Alphafoldology
ML Revolution in Structural Biology and how to use it

Marian Novotný, **Karel Berka**

1st April 2022, updated January 2024

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PŘÍRODOVĚDECKÁ FAKULTA
Univerzita Karlova

Outline

- Protein structure prediction
- CASP14
- AlphaFold2 - under the hood
- Basic uses of AF2
- AF2 DB
- AF2 publically available servers
- Limitations and challenges - Alphafoldology

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NEWS · 30 NOVEMBER 2020

‘It will change everything’: DeepMind’s AI makes gigantic leap in solving protein structures

‘The game has changed.’ AI triumphs at solving protein structures

We have been stuck on this one problem – how do proteins fold up – for nearly 50 years. To see DeepMind produce a solution for this, having worked personally on this problem for so long and after so many stops and starts, wondering if we’d ever get there, is a very special moment.

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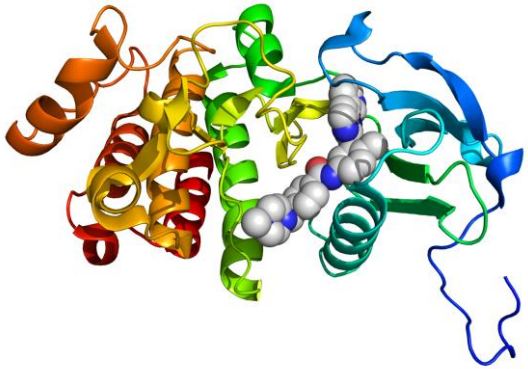
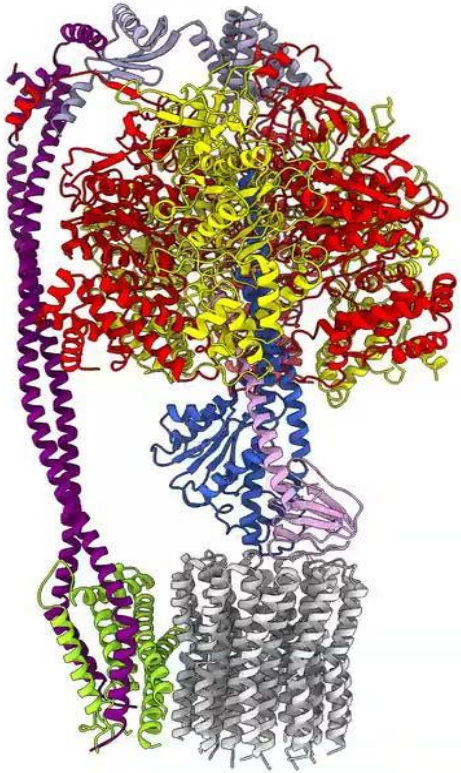
PROFESSOR JOHN MOULT
CO-FOUNDER AND CHAIR OF CASP, UNIVERSITY OF MARYLAND

Knowing structure helps to understand the function



wikipedia/imatinib



Guo et al., 2019

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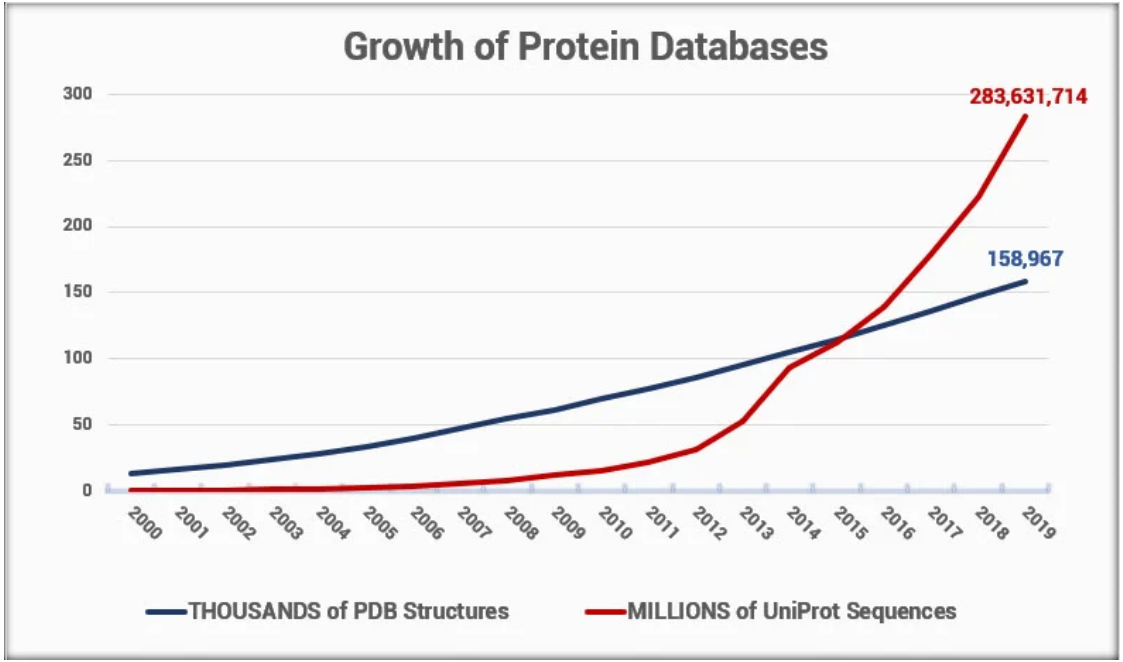
Solving 3D structures is still difficult...



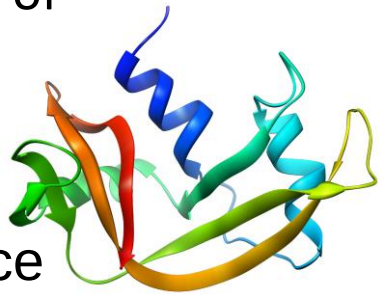
https://www.dnastar.com/blog/structural-biology/why-structure-prediction-matters

The gap between numbers of experimental structures and sequences is increasing over time

Can we use sequence to predict 3D structure?

- C.B. Anfinsen received Nobel prize in Chemistry (1972) for describing the relationship between sequence and structure

"The native conformation is determined by the totality of interatomic interactions and hence by the amino acid sequence, in a given environment."

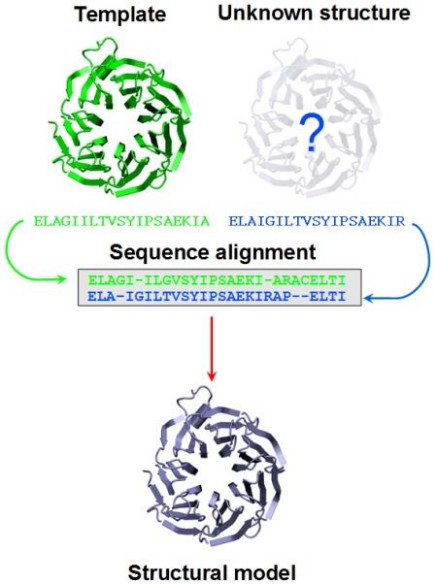


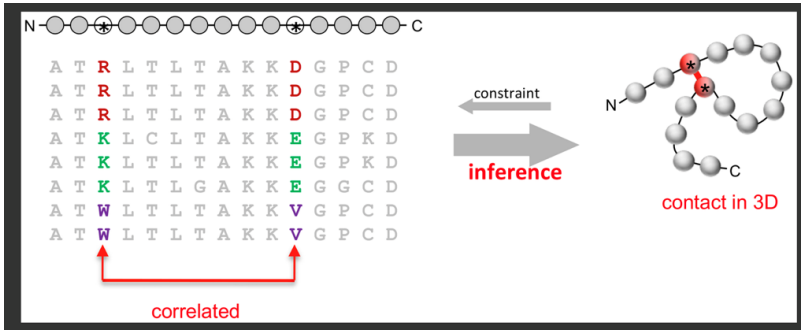
all be possible to predict structure from sequence

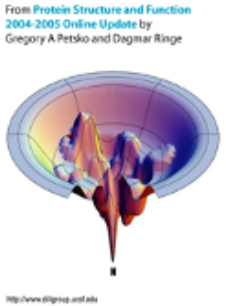
z

wikipedia

Principles of prediction from sequence







https://www.unil.ch/pmf/en/home/menuinst/technologies/homology-modeling.html

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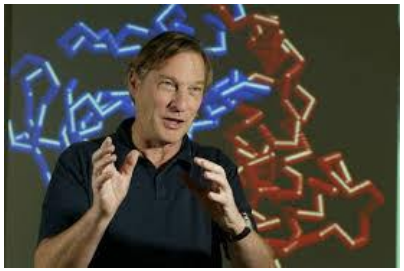
How to move the prediction field forward?

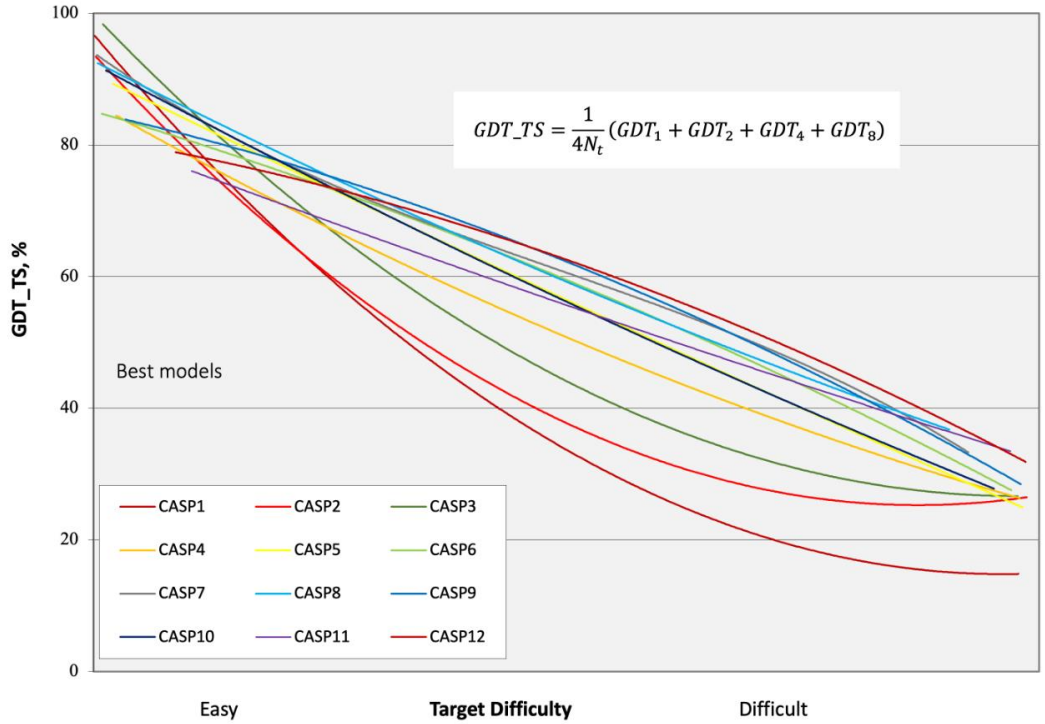
- transparent competition
- provide an “environment” for communication and exchange of experience
- develop metrics for careful examination of predicted structures



- **CASP – critical assessment of protein structure prediction**
- once in two years since 1994
- compare with experimentally solved structures

CASP

How to compare structures?

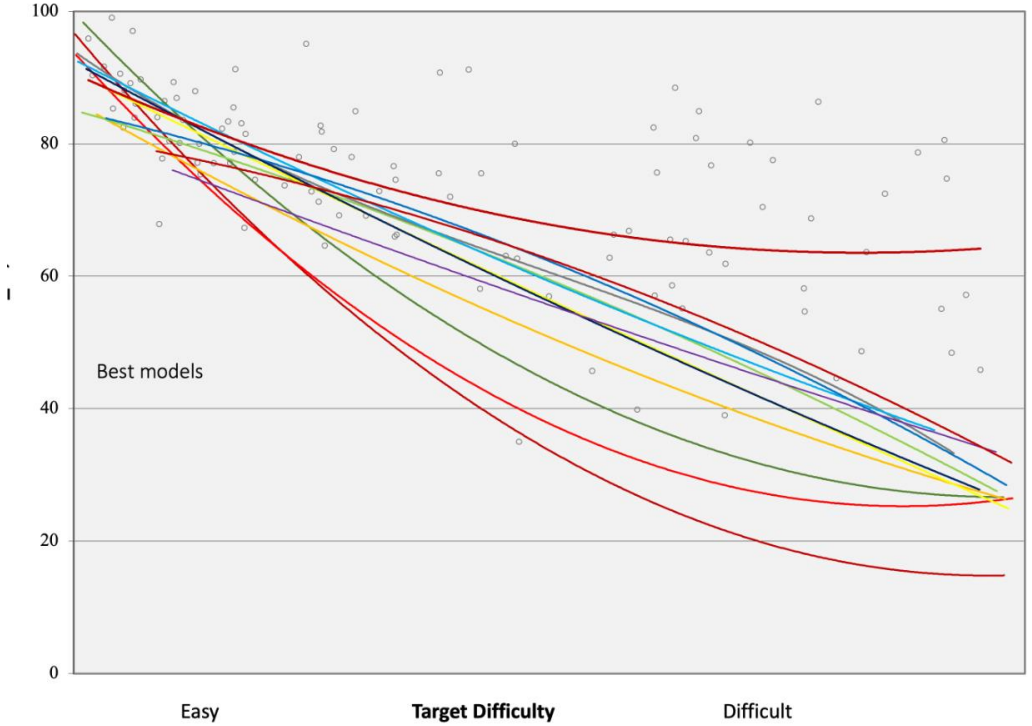


https://predictioncenter.org/casp14/doc/presentations/2020_11_30_CASP14_Introduction_Moult.pdf

GDT_TS = Global distance test - total score (max 100%)

The conventional GDT_TS total score in CASP is the average result of cutoffs at 1, 2, 4, and 8 Å falling within experimental position

2018: AlphaFold enters...



https://predictioncenter.org/casp14/doc/presentations/2020_11_30_CASP14_Introduction_Moult.pdf

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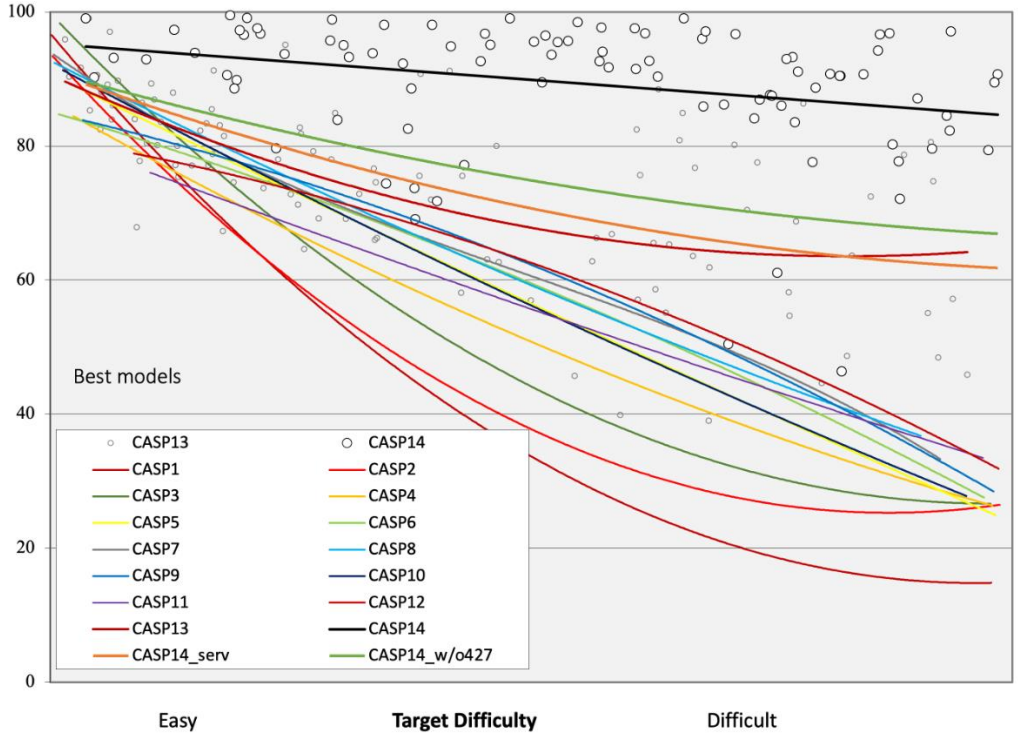
2020: Alphafold2 wins



https://predictioncenter.org/casp14/doc/presentations/2020_11_30_CASP14_Introduction_Moult.pdf

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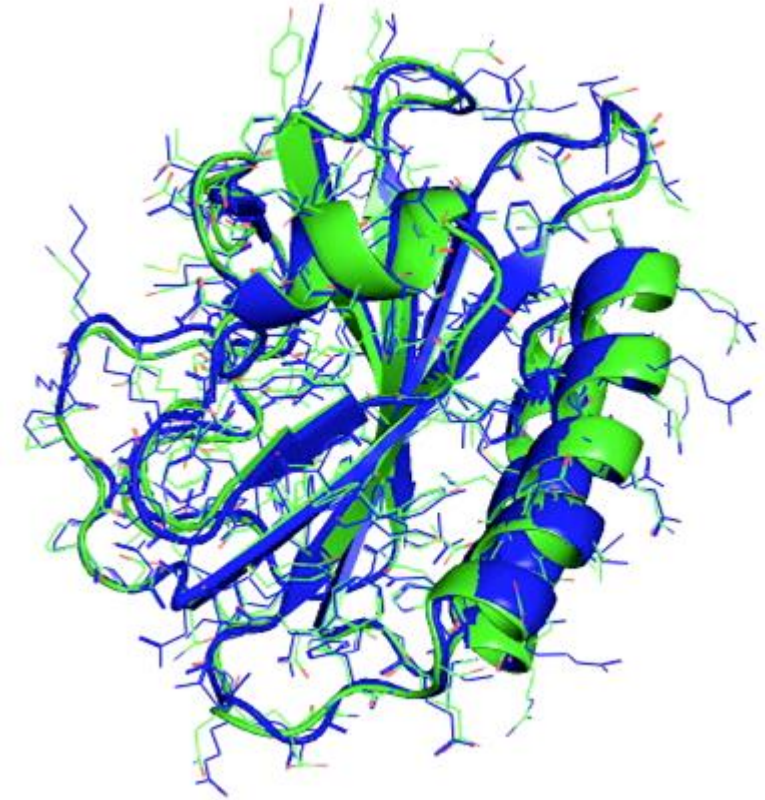
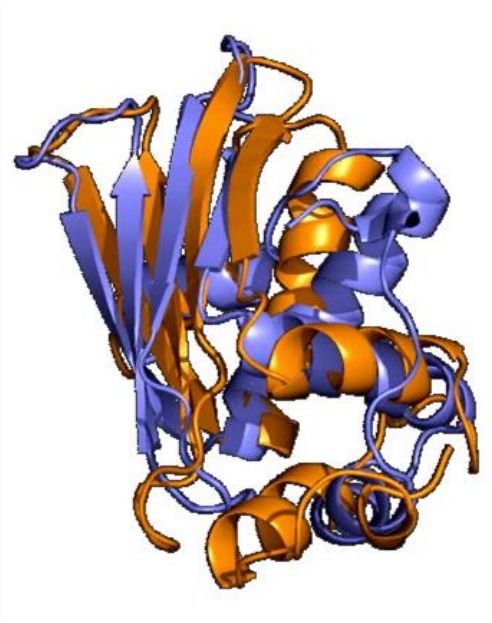
How does good/bad prediction look like?



GDT_TS = 96.5



GDT_TS = 44.6

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CASP14 vs CASP15 comparison

Best CASP15 broadly in line with best CASP14 but …

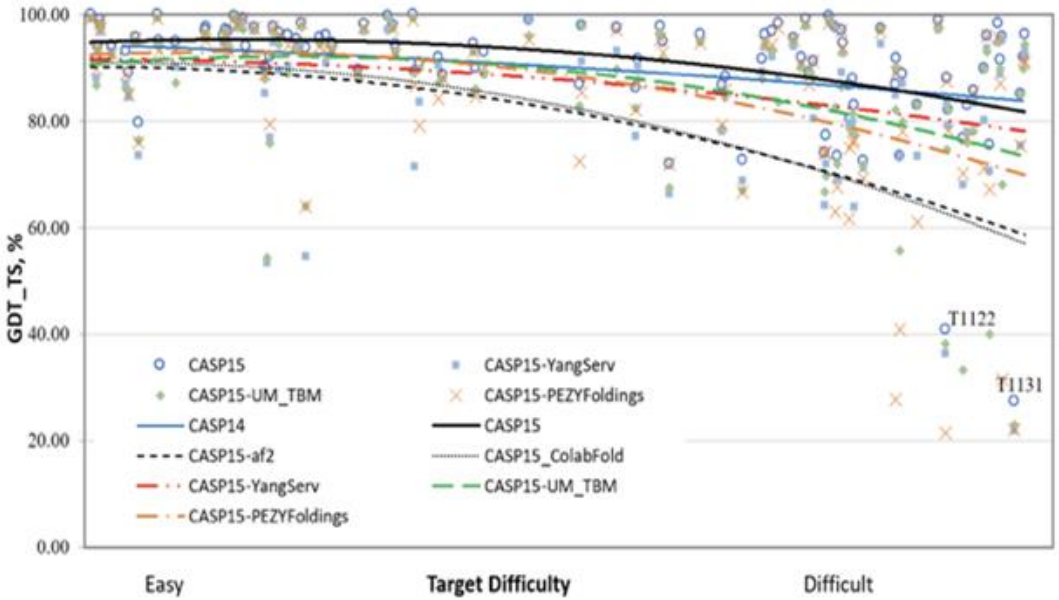
… best CASP14 (mainly AF2) consistently a little higher than best CASP15 groups

NBIS-af2-standard and ColabFold not performing at level of CASP14 DM AF2 submission

CASP invited DeepMind to informally model the set. Broadly this brings performance up to the best official CASP15 groups. vs AF2 'controls' they have

- retrained on current PDB
- increased sampling and crop size
- made some human interventions

So why persistent gap? Are CASP15 targets harder in ways not captured by this scale?



Dan Rigden's slides from CASP 15 conference

AlphaFold2
- under the hood

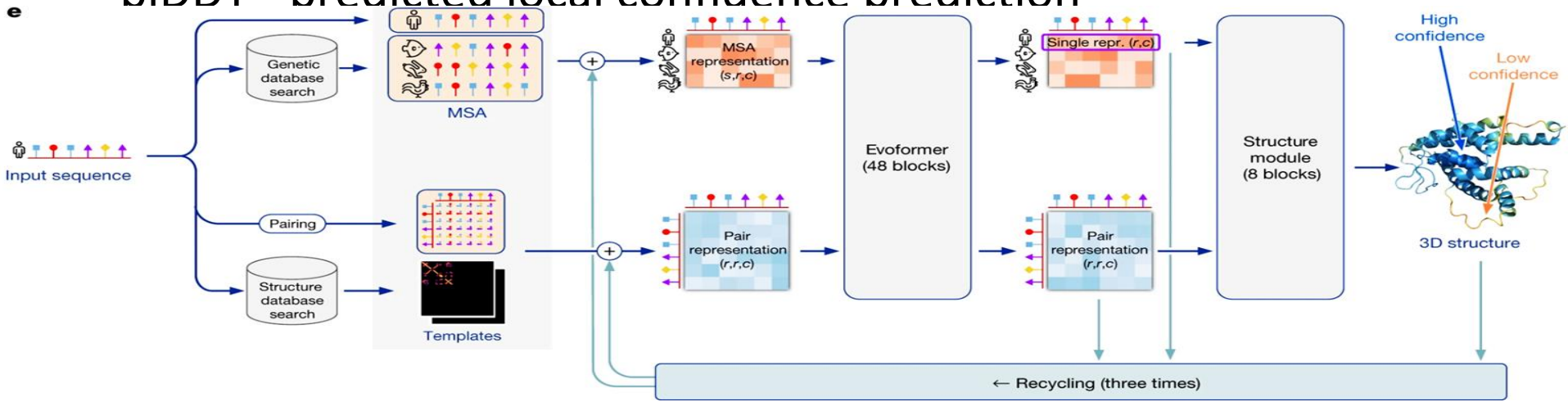
AlphaFold2

Input: sequence

extended by MSA + structural templates

Evoformer and Structure model (w Amber MD simulation)

plDDT - predicted local confidence prediction



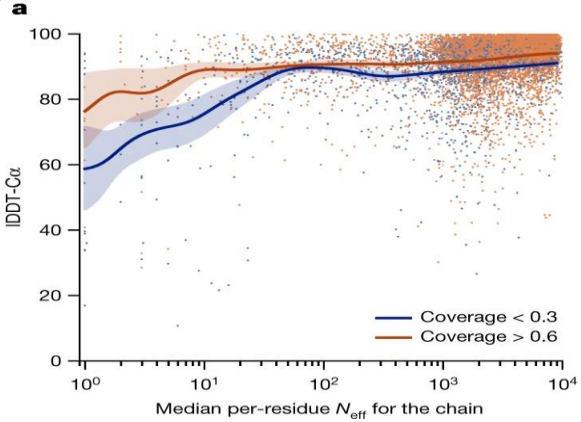
https://www.nature.com/articles/s41586-021-03819-2

MSA - multiple sequence alignment

using standard tools - jackhmmer, HHBlits

- sequence DBs:
  - *UniRef90*
  - *UniClust30* = for sequence self-distilation
- metagenomicsDBs - to fully cover classes underepresented in UniRef90
  - *Big Fantastic database (BFD)* = 66M protein families from 2.2G protein sequences
  - clustered *MGnify*

needed at least 30 sequences per MSA otherwise quality deteriorated>



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

Training

PDB database + PDB70 clusters

training db:

40% identity clusters, crop to 258 residues, batches by 128 per Tensor processing unit (TPU)

enhance accuracy by **noisy student self-distillation**

predict 350000 structures from UniRef30 using trained network

filter to high confidence subset

then train again from scratch with mixture of PDB and UniRef30

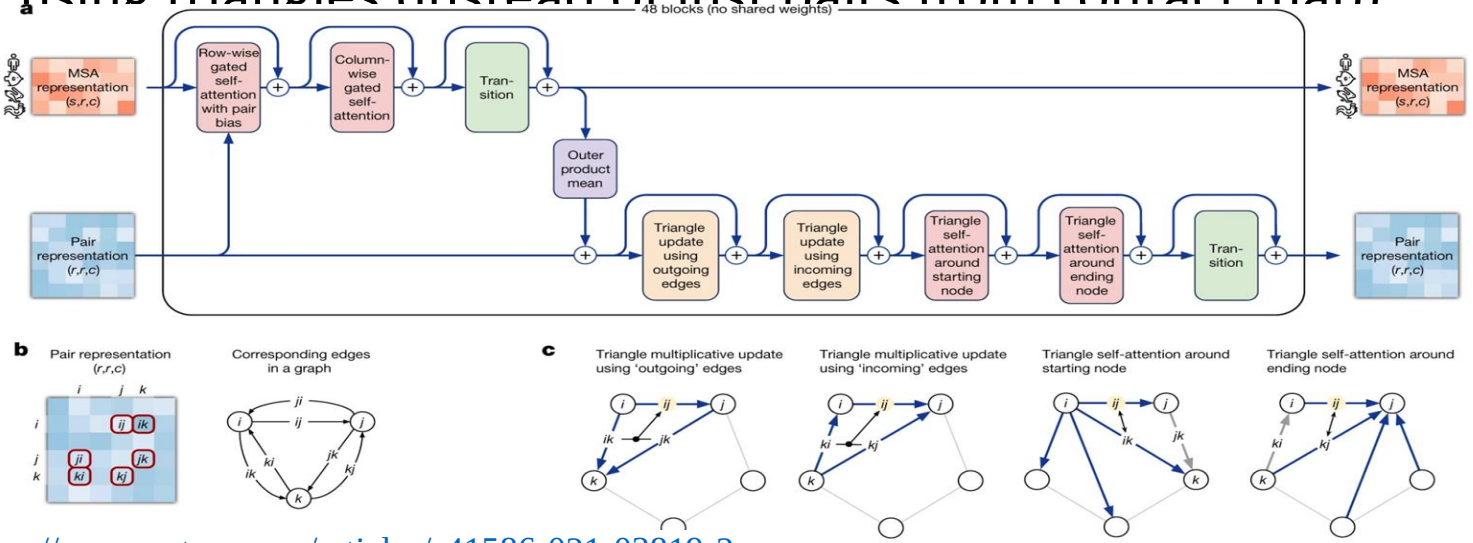
=> effective use of unlabelled sequence data

randomly mask or mutate individual residues from MSA using BERT (bidirectional encoder representations from Transformers => to predict masked elements within MSA

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

EvoFormer

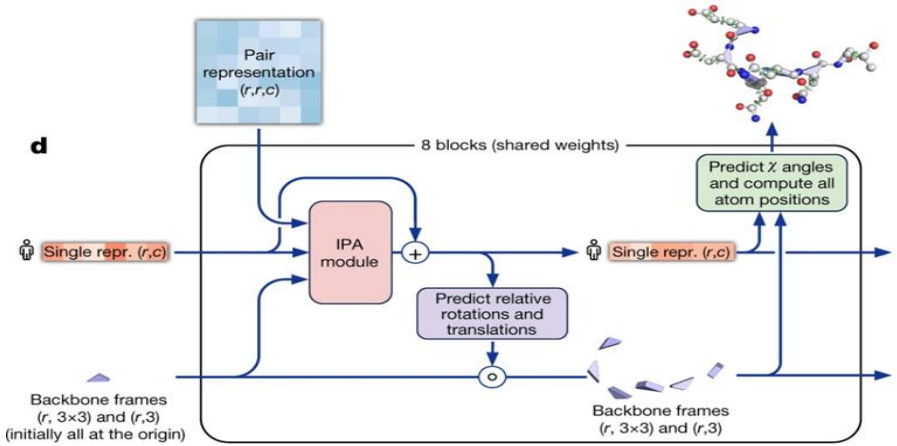
- mixing MSA and pairs via updates
- graph inference problem in 3D space
  - edges = residues in proximity
  - updates per each block (48 blocks) separately (AF1 updated all network at once)
- using triangles (instead of just pairs from contact map)

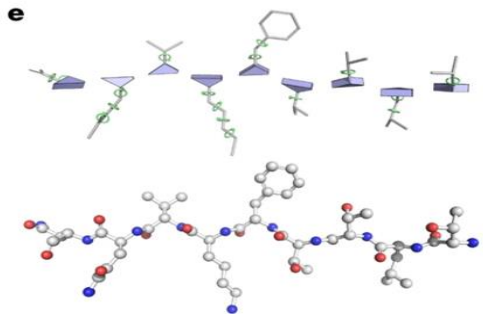


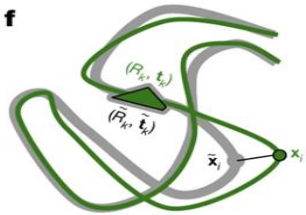
https://www.nature.com/articles/s41586-021-03819-2

Structure model

- prioritize backbone positions+orientations
  - residue gas - free floating rigid body rotations and translation
  - updates
    - IPA (invariant point attention) - neural activations only in rigid 3D
    - equivariant update using updated activations
- later fix backbone geometry
  - avoid loop closure problem)
- sidechain final refinement:
  - OpenMM with Amber 99sb forcefield





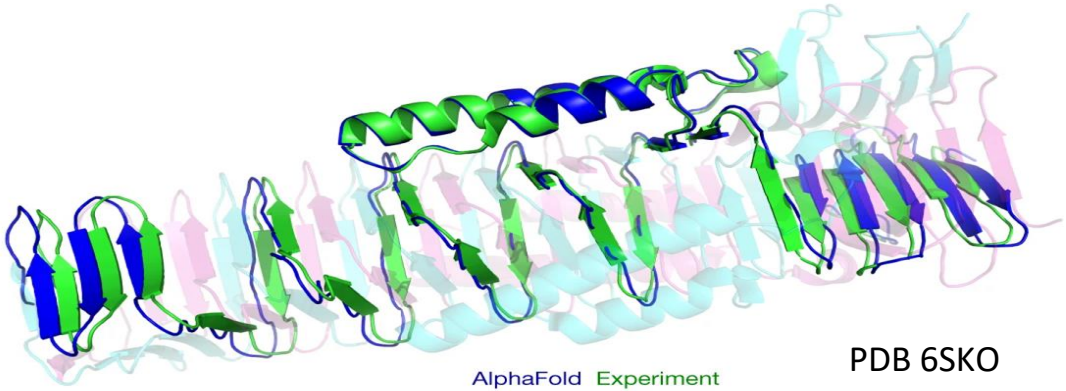


https://www.nature.com/articles/s41586-021-03819-2

Effect of cross-chain contacts.

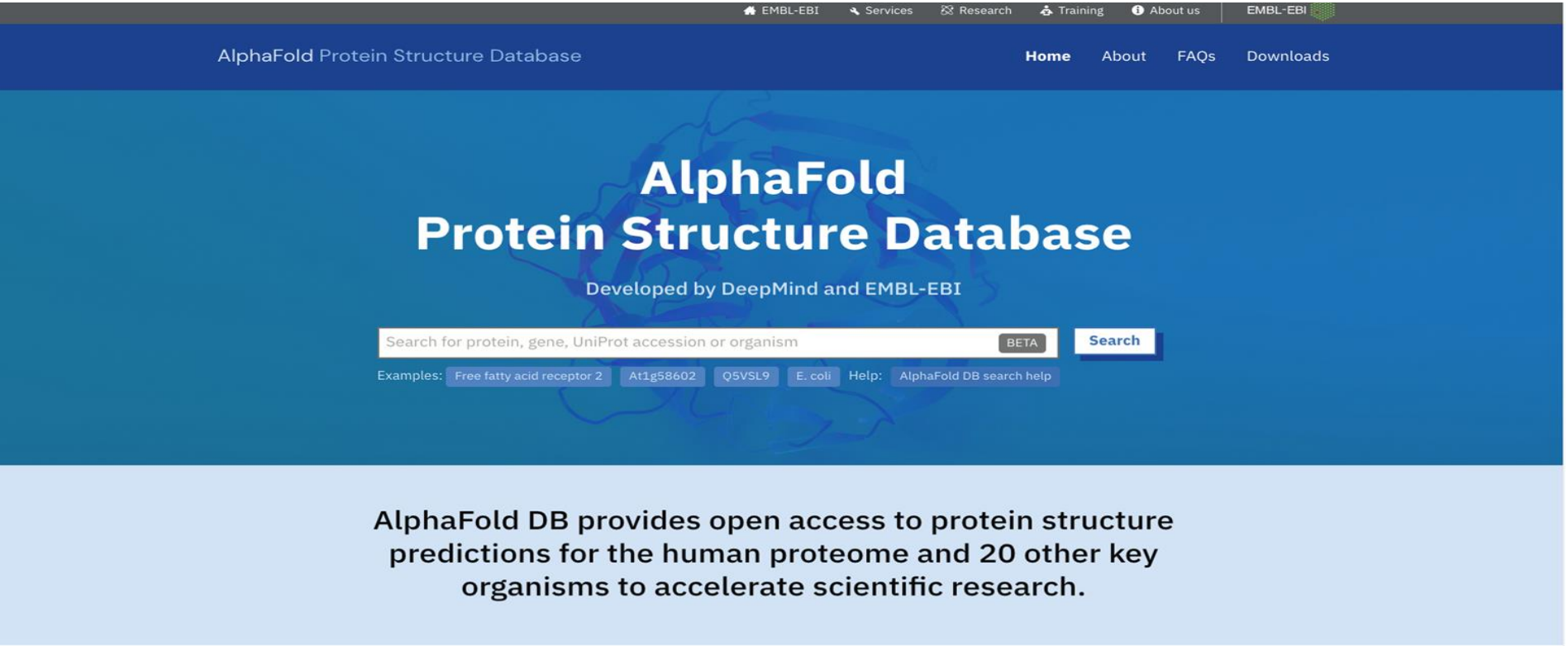
prediction is worse for **heterotropic** contacts (large complexes where 3D structure is dictated by other chains in complex)

homotropics yields high-accuracy even when chains are intertwinned



PDB 6SKO

AlphaFoldDB



"This will be one of the most important datasets since the mapping of the Human Genome."
Professor Ewan Birney
EMBL Deputy Director General and EMBL-EBI Director

https://www.alphafold.ebi.ac.uk/

Complete structures of 48 model organism proteomes

AlphaFold DB currently provides predicted structures for the 48 organisms listed below, as well as the majority of Swiss-Prot. > 200 M structures

Compressed prediction files for model organism proteomes:

Species	Common Name	Reference Proteome	Predicted Structures	Download
Arabidopsis thaliana	*Arabidopsis*	UP000006548	27,434	Download (3,678 MB)
Caenorhabditis elegans	Nematode worm	UP000001940	19,694	Download (2,626 MB)
Candida albicans	*C. albicans*	UP000000559	5,974	Download (974 MB)
Danio rerio	Zebrafish	UP000000437	24,664	Download (4,180 MB)

Compressed prediction files for global health proteomes:

Species	Common Name	Reference Proteome	Predicted Structures	Download
Ajellomyces capsulatus	Ajellomyces capsulatus	UP000001631	9,199	Download (1,351 MB)
Brugia malayi	Brugia malayi	UP000006672	8,743	Download (1,274 MB)
Campylobacter jejuni	*C. jejuni*	UP000000799	1,620	Download (173 MB)
Cladophialophora carrionii	Cladophialophora carrionii	UP000094526	11,170	Download (1,716 MB)

Compressed prediction files for Swiss-Prot:

File type	Predicted Structures	Download
Swiss-Prot (CIF files)	542,380	Download (36,896 MB)
Swiss-Prot (PDB files)	542,380	Download (26,935 MB)

SNW domain-containing protein 1

AlphaFold structure prediction

Download **PDB file** **mmCIF file** **Predicted aligned error**

Information

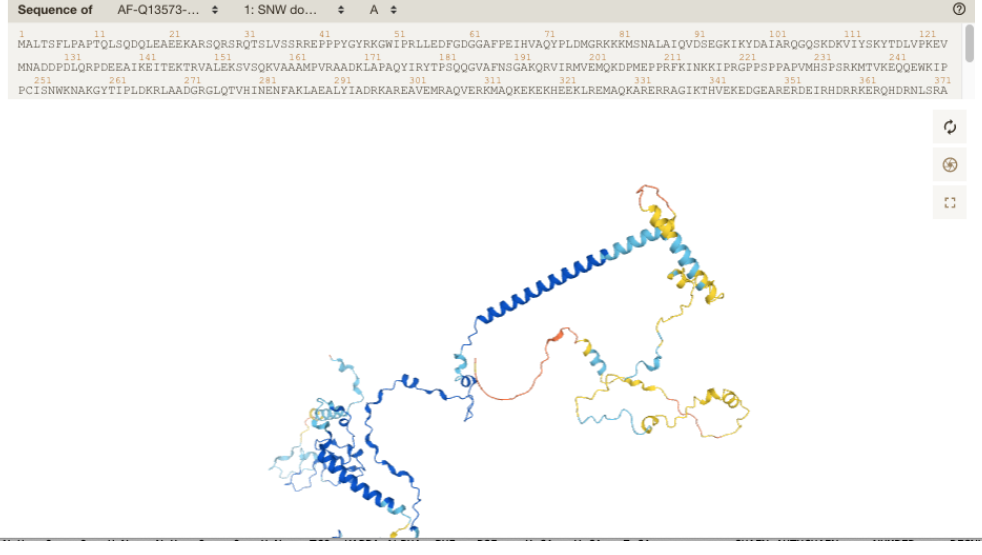
Protein	SNW domain-containing protein 1
Gene	SNW1
Source organism	Homo sapiens go to search
UniProt	Q13573 go to UniProt
Experimental structures	17 structures in PDB for Q13573 go to PDBe-KB
Biological function	(Microbial infection) Proposed to be involved in transcriptional activation by EBV EBNA2 of CBF-1/RBPJ-repressed promoters. go to UniProt

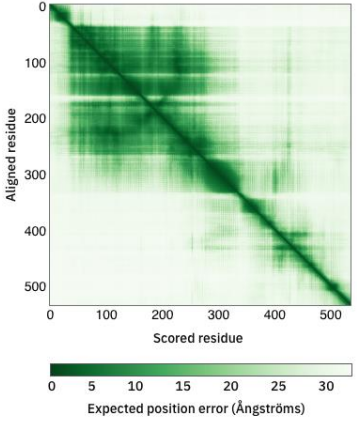
3D viewer

Model Confidence:

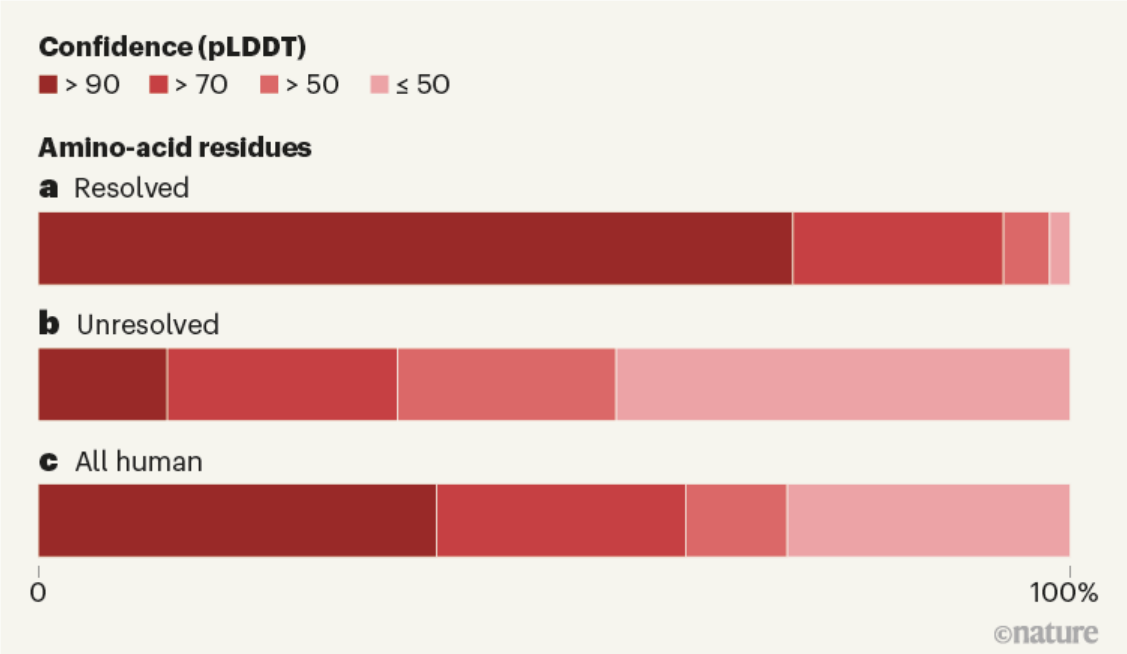
- Very high (pLDDT > 90)
- Confident (90 > pLDDT > 70)
- Low (70 > pLDDT > 50)
- Very low (pLDDT < 50)

AlphaFold produces a per-residue confidence score (pLDDT) between 0 and 100. Some regions below 50 pLDDT may be unstructured in isolation.





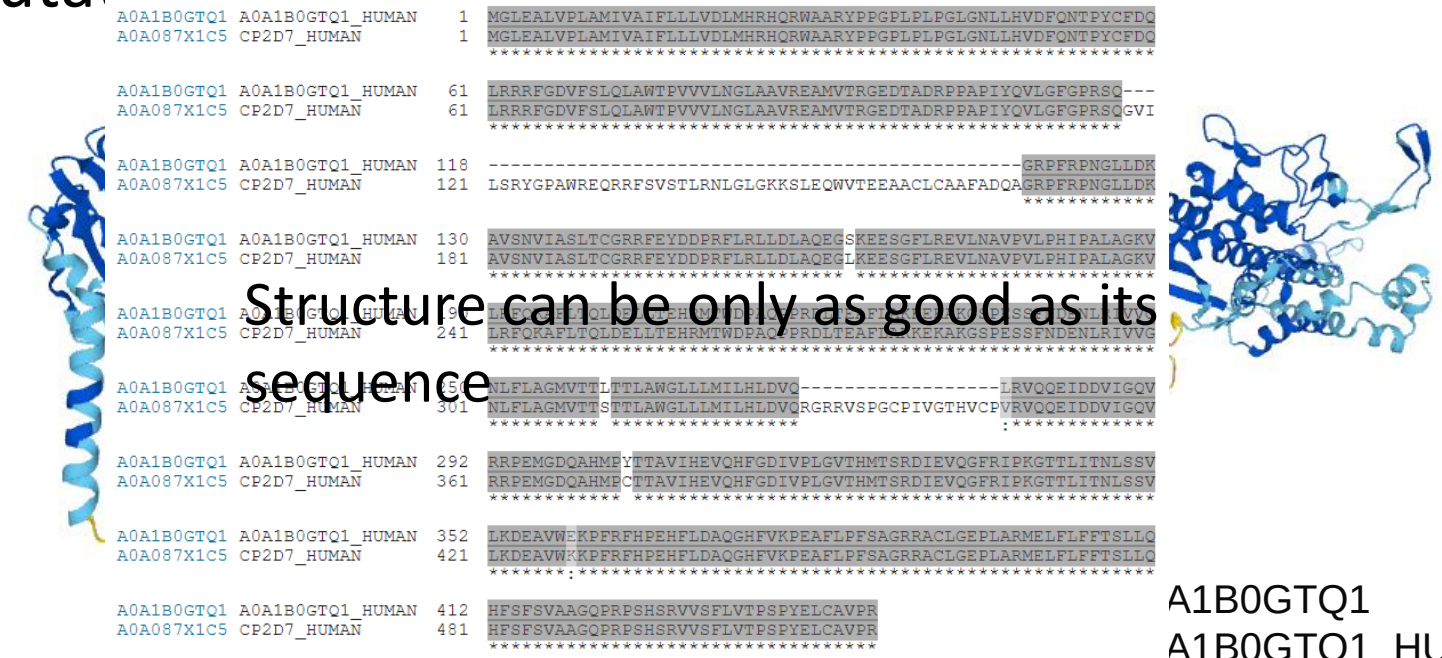
How good are the predictions of human proteins?



pLDDT - per-residue estimate of its confidence on a scale from 0 - 100
model's predicted score on the lDDT-Cα metric (local superposition-free score for comparing protein structures and models using distance difference tests).

But one still needs to be careful…

putative human cytochrome P450 2C7



Structure can be only as good as its sequence

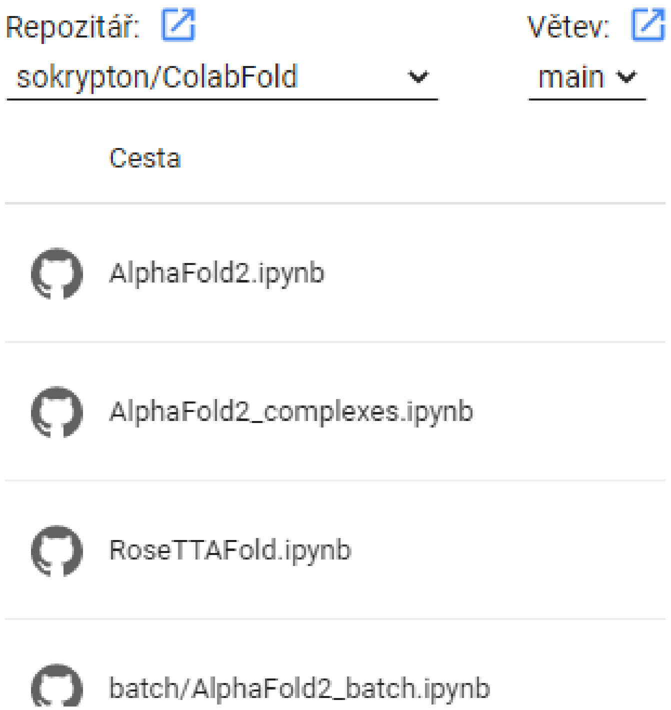
Where to run

AlphaFold in Google Colab

Github enabled JupyterNotebooks running in Google Colab environment

limitation in size (time)

start also from Chimera

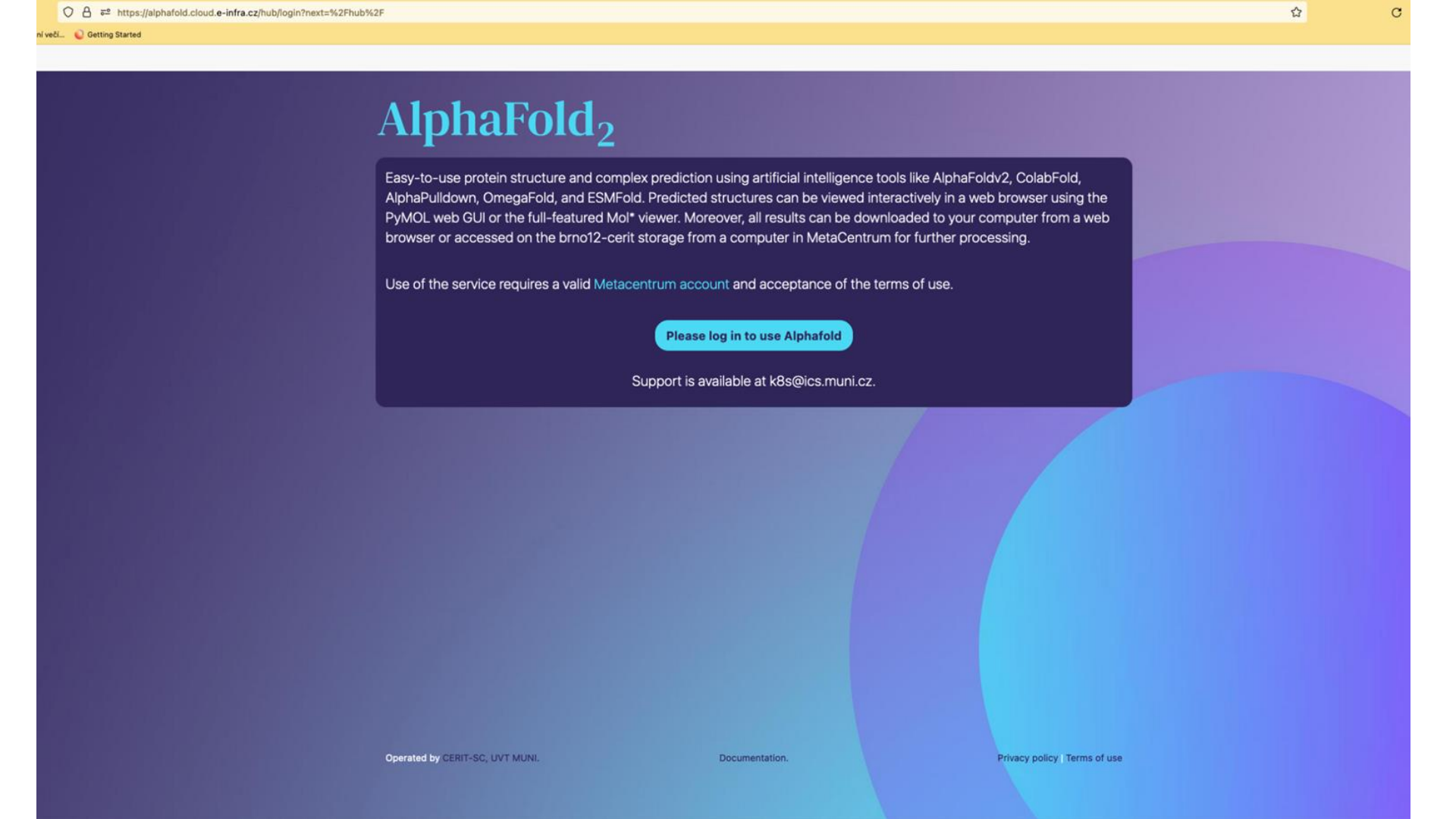


[Mirdita M, Ovchinnikov S, Steinegger M. ColabFold - Making protein folding accessible to all. *bioRxiv*, 2021](https://doi.org/10.1101/2021.08.15.456425) https://doi.org/10.1101/2021.08.15.456425
https://colab.research.google.com/github/sokrypton/ColabFold/

Alphafold 2 on ELIXIR CZ

- Alphafold “needs” TPU to run -> not many people have it on their PC
- Alphafold has been installed on Elixir CZ hardware
- Alphafold (Multimer) in the newest version 2.2.0 is accessible through Metacentrum
- speed is dependent on size of predicted protein (complex)

https://wiki.metacentrum.cz/wiki/AlphaFold


https://alphafold.cloud.e-infra.cz/hub/login?next=%2Fhub%2F
Getting Started
AlphaFold2
Easy-to-use protein structure and complex prediction using artificial intelligence tools like AlphaFoldv2, ColabFold, AlphaPulldown, OmegaFold, and ESMFold. Predicted structures can be viewed interactively in a web browser using the PyMOL web GUI or the full-featured Mol* viewer. Moreover, all results can be downloaded to your computer from a web browser or accessed on the brno12-cerit storage from a computer in MetaCentrum for further processing.
Use of the service requires a valid Metacentrum account and acceptance of the terms of use.
Please log in to use Alphafold
Support is available at k8s@ics.muni.cz.
Operated by CERIT-SC, UVT MUNI.
Documentation.
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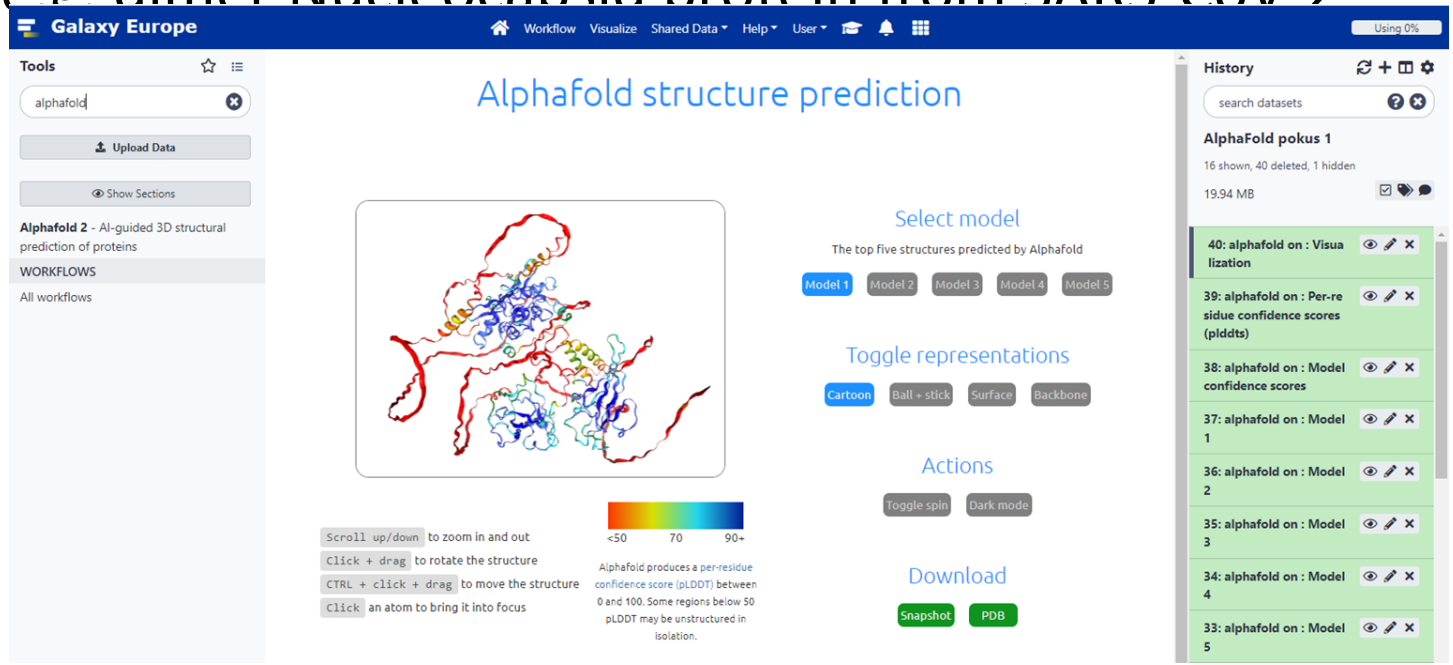
AlphaFold in UseGalaxy.eu

e.g. dimer Nucleocapsid protein from SARS-CoV-2

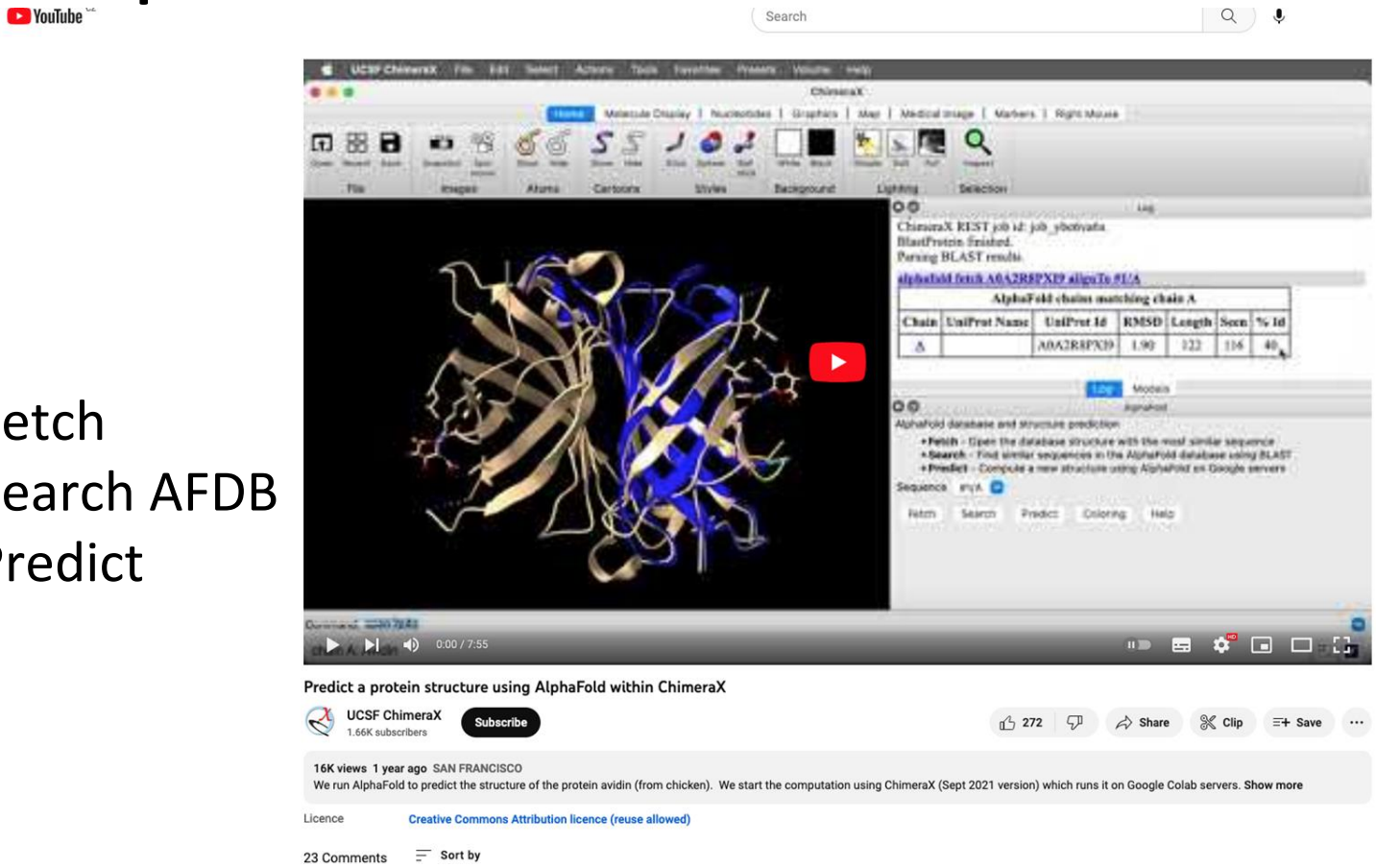


trick - dimerization fake as long disordered poly-N chain

https://usegalaxy.eu/tool_runner?tool_id=toolshed.g2.bx.psu.edu%2Frepos%2Fgalaxy-australia%2Falphafold2%2Falphafold%2F2.1.2%2Bgalaxy0

AlphaFold within ChimeraX

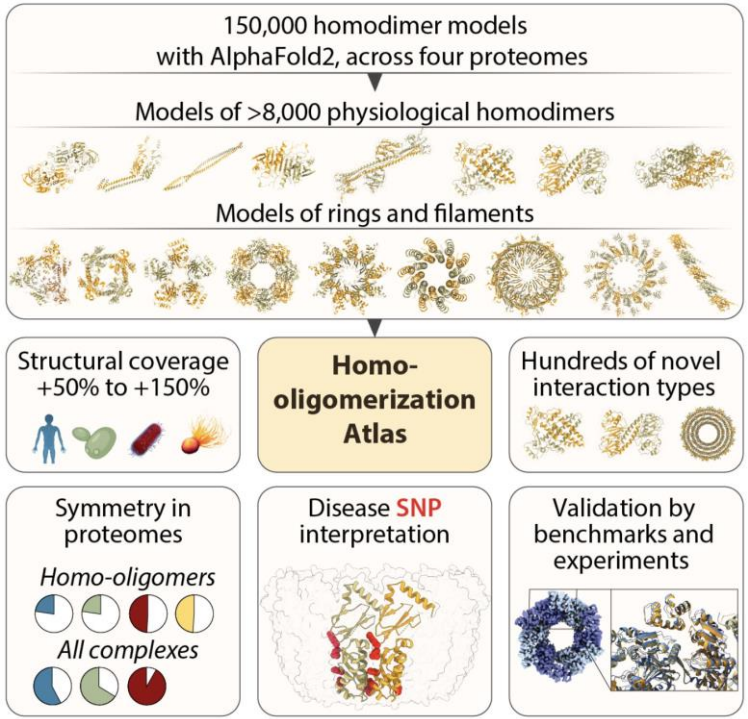
Fetch
Search AFDB
Predict



Limitations

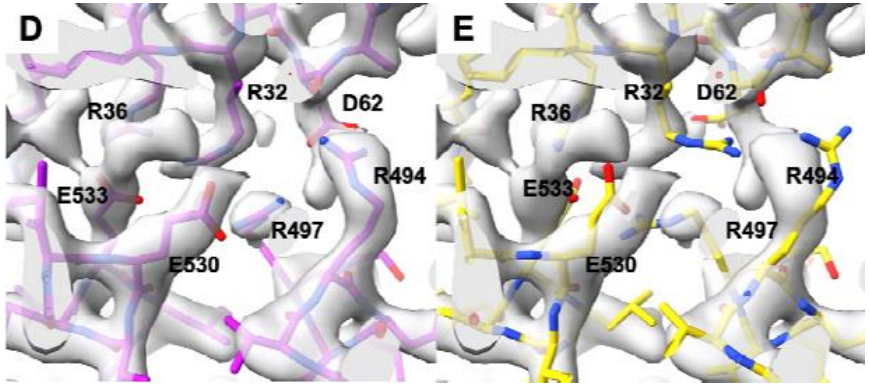
How much does the tertiary structure tell?

- 50% of archaeal, 45% of bacterial, and 20% of eukaryotic proteomes form homomers
- coiled-coil regions as major enablers of quaternary structure evolution in Eukaryotes
- disease mutations are enriched at interfaces



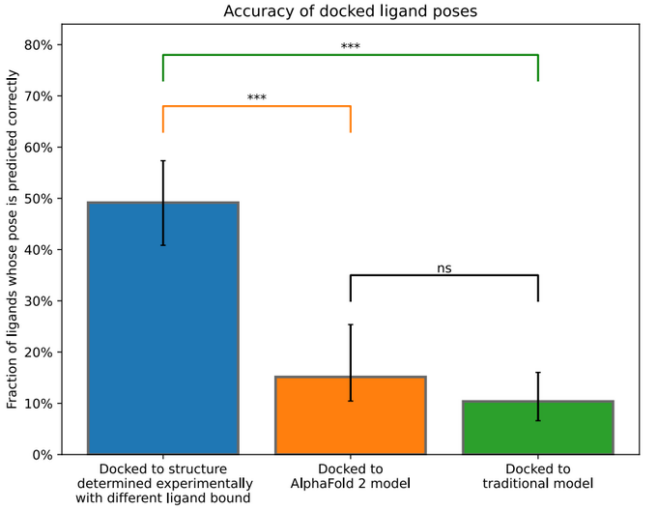
https://www.biorxiv.org/content/10.1101/2023.06.09.544317v1

How accurate are the models?



AlphaFold predictions are valuable hypotheses, and accelerate but do not replace experimental structure determination

Thomas C. Terwilliger, Dorothee Liebschner, Tristan I. Croll, Christopher J. Williams, Airlie J. McCoy, Billy K. Poon, Pavel V. Afonine, Robert D. Oeffner, Jane S. Richardson, Randy J. Read, Paul D. Adams



How accurately can one predict drug binding modes using AlphaFold models?

Masha Karelina, Joseph J. Noh, Ron O. Dror

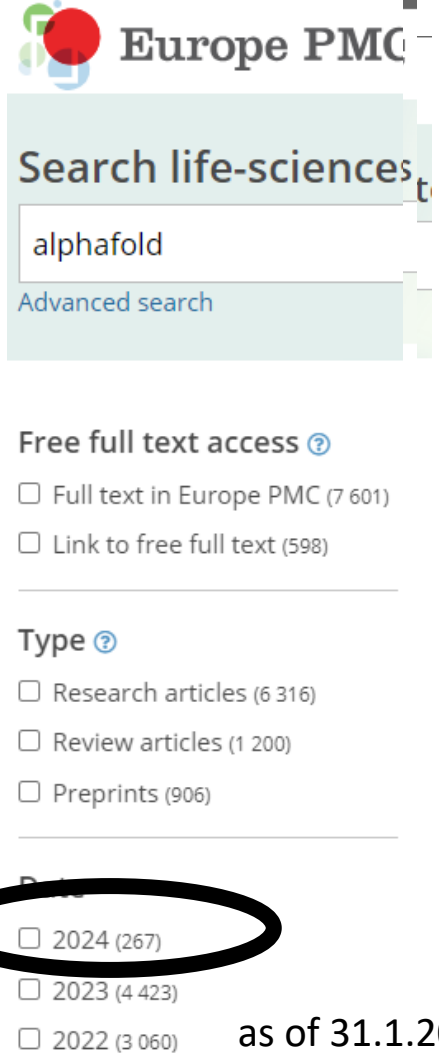
doi: https://doi.org/10.1101/2023.05.18.541346

This article is a preprint and has not been certified by peer review [what does this mean?].

Alphafold is just a start...

- use Alphafold ideas for development of their own 3D structure predictions
  - RoseTTAfold
  - ESMfold
  - OpenFold
  - Chroma
- prediction of designed proteins

...



as of 31.1.2024

Are structural biologists and bioinformaticians on the job market?

- Alphafold does not tell much about **folding process**
- Alphafold can not do **point mutations** - design of functions
- Alphafold is not usable for **drug design**
- Alphafold can not do **conformational changes** or **dynamics**
- Alphafold can not do **multiprotein complexes –** interactions
- Alphafold can not do effects of **post-translational protein modifications**
- Alphafold can not do **ligand effects**
- Alphafold is not good with **orphan sequences**
- **or is it?**

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Alphafold can describe **folding process** to some level
Was Anfinsen right?

New Results

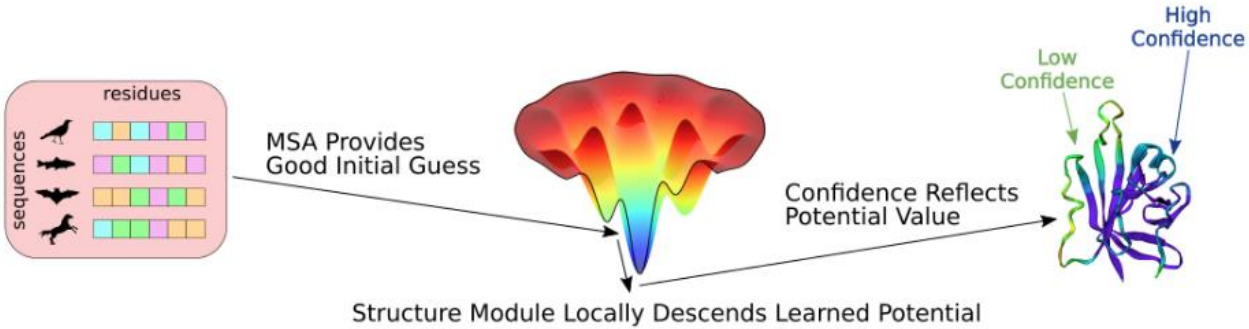
Follow this preprint

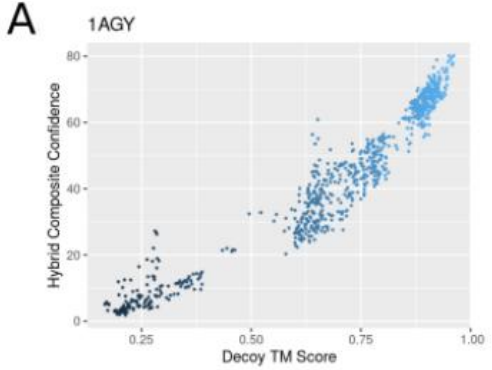
State-of-the-Art Estimation of Protein Model Accuracy using AlphaFold

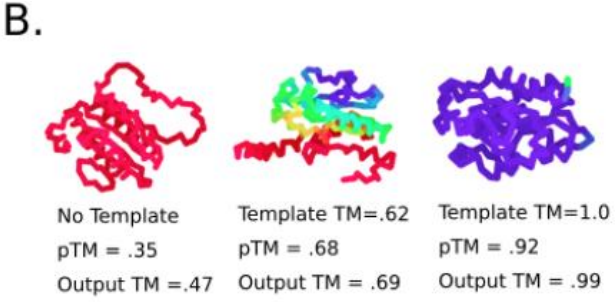
James P. Roney, Sergey Ovchinnikov

doi: https://doi.org/10.1101/2022.03.11.484043

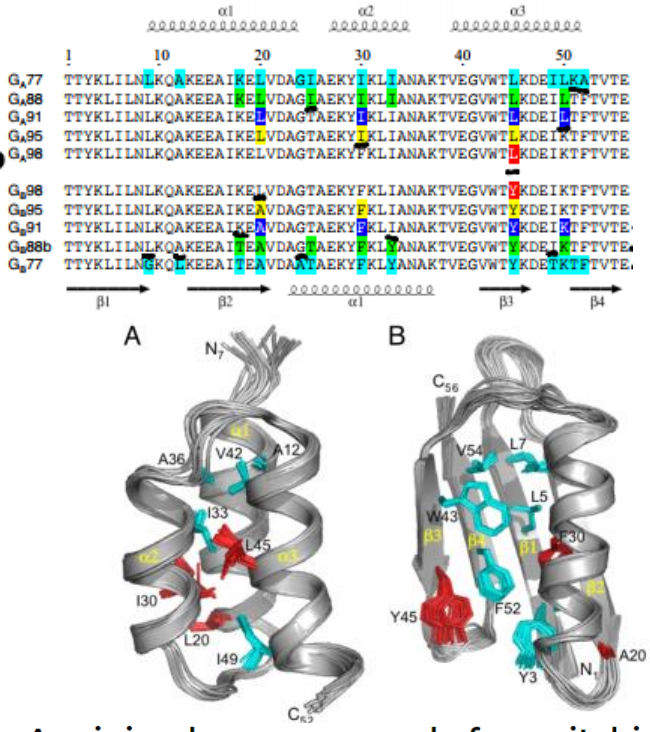
This article is a preprint and has not been certified by peer review [what does this mean?].







Alphafold can do **point-mutations effects**
Fold-switching proteins



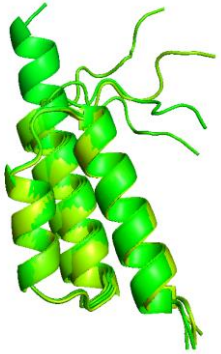
0

A minimal sequence code for switching protein structure and function

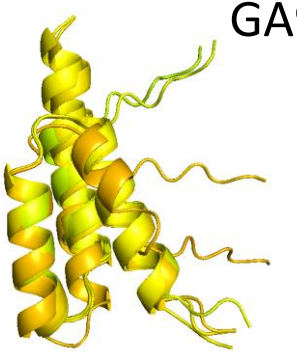
Patrick A. Alexander, Yanan He, Yihong Chen, +1, and Philip N. Bryan Authors Info & Affiliations

December 15, 2009 | 106 (50) 21149-21154 | https://doi.org/10.1073/pnas.0906408106

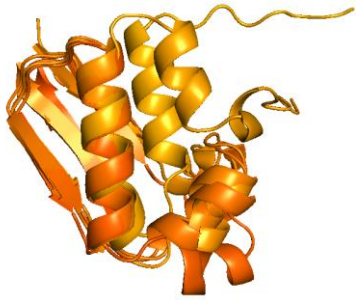
L45Y



GA77



GA98



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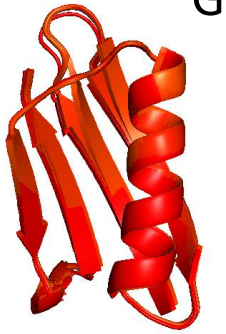
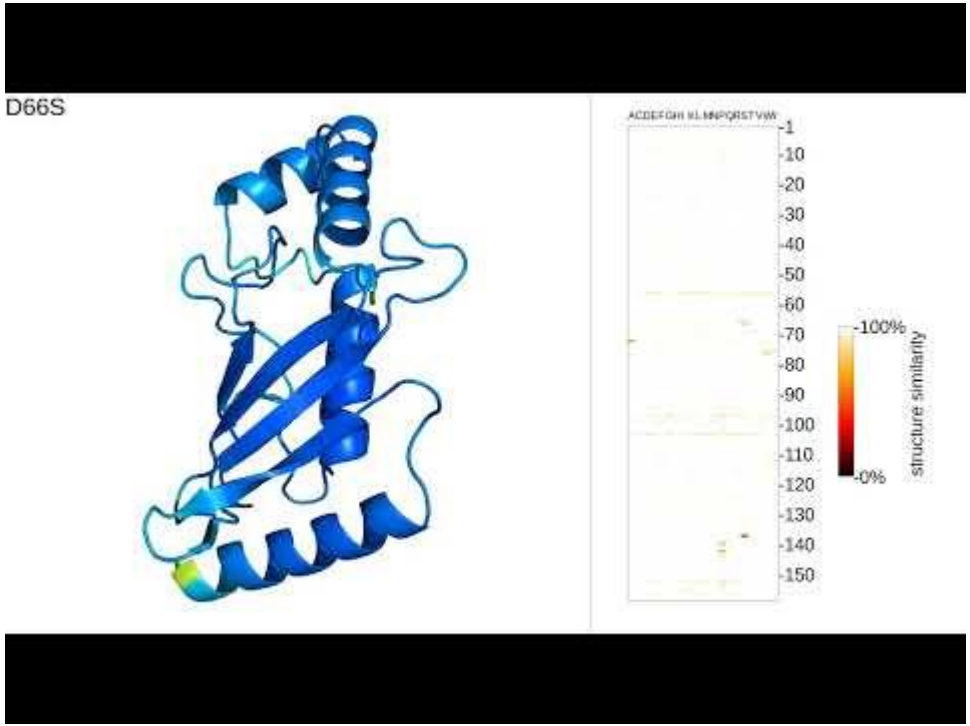


GB77

GB98 models shows mix between **3α** to **α+β**
own calculations

MutAmore

- generate all SNPs of protein
- using ESMfold/OpenFold



Rendering protein mutation movies with MutAmore

Konstantin Weissenow, Burkhard Rost

doi: https://doi.org/10.1101/2023.09.15.557870

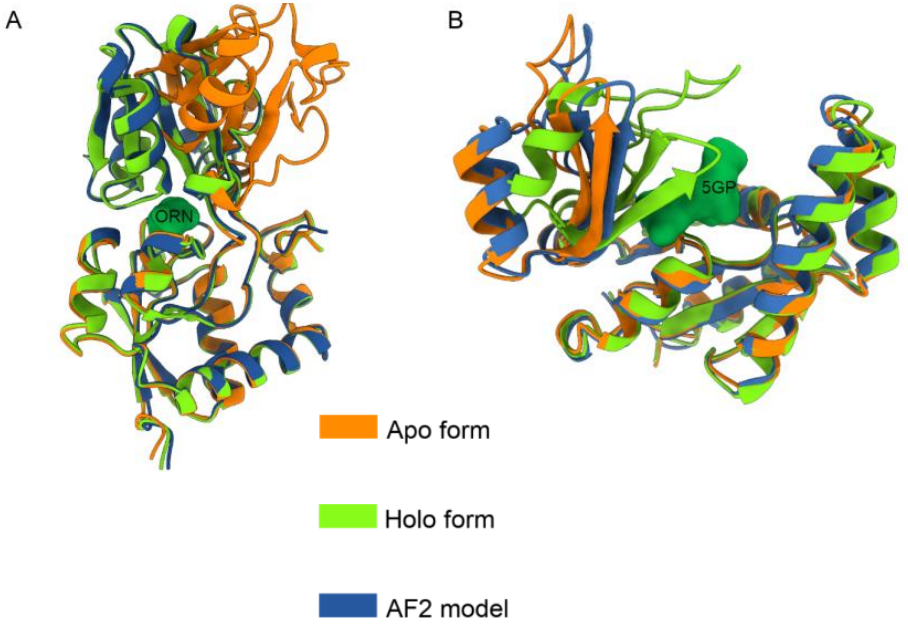
https://www.youtube.com/watch?v=1XgiFXg-Xrs&list=PL0QUUE_zWBuJ6Y5NWtDoY93FUweUUGVuf

https://www.biorxiv.org/content/10.1101/2023.09.15.557870v1

https://github.com/kWeissenow/MutAmore

AlphaFold models good enough for **drug design**?

- AlphaFold2 predicts **holo** protein in 70% => it can be used for drug designing
- pLDDT values in a single 3D model could be used to infer local conformational changes linked to ligand binding transitions.
- locally AlphaFold2 can be there - but it needs validation (as always)



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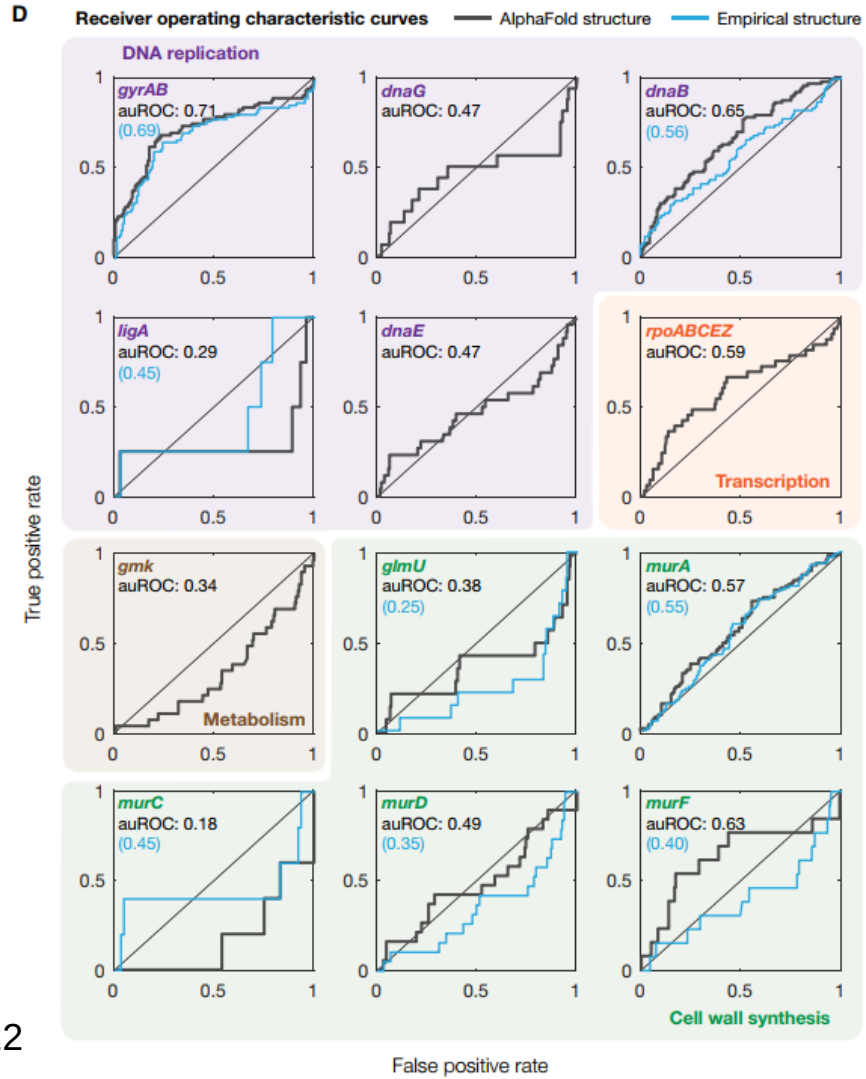
Impact of protein conformational diversity on AlphaFold predictions

Tadeo Saldaño, Nahuel Escobedo, Julia Marchetti, Diego Javier Zea, Juan Mac Donagh, Ana Julia Velez Rueda, Eduardo Gonik, Agustina García Melani, Julieta Novomisky Nechcoff, Martín N. Salas, Tomás Peters, Nicolás Demitroff, Sebastian Fernandez Alberti, Nicolas Palopoli, Maria Silvina Fornasari, Gustavo Parisi

doi: https://doi.org/10.1101/2021.10.27.466189

AlphaFold docking antibiotics example

- benchmarking docking by metabolic activity of 12 essential proteins
- auROC = 0.48 (Vina on AF2)
- rescoring -> auROC 0.63
- auROC = 0.46 (Vina on experimental structures)
- both bad (auROC random is 0.5)

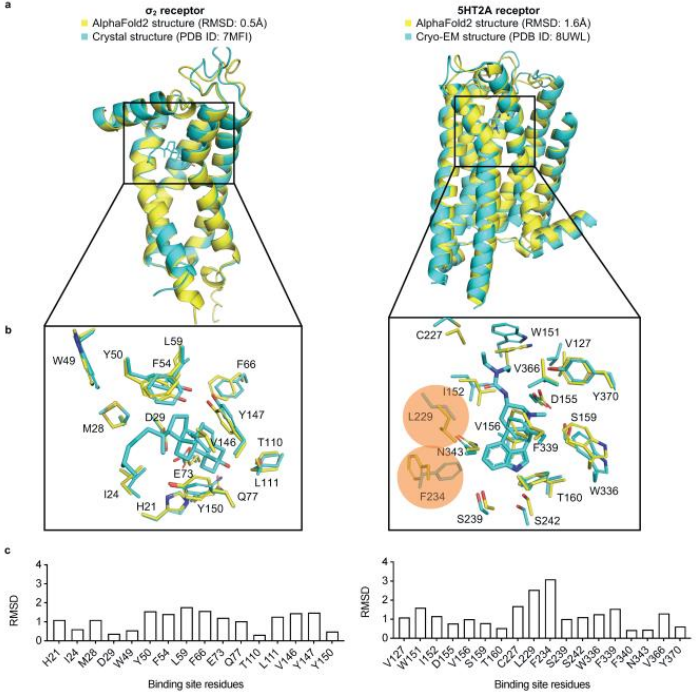


Felix Wong et al. Molecular Systems Biology 18: e11081 | 2022

AlphaFold2 structures template ligand discovery

prospective screen

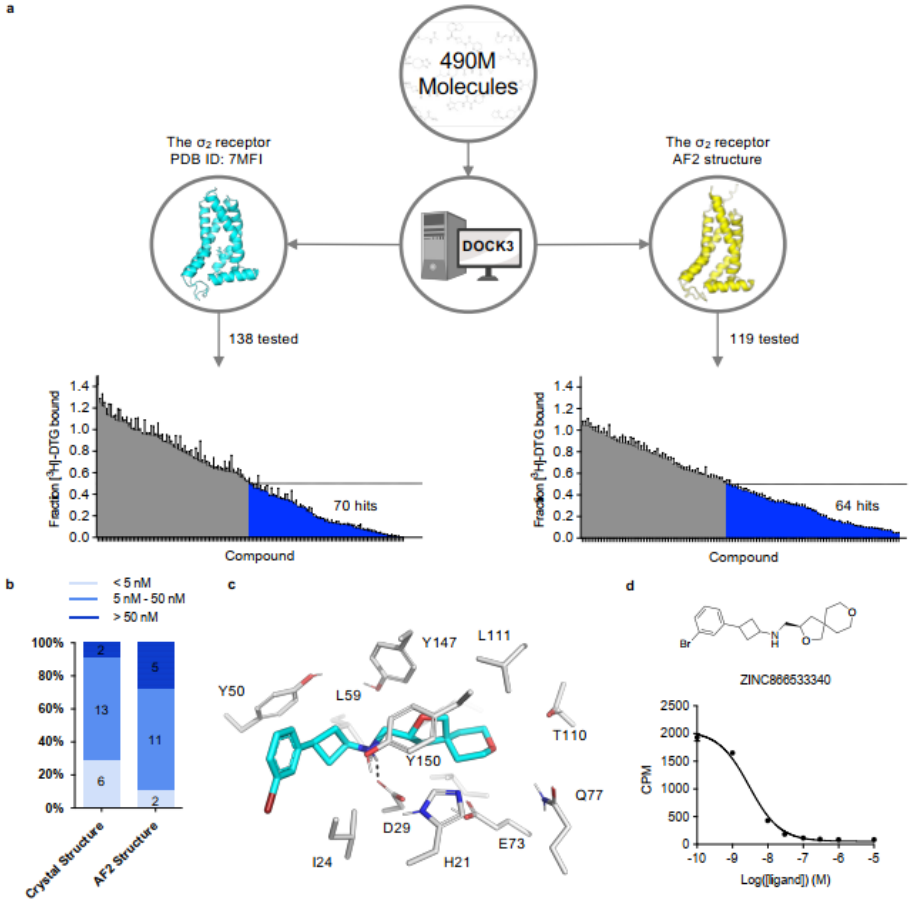
different binding site conformation



average Tc of 0.32, not far from random for this fingerprint. Consistent with the diversit

the most potent ligand from the AF2 campaign, ZINC866533340 (Ki 1.6 nM), represente

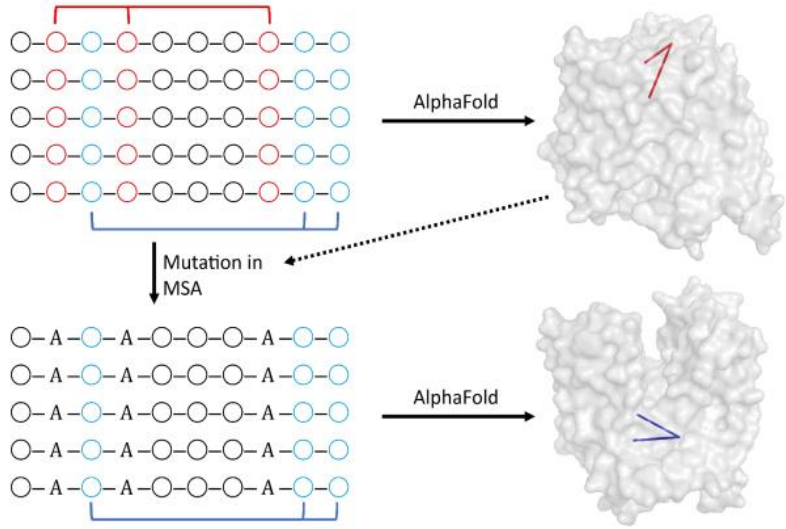
a chemotype previously unseen for the σ_2 receptor (**Fig 2c** and **2d**).



bioRxiv preprint doi: https://doi.org/10.1101/2023.12.20.572662

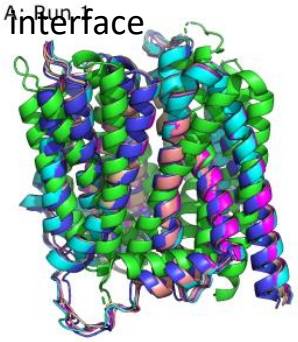
Alphafold can do **conformational changes**

- manipulation with MSA allows selection of multiple conformers via mutation of contact points in MSA

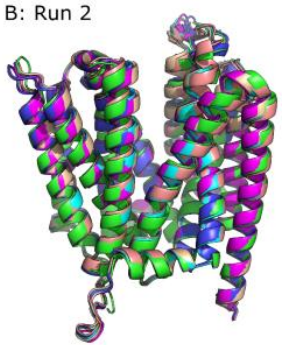


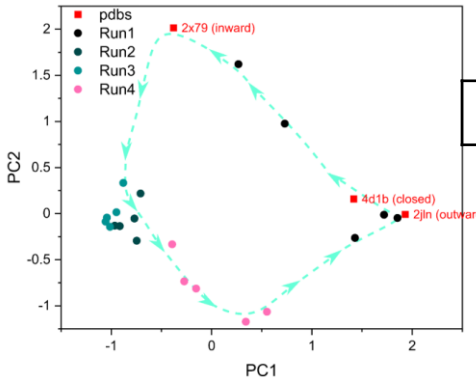
LmrP transporter

default



after mutation on interface





Mhp1

Modeling Alternate Conformations with Alphafold2 via Modification of the Multiple Sequence Alignment

Richard A. Stein, Hassane S. Mchaourab

doi: https://doi.org/10.1101/2021.11.29.470469

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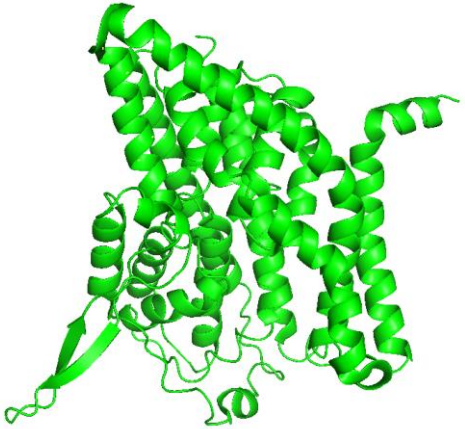
Alphafold can predict **dynamics**

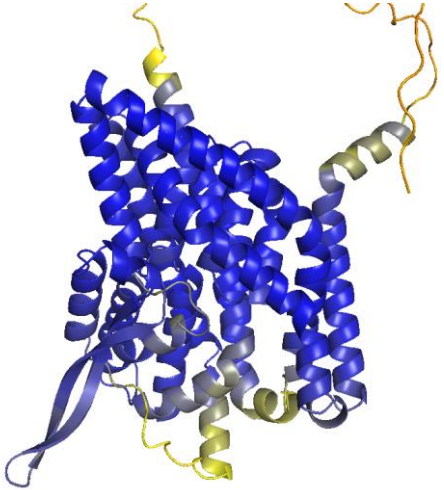
pLDDT shows flexibility

SLC1A5



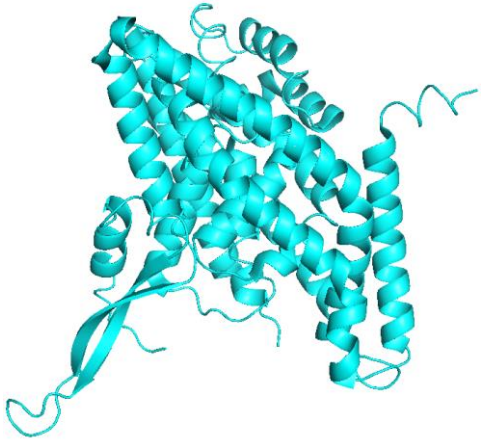
6mp6

Outward-Facing



6rvx

Inward-Facing



AlphaFold

similar to OF

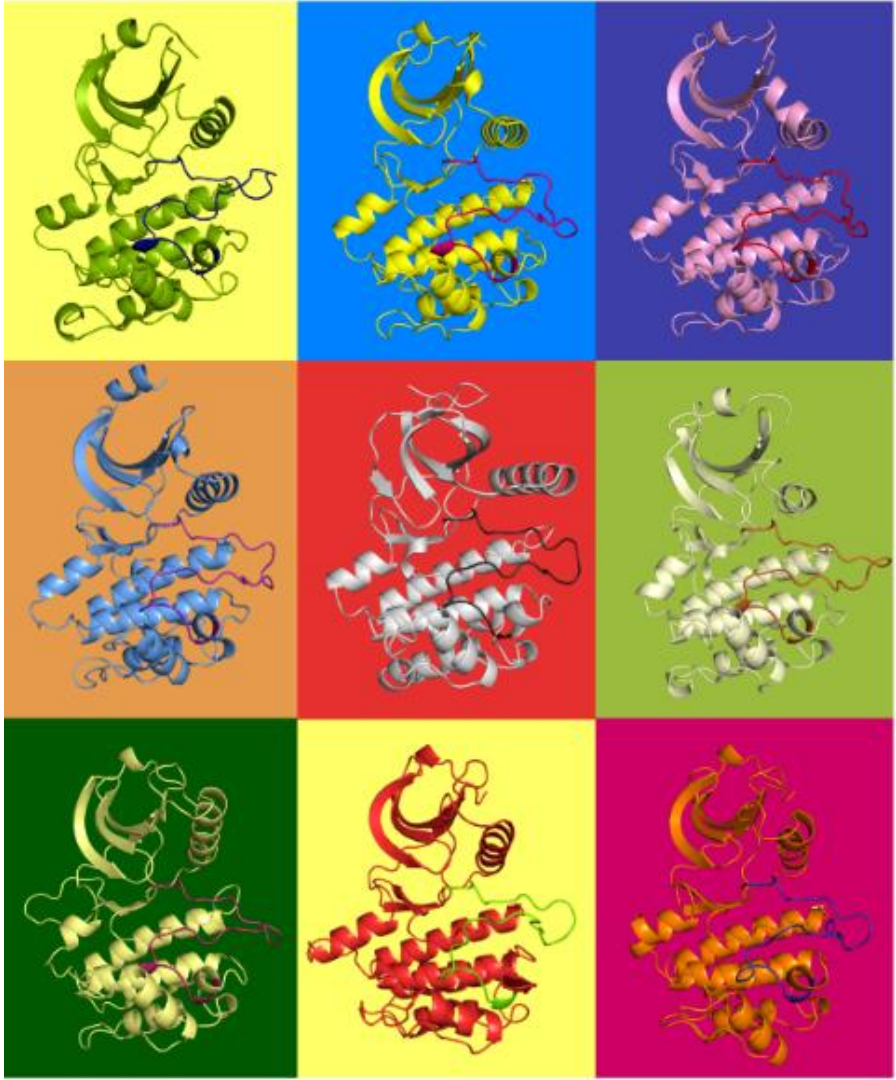
AlphaFold2 models of the active form of human typical protein kinase domains

- Humans - 437 active kinases
- PDB - 268 kinases (155 actives)
- AFDB - 209 of the 437 (48%) catalytic human protein kinases have a fully active model in the EBI data set

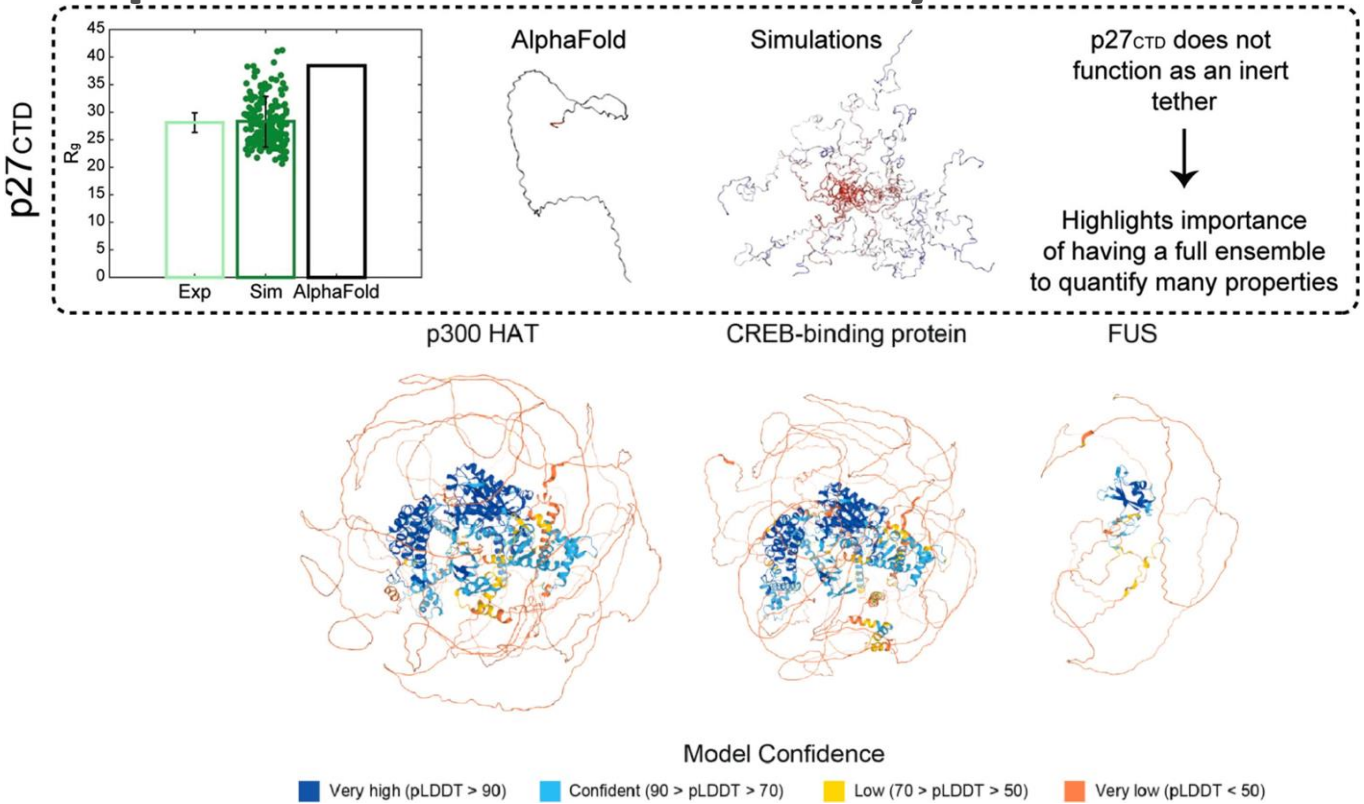
pipeline to produce actives:

- MSA for templates in active forms (including non human kinases)
- multiple depths MSA (1-90 seqs) -> different models -> check active conformation -> combine models

http://dunbrack.fccc.edu/kincore/activemodels

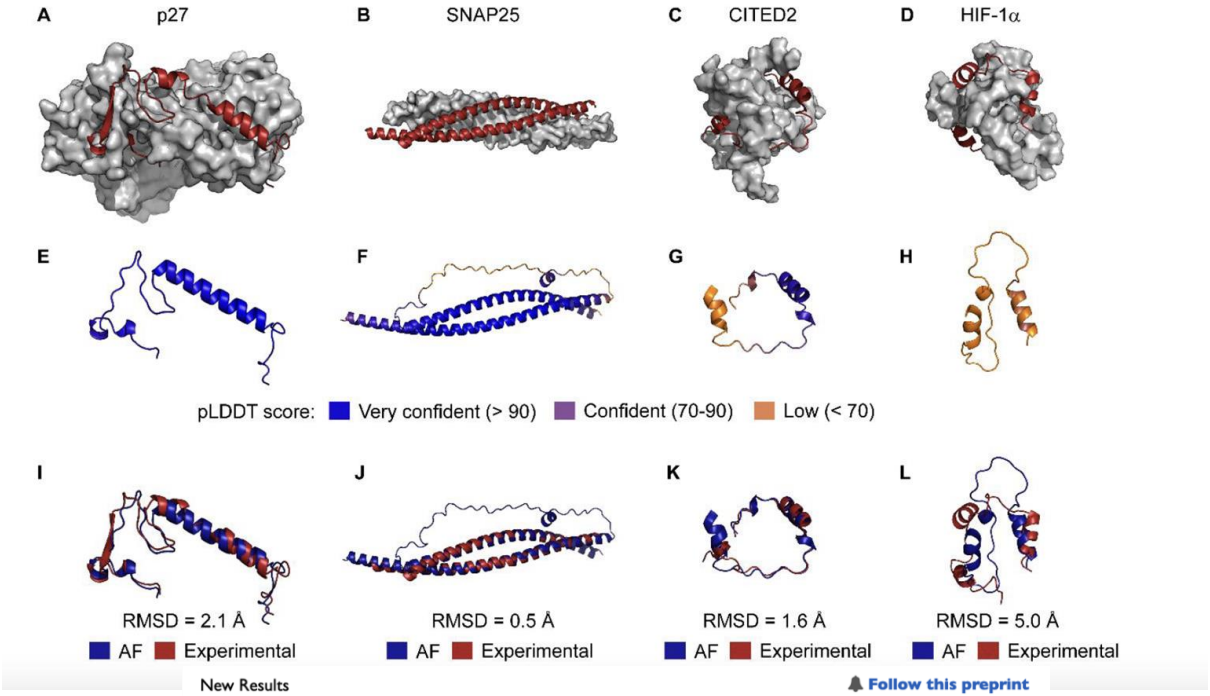


AlphaFold and Intrinsically Disordered Proteins



Ruff KM, Pappu RV ,AlphaFold and Implications for Intrinsically Disordered Proteins, J Mol Biol. 2021, https://doi.org/10.1016/j.jmb.2021.167208

AlphaFold and Intrinsically Disordered Proteins



New Results

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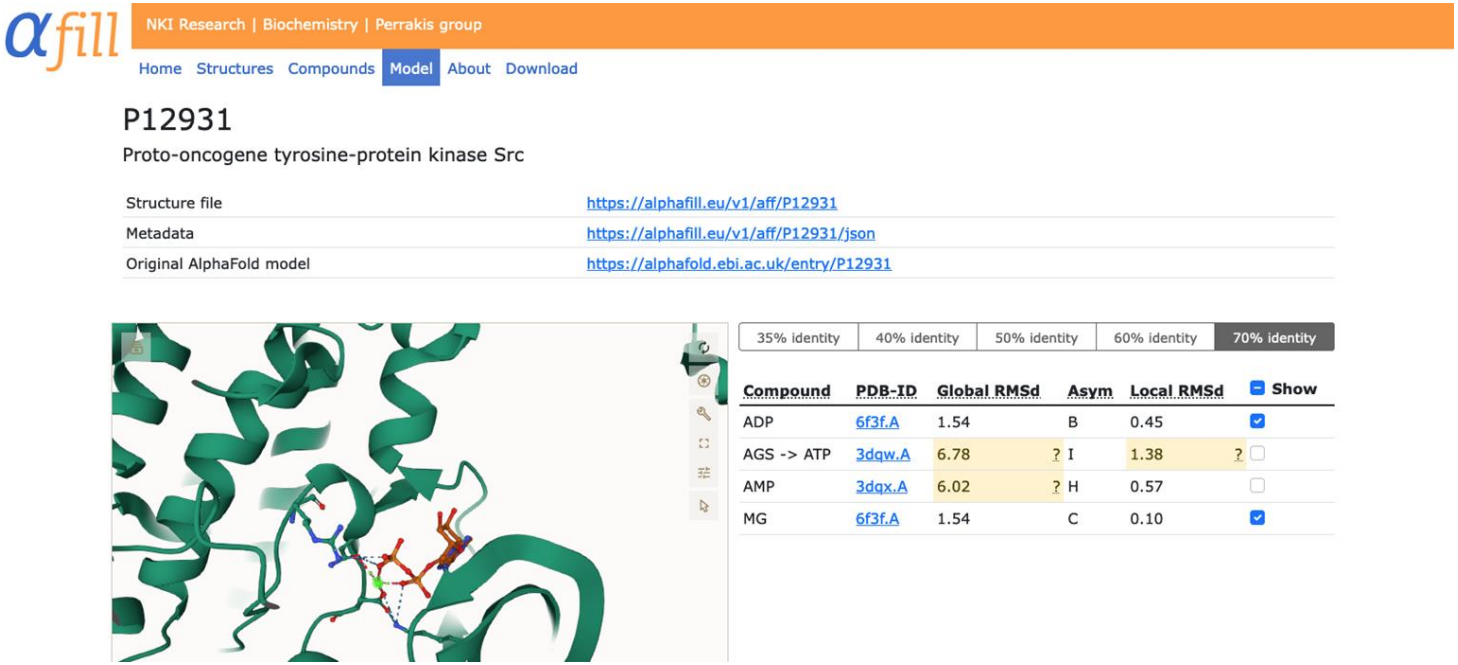
Systematic identification of conditionally folded intrinsically disordered regions by AlphaFold2

T. Reid Alderson, Iva Pritišanac, Alan M. Moses, Julie D. Forman-Kay

doi: https://doi.org/10.1101/2022.02.18.481080

Alphafold can be filled with **ligands**



Alphafold can work with **orphan sequences**

Single-sequence protein structure prediction using language models (pLM) - e.g. **ESMfold**

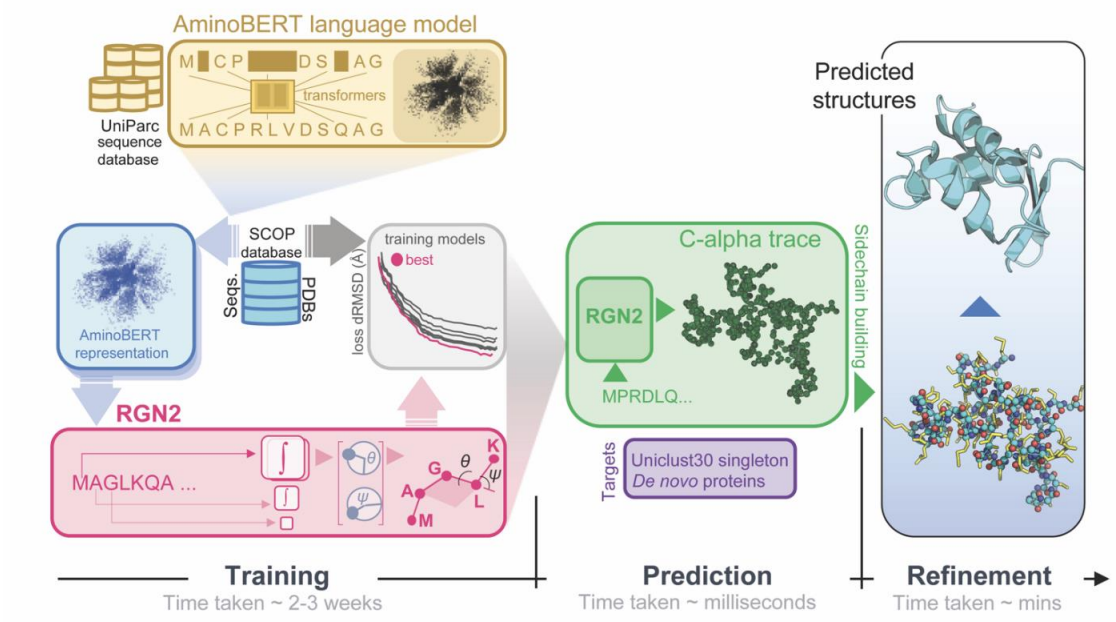


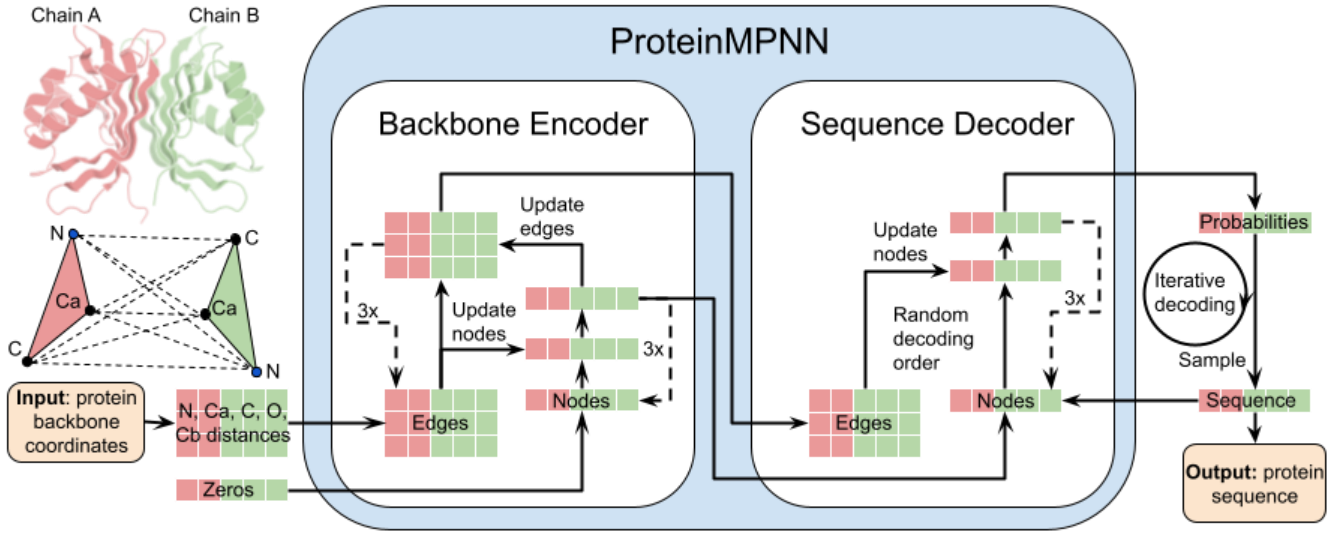
Figure 1. Organization and application of RGN2. RGN2 combines a Transformer-based protein language model (AminoBERT) with a recurrent geometric network that utilizes Frenet-Serret frames to generate the backbone structure of a protein. Placement of side chain atoms and refinement of hydrogen-bonded networks are subsequently performed using the Rosetta energy function.

https://www.youtube.com/watch?v=eobc7cMMpeY&feature=youtu.be

Reversed prediction - ProteinMPNN

find sequence to a given structural feature

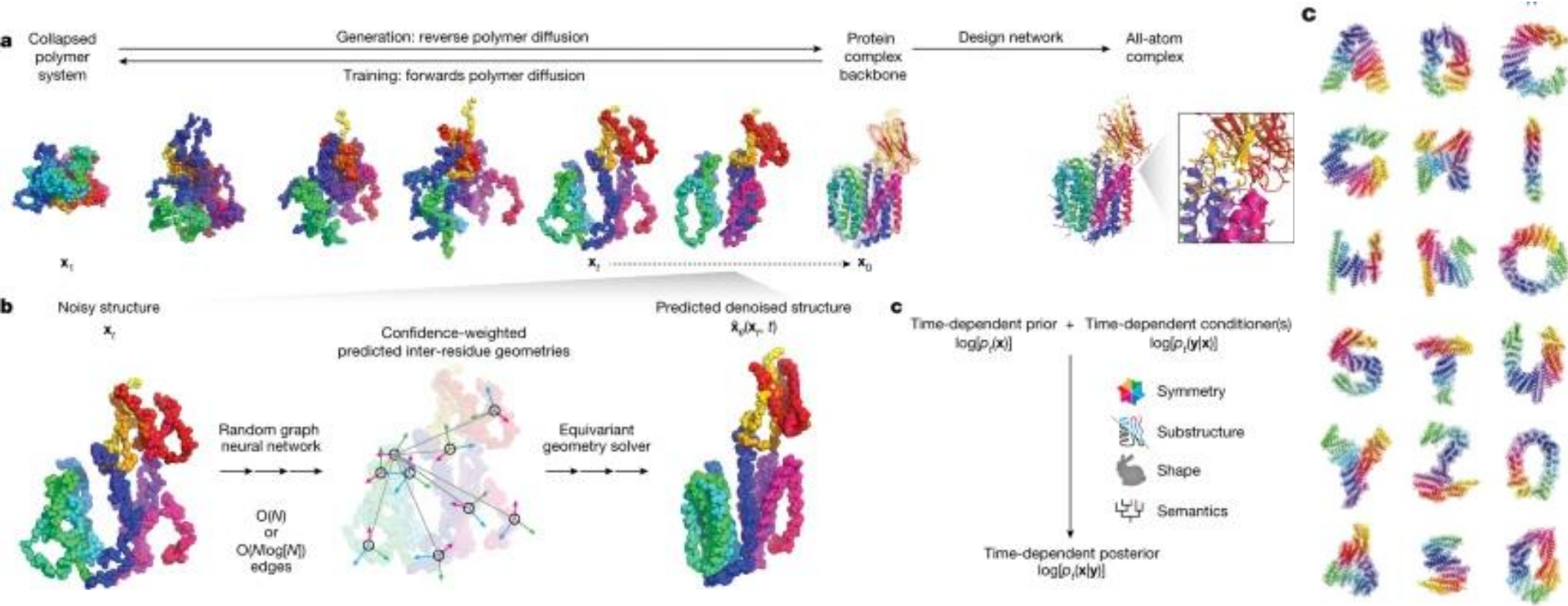
-> applicability to almost any protein sequence design problem



DOI: 10.1126/science.add2187

https://github.com/dauparas/ProteinMPNN

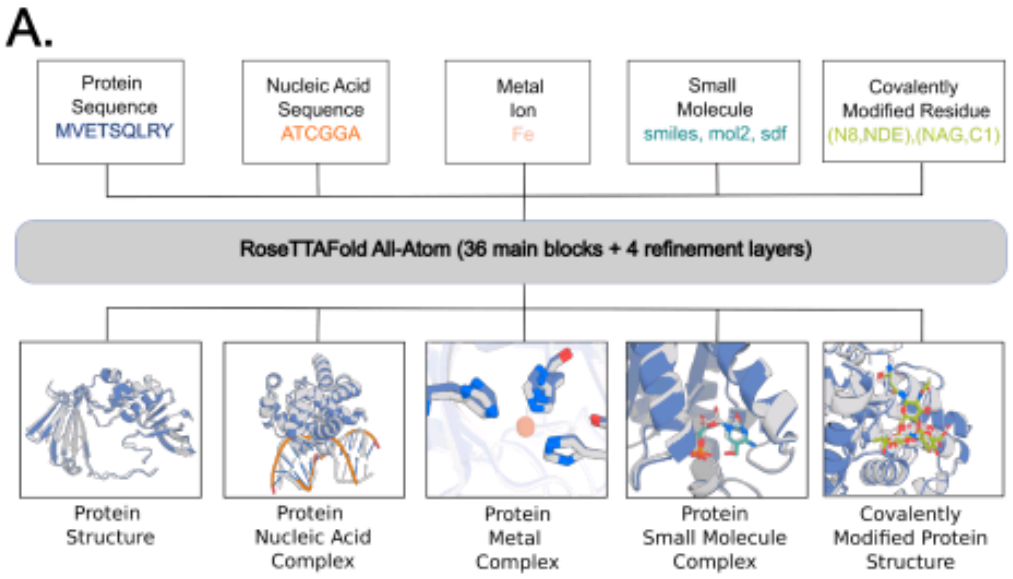
Chroma

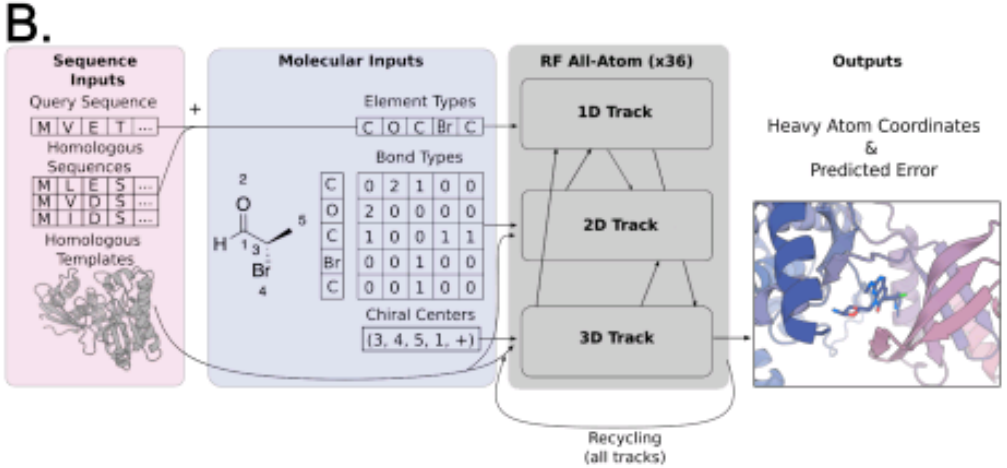


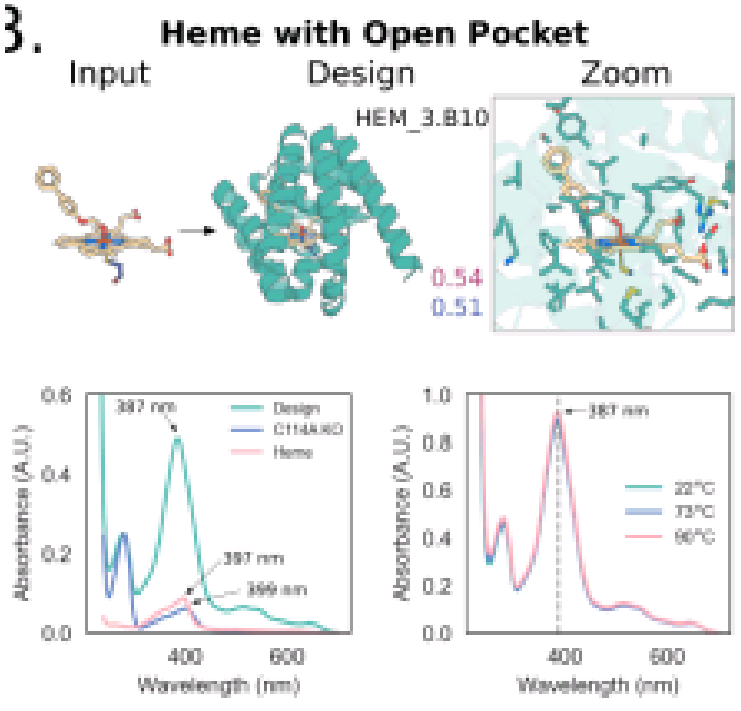
Ingraham, J.B et al *et al.* Illuminating protein space with a programmable generative model. *Nature* 623, 1070–1078 (2023). https://doi.org/10.1038/s41586-023-06728-8 https://github.com/generatebio/chroma

RoseTTAFold All-Atom

building protein around ligand



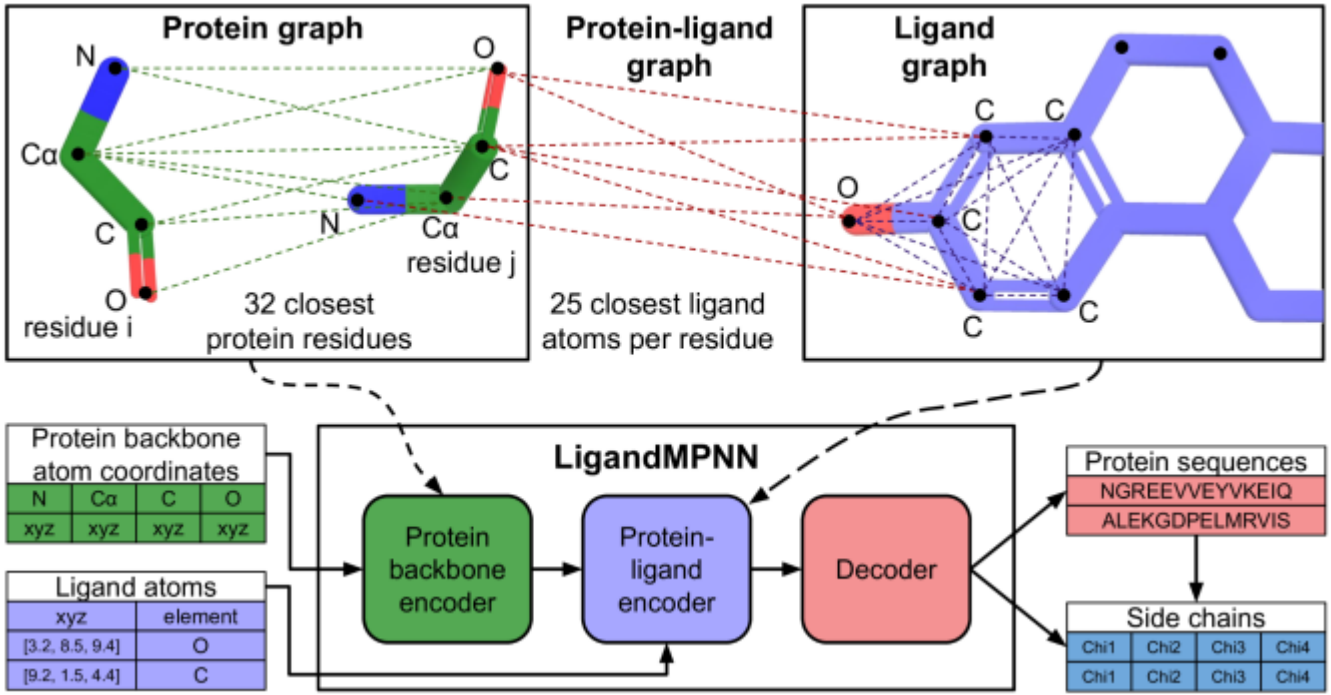




https://doi.org/10.1101/2023.10.09.561603

LigandMPNN

deep learning-based protein sequence design method that explicitly models all non-protein components of biomolecular systems



bioRxiv preprint https://doi.org/10.1101/2023.12.22.573103 https://github.com/dauparas/LigandMPNN

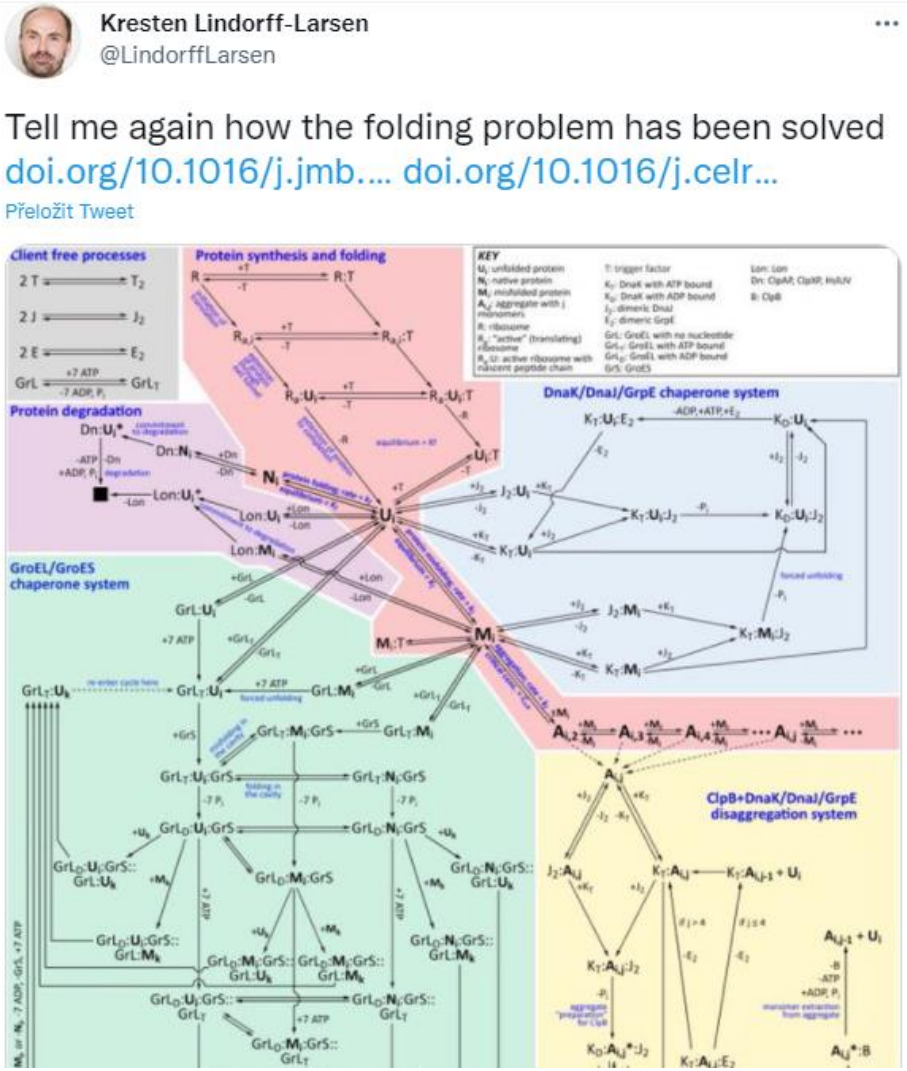
Summary

- Alphafold2 made a huge leap in **prediction accuracy**
- Role of **open science and publicly available data** can not be overstated
- **CASP competition** was a driver of the change
- Alphafold is **publicly available** and can be run from many places including ELIXIR CZ
- Alphafold has **inspired many "Alphafoldology" tools and uses** already
- Alphafold limits are yet to be fully described, but we learning more each day

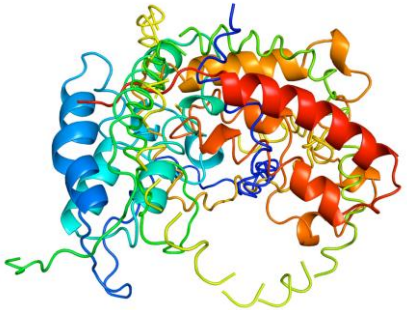
Thank you for your attention.

Any

tion


Kresten Lindorff-Larsen
@LindorffLarsen
Tell me again how the folding problem has been solved
doi.org/10.1016/j.jmb.... doi.org/10.1016/j.celr...
Přeložit Tweet
Client free processes
Protein synthesis and folding
KEY
Protein degradation
DnaK/DnaJ/GrpE chaperone system
GroEL/GroES chaperone system
ClpB+DnaK/DnaJ/GrpE disaggregation system

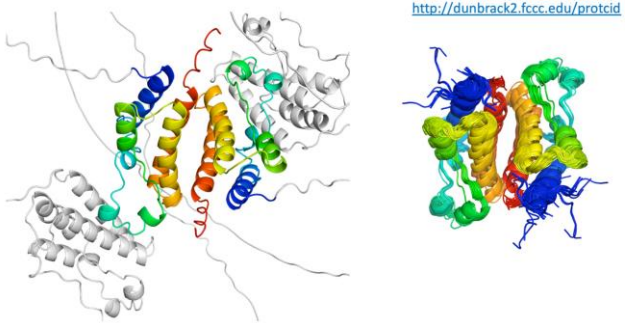
Alphafold can do **multiprotein complexes** – interactions



Alphafold-Multimer v2 reproduces dimer of Bromodomains BD2 of BET proteins observed in crystal structures

AF2mult_v2 homodimer of BRD2_HUMAN Bromodomain B2 in rainbow; BD1 in gray

ProtCID cluster of dimers of BD2 domains of human BRD2, BRD3, BRD4, mouse BRDT
http://dunbrack2.fccc.edu/protcid



https://twitter.com/RolandDunbrack/status/1502818748868317188

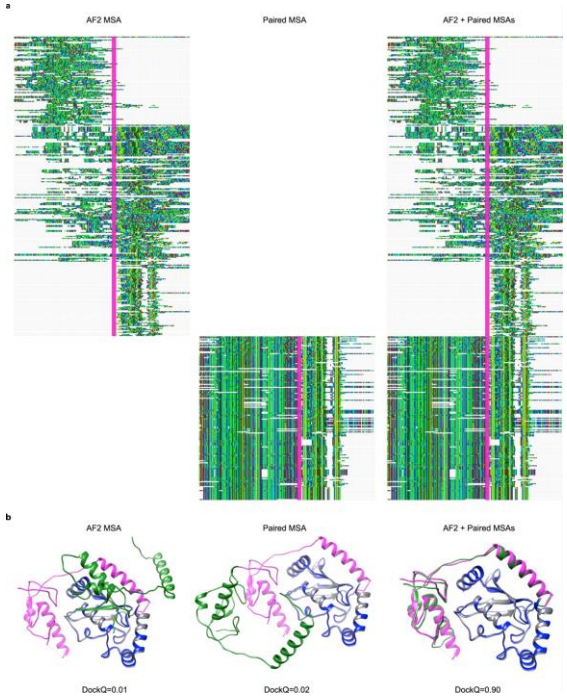
DeepMind

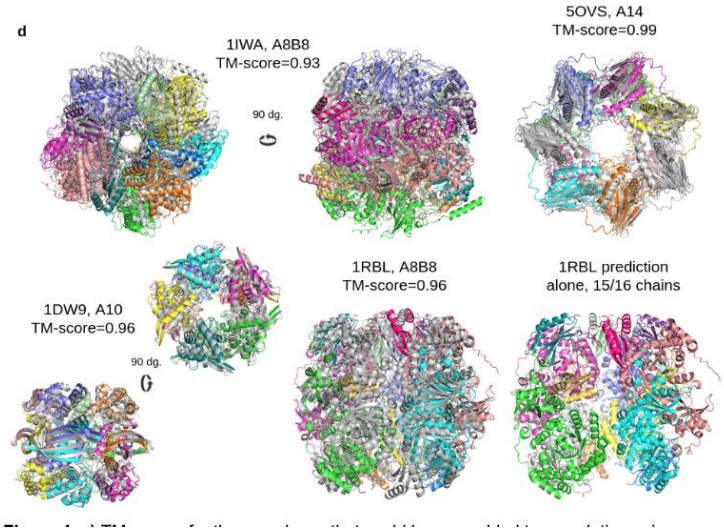
2022-03-10

Protein complex prediction with AlphaFold-Multimer

Richard Evans[1*], Michael O'Neill[1*], Alexander Pritzel[1*], Natasha Antropova[1*], Andrew Senior[1], Tim Green[1], Augustin Žídek[1], Russ Bates[1], Sam Blackwell[1], Jason Yim[1], Olaf Ronneberger[1], Sebastian Bodenstein[1], Michal

Alphafold can do **multiprotein complexes** – interactions





Article | Open Access | Published: 10 March 2022

Improved prediction of protein-protein interactions using AlphaFold2

Patrick Bryant, Gabriele Pozzati & Arne Elofsson

Nature Communications **13**, Article number: 1265 (2022) | Cite this article

6092 Accesses | **27** Altmetric | Metrics

New Results

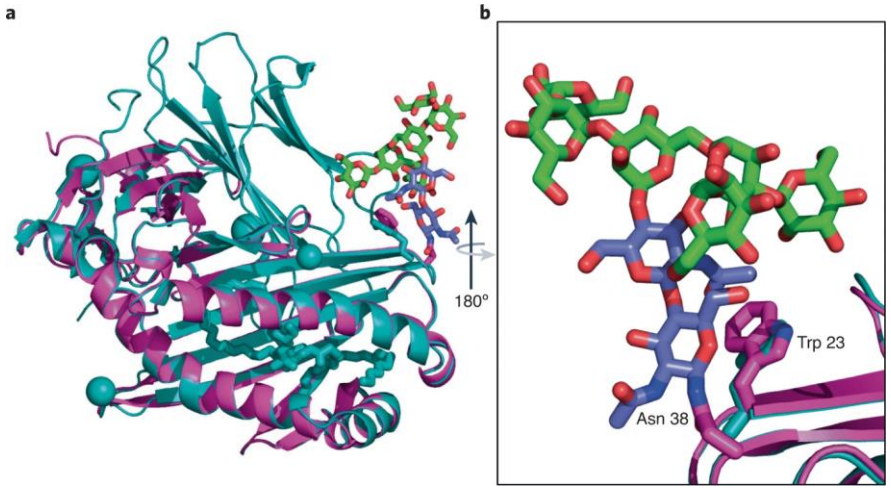
Follow this preprint

Predicting the structure of large protein complexes using AlphaFold and sequential assembly

Patrick Bryant, Gabriele Pozzati, Wensi Zhu, Aditi Shenoy, Petras Kundrotas, Arne Elofsson

doi: https://doi.org/10.1101/2022.03.12.484089

- Alphafold can not do effects of **post-translational protein modifications** (by itself)



Correspondence | Published: 29 October 2021

The case for post-predictional modifications in the AlphaFold Protein Structure Database

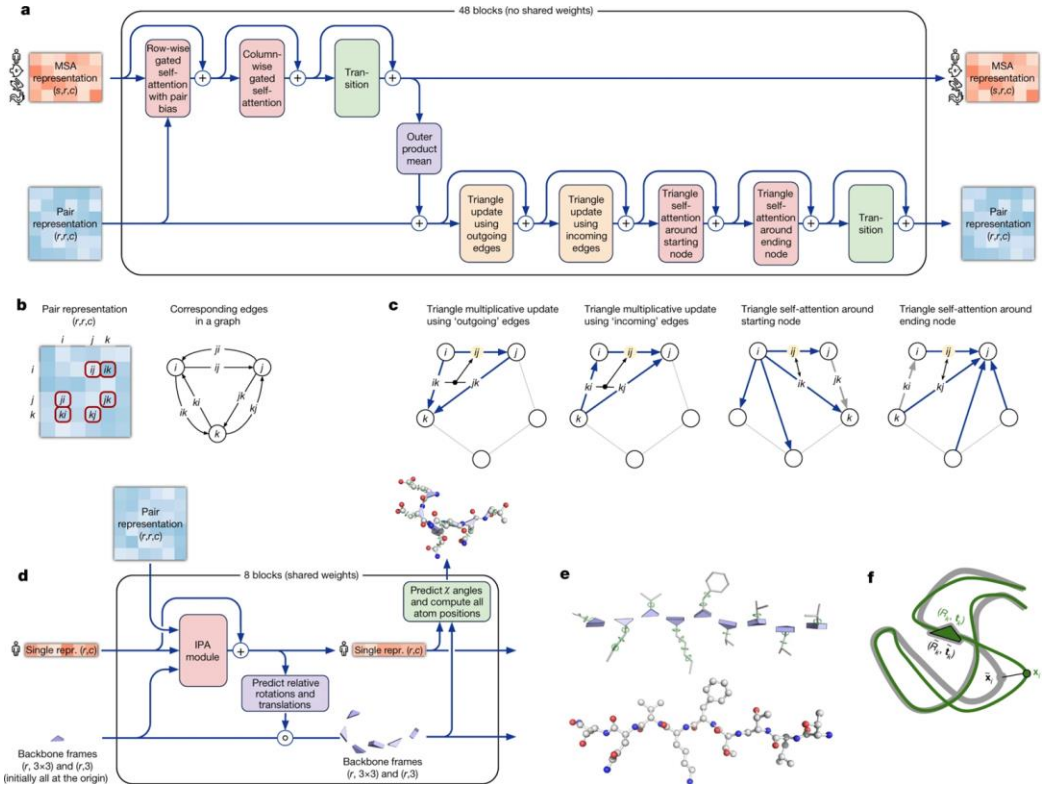
Haroldas Bagdonas, Carl A. Fogarty, Elisa Fadda & Jon Agirre

Nature Structural & Molecular Biology **28**, 869–870 (2021) | Cite this article

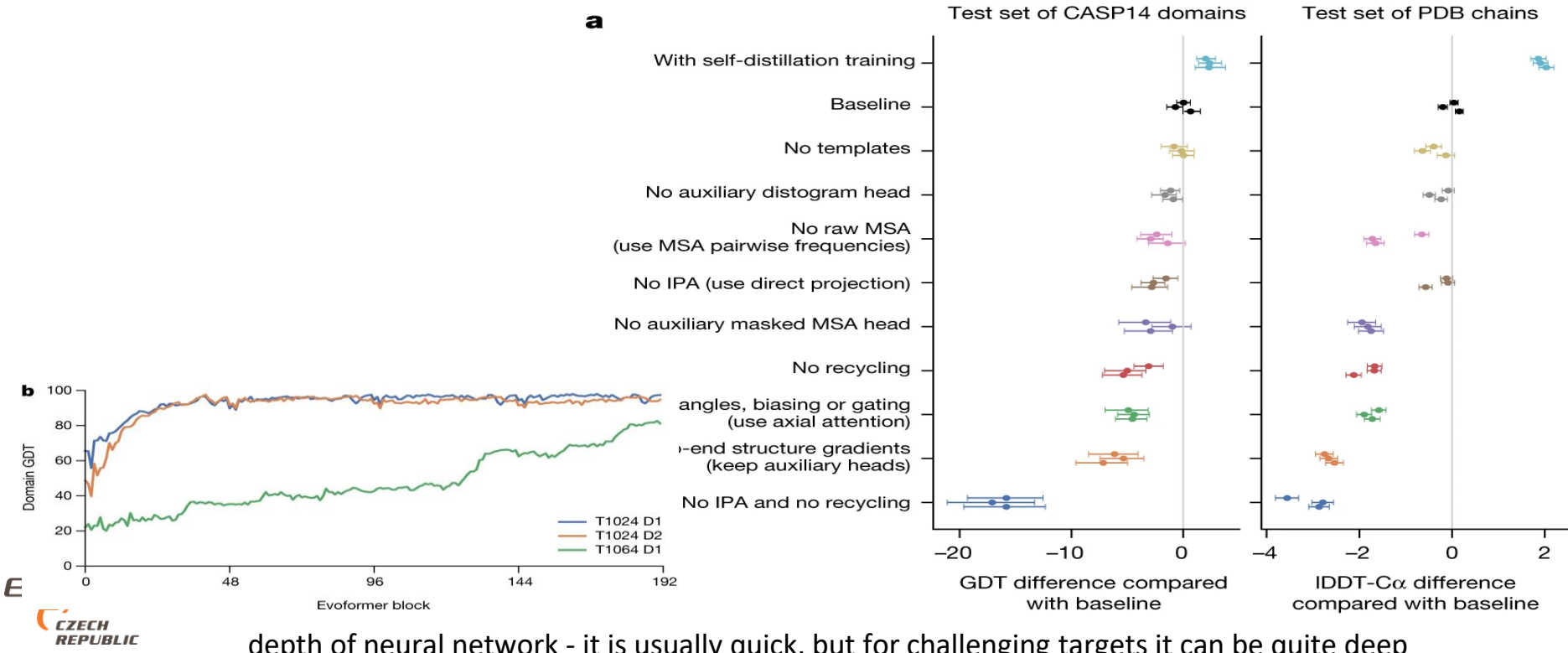
10k Accesses | **2** Citations | **151** Altmetric | Metrics

Extra slides

Architectural details.



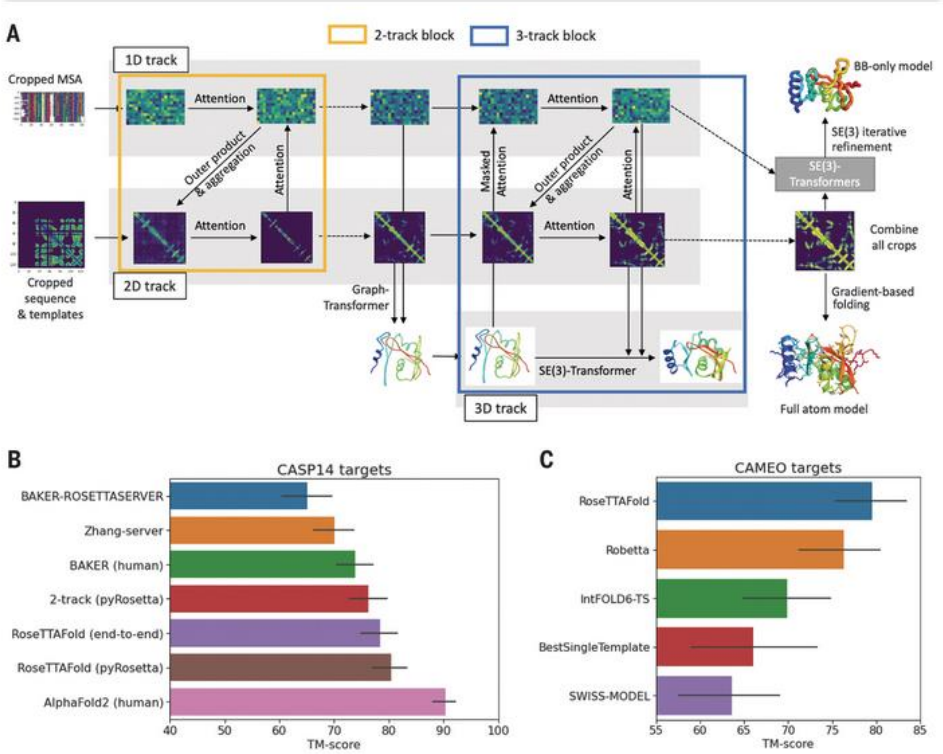
Interpreting the neural network



depth of neural network - it is usually quick, but for challenging targets it can be quite deep

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

Accurate prediction of protein structures and interactions using a three-track neural network



https://www.science.org/doi/full/10.1126/science.abj8754

USING ALPHAFOLD FOR RAPID AND ACCURATE FIXED BACKBONE PROTEIN DESIGN

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ABSTRACT

The prediction of protein structure and the design of novel protein sequences and structures have long been intertwined. The recently released AlphaFold has heralded a new generation of accurate protein structure prediction, but the extent to which this affects protein design stands yet unexplored. Here we develop a rapid and effective approach for fixed backbone computational protein design, leveraging the predictive power of AlphaFold. For several designs we demonstrate that not only are the AlphaFold predicted structures in agreement with the desired backbones, but they are also supported by the structure predictions of other supervised methods as well as *ab initio* folding. These results suggest that AlphaFold, and methods like it, are able to facilitate the development of a new range of novel and accurate protein design methodologies.

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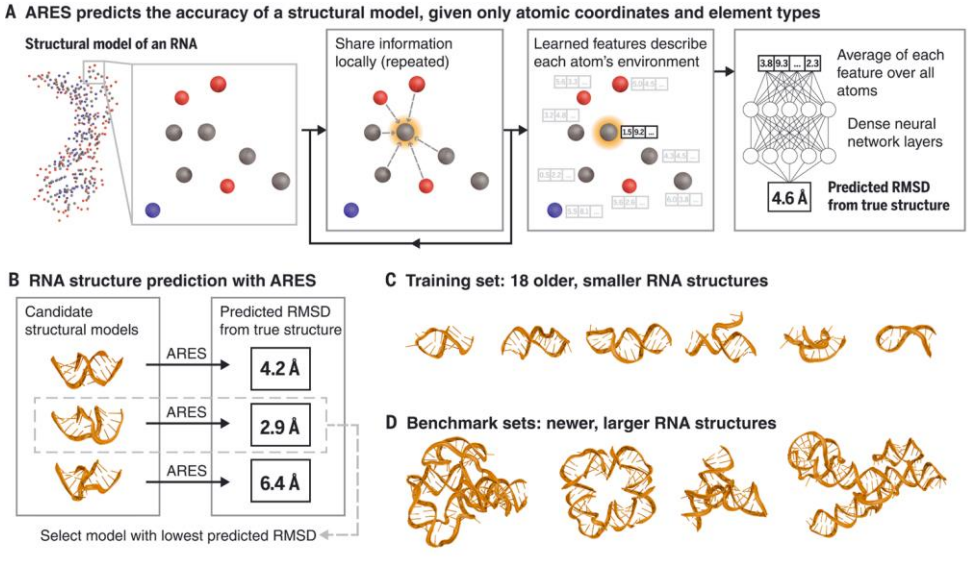
Geometric deep learning of RNA structure



https://www.science.org/doi/10.1126/science.abe5650

RoseTTAfold2 from Pymol