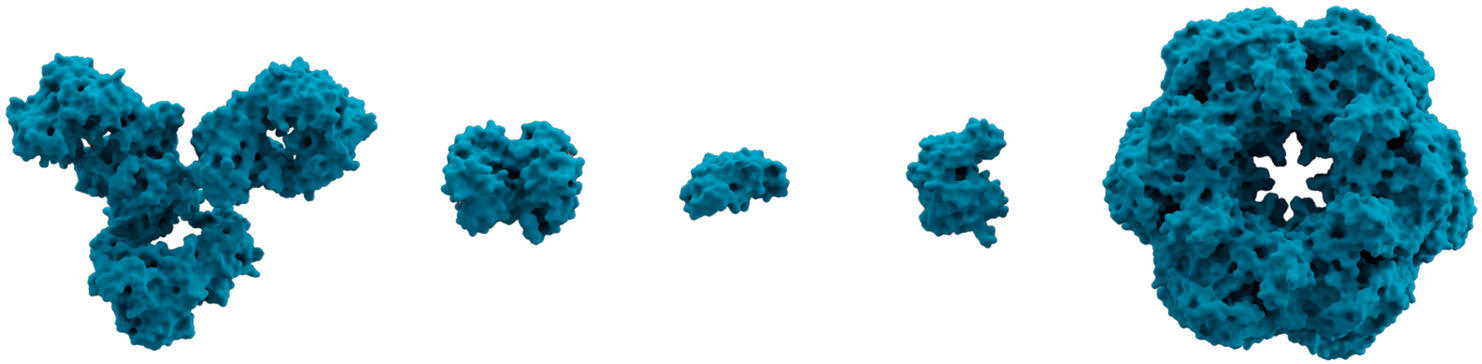

IgG hemoglobin insulin adenylate kinase glutamine synthetase

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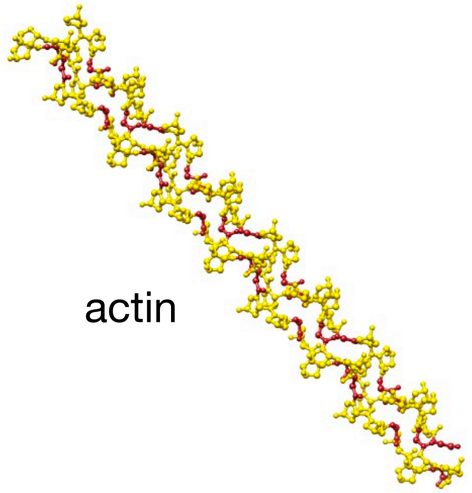
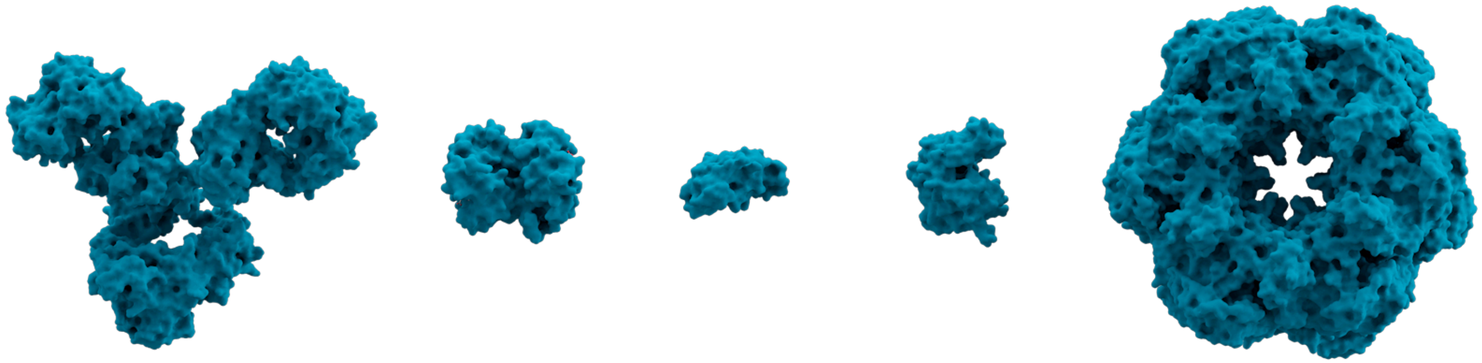


actin



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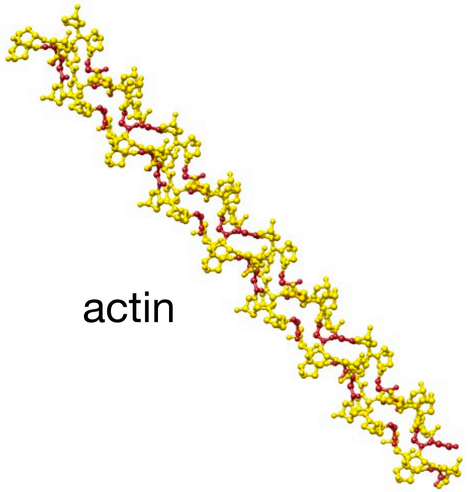

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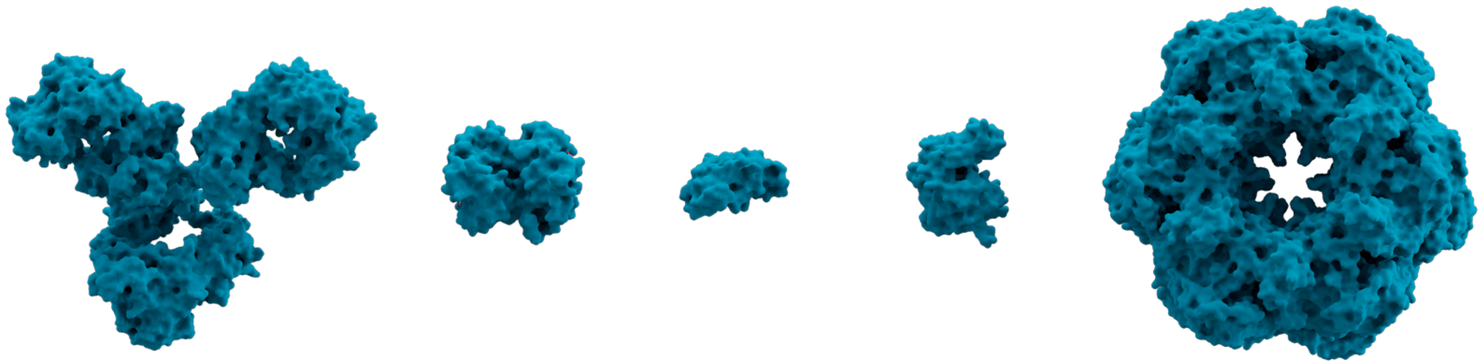
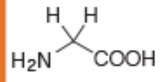


IgG hemoglobin insulin adenylate kinase glutamine synthetase

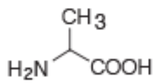
luciferase

Diversity arises from 20 building blocks

SMALL

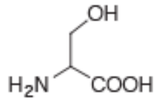


Glycine (Gly, G)
MW: 75.07

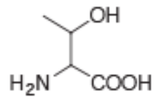


Alanine (Ala, A)
MW: 89.09

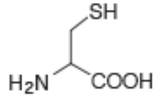
NUCLEOPHILIC



Serine (Ser, S)
MW: 105.09, $pK_a \sim 16$

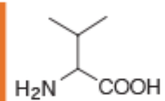


Threonine (Thr, T)
MW: 119.1, $pK_a \sim 16$

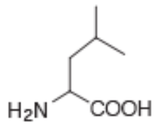


Cysteine (Cys, C)
MW: 121.2, $pK_a = 8.18$

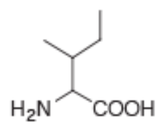
HYDROPHOBIC



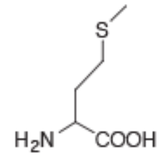
Valine (Val, V)
MW: 117.1



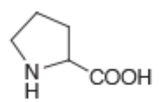
Leucine (Leu, L)
MW: 131.2



Isoleucine (Ile, I)
MW: 131.2

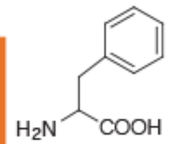


Methionine (Met, M)
MW: 149.2

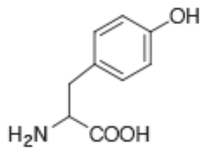


Proline (Pro, P)
MW: 115.1

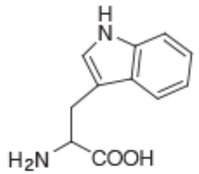
AROMATIC



Phenylalanine (Phe, F)
MW: 165.2

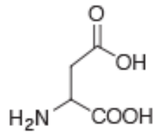


Tyrosine (Tyr, Y)
MW: 181.2, $pK_a = 10.46$

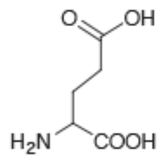


Tryptophan (Trp, W)
MW: 204.2

ACIDIC

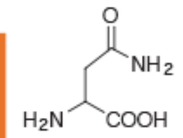


Aspartic Acid (Asp, D)
MW: 133.1, $pK_a = 3.9$

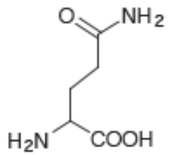


Glutamic Acid (Glu, E)
MW: 147.1, $pK_a = 4.07$

AMIDE

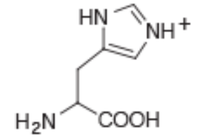


Asparagine (Asn, N)
MW: 132.1

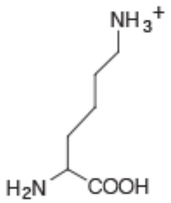


Glutamine (Gln, Q)
MW: 146.1

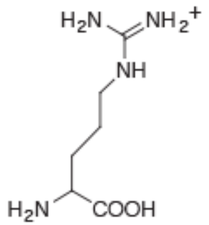
BASIC



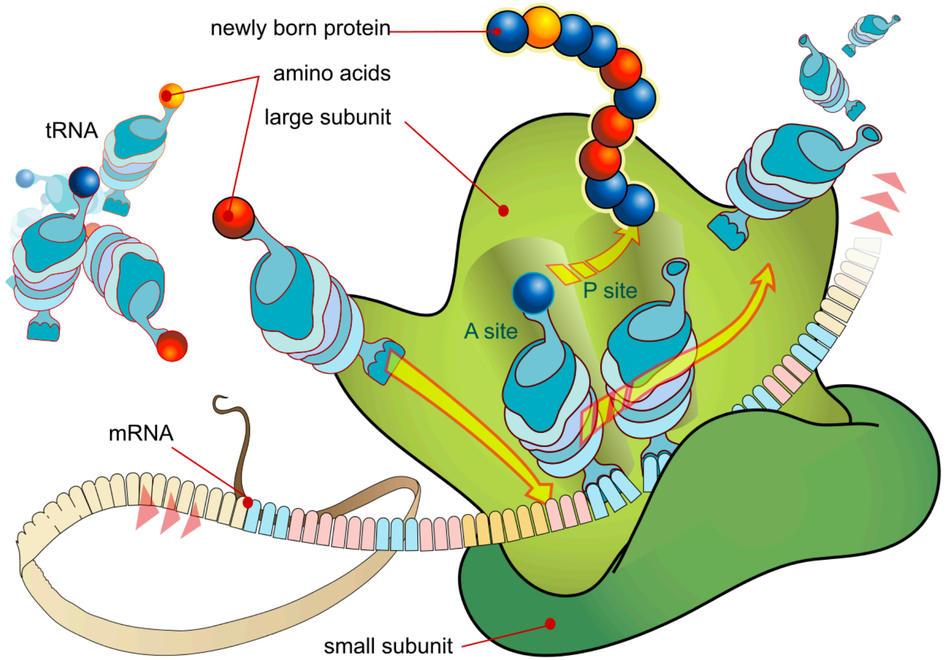
Histidine (His, H)
MW: 155.2, $pK_a = 6.04$



Lysine (Lys, K)
MW: 146.2, $pK_a = 10.79$



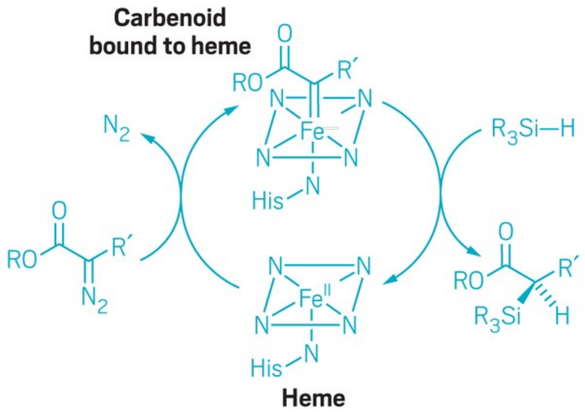
Arginine (Arg, R)
MW: 174.2, $pK_a = 12.48$



Why design proteins?

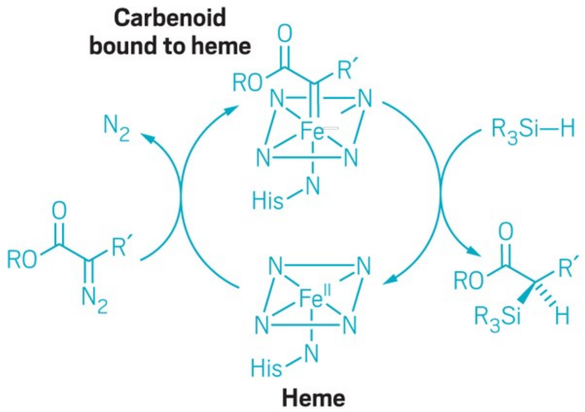
Why design proteins?

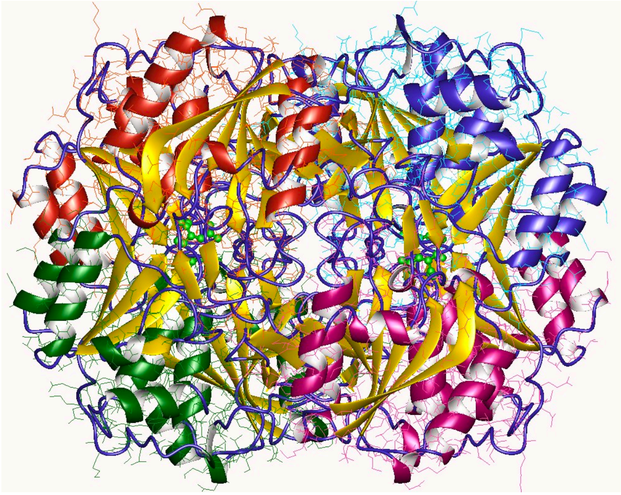
- New chemistry



Why design proteins?

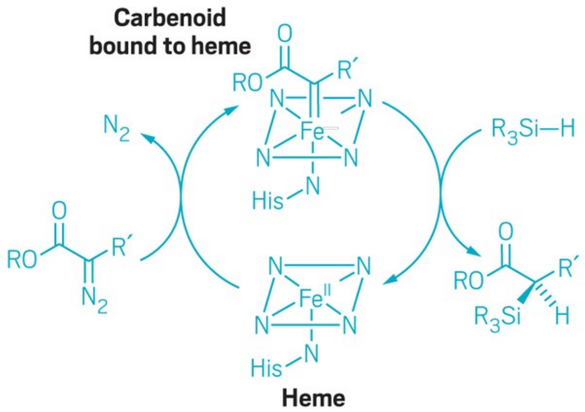
- New chemistry
- Therapeutics

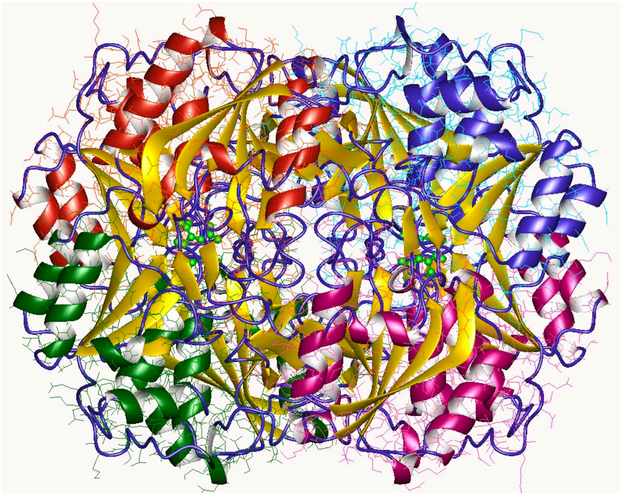


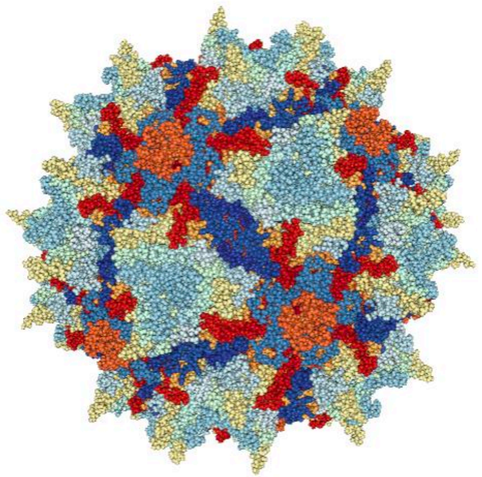


Why design proteins?

- New chemistry
- Therapeutics
- To learn how they work

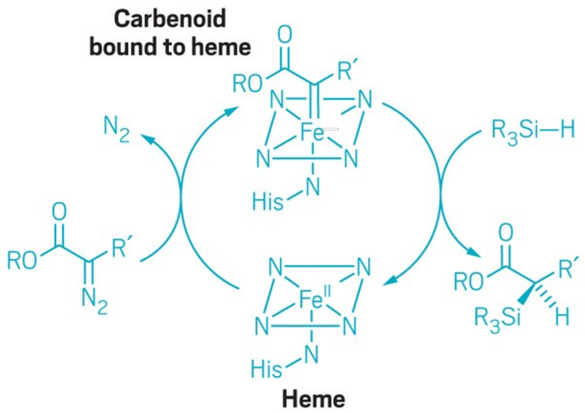


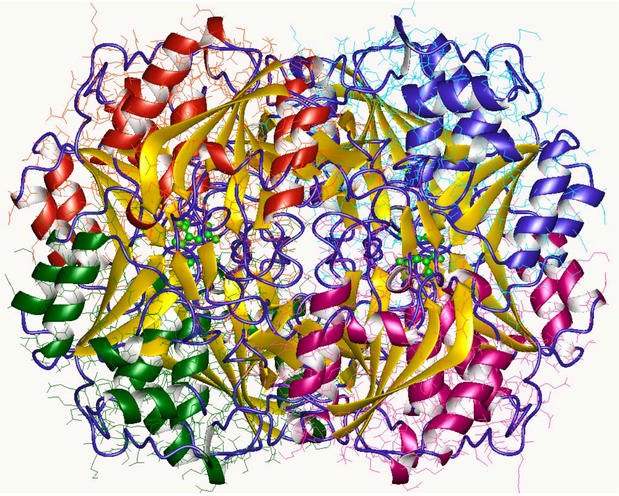


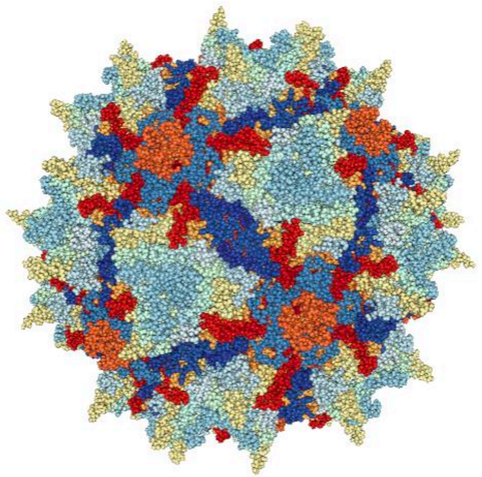


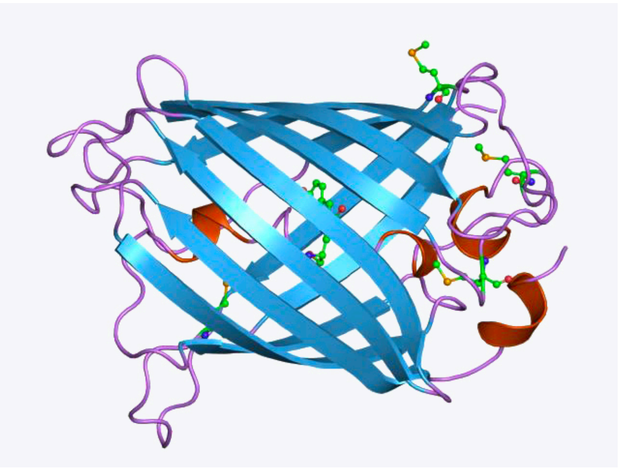
Why design proteins?

- New chemistry
- Therapeutics
- To learn how they work
- Molecular tools









The protein design problem

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MGTGDHDD...

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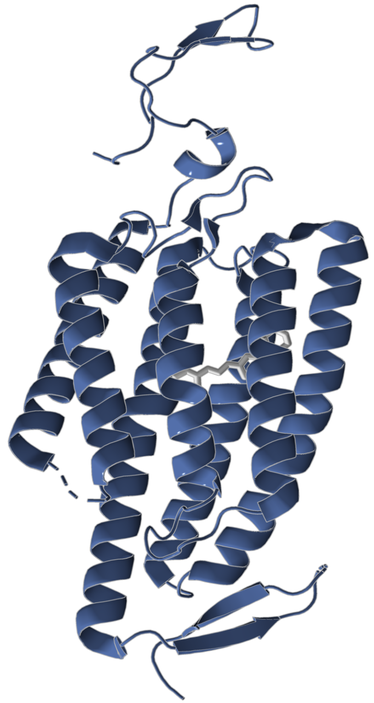
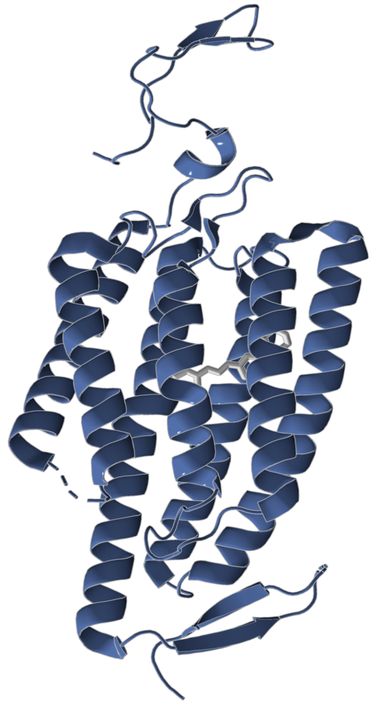
MGTGDHDD...



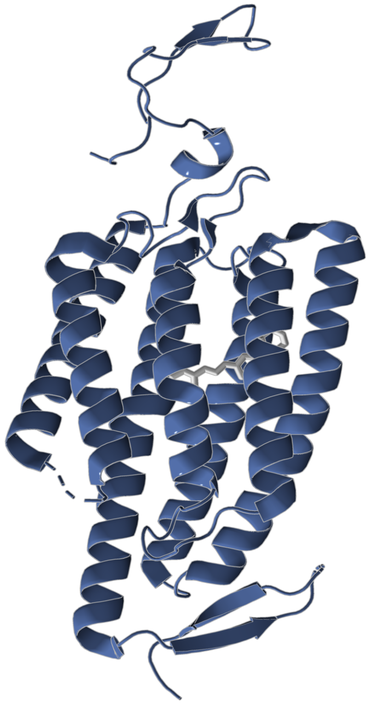
The protein design problem

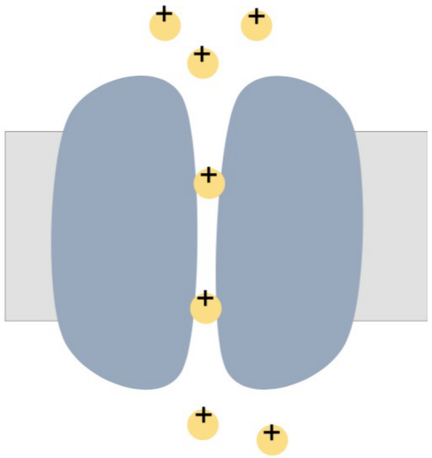
MGTGDHDD... ? 

The protein design problem

MGTGDHDD...

?

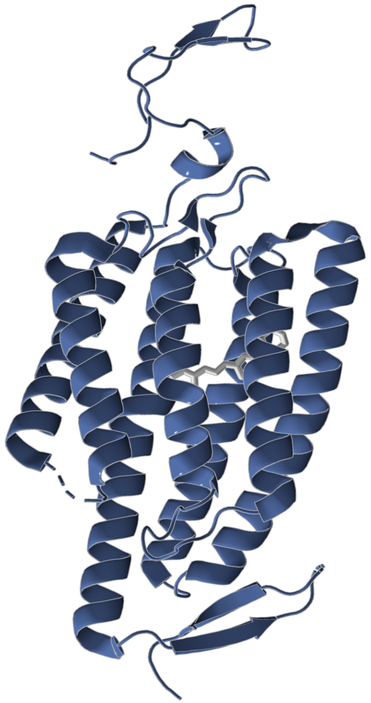




The protein design problem

MGTGDHDD...

?



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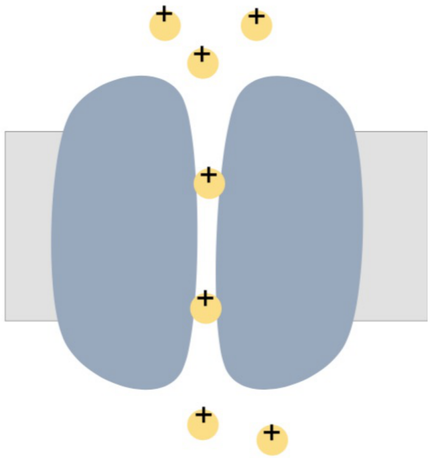
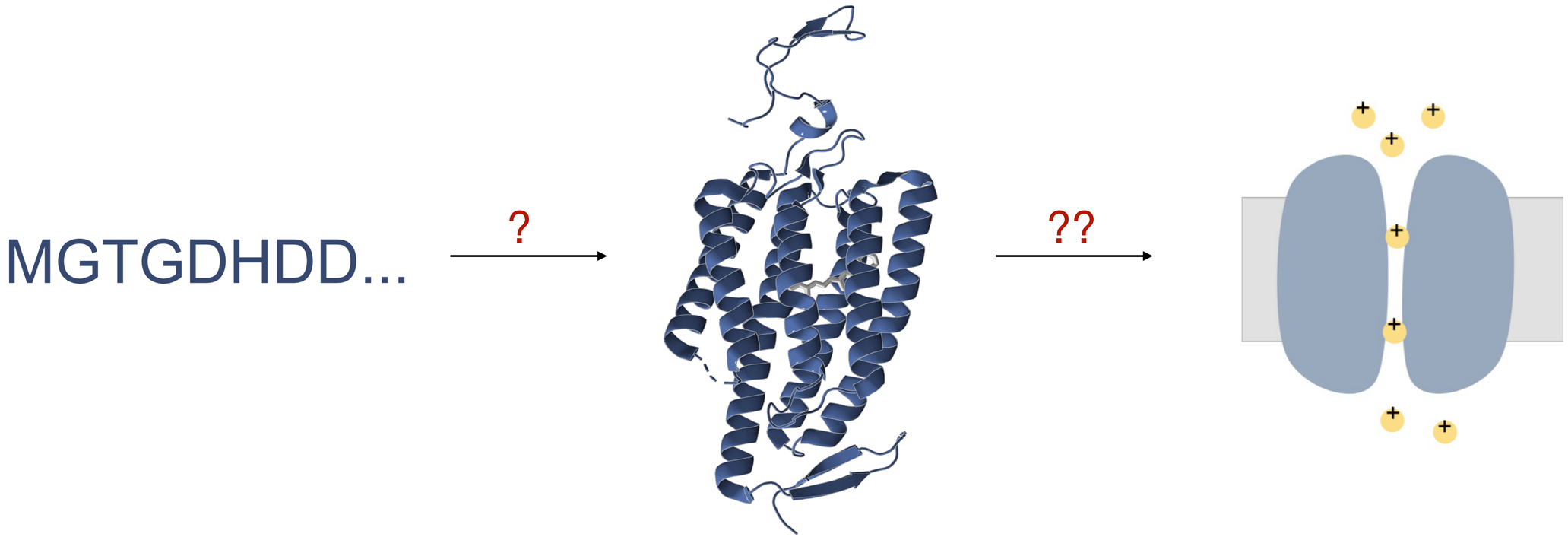


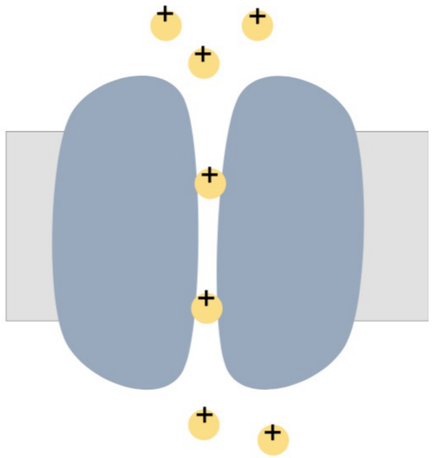
The protein design problem

MGTGDHDD...



What sequence will give the desired function?

The protein design problem

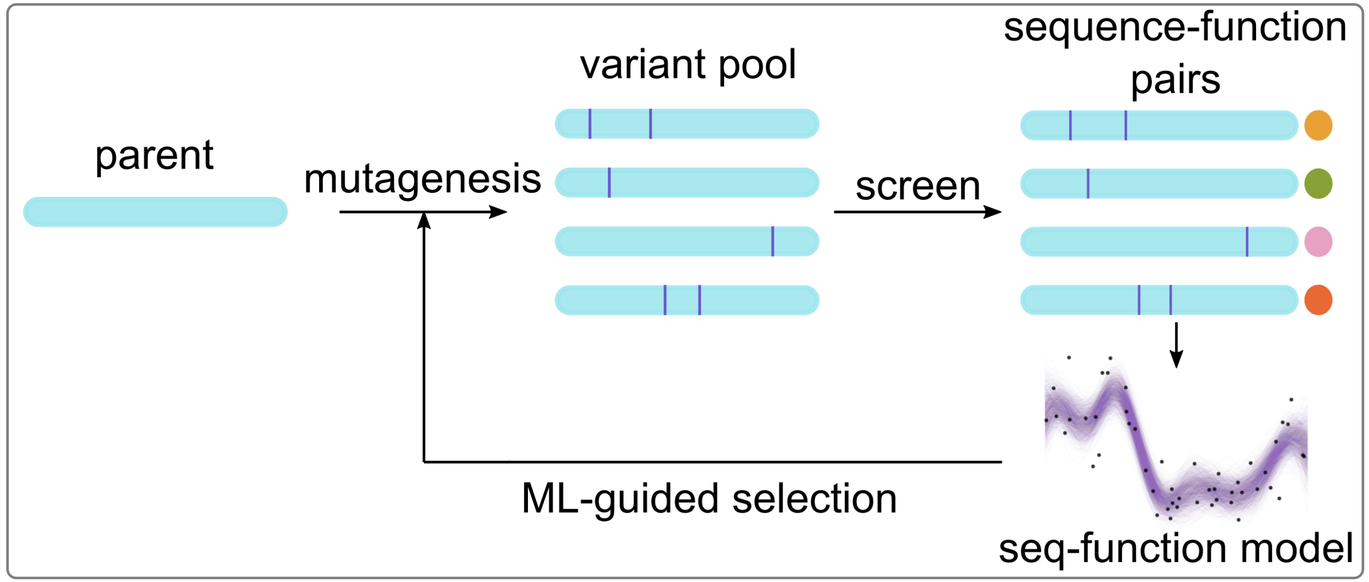


???

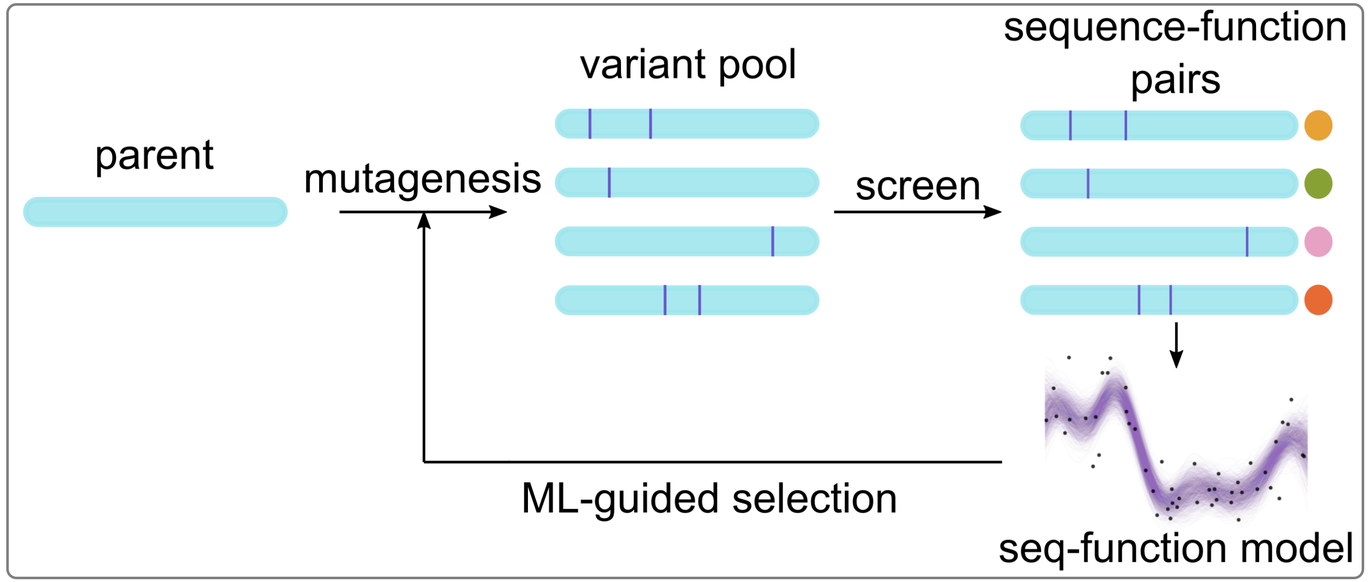
MGTGDHDD...

What sequence will give the desired function?

Machine learning enables optimization with fewer measurements

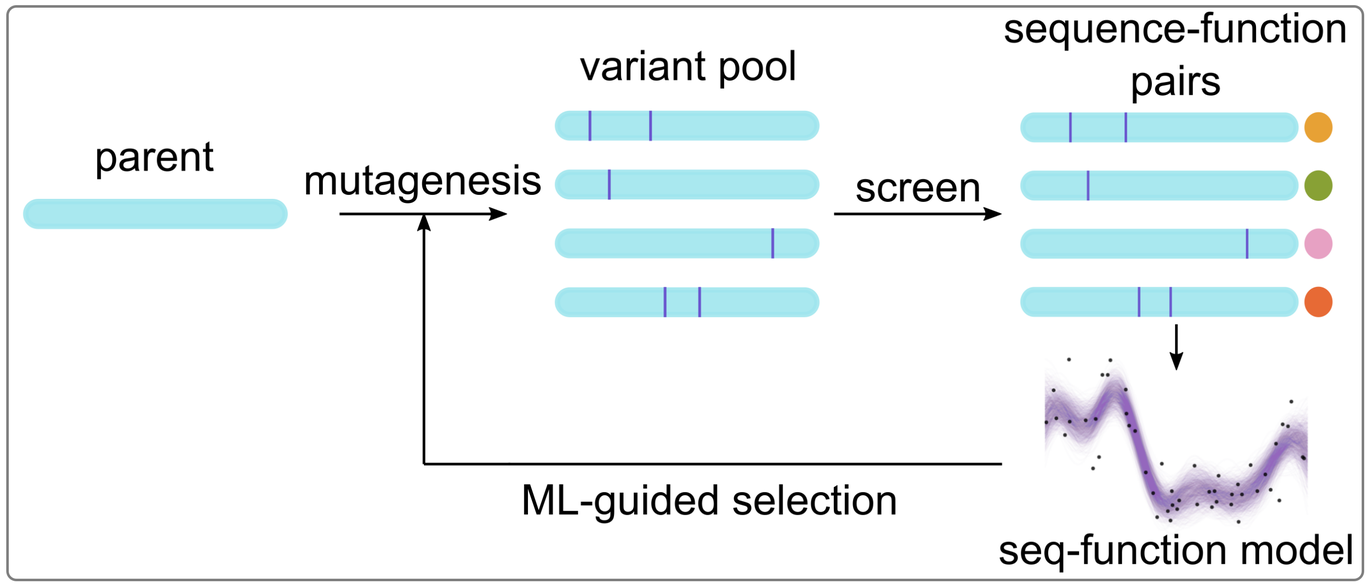


Machine learning enables optimization with fewer measurements



Channelrhodopsin current
~200 measurements (Bedbrook 2019)

Machine learning enables optimization with fewer measurements



Channelrhodopsin current
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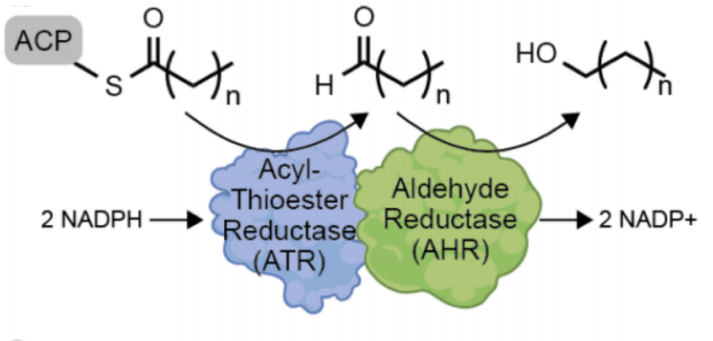
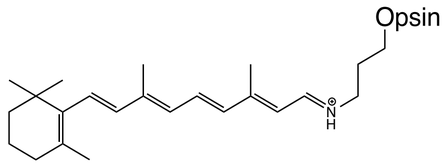


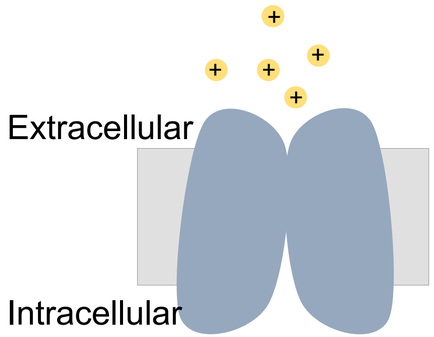
acyl-ACP reductase fatty alcohol synthesis
~100 measurements (Greenhalgh 2021)

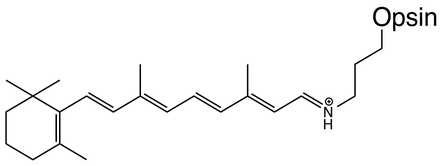
Channelrhodopsins: light-gated ion channels

Channelrhodopsins: light-gated ion channels

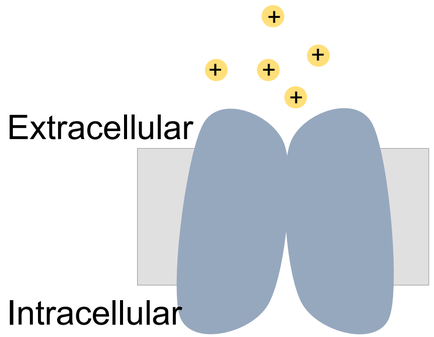


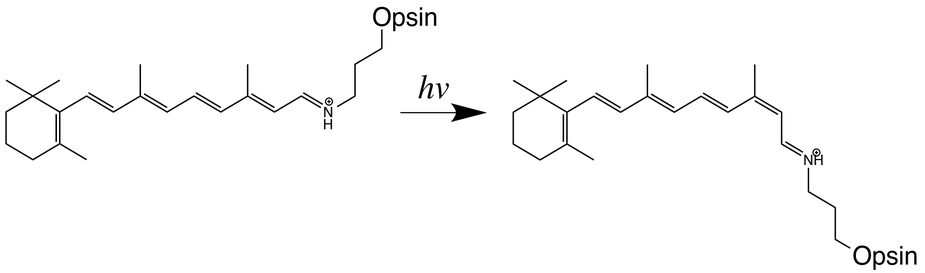
Channelrhodopsins: light-gated ion channels



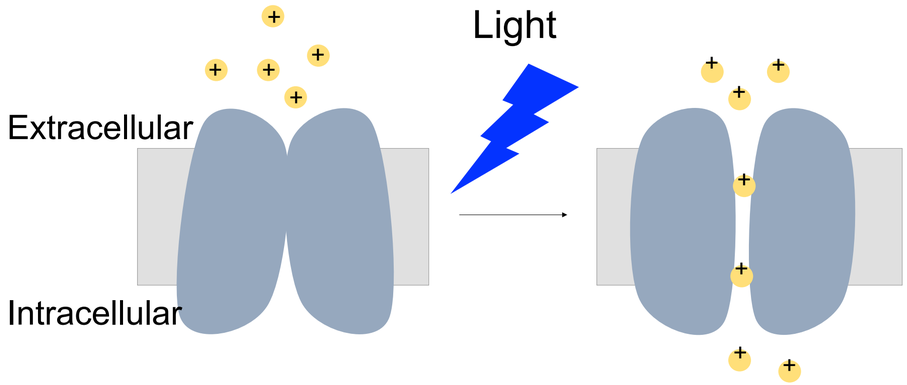


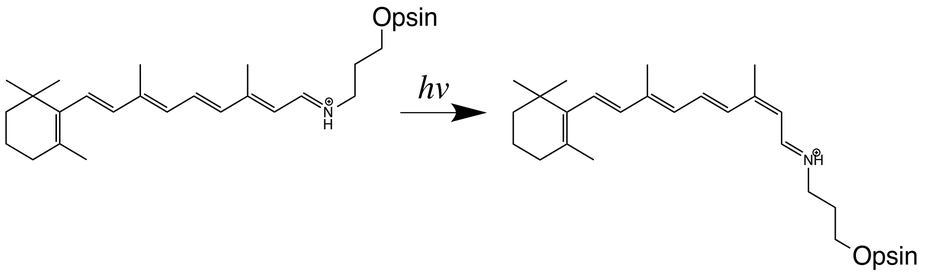
Channelrhodopsins: light-gated ion channels



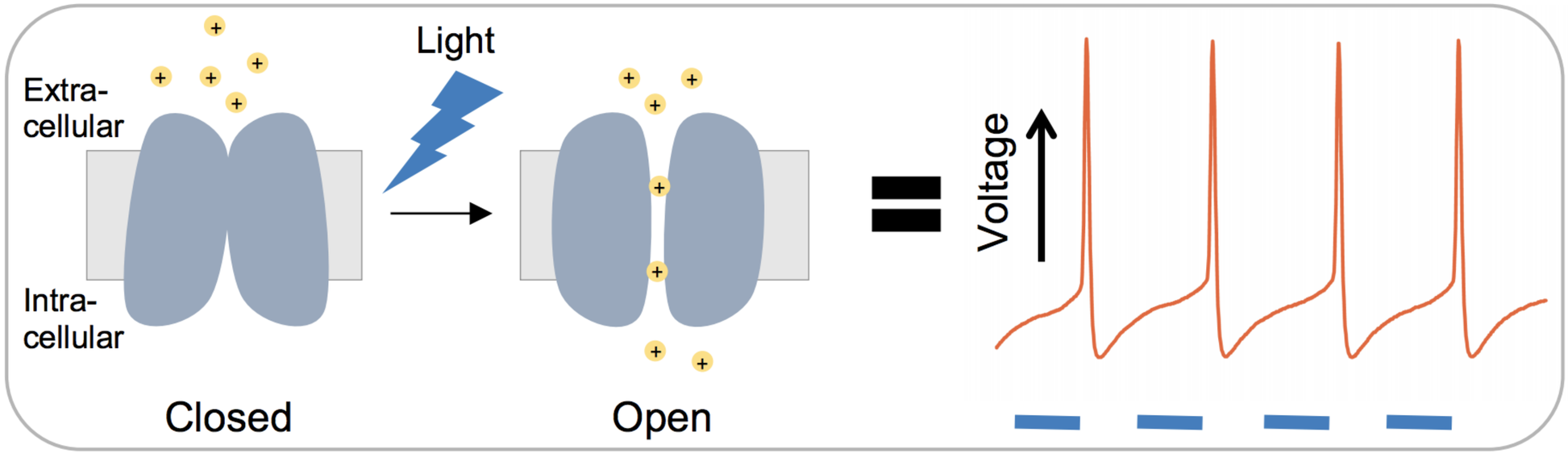


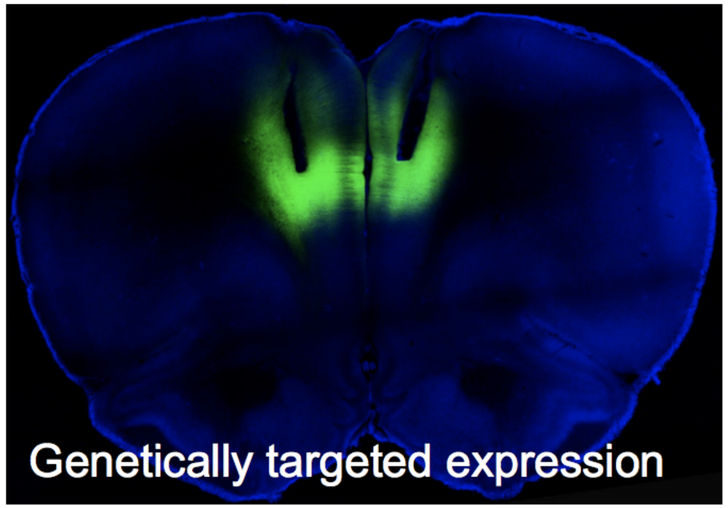
Channelrhodopsins: light-gated ion channels





ChRs are optogenetic tools



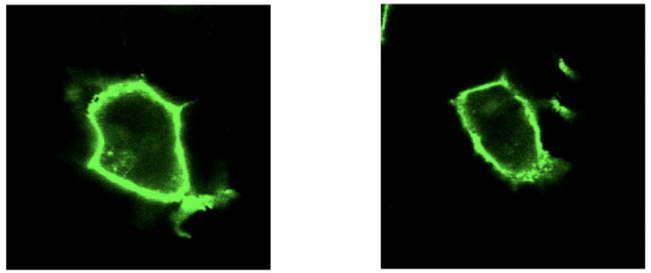


Optogenetics, Nature Method of the year, 2010

Multiple engineering goals

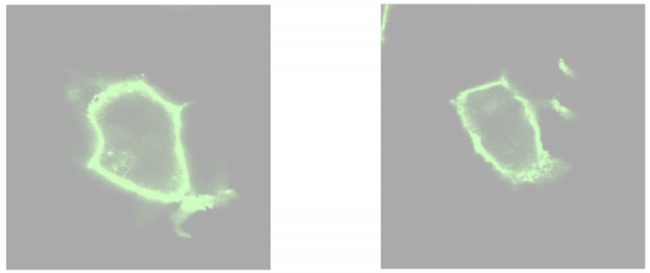
Multiple engineering goals

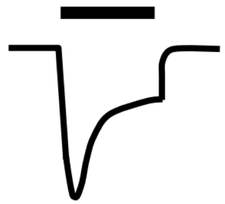
- Heterologous membrane localization



Multiple engineering goals

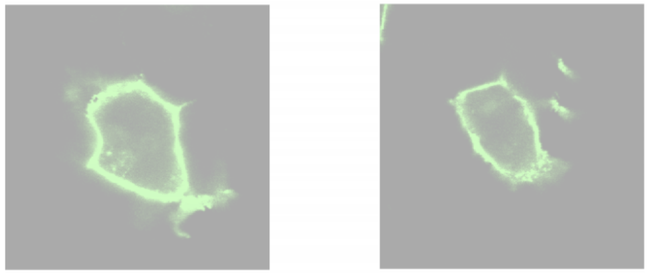
- Heterologous membrane localization
- Increased sensitivity

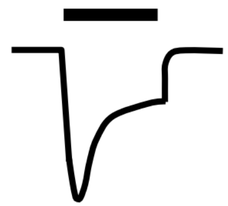




Multiple engineering goals

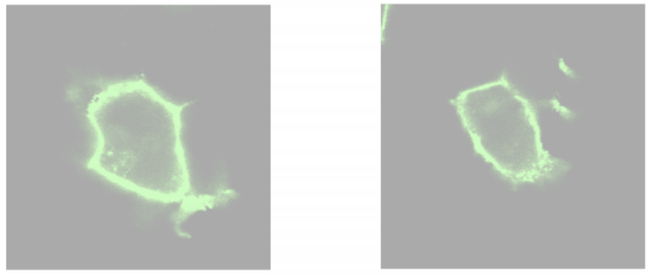
- Heterologous membrane localization
- Increased sensitivity
- Different activation wavelengths



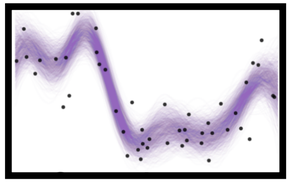


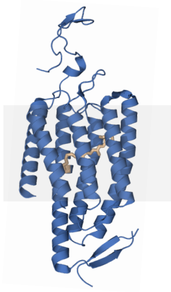
Multiple engineering goals

- Heterologous membrane localization
- Increased sensitivity
- Different activation wavelengths
- Different on/off kinetics



Machine learning enables optimization with fewer measurements





Channelrhodopsin current
~200 measurements (Bedbrook 2019)

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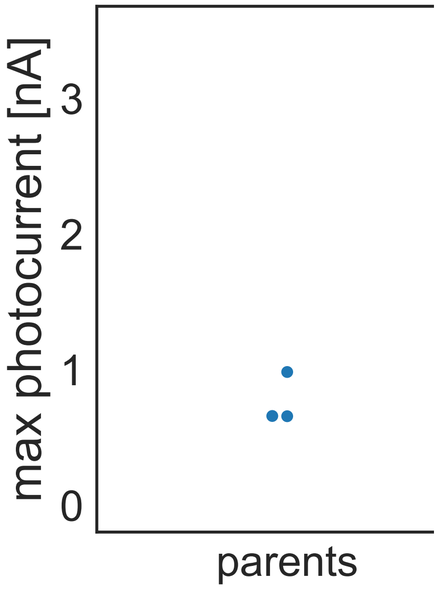

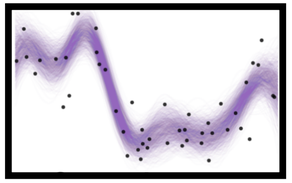

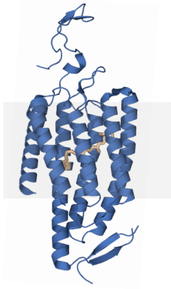

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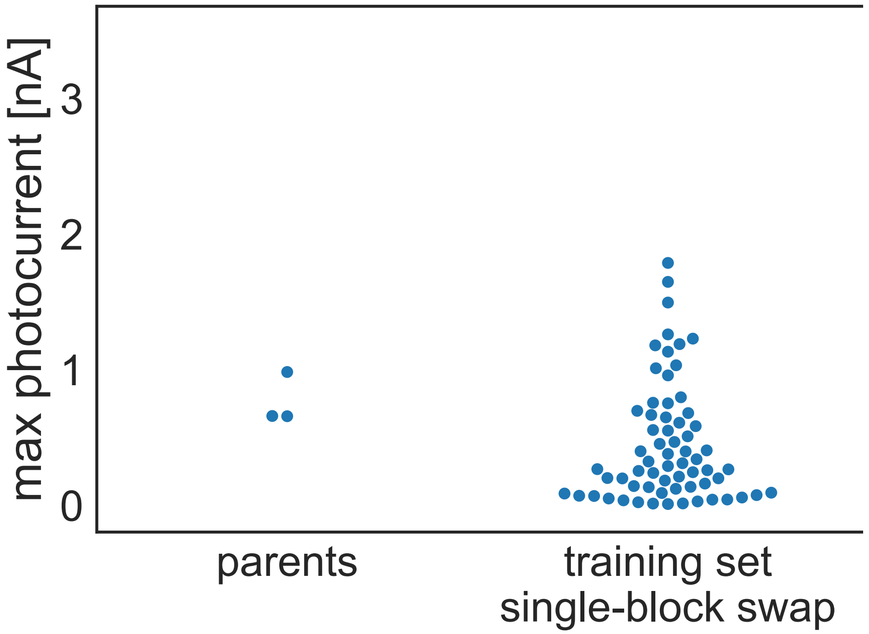

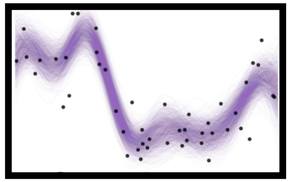

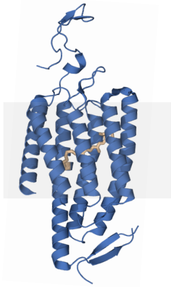

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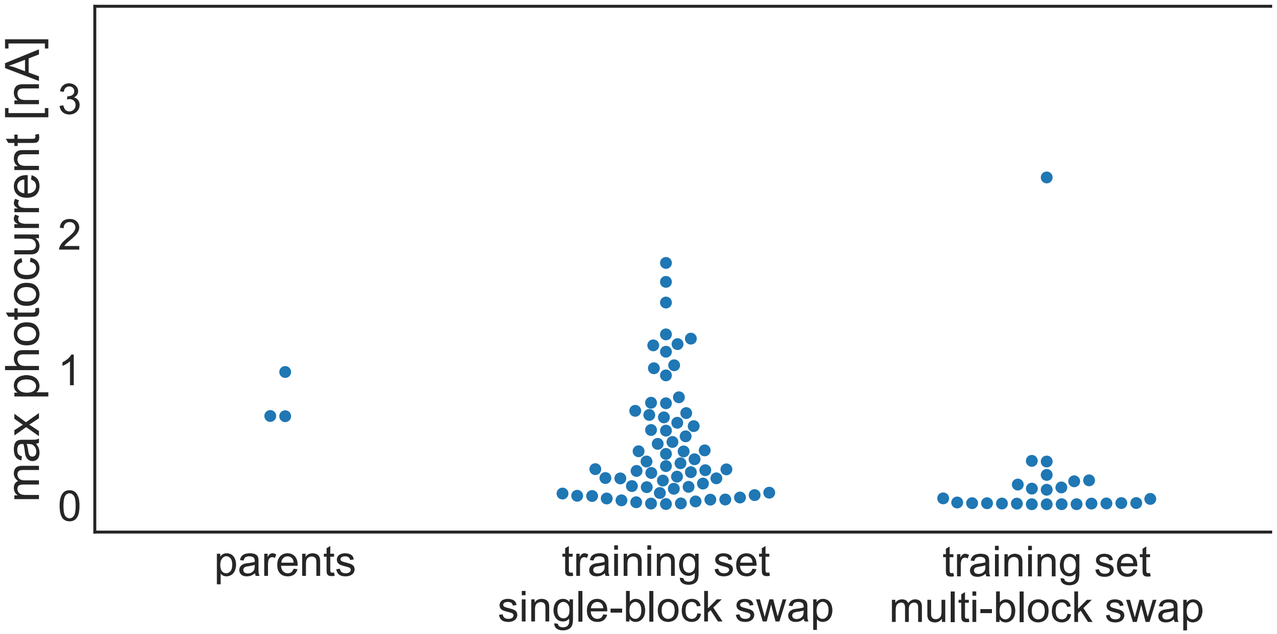

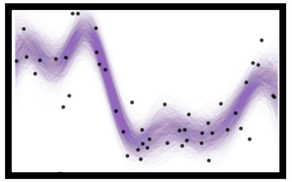

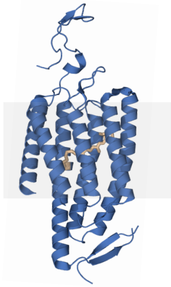

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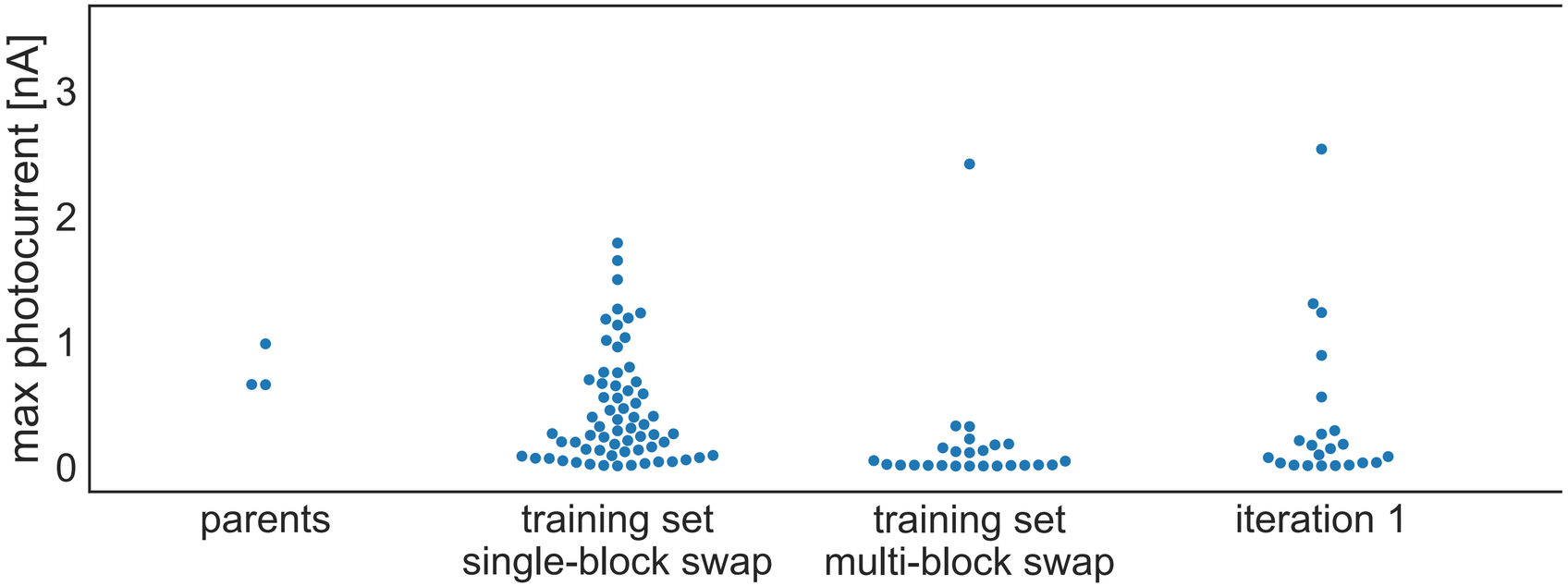

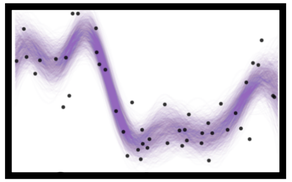

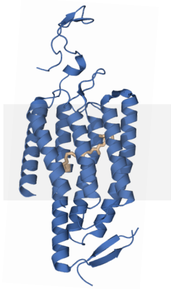

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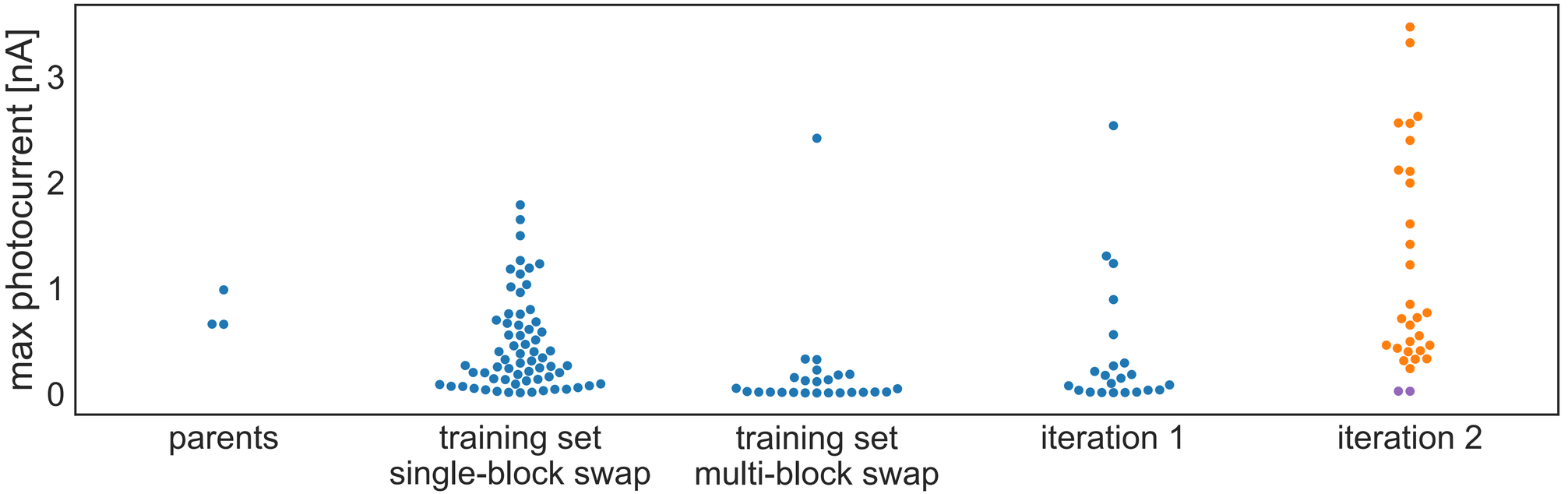

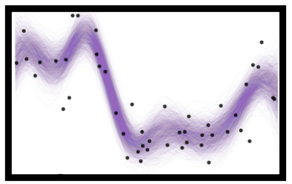

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Engineered ChRs control mouse neurons without skull removal

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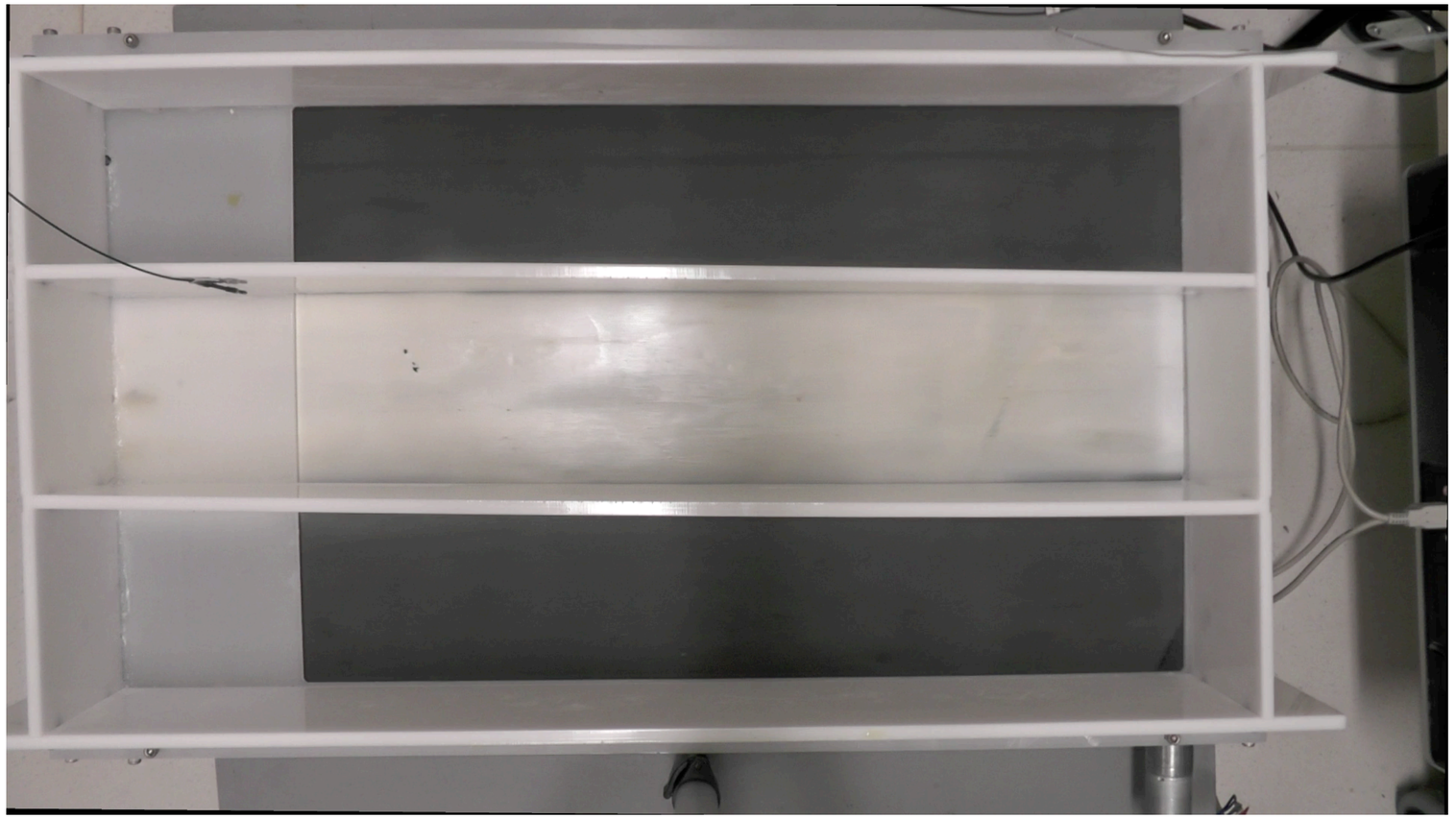
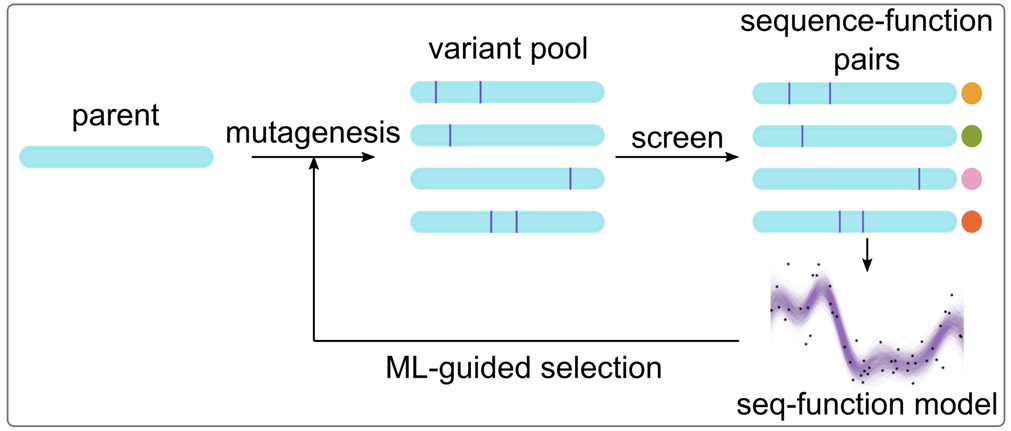


MLDE: successes and limitations



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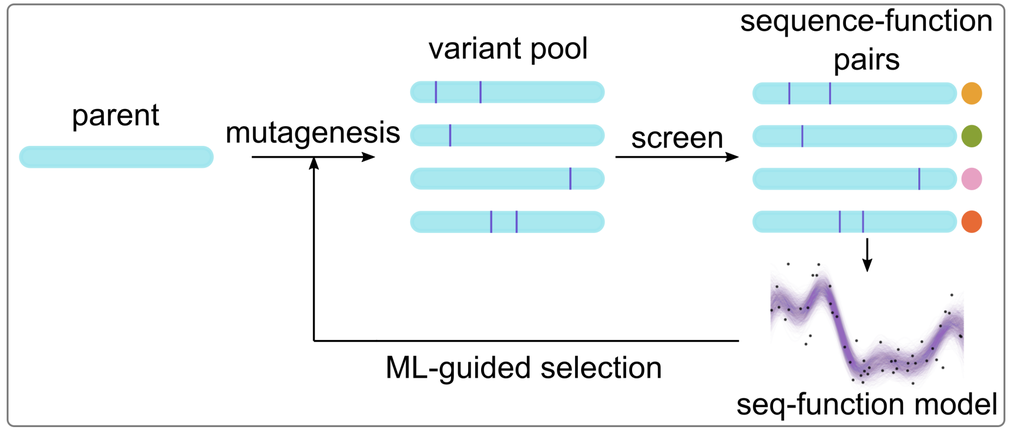
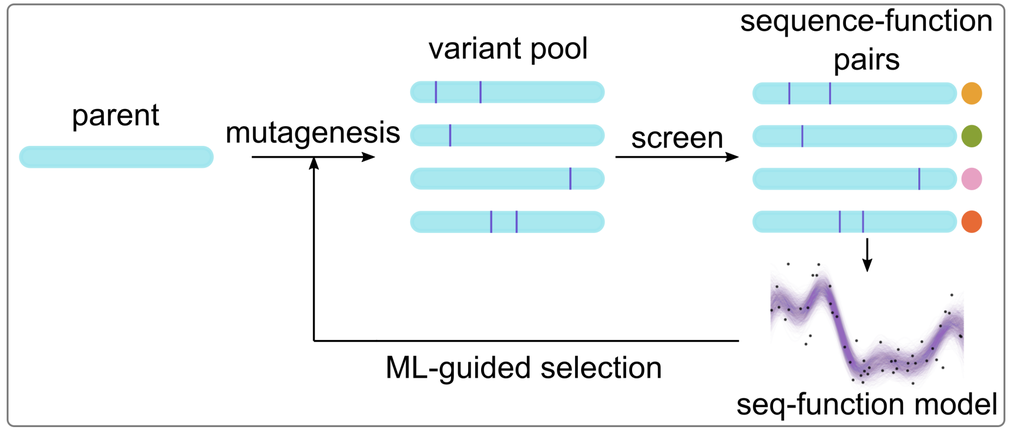


- Accurate models with < 200 measurements

MLDE: successes and limitations



- Accurate models with < 200 measurements
- Find rare, improved sequences with < 200 measurements

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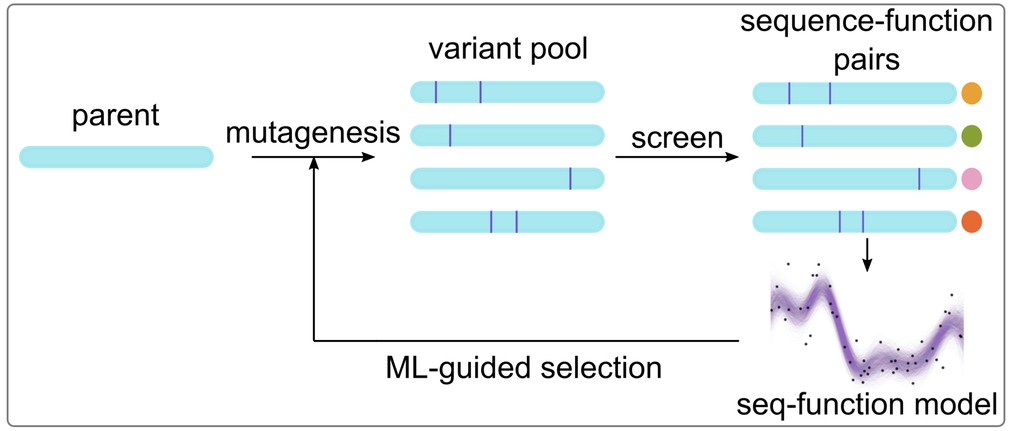

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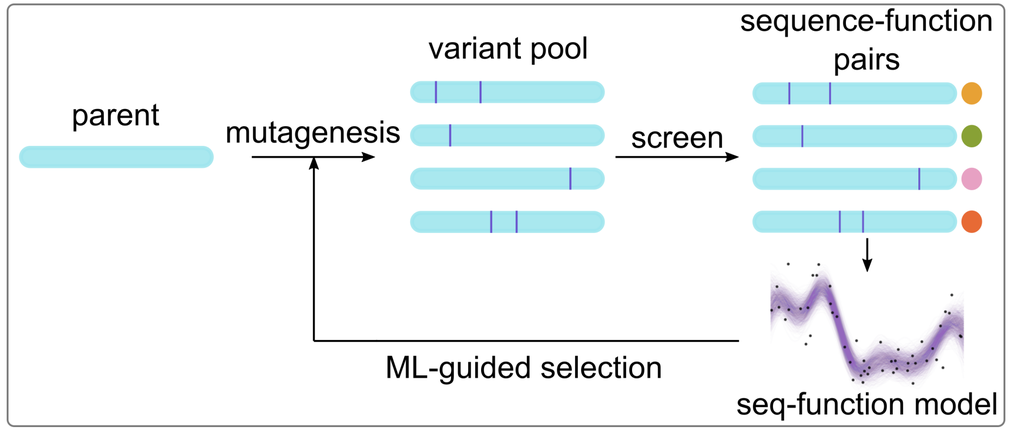
Still requires starting point!

MLDE: successes and limitations



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Still requires starting point!

Ignores mountains of protein data

Pretraining can leverage large sequence and structure databases

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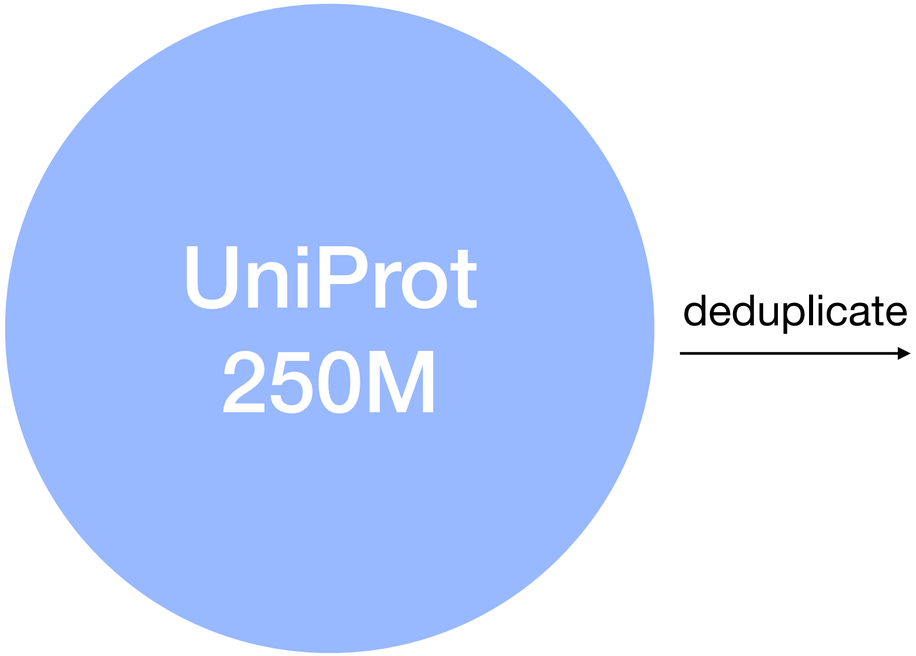
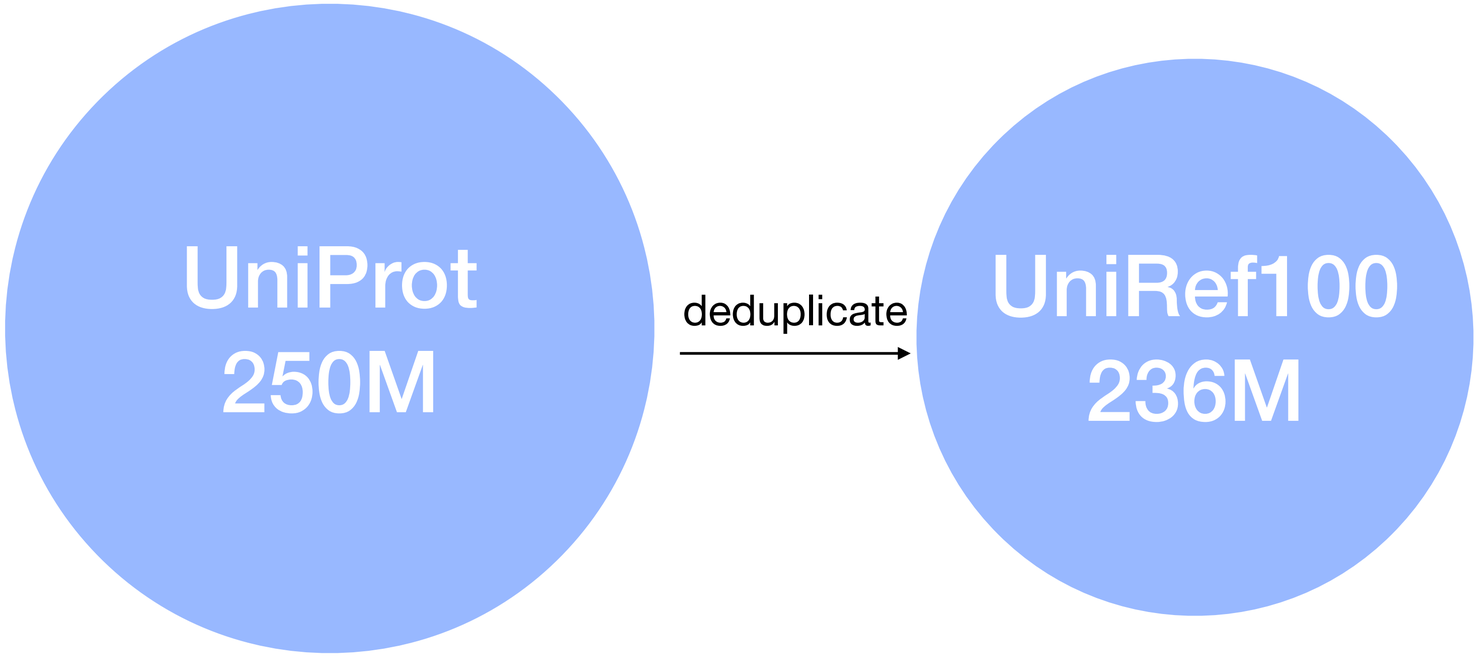


Pretraining can leverage large sequence and structure databases



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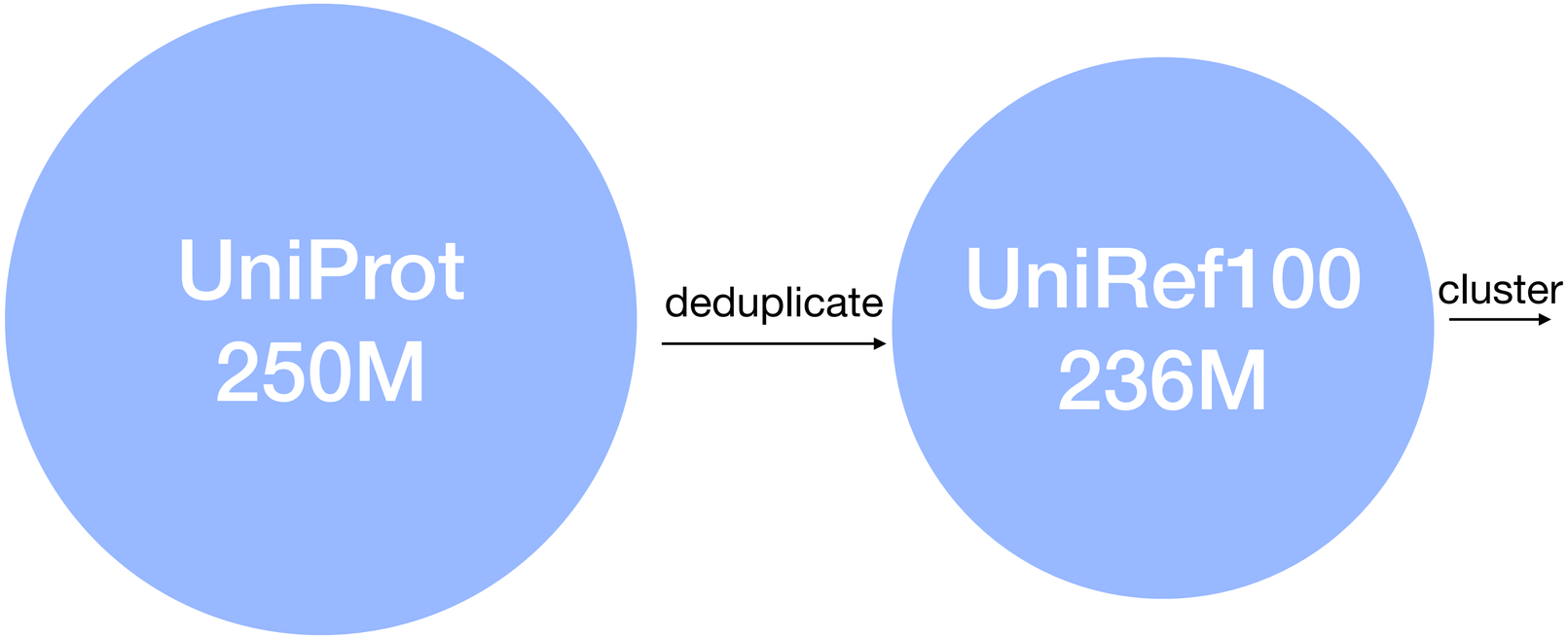

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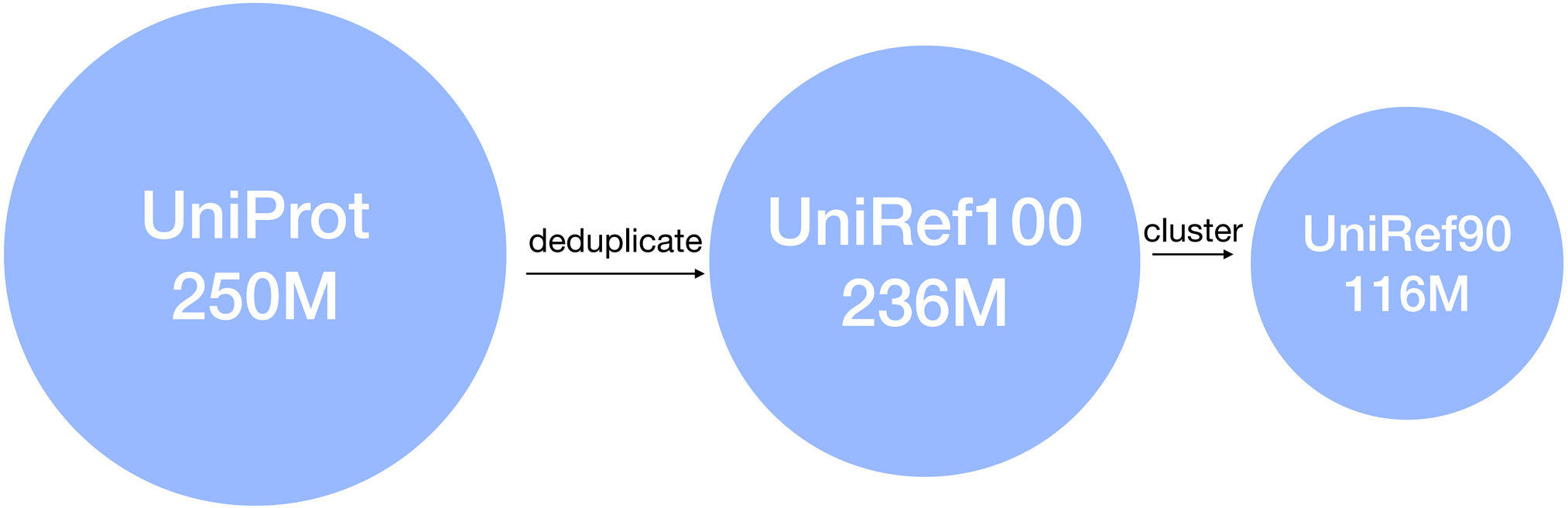

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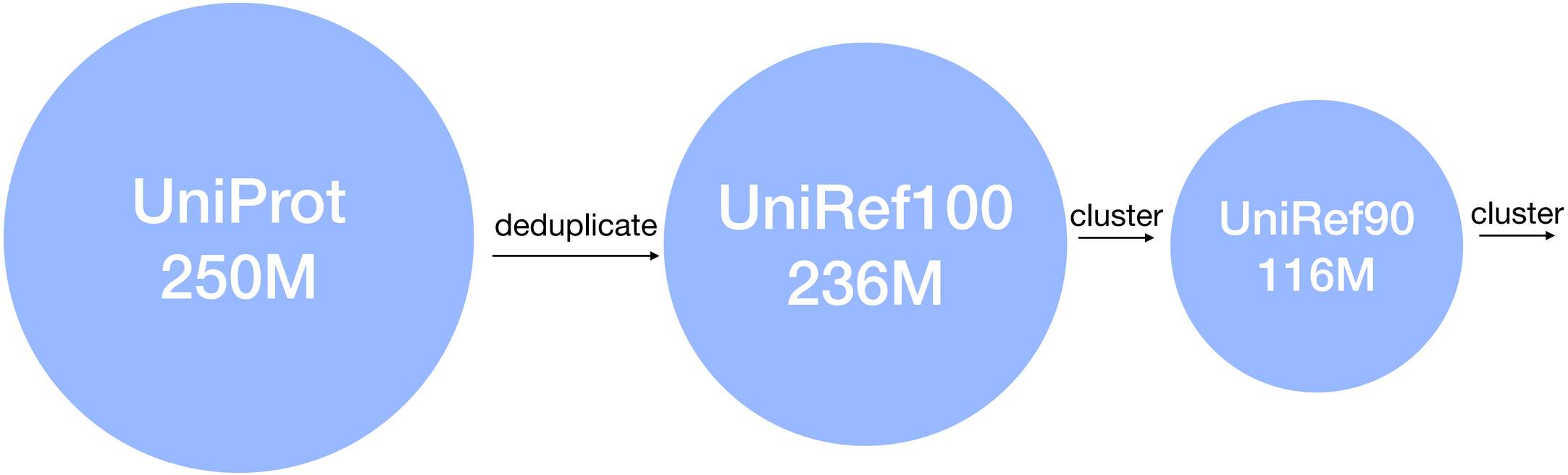

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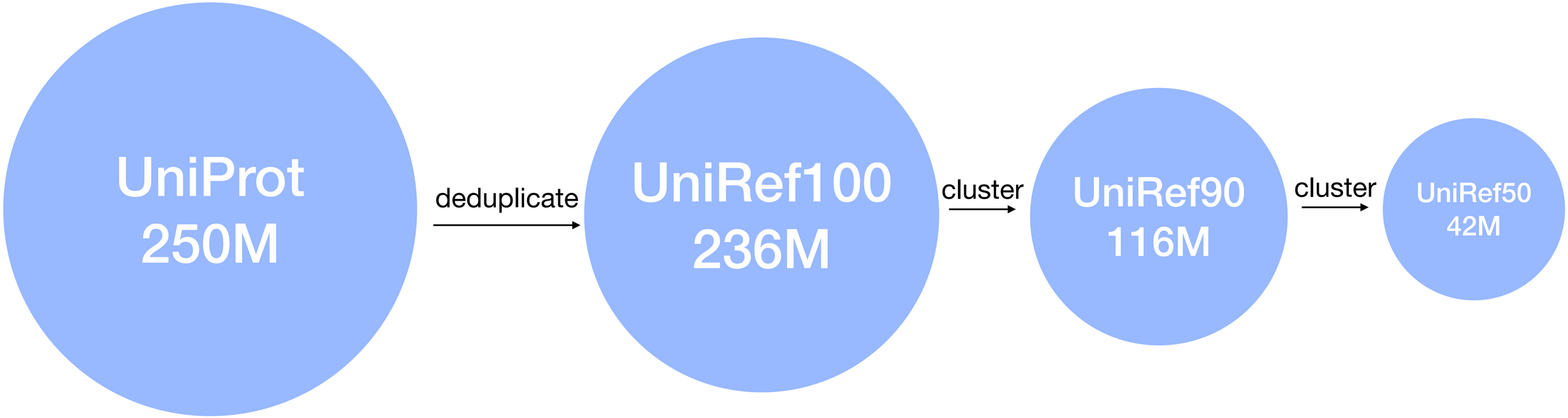

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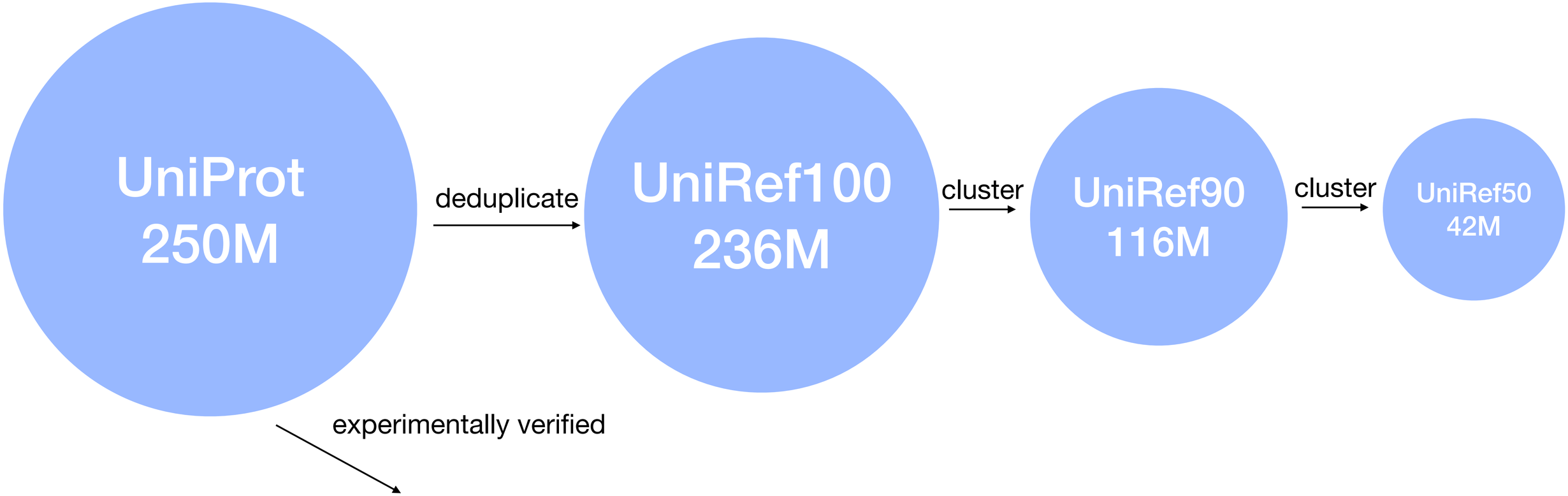

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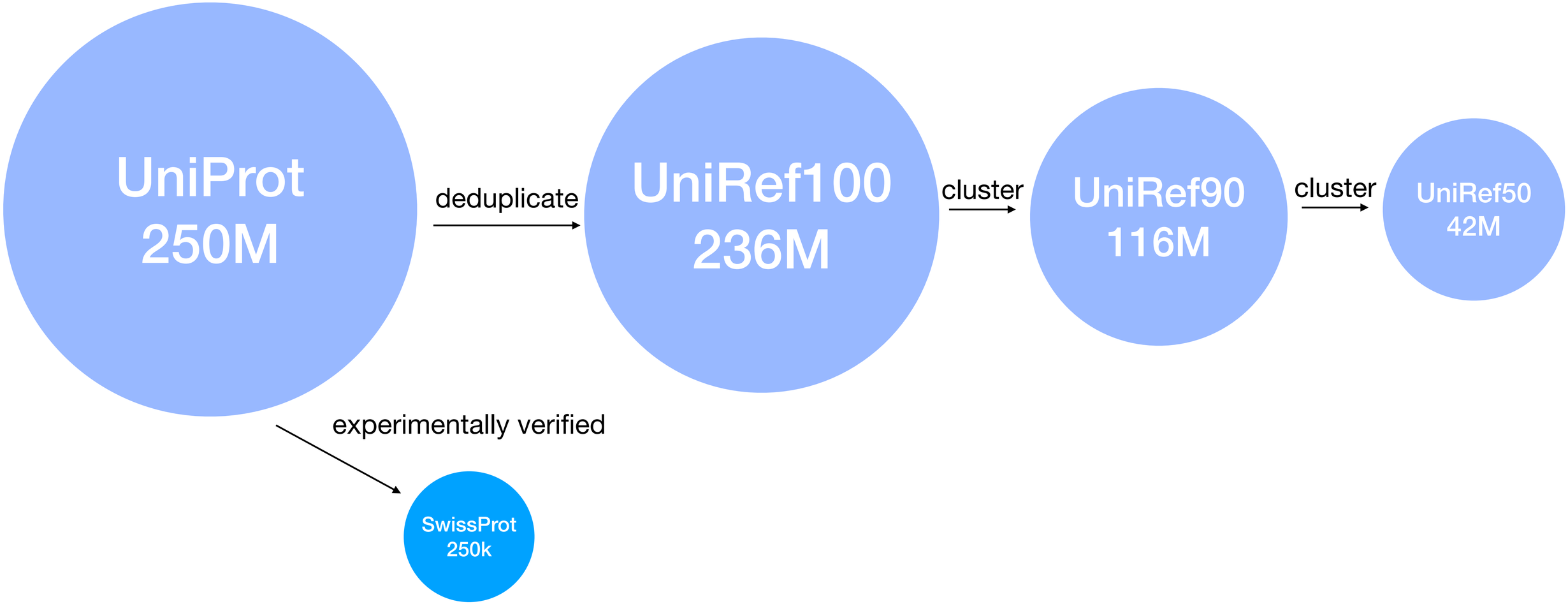

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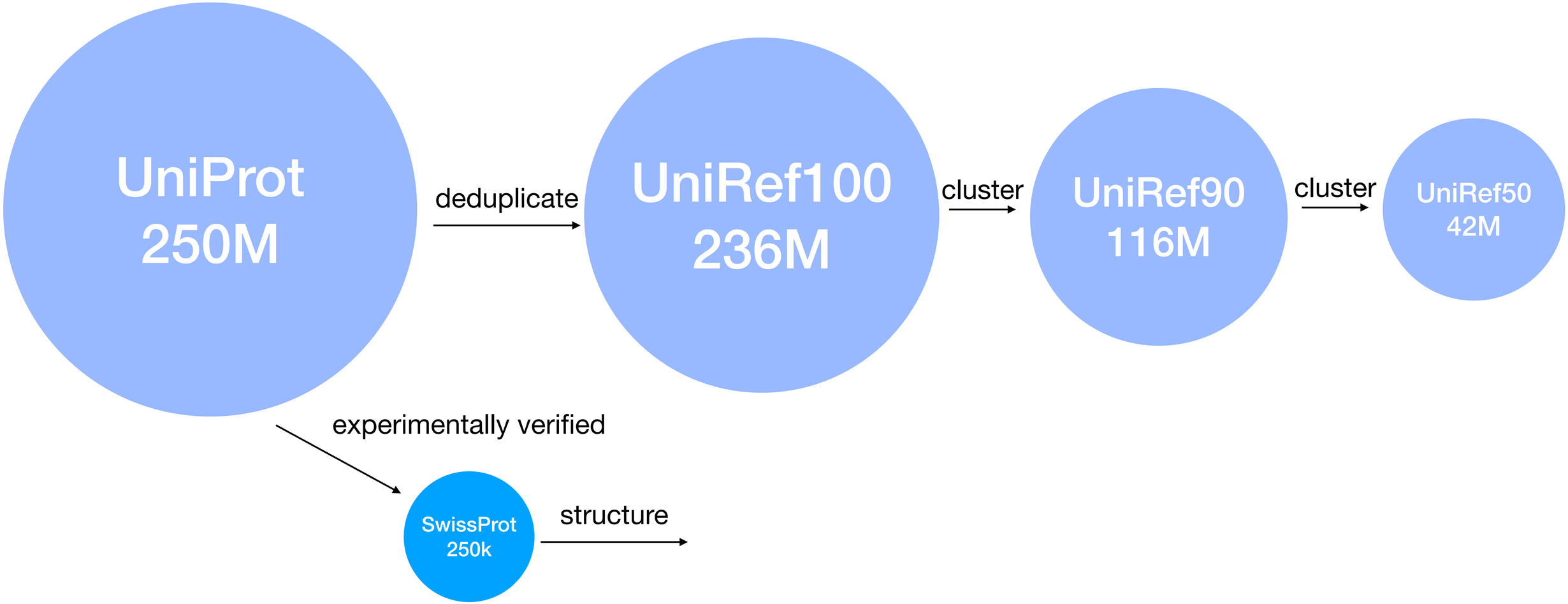

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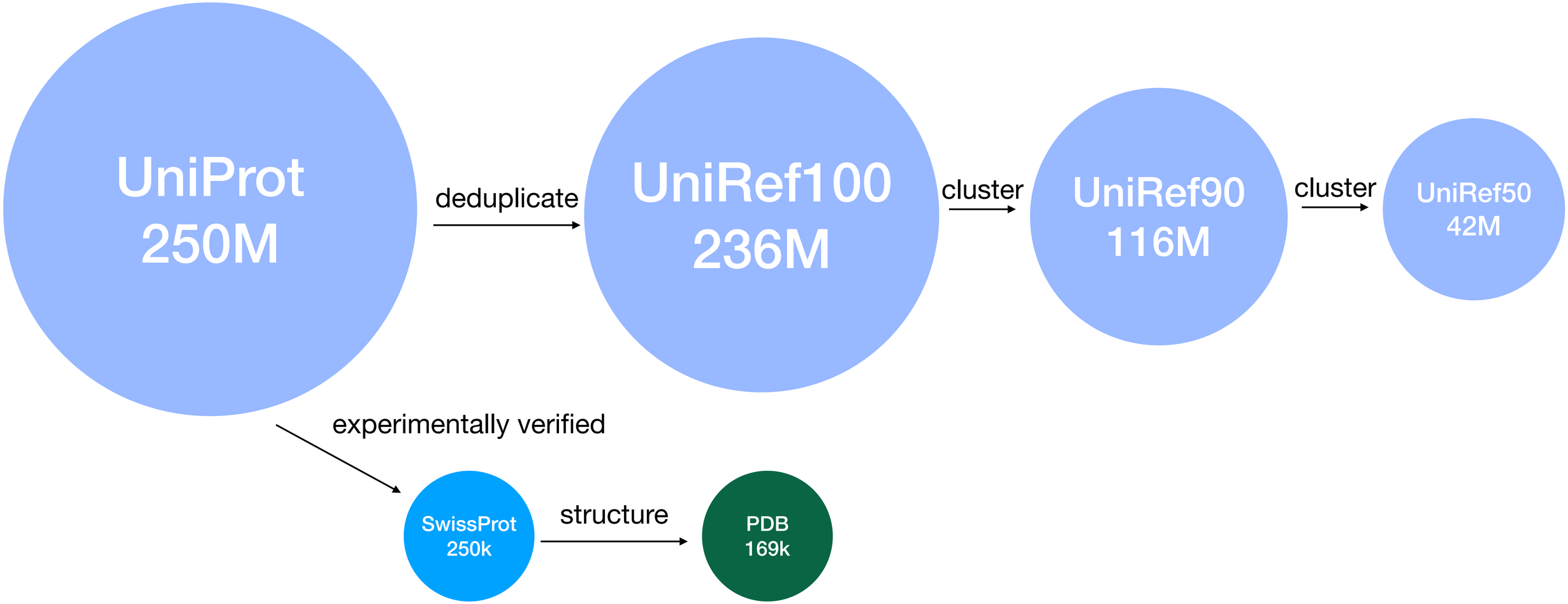


Pretraining can leverage large sequence and structure databases

UniProt 250M

deduplicate

UniRef100 236M

cluster

UniRef90 116M

cluster

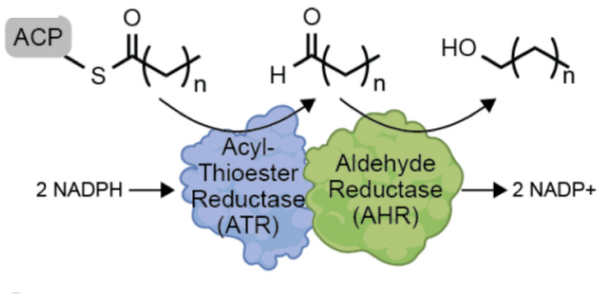
UniRef50 42M

experimentally verified

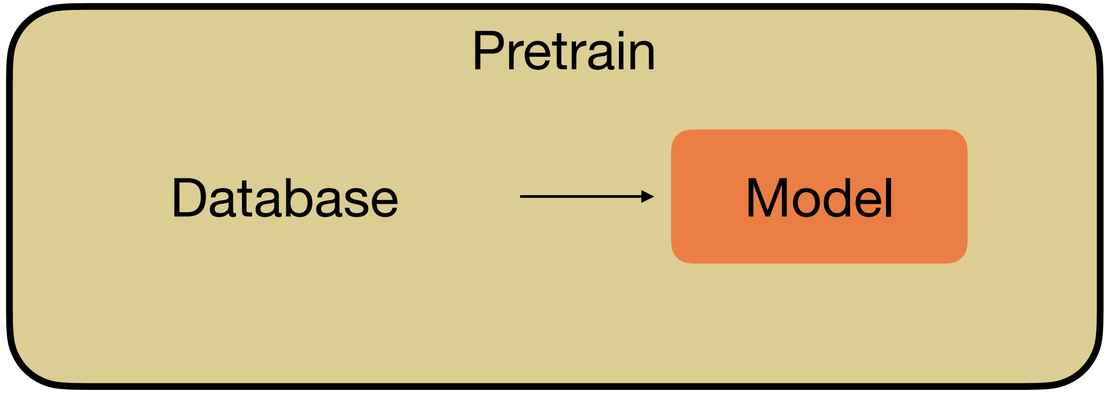
SwissProt 250k

structure

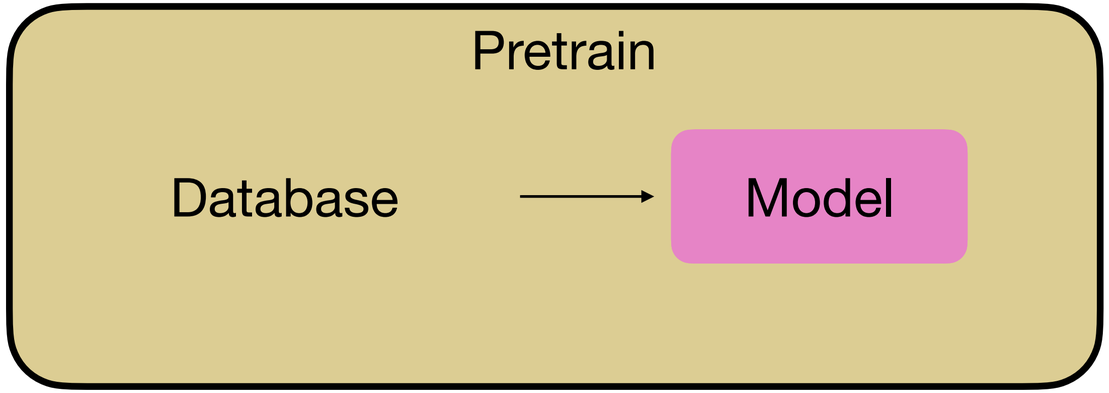
PDB 169k



Pretraining allows us to transfer knowledge



Pretraining allows us to transfer knowledge



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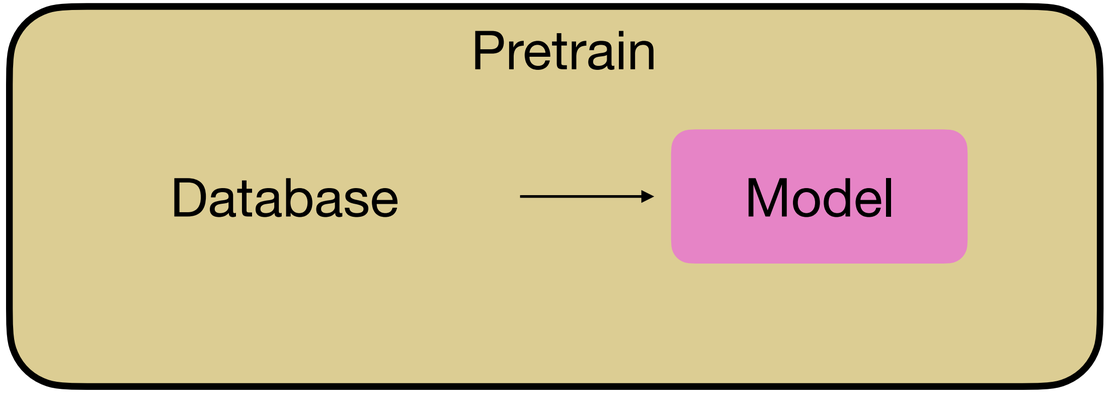
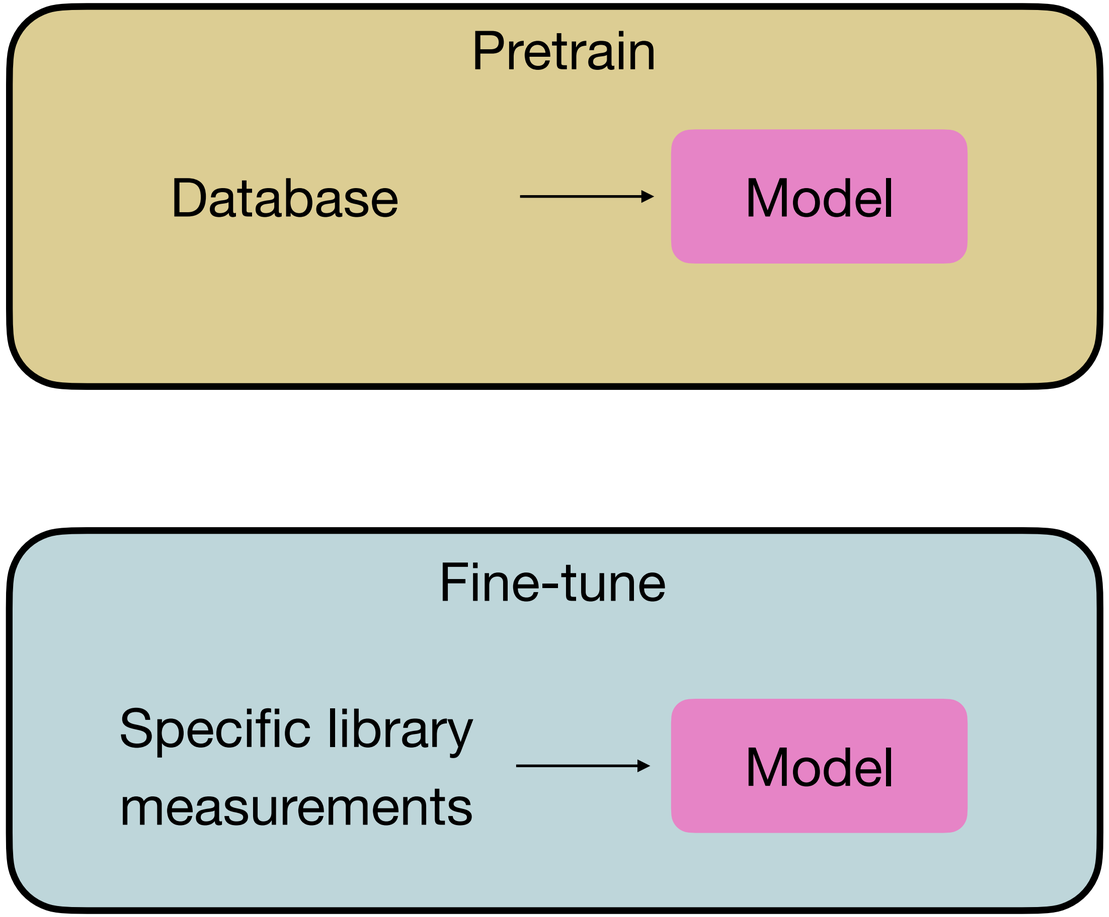


Model

Pretraining allows us to transfer knowledge



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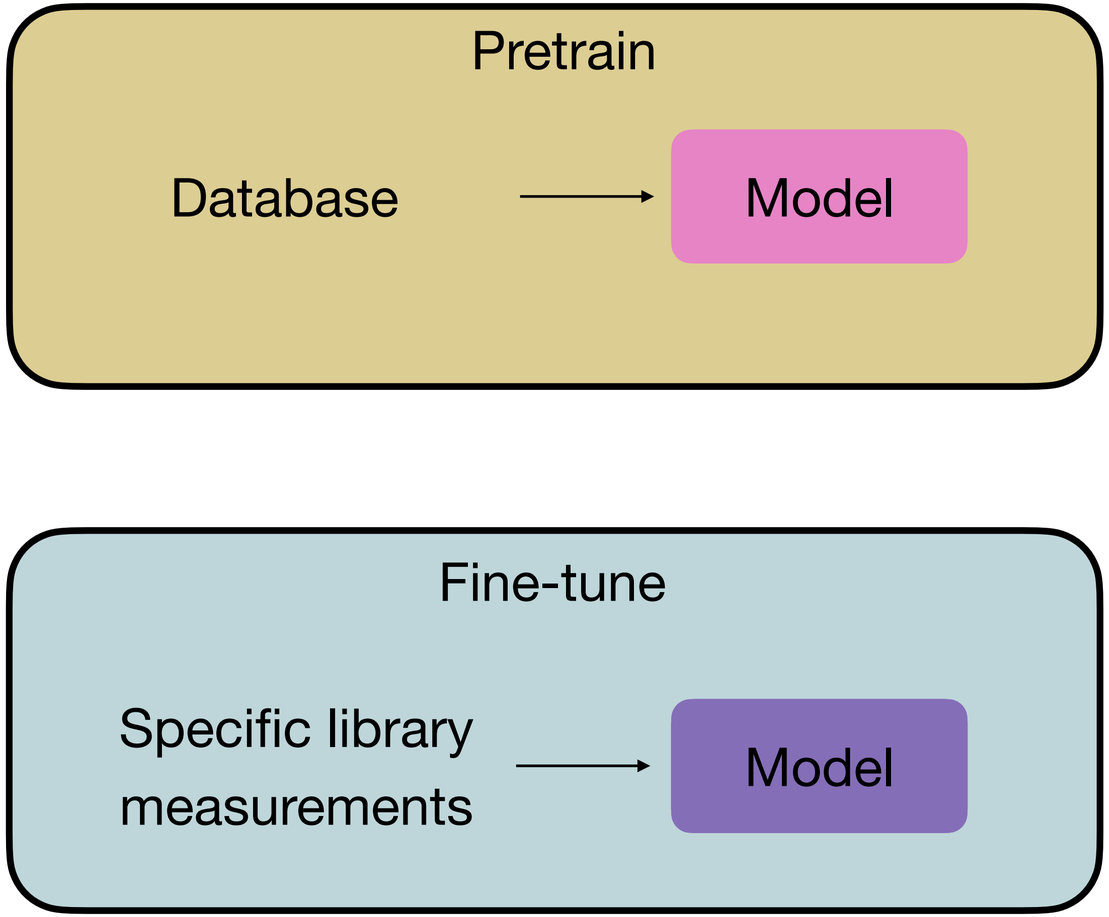

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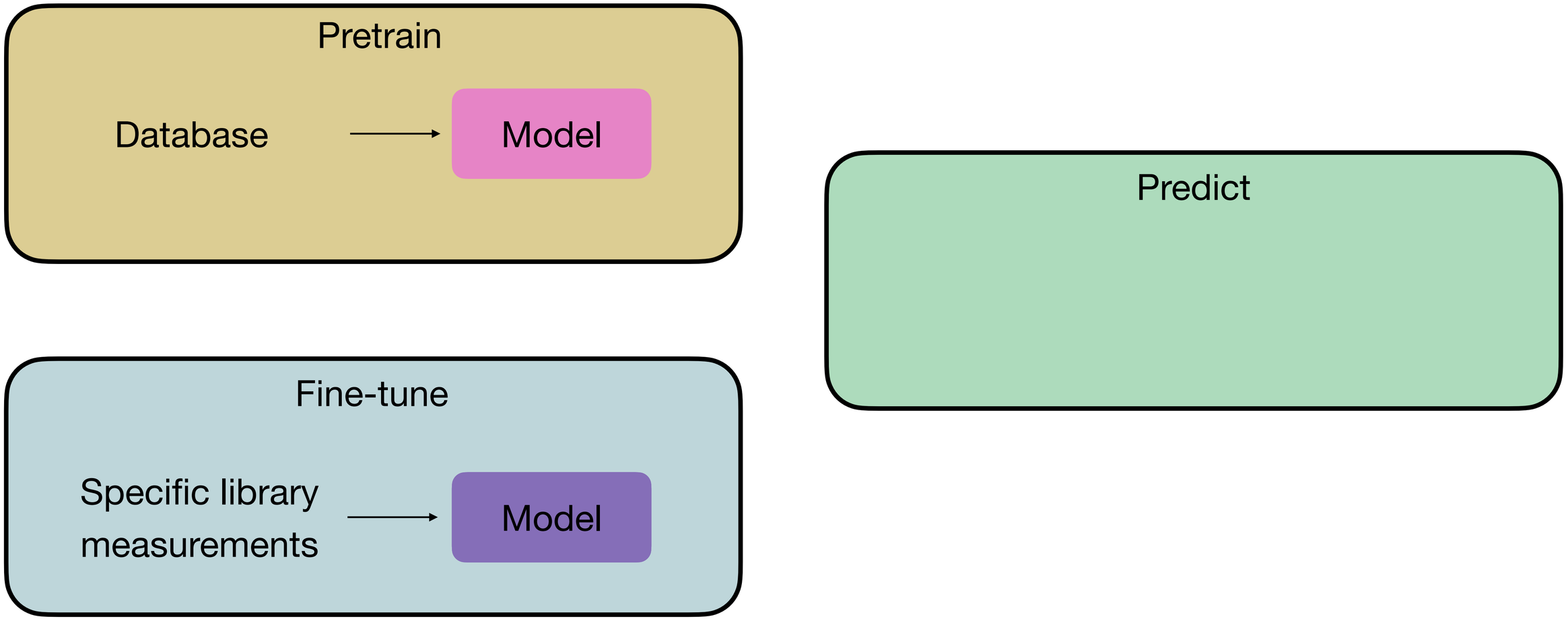

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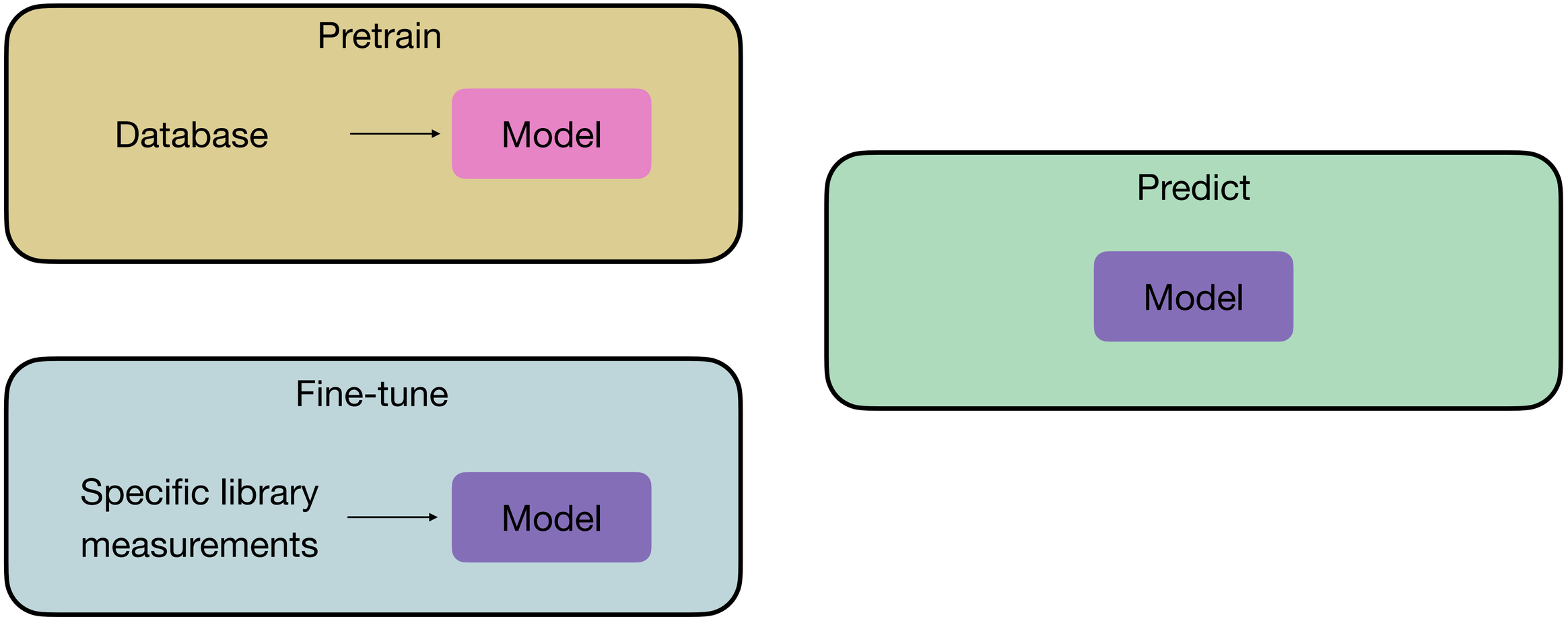

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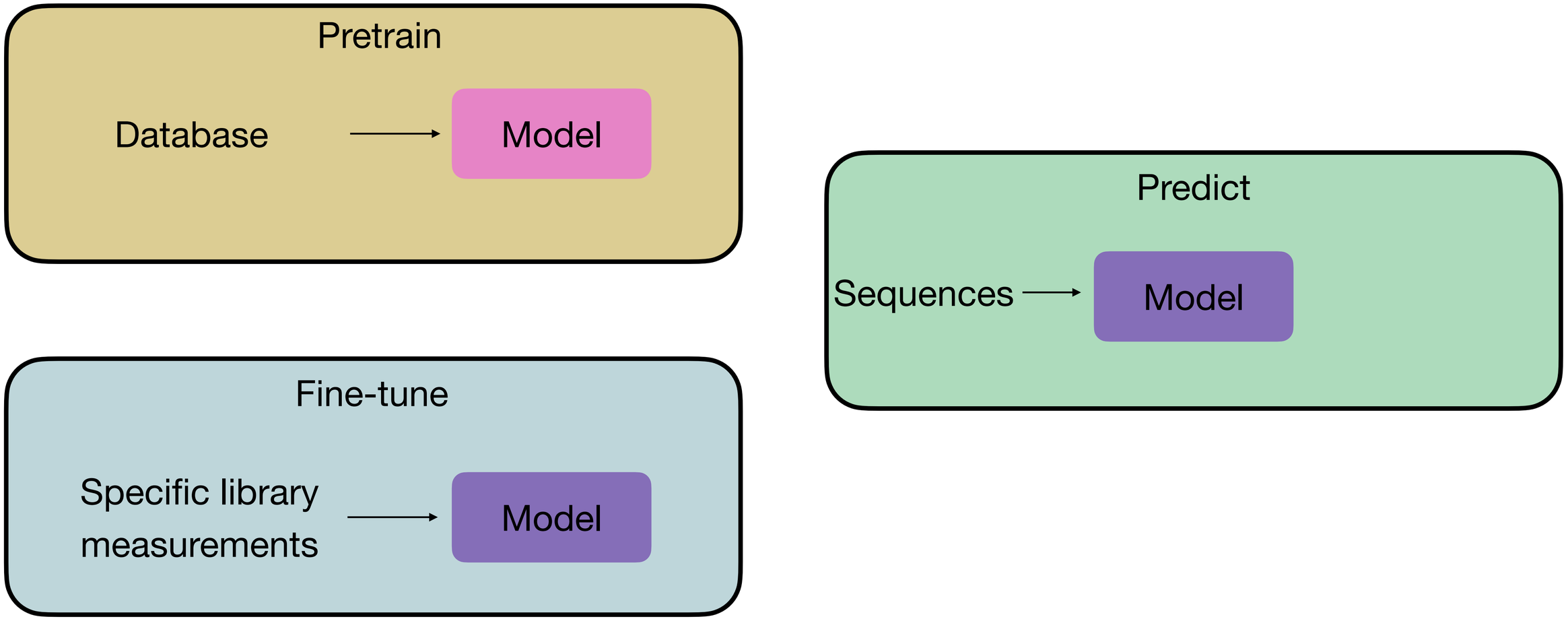

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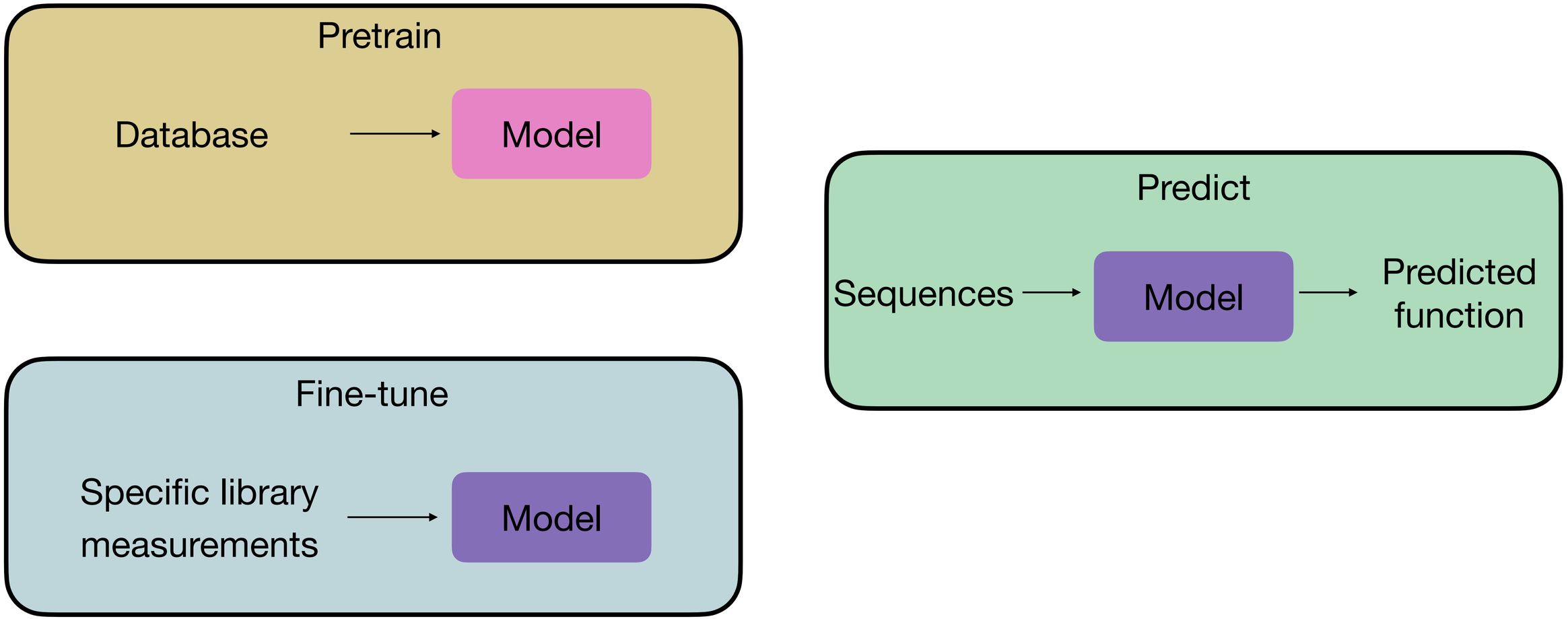

Many methods pretend proteins are language

MFTGNDAGH

Many methods pretend proteins are language

MFTGNDAGH

Treat amino acids like tokens

Many methods pretend proteins are language

MFTGNDAGH

Treat amino acids like tokens

Use tools originally developed for language

Many methods pretend proteins are language

MFTGNDAGH

Many methods pretend proteins are language

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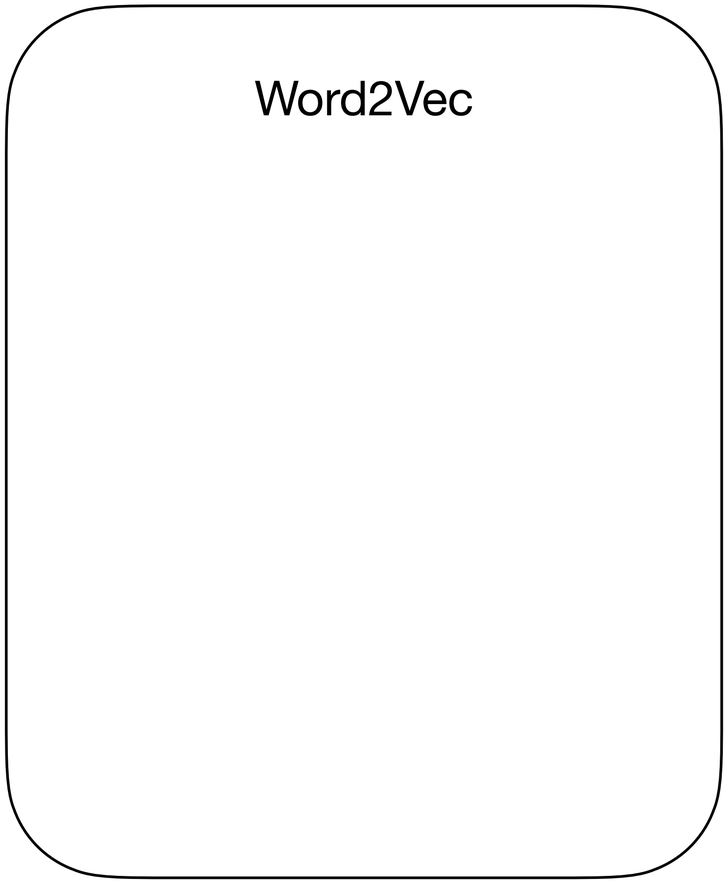

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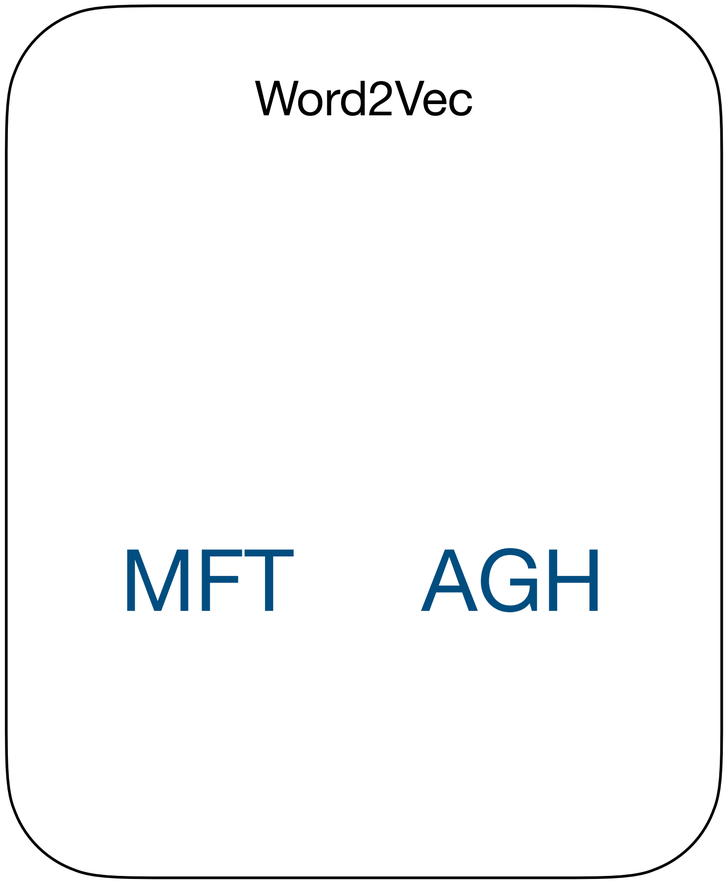

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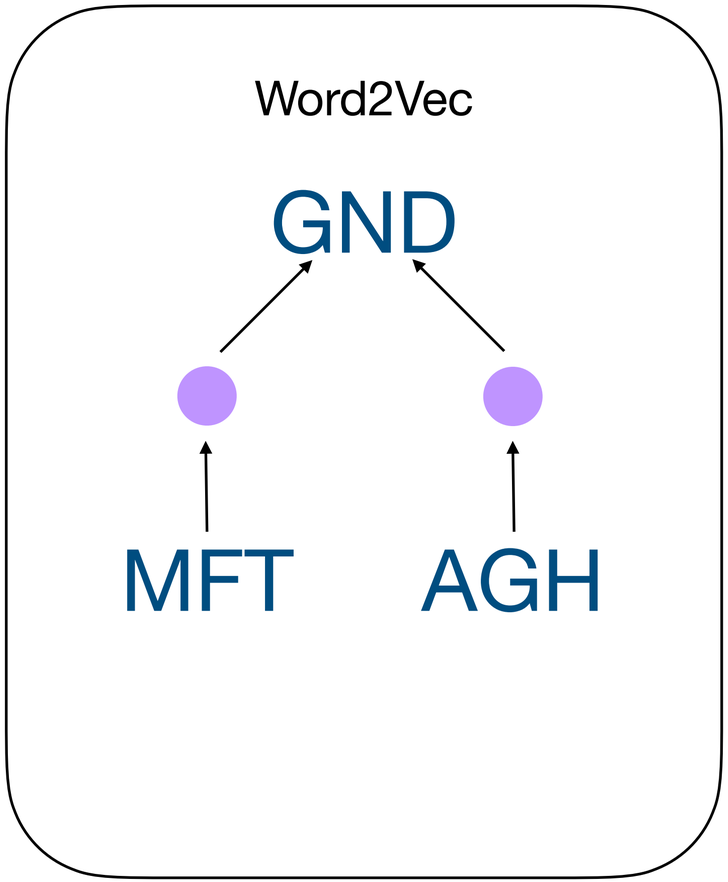

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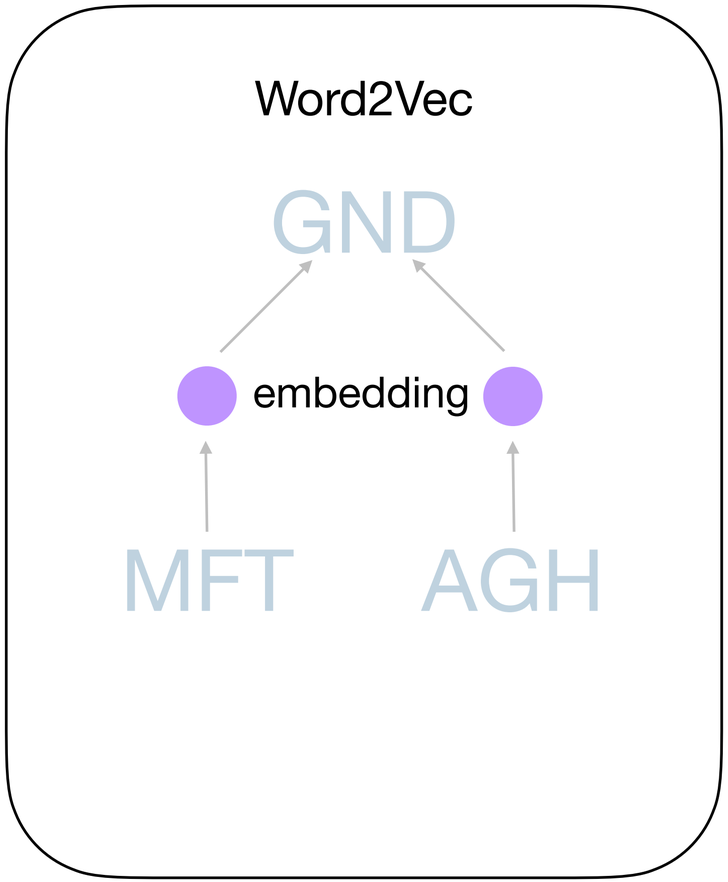

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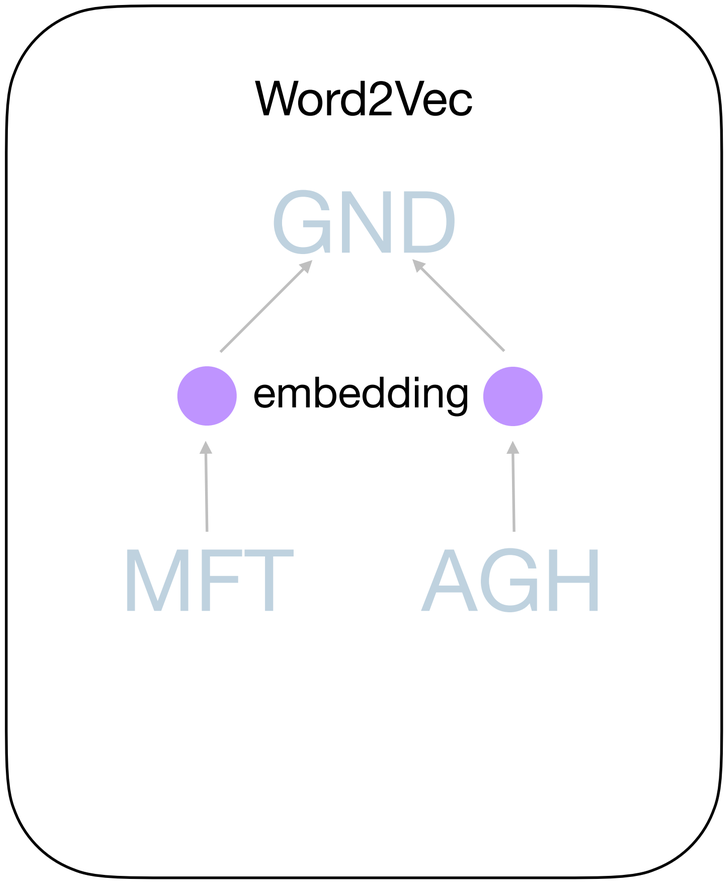

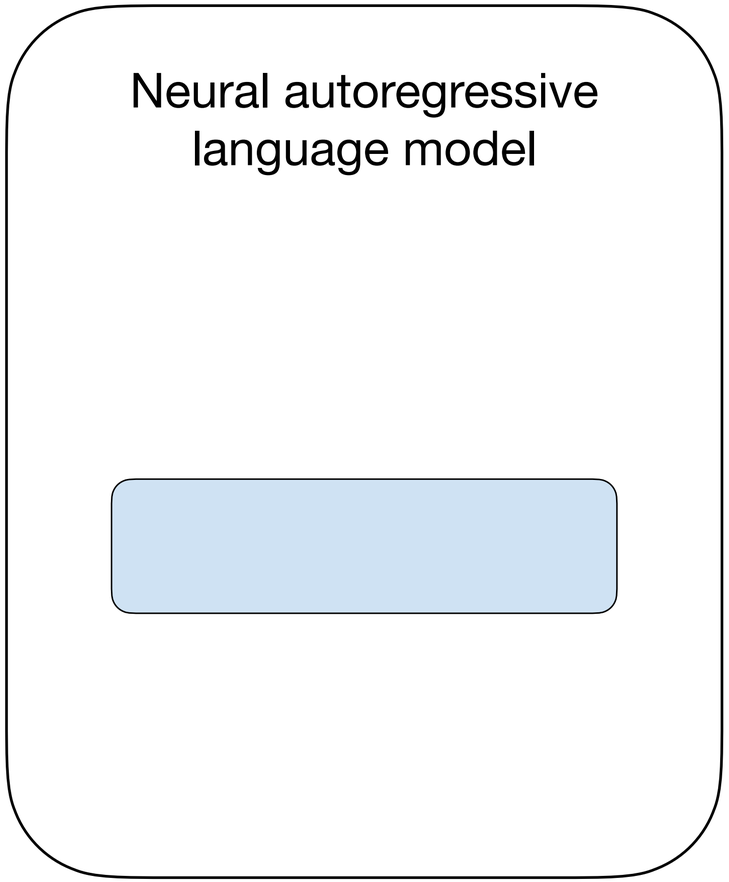

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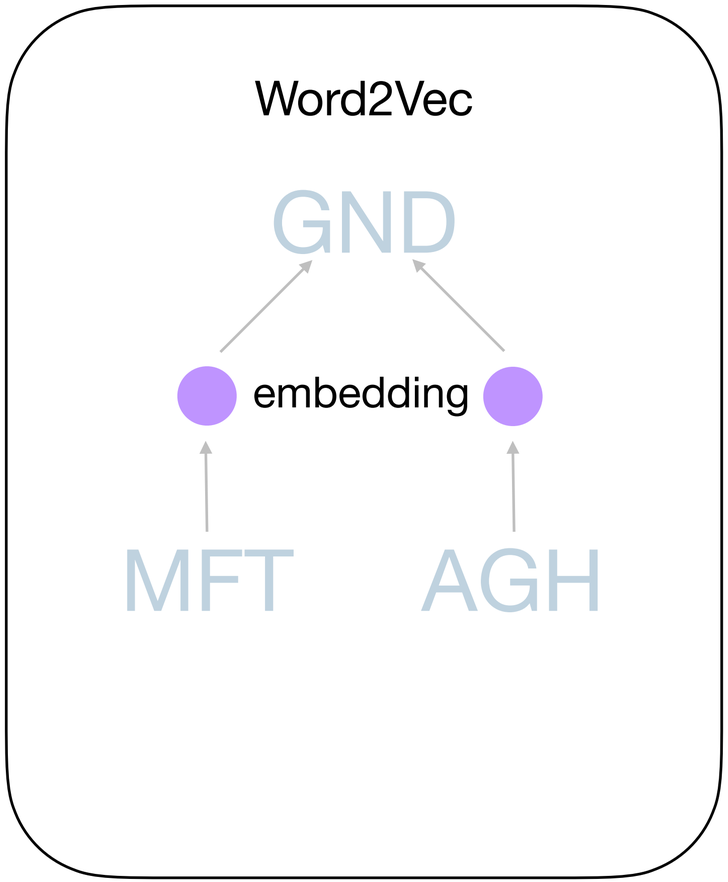

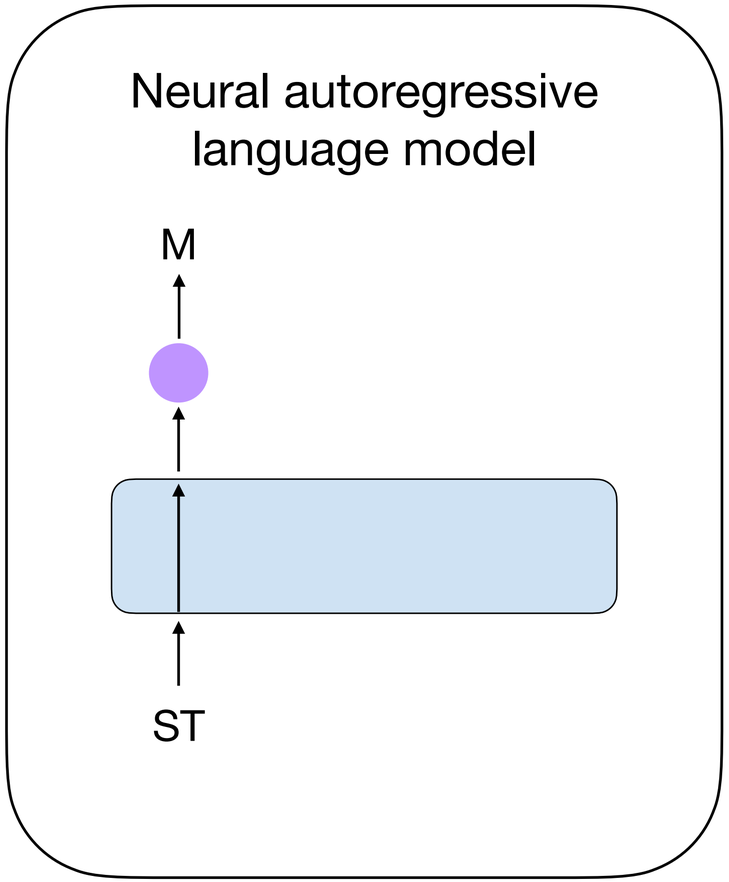

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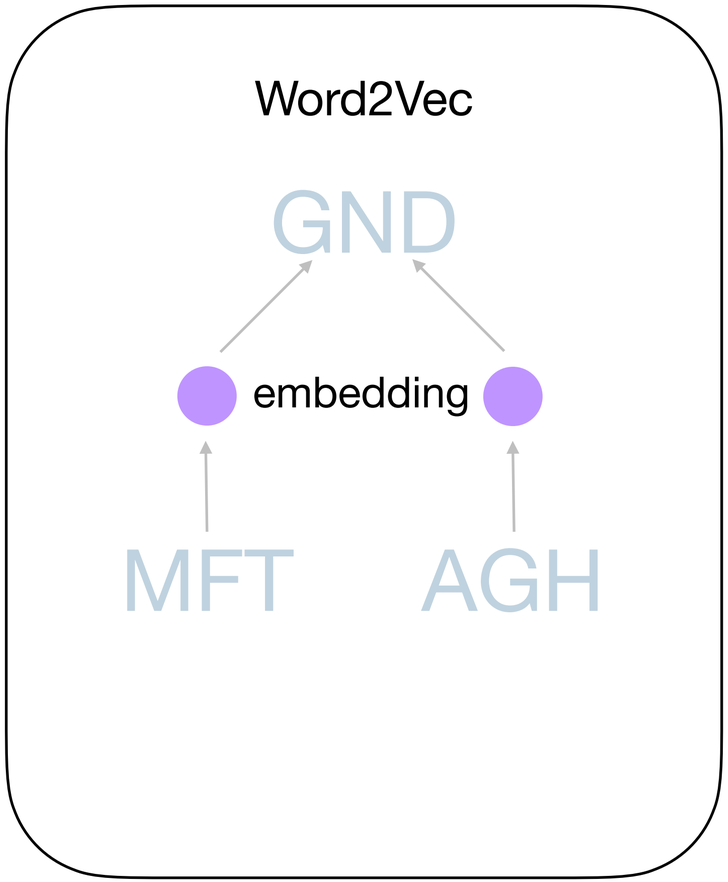

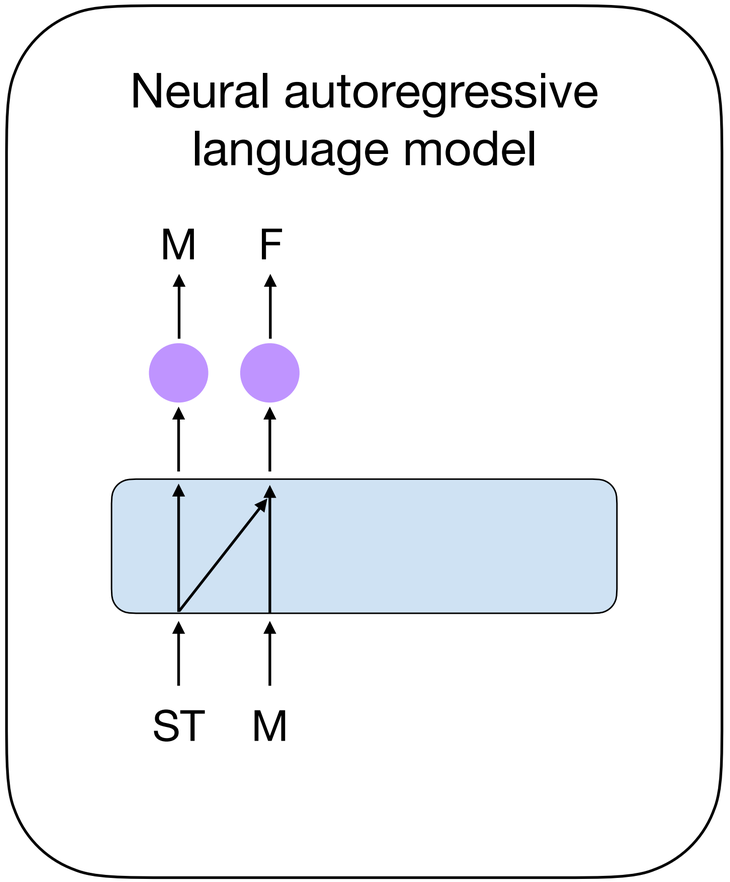

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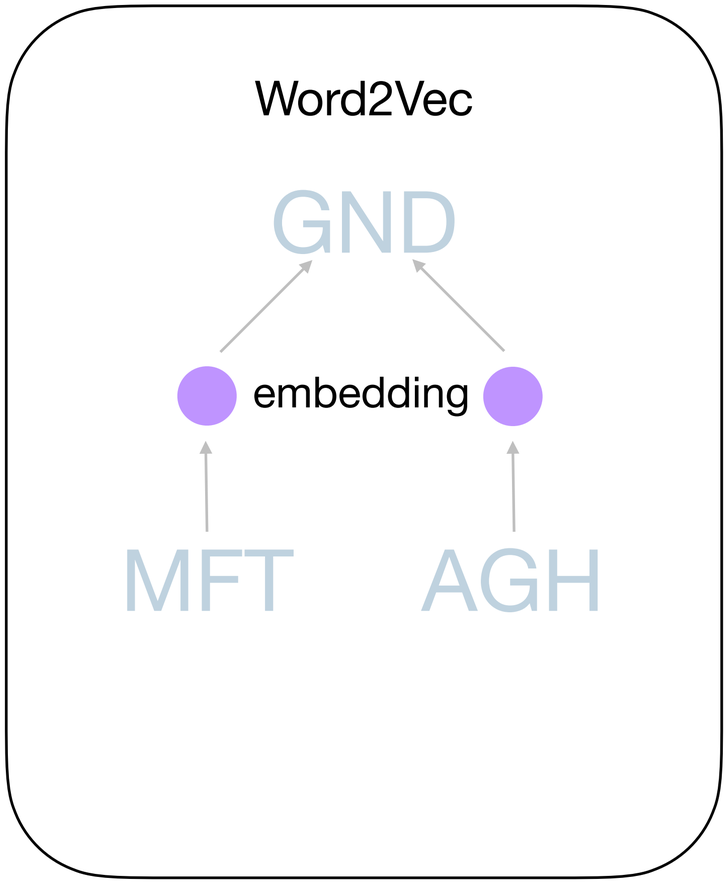

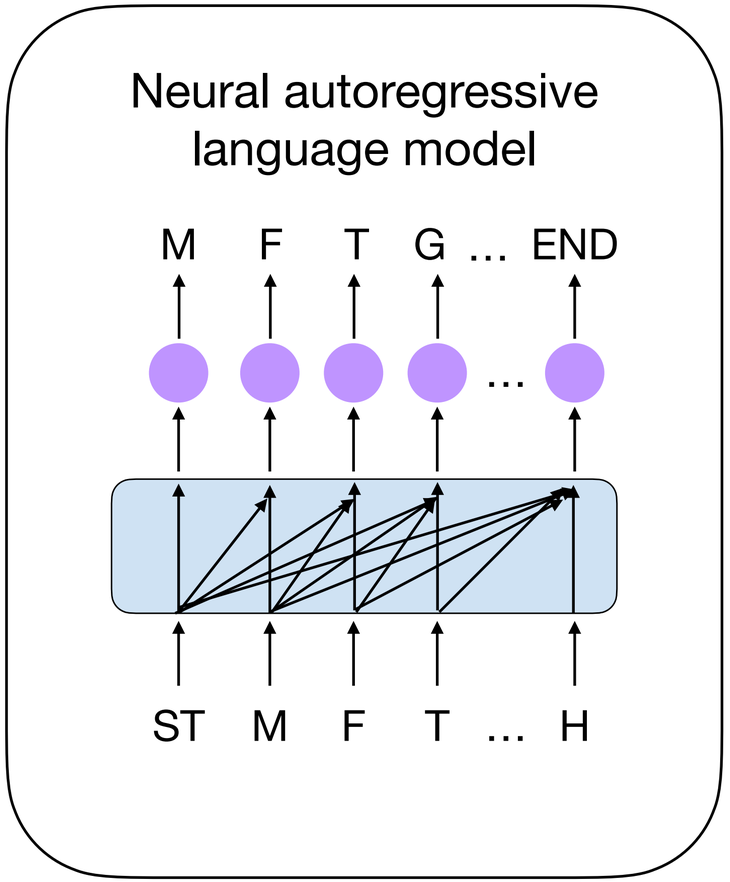

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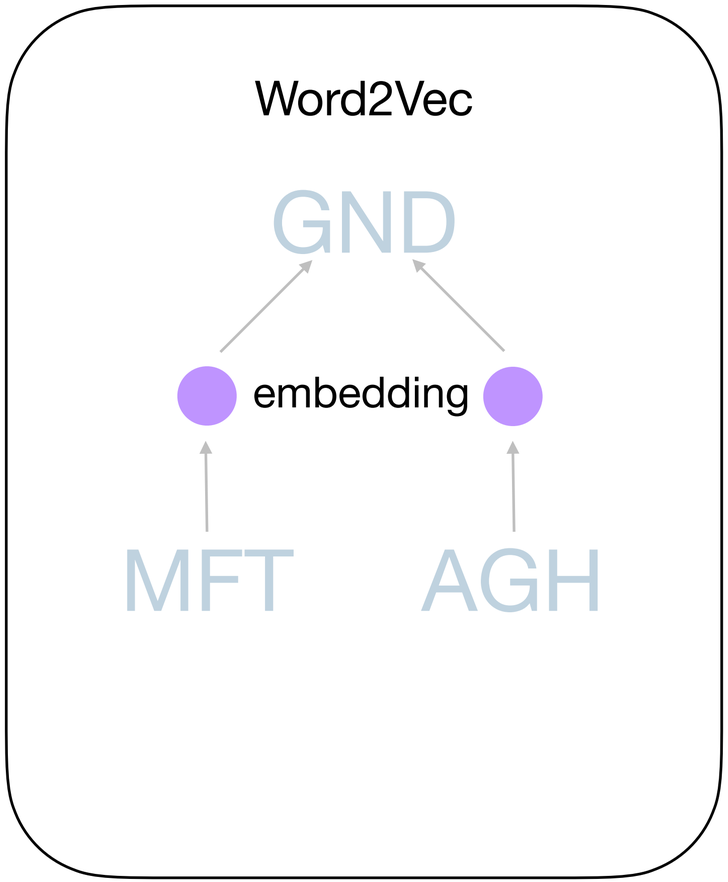

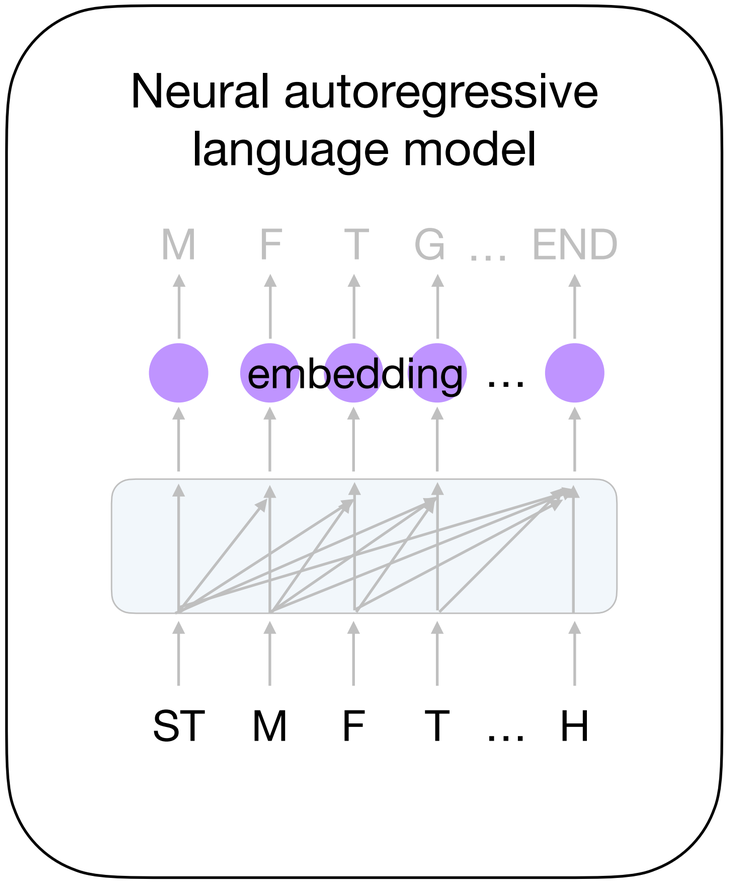

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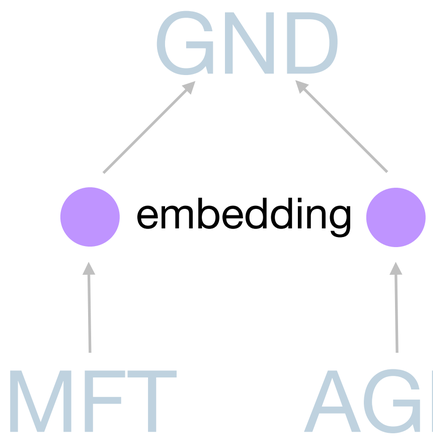
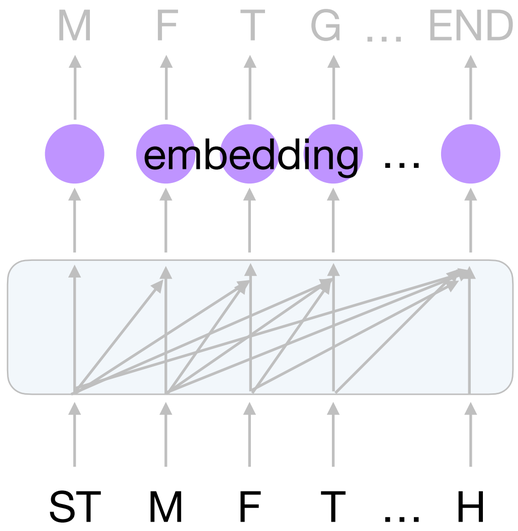
Word2Vec



Neural autoregressive language model



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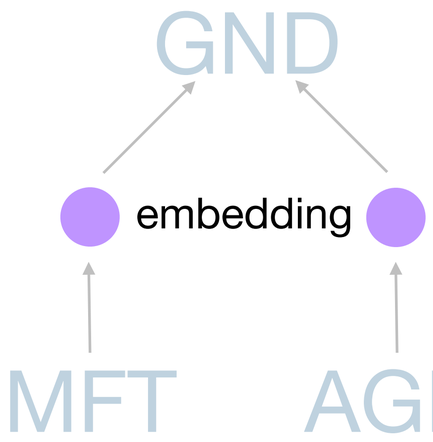

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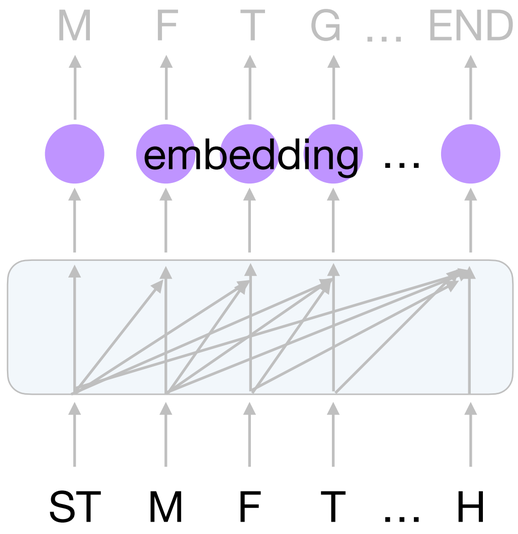

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M F T G … H

MFTGNDAGH

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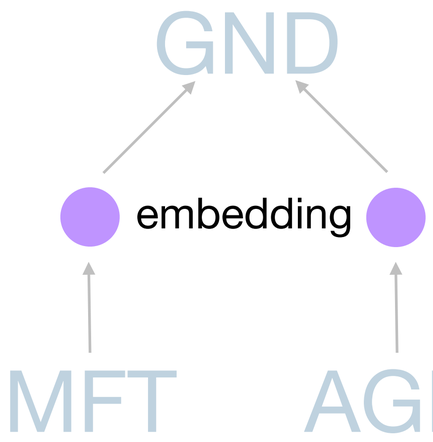

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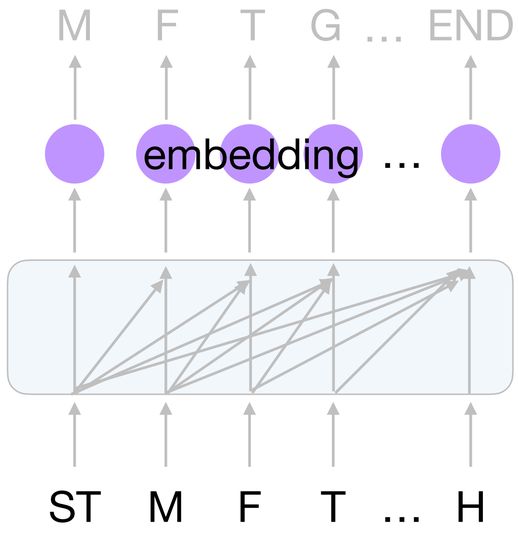

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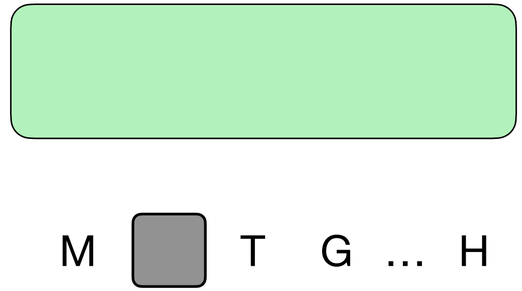

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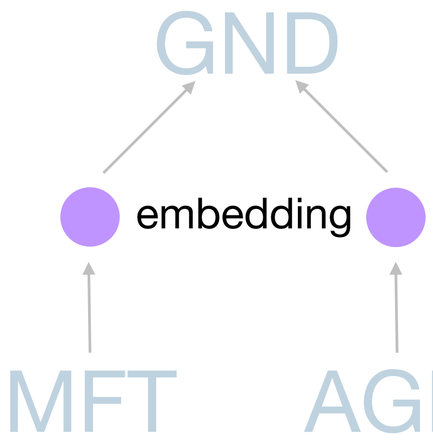

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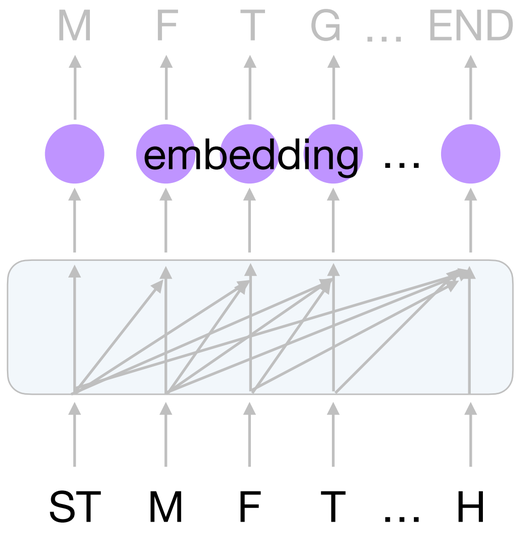

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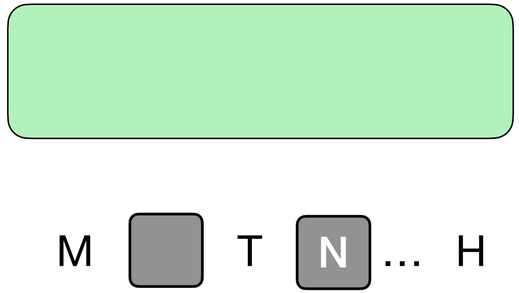

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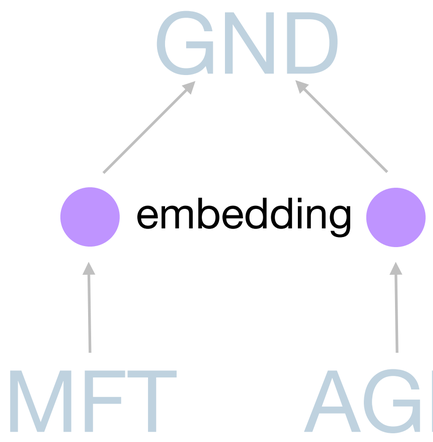

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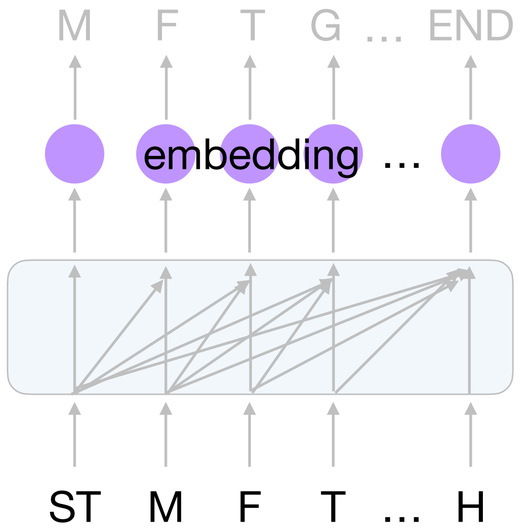

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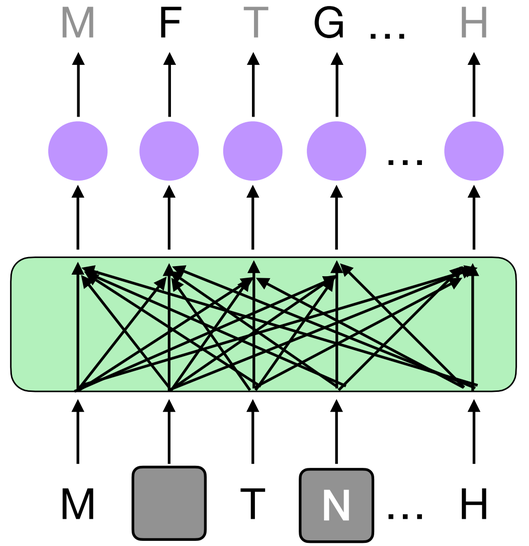

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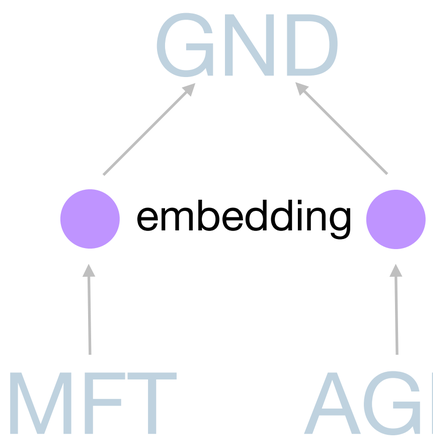

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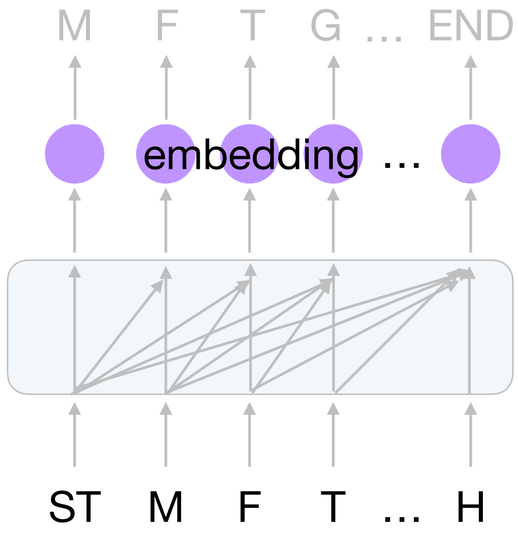

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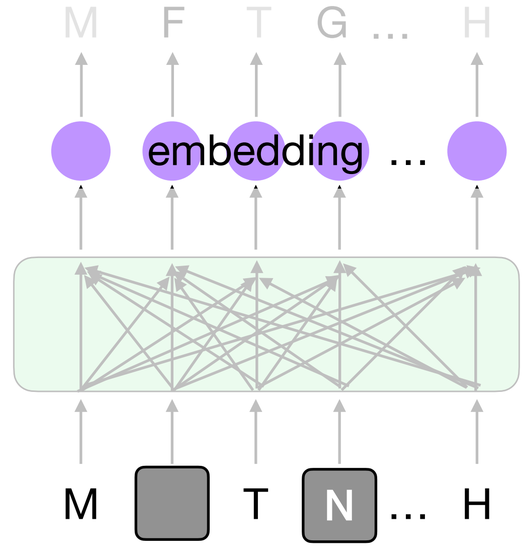

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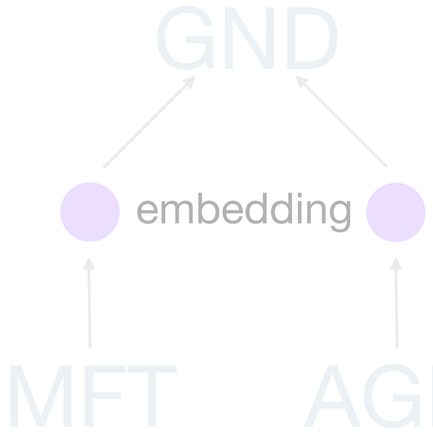

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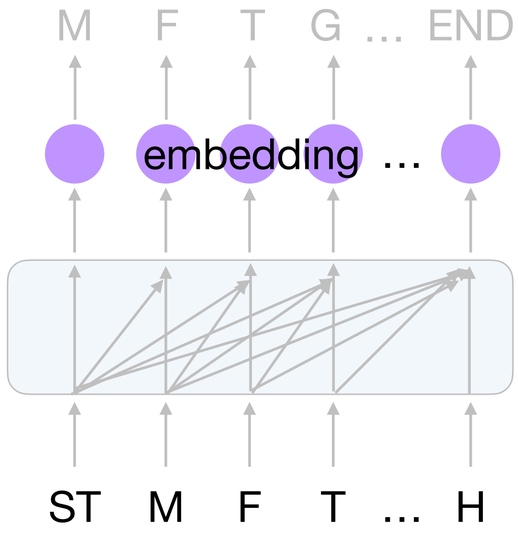

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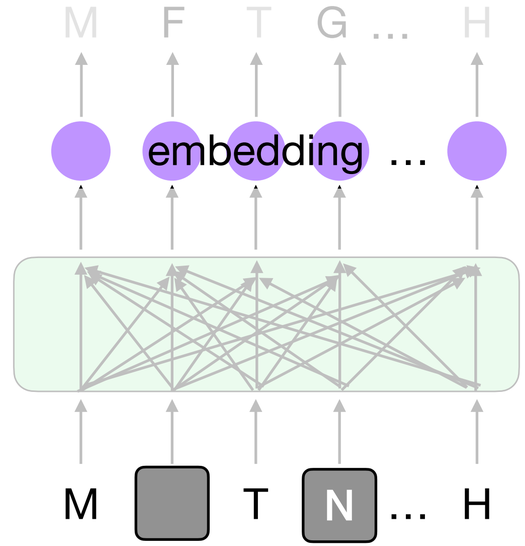

MFTGNDAGH

Architecture, dataset, and task all influence representation quality

Detlefsen *et al.* 2022

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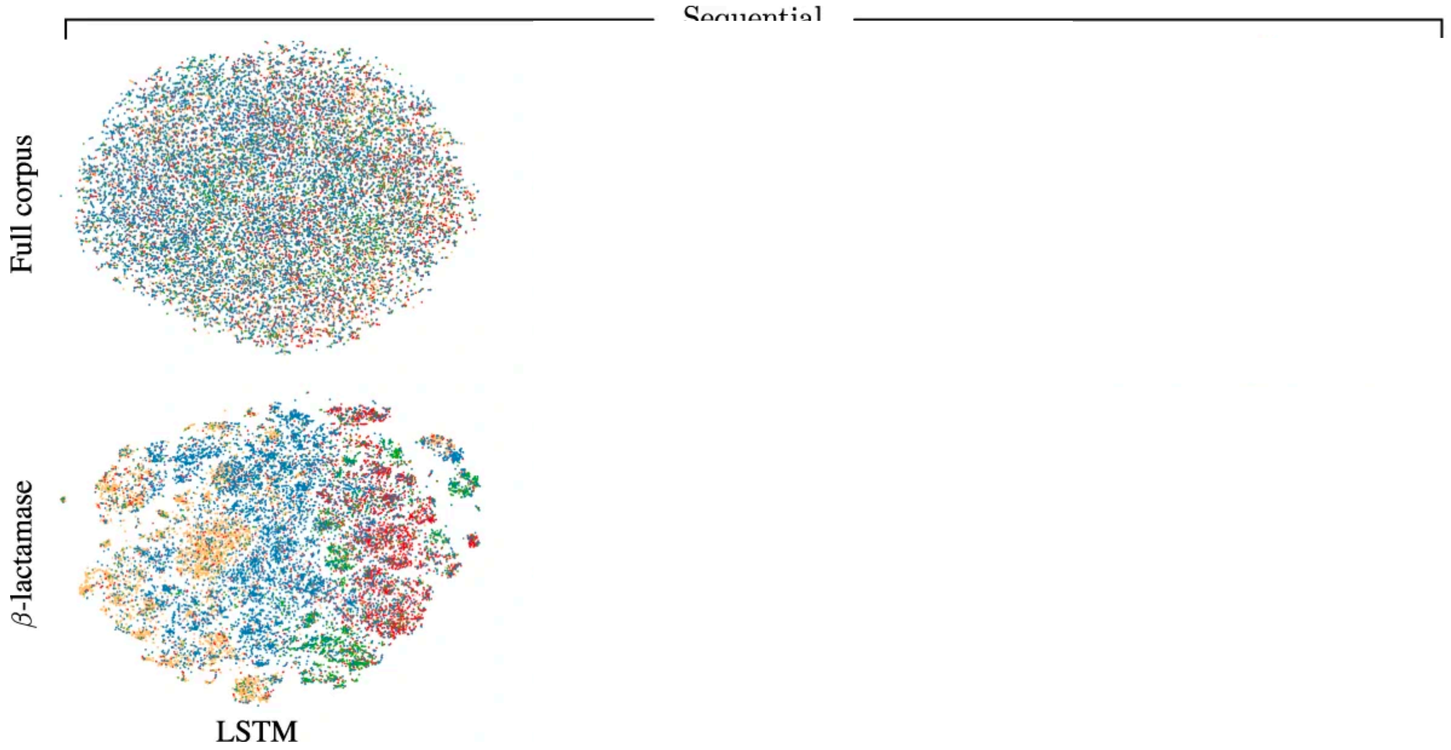

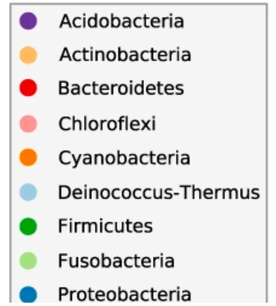

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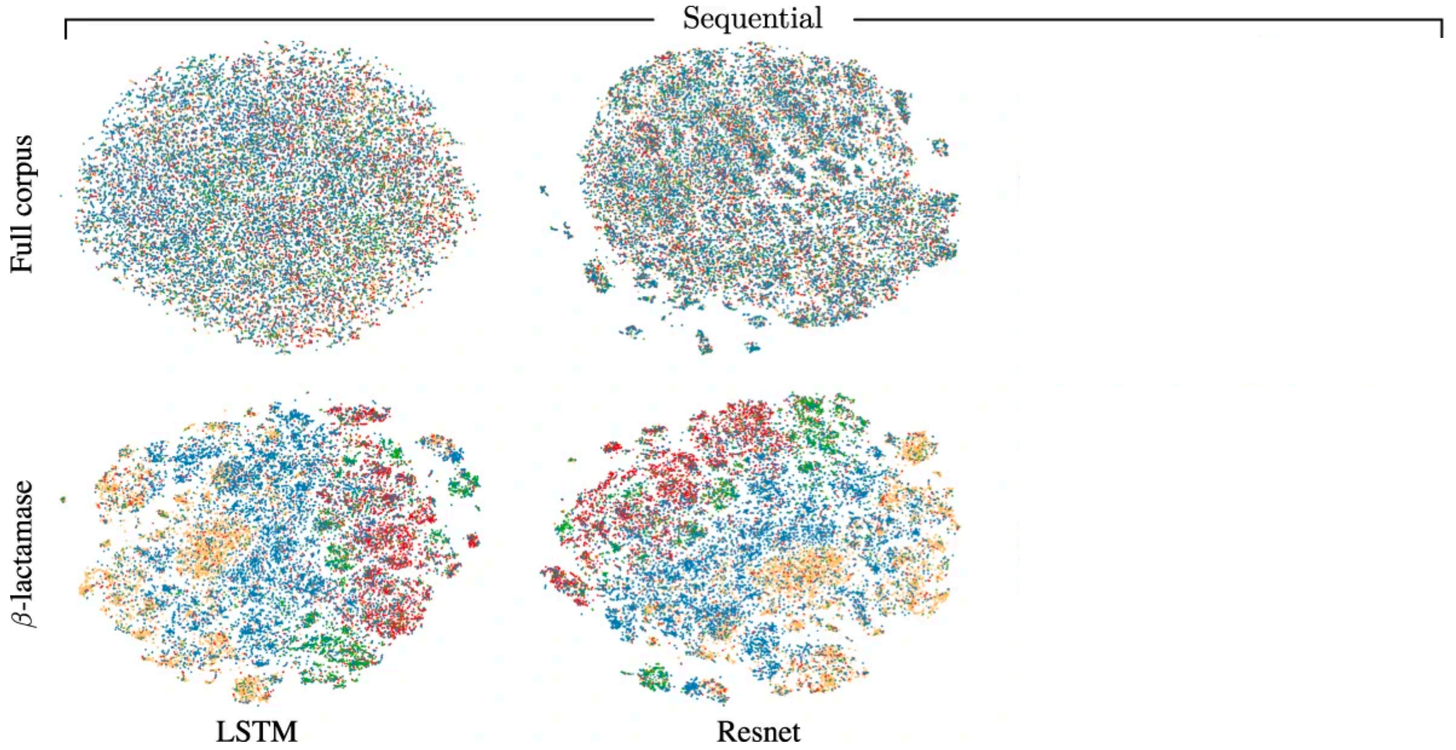

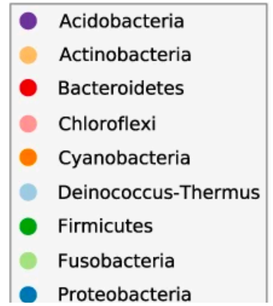

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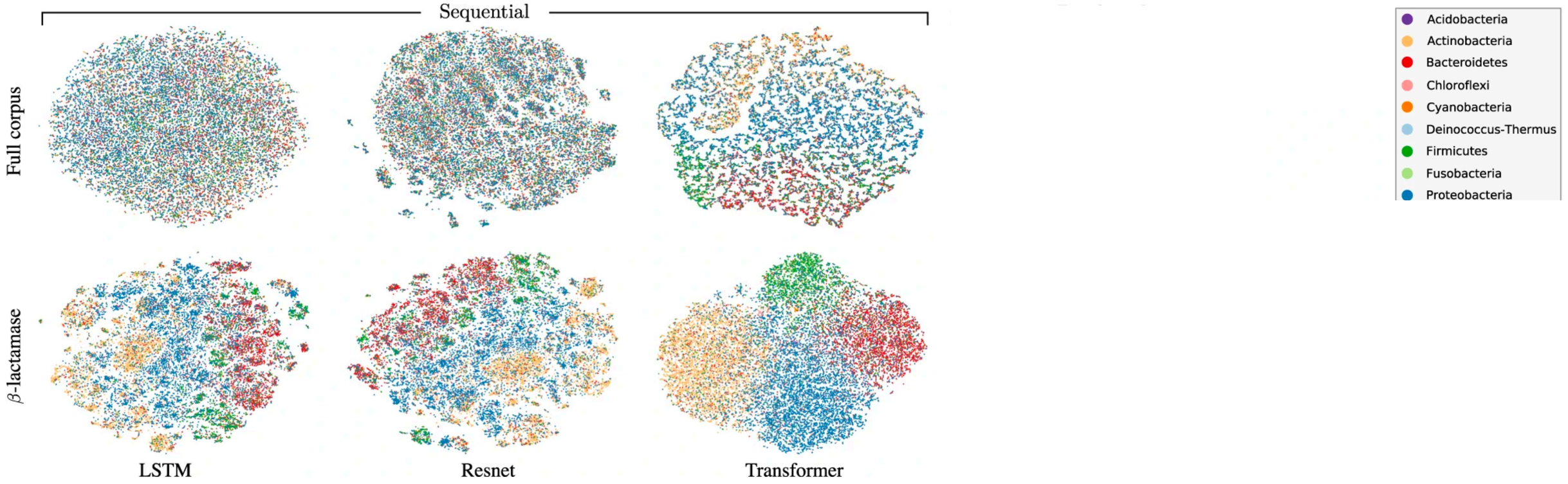

Detlefsen *et al.* 2022

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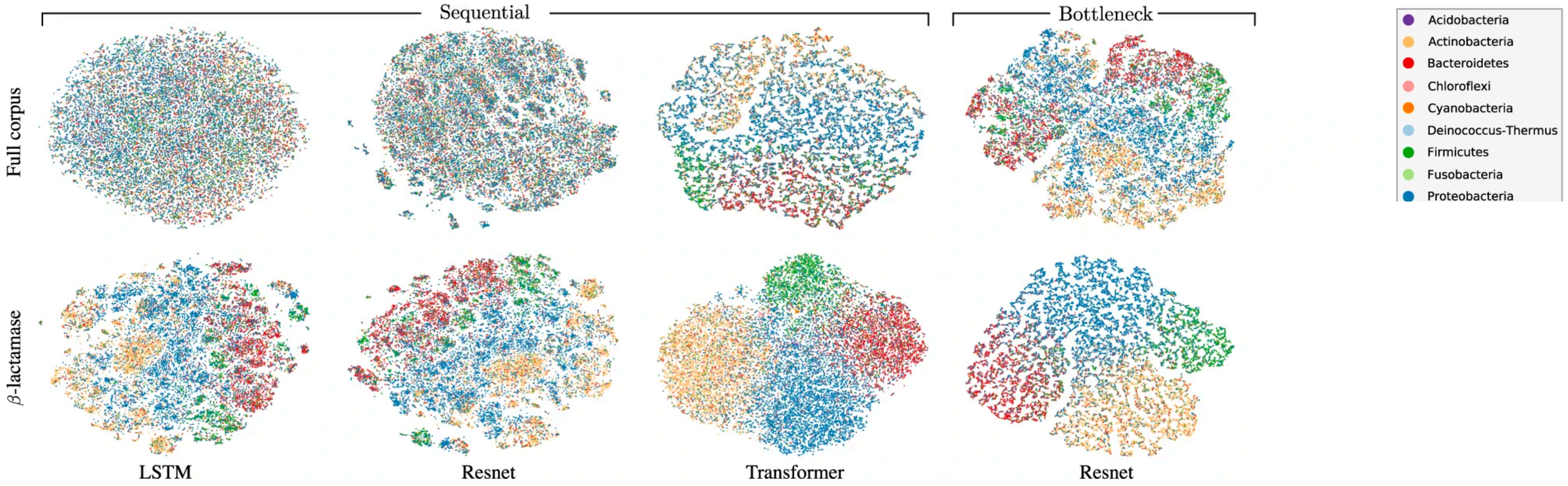

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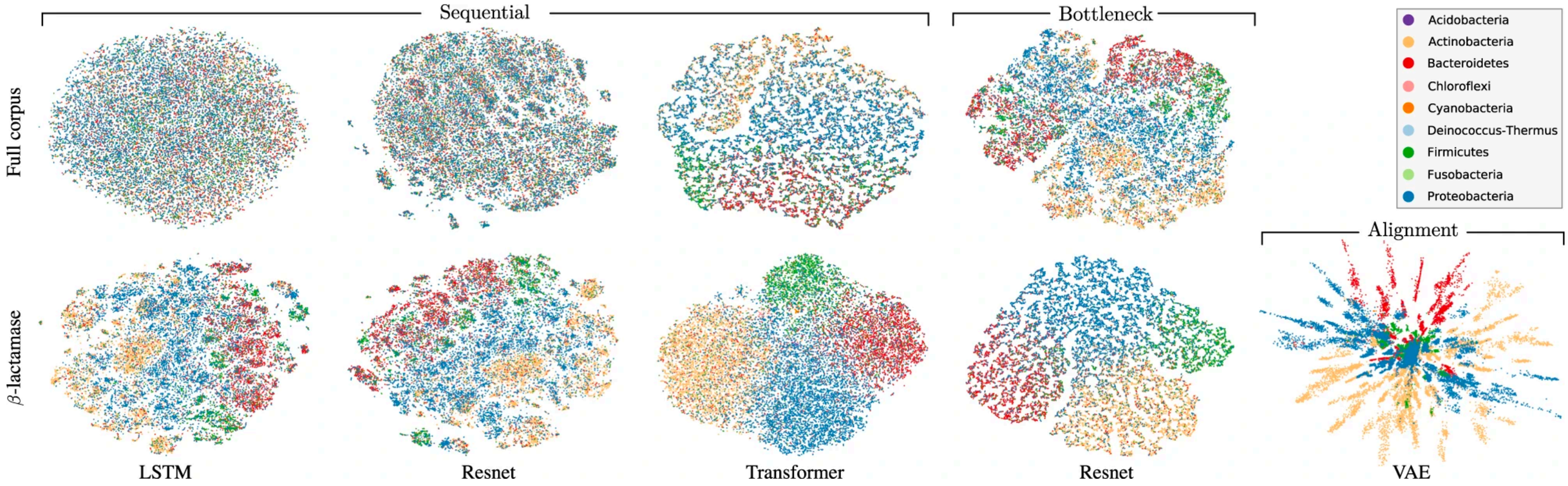

Detlefsen *et al.* 2022

Transformer masked language models are currently popular

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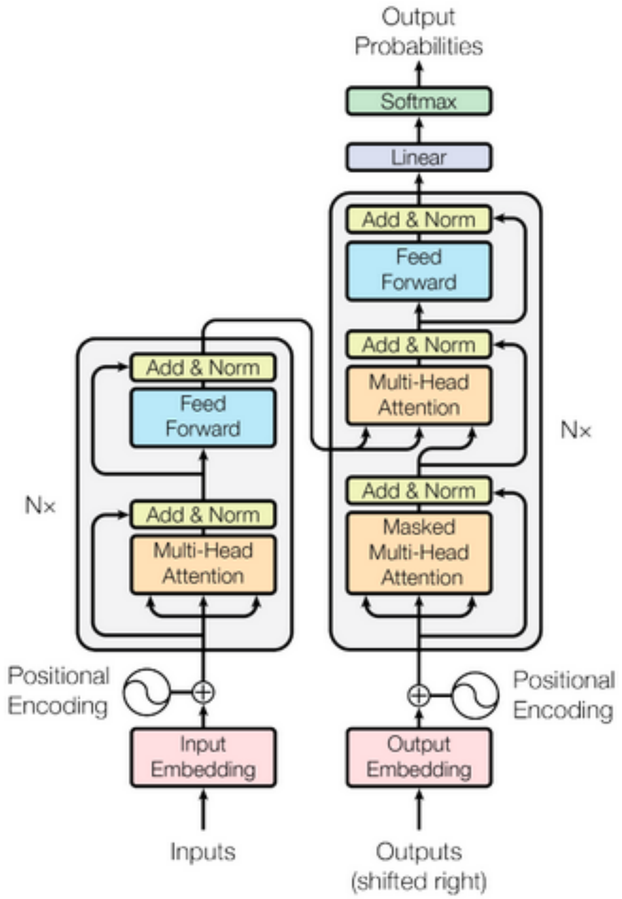
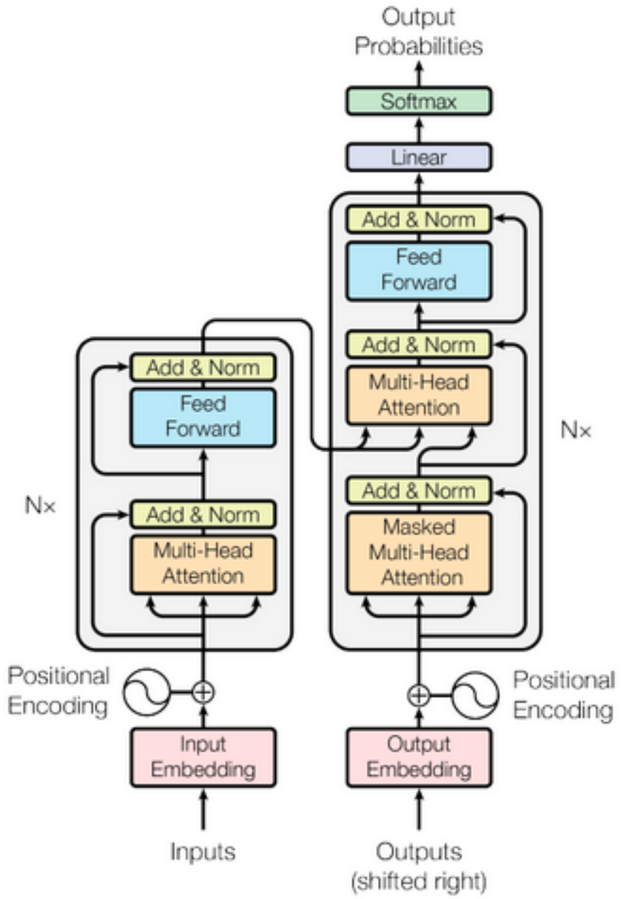


Transformer masked language models are currently popular



UniRef50
42M

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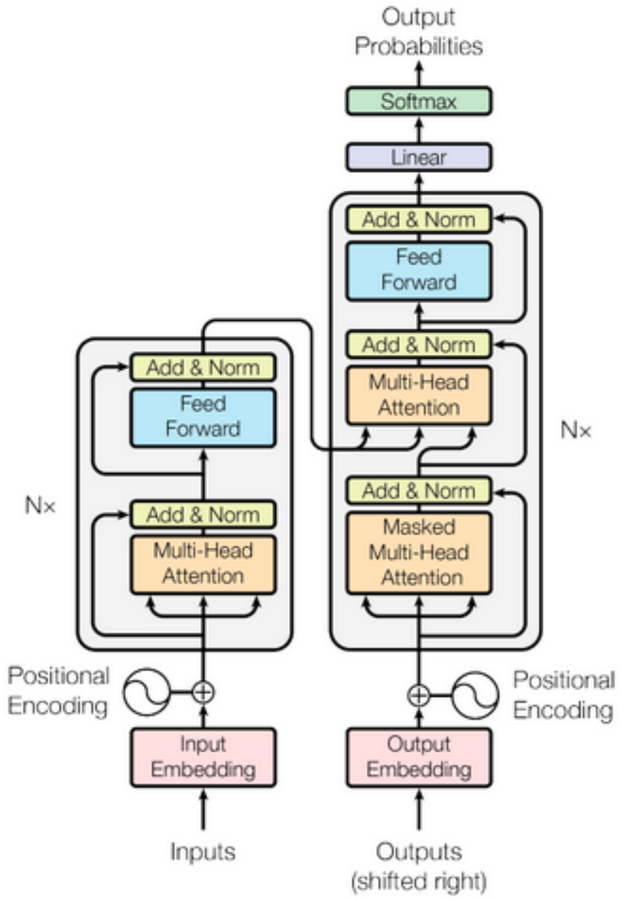

UniRef50 42M → ESM-1b

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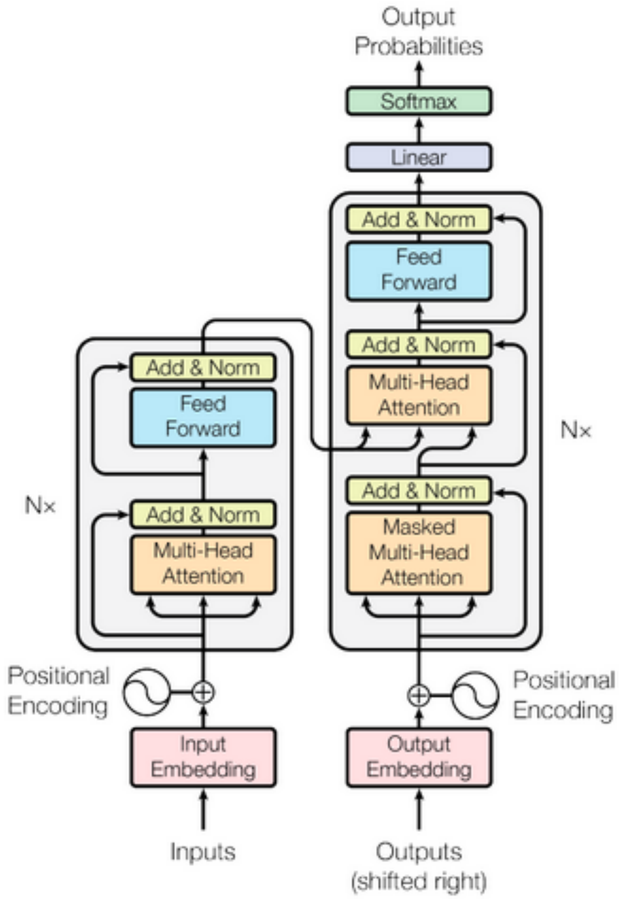

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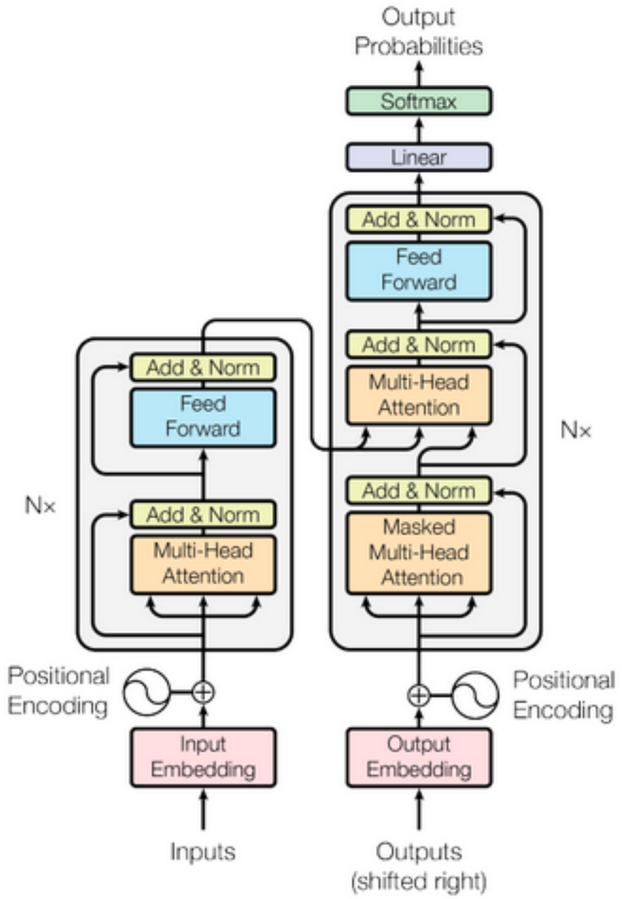

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UniRef90 116M

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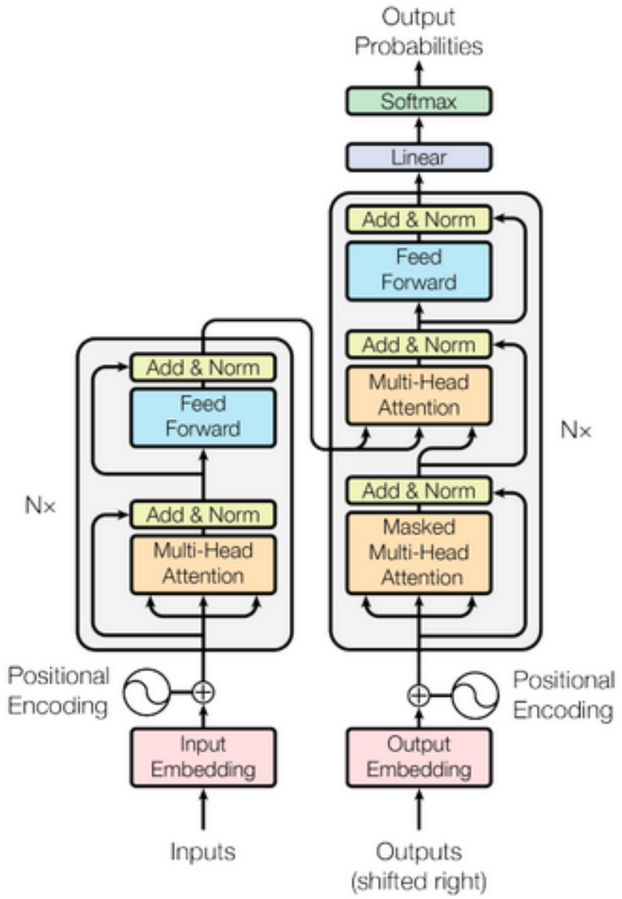

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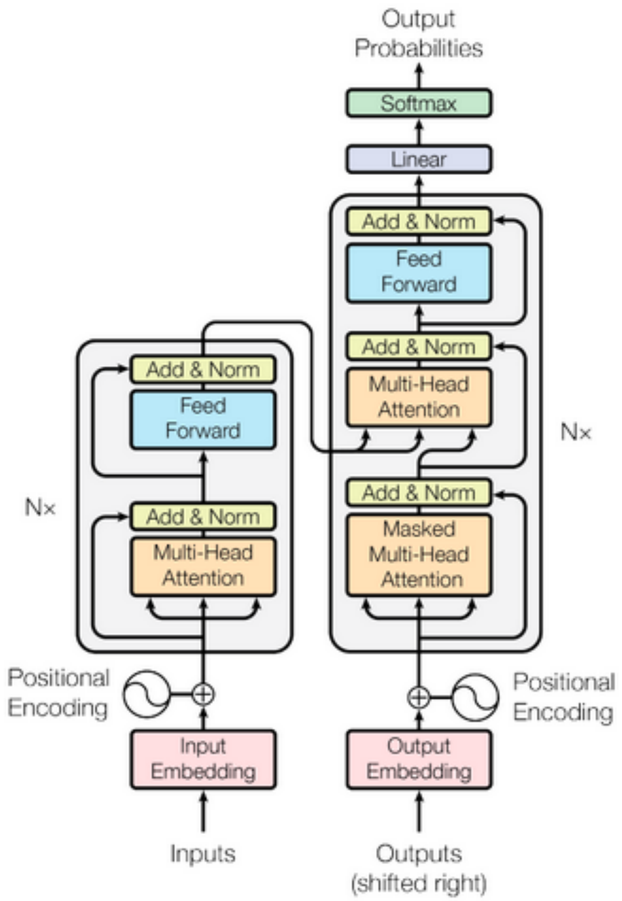

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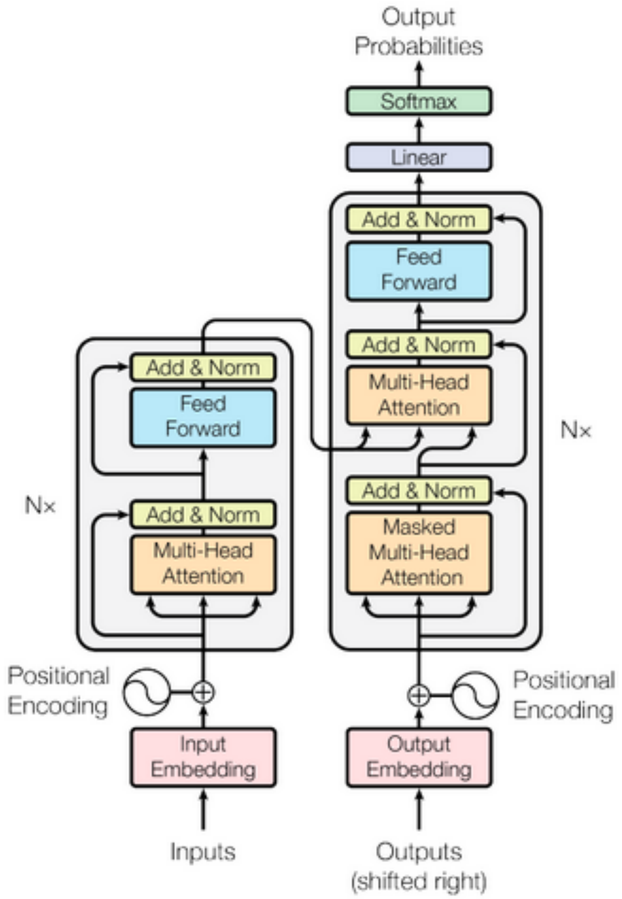
UniRef90 116M → ESM-1v

Best at variant effect prediction

Transformer masked language models are currently popular



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Best at variant effect prediction

BFD 1.2B

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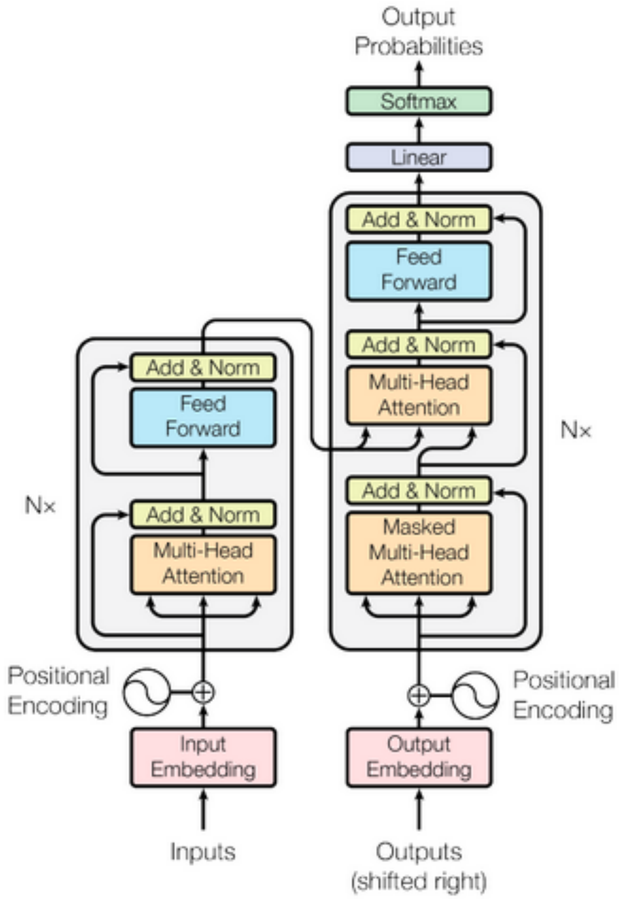

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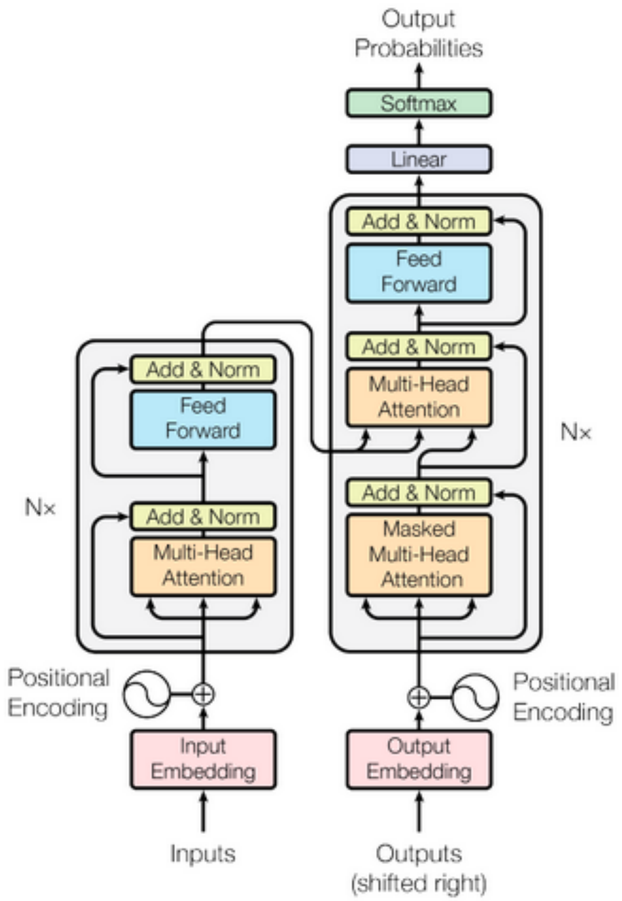

UniRef50 42M → ESM-1b

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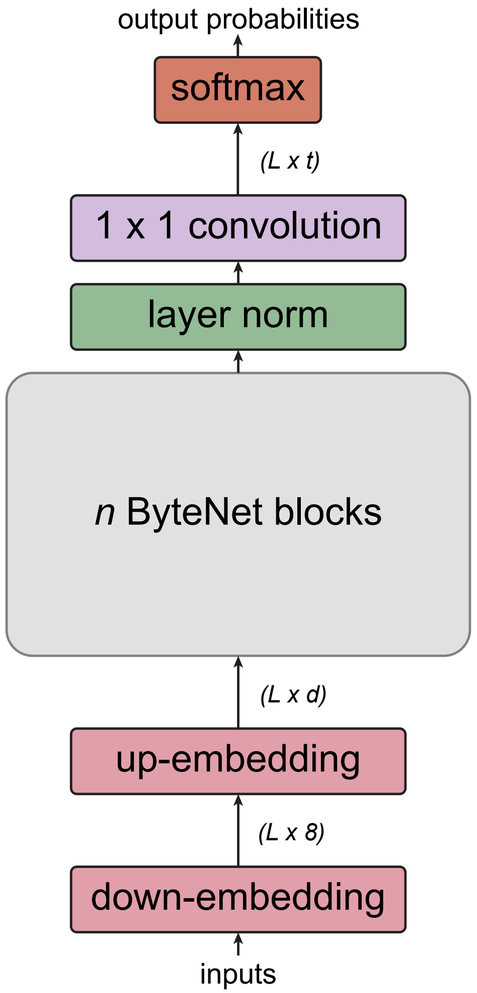
Having many more (redundant) sequences doesn't help

CNNs are competitive with transformers for pretraining

CNNs are competitive with transformers for pretraining



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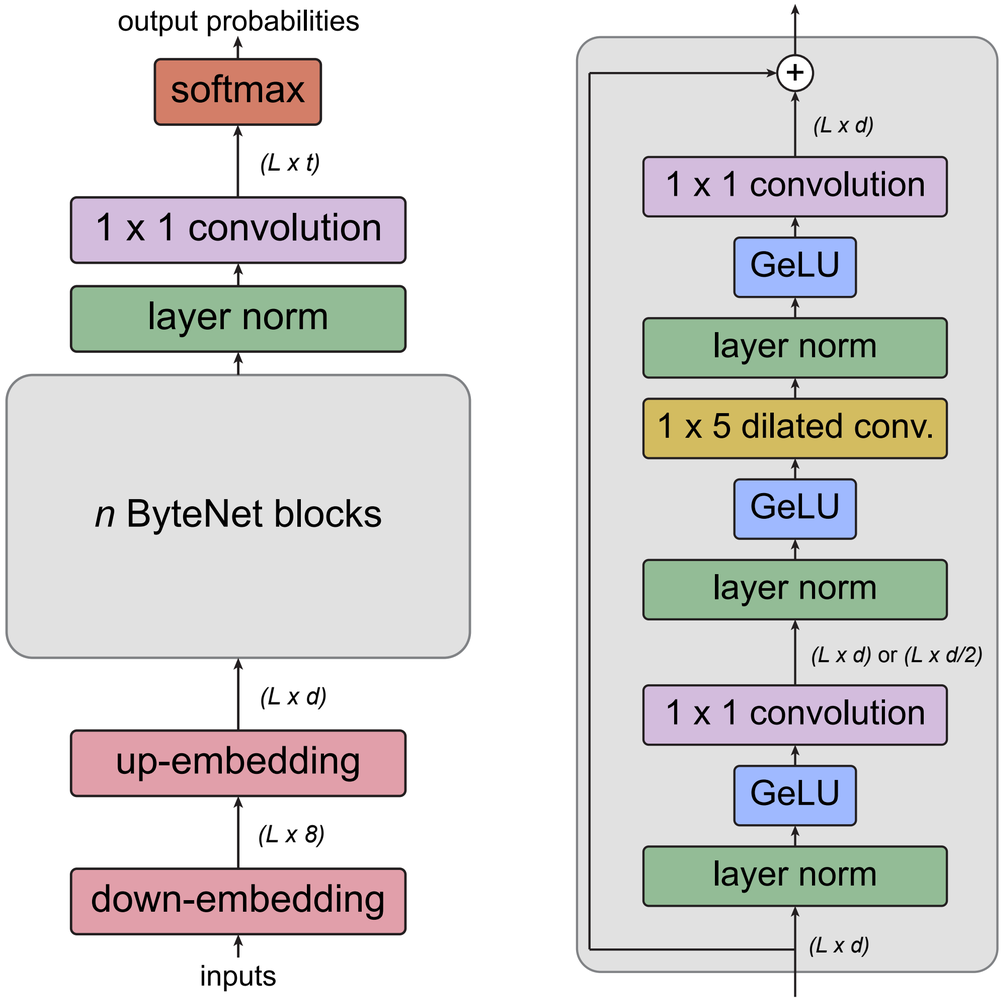

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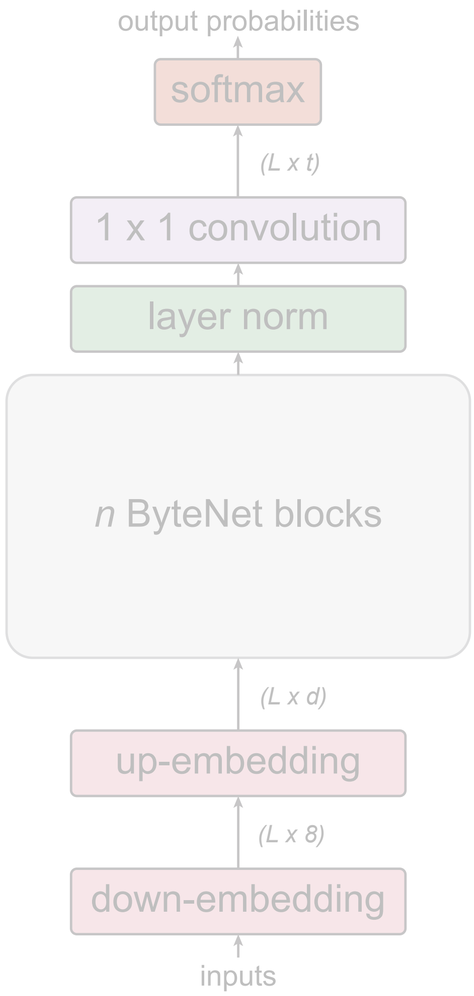

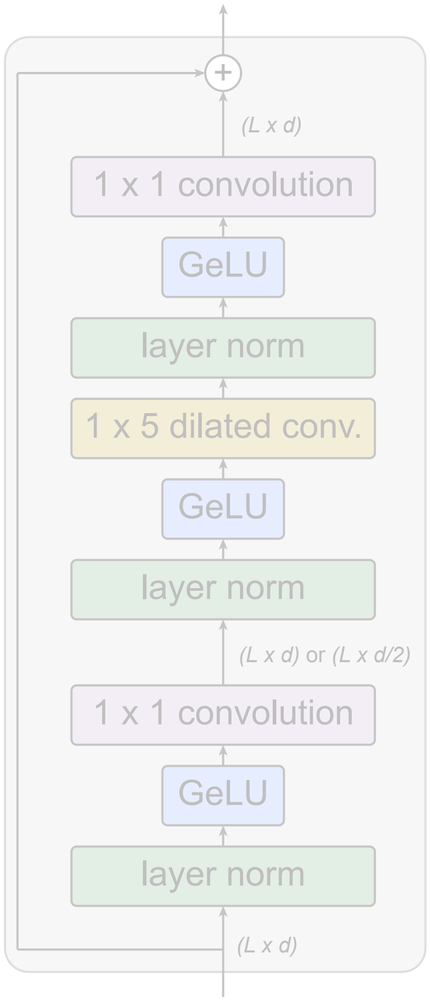

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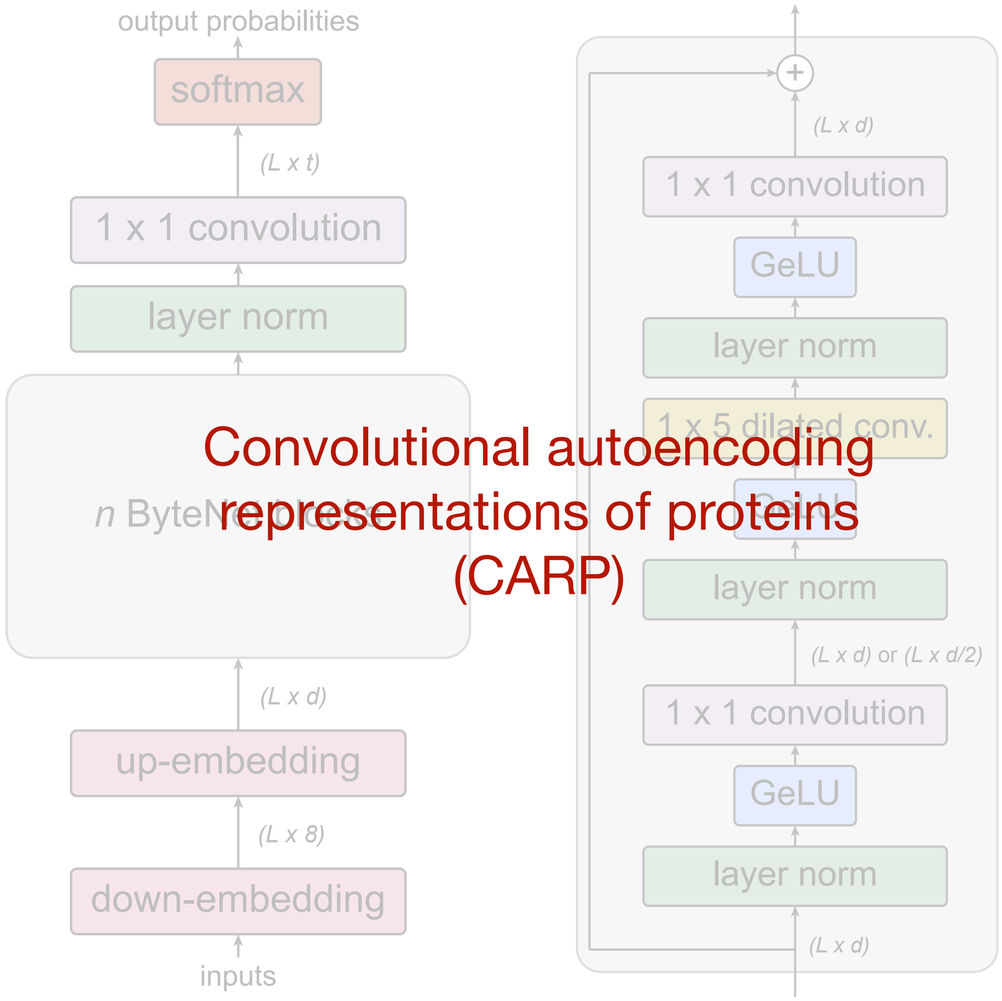
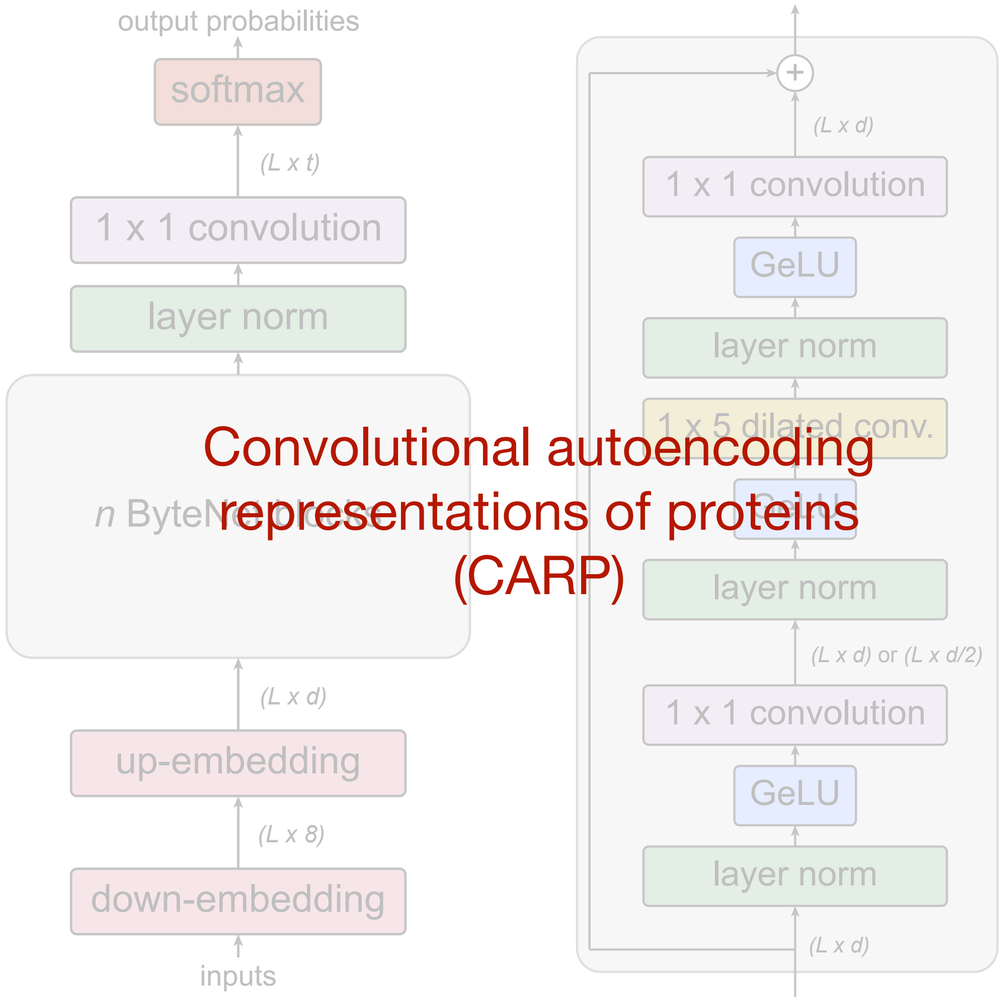


Convolutional autoencoding representations of proteins (CARP)

CNNs are competitive with transformers for pretraining



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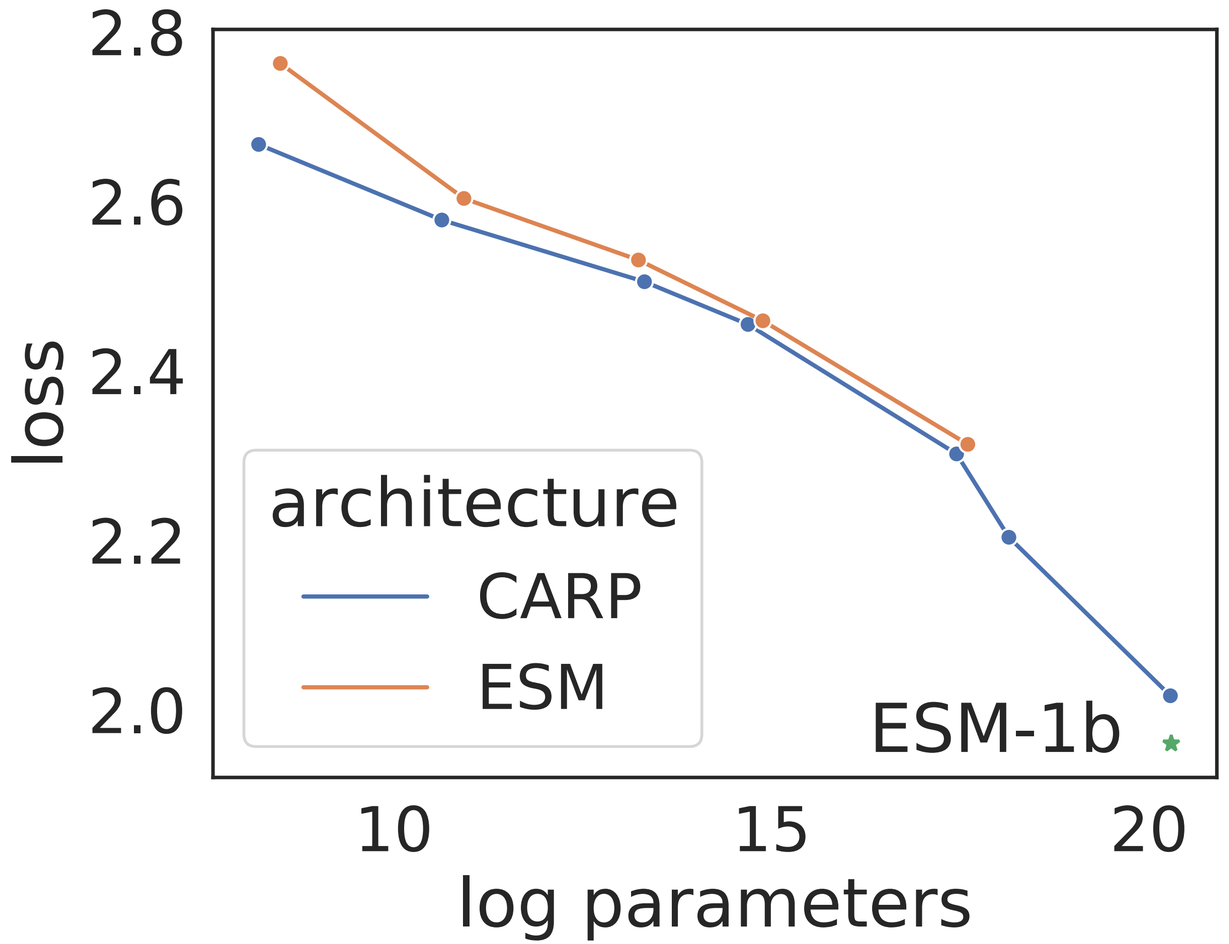
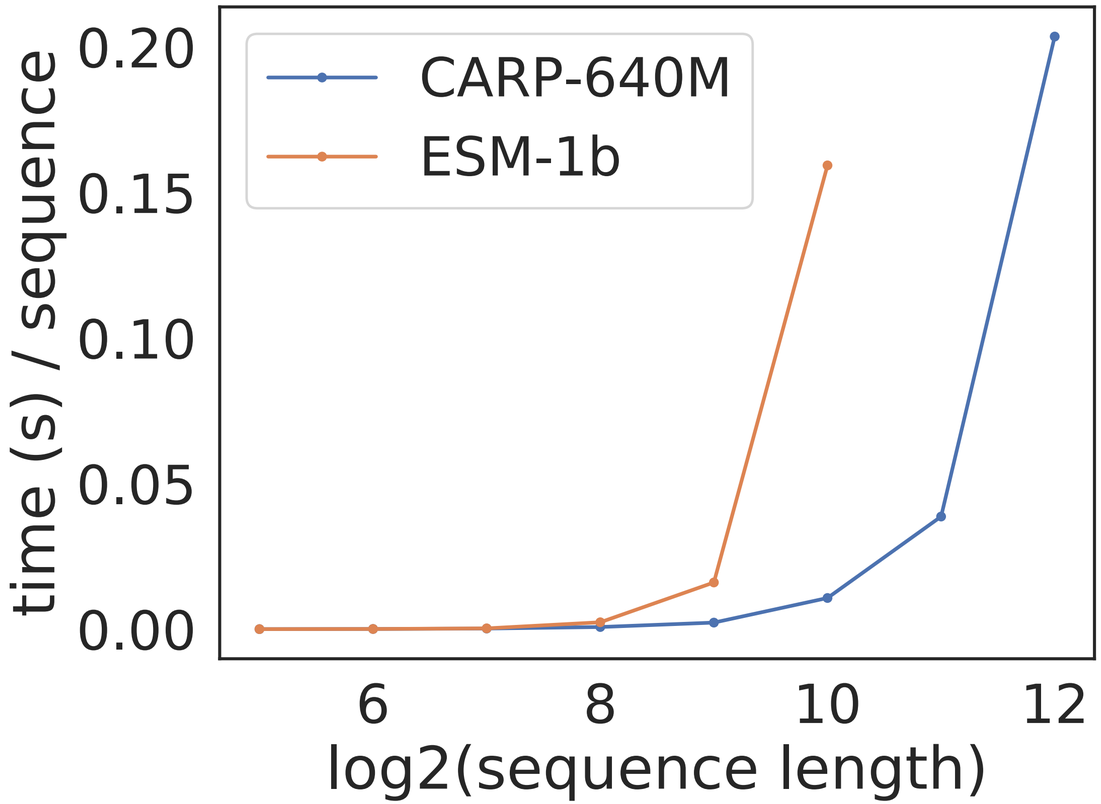


CNNs scale better with length



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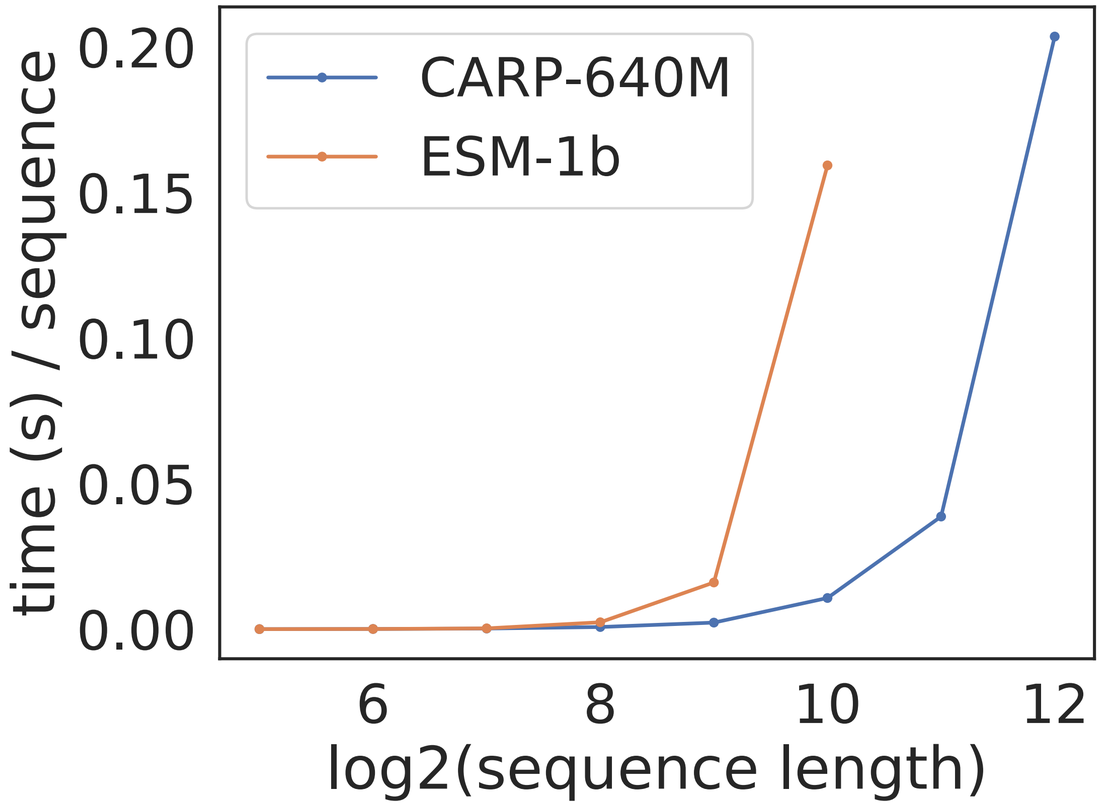
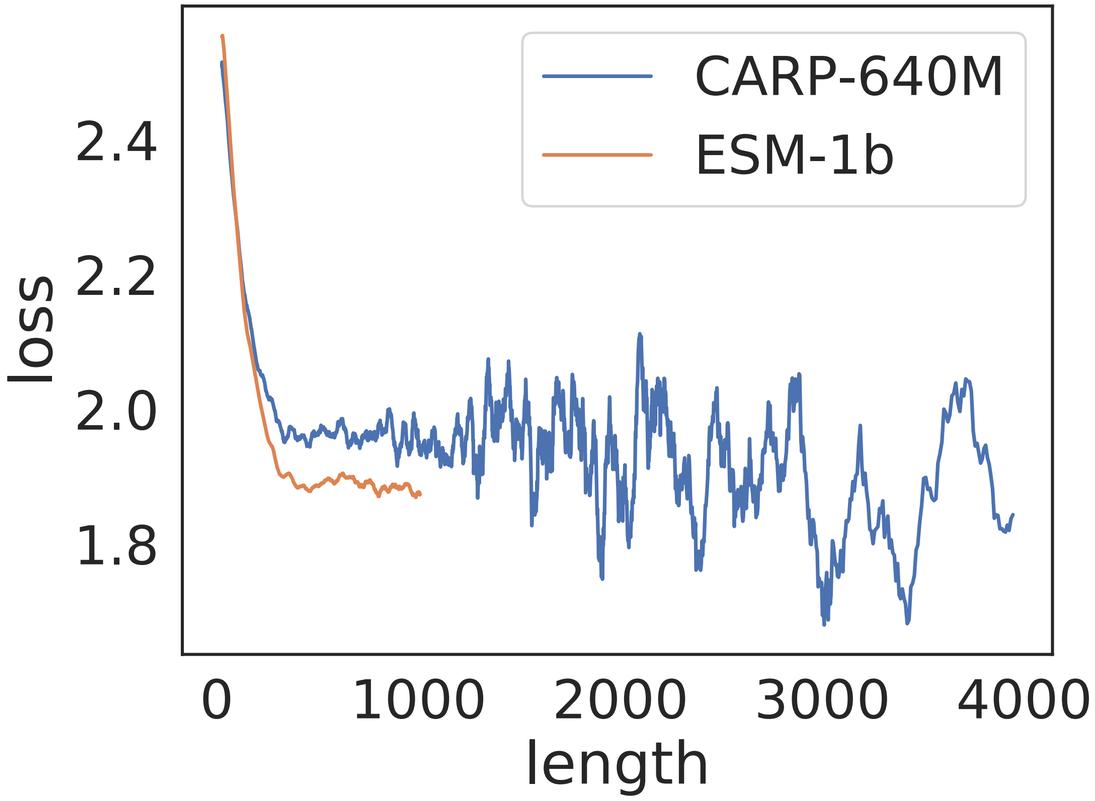
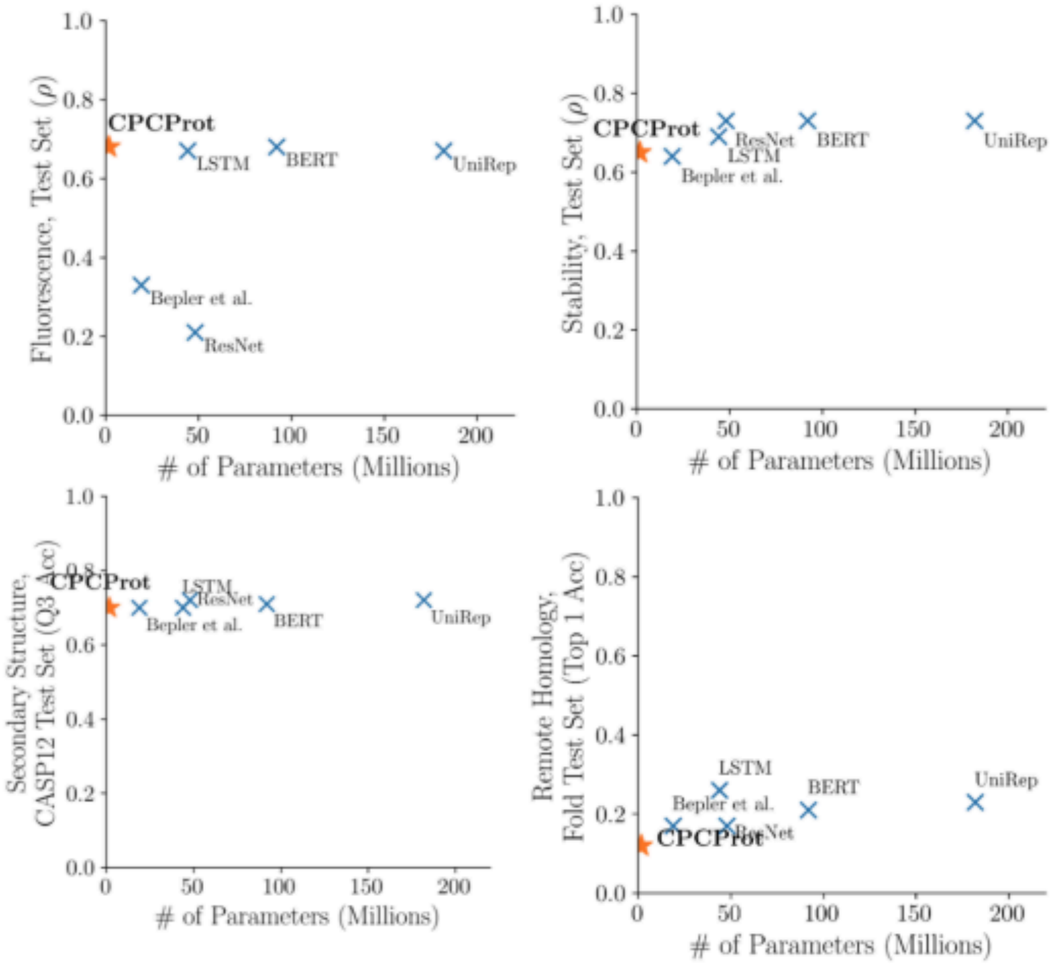


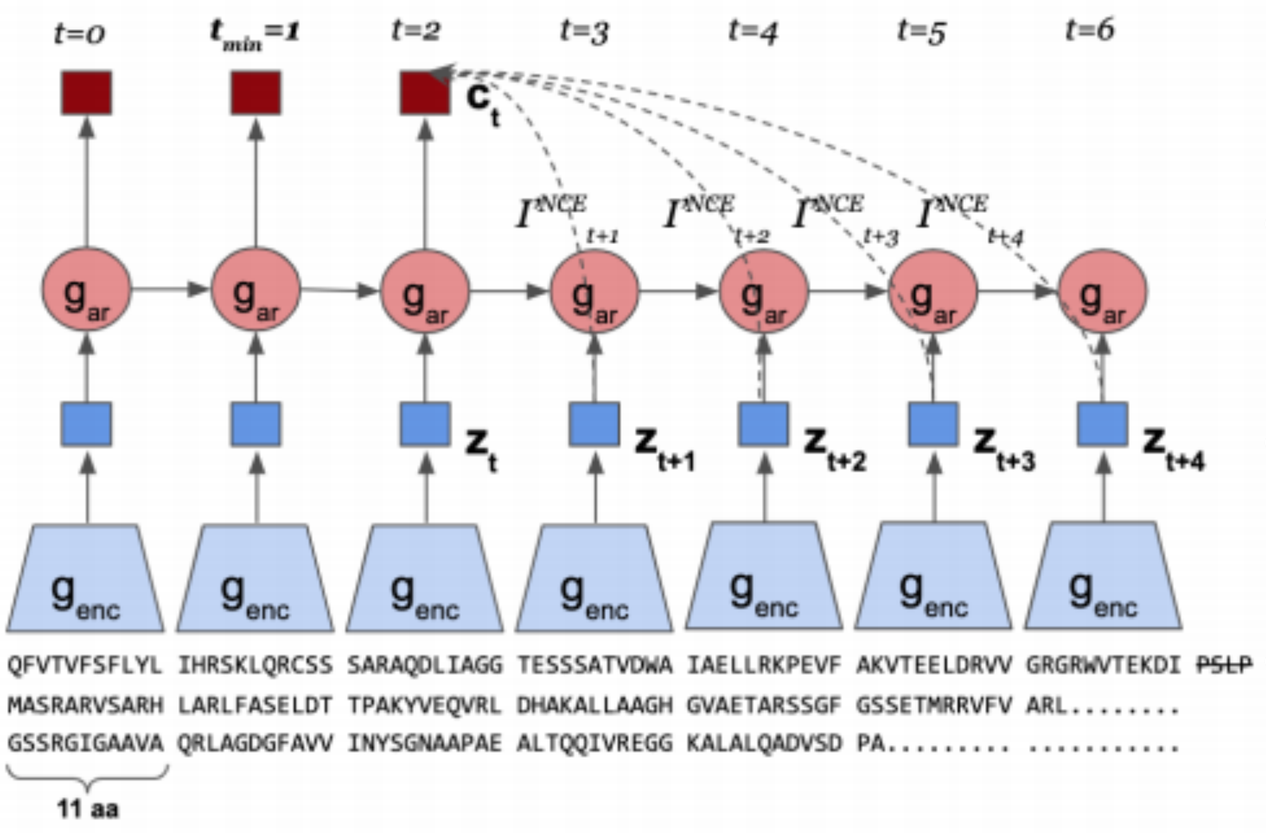


Contrastive learning may require fewer parameters



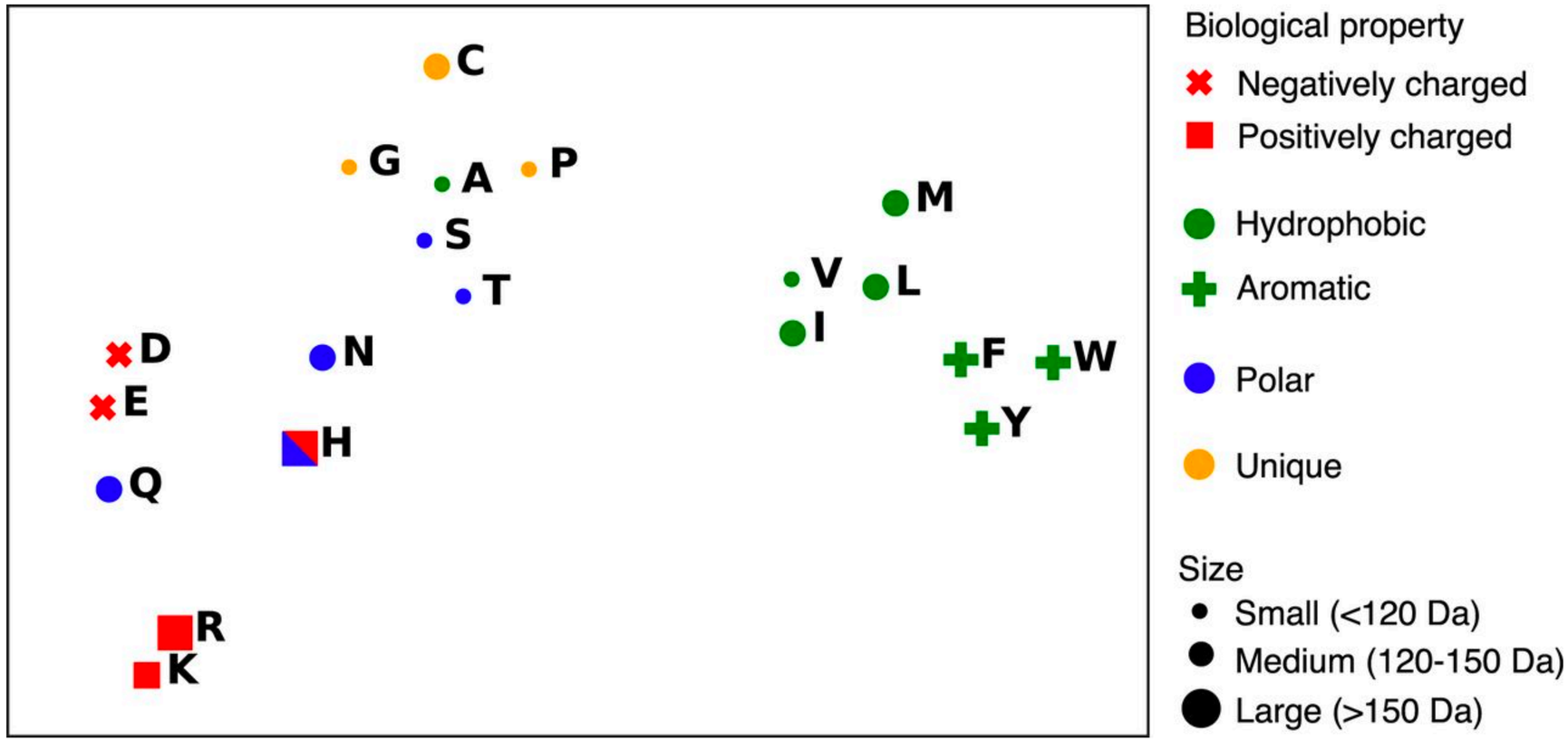
	# of Embedding Parameters	Remote Homology			Secondary Structure			Stability	Fluorescence
		Fold	Superfamily	Family	CB513	CASP12	TS115		
Unirep	182M	0.23	0.38	0.87	0.73	**0.72**	0.77	**0.73**	0.67
BERT	92M	0.21	0.34	0.88	0.73	0.71	0.77	**0.73**	**0.68**
ResNet	48M	0.17	0.31	0.77	**0.75**	**0.72**	**0.78**	**0.73**	0.21
LSTM	44M	**0.26**	**0.43**	**0.92**	**0.75**	0.70	**0.78**	0.69	0.67
Bepler et al.	19M	0.17	0.20	0.79	0.73	0.70	0.76	0.64	0.33
One Hot	0	0.09	0.08	0.39	0.69	0.68	0.72	0.19	0.14
CPCProt	1.7M	0.12	0.12	0.48	0.69	0.70	0.73	0.65	**0.68**
$\text{CPCProt}_{\text{GRU\_large}}$	8.4M	0.13	0.14	0.52	0.70	0.70	0.73	0.65	**0.68**
$\text{CPCProt}_{\text{LSTM}}$	71M	0.11	0.11	0.47	0.68	0.66	0.70	0.68	**0.68**

But is it really the contrastive learning that helps?



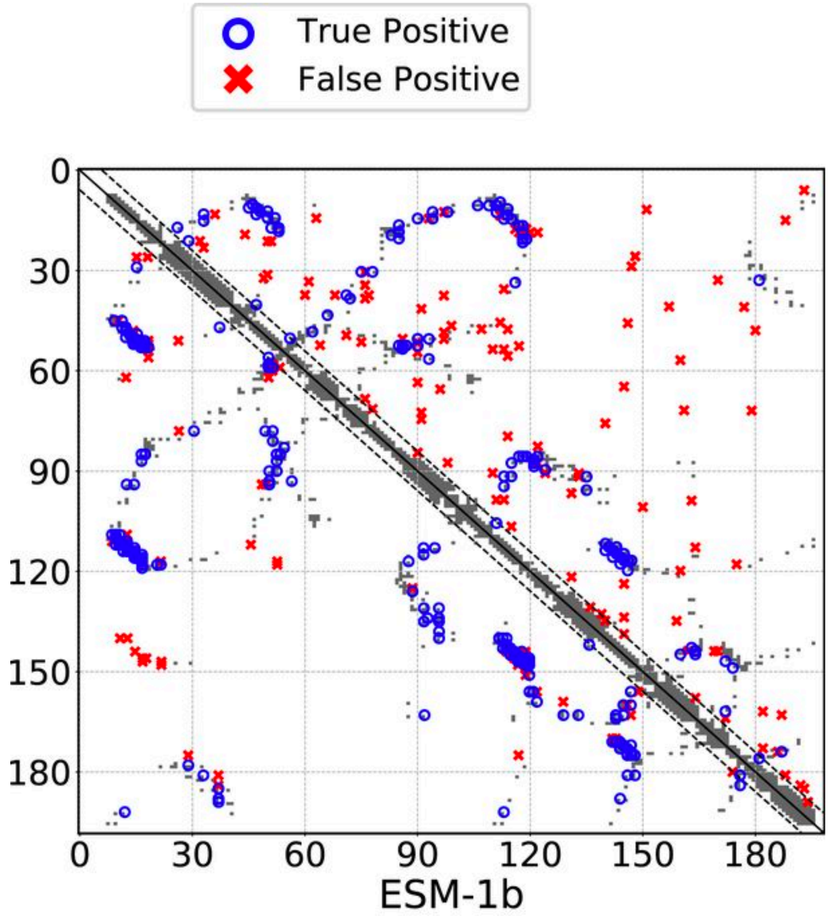
- In images, the augmentation pipeline is most important
- Maybe we just need to be predicting larger blocks?
- Or have better negatives

Deep sequence embeddings recapitulate biophysical properties



Rives *et al. PNAS* 2021

Deep sequence embeddings contain structural information



Rives *et al. PNAS* 2021

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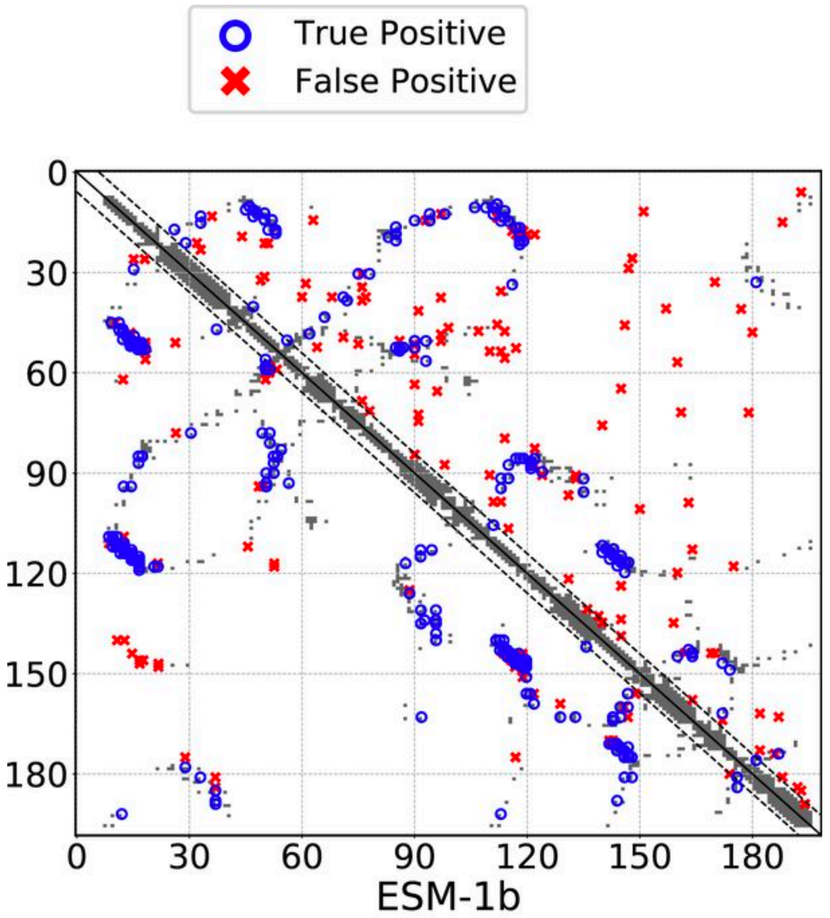
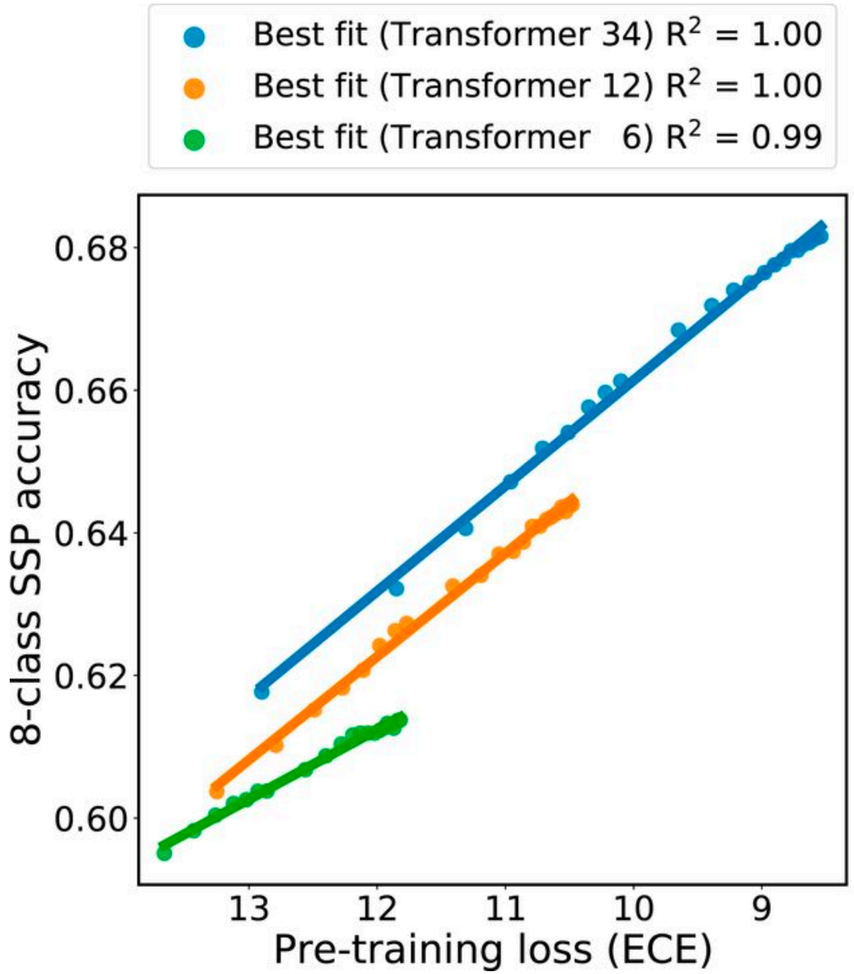
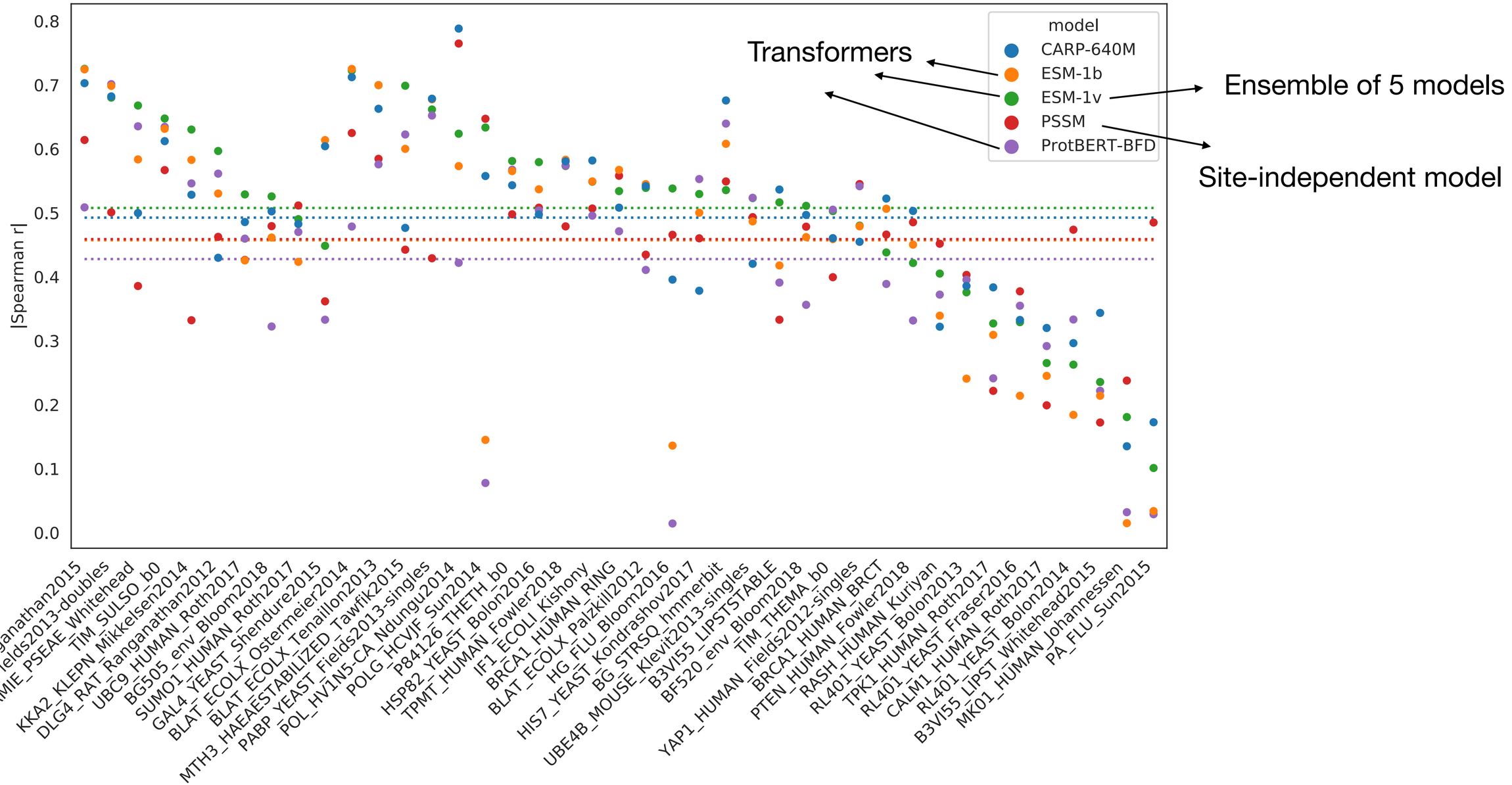




Rives *et al. PNAS* 2021

MLM pseudo likelihood predicts mutant fitness



Pretrained models contain evolutionary information

Hie *et al.* 2022

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Pseudolikelihood correlates with mutational tolerance

Hie *et al.* 2022

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Pseudolikelihood correlates with mutational tolerance

$$\frac{p(\text{mutation})}{p(\text{wild type})}$$

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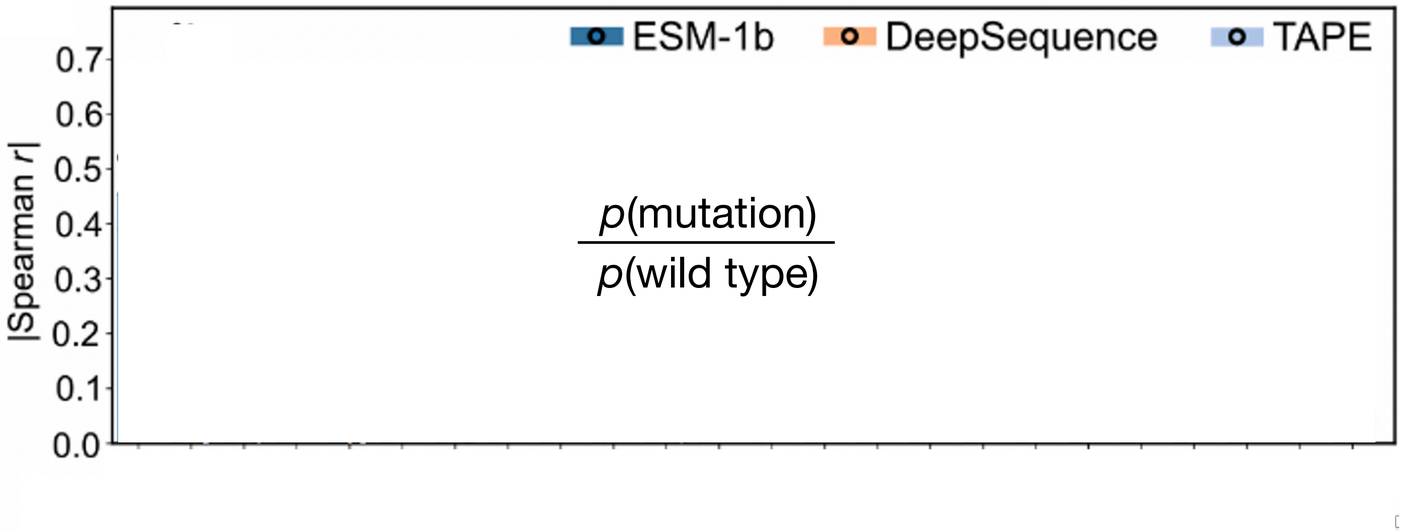

Hie *et al.* 2022

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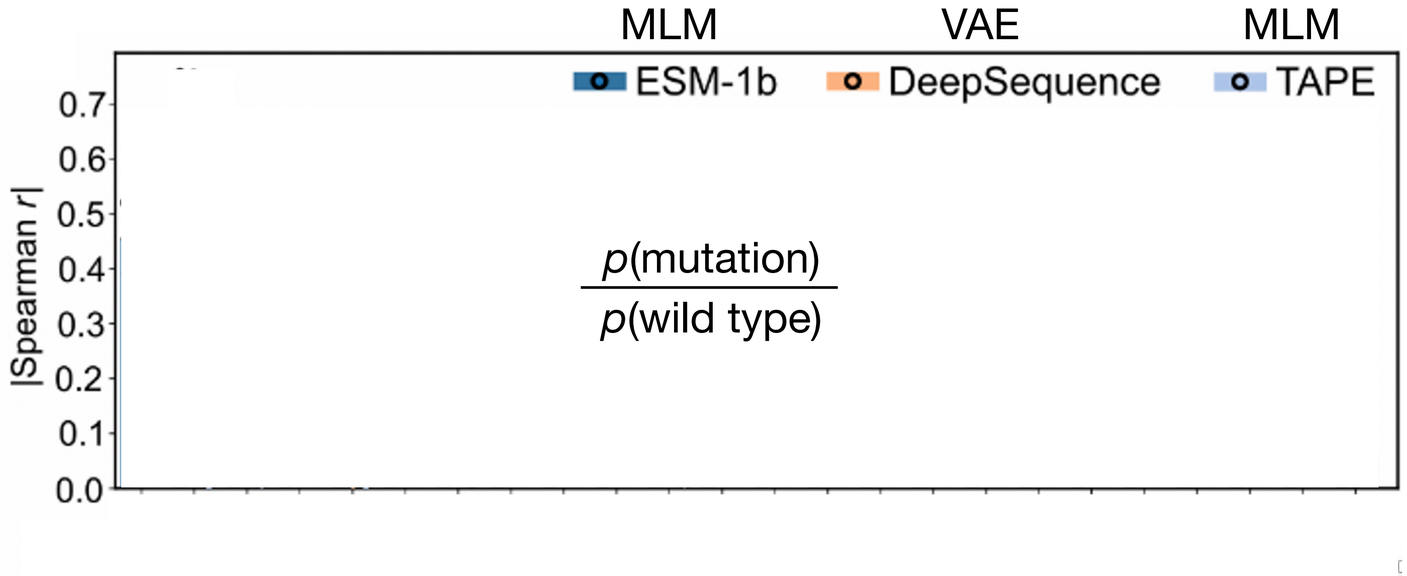

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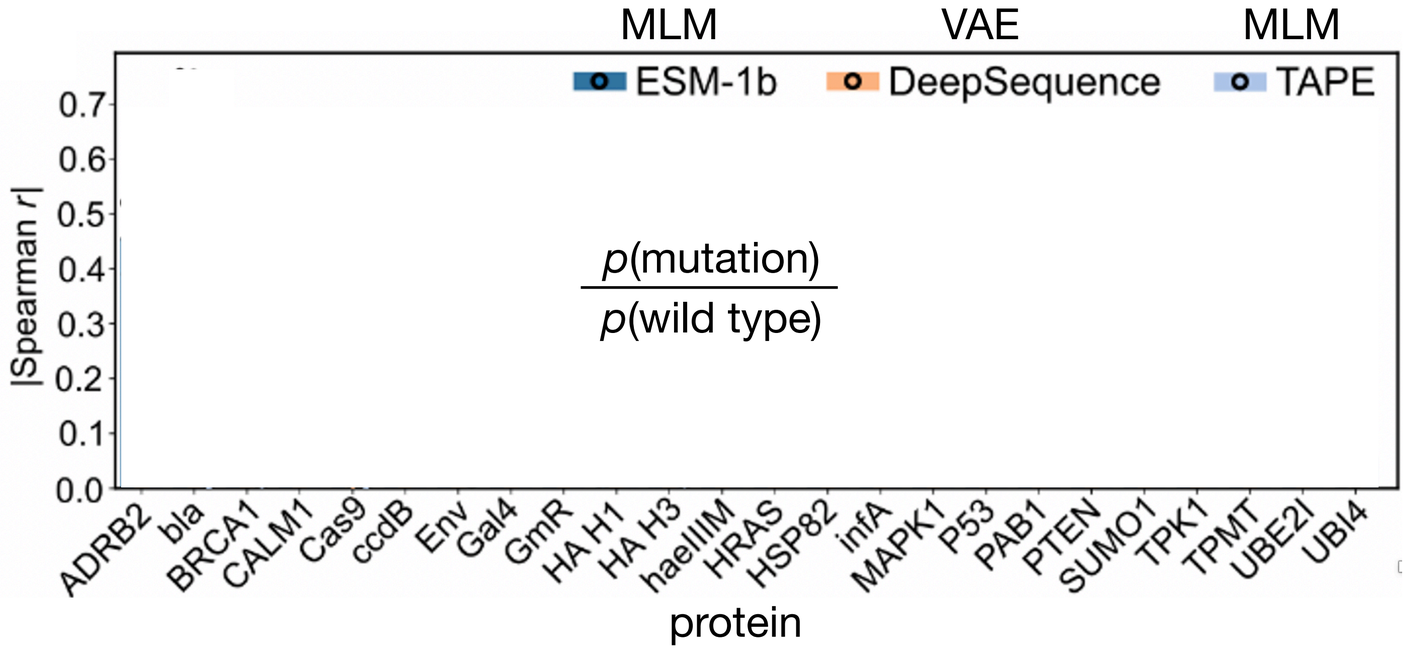

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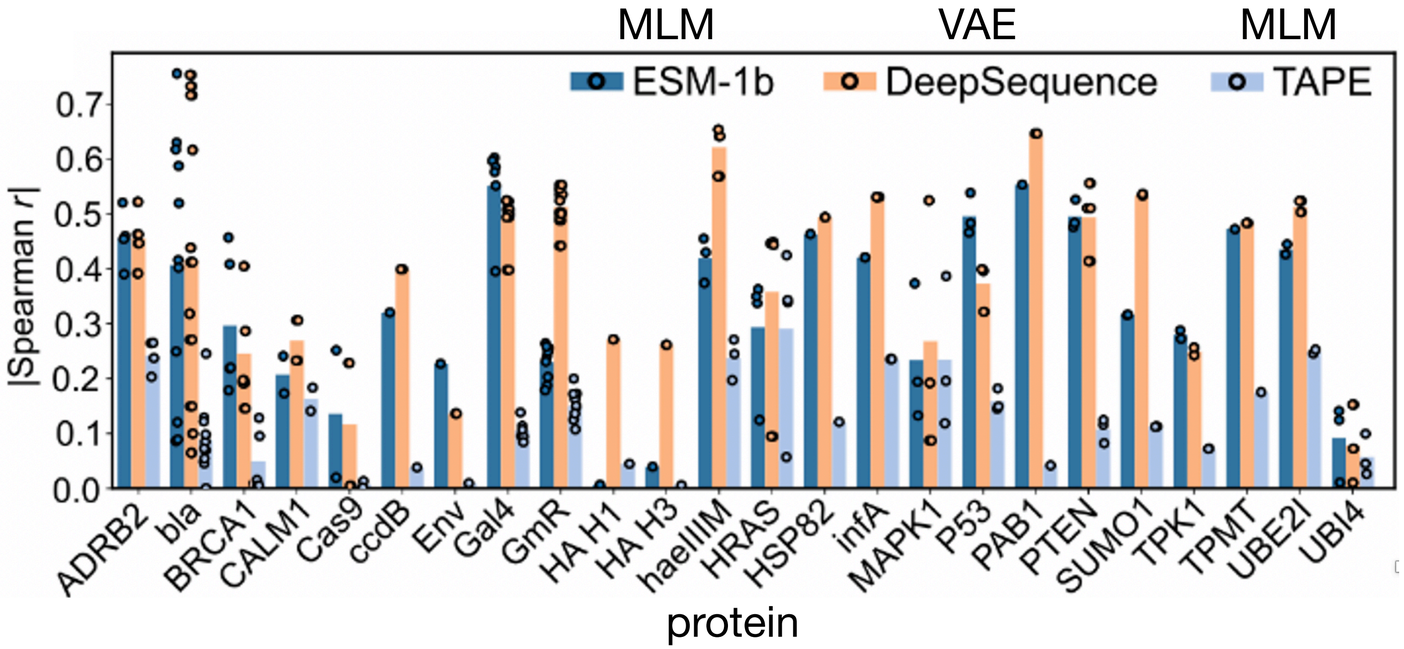

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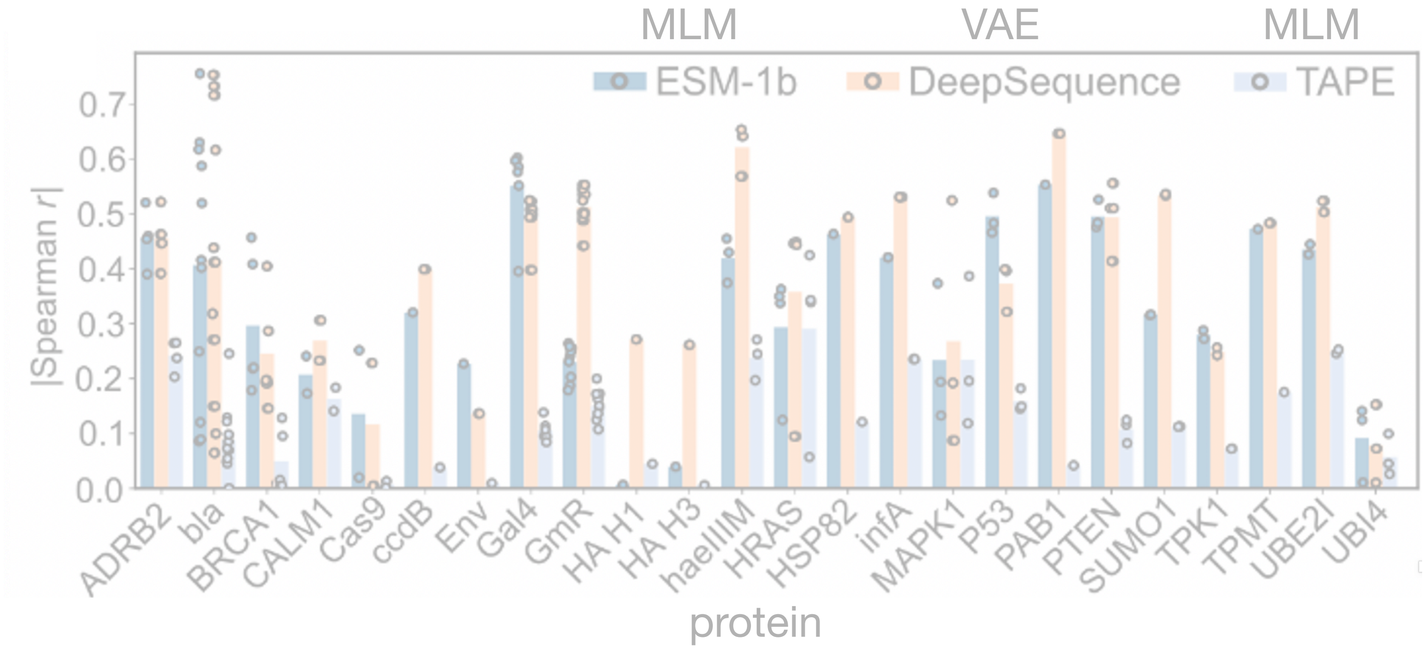

Use pseudolikelihood to predict evolutionary vector field

Hie *et al.* 2022

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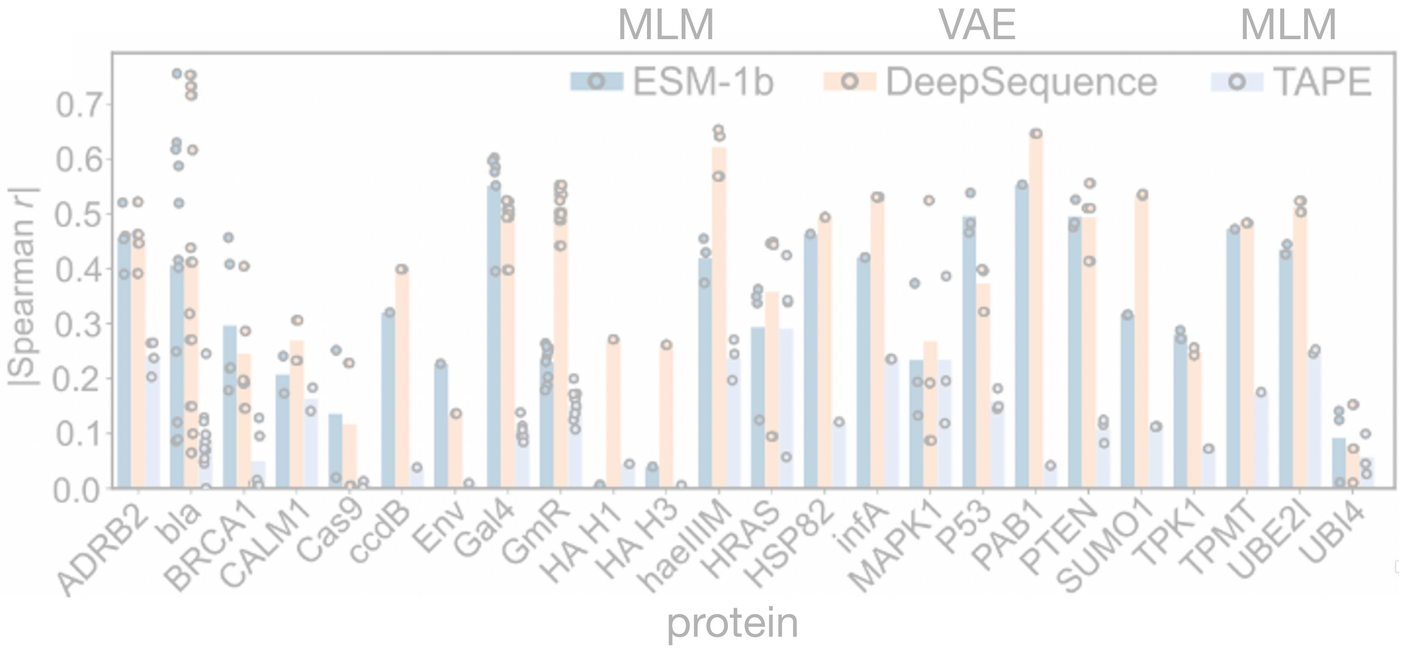

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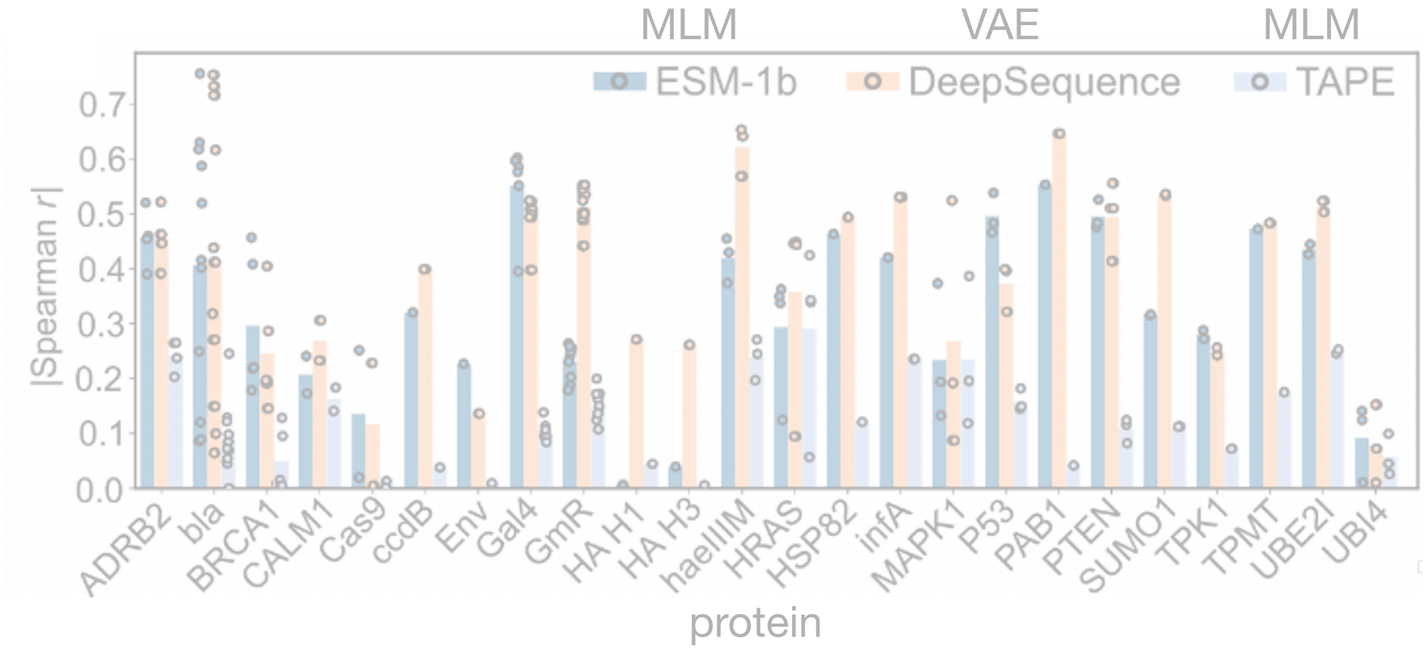

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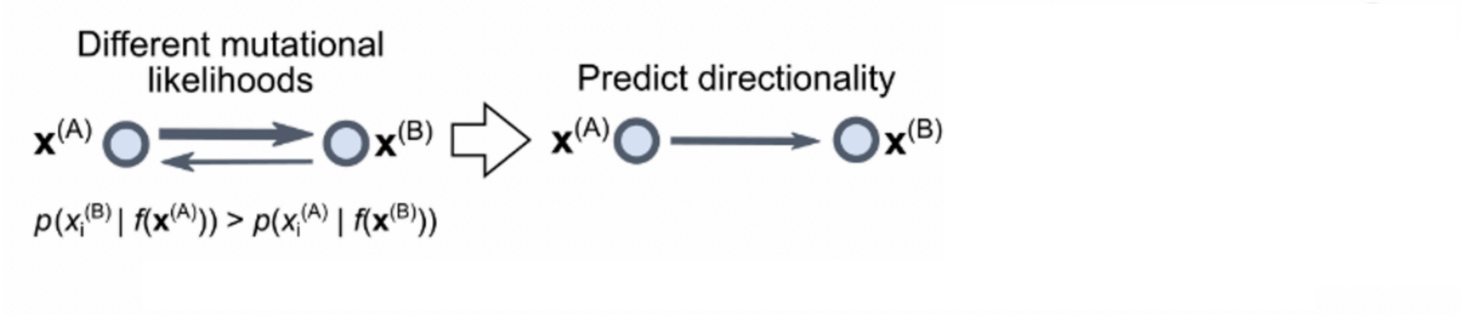

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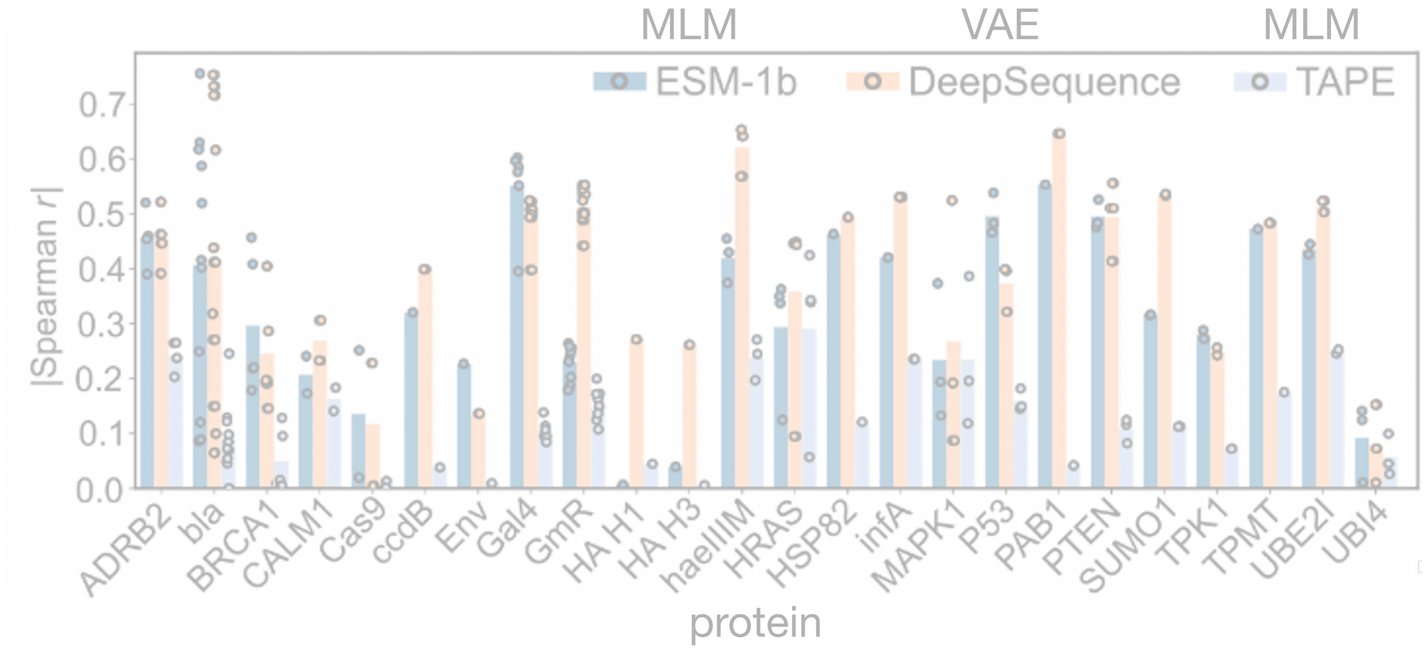

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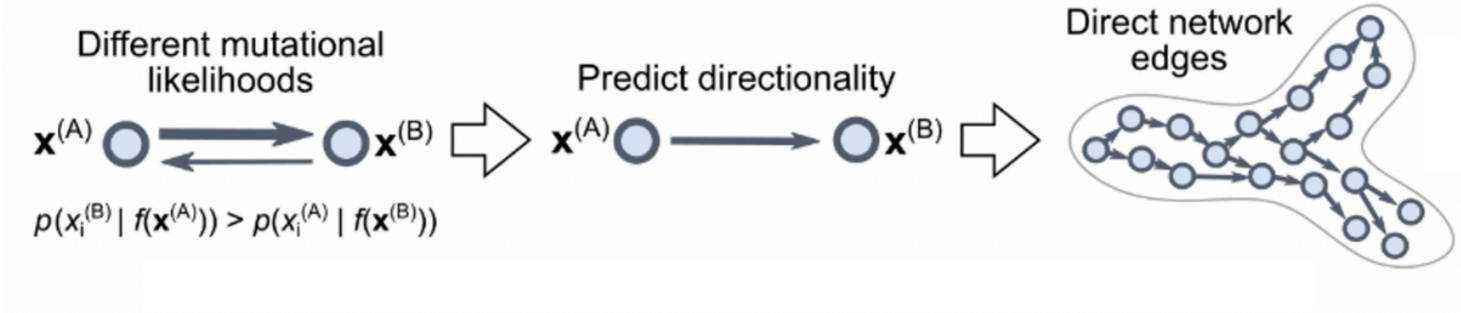

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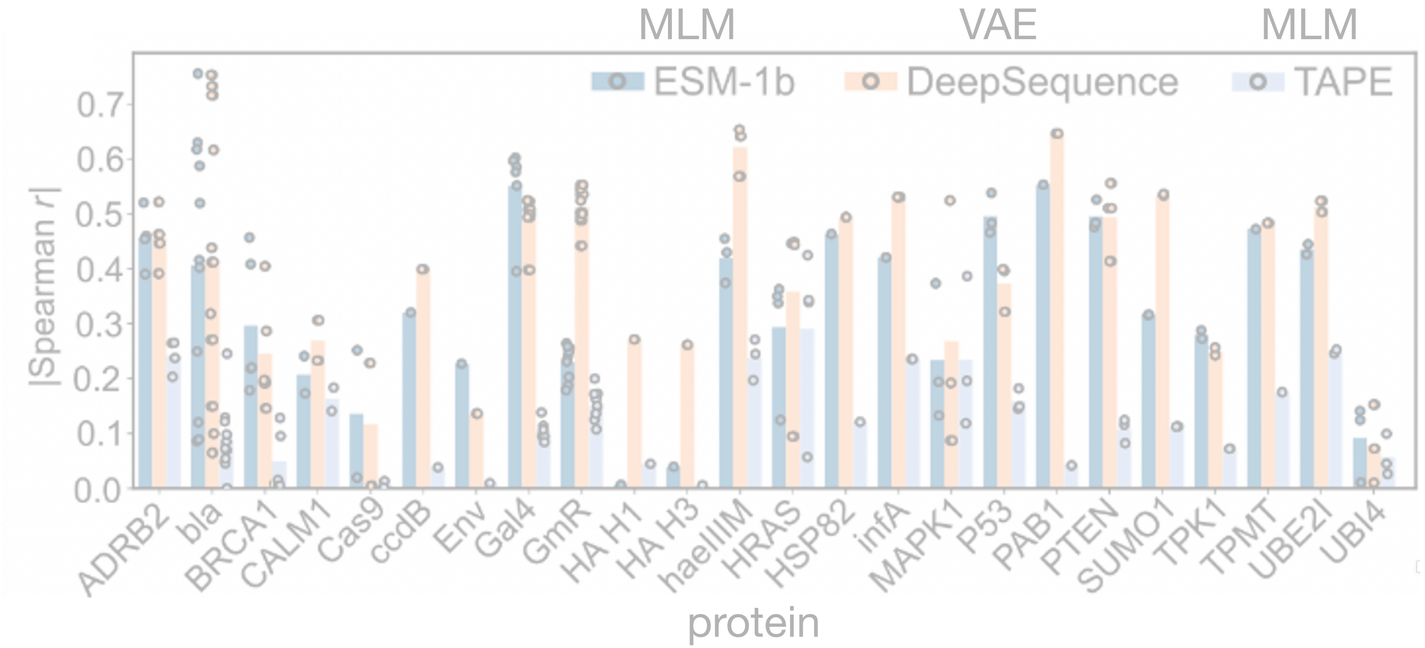

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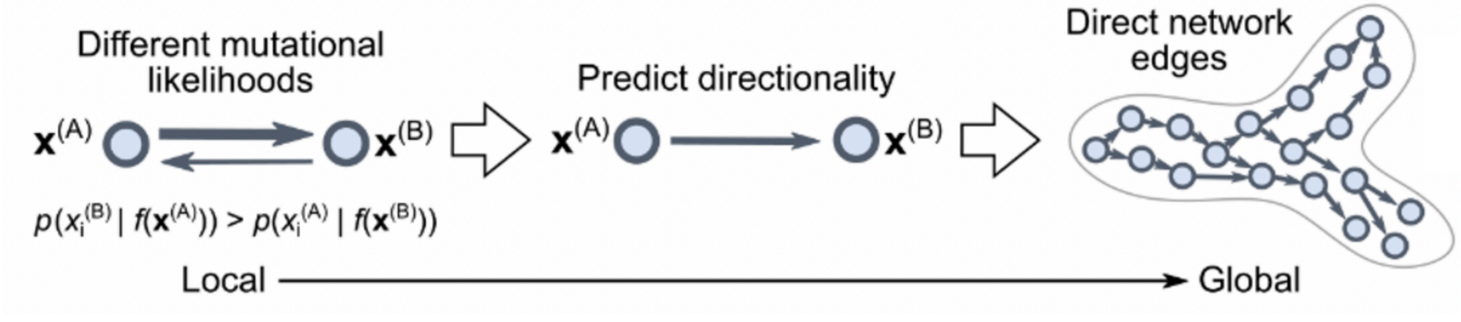

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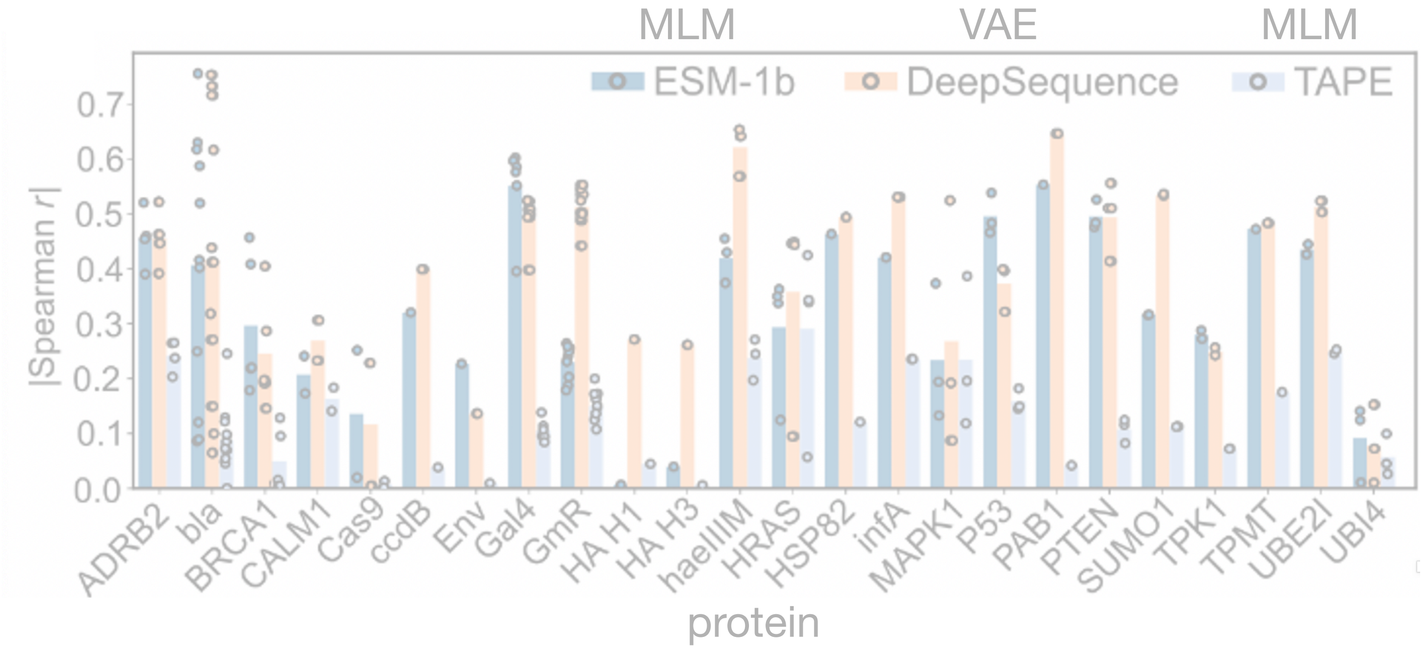

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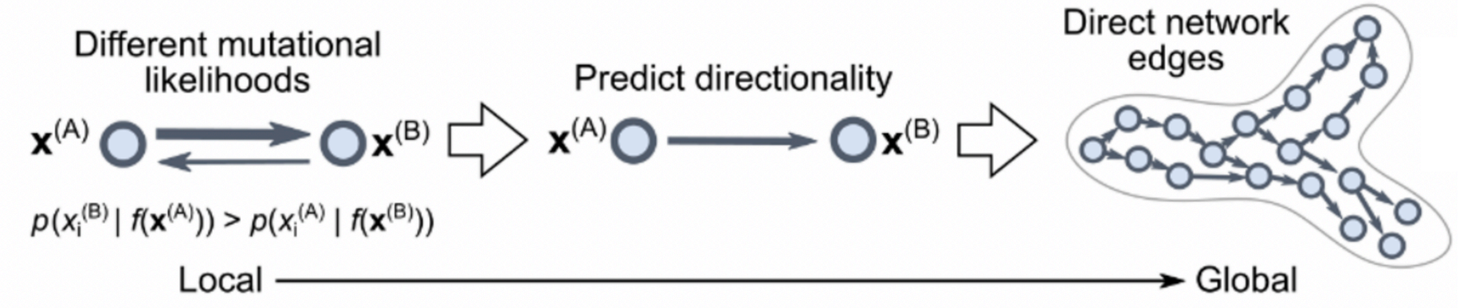
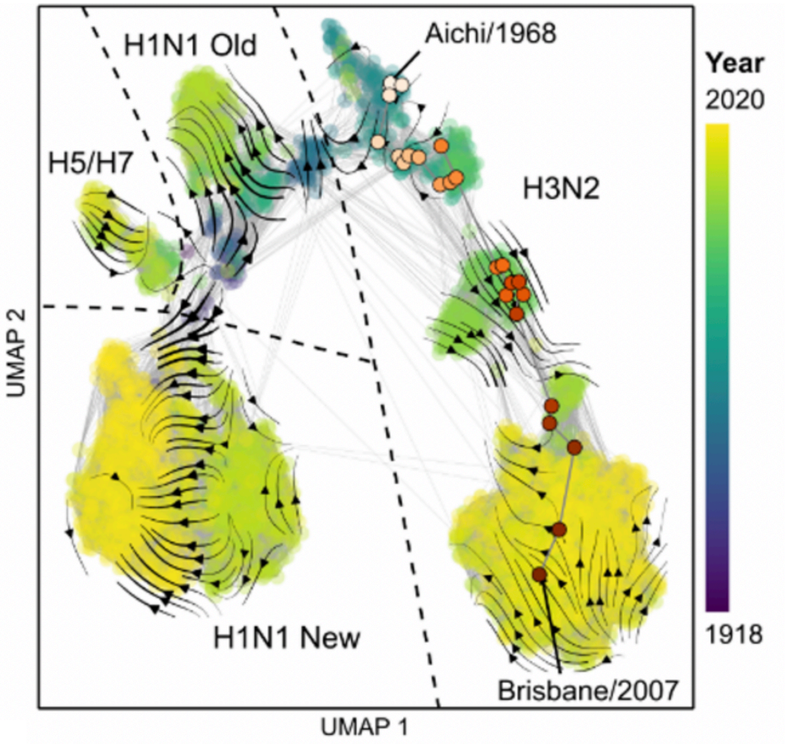


Influenza A nucleoprotein

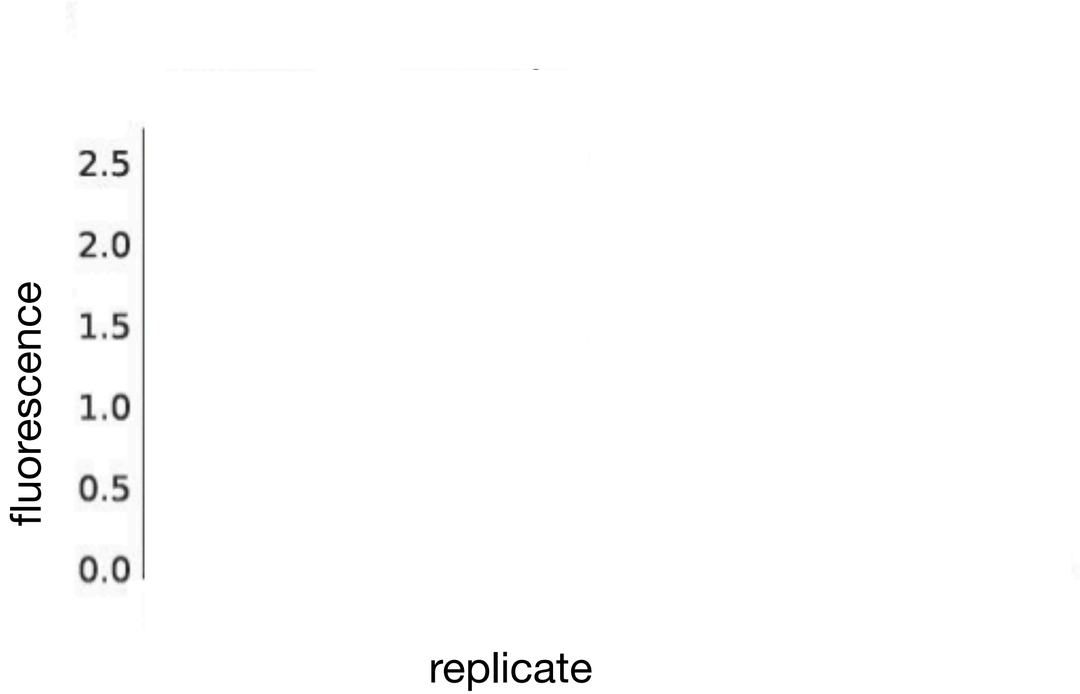


Hie *et al.* 2022

Pretraining guides search away from loss-of-function sequences

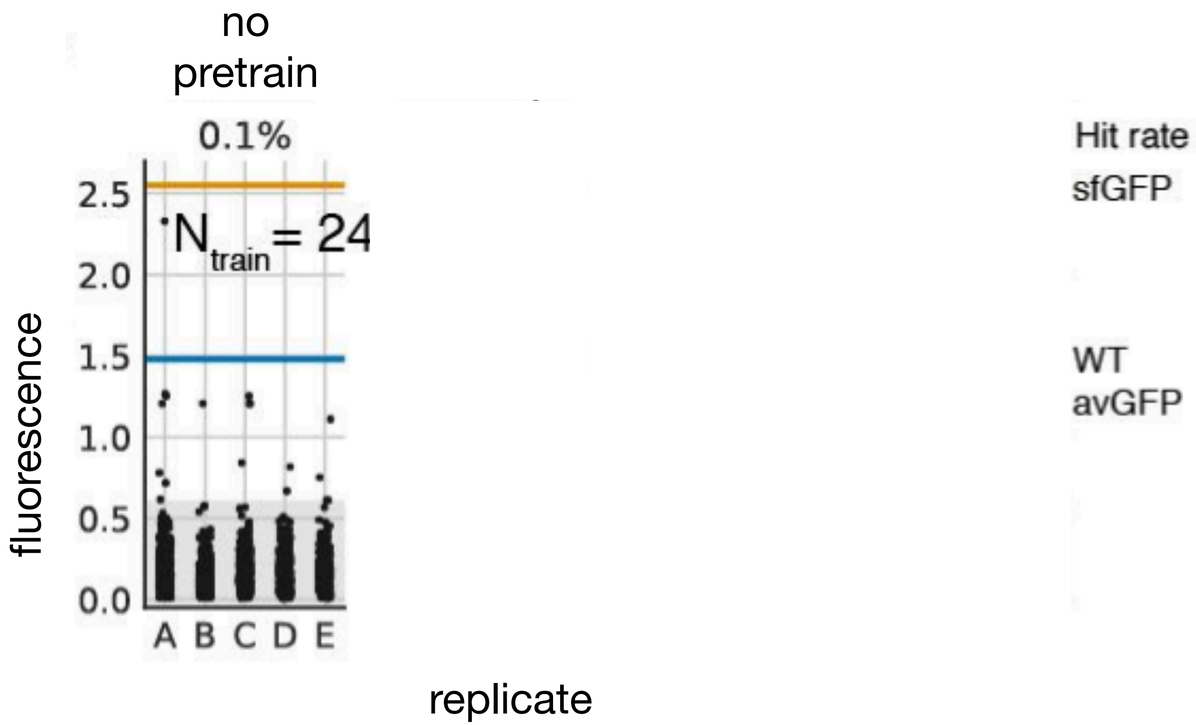
Biswas *et al. Nature Methods* 2021

Pretraining guides search away from loss-of-function sequences



Biswas *et al. Nature Methods* 2021

Pretraining guides search away from loss-of-function sequences



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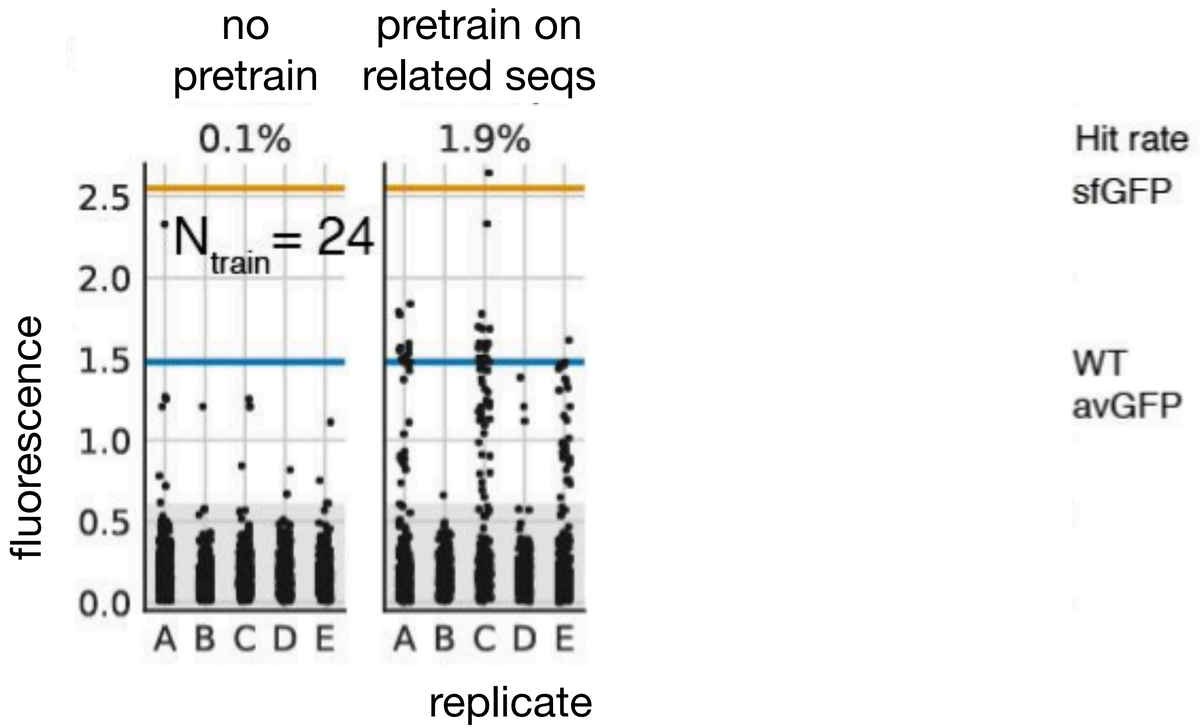

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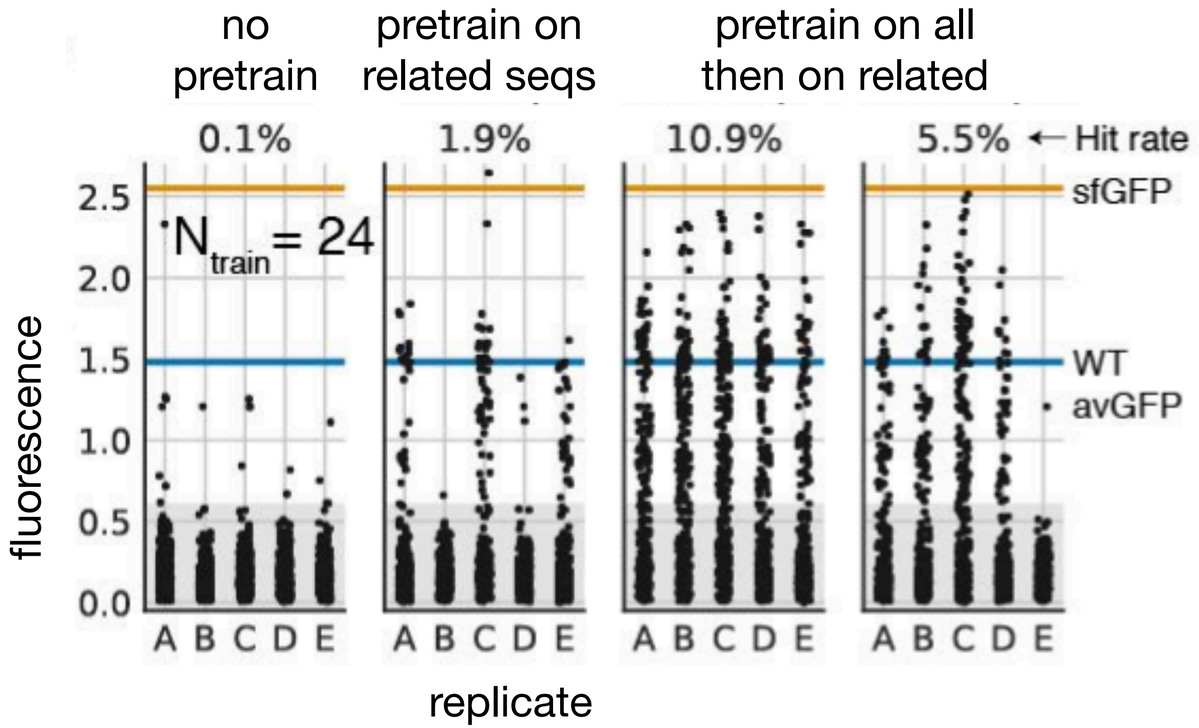

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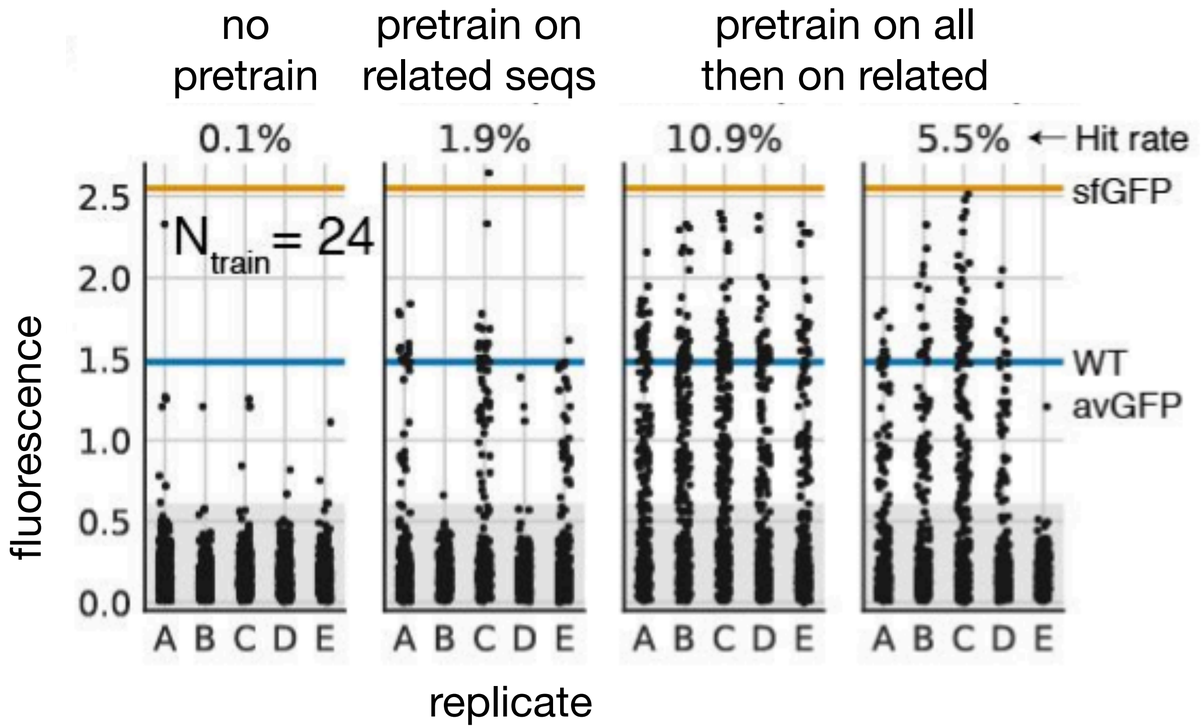

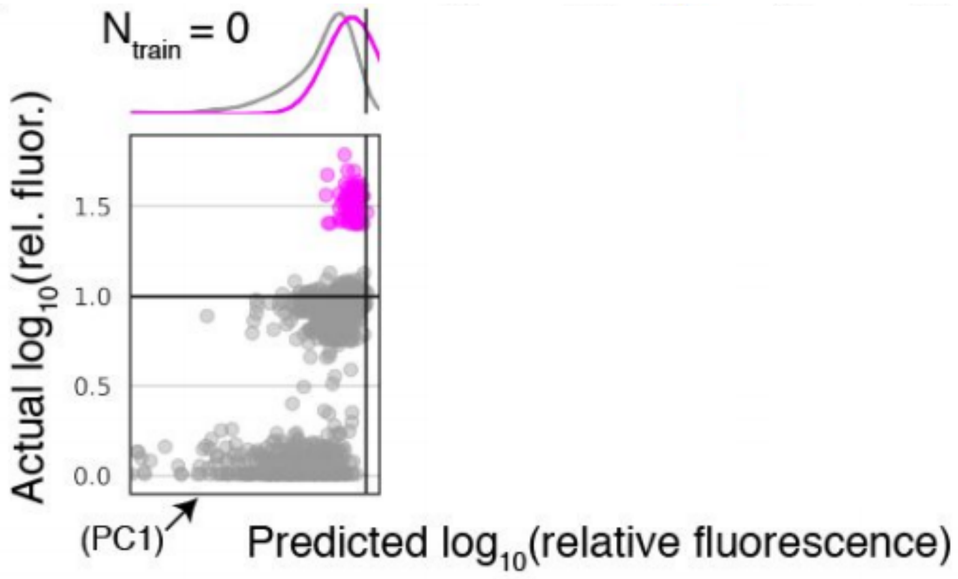

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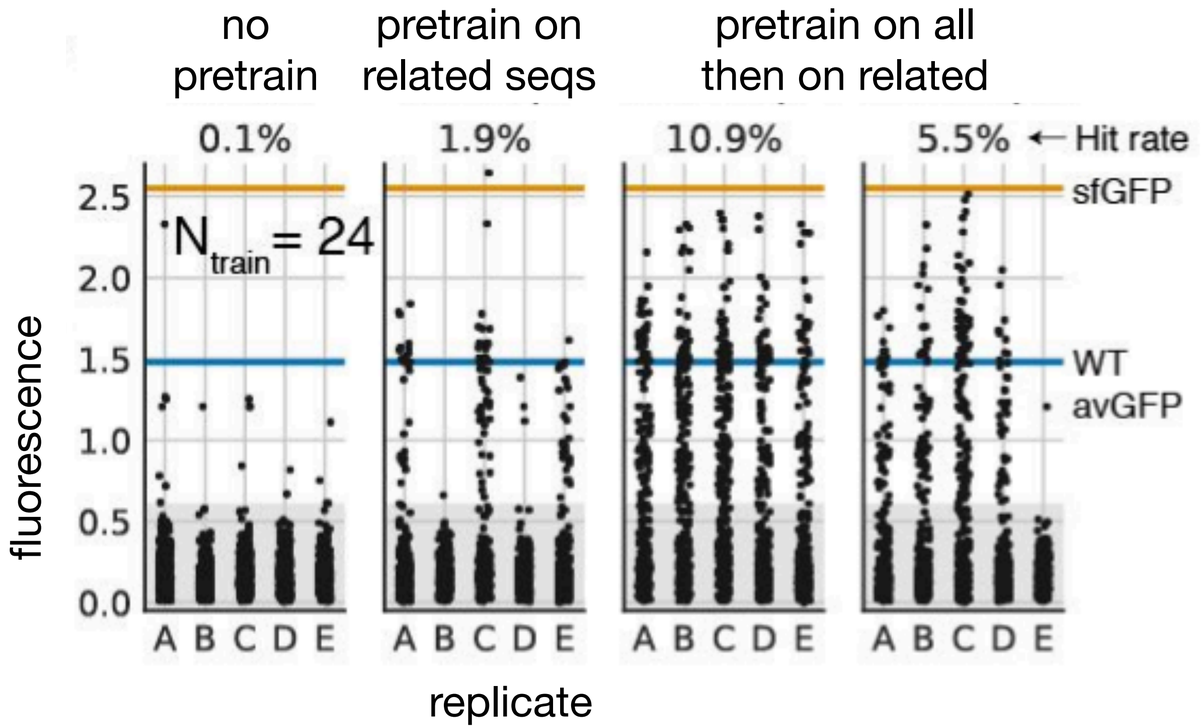

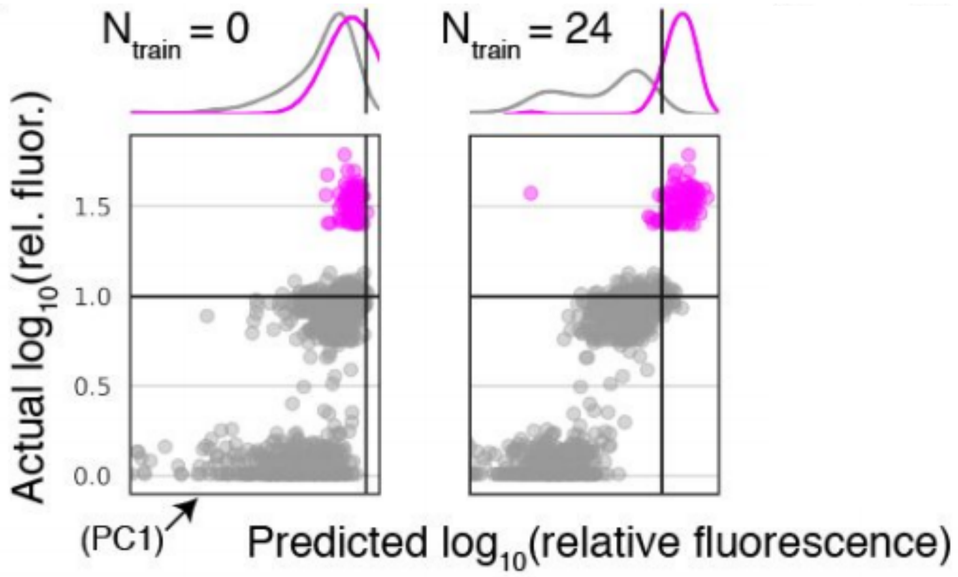

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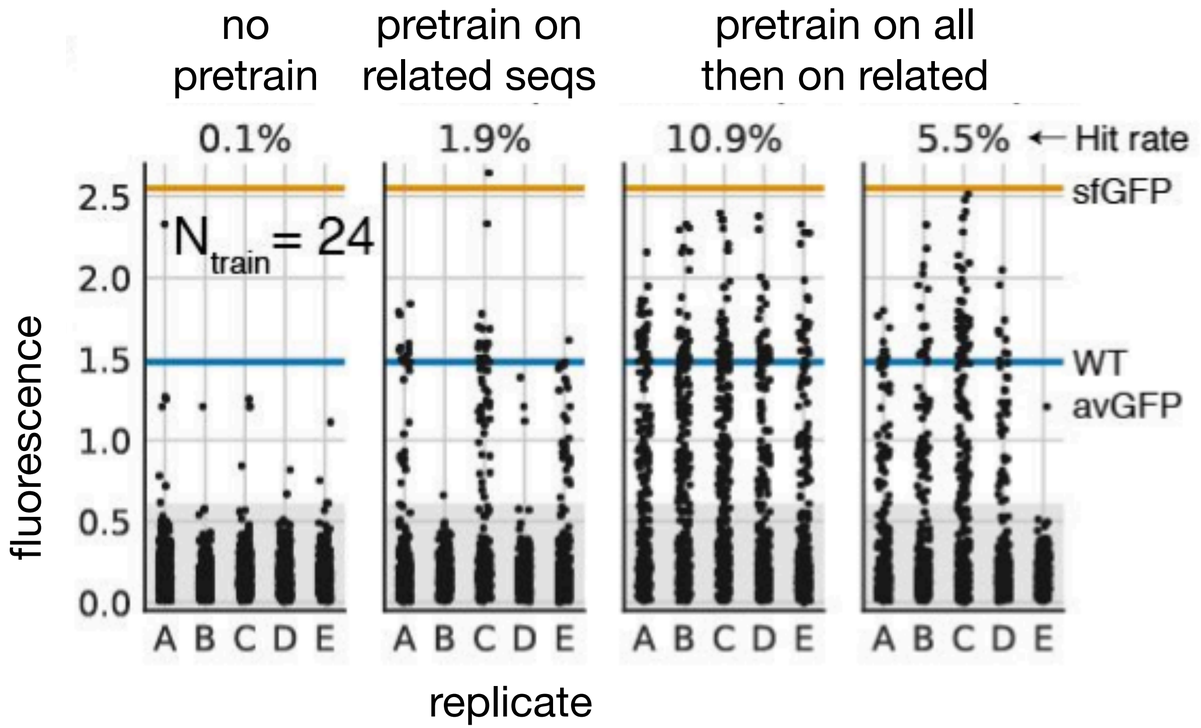

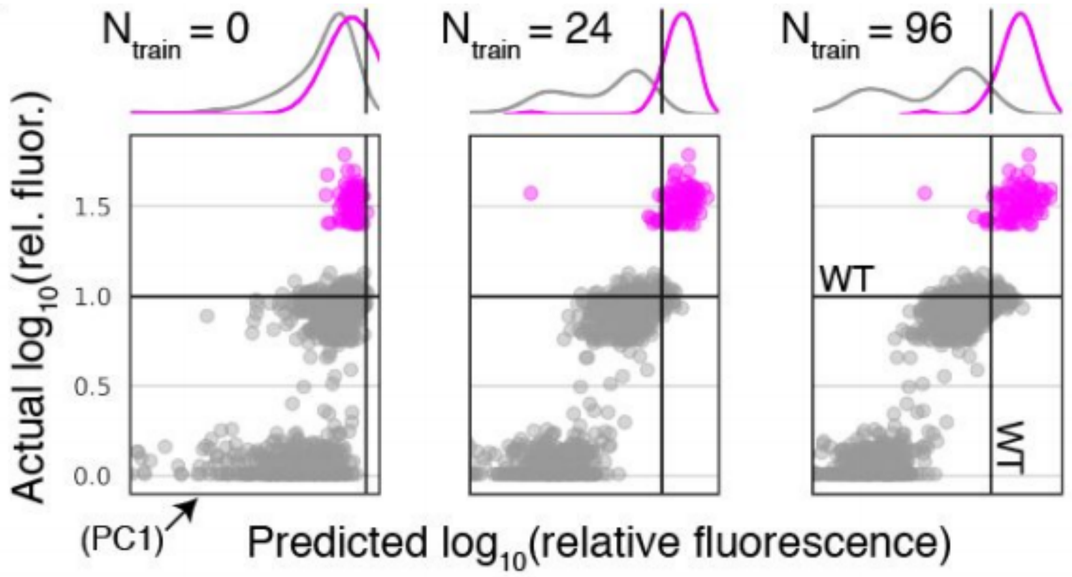

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Pretrained models propose high-fitness sequences

Hie *et al.* 2022

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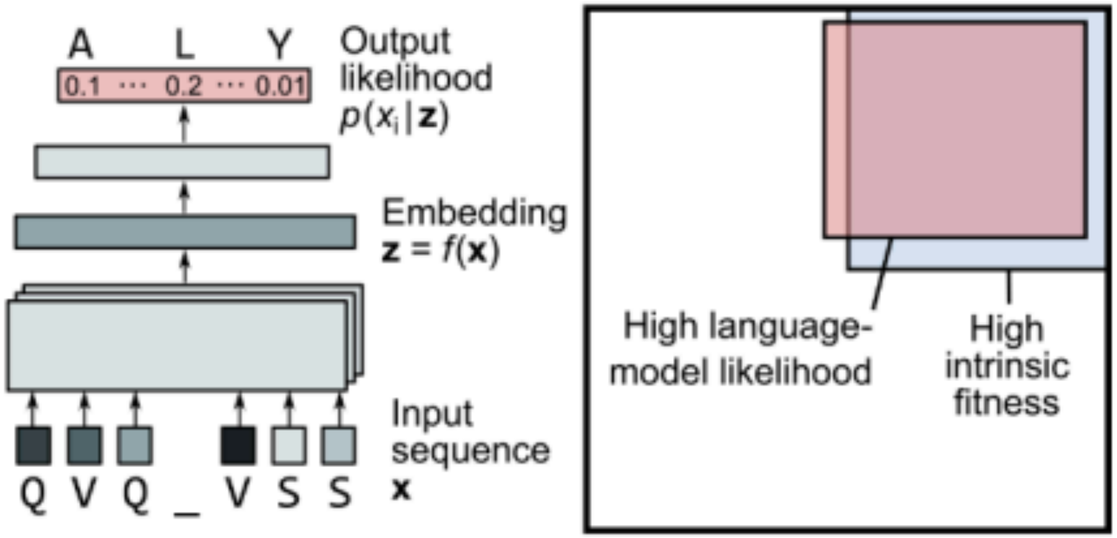

Experiment: Approximate intrinsic fitness with language-model likelihood, measure extrinsic fitness

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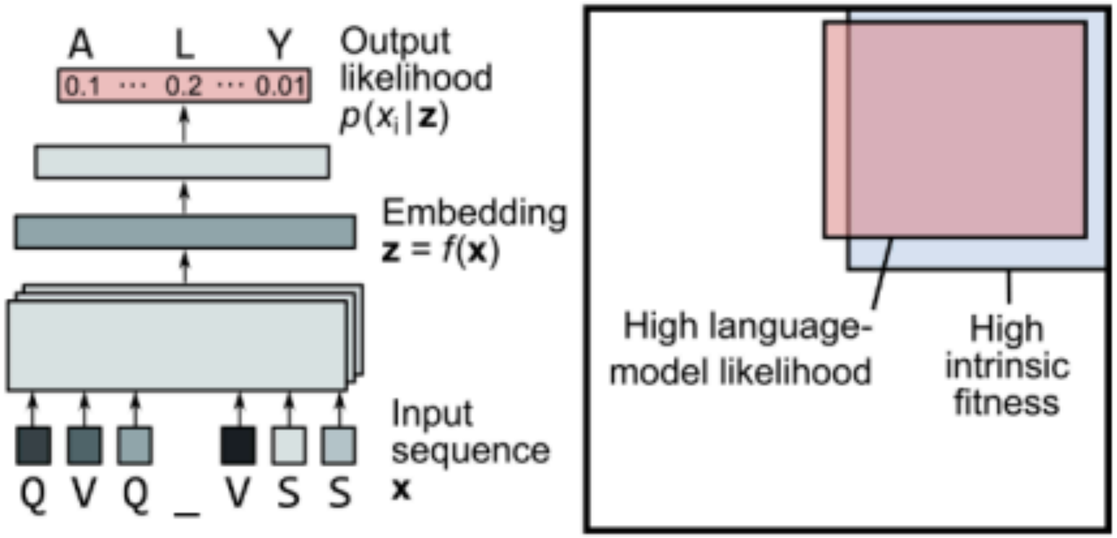

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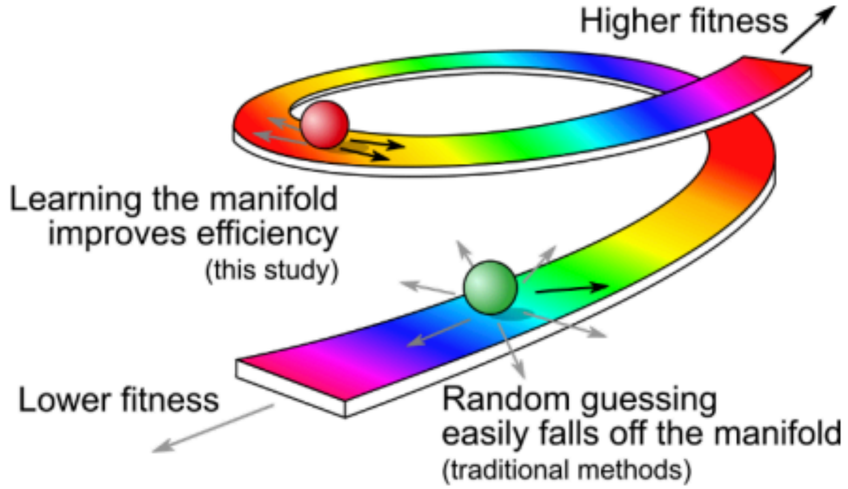

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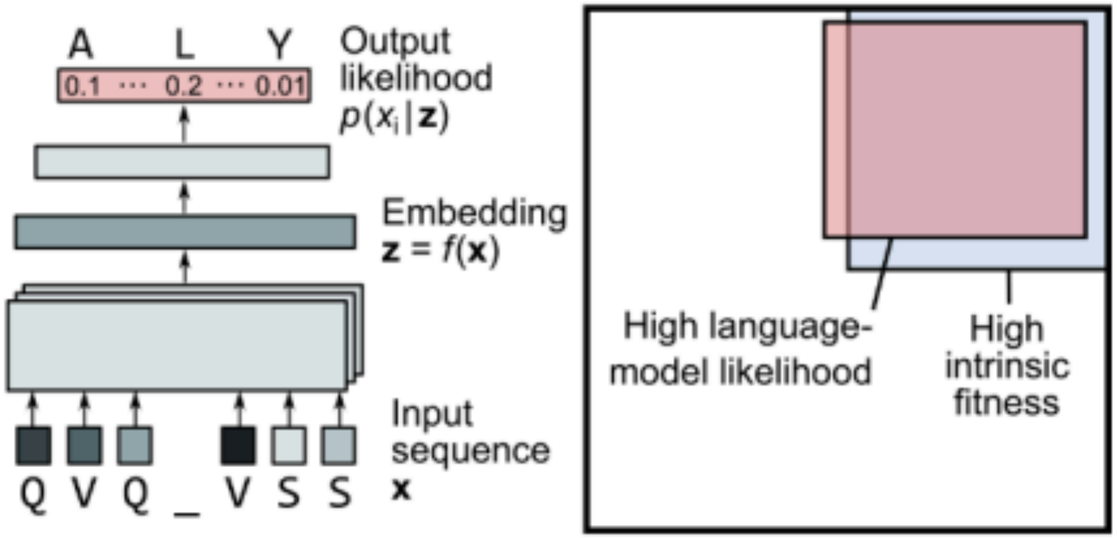

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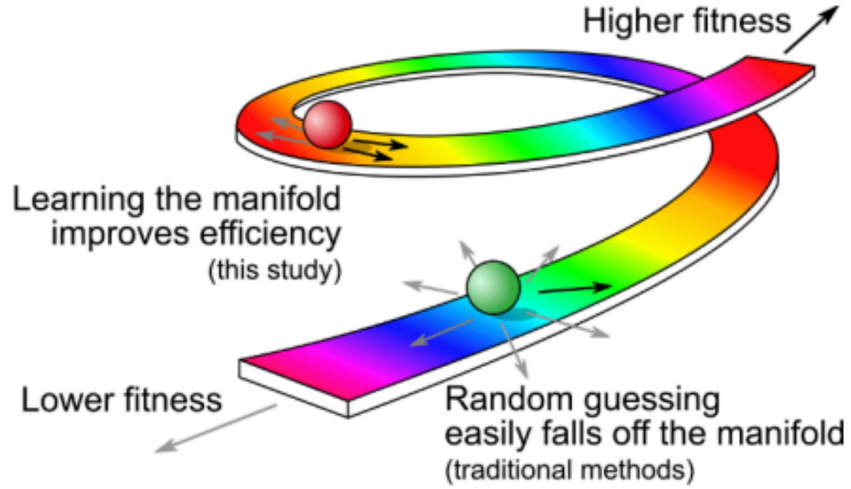

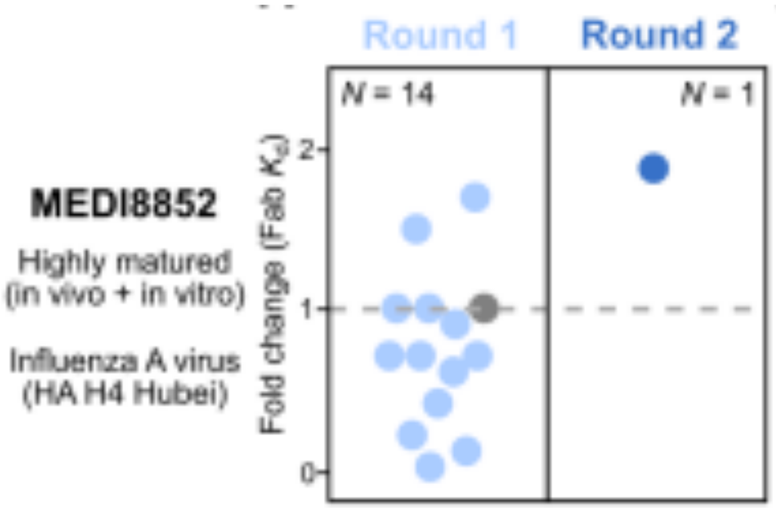

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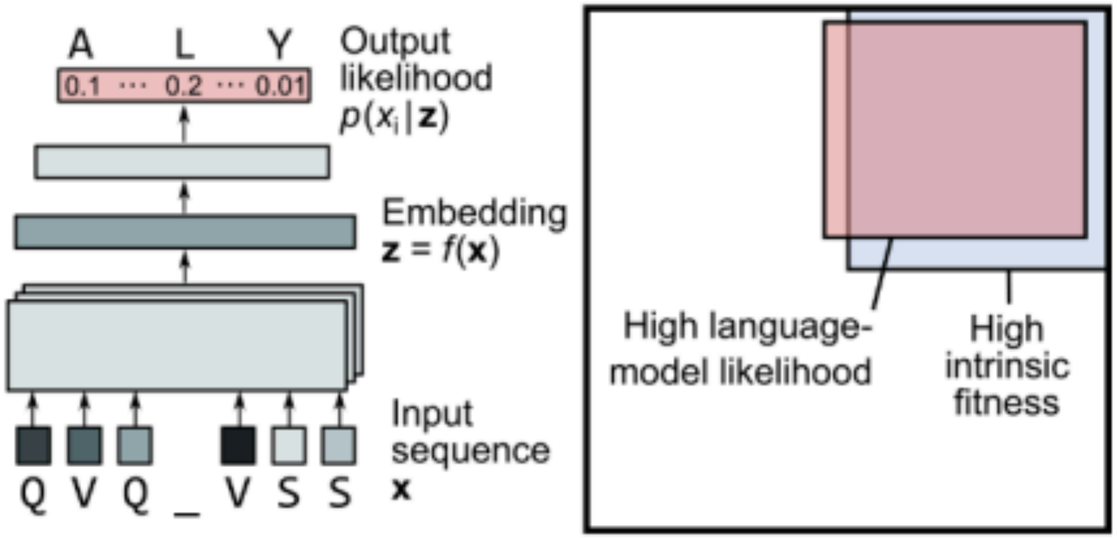

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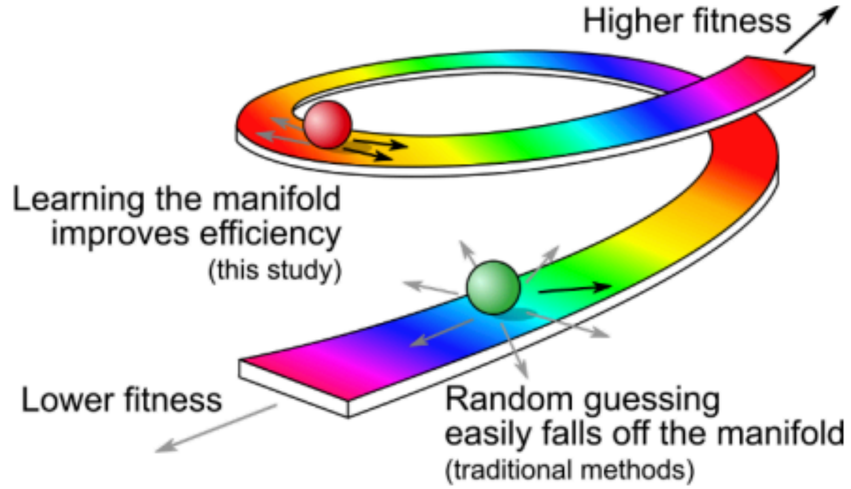

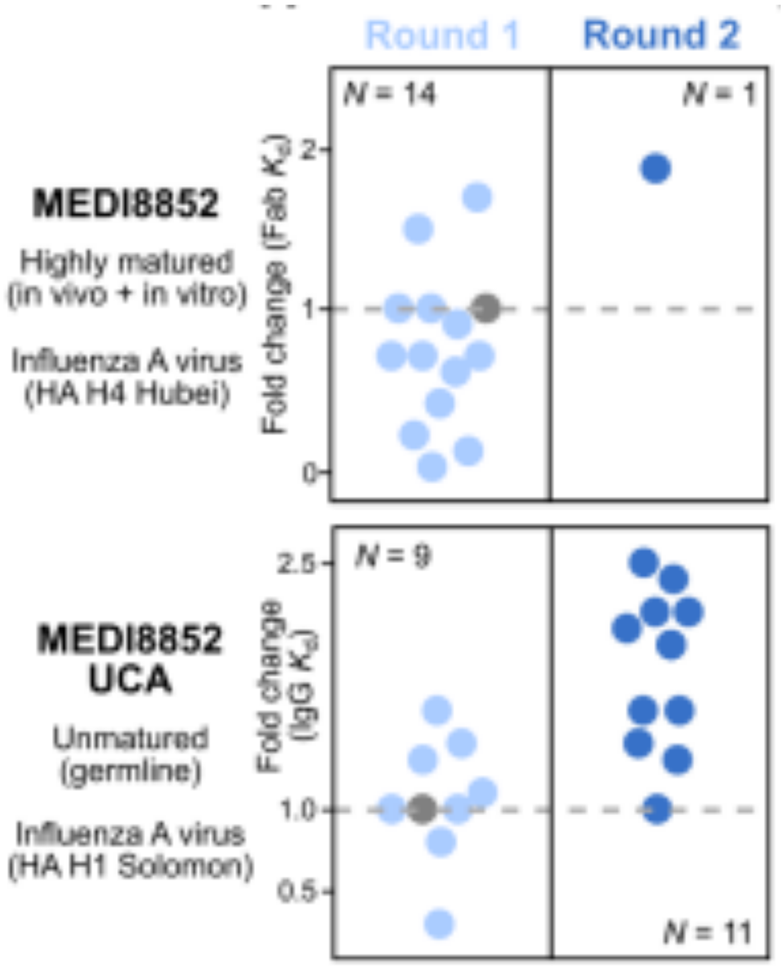

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Need benchmarks for protein function ML

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SuperGLUE

Need benchmarks for protein function ML

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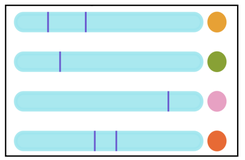
SuperGLUE

Focus on sequence -> fitness



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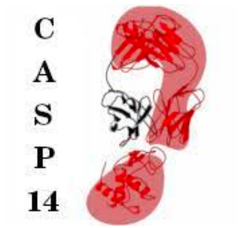
SuperGLUE

CASP14



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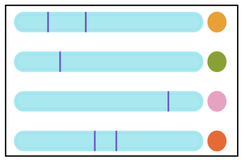

TAPE function datasets do not discriminate well

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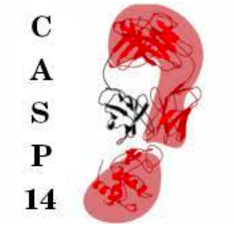

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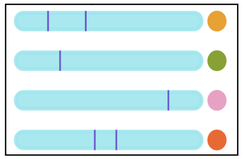

TAPE function datasets do not discriminate well

Model	Pretraining	Fluorescence	Stability

Need benchmarks for protein function ML

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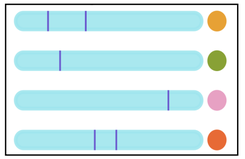

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Model	Pretraining	Fluorescence	Stability
ESM (Rives *et al.*)	MLM	0.68	0.71

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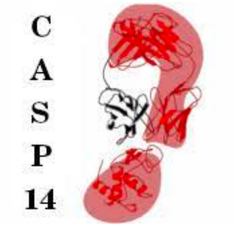

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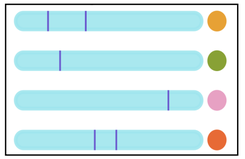

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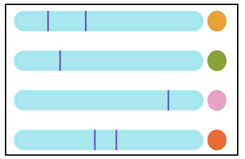

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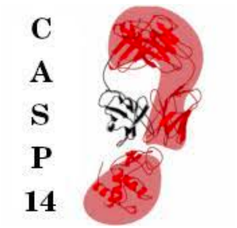

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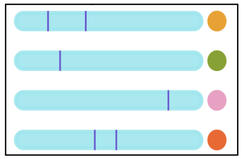

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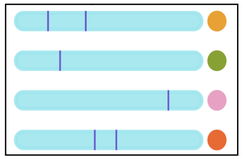

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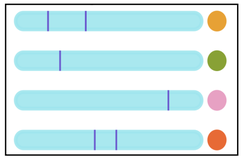

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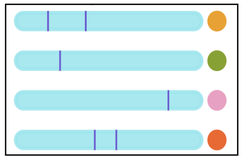

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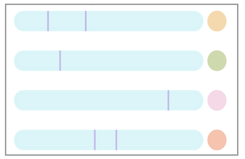

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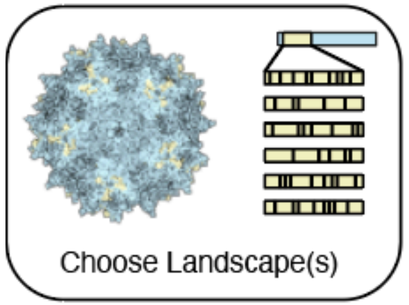

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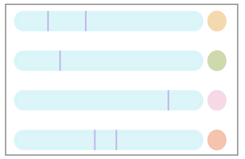

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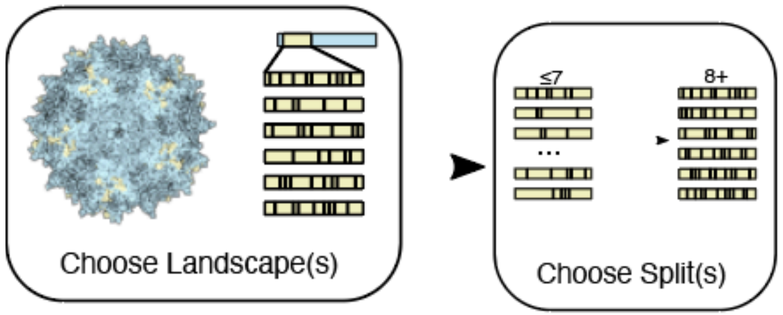

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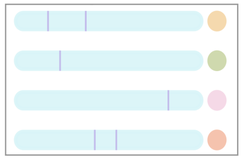

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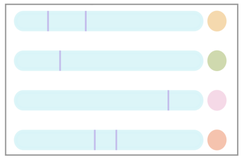

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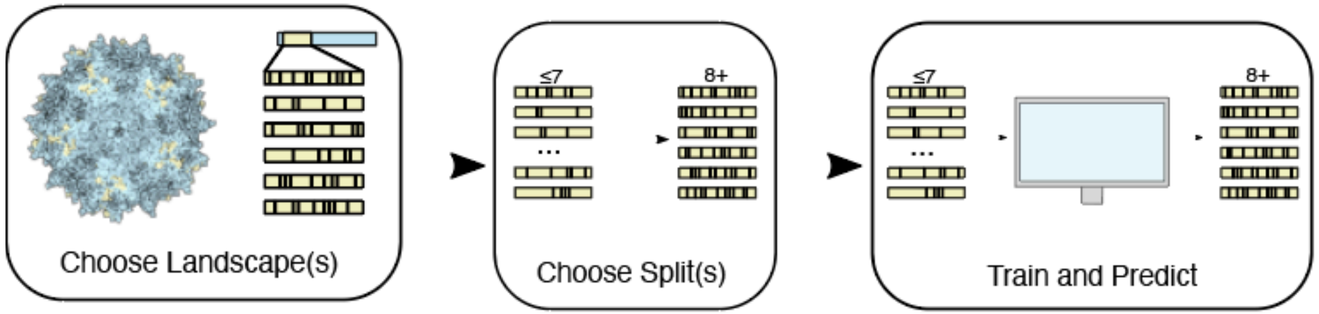

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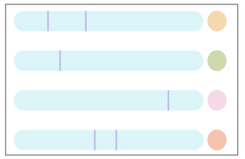

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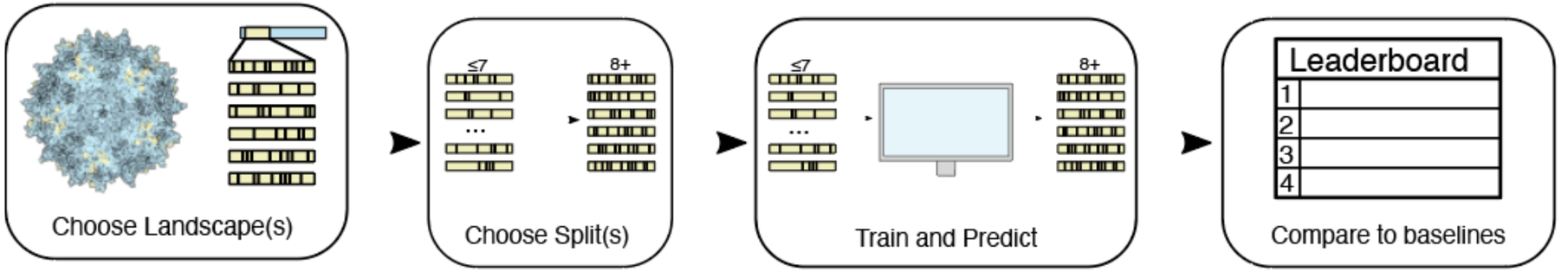
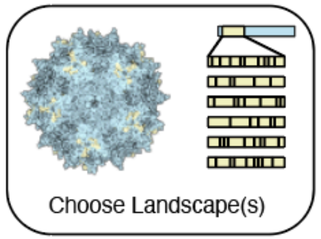
TAPE transformer	MLM	0.68	0.73
CPCProt (Lu *et al.*)	contrastive	0.68	0.65
Linear regression	none	0.68	0.48
CNN	none	0.67	0.51
CARP-640M	MLM	0.68	0.72

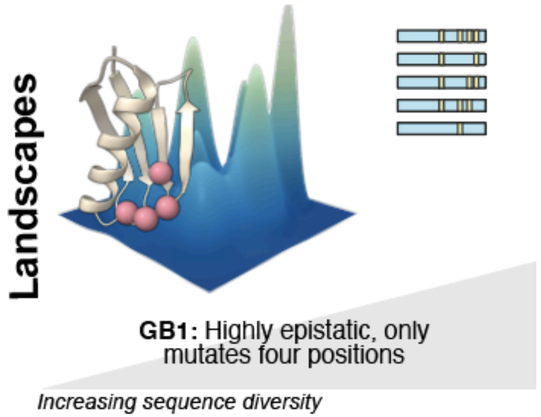
Christian Dallago, Jody Mou, Kadina Johnston, Bruce Wittmann, Nick Bhattacharya, Samuel Goldman, Ali Madani

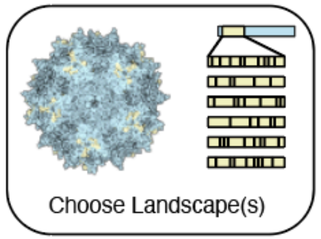


Choose three landscapes



Choose three landscapes





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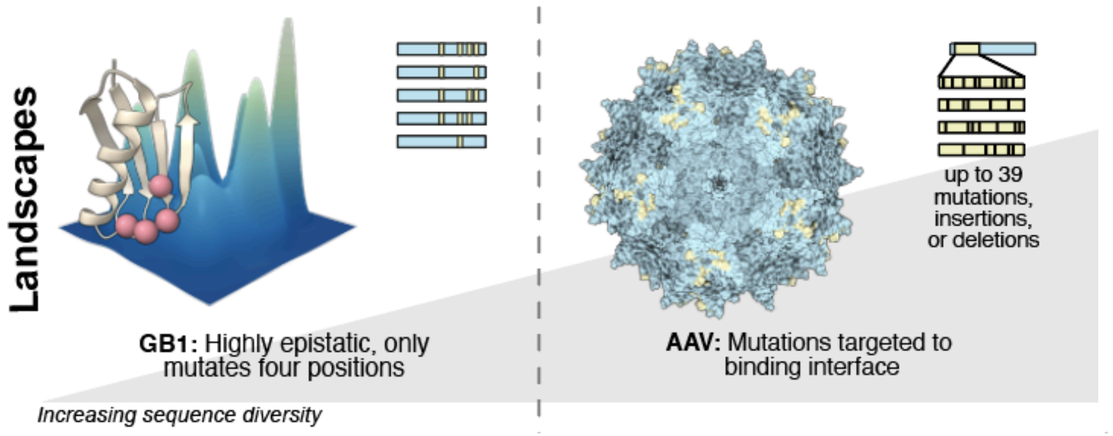
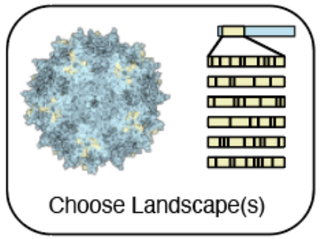
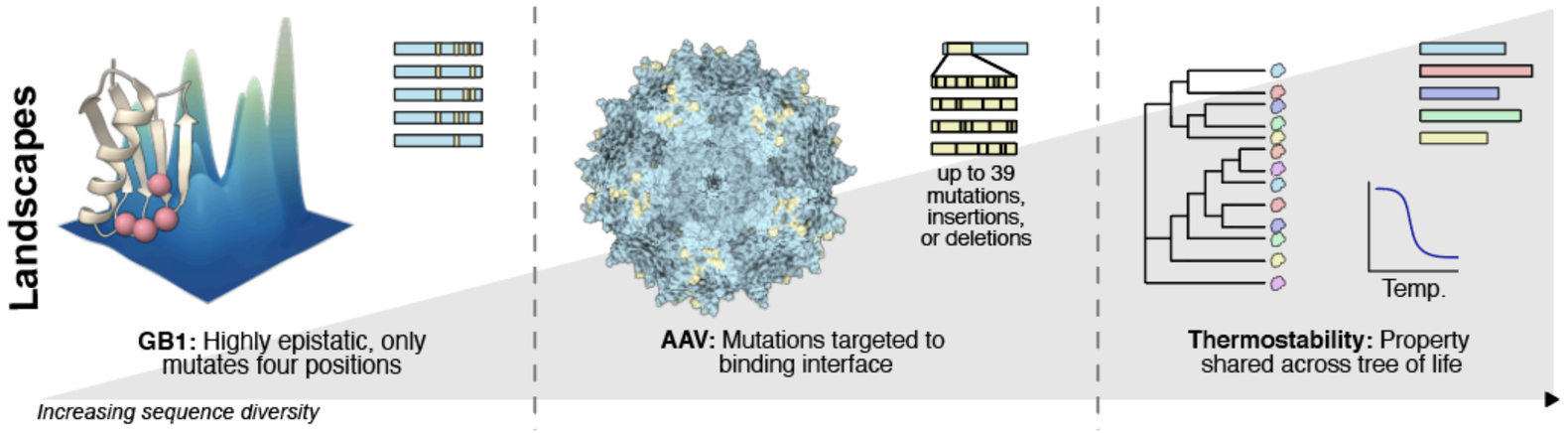
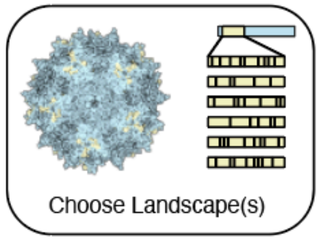


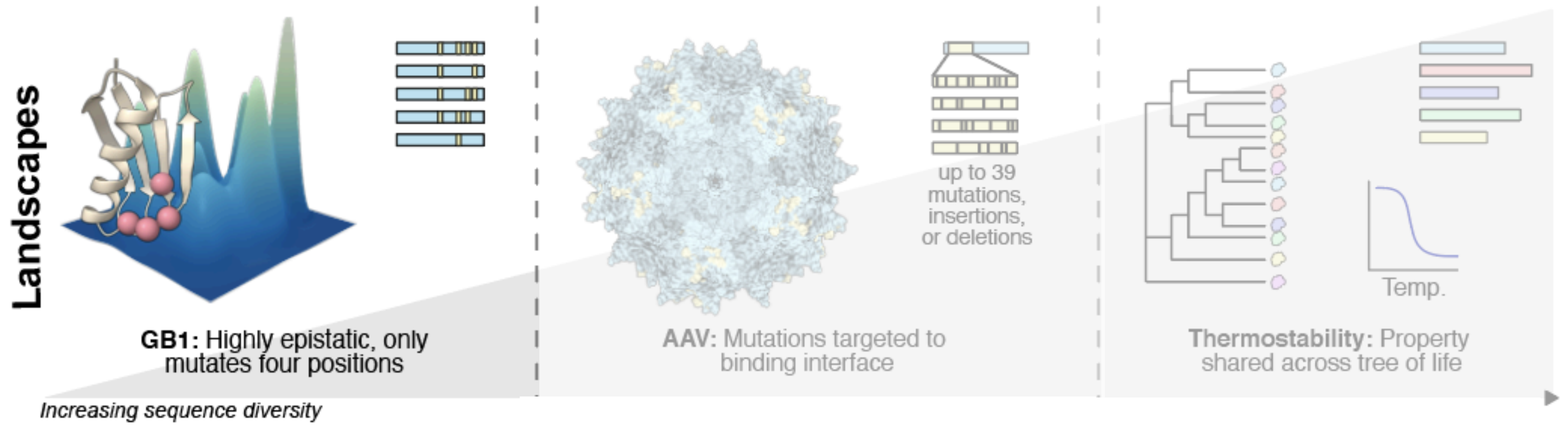


Choose three landscapes

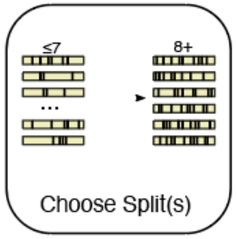




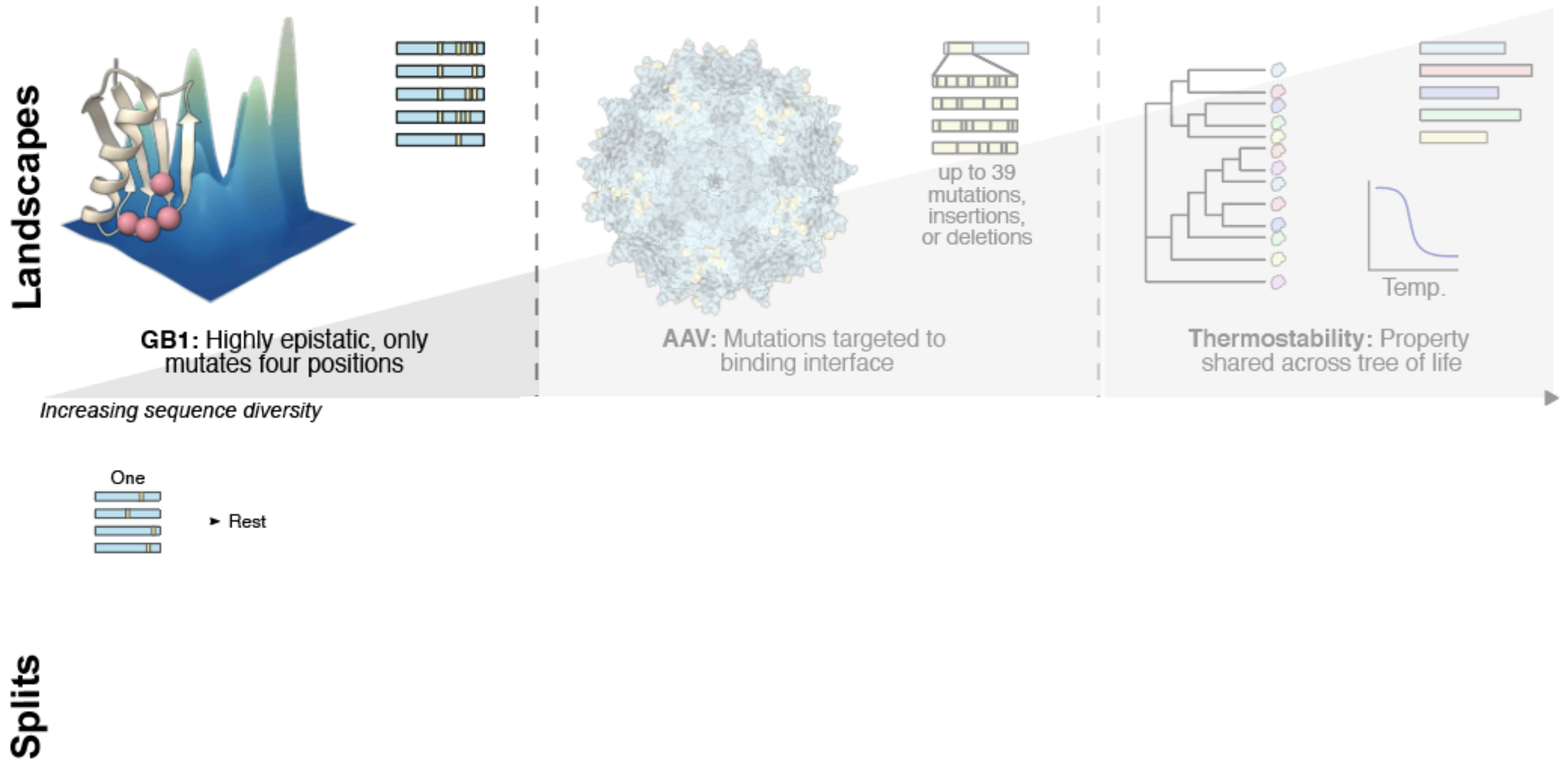
Make biologically-relevant train/test splits

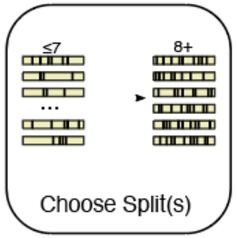


Splits

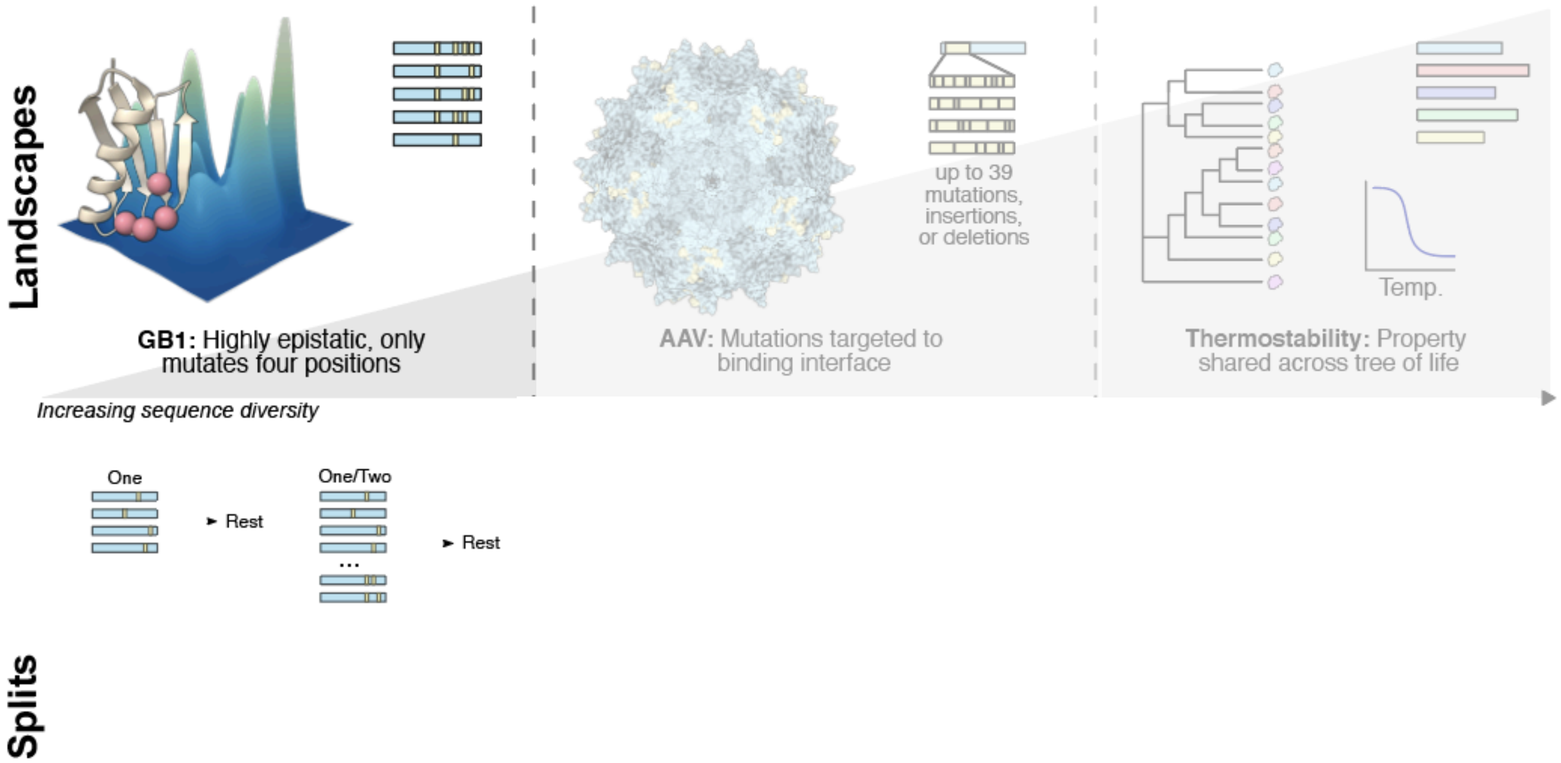


Make biologically-relevant train/test splits

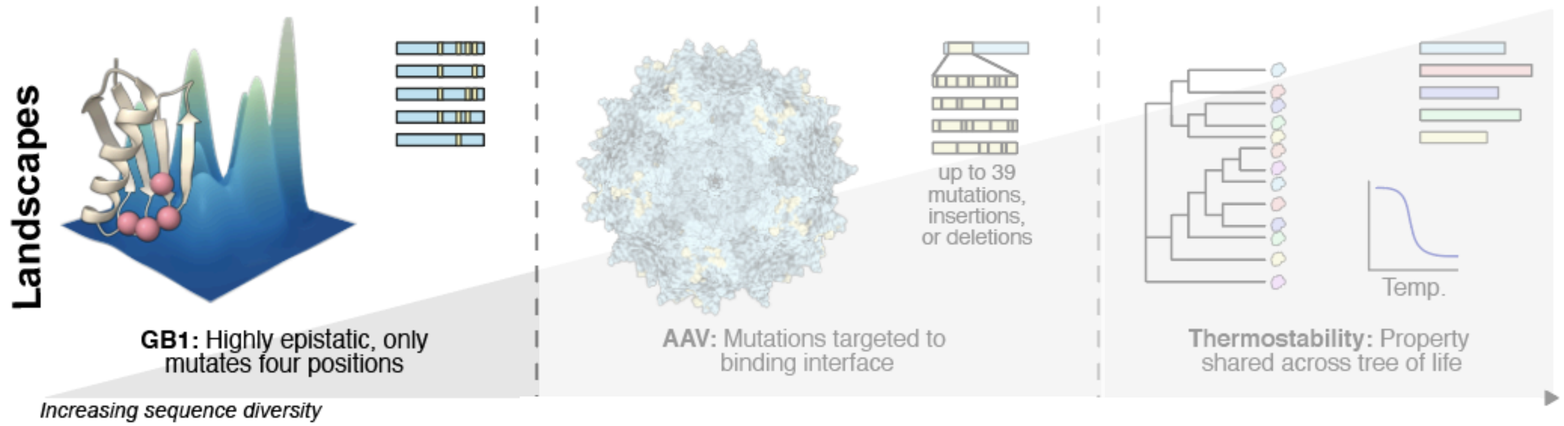


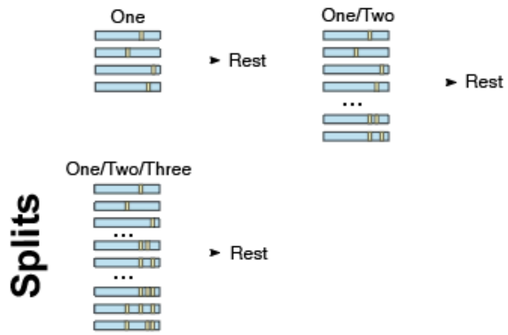


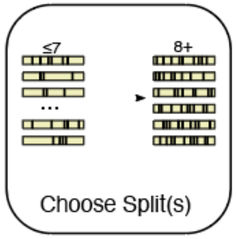
Make biologically-relevant train/test splits



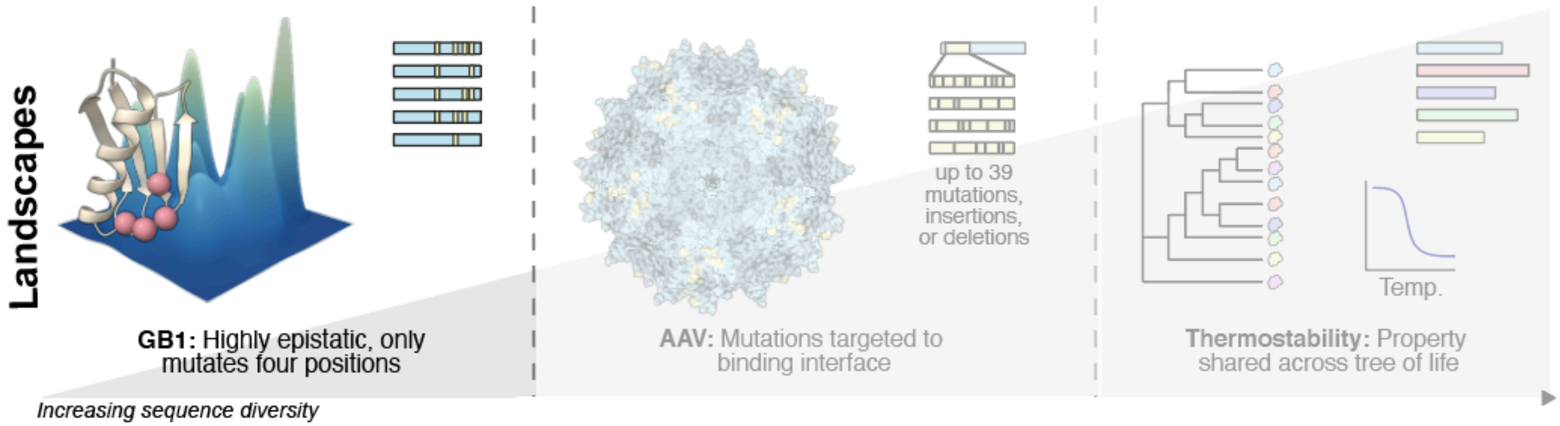
Make biologically-relevant train/test splits

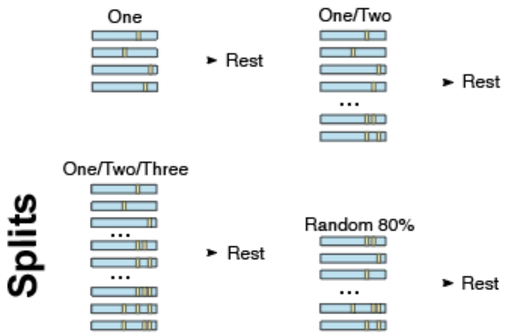


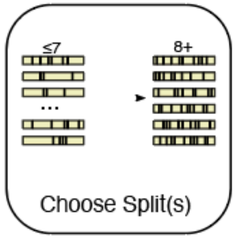




Make biologically-relevant train/test splits







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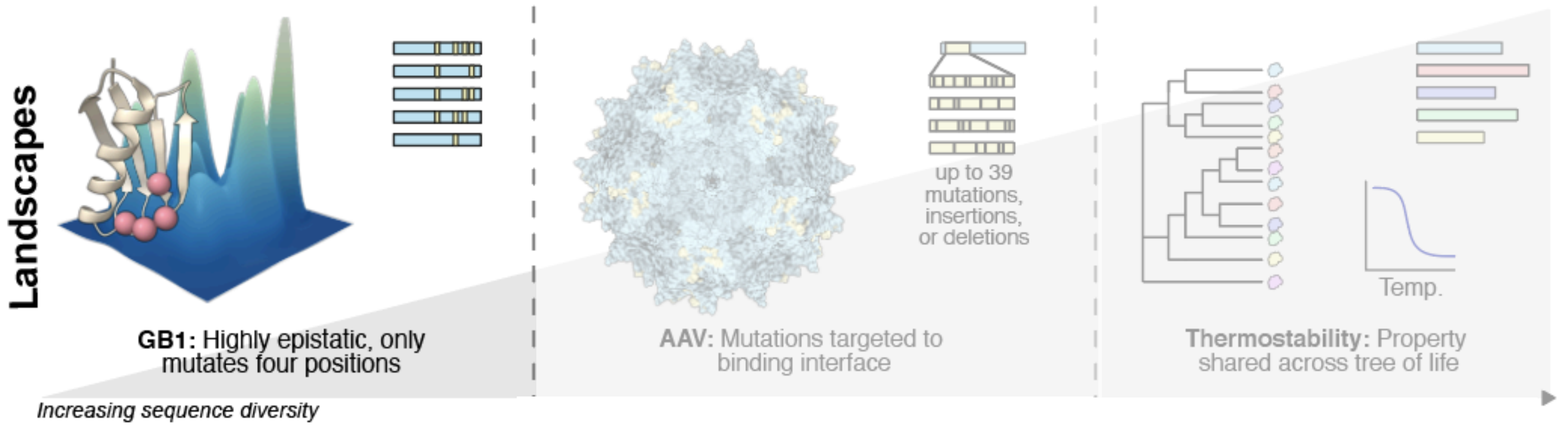
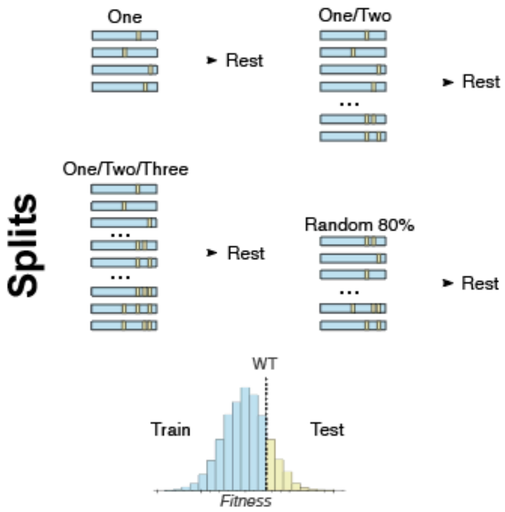
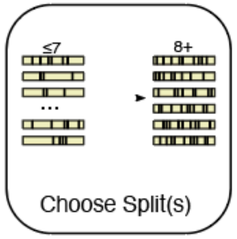
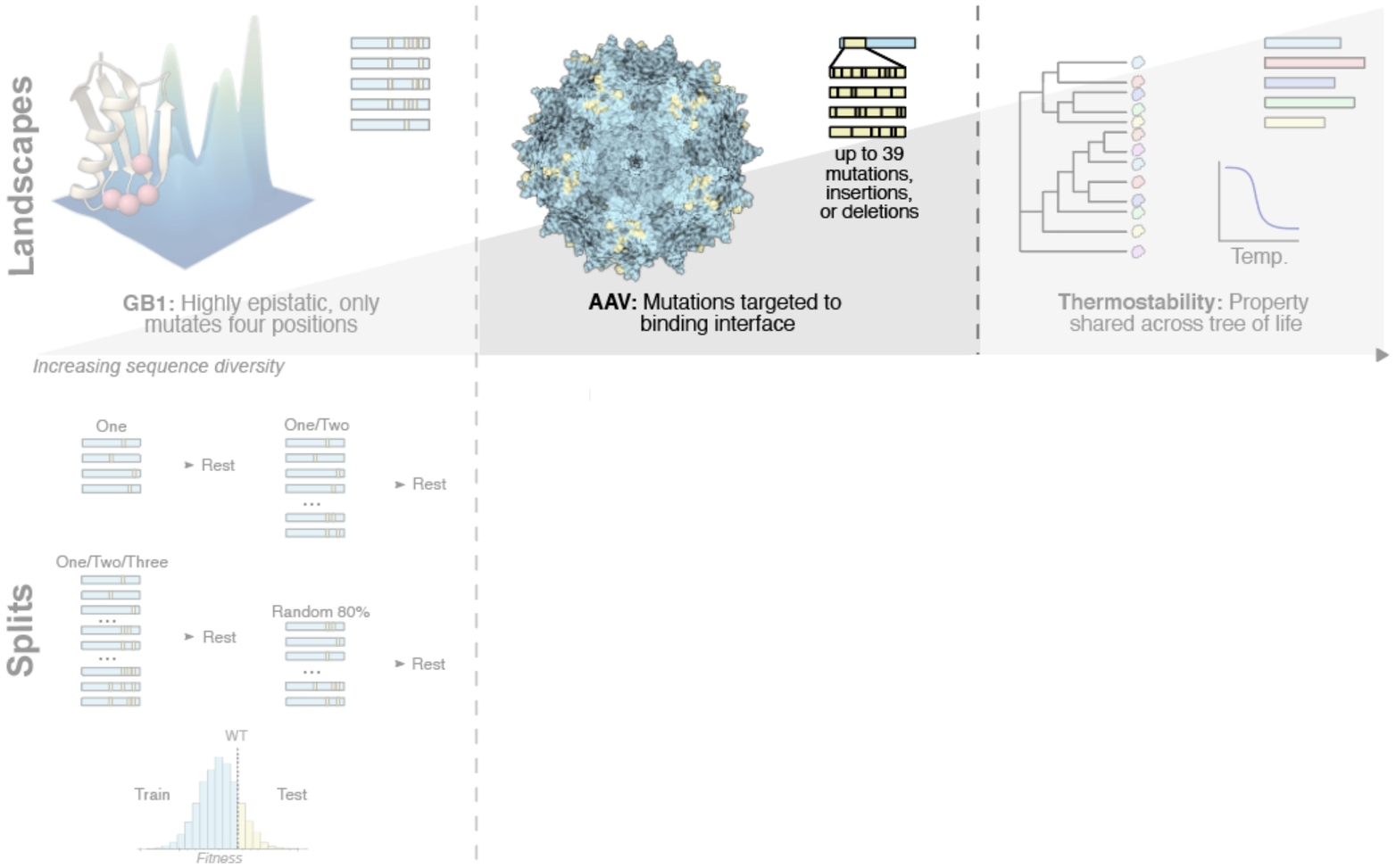
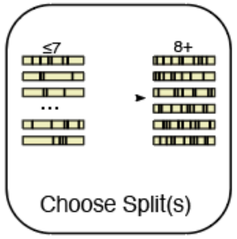






Make biologically-relevant train/test splits





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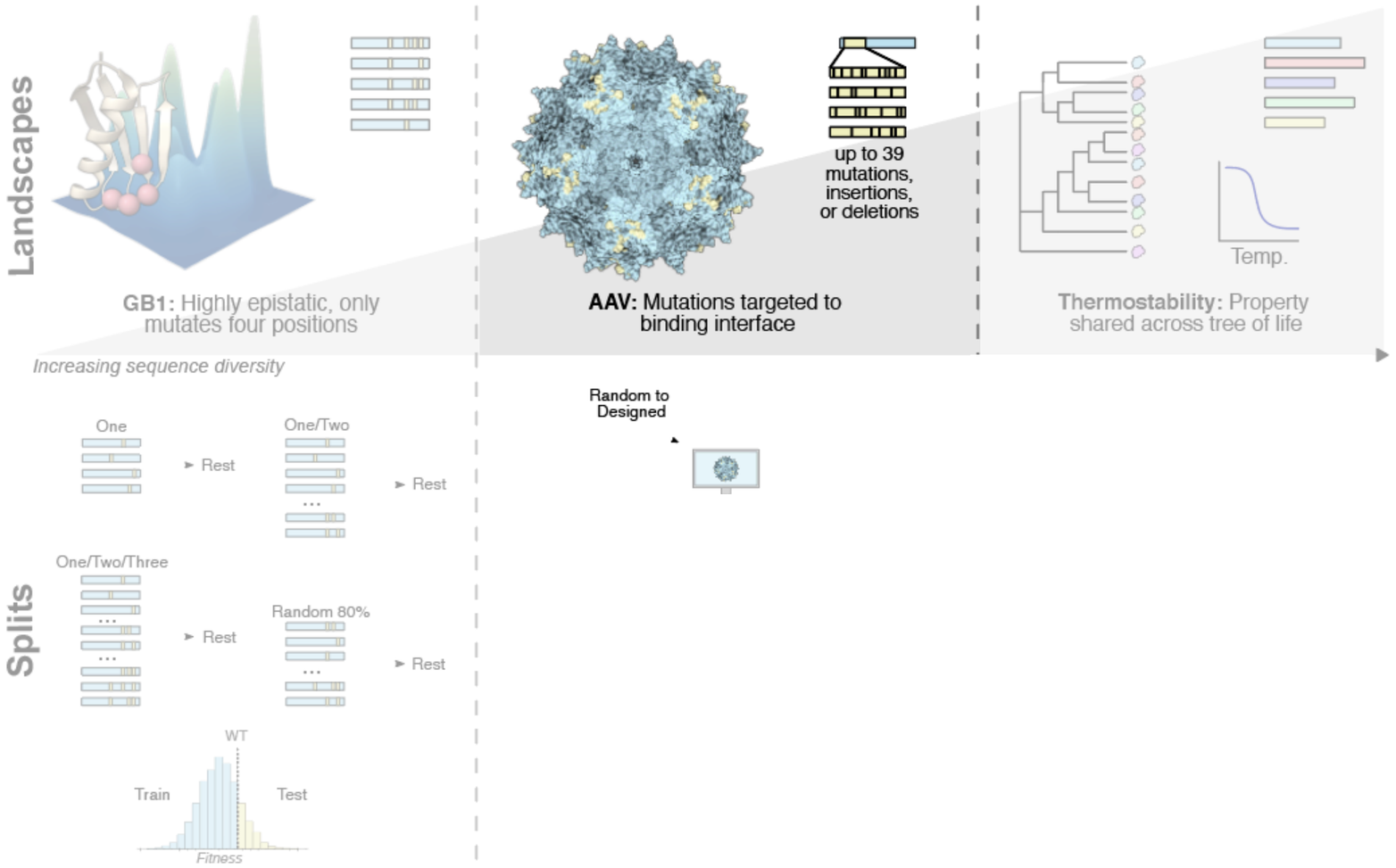

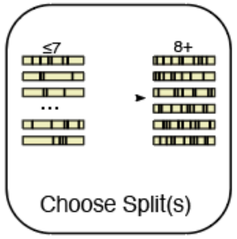

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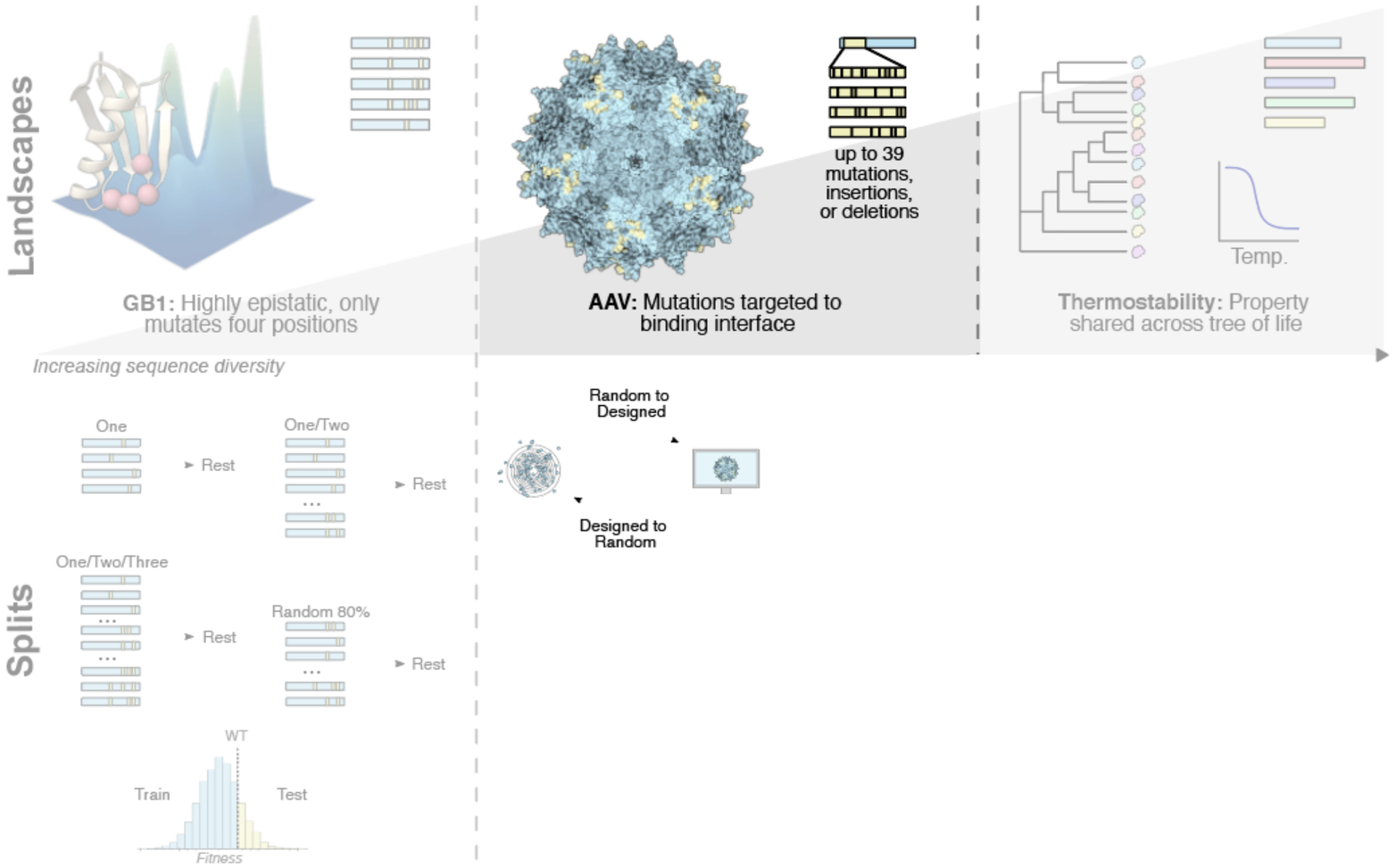

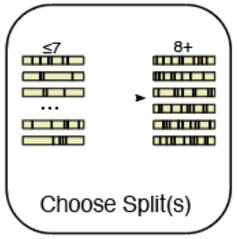

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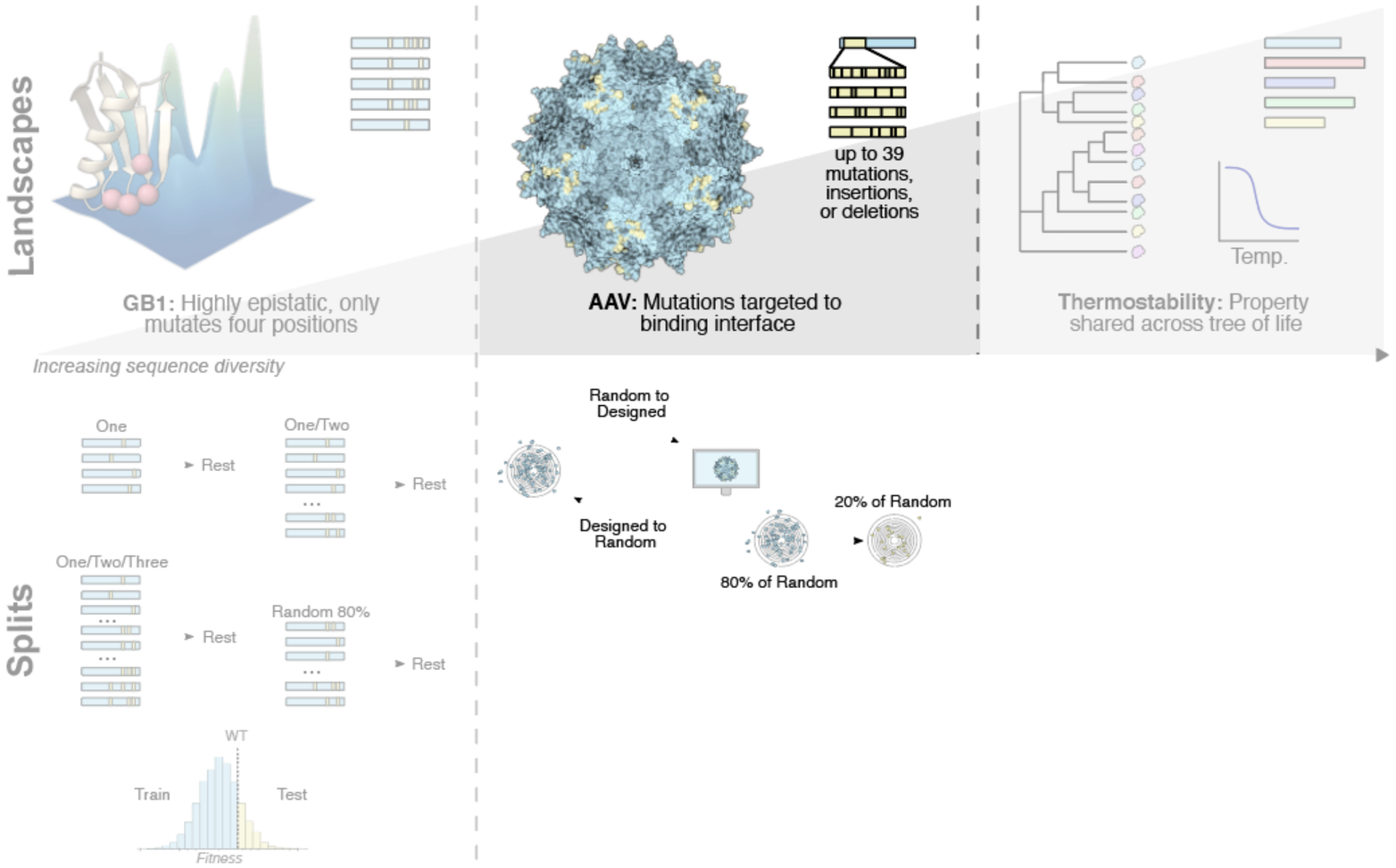

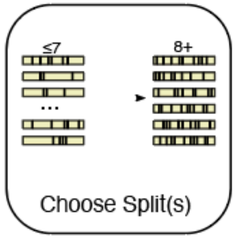

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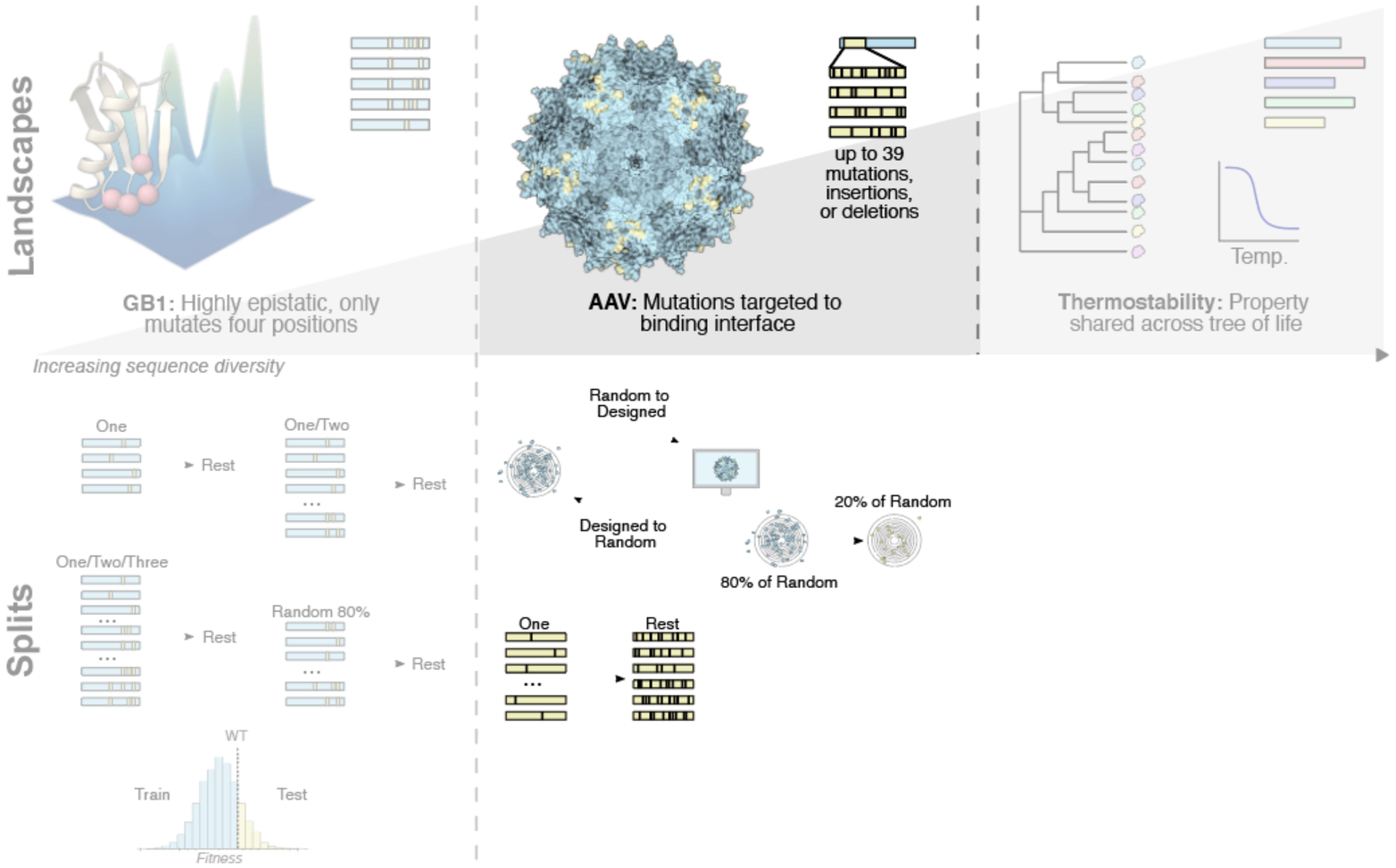

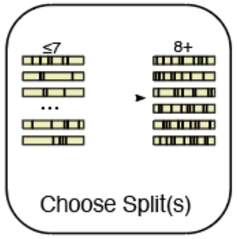

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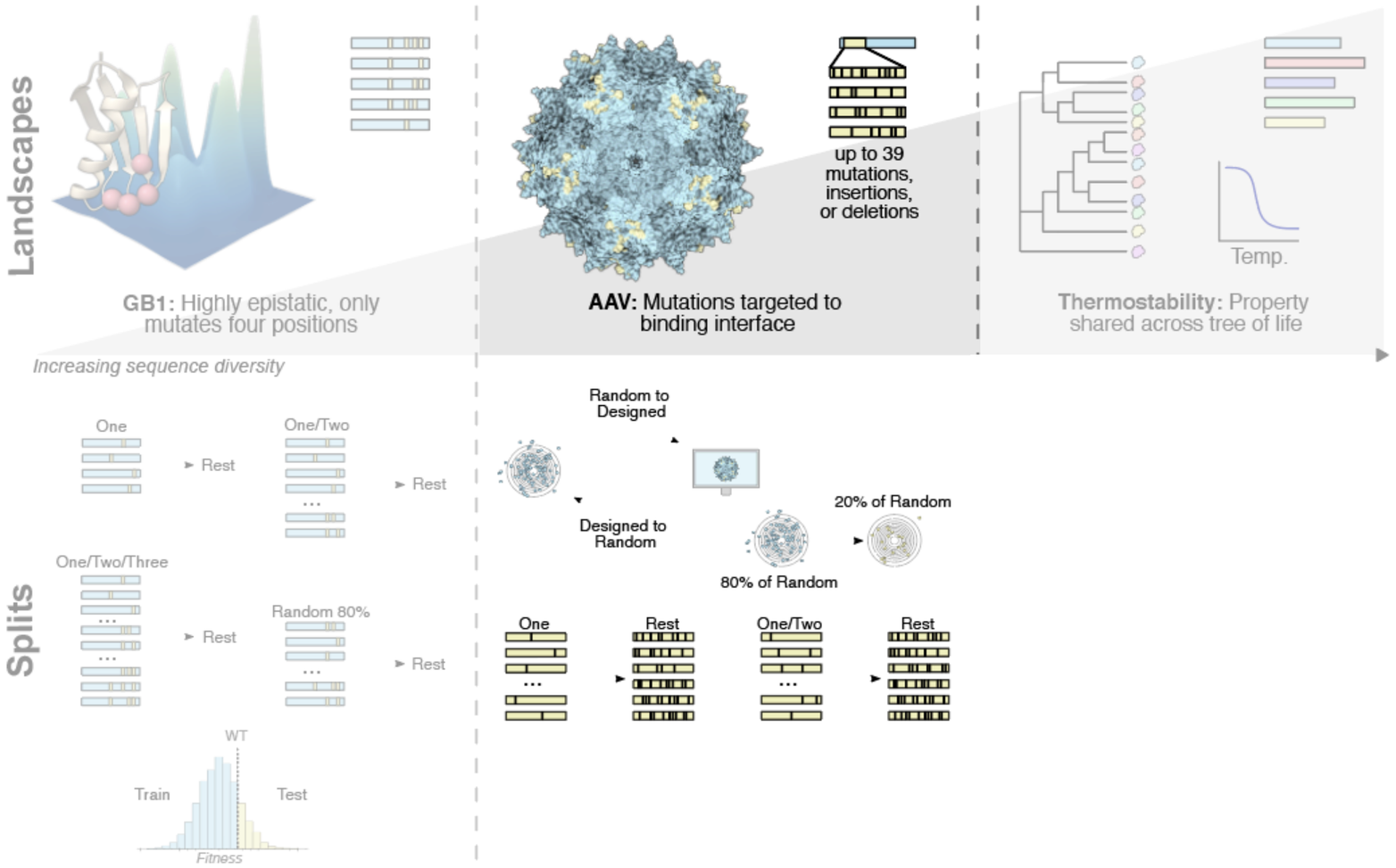

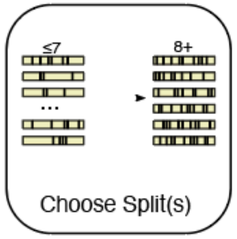

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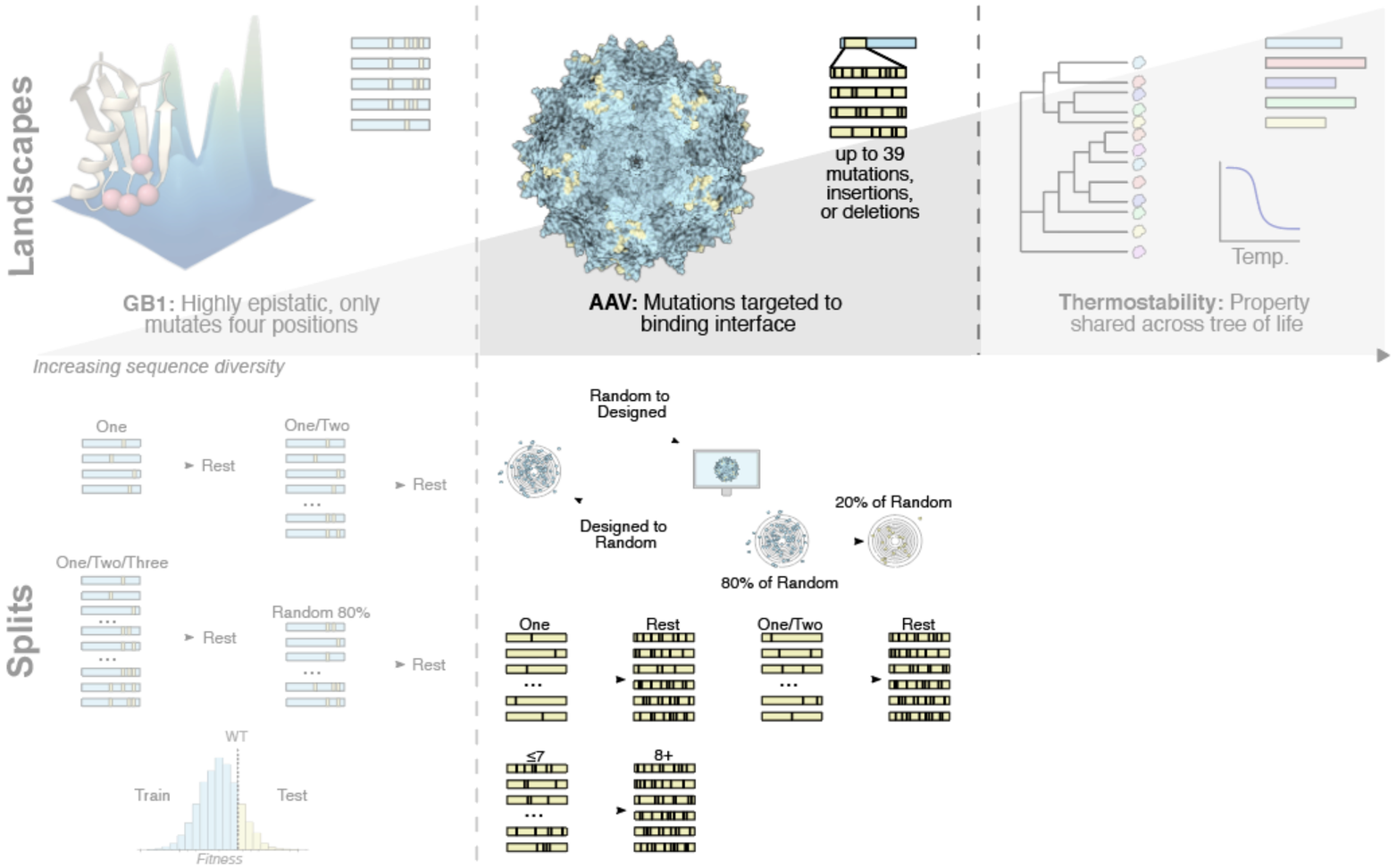

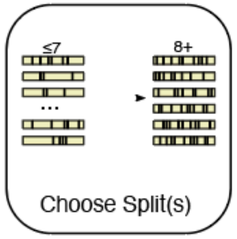

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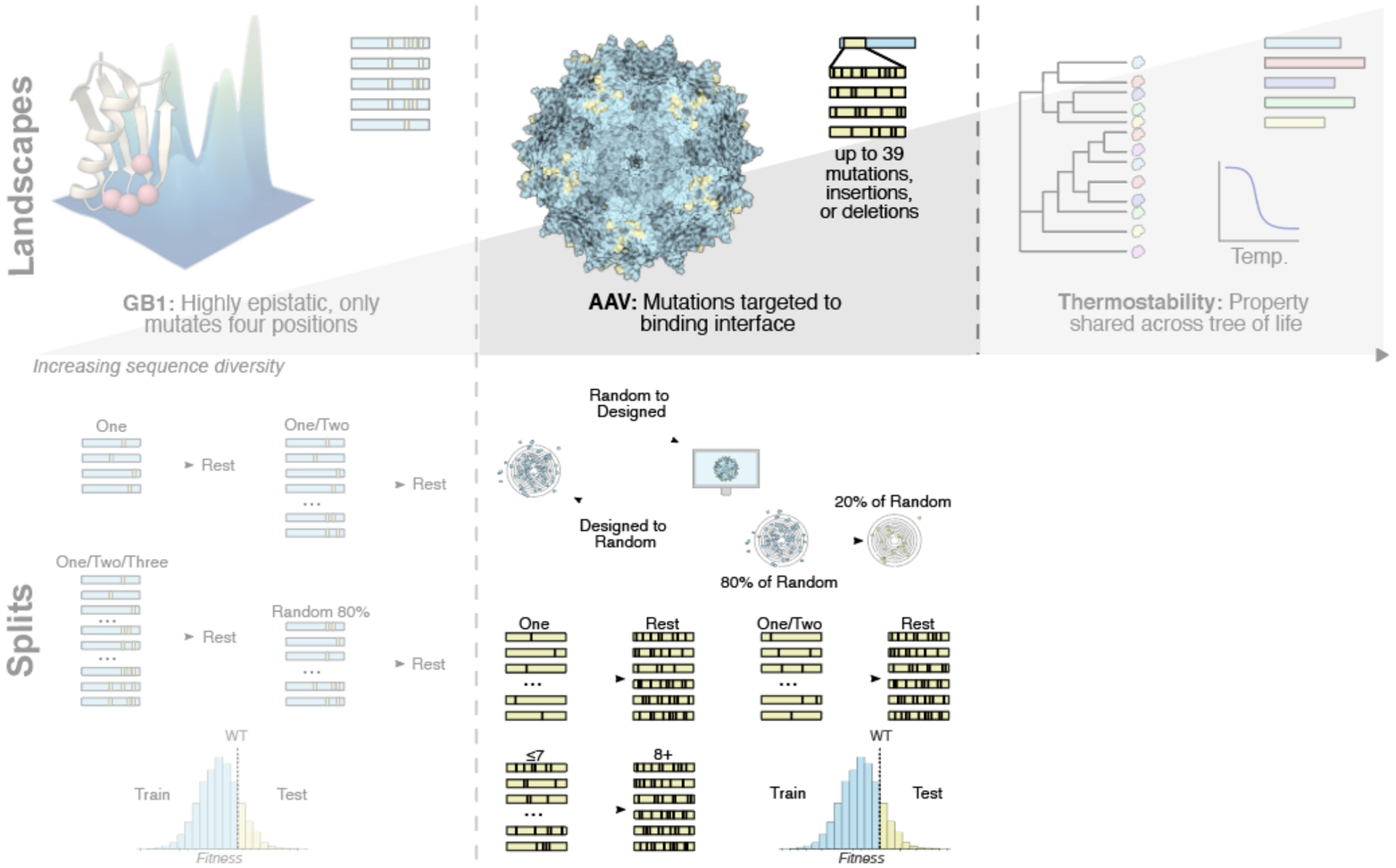

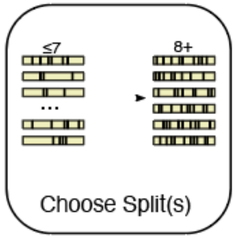

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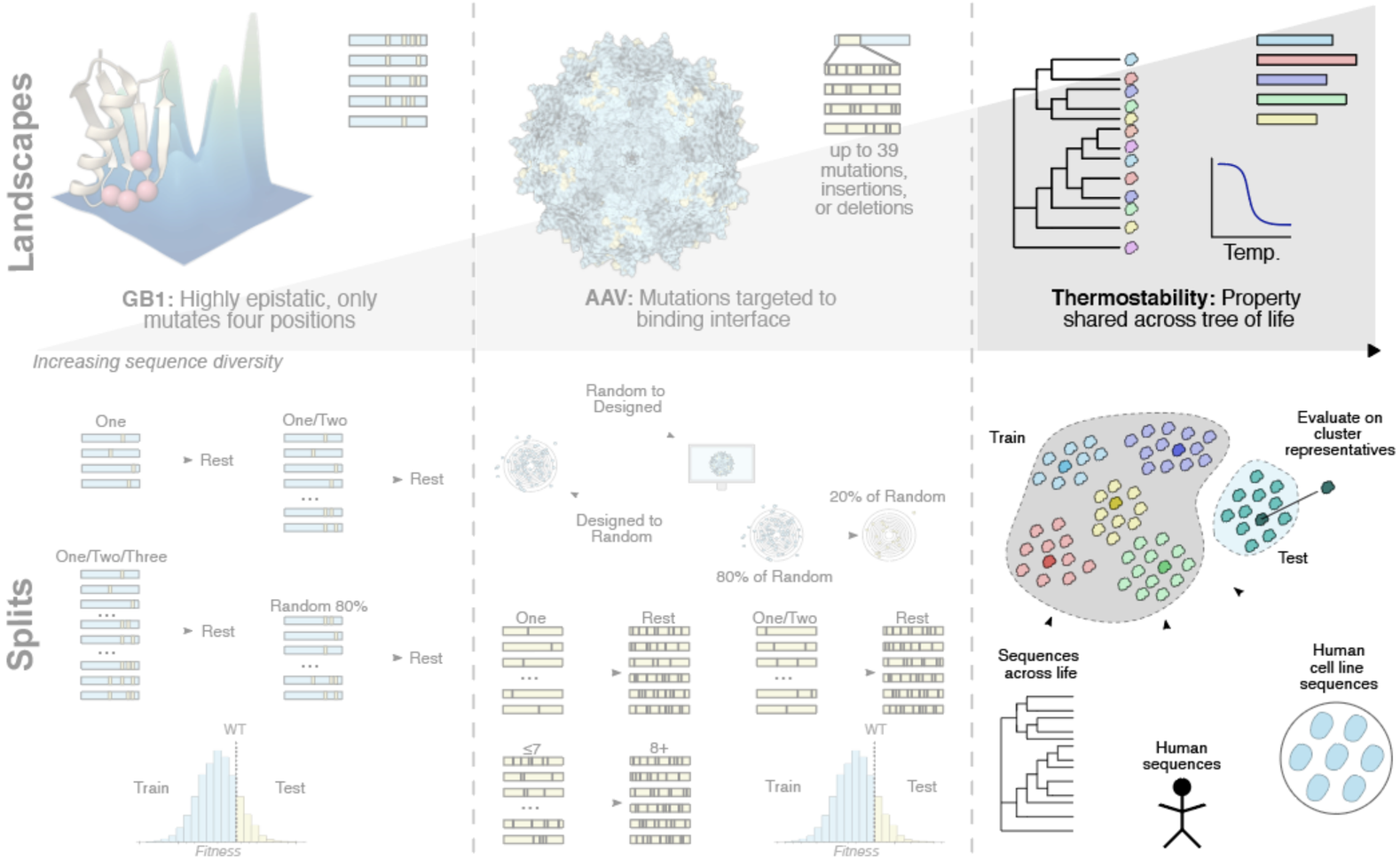
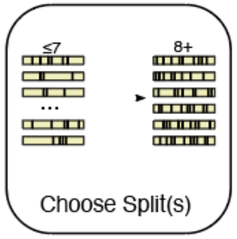
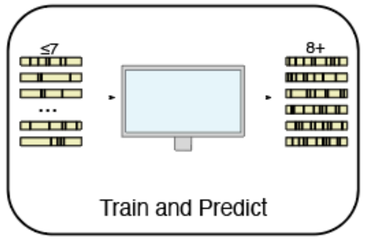




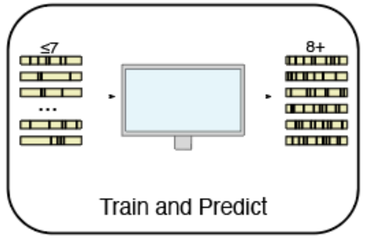
Evaluate many baseline models



Dallago *et al.* 2021

Evaluate many baseline models

Sequence distance

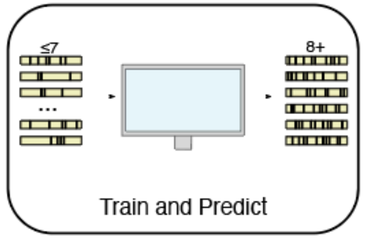


Dallago *et al.* 2021

Evaluate many baseline models

Sequence distance

Levenshtein distance



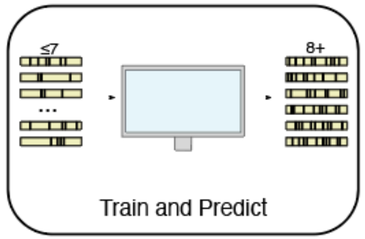
Dallago *et al.* 2021

Evaluate many baseline models

Sequence distance

Levenshtein distance

BLOSUM62



Dallago *et al.* 2021

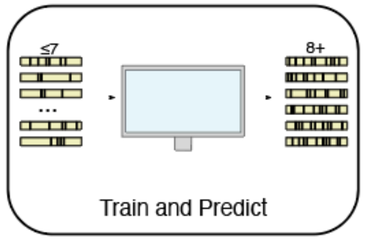
Evaluate many baseline models

Sequence distance

Levenshtein distance

BLOSUM62

Supervised models



Dallago *et al.* 2021

Evaluate many baseline models

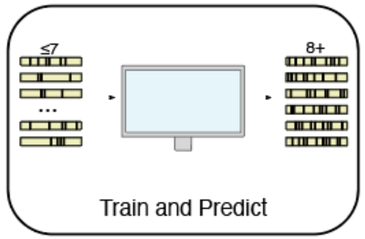
Sequence distance

Levenshtein distance

BLOSUM62

Supervised models

Ridge regression



Dallago *et al.* 2021

Evaluate many baseline models

Sequence distance

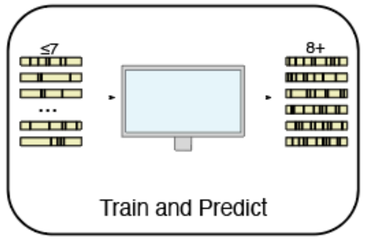
Levenshtein distance

BLOSUM62

Supervised models

Ridge regression

small CNN



Dallago *et al.* 2021

Evaluate many baseline models

Sequence distance

Levenshtein distance

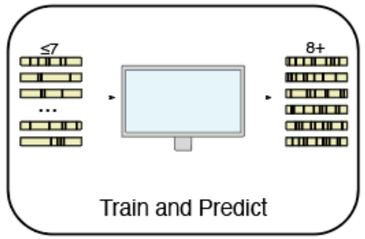
BLOSUM62

Supervised models

Ridge regression

small CNN

ESM-untrained
(750M par. transformer)



Dallago *et al.* 2021

Evaluate many baseline models

Sequence distance

Levenshtein distance

BLOSUM62

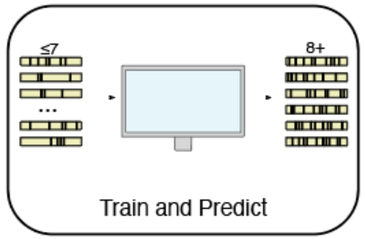
Supervised models

Ridge regression

small CNN

ESM-untrained
(750M par. transformer)

Pretrained models



Dallago *et al.* 2021

Evaluate many baseline models

Sequence distance

Levenshtein distance

BLOSUM62

Supervised models

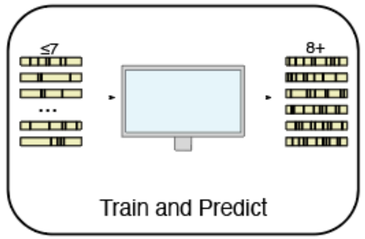
Ridge regression

small CNN

ESM-untrained
(750M par. transformer)

Pretrained models

ESM-1b
(pretrained on UniRef50)



Dallago *et al.* 2021

Evaluate many baseline models

Sequence distance

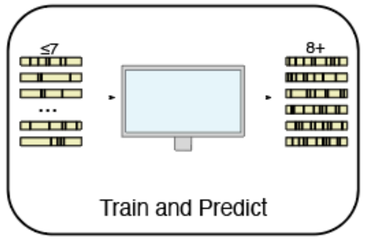
- Levenshtein distance
- BLOSUM62

Supervised models

- Ridge regression
- small CNN
- ESM-untrained (750M par. transformer)

Pretrained models

- ESM-1b (pretrained on UniRef50)
- ESM-1v (pretrained on UniRef90)



Dallago *et al.* 2021

Evaluate many baseline models

Sequence distance

- Levenshtein distance
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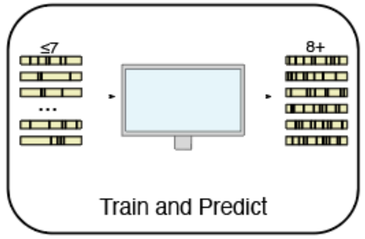
Best on highly-diverse landscapes (thermostability) or when data is very limited



Dallago *et al.* 2021

Evaluate many baseline models

Sequence distance

- Levenshtein distance
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Supervised models

- Ridge regression
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Strong performance on most landscapes

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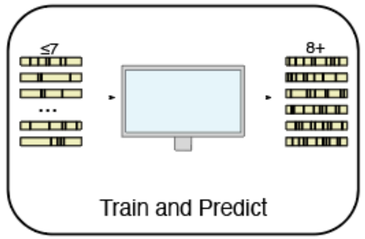
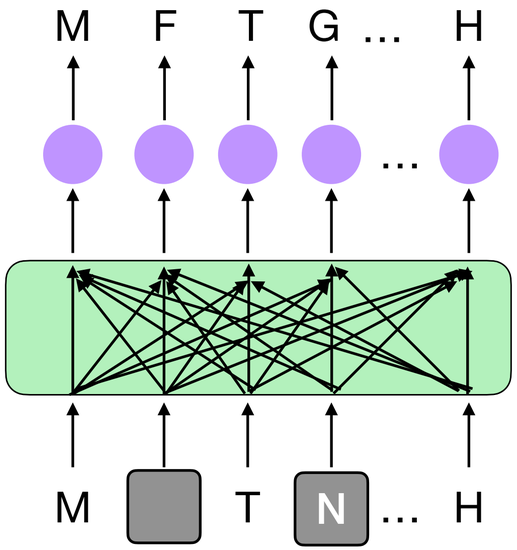


Dallago *et al.* 2021

Try your models!

https://benchmark.protein.properties/home

Local-to-global aggregation affects model performance



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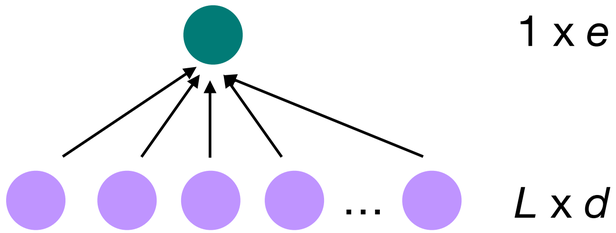

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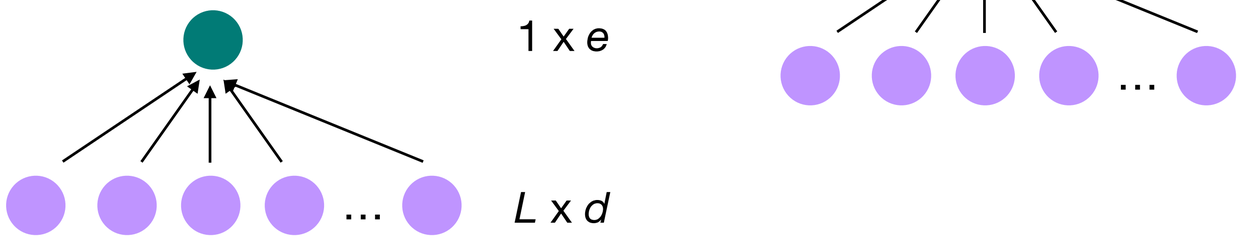

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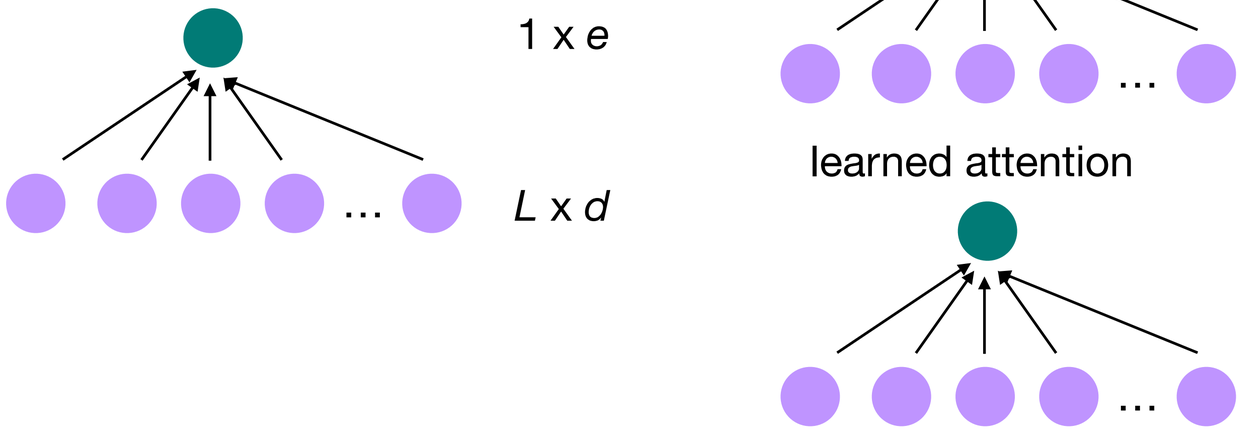

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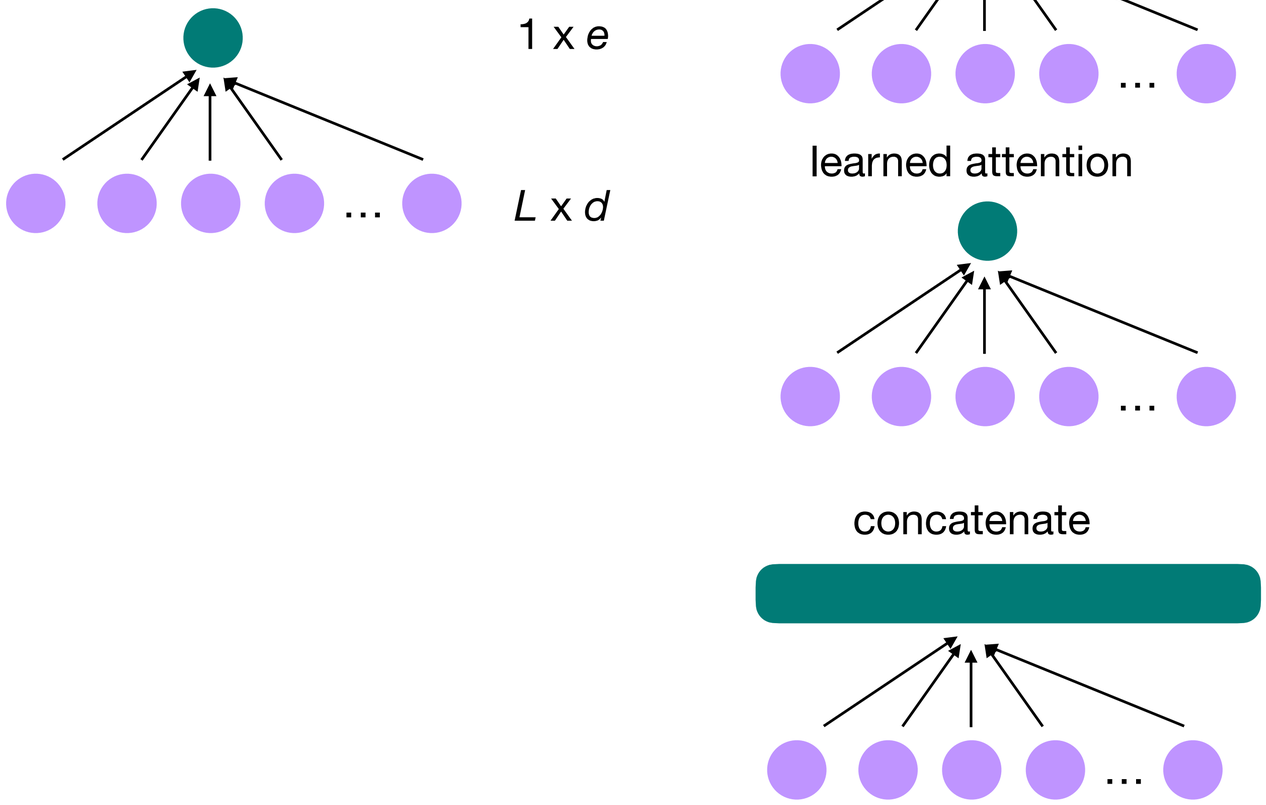

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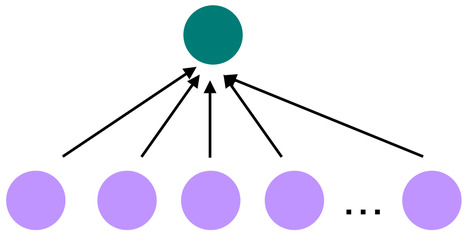
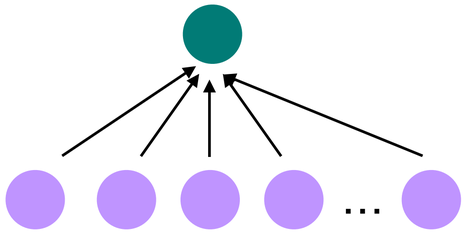


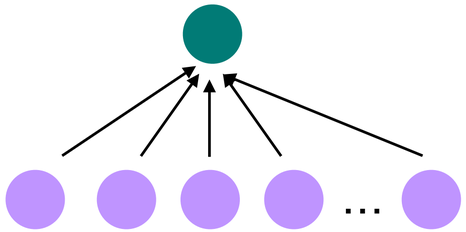
1 x *e*

L x *d*

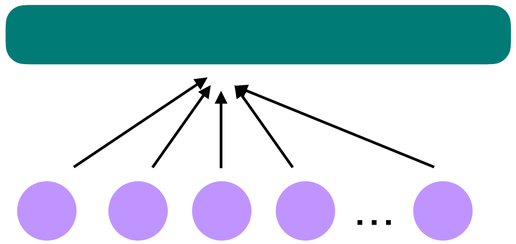
mean



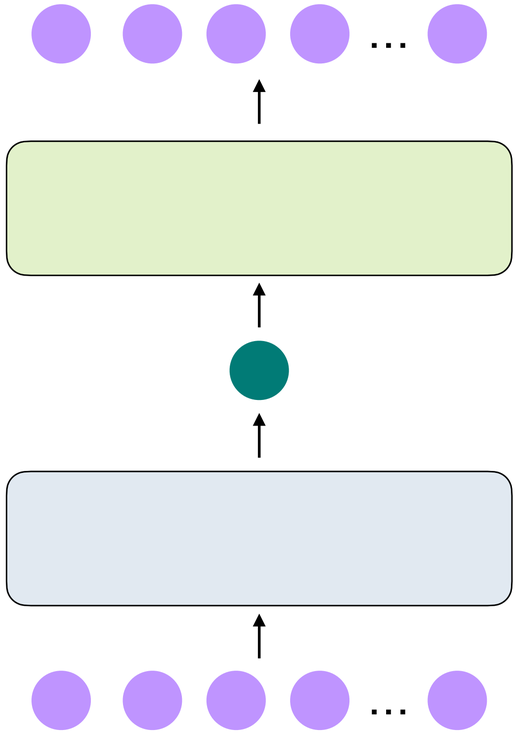
learned attention



concatenate



bottleneck



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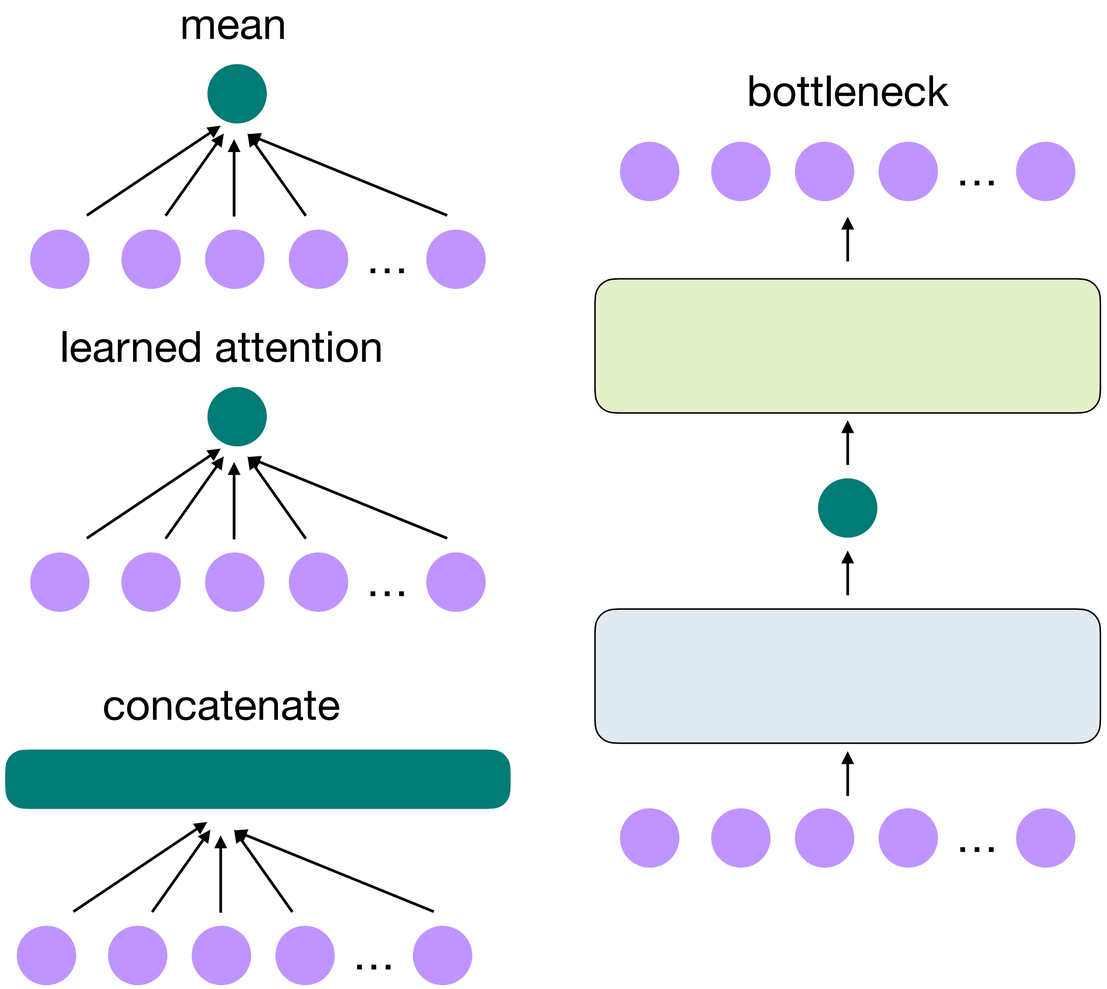


	Stability (Corr.)	Fluorescence (Corr.)	Homology (Acc.)
Mean	0.42	0.19	0.27
Attention	0.65	0.23	0.27
Light Att.	0.66	0.23	0.27
Maximum	0.02	0.02	0.28
MeanMax	0.37	0.15	0.26
KMax	0.10	0.11	0.27
Concat	0.74	0.69	0.34
Bottleneck	**0.79**	**0.78**	**0.41**

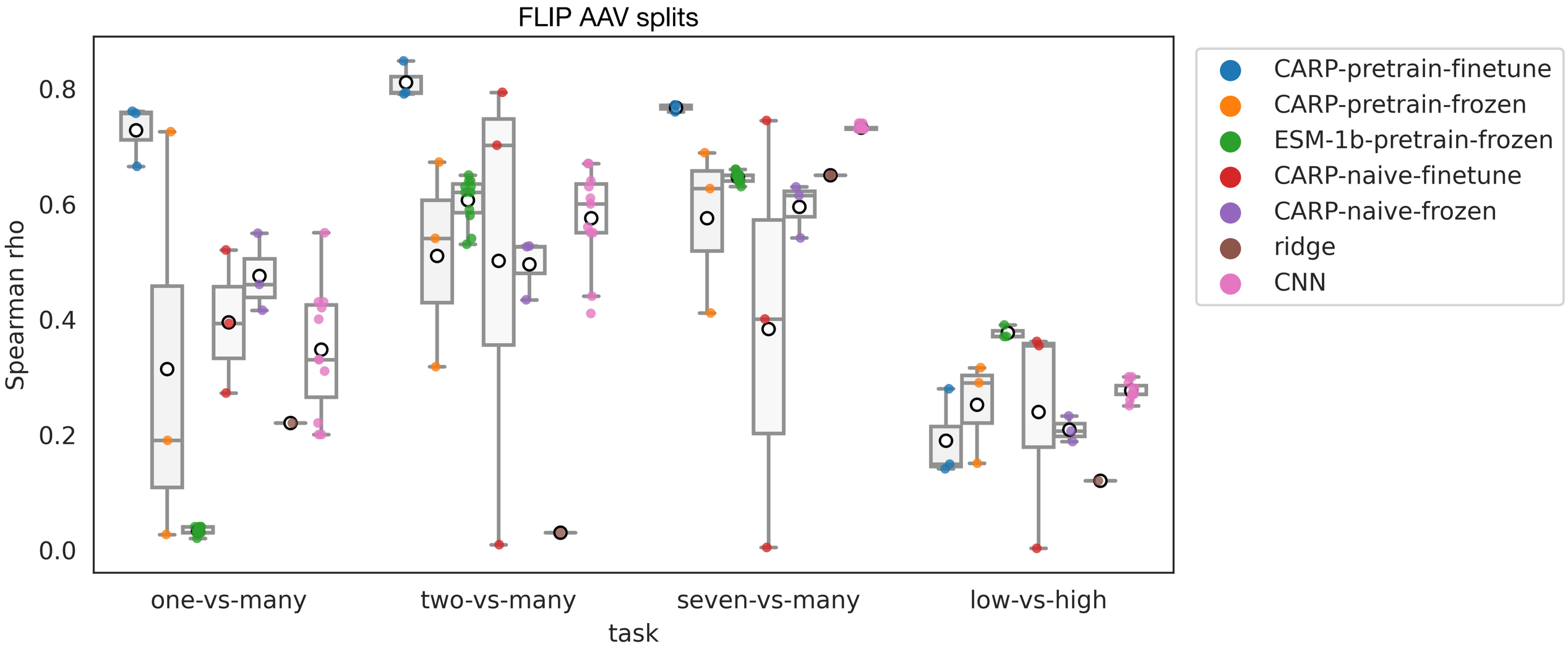
Detlefsen *et al.* 2022

Finetuning/fixing pretrained weights also matters

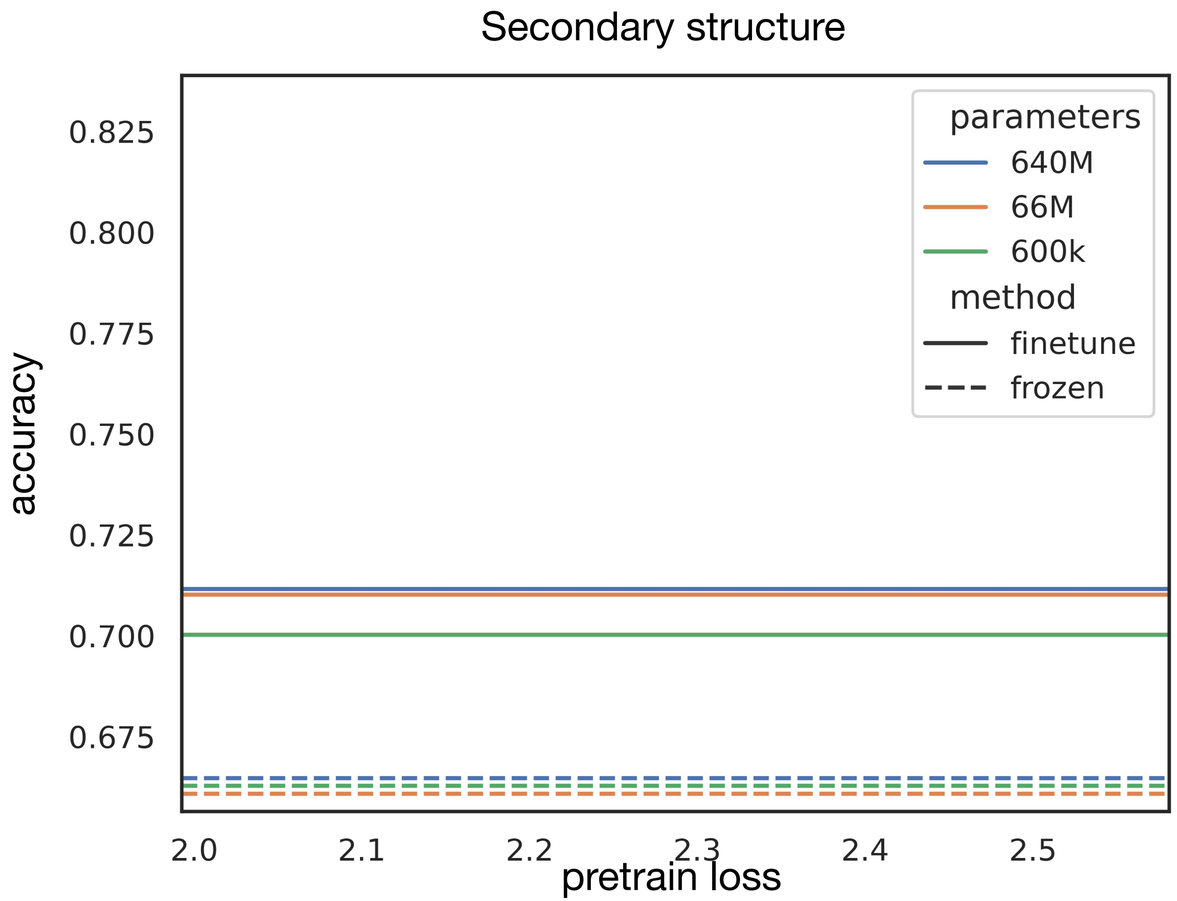
	Remote Homology			Fluorescence			Stability		
	Resnet	**LSTM**	**Trans**	**Resnet**	**LSTM**	**Trans**	**Resnet**	**LSTM**	**Trans**
PRE+FIX	0.27	**0.37**	0.27	0.23	**0.74**	0.48	0.65	0.70	0.62
PRE+FIN	0.17	0.26	0.21	0.21	0.67	0.68	**0.73**	0.69	**0.73**
RNG+FIX	0.03	0.10	0.04	0.25	0.63	0.14	0.21	0.61	–
RNG+FIN	0.10	0.12	0.09	−0.28	0.21	0.22	0.61	0.28	−0.06
Baseline	0.09 (Accuracy)			0.14 (Correlation)			0.19 (Correlation)		

Detlefsen *et al.* 2022

Finetuning/fixing pretrained weights also matters



When does pretraining help?



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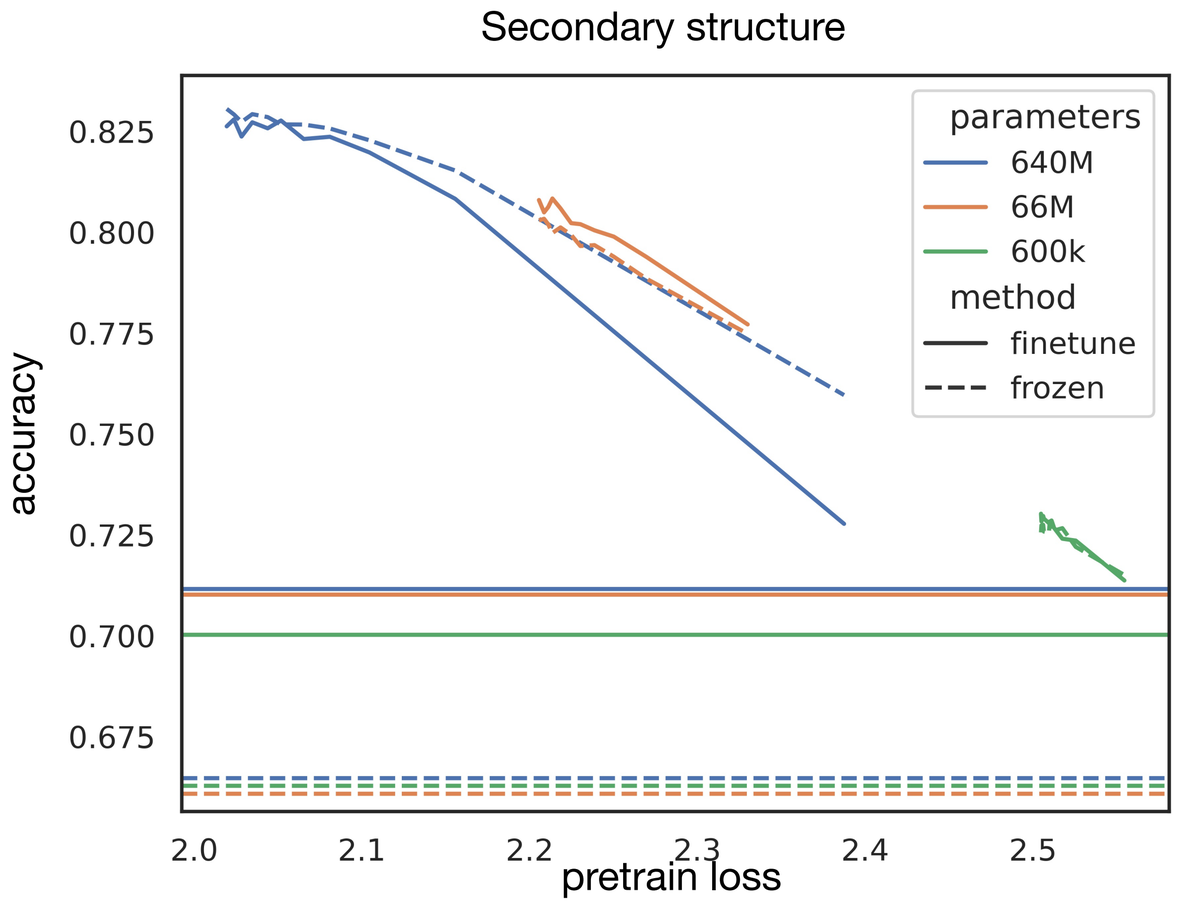

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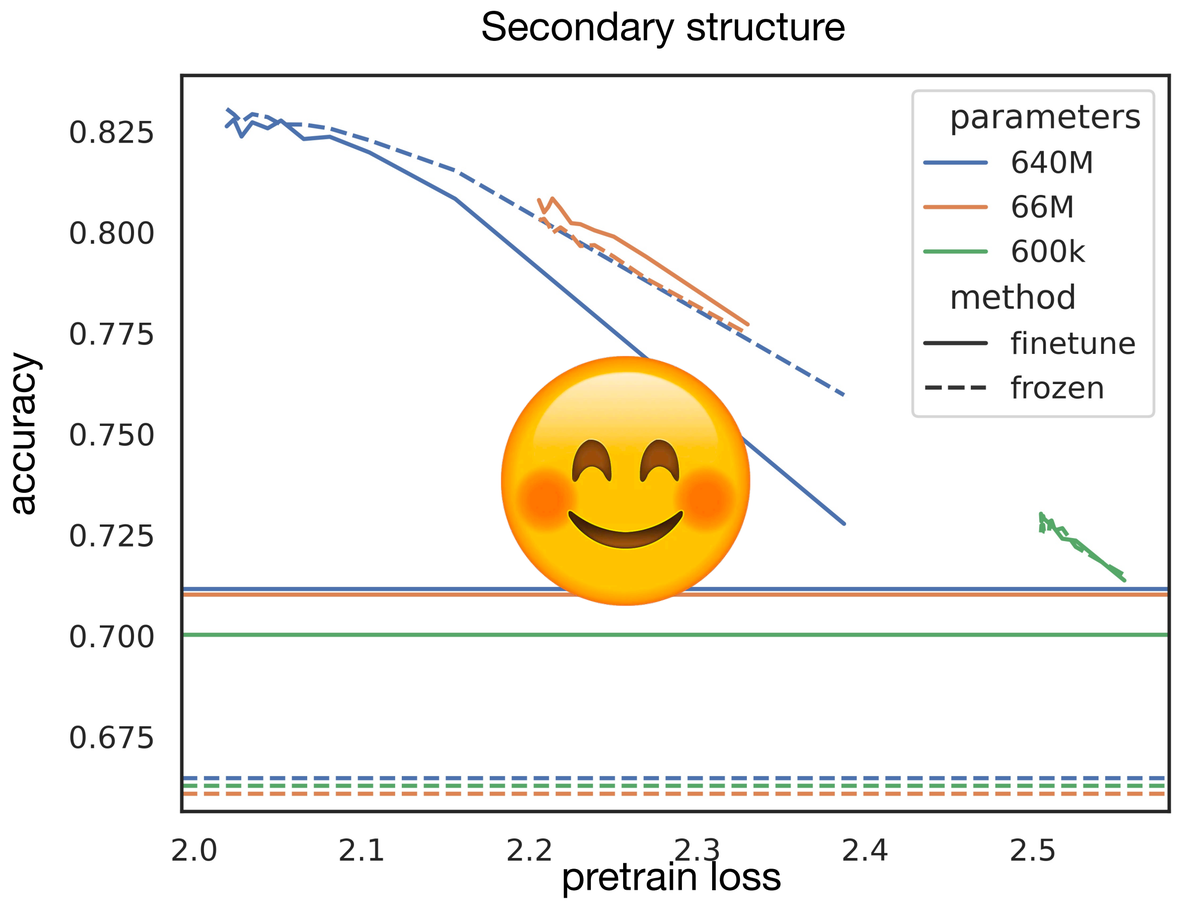

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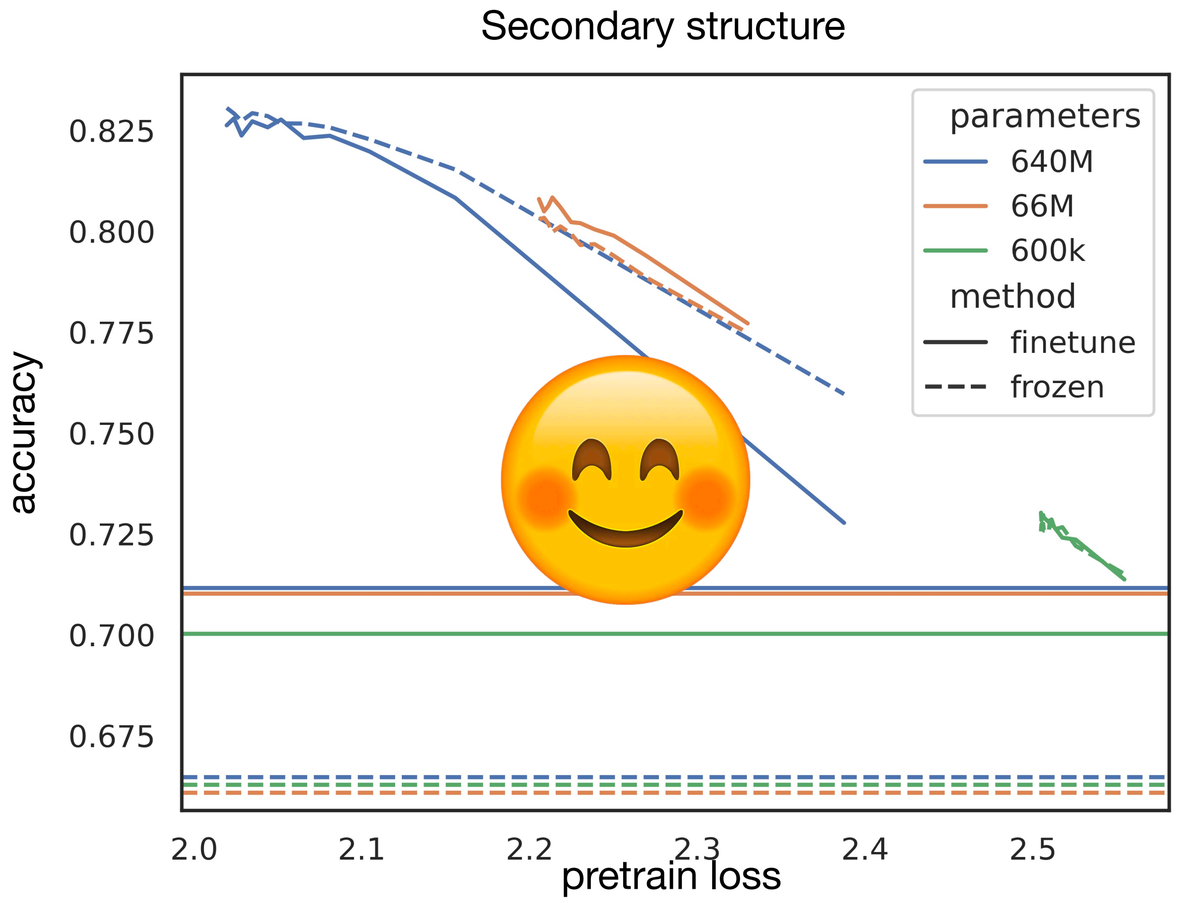

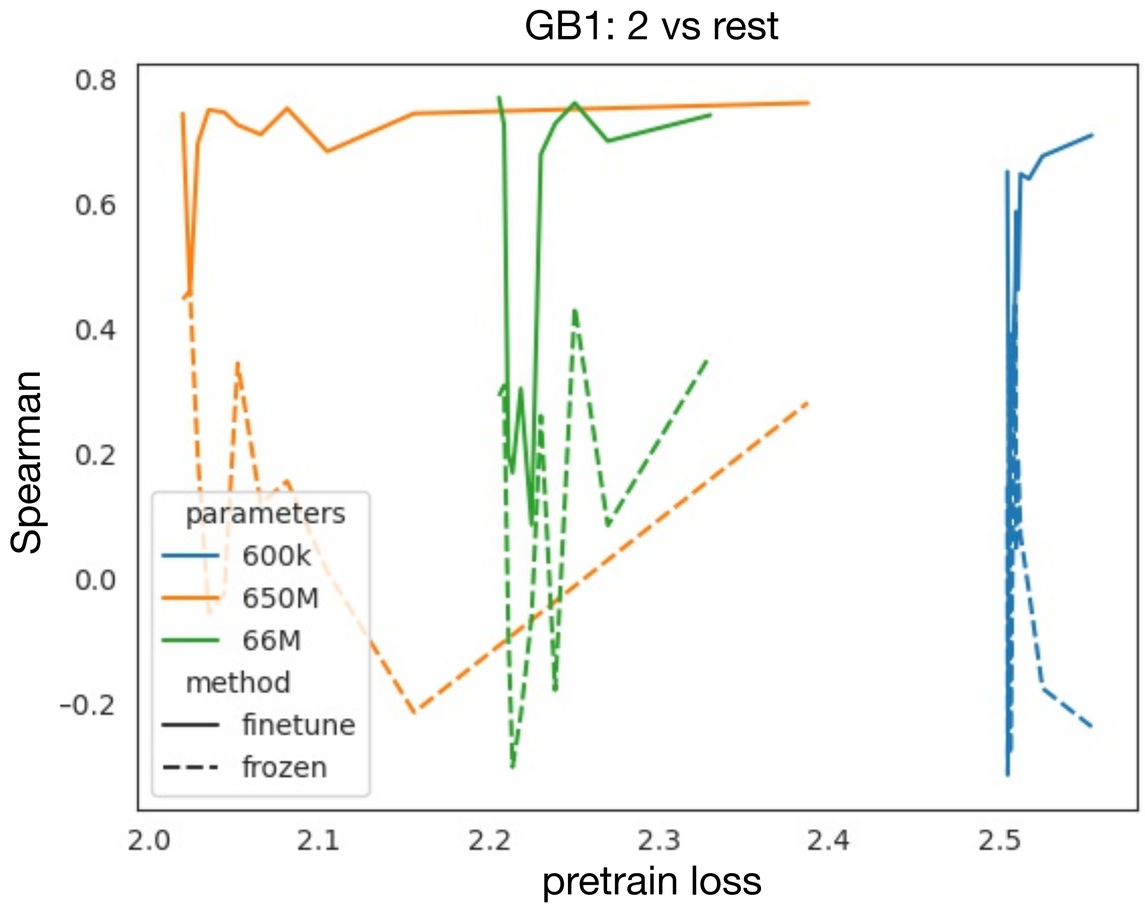

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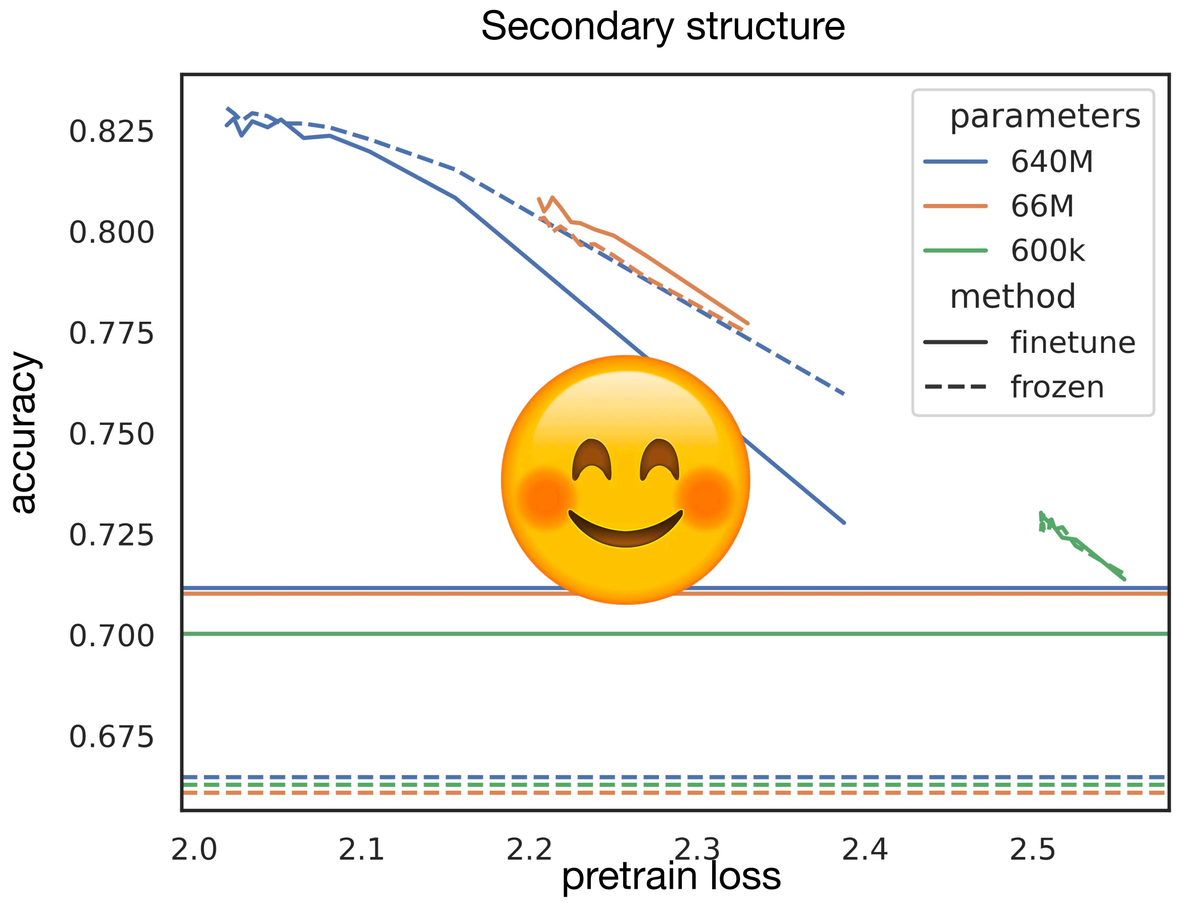

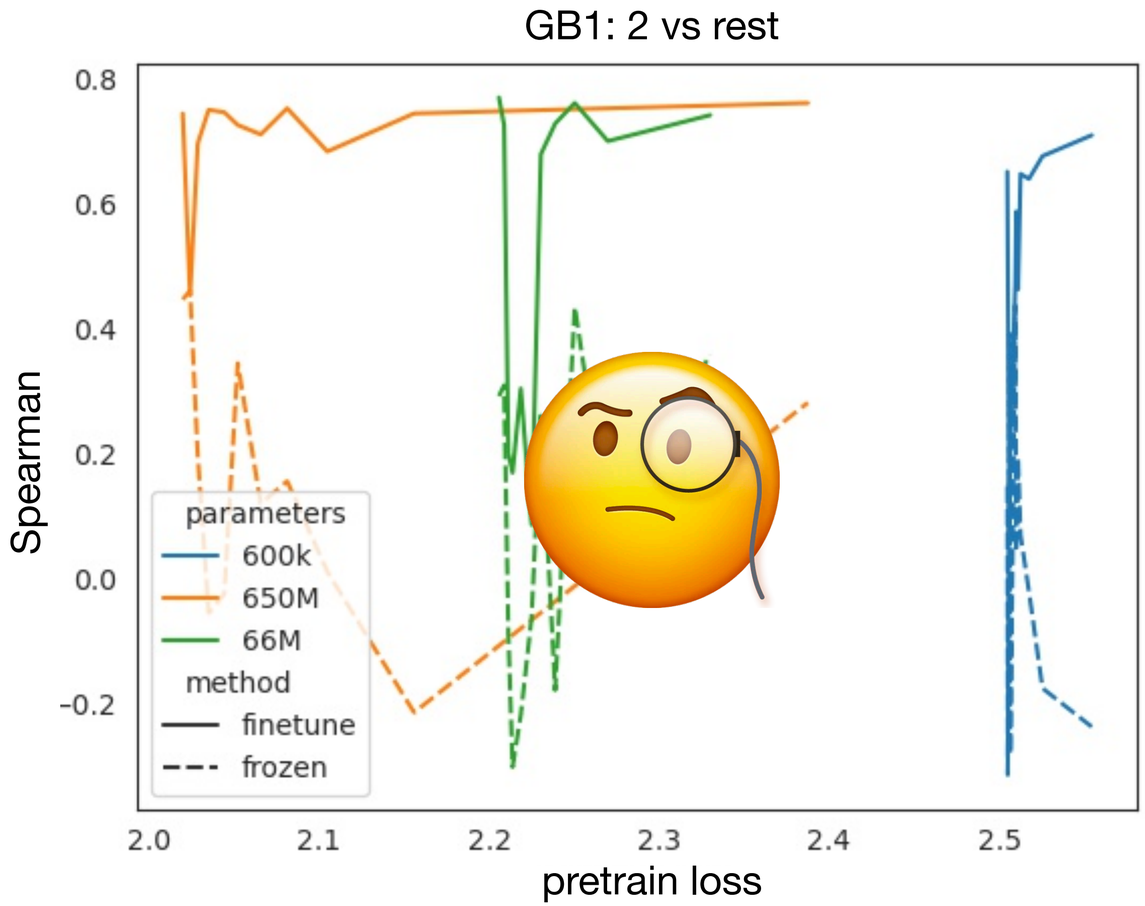

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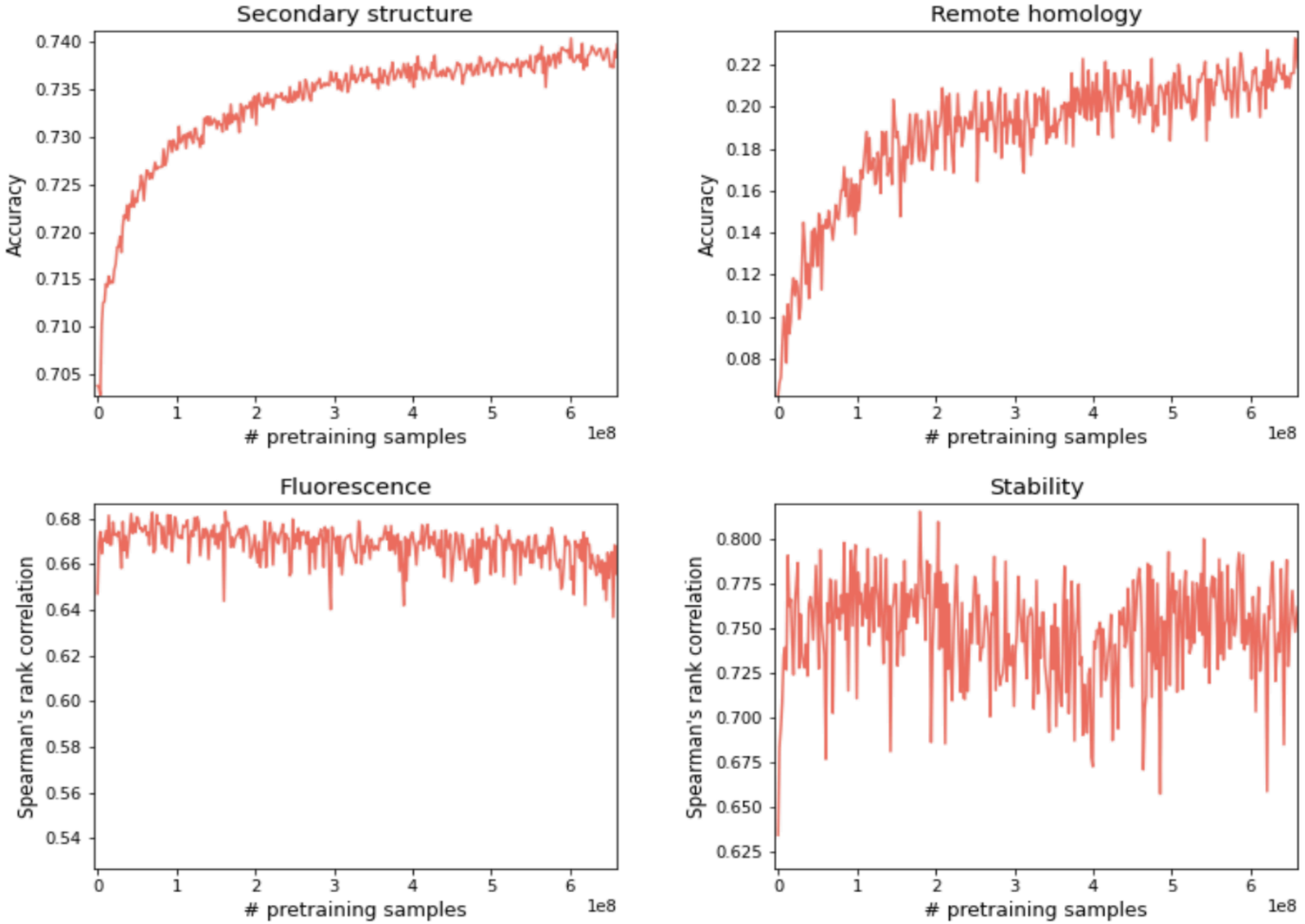

Brandes *et al.* 2021

Protein sequences are not language

Protein sequences are not language

Differences between proteins and NL

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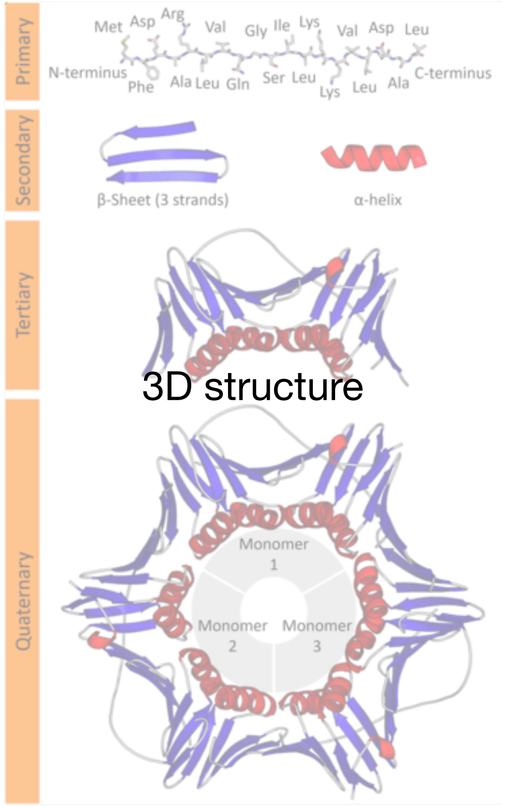
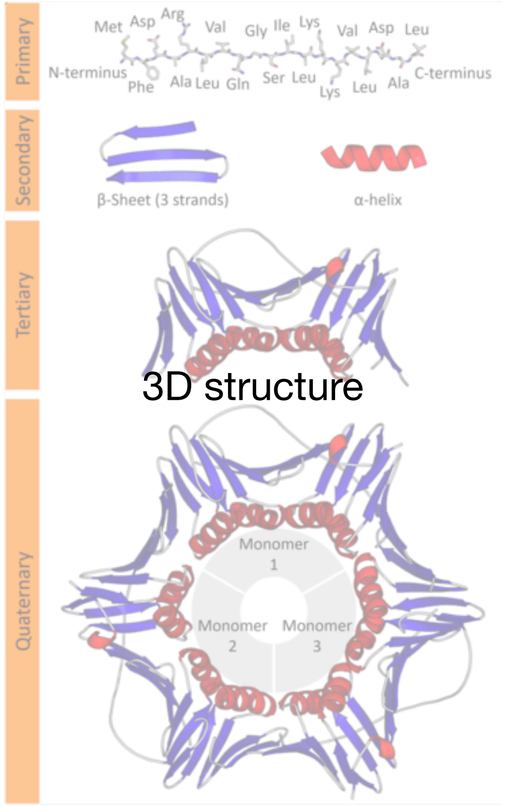
Differences between proteins and NL



Thomas Shafee

Protein sequences are not language

Differences between proteins and NL



Thomas Shafee

ACDEFGHIKLMNPQRSTVWY
vs
words and subwords

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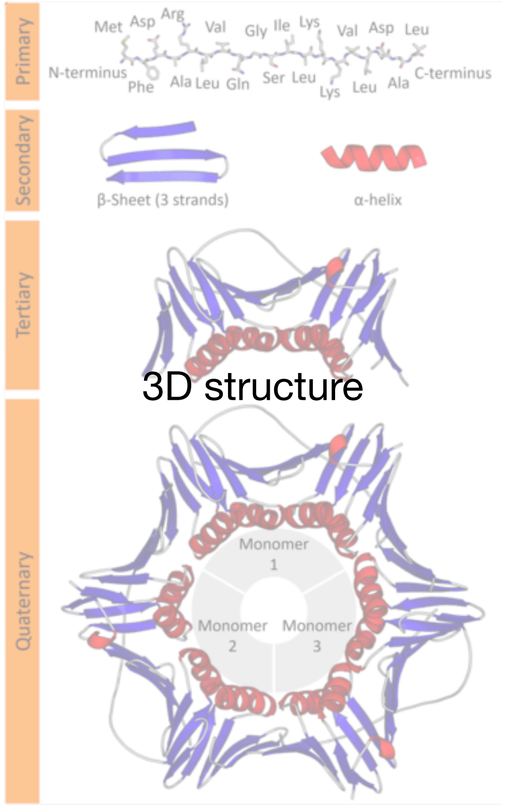

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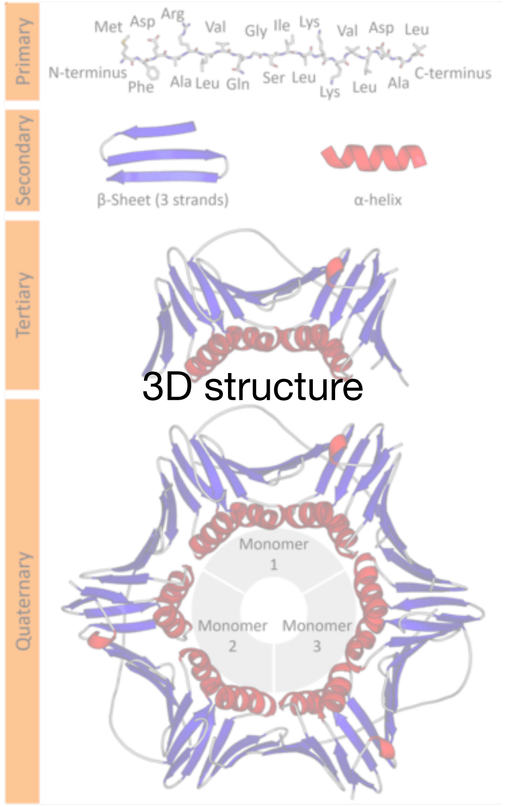

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evolution + sequencing

Multi-modal models

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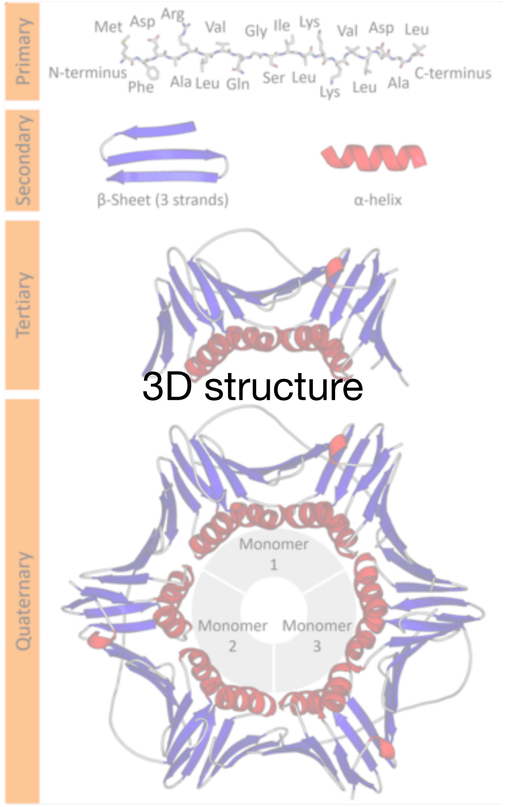

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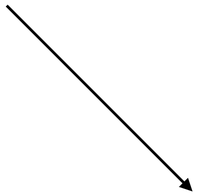
sequence `MGHTQWI...`



model

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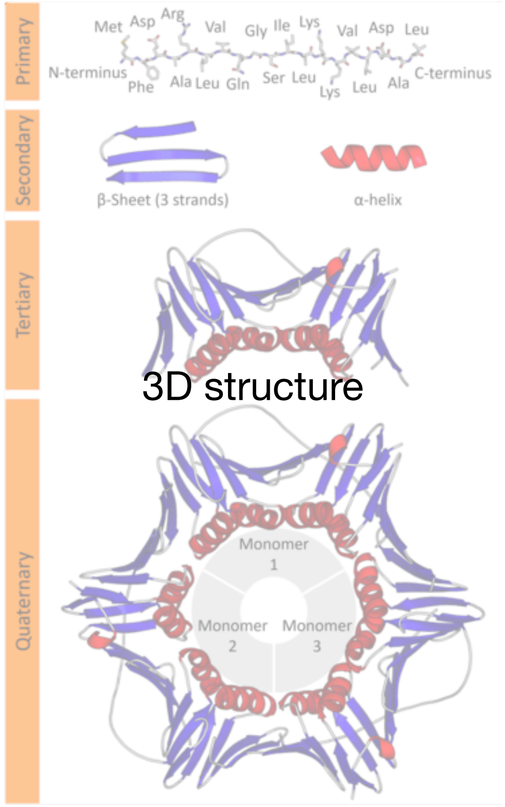
Differences between proteins and NL



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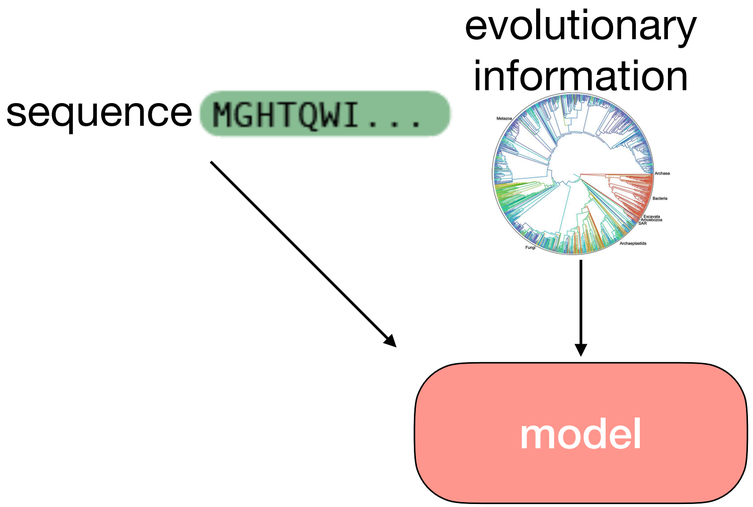

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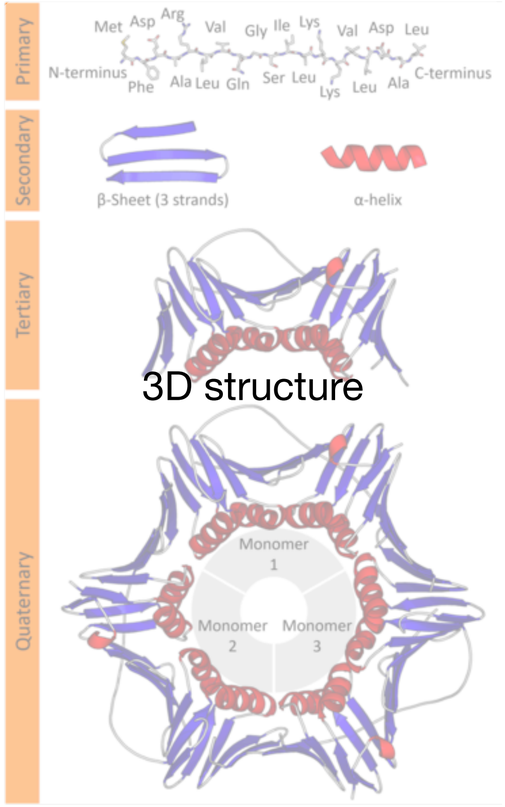

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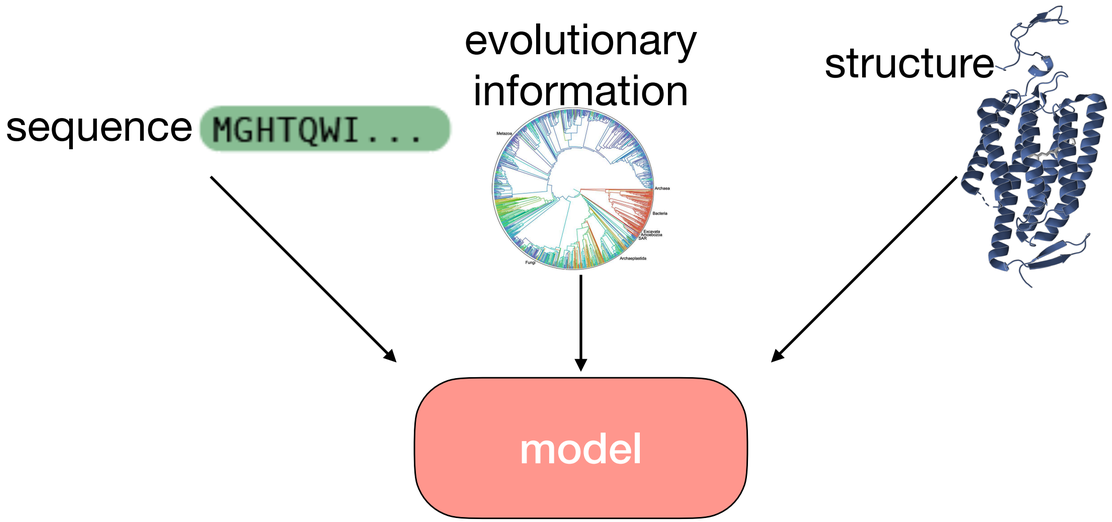

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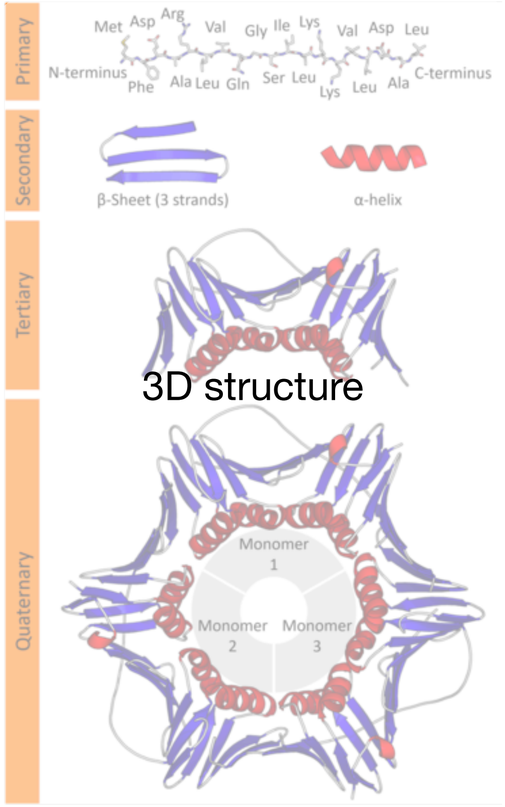

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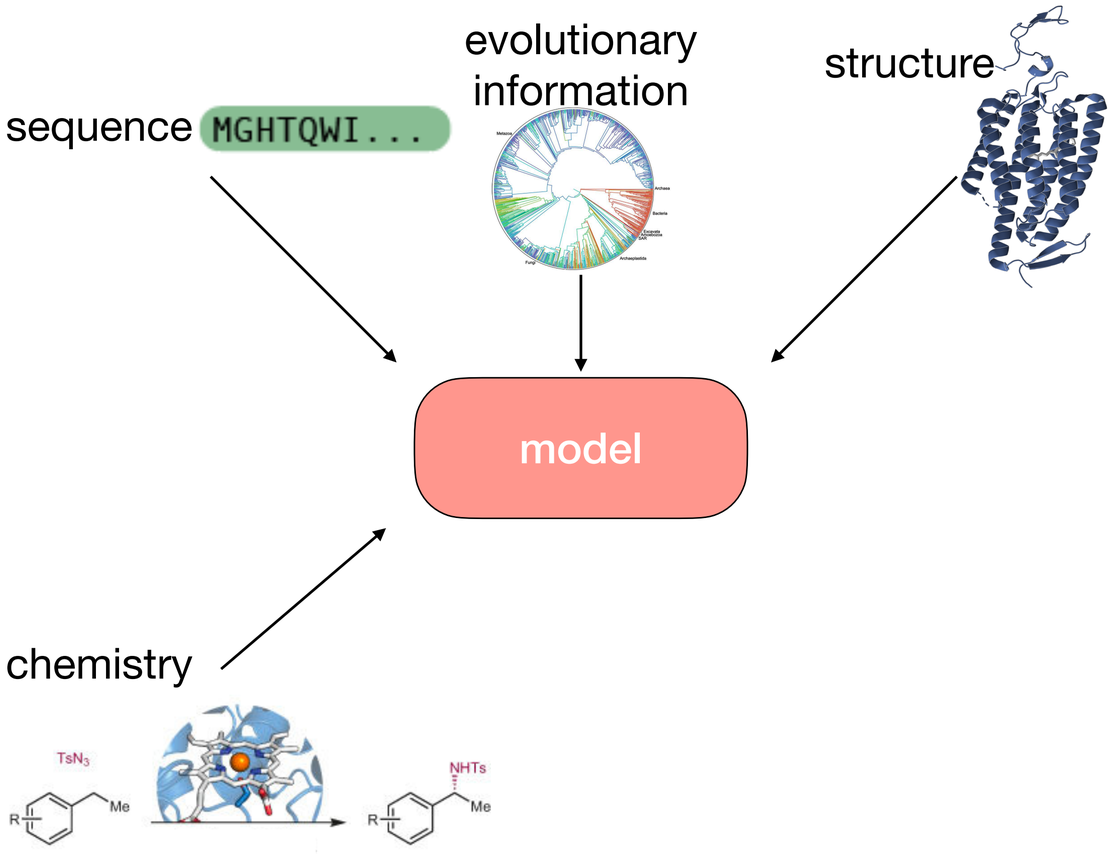

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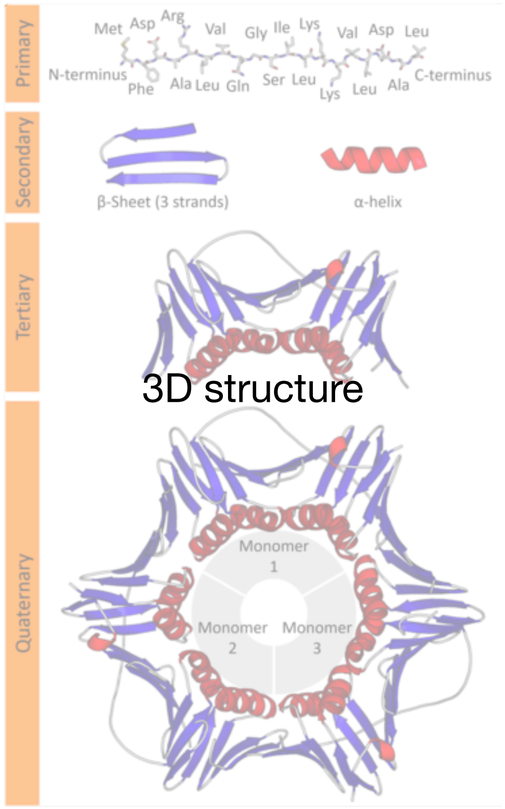

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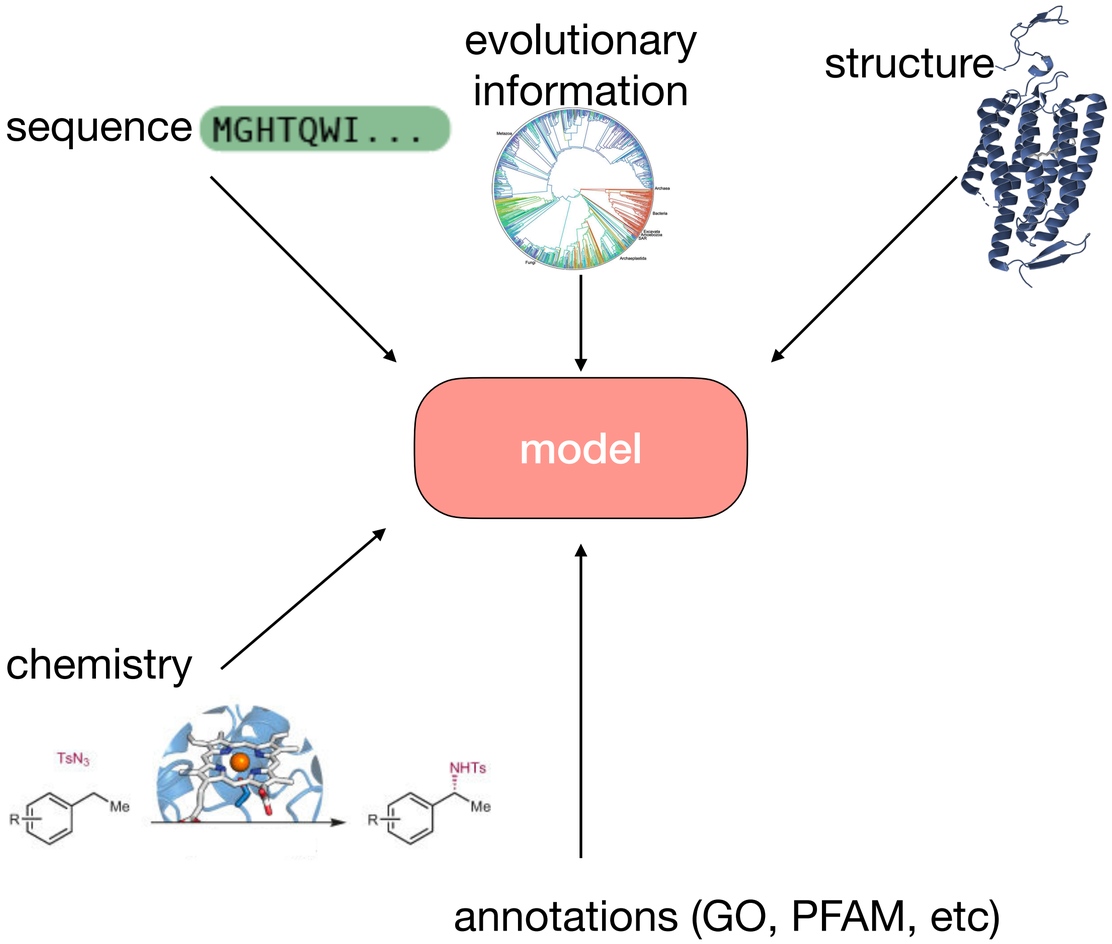

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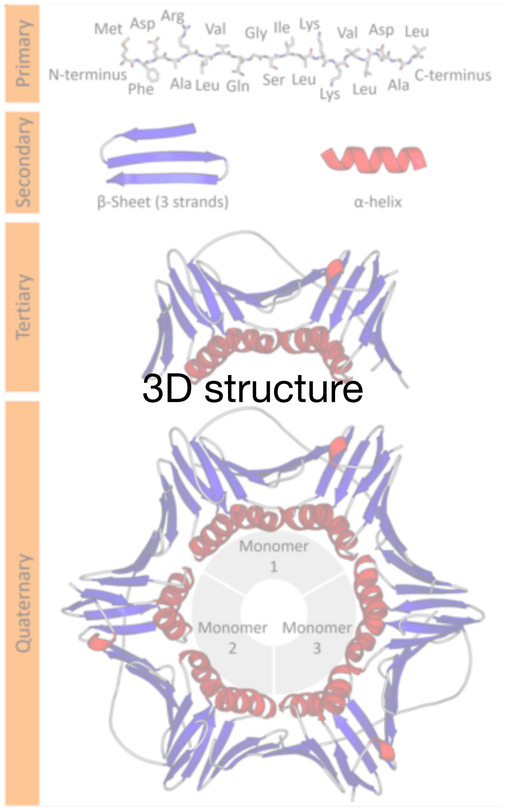

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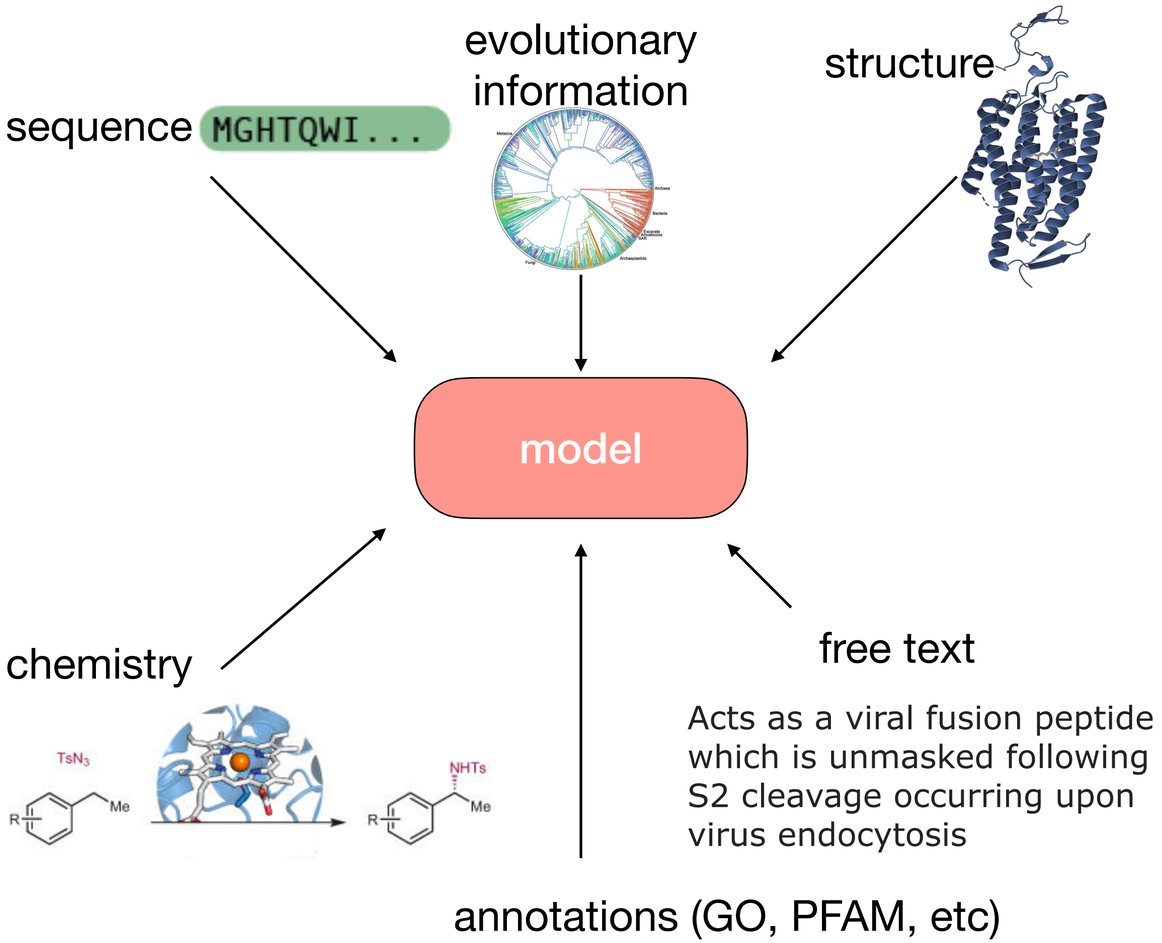
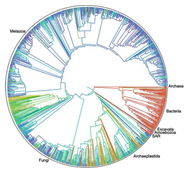


Multiple sequence alignments encode structural information

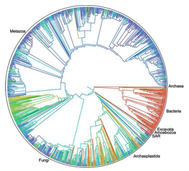
evolutionary information



Multiple sequence alignments encode structural information

Alignments contain information about contacts

evolutionary information



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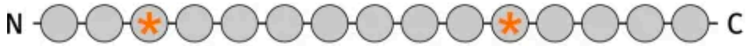
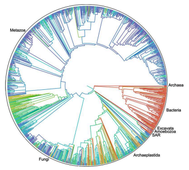


evolutionary information



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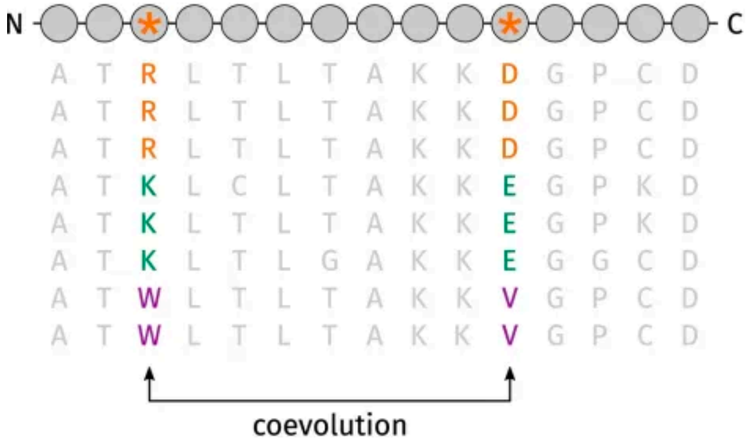
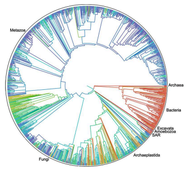
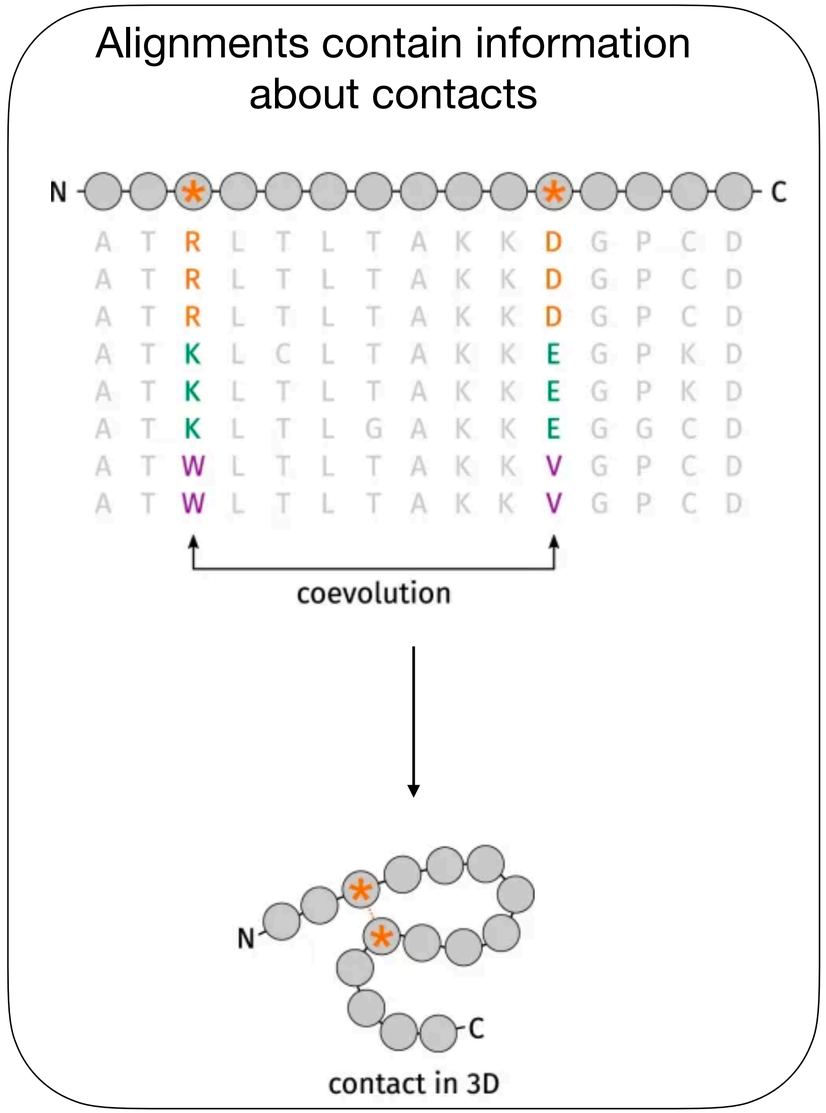


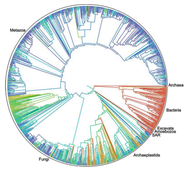
evolutionary information



Multiple sequence alignments encode structural information

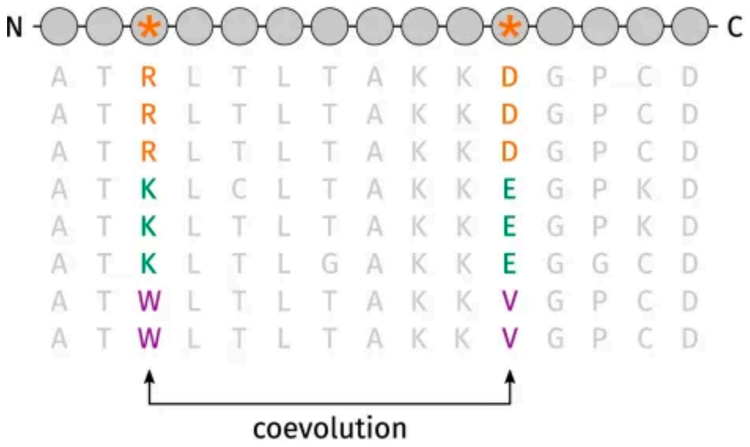


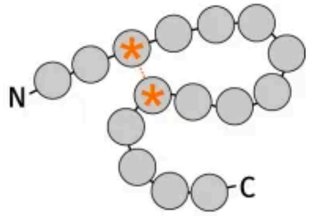
evolutionary information



Multiple sequence alignments encode structural information

Alignments contain information about contacts

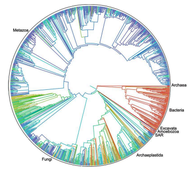




contact in 3D

Contacts constrain fold

evolutionary information



Multiple sequence alignments encode structural information

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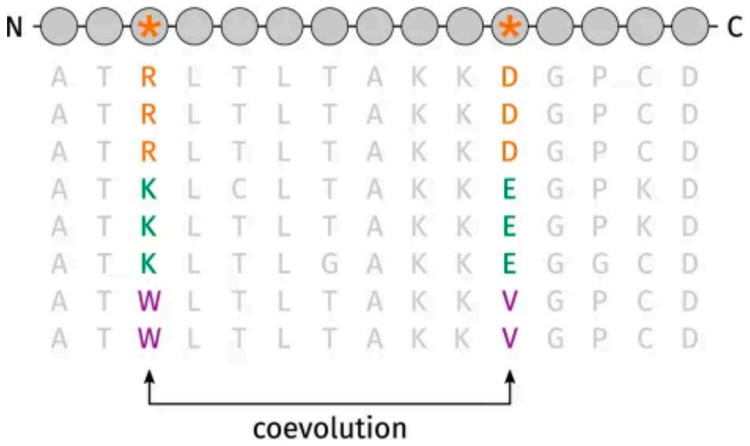

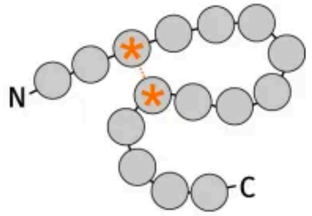

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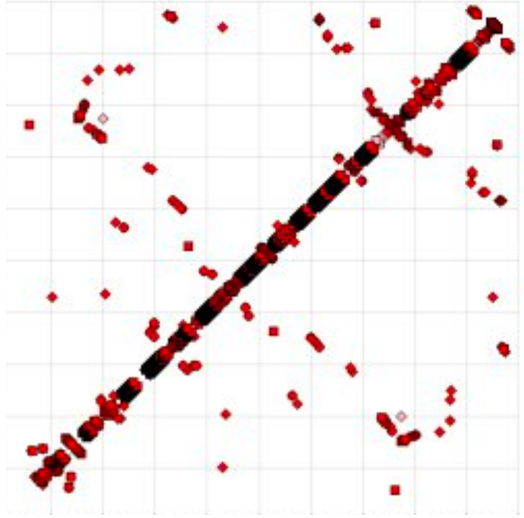
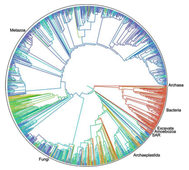


evolutionary information



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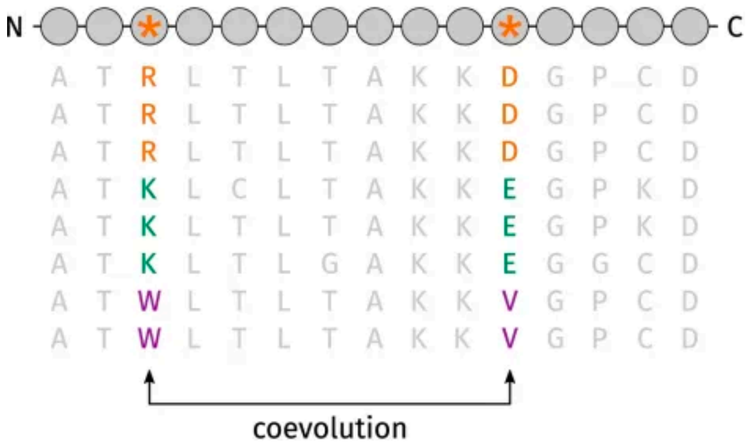
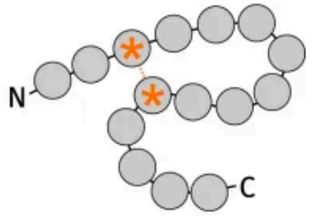
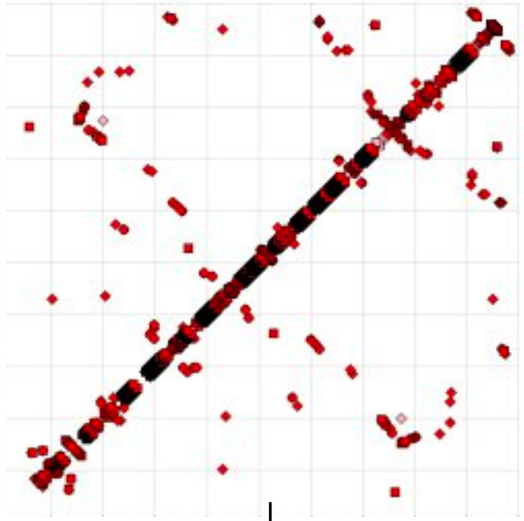
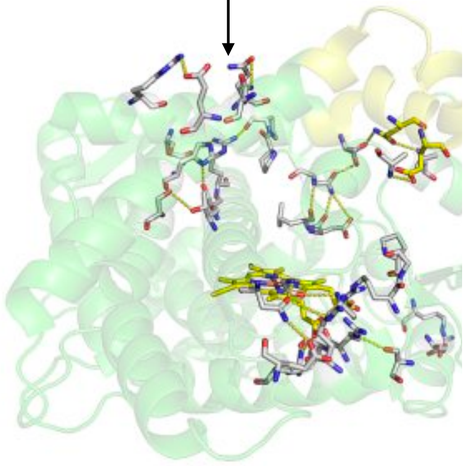




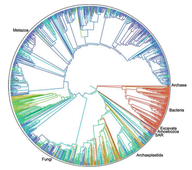
contact in 3D

Contacts constrain fold

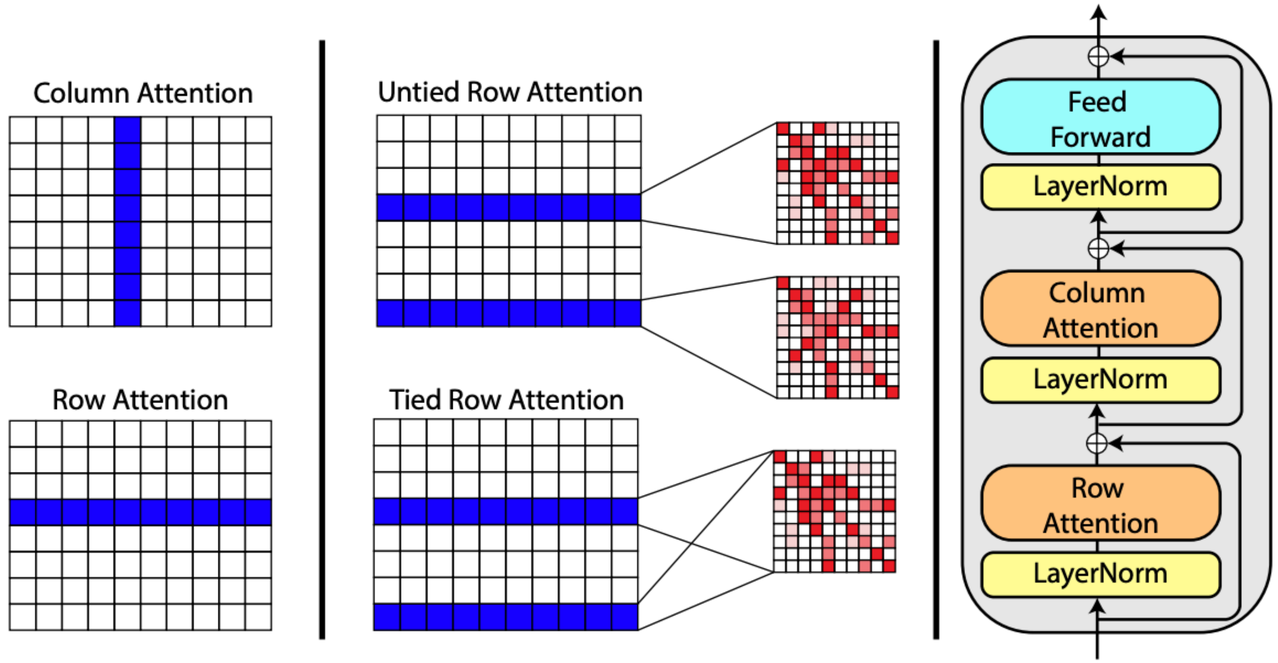




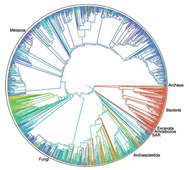
evolutionary information



MSA-Transformer extracts information from MSAs

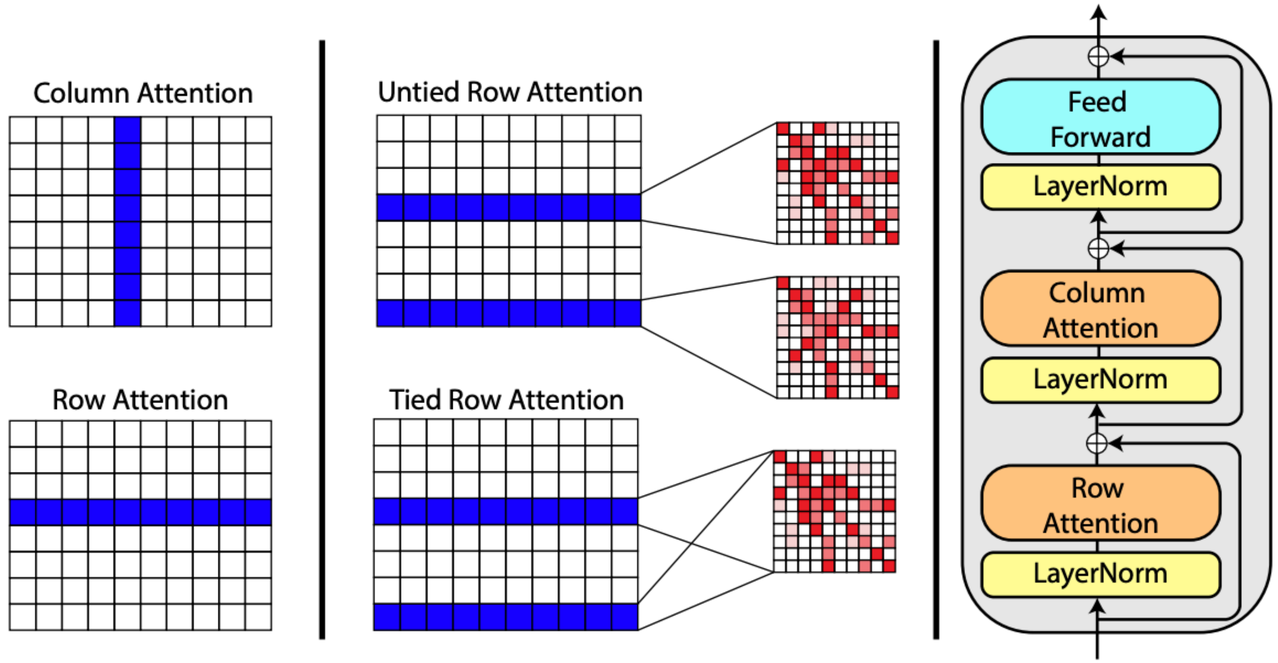


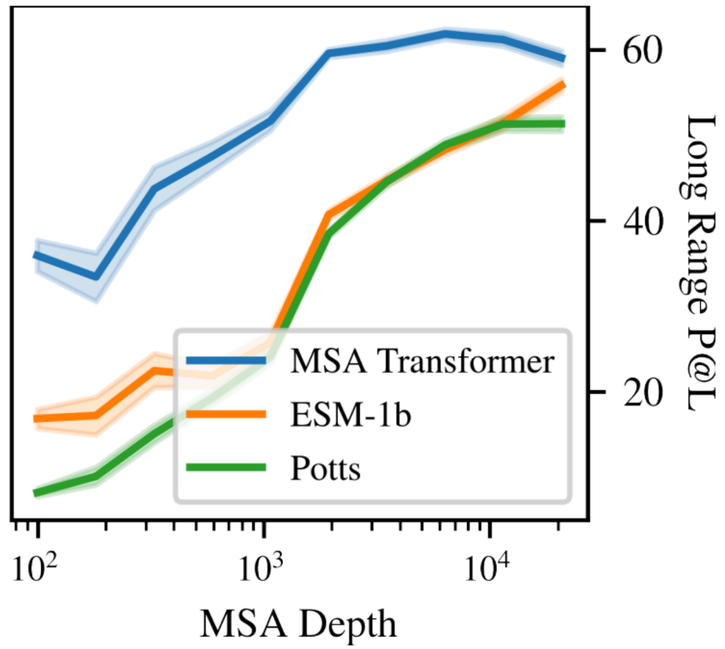
evolutionary information



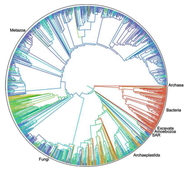
Rao *et al.* 2021

MSA-Transformer extracts information from MSAs



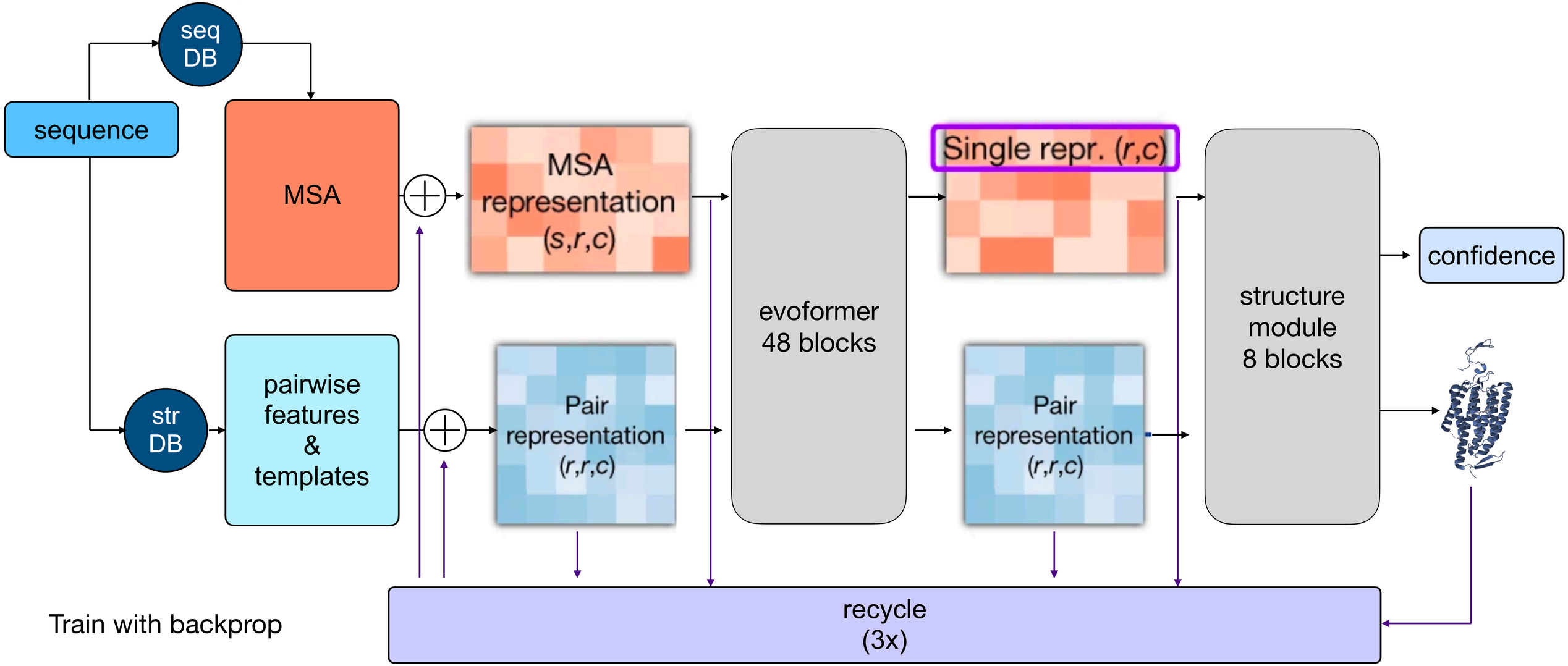


evolutionary information



Rao *et al.* 2021

AlphaFold uses MSAs and transformers

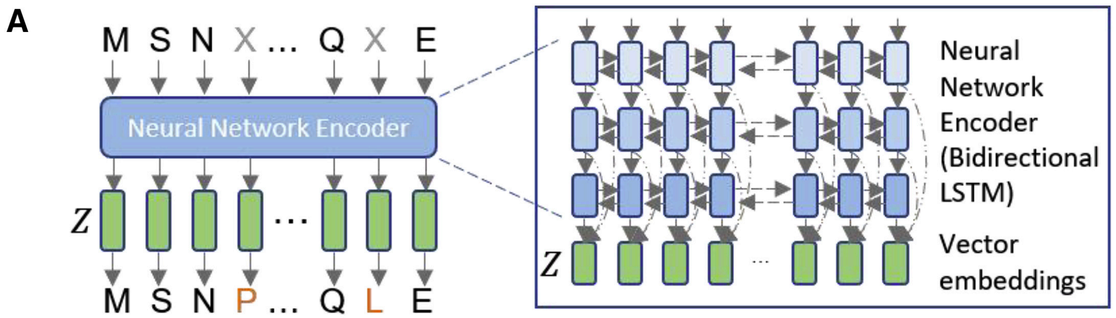


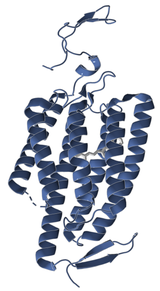
Train with backprop

16 TPUv3s for several weeks

Jumper *et al.* 2021

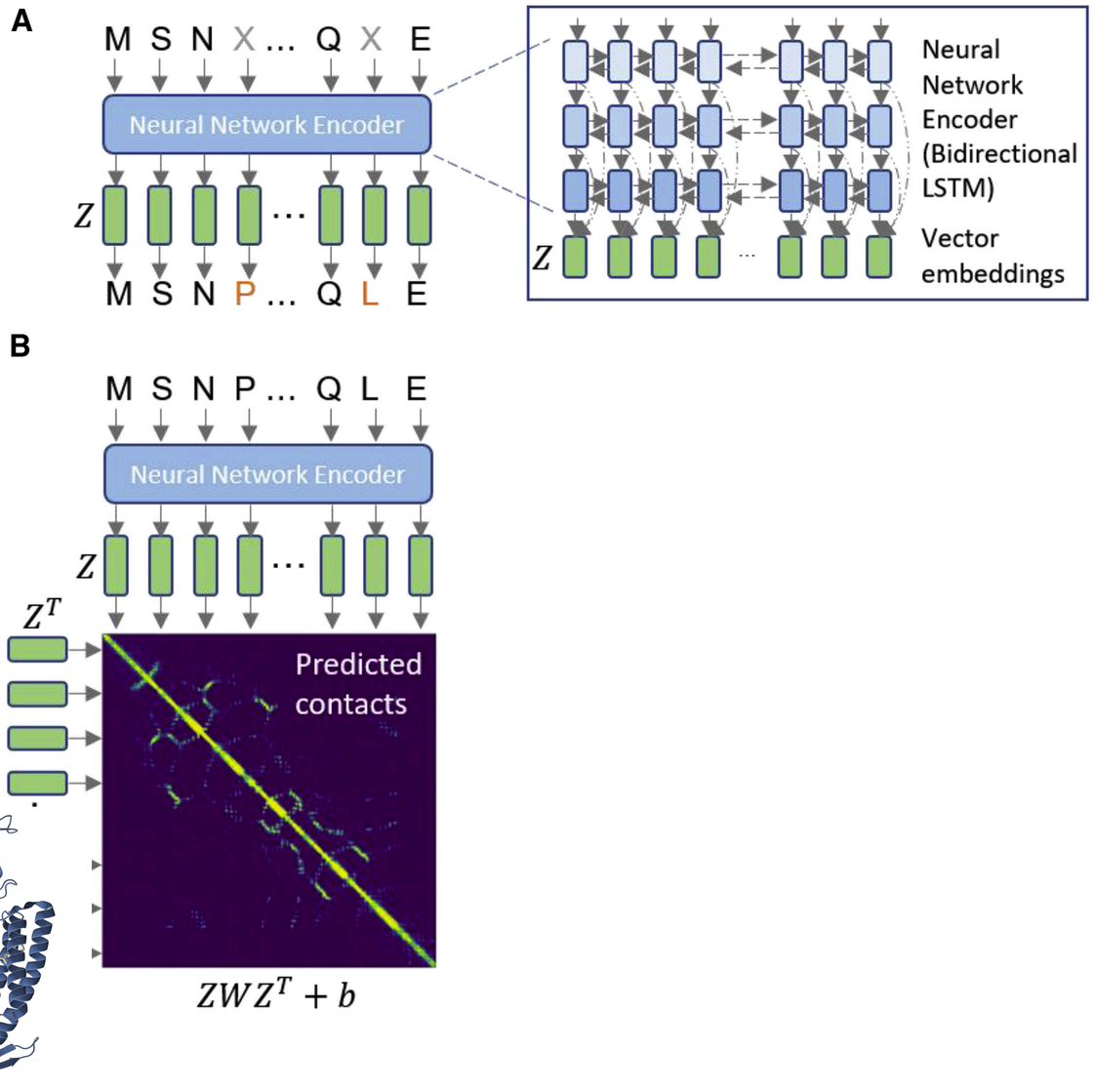
Can use structure as a pretext task





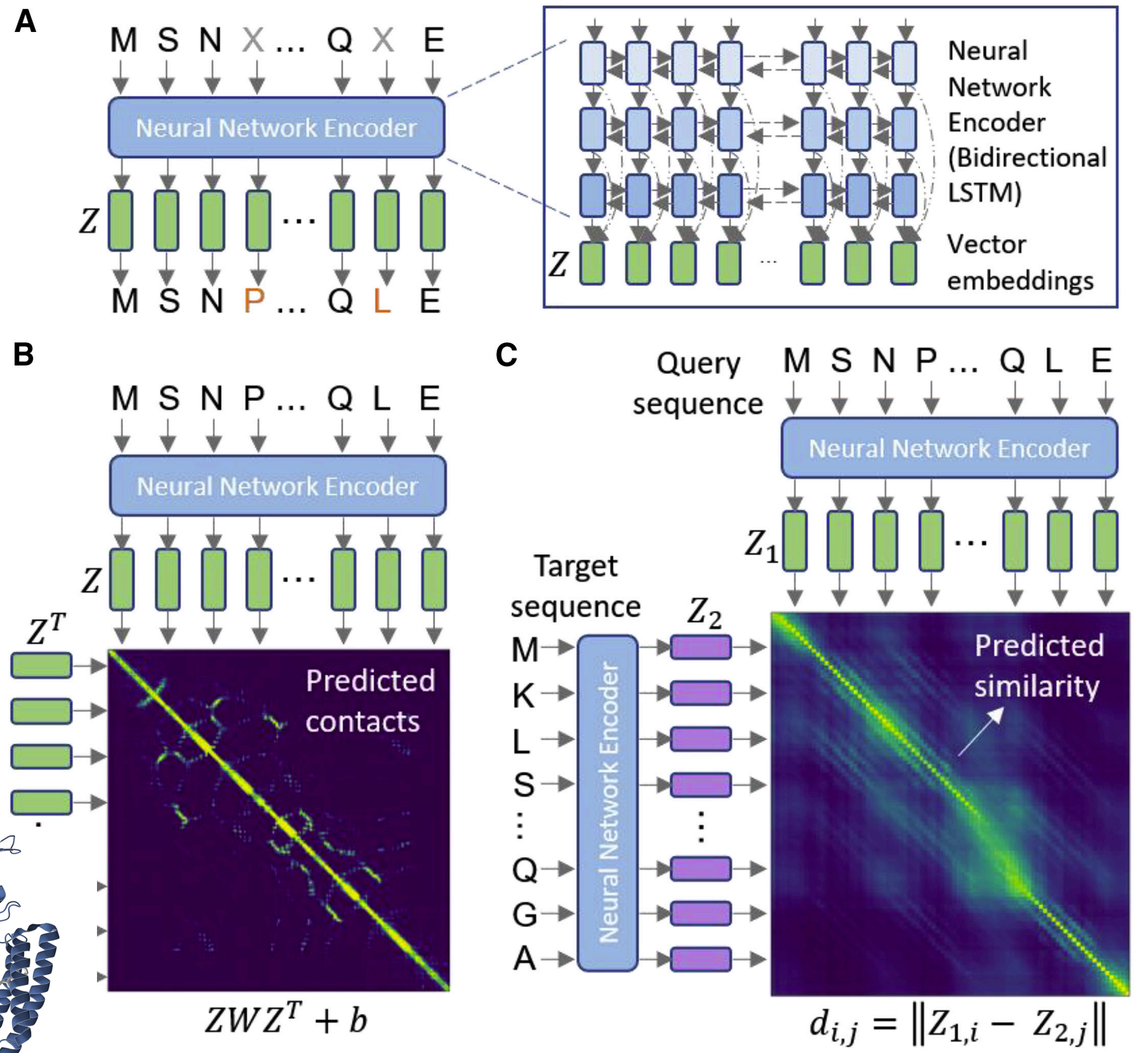
Bepler *et al. Cell Systems* 2021

Can use structure as a pretext task



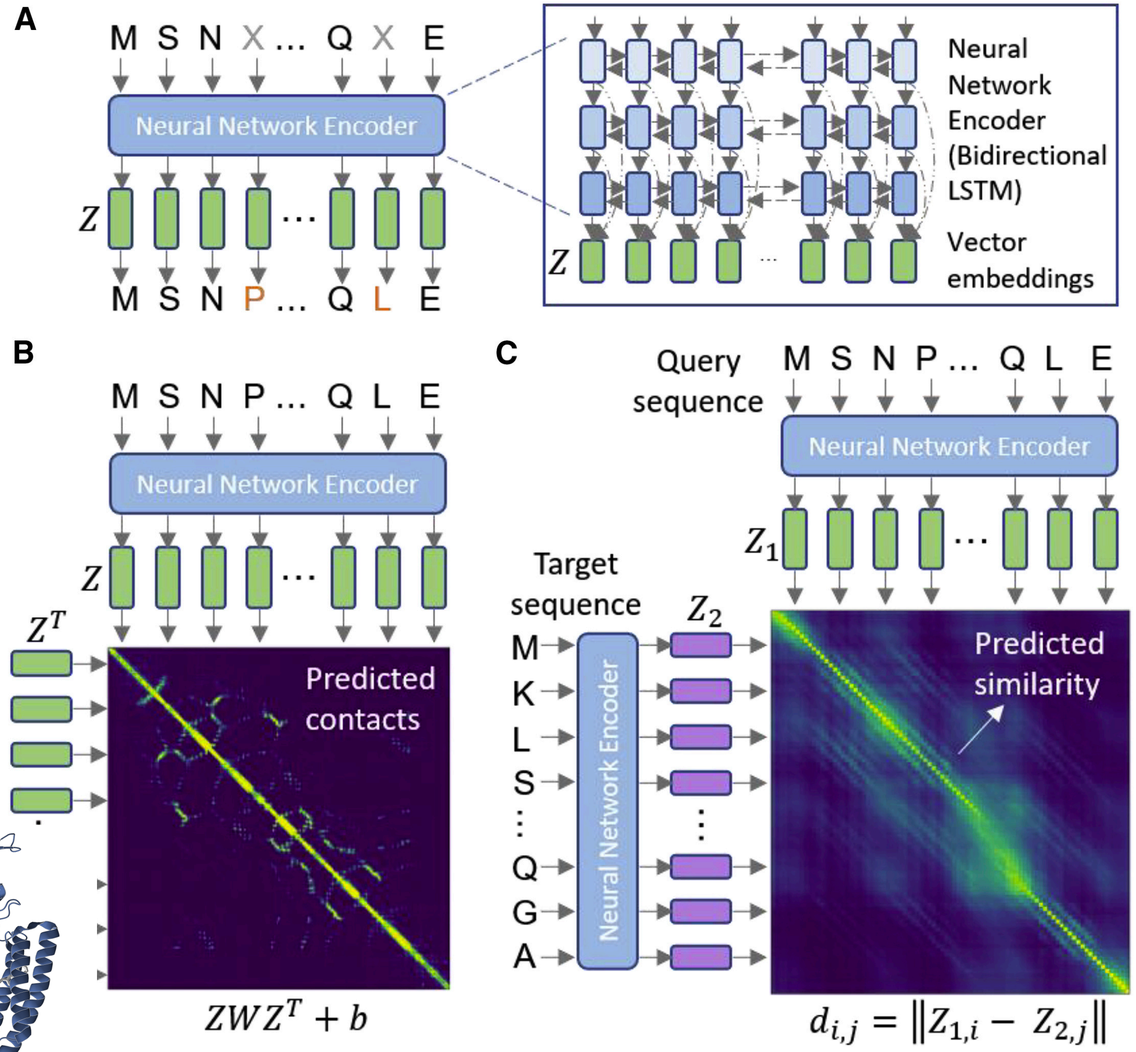
Bepler *et al. Cell Systems* 2021

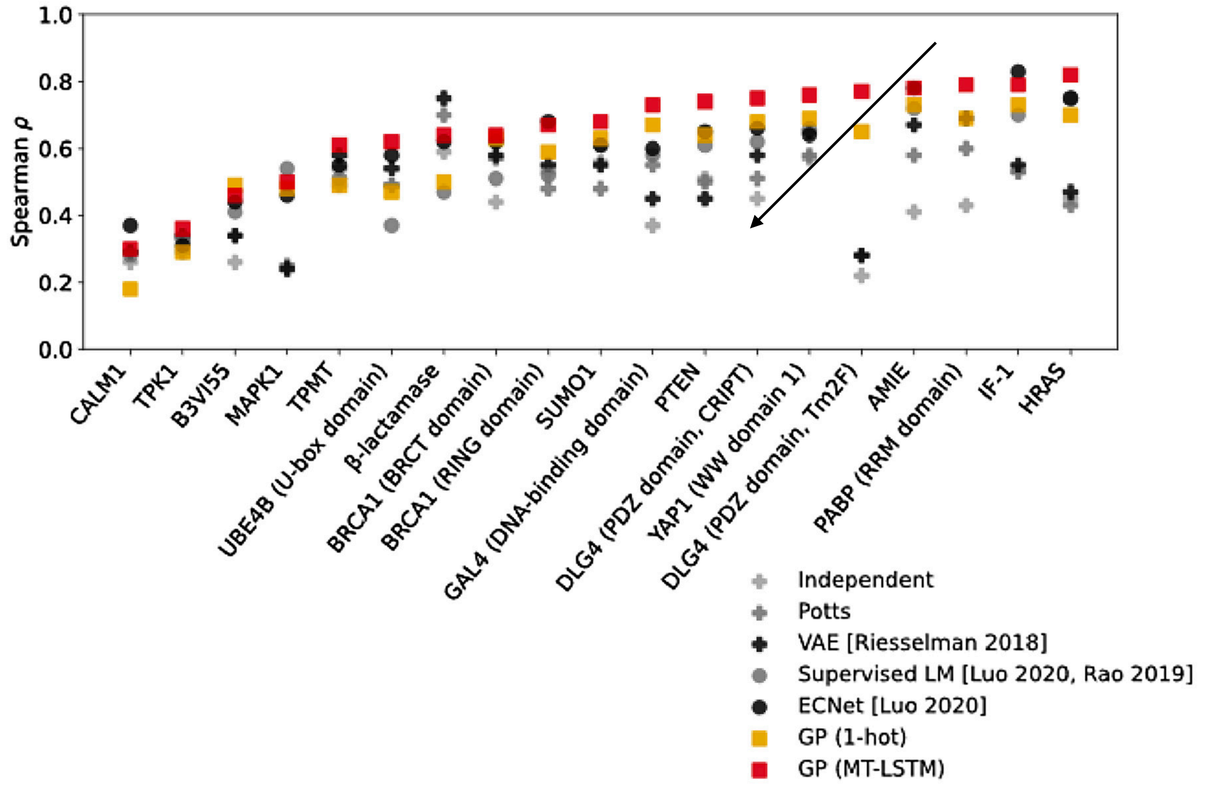
Can use structure as a pretext task



Bepler *et al. Cell Systems* 2021

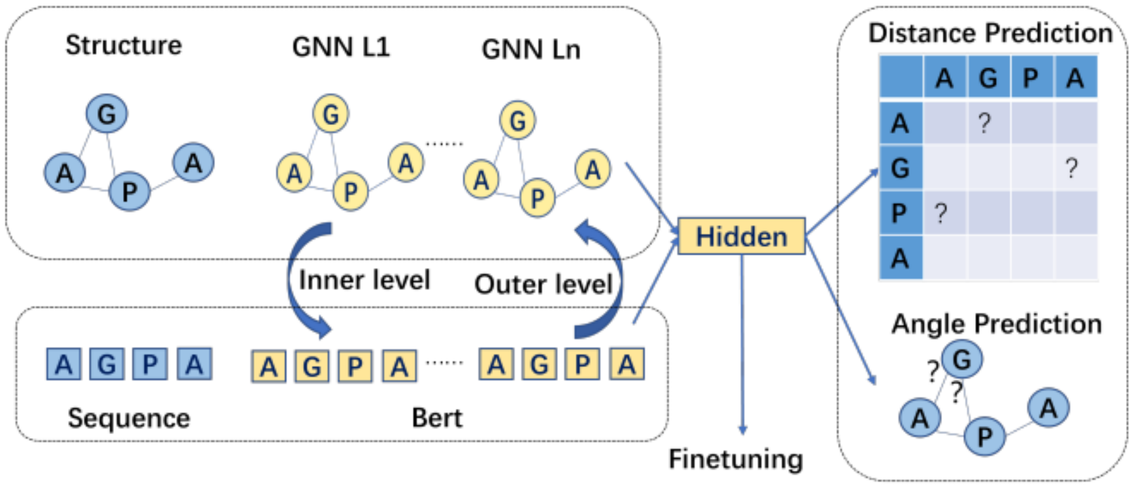
Can use structure as a pretext task





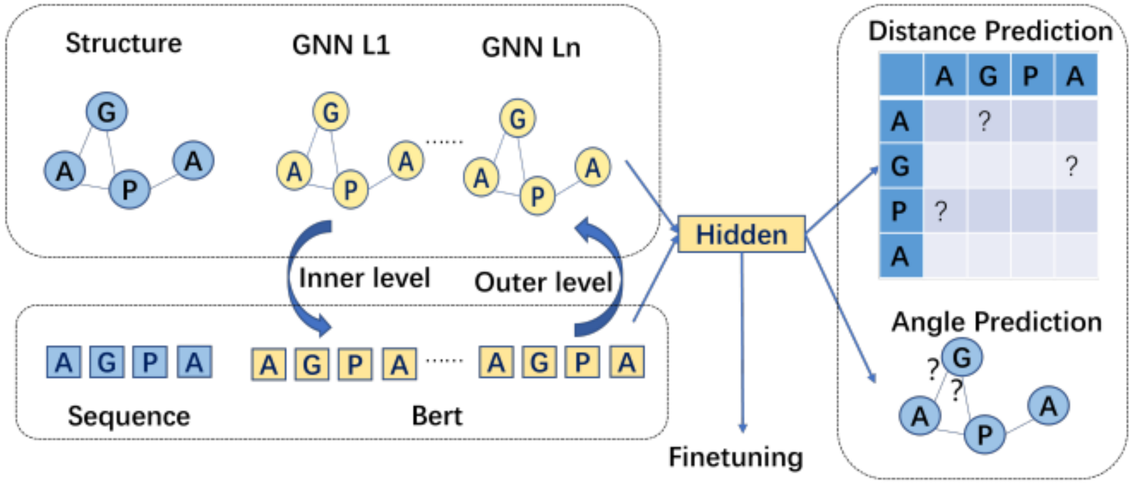
Bepler *et al. Cell Systems* 2021

Can use structure as a pretext task

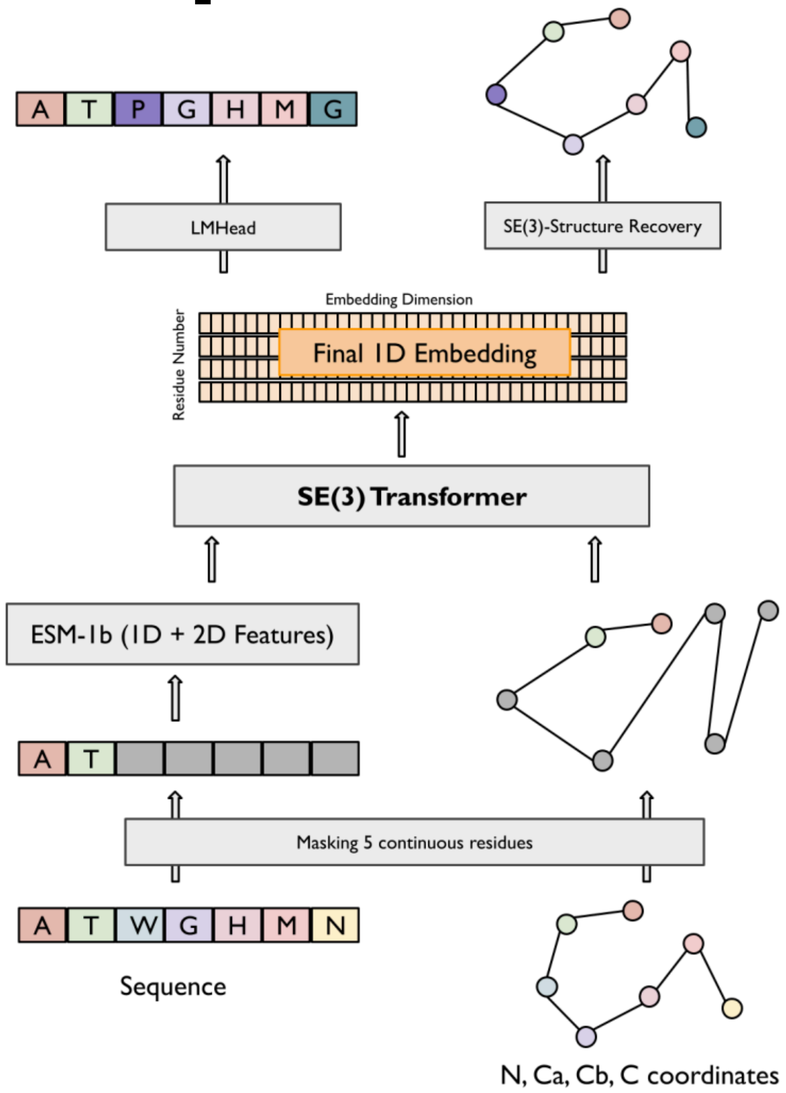


Chen *et al.* 2022

Can use structure as a pretext task



Chen *et al.* 2022



Mansoor *et al.* 2021

Conditioning on structure improves sequence reconstruction

Conditioning on structure improves sequence reconstruction

Structure-conditioned masked language model

Conditioning on structure improves sequence reconstruction

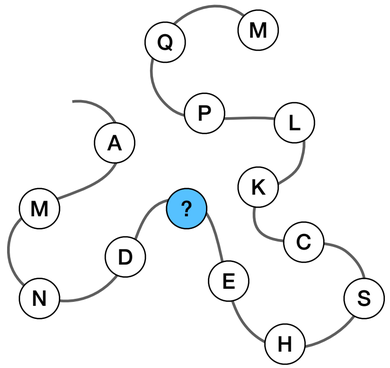
Structure-conditioned masked language model

Goal: Predict P(s_{masked} |structure, $s_{unmasked}$)

Conditioning on structure improves sequence reconstruction

Structure-conditioned masked language model

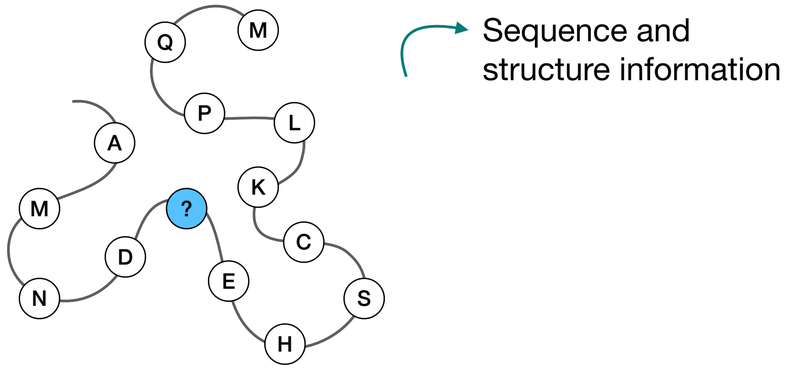
Goal: Predict P(s_{masked} |structure, $s_{unmasked}$)



Conditioning on structure improves sequence reconstruction

Structure-conditioned masked language model

Goal: Predict P(s_{masked} |structure, $s_{unmasked}$)



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Structure-conditioned masked language model

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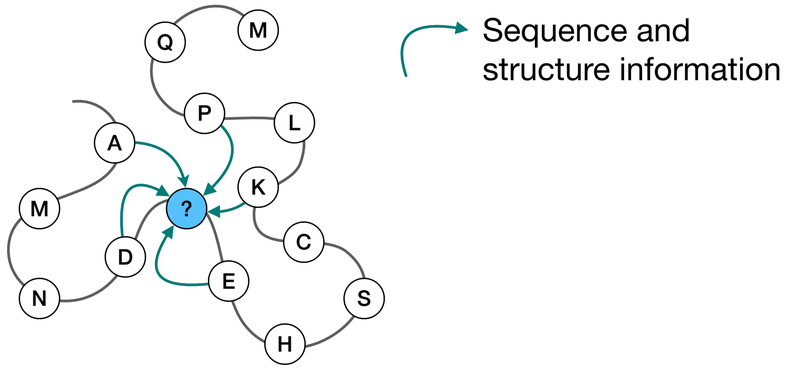

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Structure-conditioned masked language model

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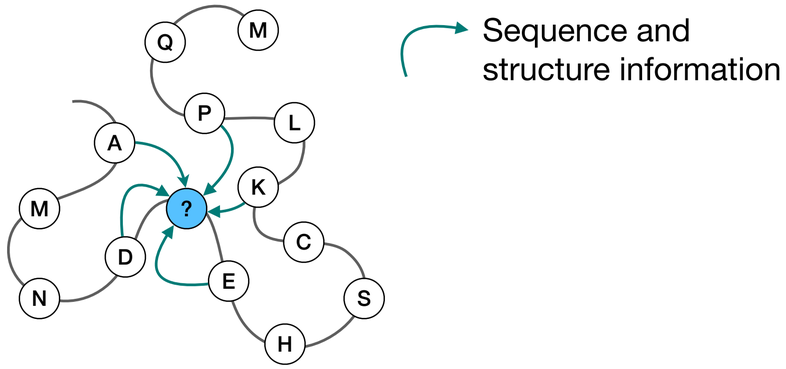
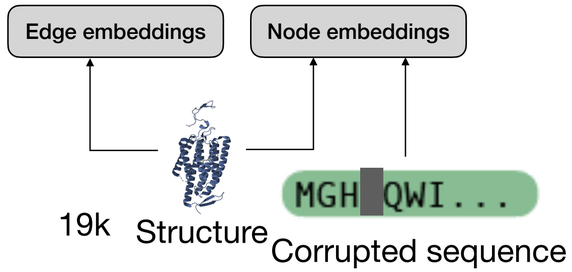


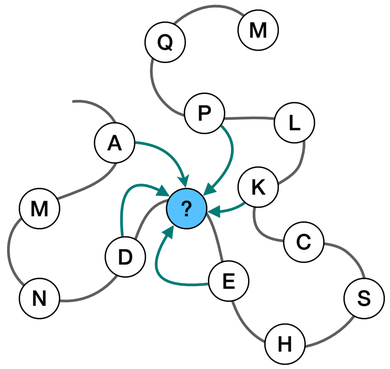
Sequence and
structure information



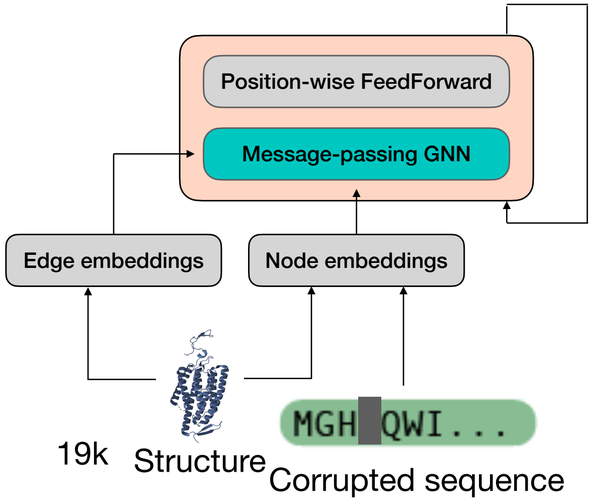
Conditioning on structure improves sequence reconstruction

Structure-conditioned masked language model

Goal: Predict P(s_{masked} |structure, $s_{unmasked}$)



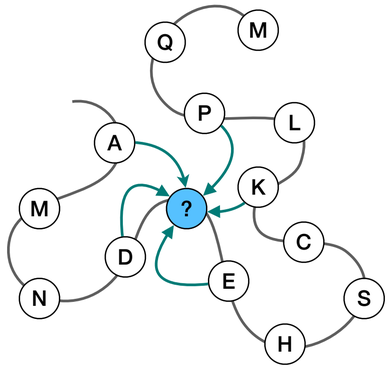
Sequence and structure information



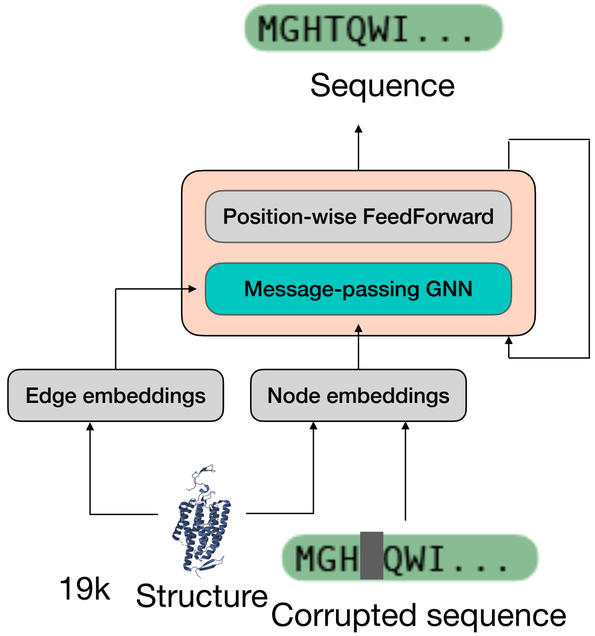
Conditioning on structure improves sequence reconstruction

Structure-conditioned masked language model

Goal: Predict P(s_{masked} |structure, $s_{unmasked}$)



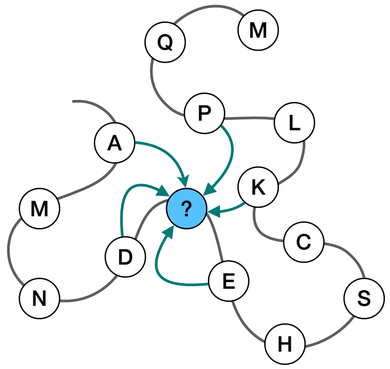
Sequence and structure information



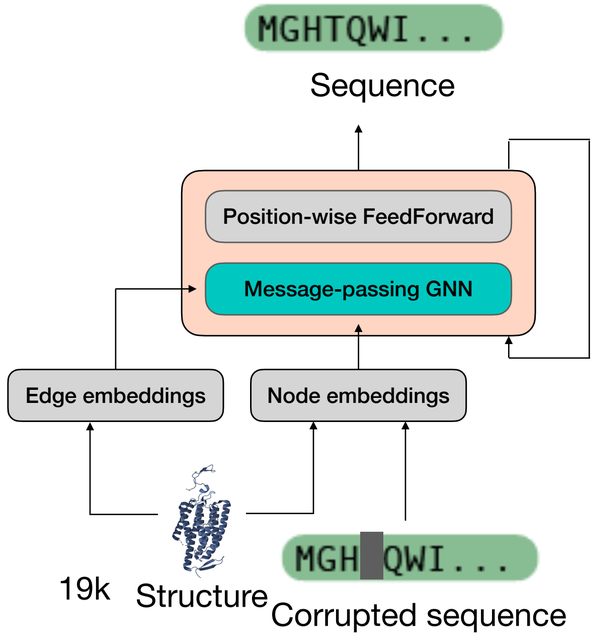
Conditioning on structure improves sequence reconstruction

Structure-conditioned masked language model

Goal: Predict P(s_{masked} |structure, $s_{unmasked}$)



Sequence and structure information

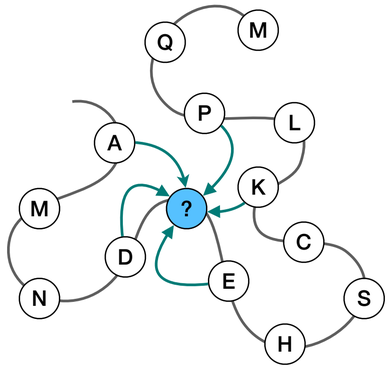


Model	Perplexity
GNN	4.96

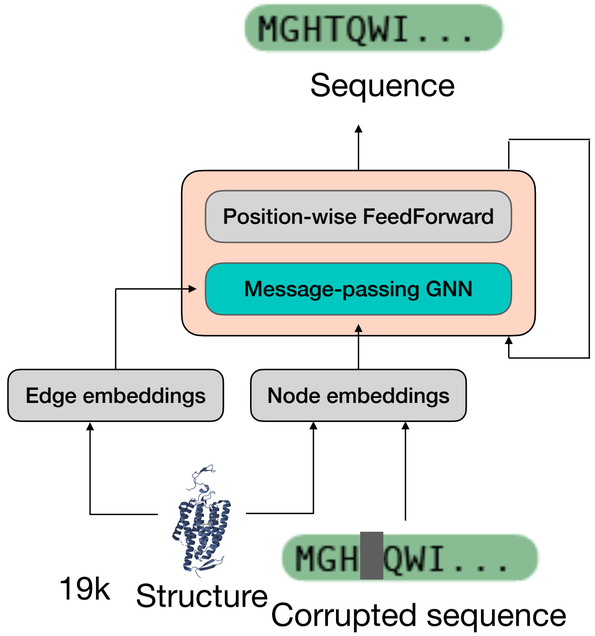
Conditioning on structure improves sequence reconstruction

Structure-conditioned masked language model

Goal: Predict P(s_{masked} |structure, $s_{unmasked}$)

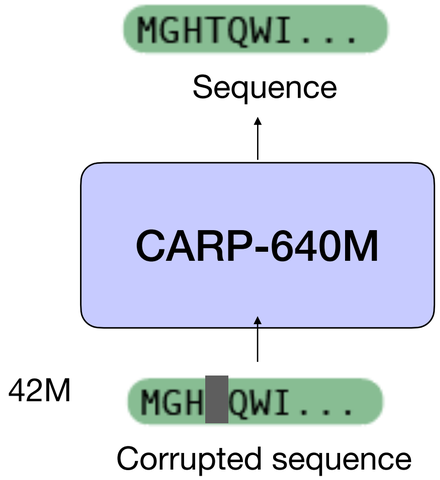


Sequence and structure information



Model	Perplexity
GNN	4.96

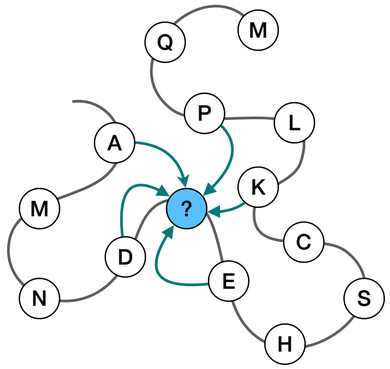
Masked language model



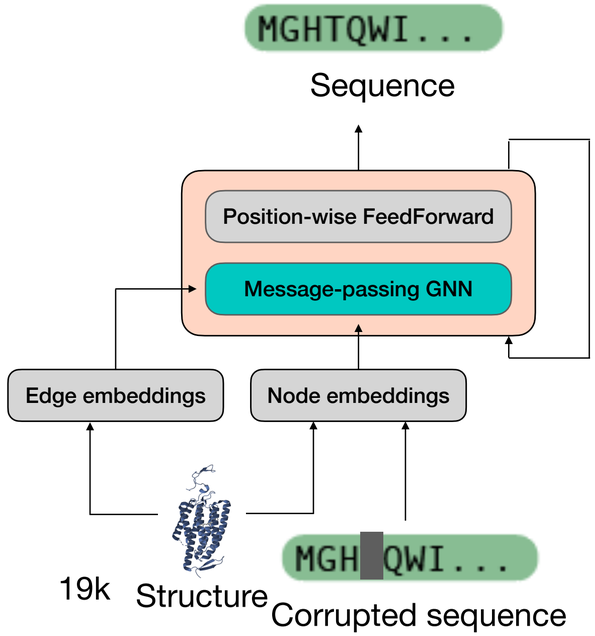
Conditioning on structure improves sequence reconstruction

Structure-conditioned masked language model

Goal: Predict P(s_{masked} |structure, $s_{unmasked}$)

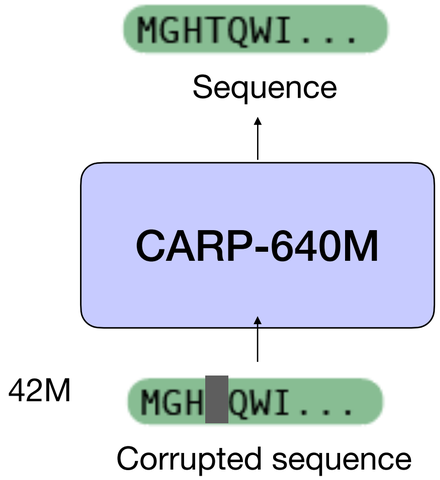


Sequence and structure information



Model	Perplexity
GNN	4.96
Sequence only	7.06

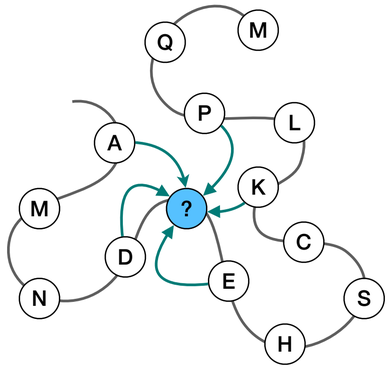
Masked language model



Conditioning on structure improves sequence reconstruction

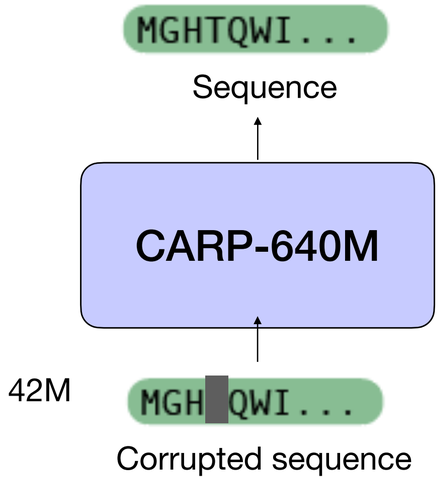
Structure-conditioned masked language model

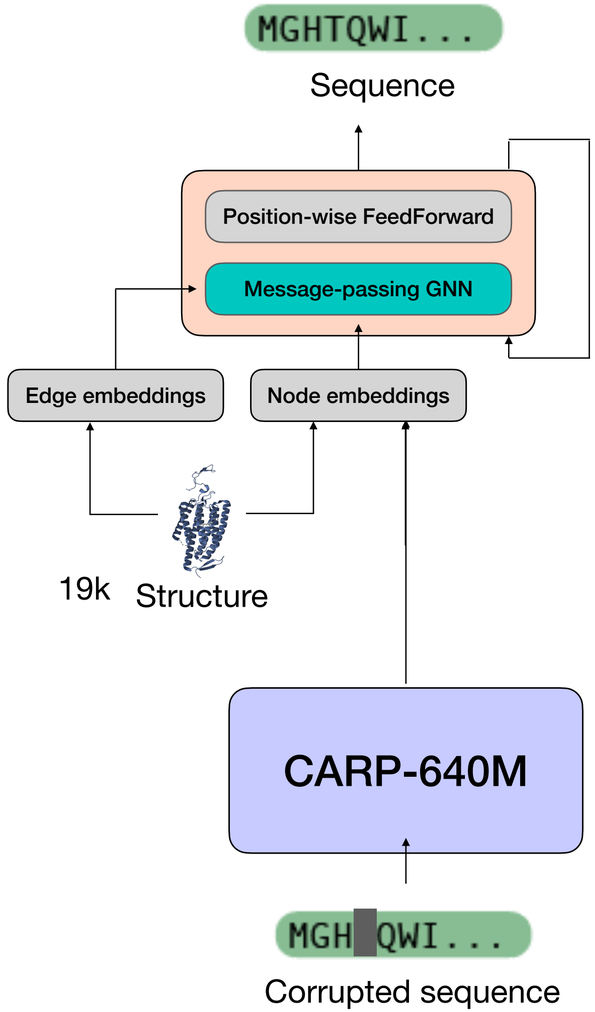
Goal: Predict P(s_{masked} |structure, $s_{unmasked}$)



Sequence and structure information

Masked language model



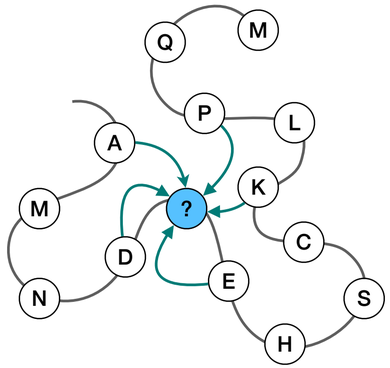


Model	Perplexity
GNN	4.96
Sequence only	7.06

Conditioning on structure improves sequence reconstruction

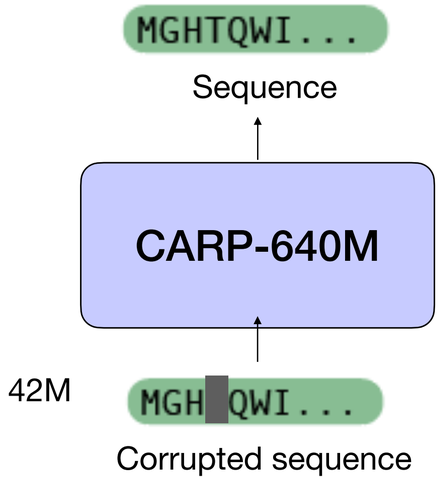
Structure-conditioned masked language model

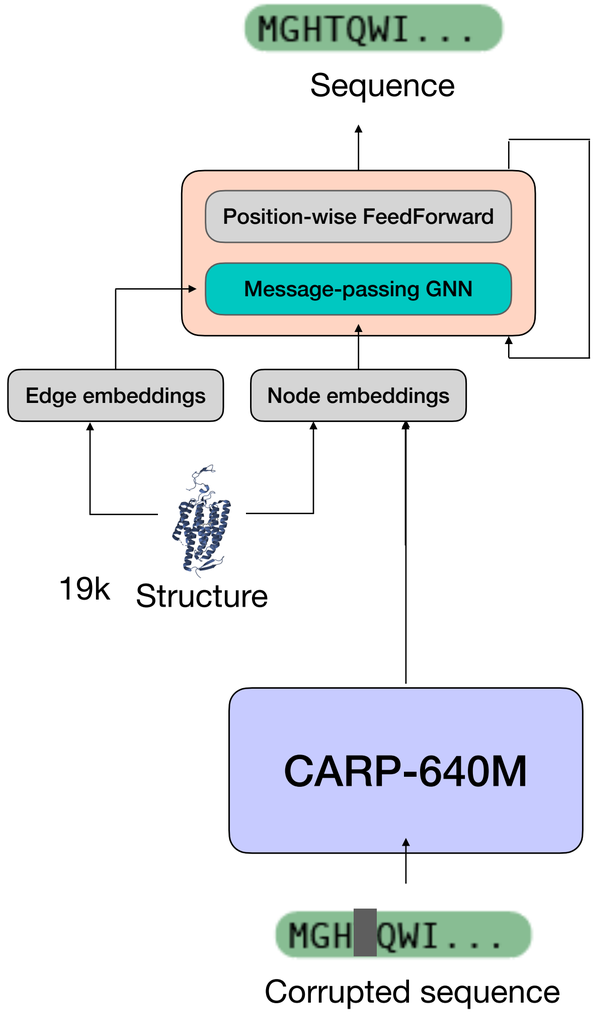
Goal: Predict P(s_{masked} |structure, $s_{unmasked}$)



Sequence and structure information

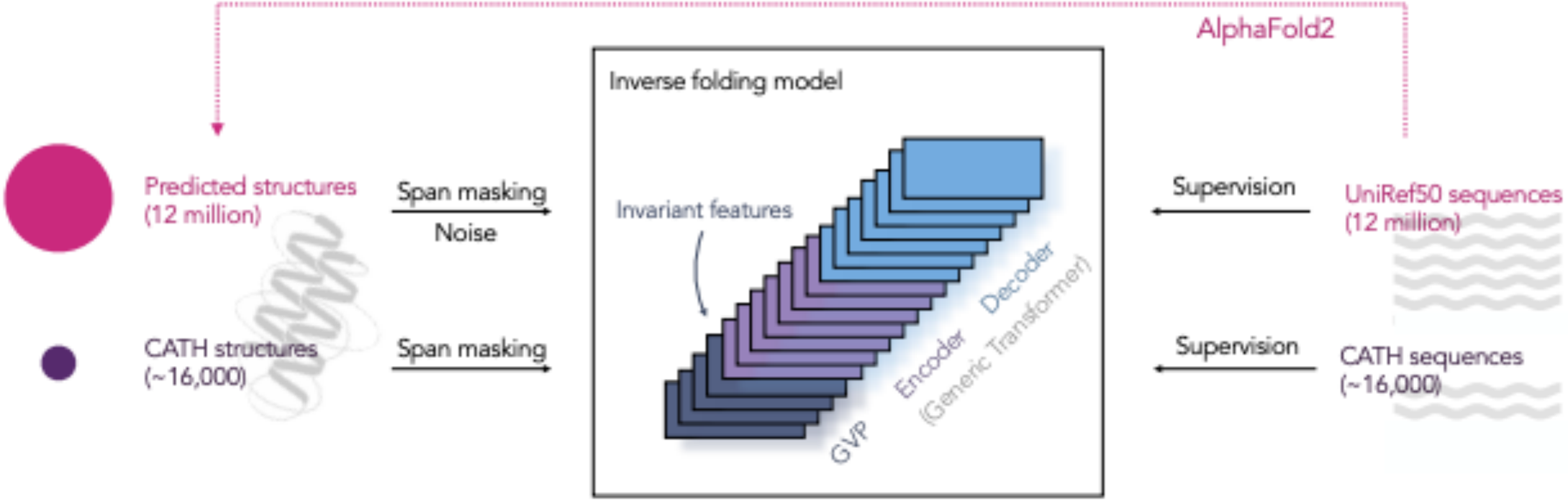
Masked language model





Model	Perplexity
GNN	4.96
Sequence only	7.06
Pretrained logits -> GNN	4.08

Adding predicted structures improves sequence reconstruction



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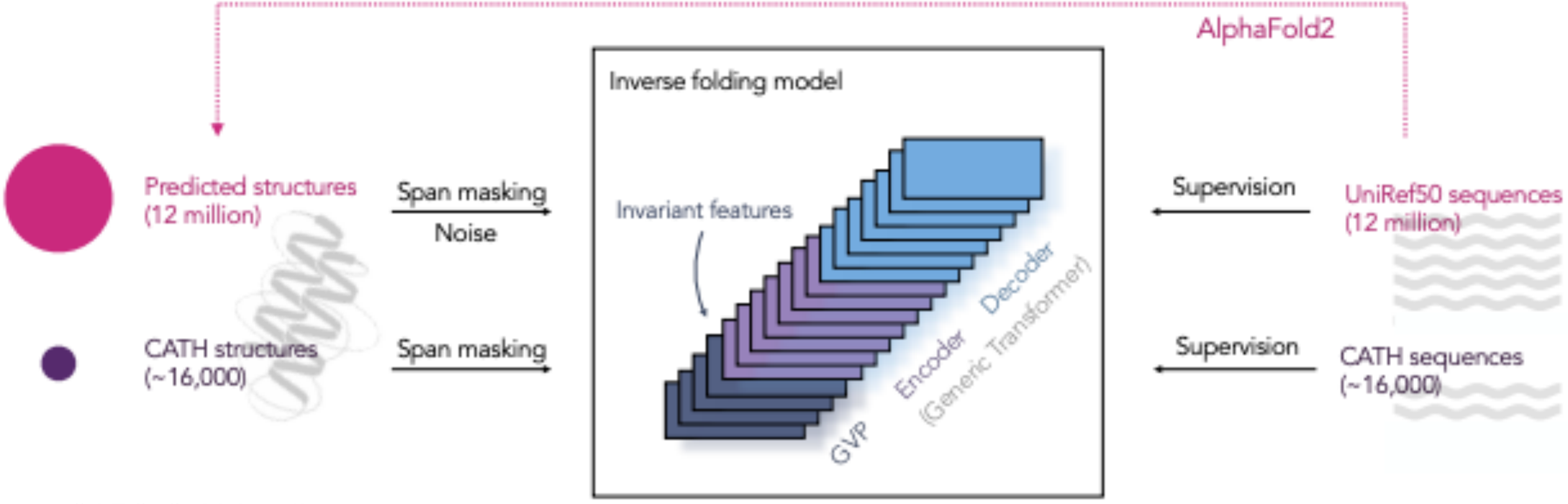
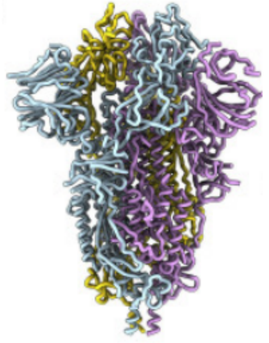
Adding predicted structures improves sequence reconstruction



SARS-CoV-2 spike receptor-binding domain



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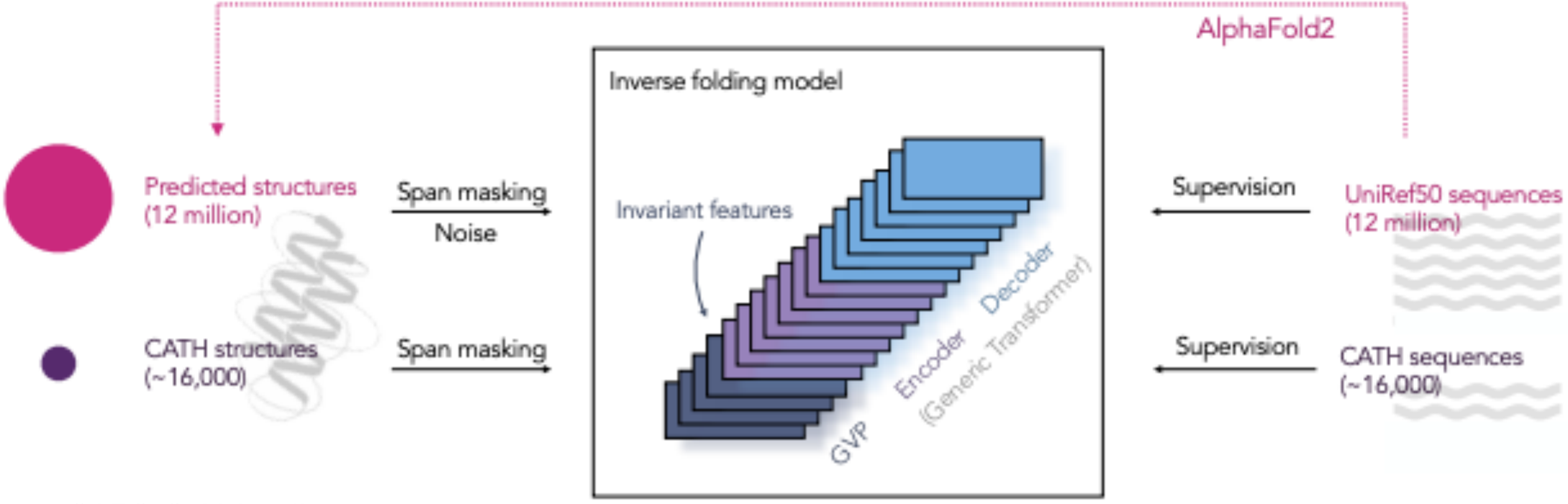
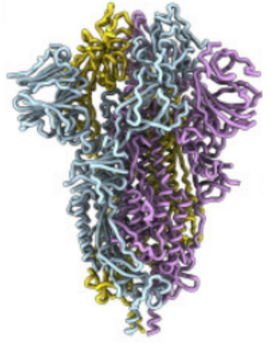
Adding predicted structures improves sequence reconstruction



SARS-CoV-2 spike receptor-binding domain



	Spearman correlation			
Model	No coords	No RBM coords	No ACE2 coords	All coords
ESM-1v	0.03			
ESM-1b	0.02			
ESM-MSA-1b (few-shot)	**0.51**			

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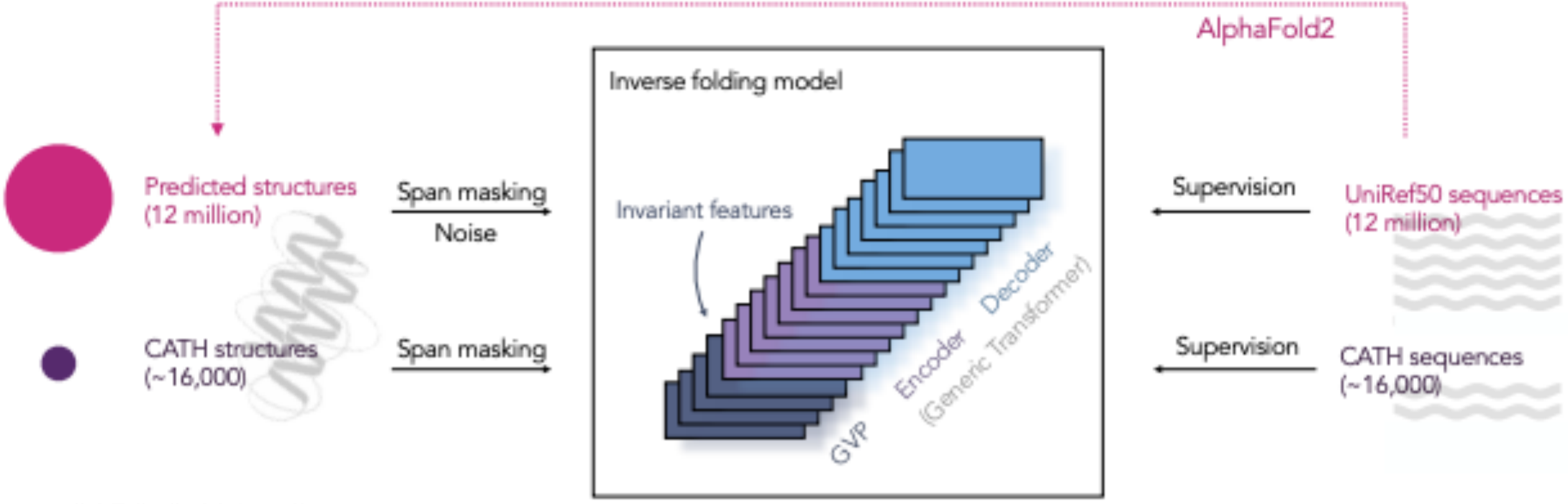
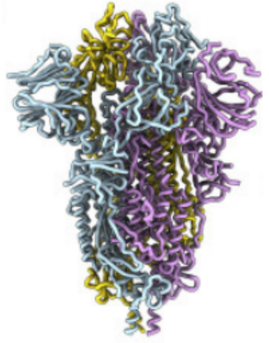
Adding predicted structures improves sequence reconstruction



SARS-CoV-2 spike receptor-binding domain



Model	Spearman correlation			
	No coords	No RBM coords	No ACE2 coords	All coords
ESM-1v	0.03			
ESM-1b	0.02			
ESM-MSA-1b (few-shot)	**0.51**			
GVP-GNN		-0.10	0.50	0.60
GVP-GNN-large+AF2		-0.05	0.52	**0.69**
GVP-Transformer+AF2		-0.06	**0.53**	0.64

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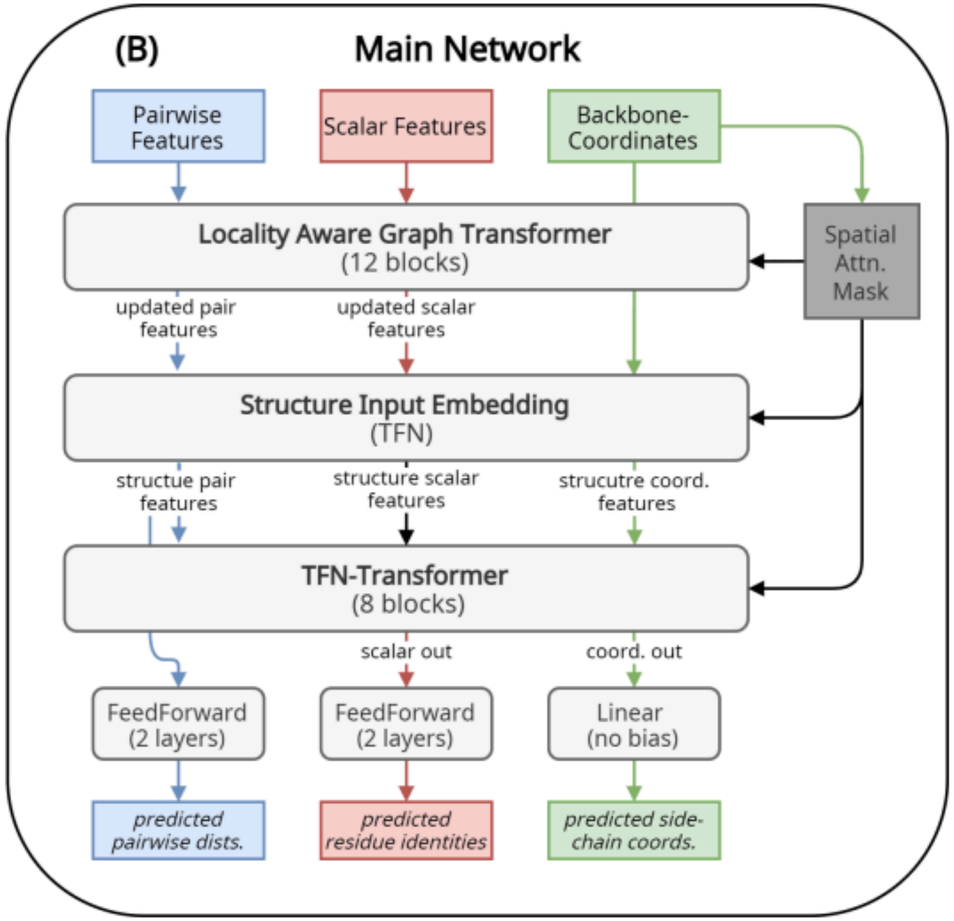
Adding predicted structures improves sequence reconstruction



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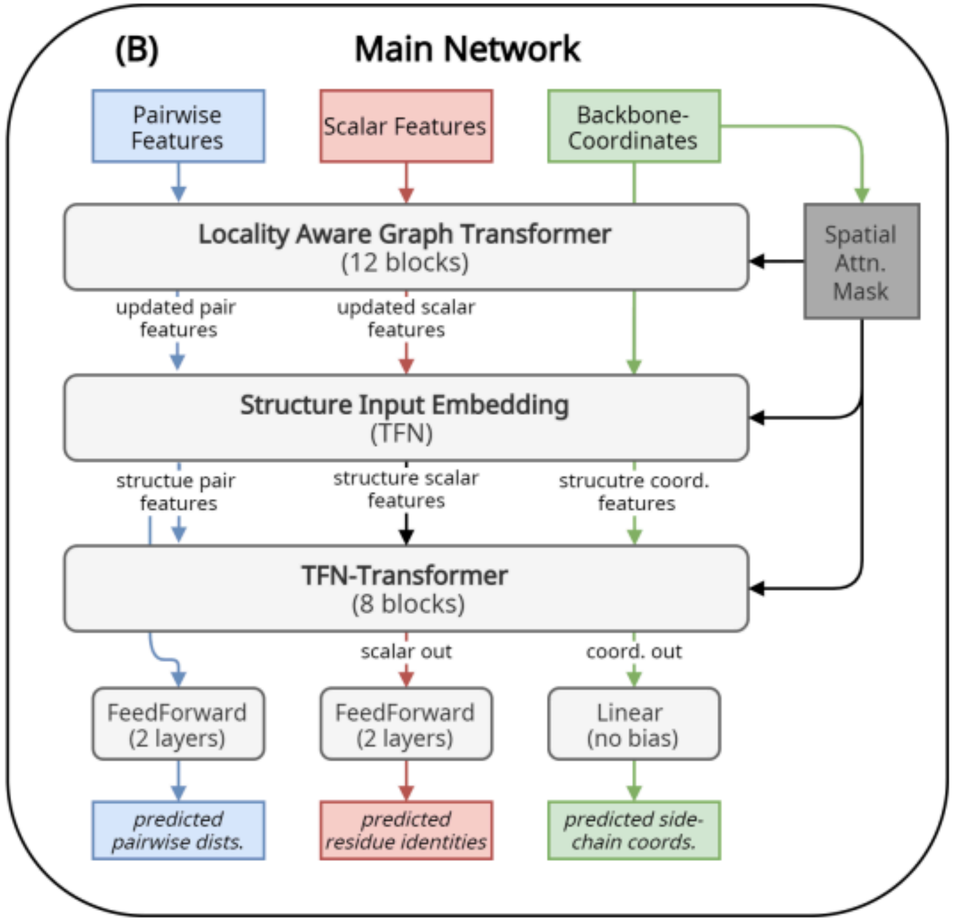
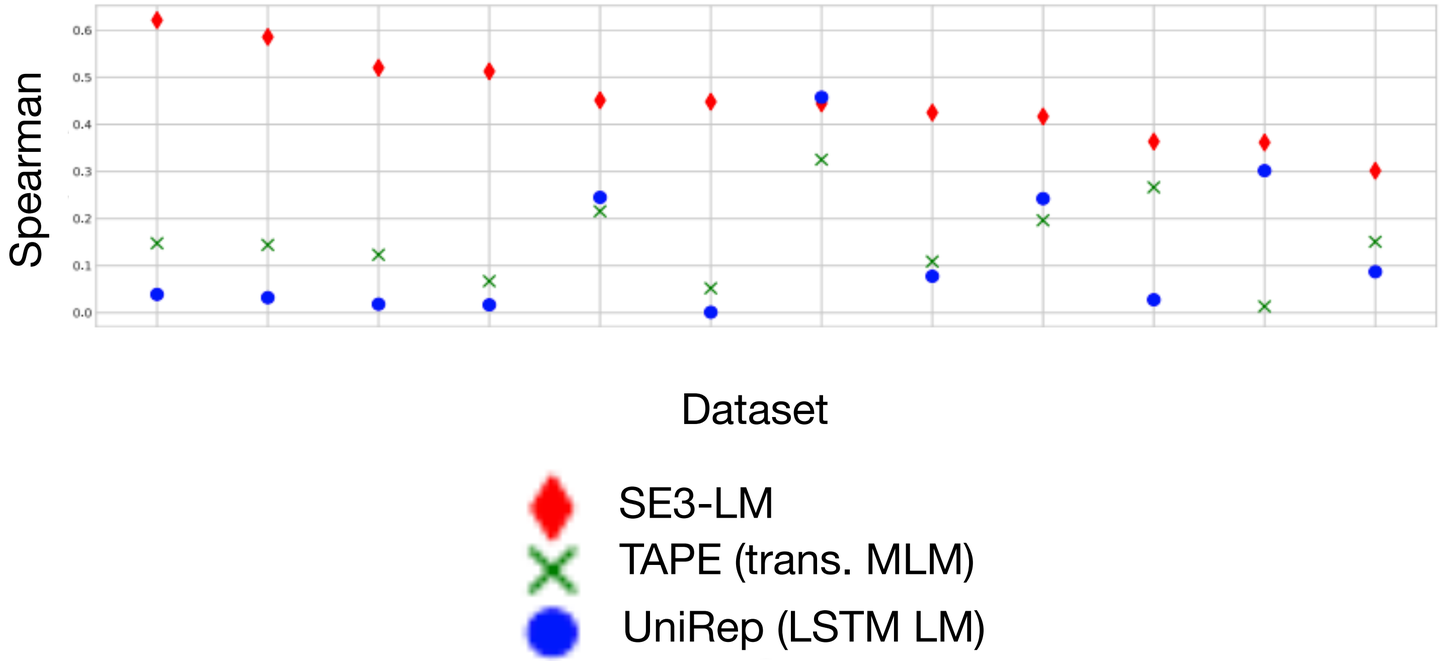
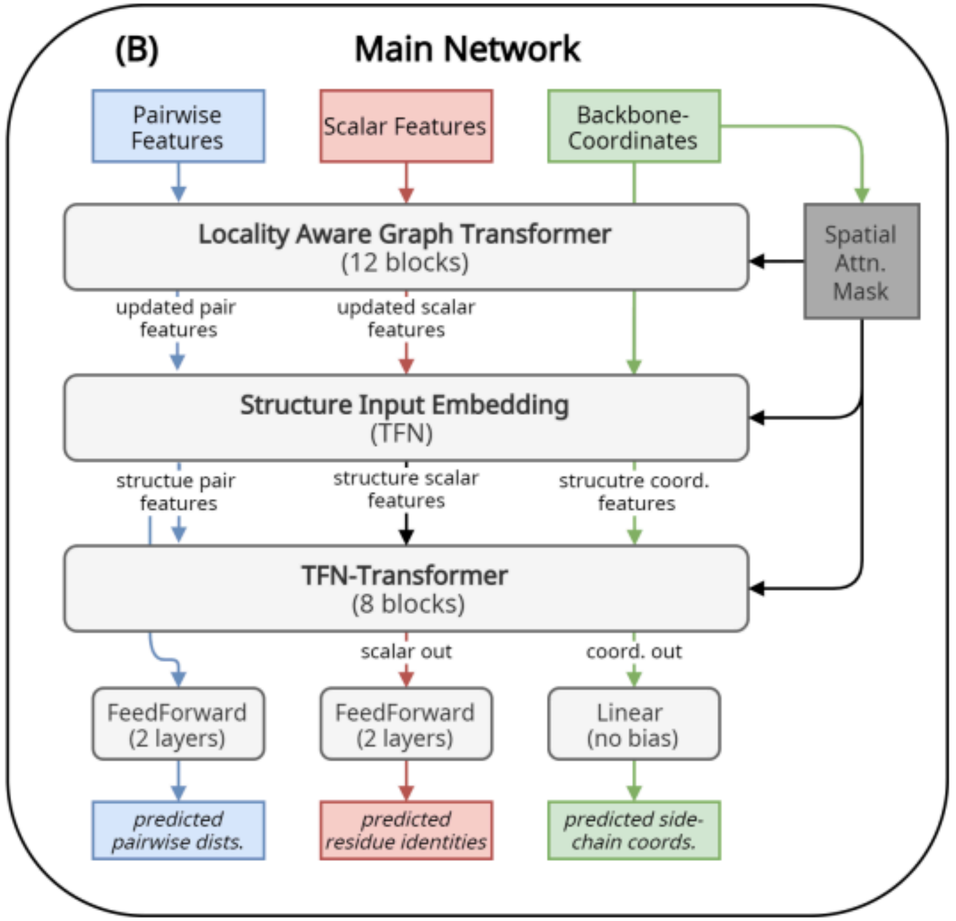
Adding predicted structures improves sequence reconstruction

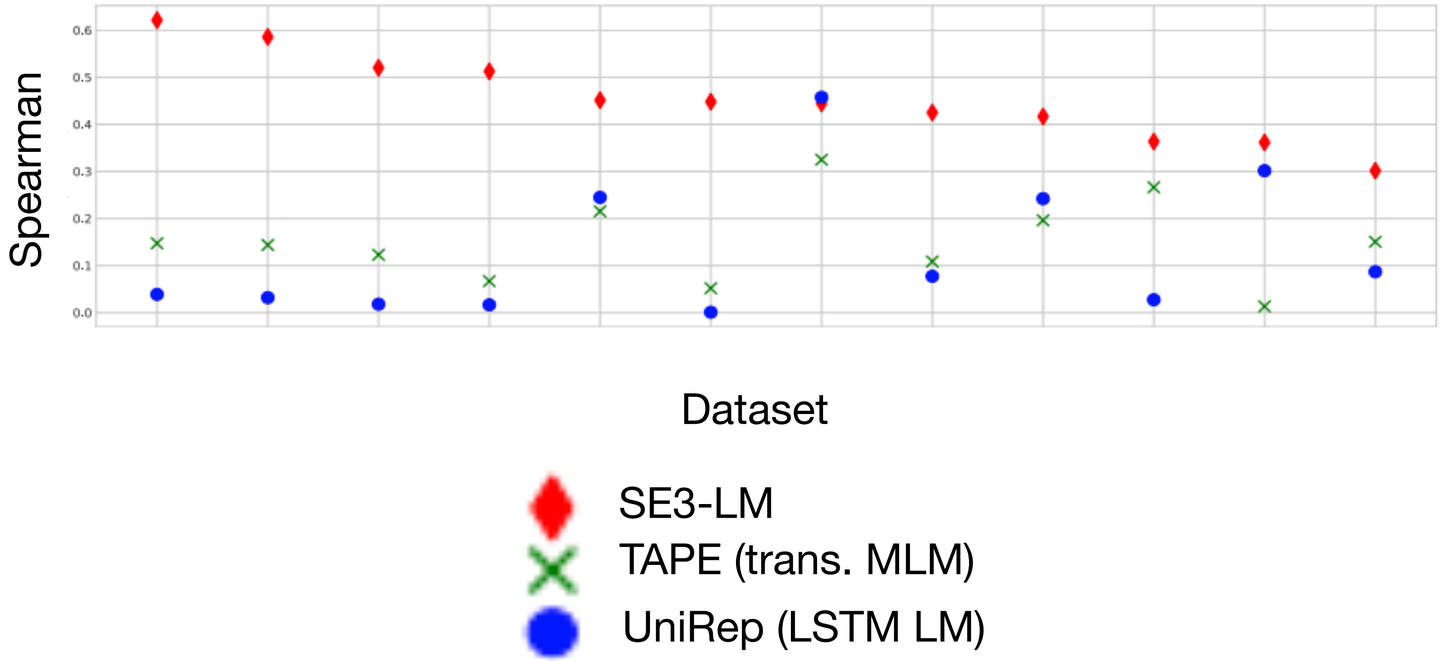




McPartlon *et al.* 2022

Adding predicted structures improves sequence reconstruction





This is all very new — evaluations are very inconsistent!

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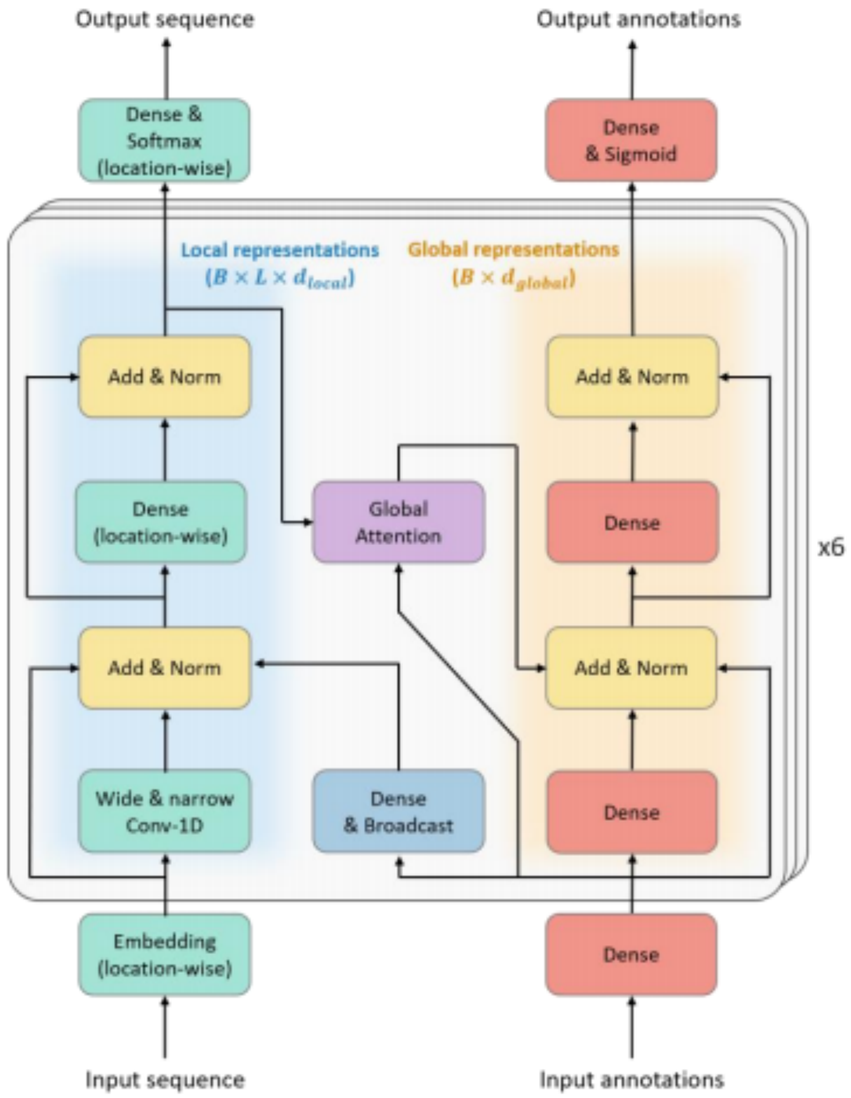
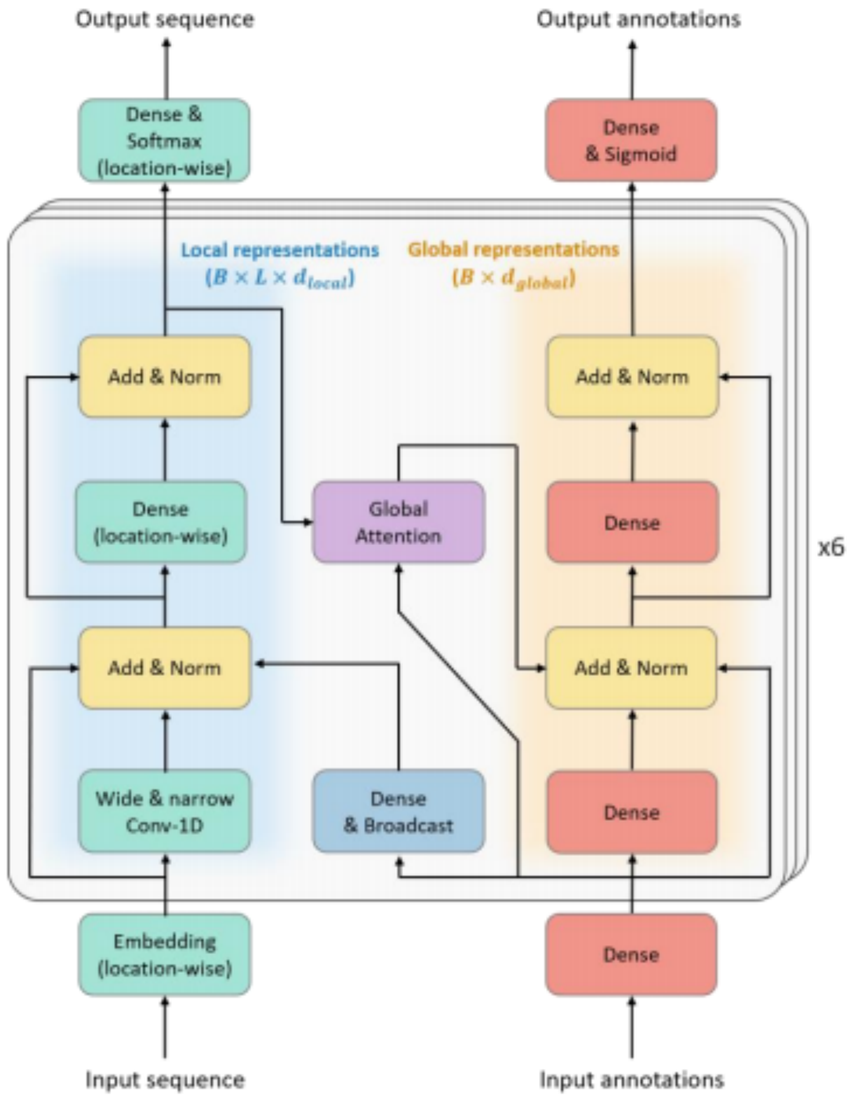
Combine sequence and annotations



Brandes *et al.* 2021

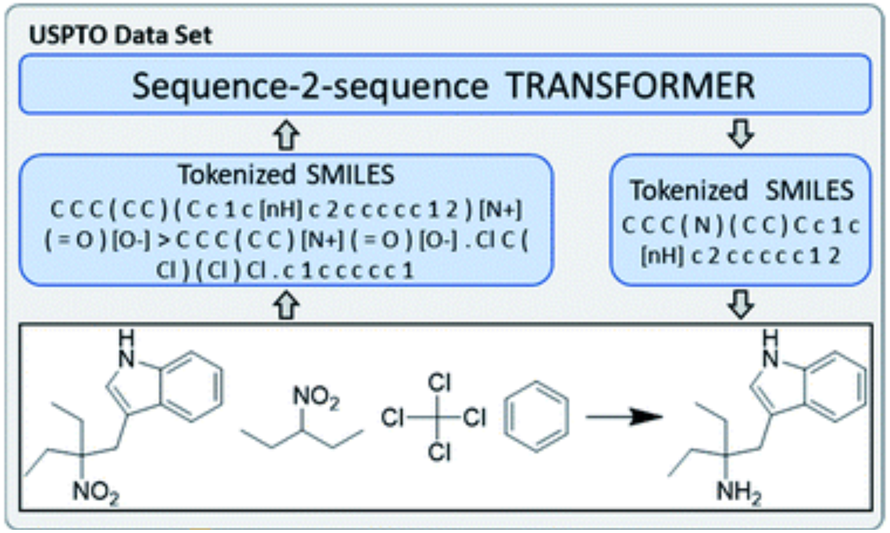
Combine sequence and annotations



	Method	Structure	Evolutionary	Engineering	
		Secondary structure	Remote homology	Fluorescence	Stability
Without Pretraining	TAPE Transformer	0.70	0.09	0.22	-0.06
	LSTM	0.71	0.12	0.21	0.28
	ProteinBERT	0.70	0.06	0.65	0.63
With Pretraining	TAPE Transformer	0.73	0.21	0.68	0.73
	LSTM	0.75	0.26	0.67	0.69
	UniRep mLSTM	0.73	0.23	0.67	0.73
	ProteinBERT	0.74	0.22	0.66	0.76

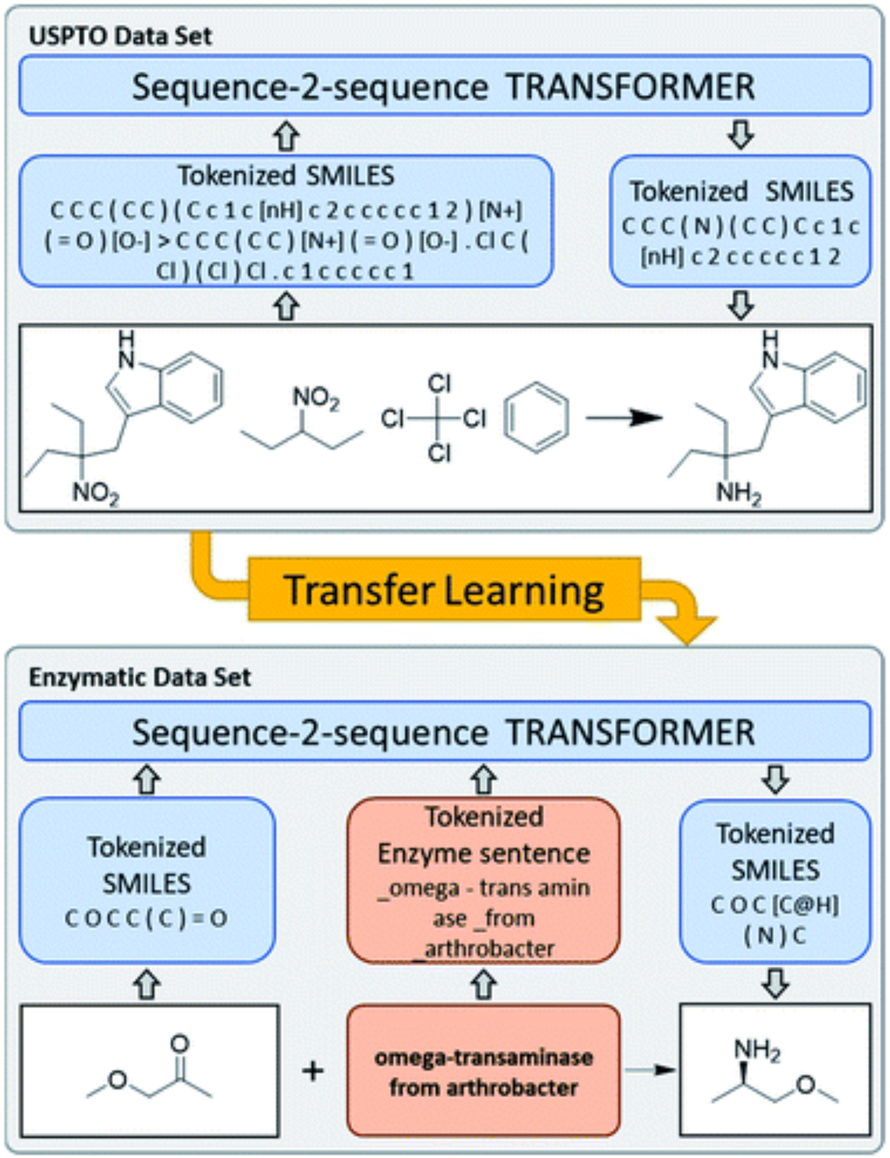
Brandes *et al.* 2021

Predict product from substrates and text



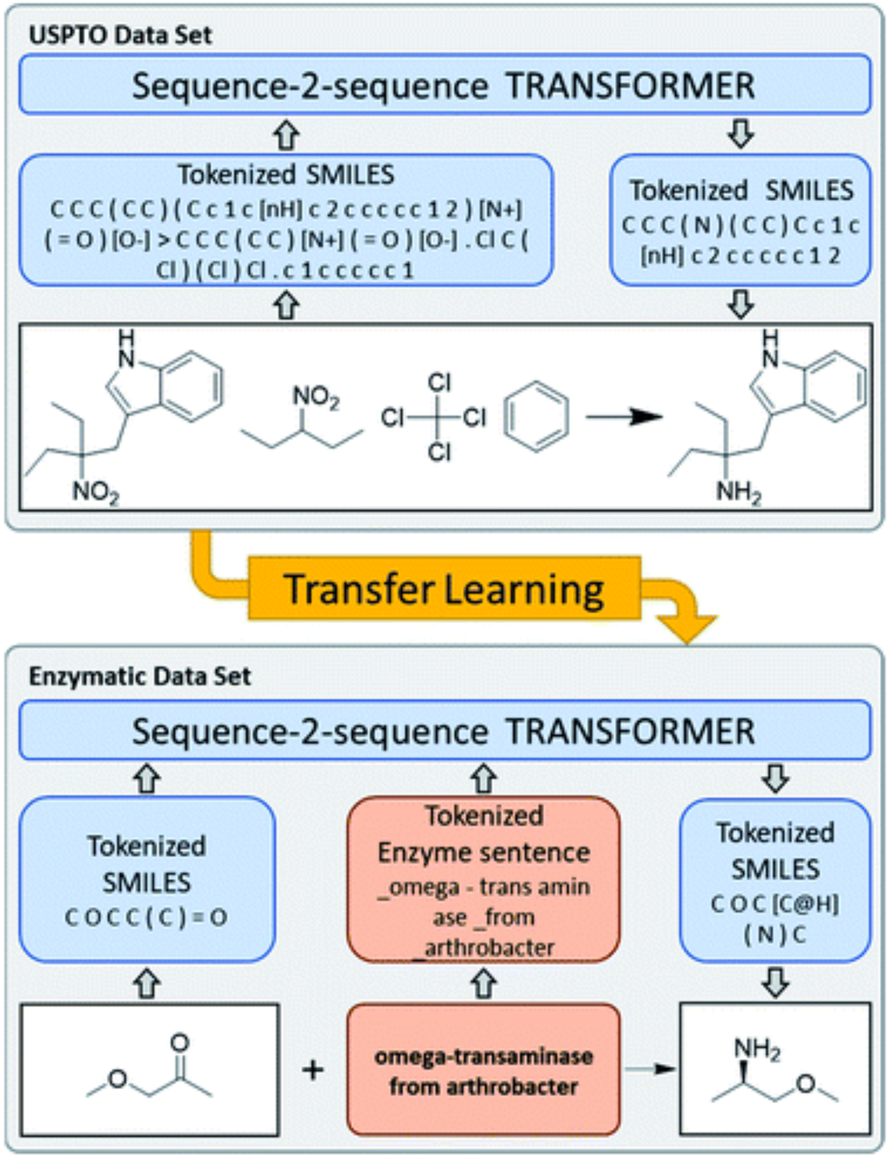
Kreutter *et al. Chem. Sci.* 2021

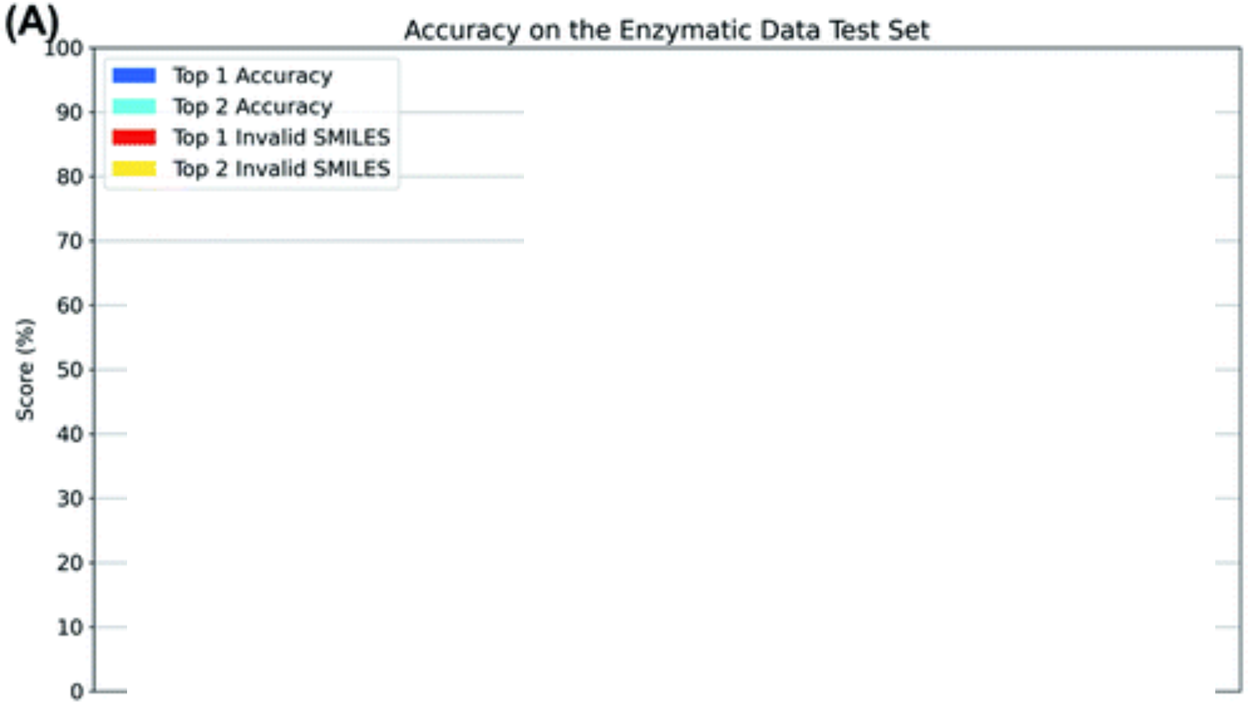
Predict product from substrates and text



Kreutter *et al. Chem. Sci.* 2021

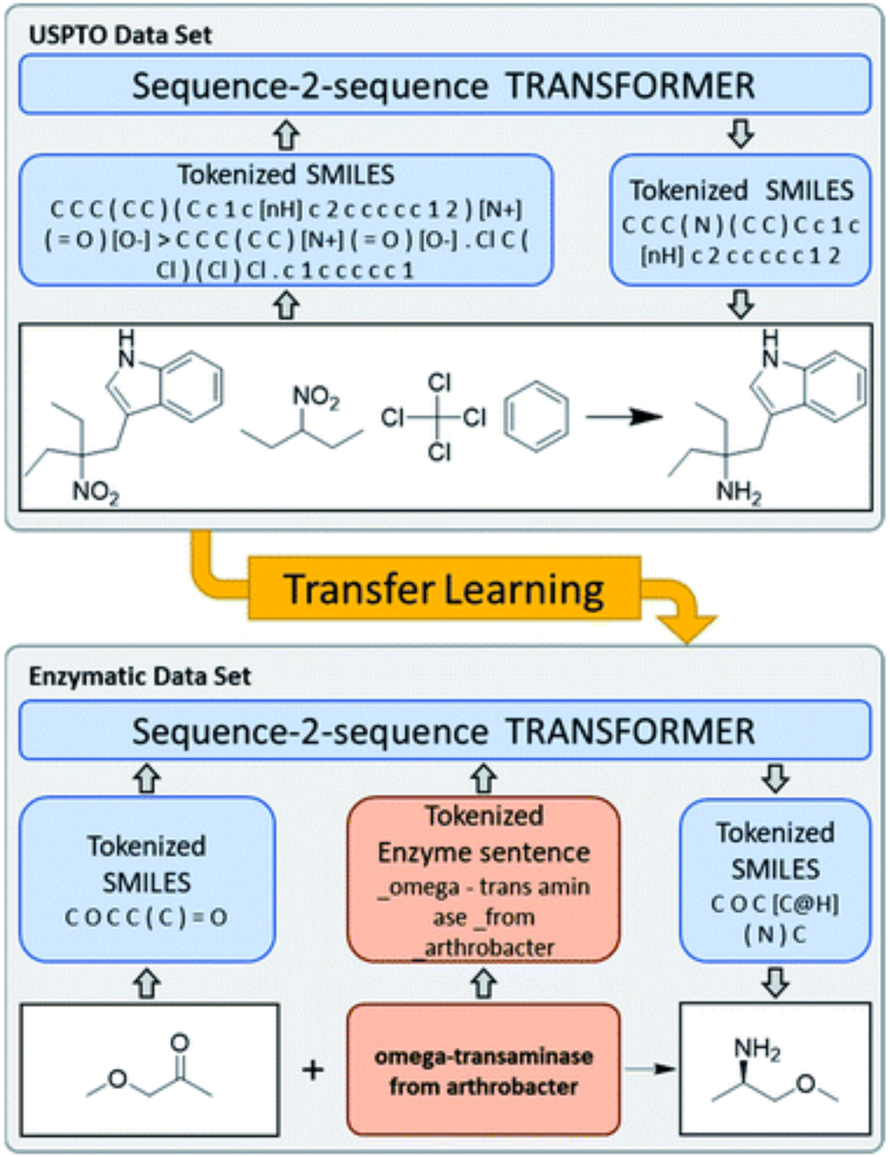
Predict product from substrates and text

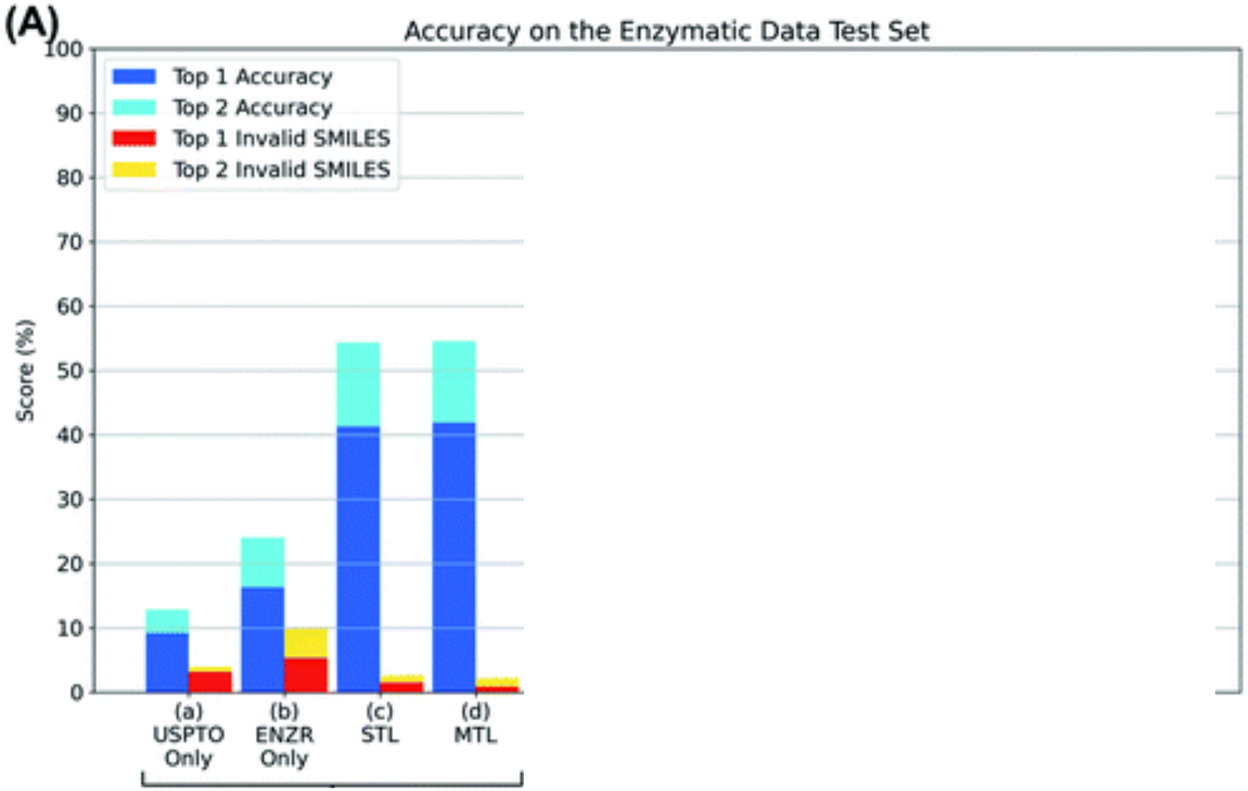




Kreutter *et al. Chem. Sci.* 2021

Predict product from substrates and text





no text

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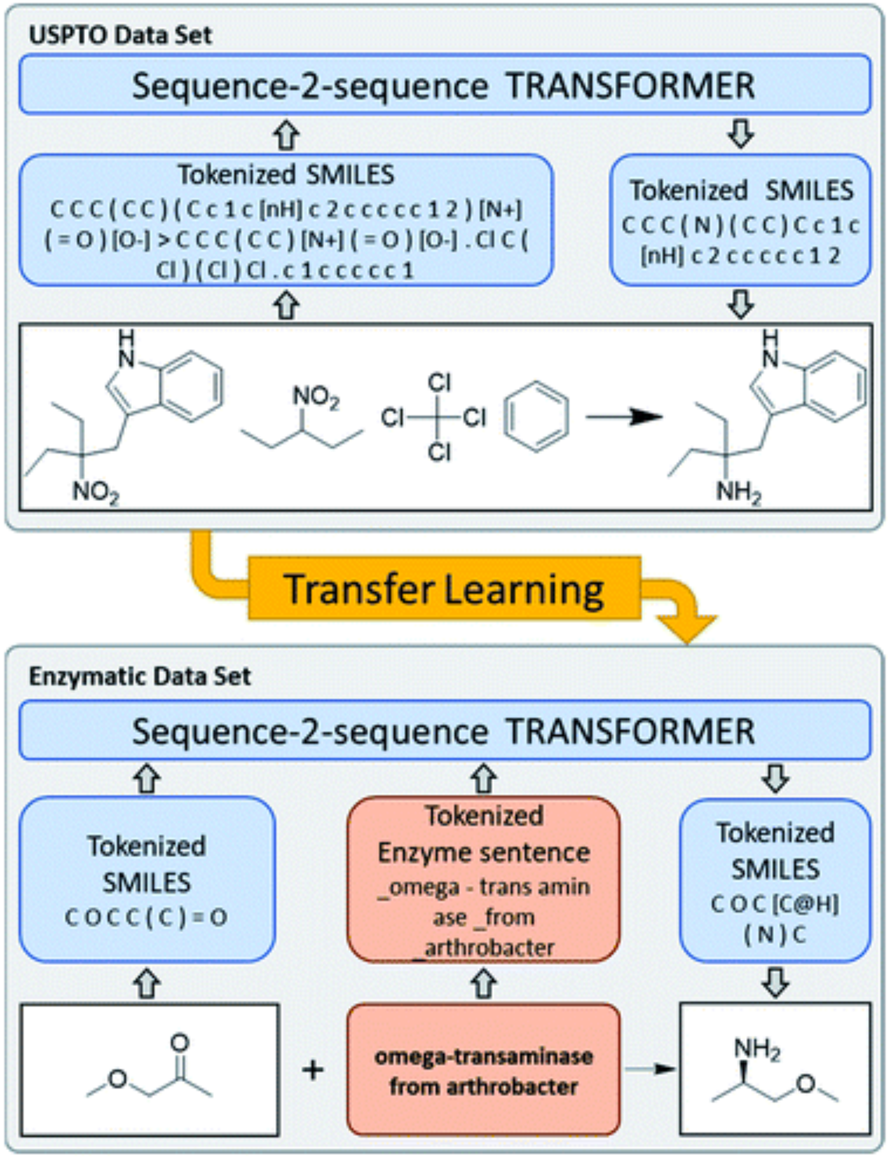
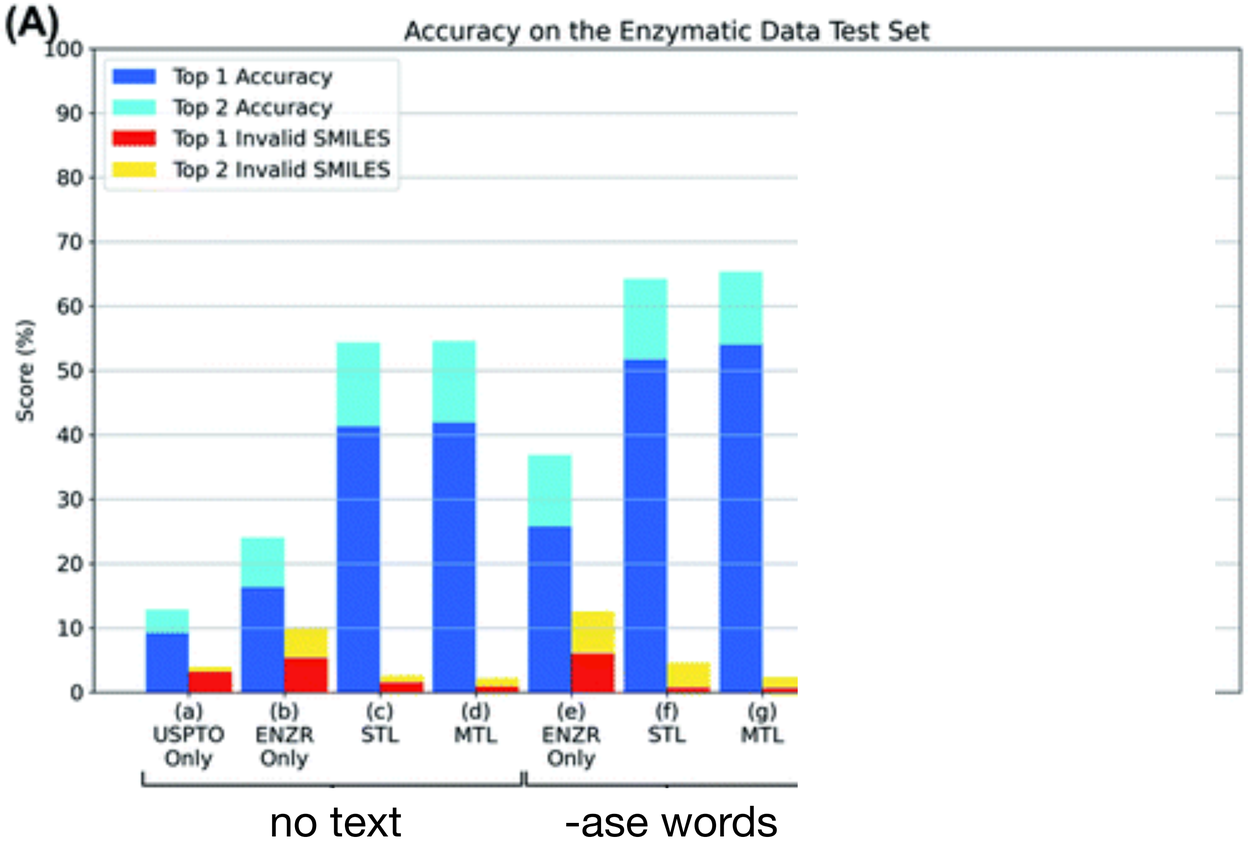
Predict product from substrates and text





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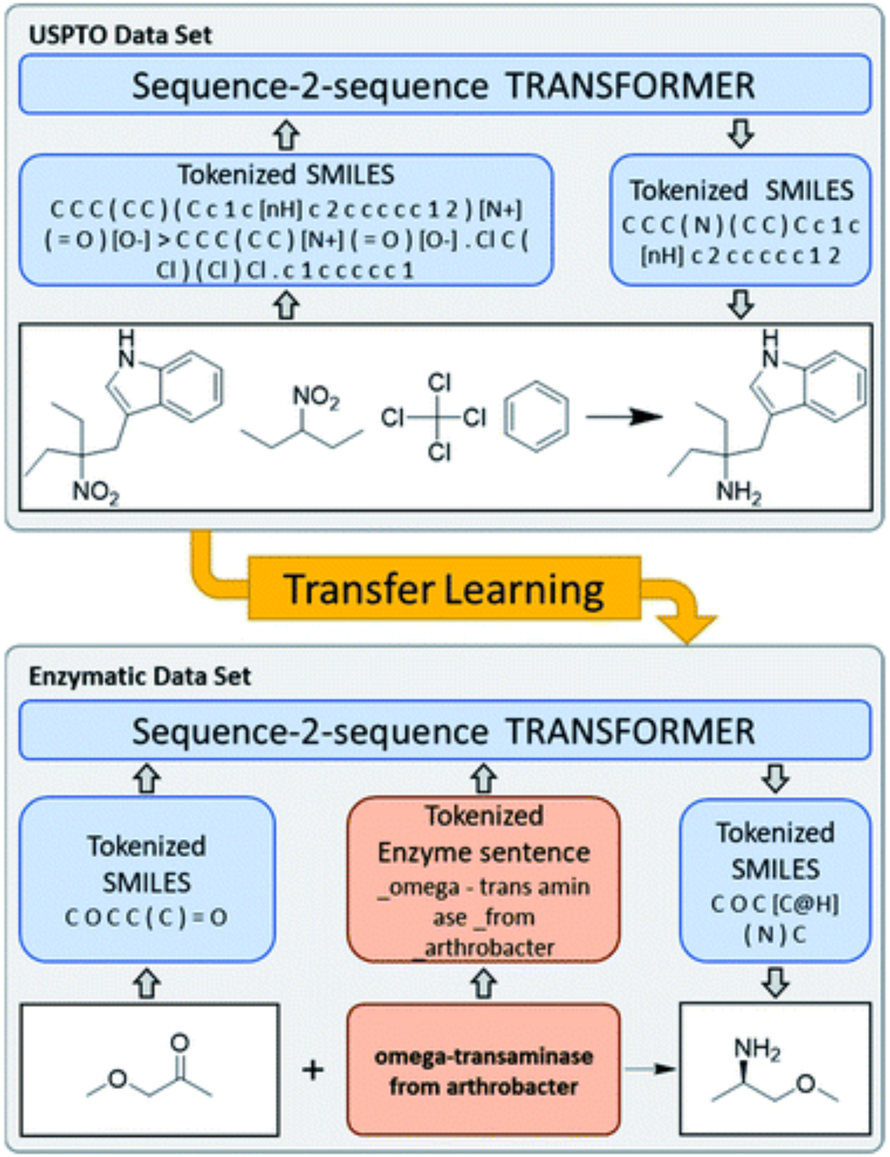
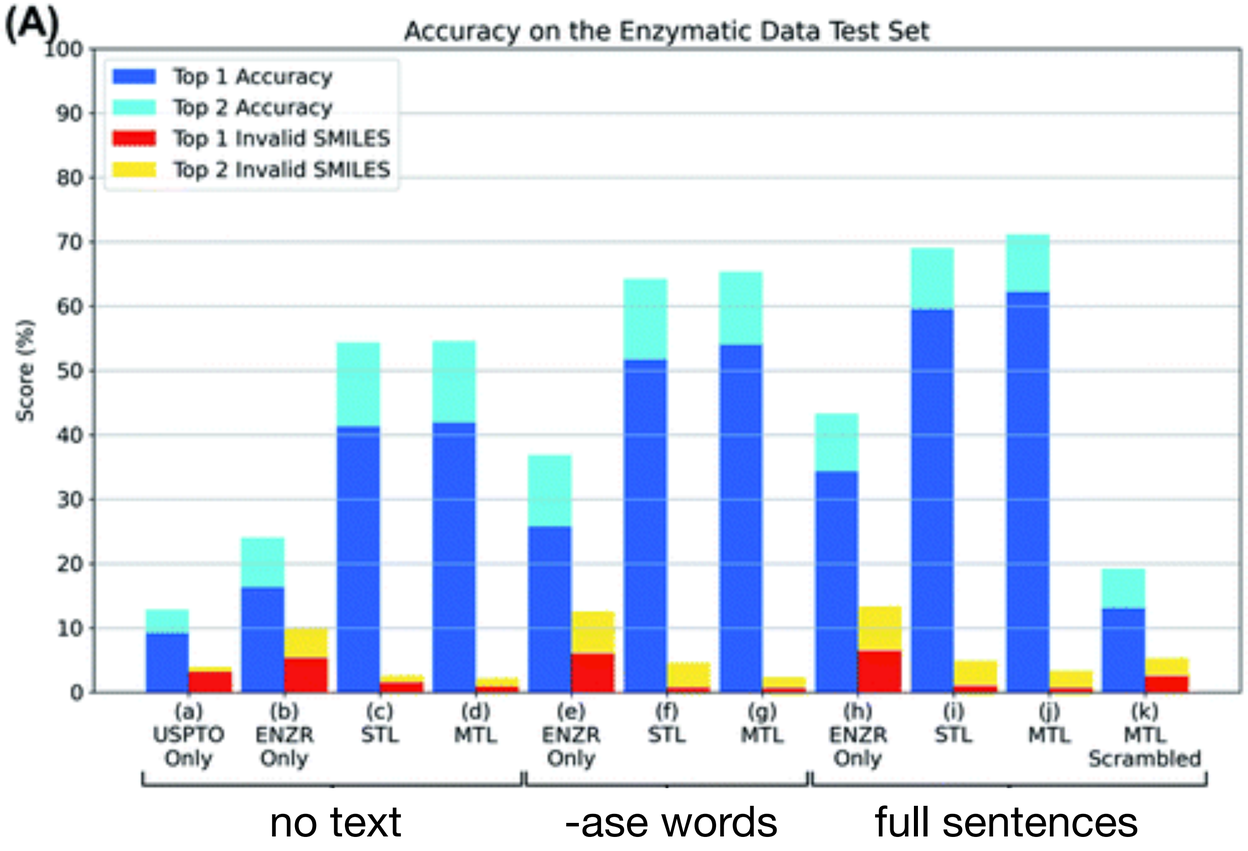
Predict product from substrates and text





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Questions

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