

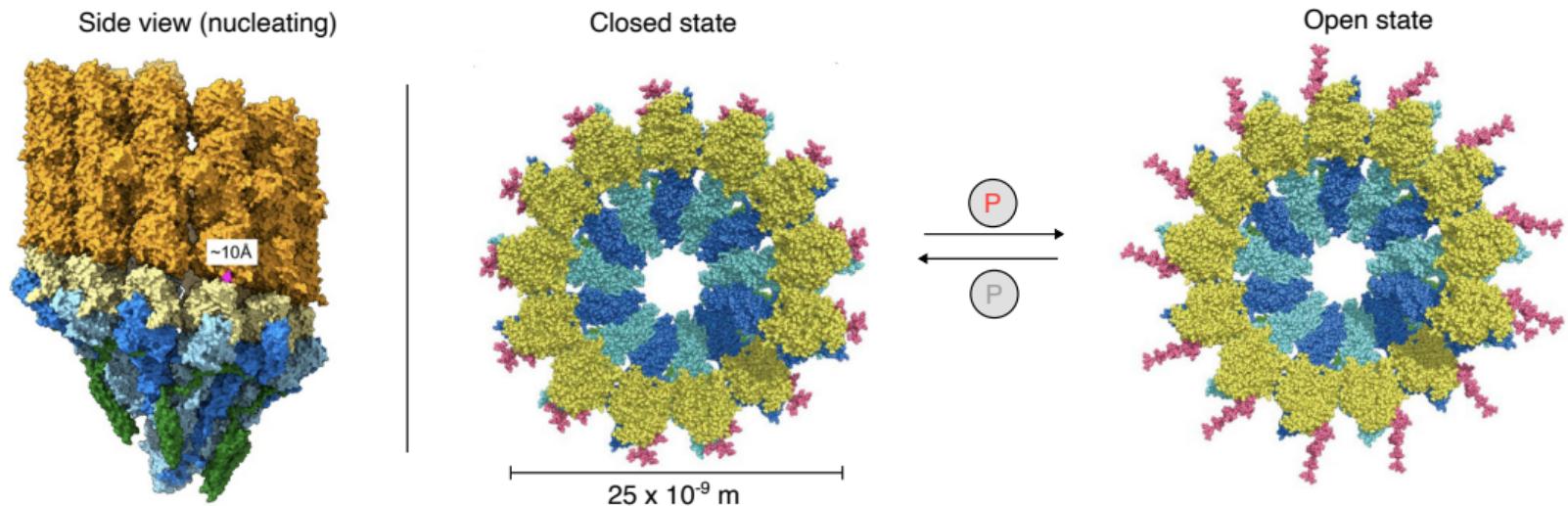
The Post-AlphaFold world: a new algorithmic landscape for structure-function modeling

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AI Days | March 6th, 2025

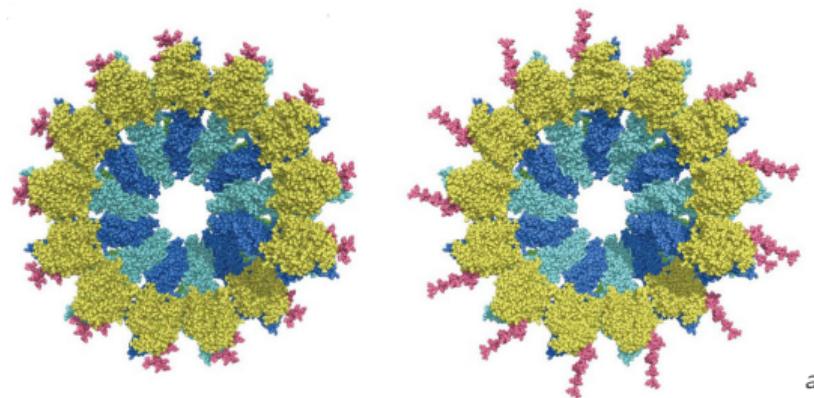
Slides: carlosoliver.co/2025/04/05/aidays.html

Structure is the language of biology



¹[Harris et al., 2018]

Driving Questions



^a[Harris et al., 2018]

- What are the **functional** components of the proteins?
- Can we detect **design** principles in these machines?
- How do we optimally **perturb** the machines?

Tasks: mapping from structure to function

Protein Classification

e.g. Gene Ontology or Enzyme Class



Residue Classification

e.g. Binding Pocket Prediction



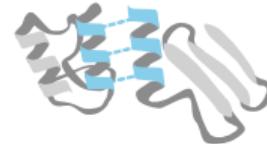
Self-Supervision

e.g. Pretraining with AlphaFold



Pairwise Residue

e.g. Binding Interface Prediction



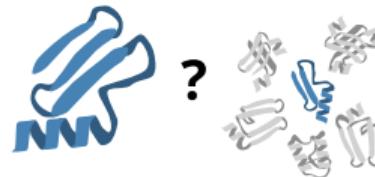
Pairwise Protein

e.g. Structure Alignment or Protein-Protein Interaction



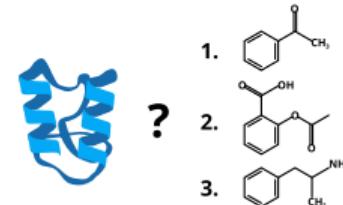
Retrieval

e.g. Similar Structure Search



Ranking

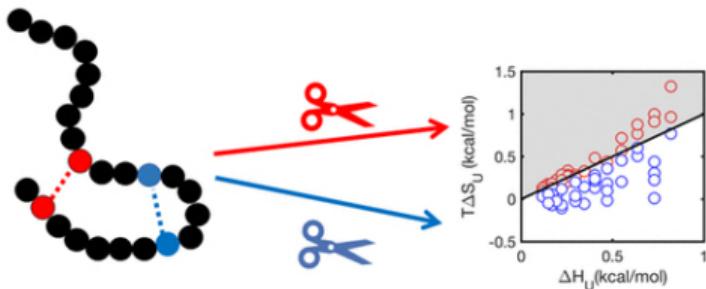
e.g. Drug Screening



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²[Kucera et al., 2023]

An approach: direct perturbation



$$\Delta G^{\text{Mutant}}_{\text{Red}} > \Delta G^{\text{Mutant}}_{\text{Blue}} > \Delta G^{\text{Wild-type}}$$

a

^aBigman, Lavi S., and Yaakov Levy., 2018

Pros

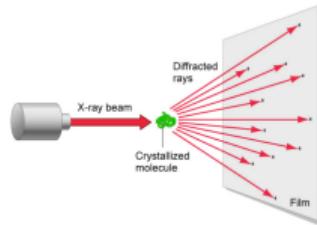
- Directly explainable

Cons

- Slow & costly
- Lack of generalization (one experiment, one story)

The data-driven approach

Structure Data



AlphaFold

Function Data



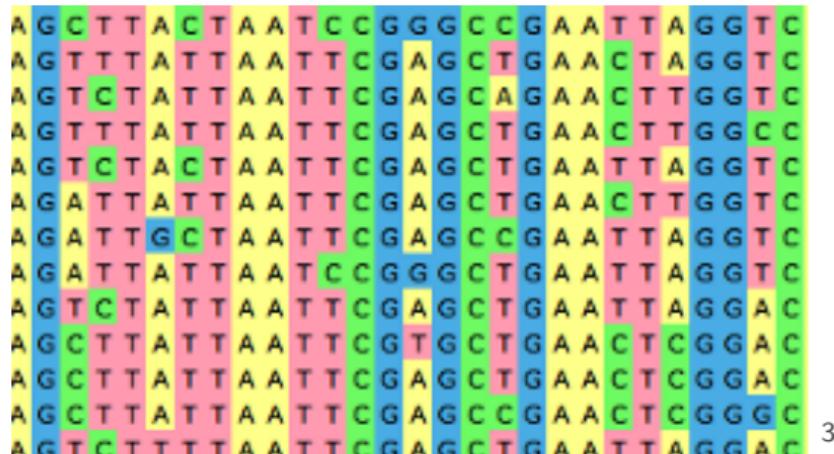
Expasy 

 PDBbind+

Pfam

Another approach: bioinformatics

We can learn more by studying relationships between many different proteins in connection to functional knowledge.

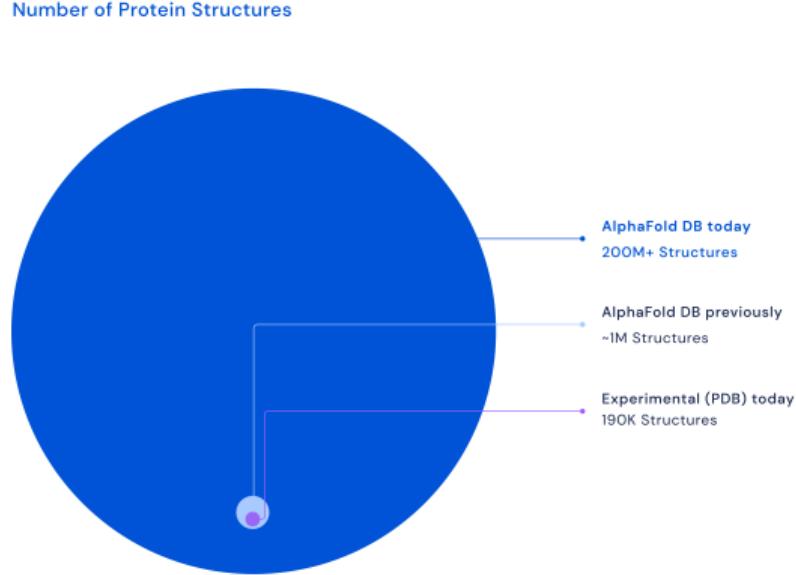


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Main focus of bioinformatics development for the past decades.

³<http://ugene.net/multiple-sequence-alignment-with-muscle/>

And then came AlphaFold...



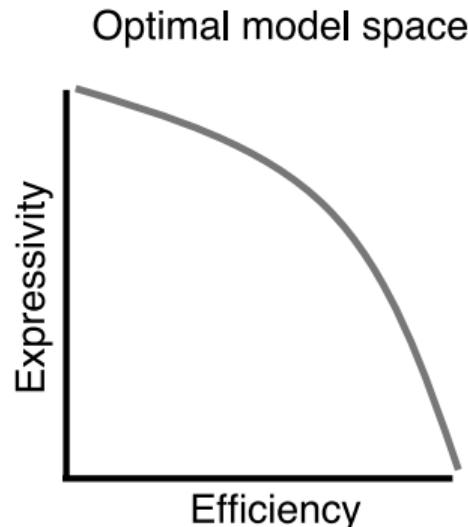
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Massive increase in complexity and scale!

⁴Source: DeepMind blog

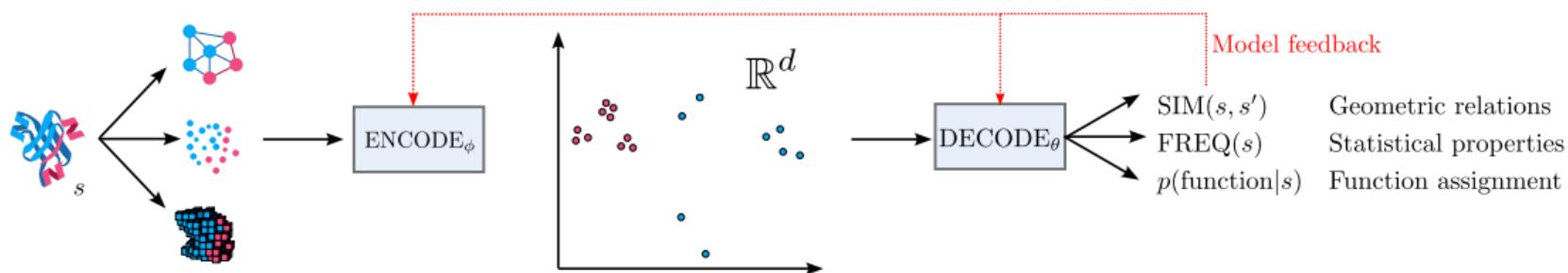
The expressivity vs efficiency tradeoff

- Models have to balance the degree biological complexity they can capture (expressivity) with the computational speed of running them (efficiency).
- Classical tools (pre-AI) tend to lie in low-expressivity regions.



How does AI make this shift possible?

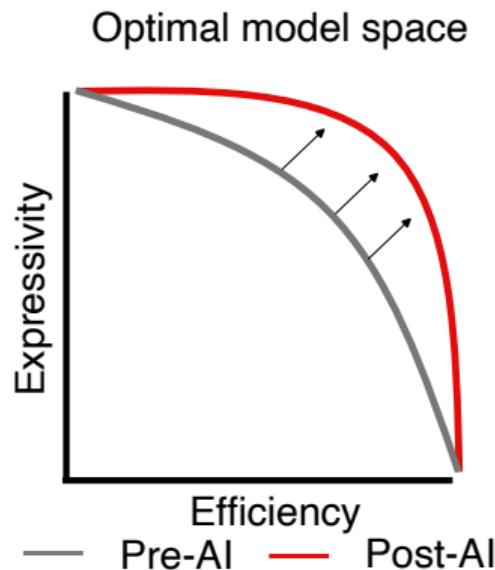
1. Neural network with parameters ϕ encodes proteins from the **structure domain** to intermediate vectorial space.
2. Neural network with parameters θ decodes proteins to the **function domain**.



Key: all steps are matrix multiplication-based (\uparrow efficiency), and neural networks can capture complex patterns (\uparrow expressivity).

The case for AI in bioinformatics

- AI models **efficiently** capture **complex** relationships that **connect** domains.



Imperative: discover the next generation of **high-capacity and scalable** bioinformatics tools.

Case study: Protein Alignment

- How do we measure the similarity of two proteins?
 - Prior: fundamental unit is single amino acids (\uparrow Efficiency)
 - Prior: substitution cost for all pairs of amino acids is fixed (\downarrow Expressivity)

Substitution Matrix (parameters)

	C	S	T	A	G	P	D	E	Q	N	H	R	K	M	I	L	V	W	F
C	9																		
T	1	5																	
A	0	1	0	4															
G	-3	0	-2	0	6														
P	-3	-1	-1	-2	7														
D	-3	8	-1	-2	-1	-1	6												
E	-4	8	-1	-1	-2	-1	2	5											
Q	-3	8	-1	-1	-2	-1	0	2	5										
N	-3	1	0	-2	0	-2	1	0	6										
H	-3	-1	-2	-2	-2	-2	-1	0	0	1	8								
R	-3	-1	-1	-1	-2	-2	-2	1	0	1	0	5							
K	-3	8	-1	-1	-2	-1	-1	1	1	6	-1	2	5						
M	-1	-1	-1	-1	-3	-2	-3	-2	0	-2	-1	-1	5						
I	-1	-2	-1	-1	-4	-3	1	4											
L	-1	-2	-1	-1	-4	-3	-4	-3	-2	-3	-3	-2	2	2	4				
V	-1	2	0	0	-3	-2	-3	-2	-3	-3	-3	-2	1	3	1	4			
W	-2	-3	-2	-3	-2	-4	-4	-3	-2	-4	-2	-3	-3	-1	-3	-2	-3	11	
Y	-2	-2	-2	-2	-3	-3	-3	-2	-1	2	-2	-2	-1	-1	-1	1	2	7	
F	-2	-2	-2	-2	-3	-4	-3	-3	-3	-3	-1	-3	0	0	0	1	3	6	
E	C	S	T	A	G	P	D	E	Q	N	H	R	K	M	I	L	V	W	

Alignment

	T	G	T	T	A	C	G	G
G	0	0	0	0	0	0	0	0
G	0	0	3	1	0	0	0	3
G	0	0	3	1	0	0	0	6
T	0	3	1	6	4	2	0	1
T	0	3	1	4	9	7	5	3
G	0	1	6	4	7	6	4	8
A	0	0	4	3	5	10	8	6
C	0	0	2	1	3	8	13	11
T	0	3	1	5	4	6	11	10
A	0	1	0	3	2	7	9	8

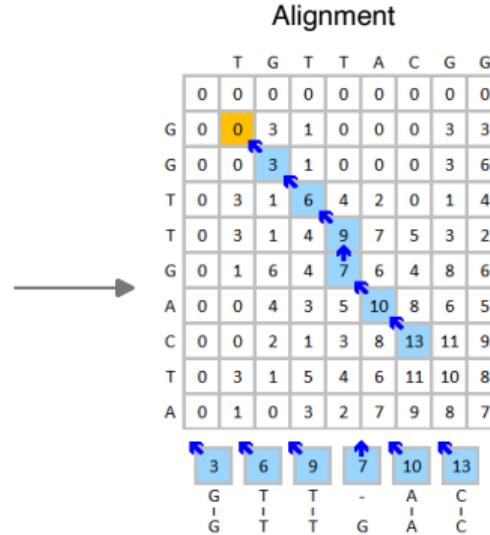
3	6	9	7	10	1
G I G	T I T	T I T	-	A I A	O I O
			G		

Case study: Protein Alignment

- How do we measure the similarity of two proteins?
- Prior: fundamental unit is single amino acids (\uparrow Efficiency)
- Prior: substitution cost for all pairs of amino acids is fixed (\downarrow Expressivity)

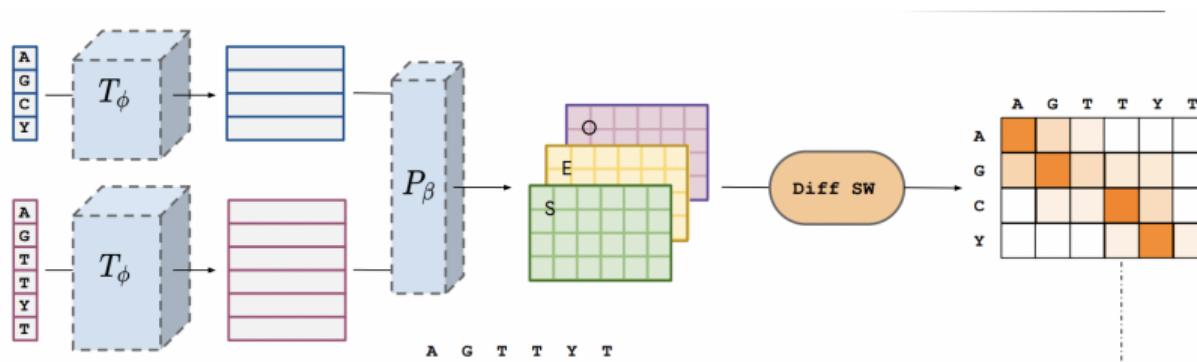
Substitution Matrix
(parameters)

C	S	T	A	G	P	D	E	Q	N	H	R	K	M	I	L	V	W	Y	F
C 9																			C
S -1 4																			S
T -1 1 5																			T
A 0 1 0 4																			A
G -3 0 -2 0 6																			G
P -3 -1 -1 -1 -2 7																			P
D -3 0 -1 -2 -1 6																			D
E -4 0 -1 -1 -2 -1 2 5																			E
Q -3 0 -1 -1 -2 -1 0 2 5																			Q
N -3 1 0 -2 0 -2 1 0 0 6																			N
H -3 -1 -2 -2 -2 -2 -1 0 0 1 8																			H
R -3 -1 -1 -1 -2 -2 -1 0 1 0 5																			R
K -3 0 -1 -1 -2 -1 -1 1 1 0 -1 2 5																			K
M -1 -1 -1 -1 -3 -2 -3 -2 0 -2 -2 -1 -1 5																			M
I -1 -2 -1 -1 -4 -3 -3 -3 -3 -3 -3 -3 -3 1 4																			I
L -1 -2 -1 -1 -4 -3 -4 -3 -2 -3 -3 -2 -2 2 2 4																			L
V -1 -2 0 -3 -3 -2 -3 -2 -2 -3 -3 -3 -2 1 3 1 4																			V
W -2 -3 -2 -3 -2 -4 -4 -3 -2 -4 -2 -3 -3 -1 -3 -2 -3 11																			W
Y -2 -2 -2 -2 -3 -3 -3 -2 -1 -2 2 -2 -2 -1 -1 -1 2 7																			Y
F -2 -2 -2 -2 -3 -4 -3 -3 -3 -1 -3 -3 0 0 -1 1 3 6 F																			F
C S T A G P D E Q N H R K M I L V W Y F																			C S T A G P D E Q N H R K M I L V W Y F



Beyond fixed substitution costs [Llinares-López et al., 2023]

- Allow flexible substitution costs (\uparrow Expressivity)
- Substitution costs become a model parameter.
- Parameter is tuned by backpropagation using function data.



Case study: Protein Alignment

- How do we measure the similarity of two proteins?
- Prior: substitution cost for all pairs of amino acids is fixed (\downarrow Expressivity)
- **Prior: fundamental unit is single amino acids (\uparrow Efficiency)**
- Solution: dynamic programming

Substitution Matrix
(parameters)

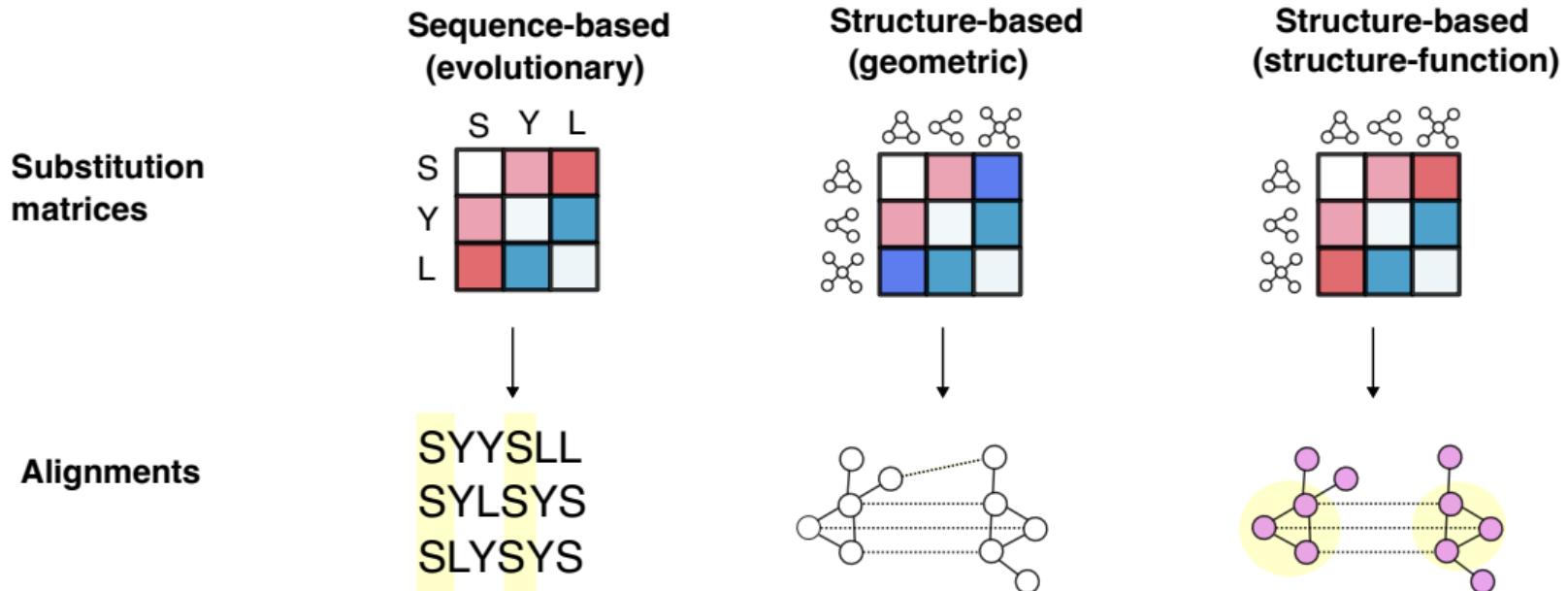
C	S	T	A	G	P	D	E	Q	N	H	R	K	M	I	L	V	W	Y	F
C	0	-1	4	1	5	0	1	0	4	0	1	0	1	0	1	0	1	0	1
S	-1	0	1	5	0	1	0	4	0	1	0	1	0	1	0	1	0	1	0
T	0	1	5	0	1	0	4	0	1	0	1	0	1	0	1	0	1	0	1
A	0	1	0	4	1	5	0	1	0	4	1	5	0	1	0	1	0	1	0
G	-3	0	-2	0	6	0	1	0	0	6	0	1	0	0	6	0	1	0	0
P	0	3	-1	-1	-2	7	0	1	0	0	6	0	1	0	0	6	0	1	0
D	-3	0	-1	-2	-1	6	0	1	0	0	5	0	1	0	0	5	0	1	0
E	-4	0	-1	-1	-2	1	2	5	0	1	0	1	0	1	0	1	0	1	0
Q	-3	0	-1	-1	-2	1	0	2	5	0	1	0	1	0	1	0	1	0	1
M	-3	1	0	-2	0	2	1	0	0	6	0	1	0	1	0	1	0	1	0
H	-3	-1	-2	-2	-2	-1	0	0	1	8	0	1	0	1	0	1	0	1	0
R	-3	-1	-1	-1	-2	-2	0	1	0	0	5	0	1	0	1	0	1	0	1
K	-3	0	-1	-1	-2	-1	1	1	0	-1	2	5	0	1	0	1	0	1	0
M	-1	-1	-1	-1	-3	-2	-3	0	-2	-2	-1	-1	5	0	1	0	1	0	1
I	-1	-2	-1	-1	-4	-3	-3	-3	-3	-3	-3	-3	1	4	0	1	0	1	0
L	-1	-1	-2	-1	-4	-3	-4	-3	-2	-3	-3	-2	-2	2	2	4	0	1	0
V	-1	-2	0	0	-3	-2	-3	-2	-3	-3	-2	1	3	1	4	0	1	0	1
W	-2	-3	-2	-3	-2	-4	-4	-3	-2	-4	-2	-3	-3	-1	-3	-2	-3	11	0
F	-2	-2	-2	-2	-3	-4	-3	-3	-3	-1	-3	-3	0	0	0	-1	2	7	0
C	3	6	9	7	10	13													

Alignment

T	G	T	T	T	A	C	G	G											
0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
G	0	0	3	1	0	0	0	0	3	3	3	3	3	3	3	3	3	3	3
G	0	0	3	1	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
T	0	3	1	6	4	2	0	1	4	4	2	0	1	4	4	2	0	1	4
T	0	3	1	4	9	7	5	3	2	9	7	5	3	2	9	7	5	3	2
G	0	1	6	4	7	6	4	8	6	7	6	4	8	6	7	6	4	8	6
A	0	0	4	3	5	10	8	6	5	10	8	6	5	10	8	6	5	10	8
C	0	0	2	1	3	8	13	11	9	8	13	11	9	8	13	11	9	8	13
T	0	3	1	5	4	6	11	10	8	4	6	11	10	8	4	6	11	10	8
A	0	1	0	3	2	7	9	8	7	2	7	9	8	7	2	7	9	8	7

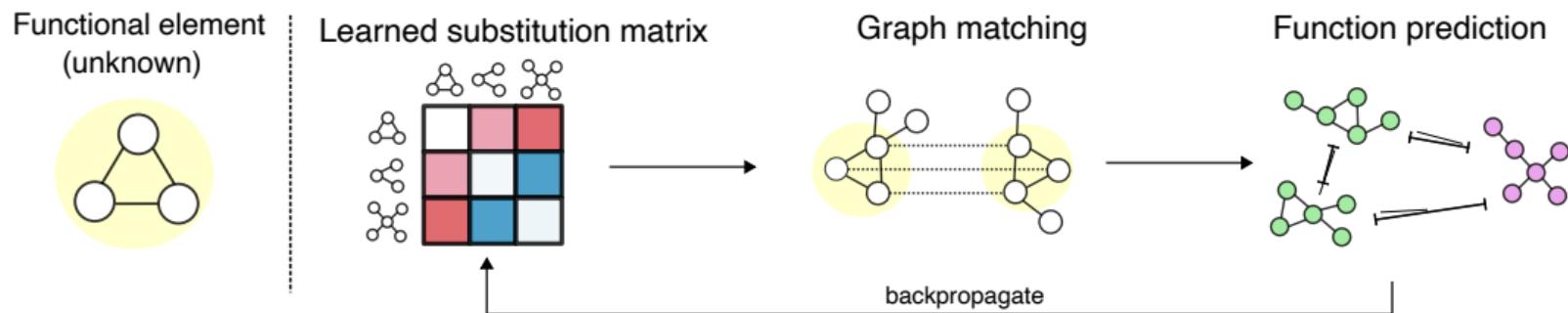
3 6 9 7 10 13
G T T G A C
I I I G A C

Beyond residue-level alphabets [Pellizzoni et al., 2024]



Learn SM via graph matching

- We decompose the protein into higher order subunits → local neighbourhoods (\uparrow expressivity).



Learned substitution costs reflect functional substructures

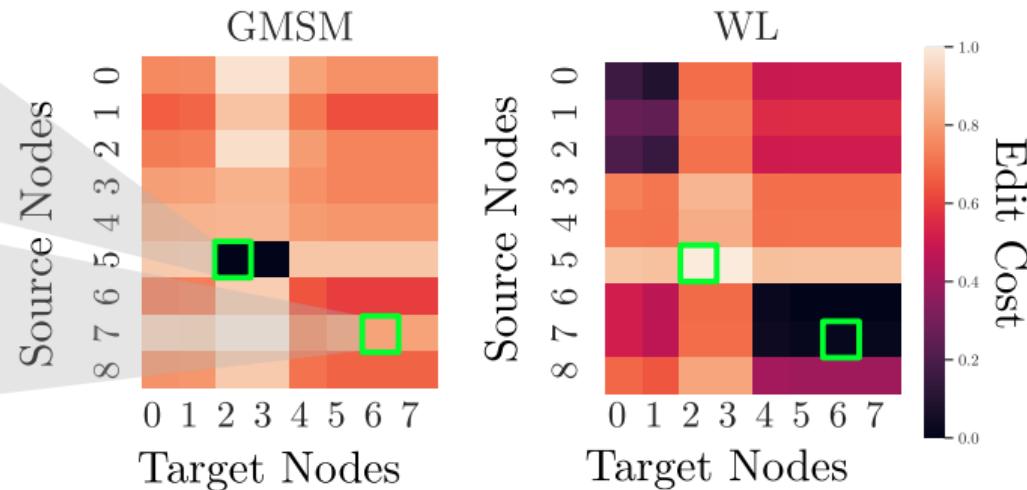
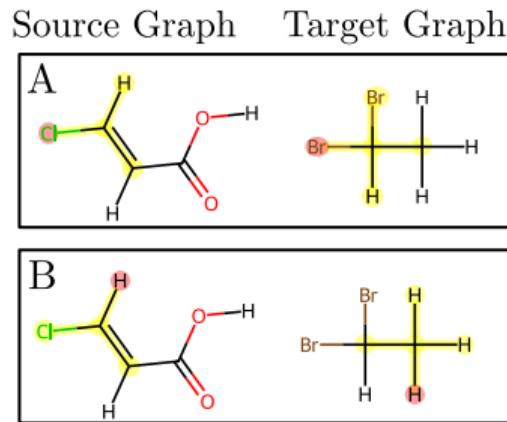
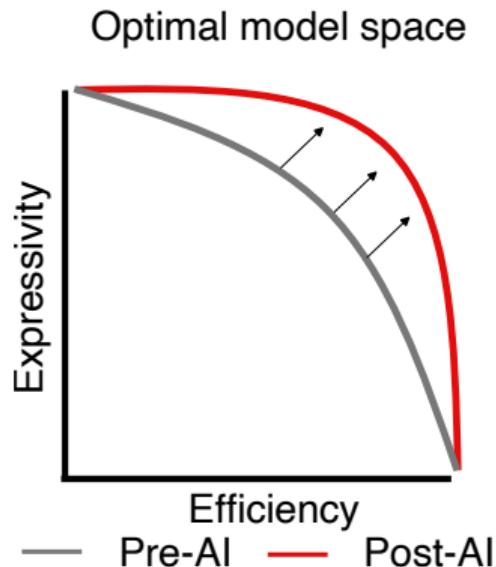


Figure: Learned substitution matrices from GMSM vs structure-only WL kernel.

Perspectives

- Many more algorithms remain to be discovered around the new Pareto front.
- Exploration will unlock insights in more complex modalities (e.g protein ensembles)

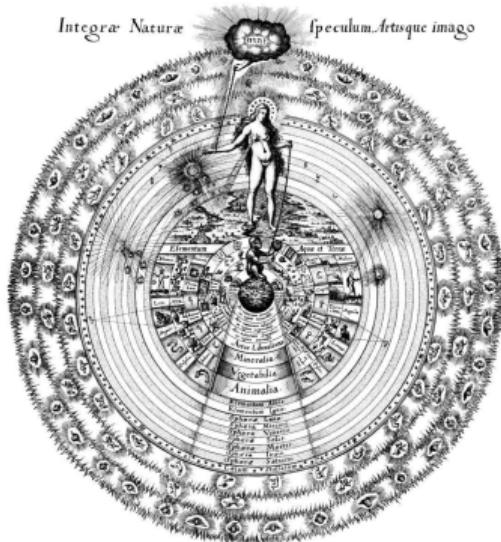


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