Sabancı Üniversitesi

TÜBİTAK

EURO 4SEE

Prediction of Protein Structures Using Deep Learning Tools

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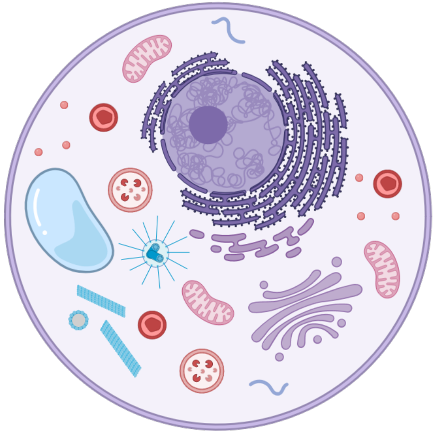
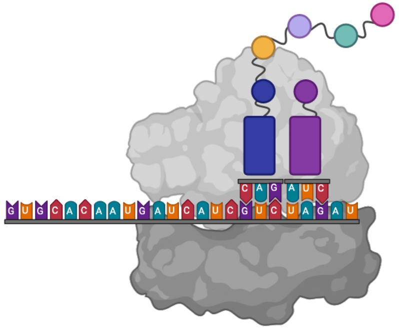
Proteins?



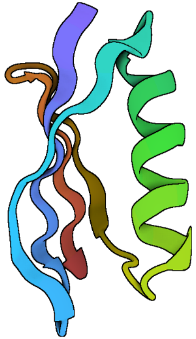
Cell

DNA

RNA

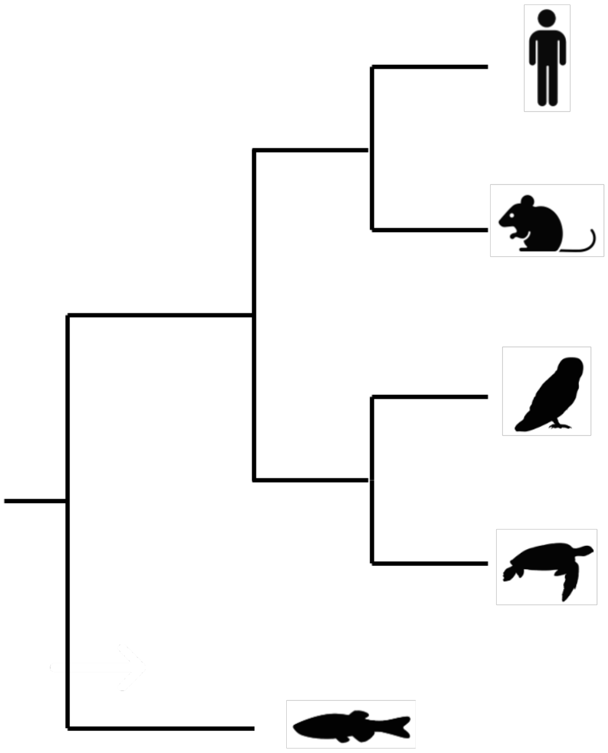


Protein
(Translation)



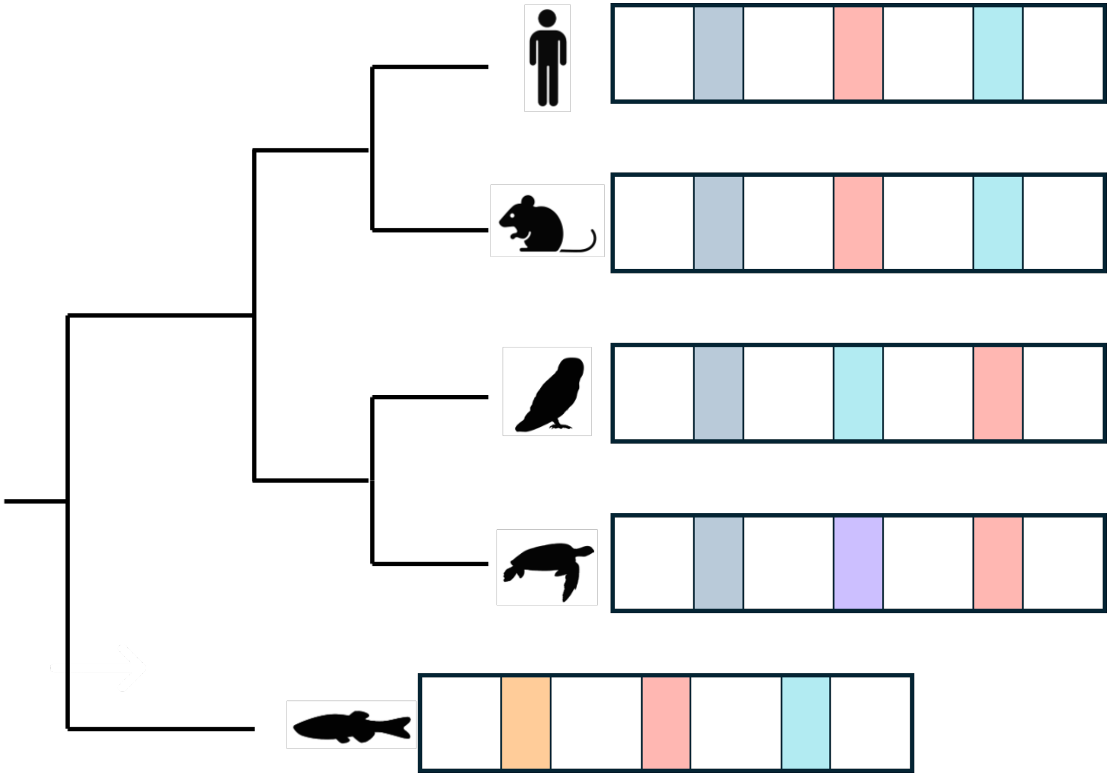
Protein
(Structure)

Evolution



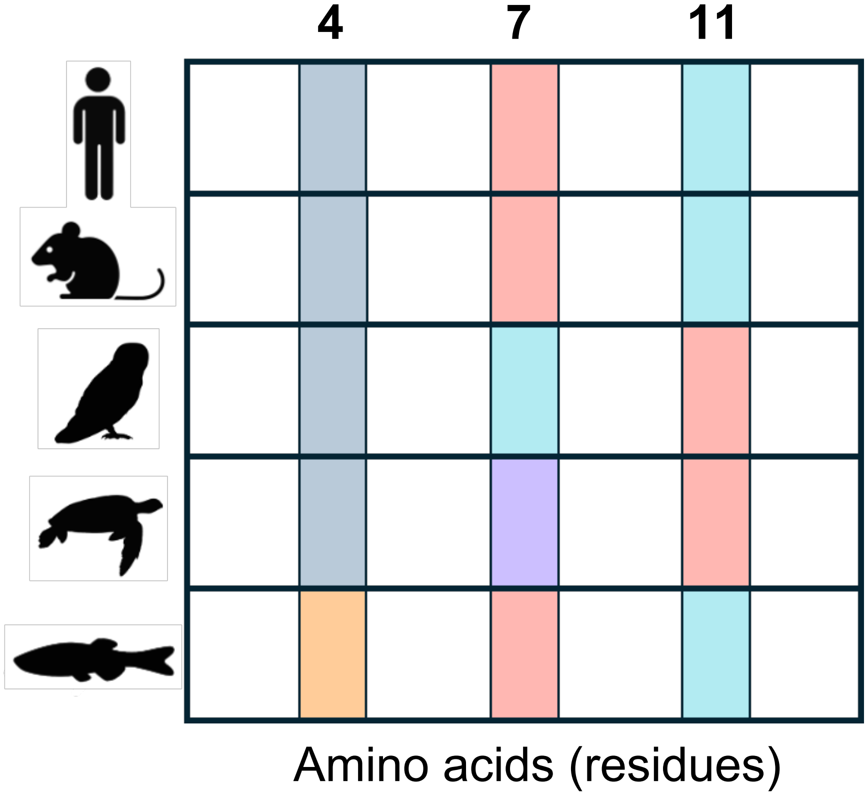
- Phylogenetic tree
- How to compare the similarities?

Evolution



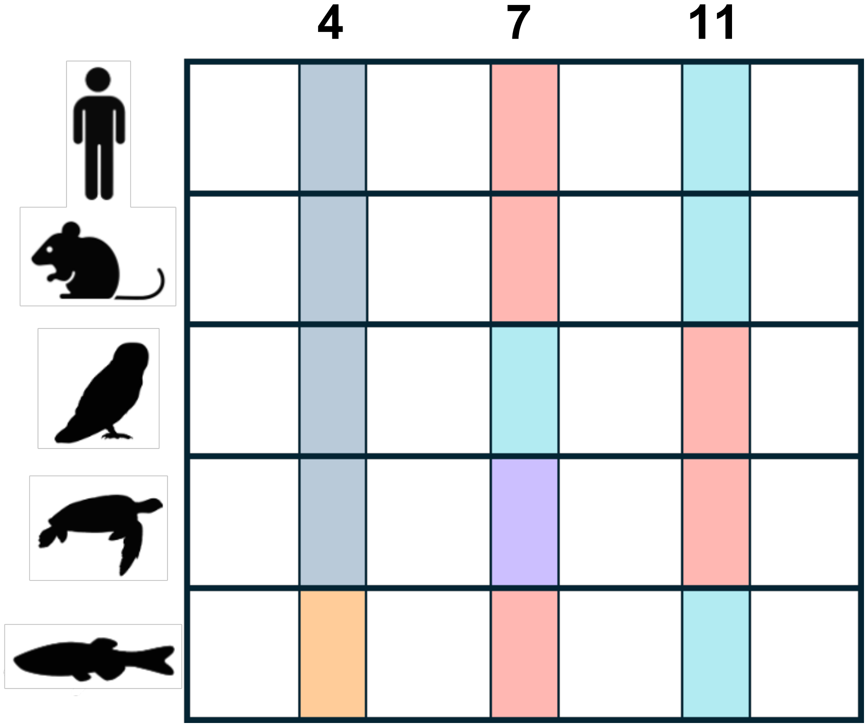
- Phylogenetic tree
- How to compare the similarities?

Multiple sequence alignment(MSA)



- MSA, amino acids (residues) change through species
- Position 4, conserved
- Position 7 and 11, coevolved

Multiple sequence alignment(MSA)



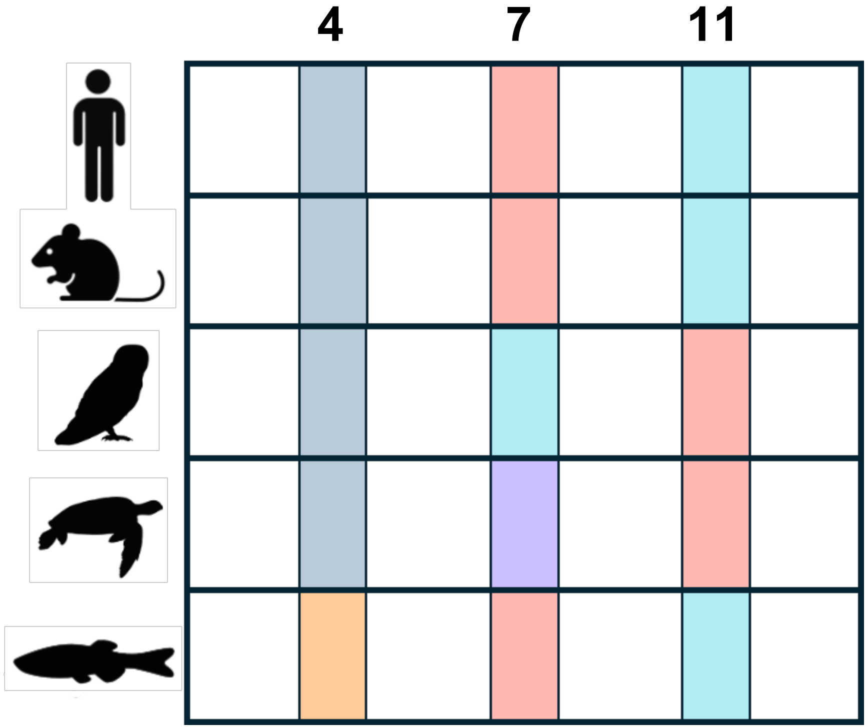
Amino acids (residues)

- **MSA tools**

MMseqs2(https://github.com/soedinglab/MMseqs2)

JackHMMER(https://www.ebi.ac.uk/Tools/hmmer/search/jackhmmer)

Multiple sequence alignment(MSA)



Amino acids (residues)

- **Conservation tool**

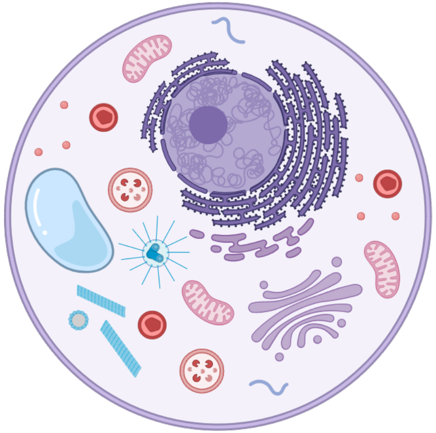
ConSurf (https://consurf.tau.ac.il/consurf_index.php)

- **Coevolution tools**

GREMLIN (https://github.com/sokrypton/GREMLIN)

EVCoupling (https://v1.evcouplings.org/)

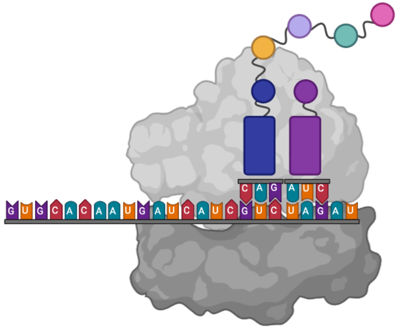
Proteins?



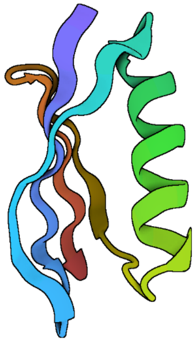
Cell

DNA

RNA



Protein
(Translation)



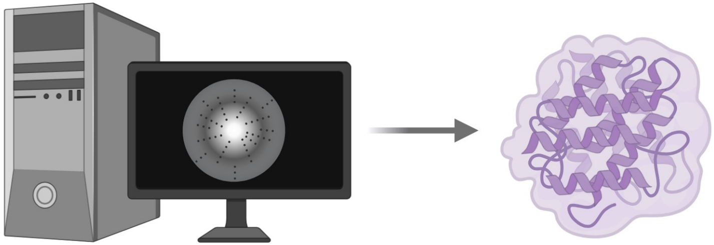
Protein
(Structure)

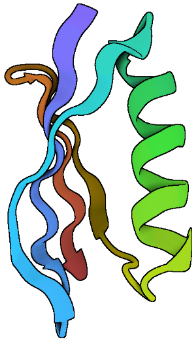
Protein Data Bank (PDB)

- Experimental structures

X-ray crystallography
NMR
Cryo-EM

Aren’t they also models?

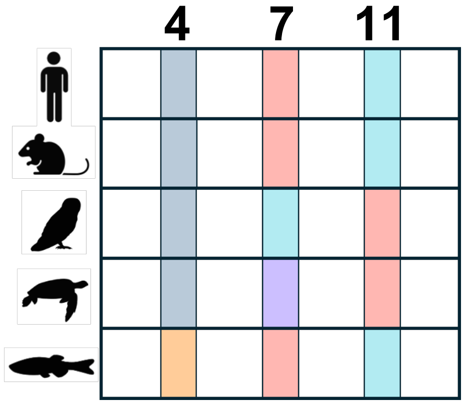


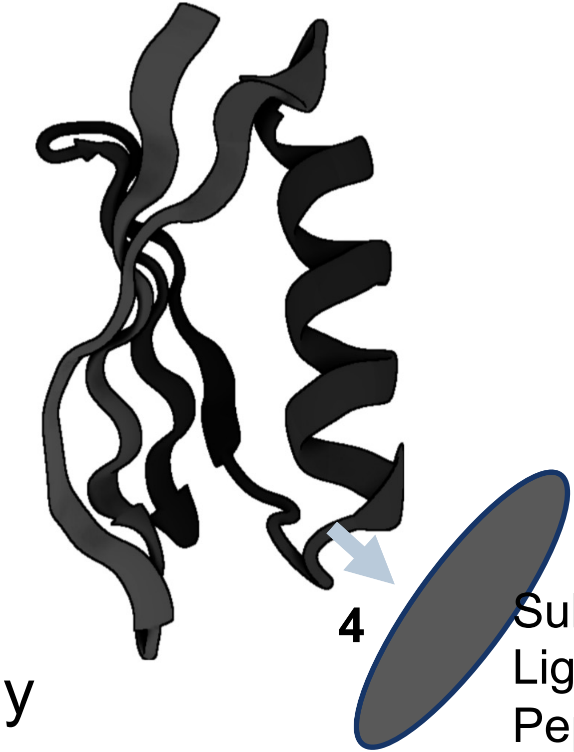


Protein
(Structure)

We have MSAs and structures, any relation?

MSA, Structure, Function?



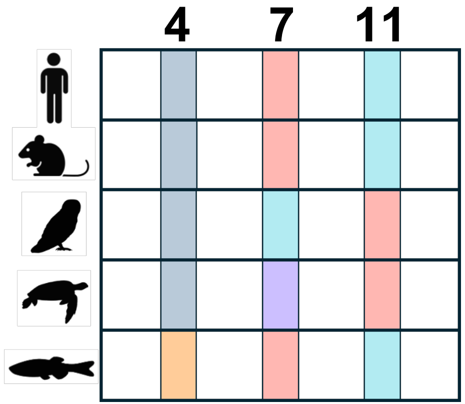


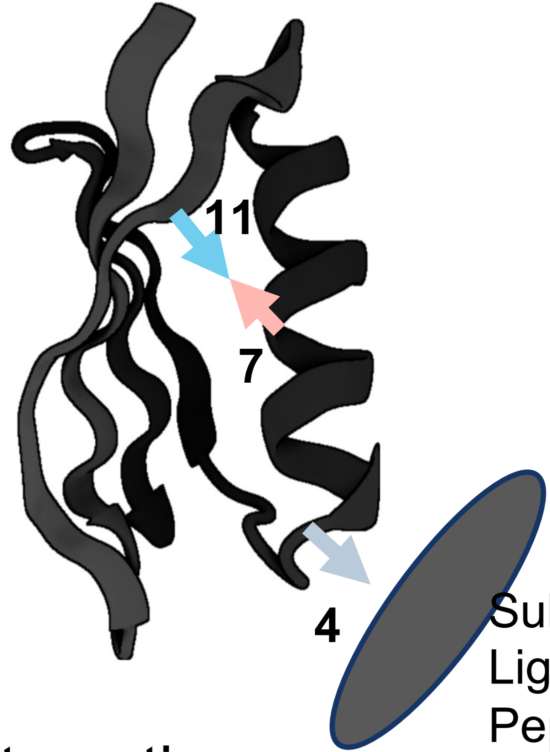
Substrate
Ligand
Peptide
Partner protein

- Conserved residues, functionally important, cannot be changed

https://www.solab.org/resources/coevolution-structure-prediction

MSA, Structure, Function?



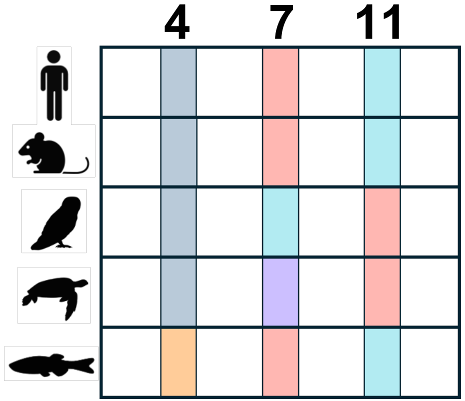


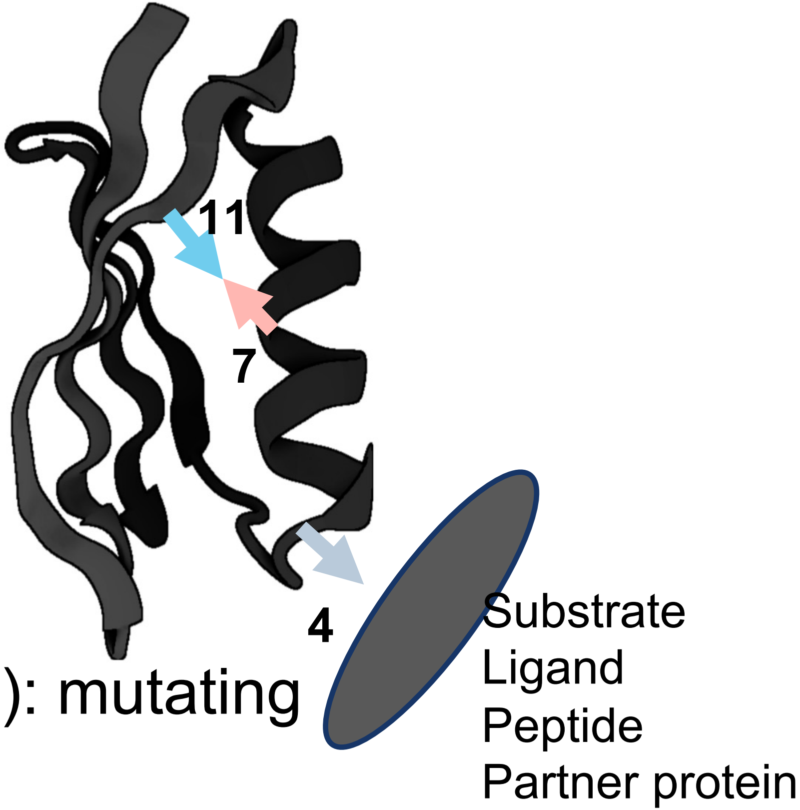
Substrate
Ligand
Peptide
Partner protein

- Co-evolved residues, coupling information, structurally close, interacting

https://www.solab.org/resources/coevolution-structure-prediction

MSA, Structure, Function?



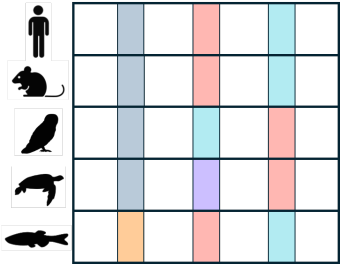


- Deep mutational scanning (DMS): mutating contact residues affects function

https://www.nature.com/articles/s41588-019-0431-x && https://www.nature.com/articles/s41588-019-0432-9

Now that we know sequence, structure, and function are related, what comes next?

Predicting the structure from seq



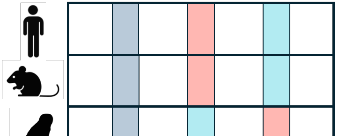
~4.7B protein sequences

https://data.mmseqs.com/

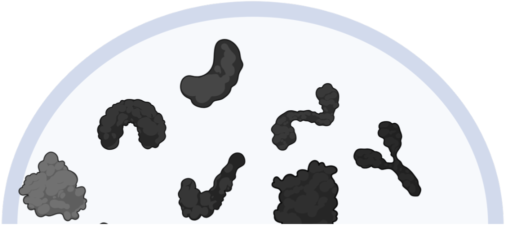
~240K protein structures

https://www.rcsb.org/pages/about-us/index

Predicting the structure from seq



+



AlphaFold!

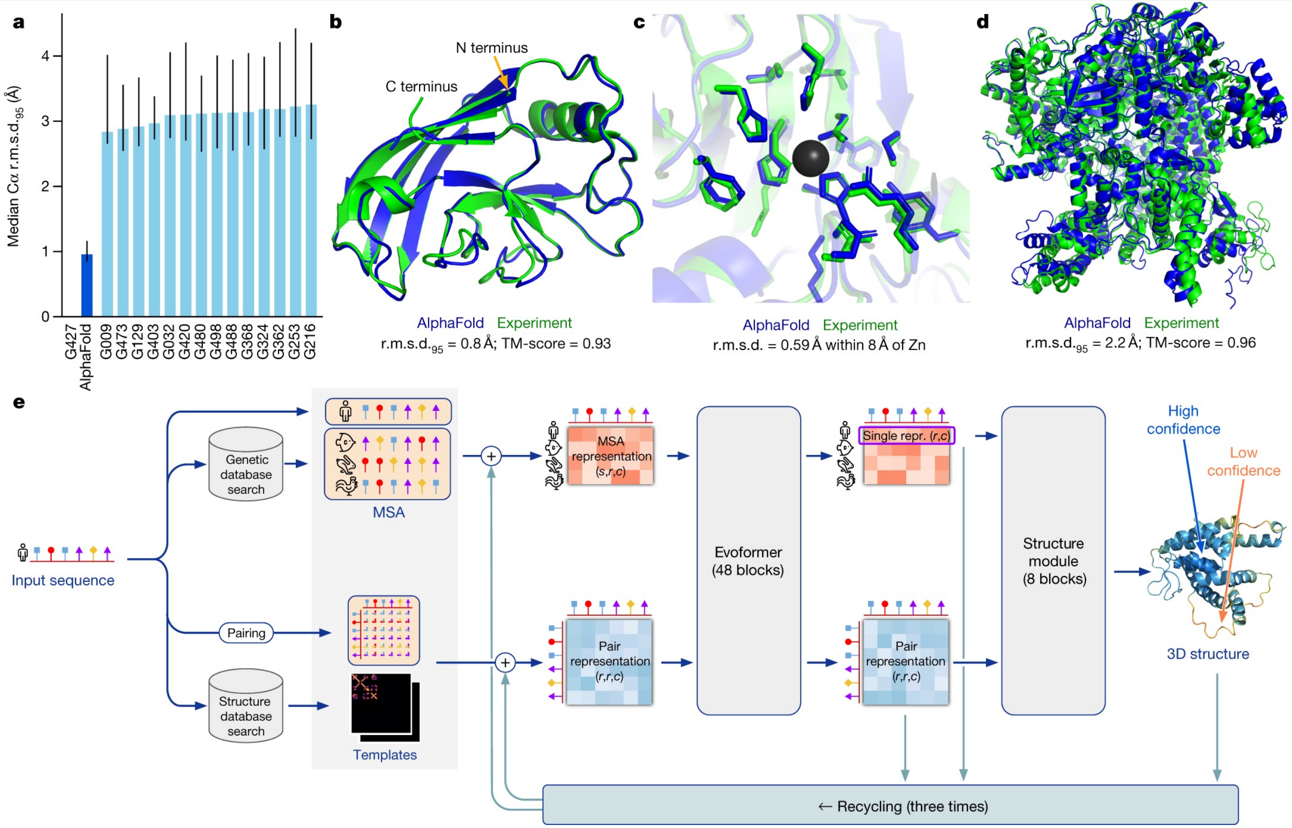
~4.7B protein sequences

https://data.mmseqs.com/

~240K protein structures

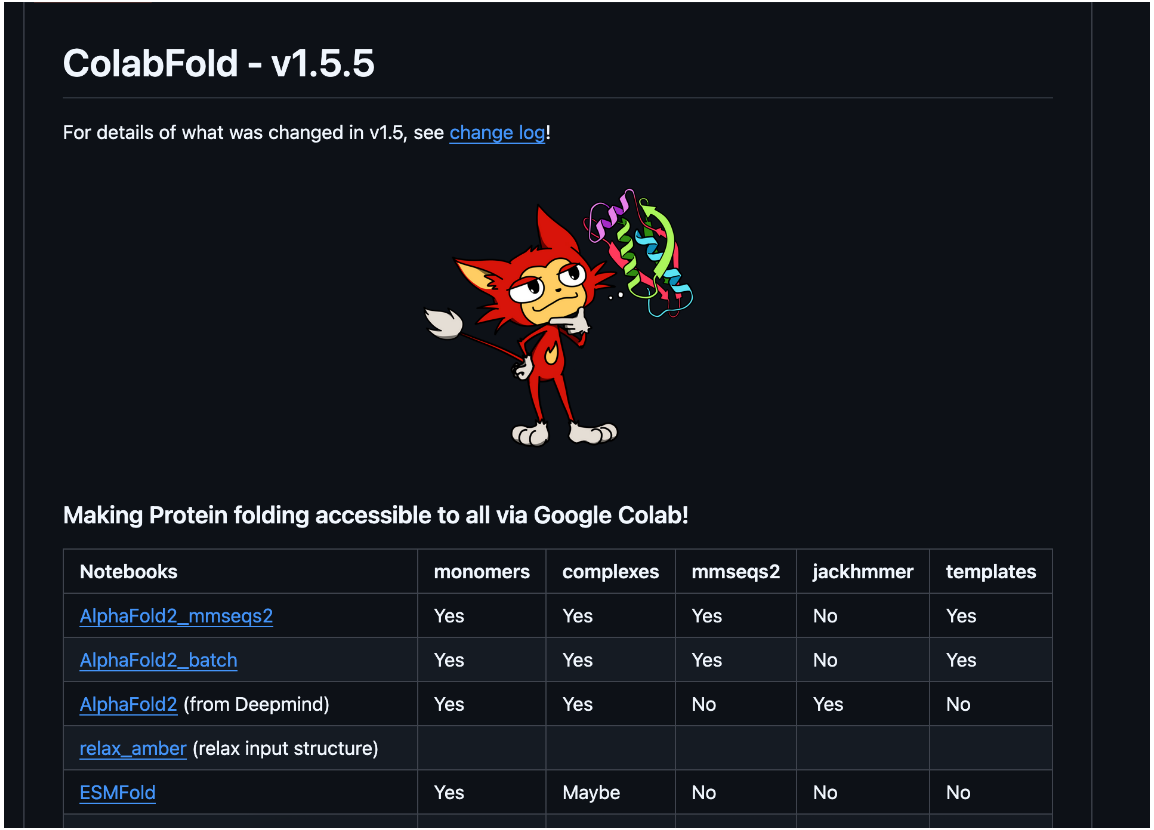
https://www.rcsb.org/pages/about-us/index

AlphaFold2



https://www.nature.com/articles/s41586-021-03819-2

MMseqs2 + AlphaFold2 = ColabFold



ColabFold - v1.5.5

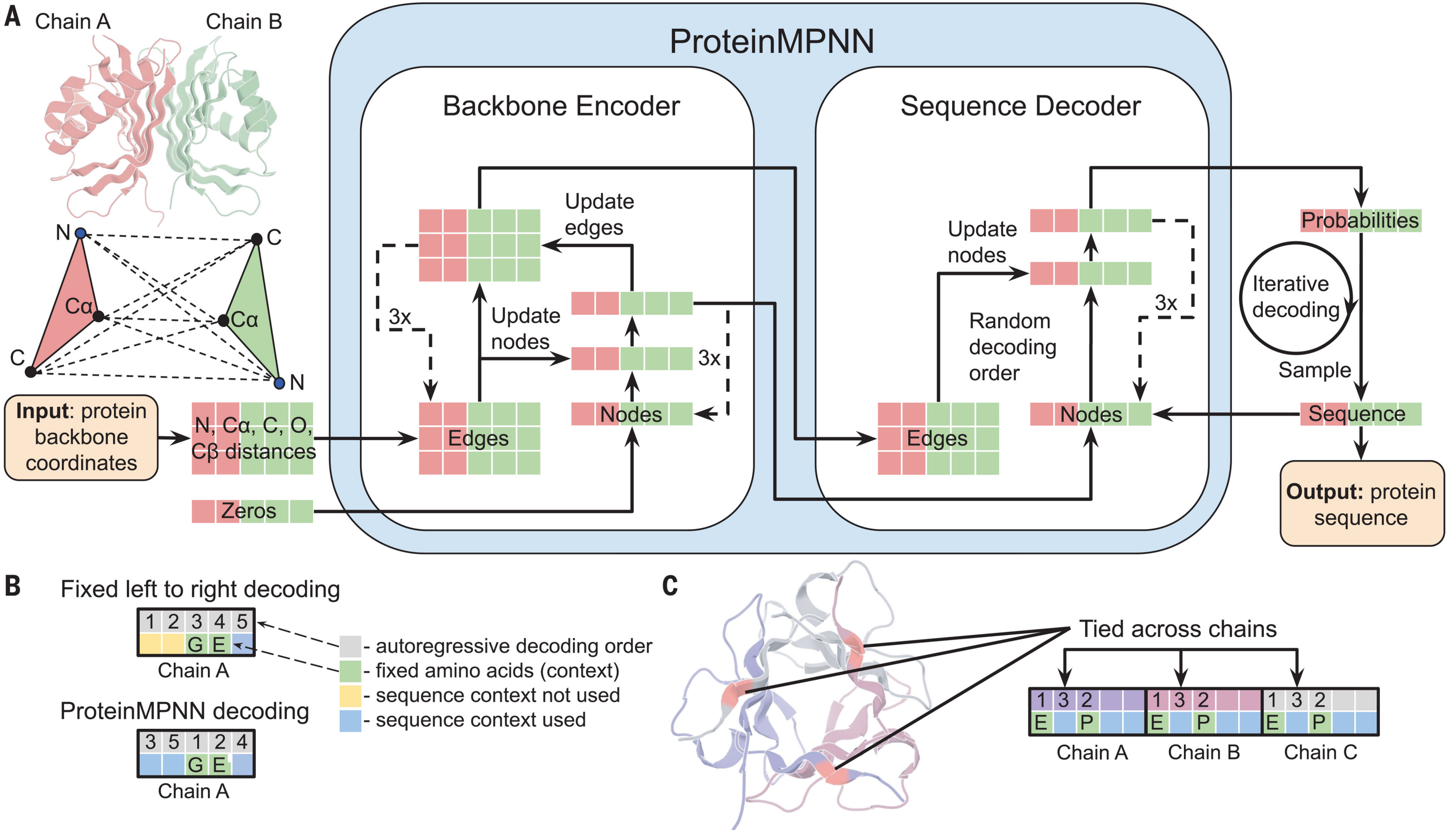
For details of what was changed in v1.5, see change log!

Making Protein folding accessible to all via Google Colab!

Notebooks	monomers	complexes	mmseqs2	jackhmmer	templates
AlphaFold2_mmseqs2	Yes	Yes	Yes	No	Yes
AlphaFold2_batch	Yes	Yes	Yes	No	Yes
AlphaFold2 (from Deepmind)	Yes	Yes	No	Yes	No
relax_amber (relax input structure)					
ESMFold	Yes	Maybe	No	No	No

https://github.com/sokrypton/ColabFold

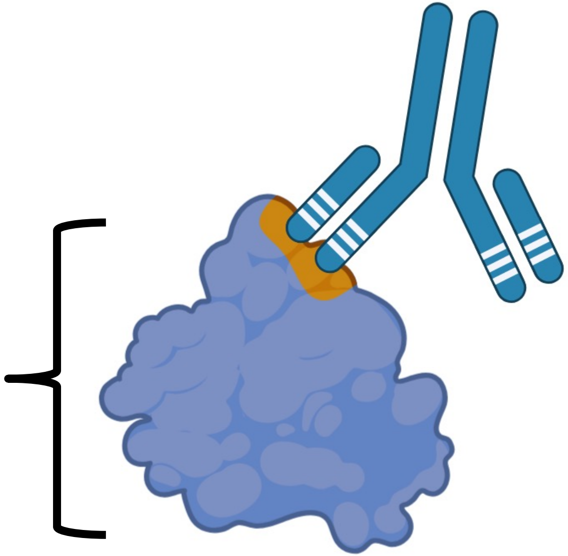
Reversing the process - ProteinMPNN



https://www.science.org/doi/10.1126/science.add2187

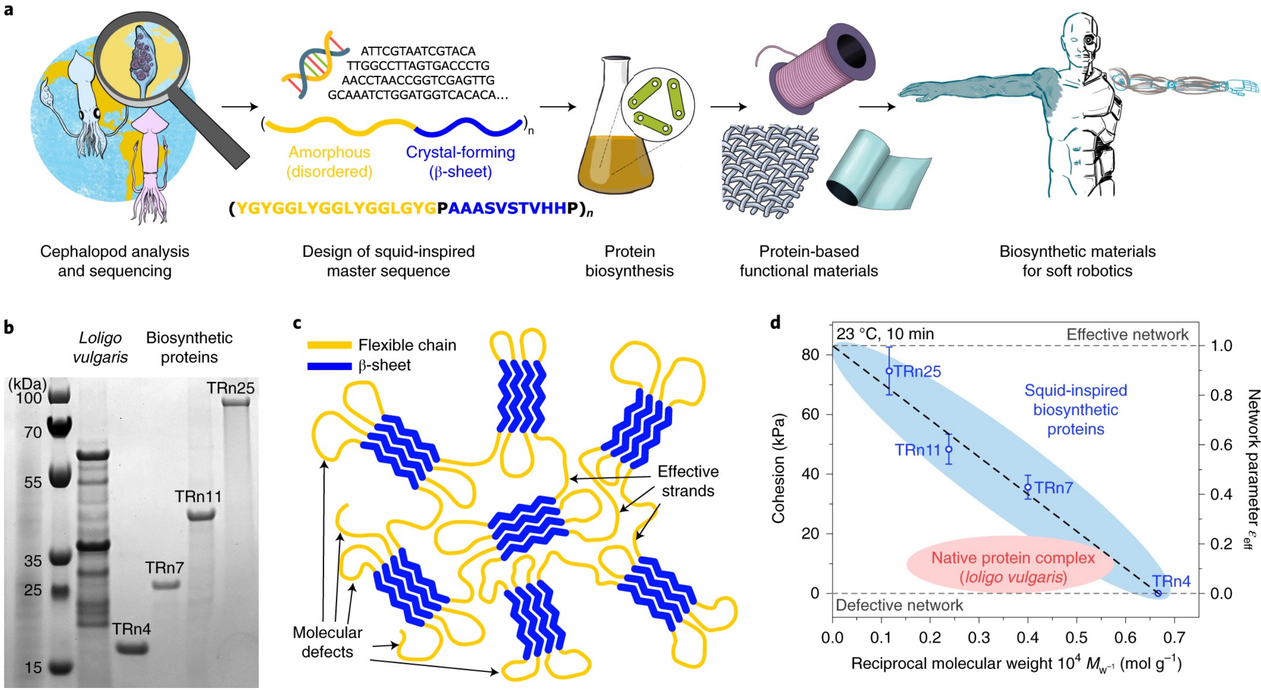
ProteinMPNN

- Binder design
- Biomaterials design



ProteinMPNN

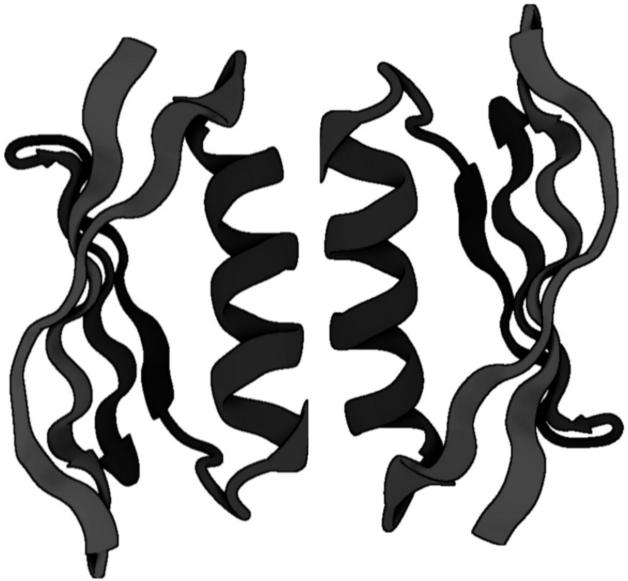
- Binder design
- Biomaterials design



https://www.nature.com/articles/s41563-020-0736-2

What about multimers?

How do non-bonded interactions differ between two distant amino acids in a single protein and those between multiple proteins?

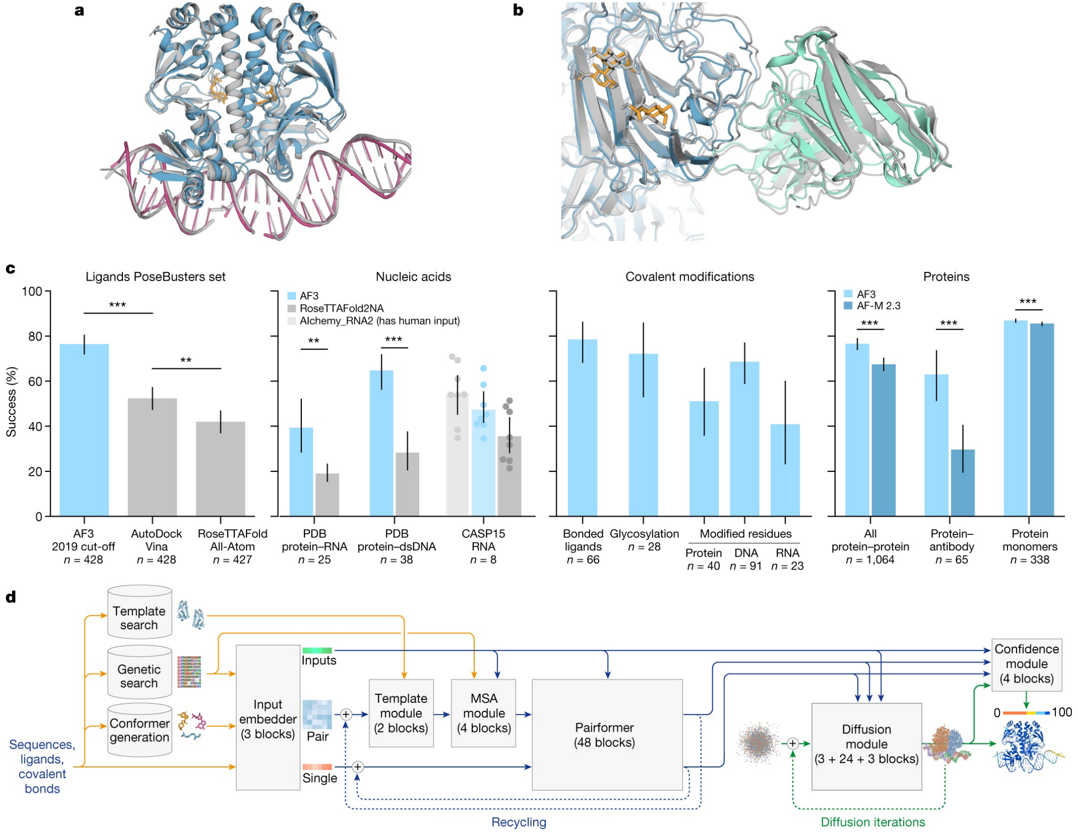


AlphaFold3

- Multimers
- DNA, RNA
- Ligands

and an online server!

https://alphafoldserver.com/

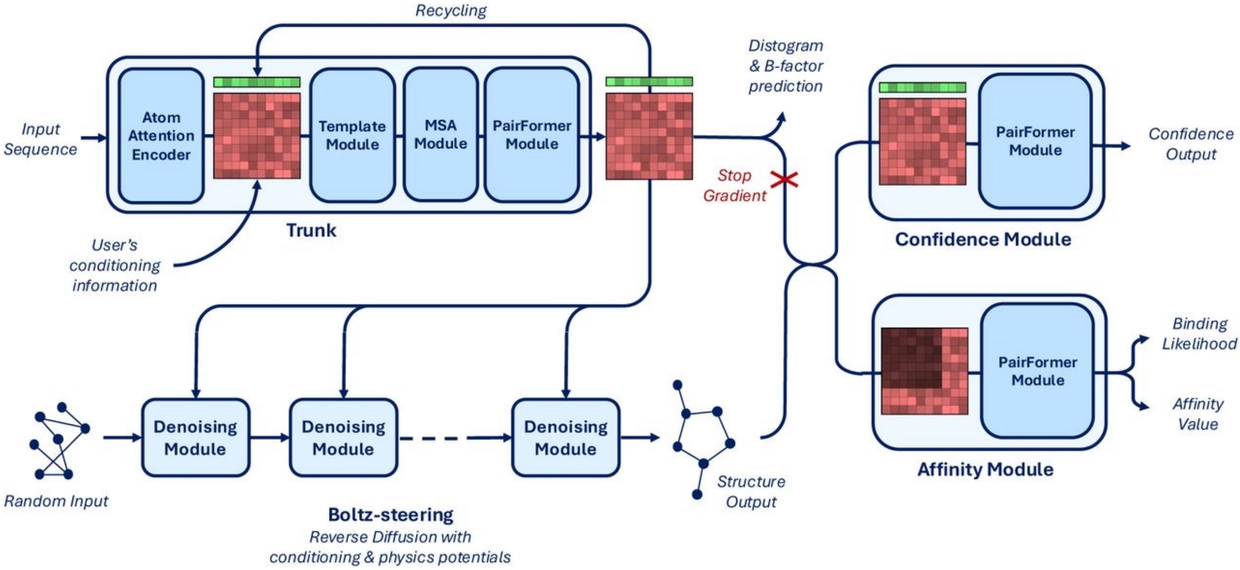


https://www.nature.com/articles/s41586-024-07487-w

Boltz-2

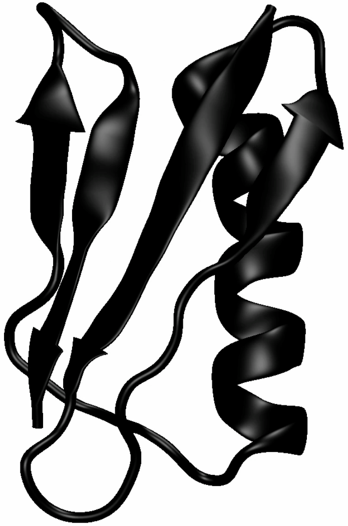
- Drugs, ligands
- Affinities!

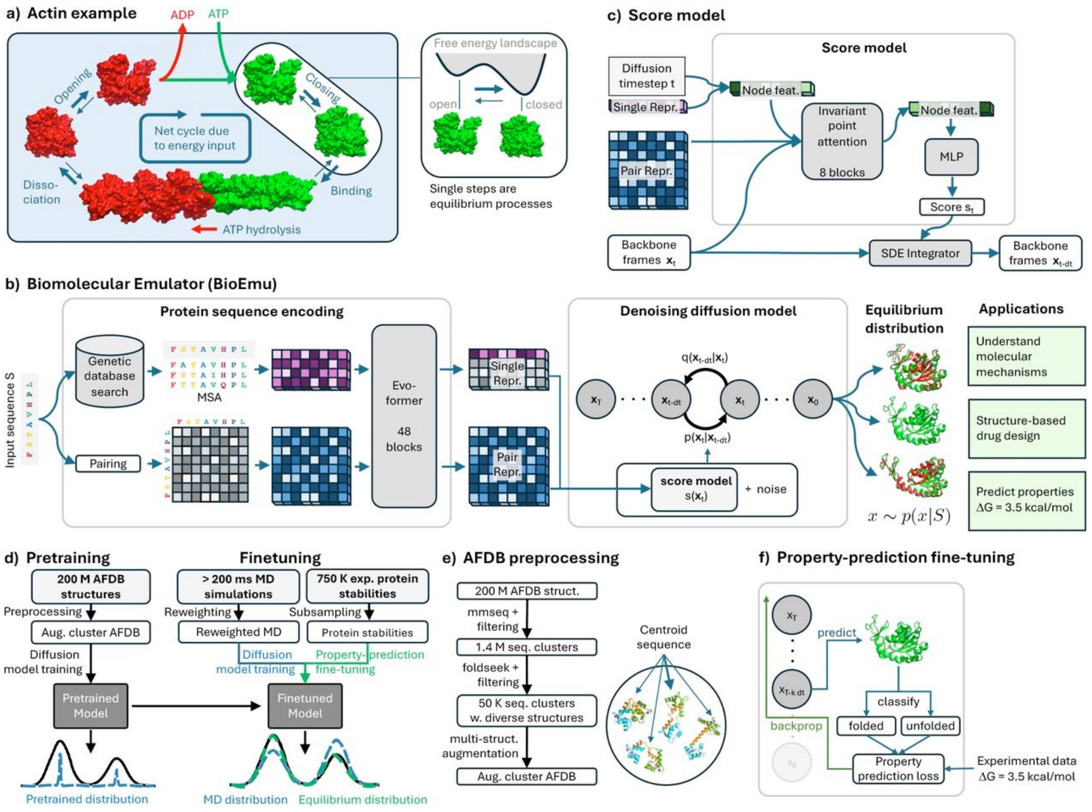
and Open Access!



https://www.biorxiv.org/content/10.1101/2025.06.14.659707v1

BioEmu – proteins are NOT static!

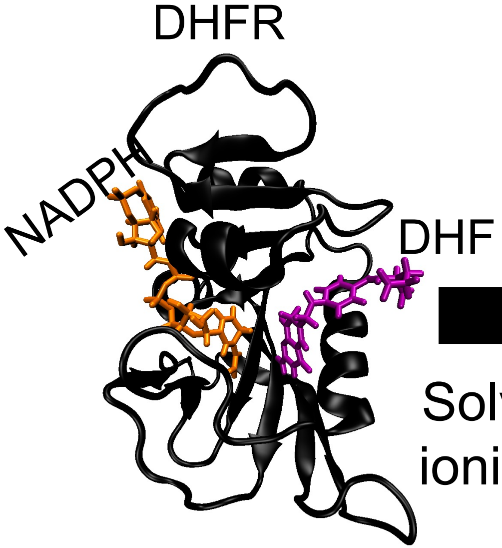




https://www.science.org/doi/10.1126/science.adv9817

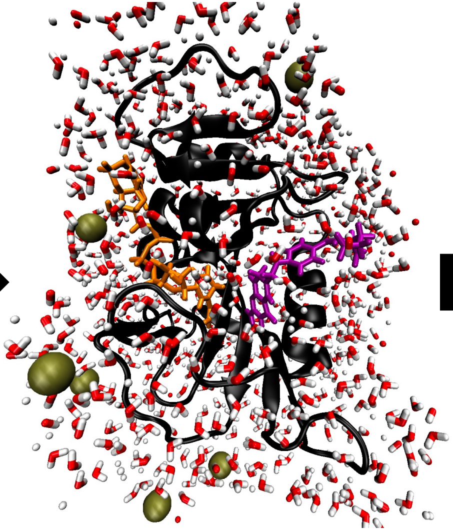
Physics-based methods?

Molecular Dynamics (MD) simulations



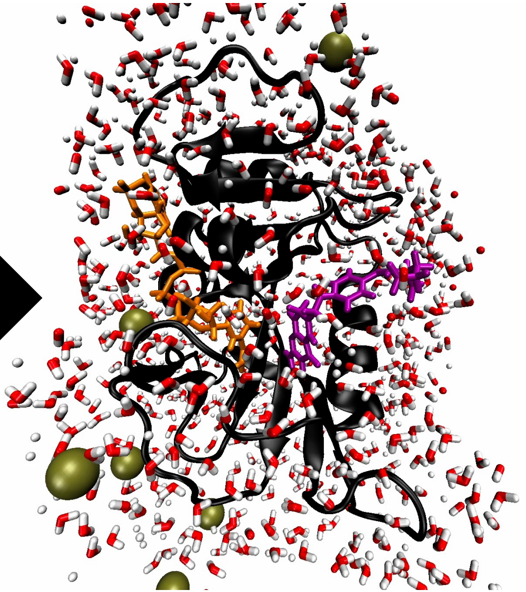
Experimentally solved
structure
(Protein Data Bank)

Solvation
ionization



Isotonic solution
Water +
0.15 M KCl salt

MD



Molecular dynamics
simulations at 310 K
CHARMM36 force-field
Namd3 software

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Thanks!

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the European Union

EuroHPC
Joint Undertaking

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