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Protein Structure Prediction and Using AlphaFold

Day 10: Friday 31st March

3D Structure Prediction

- Yesterday we learnt about experimental approaches to determine protein structure:
  - NMR
  - X-ray crystallography
  - Electron microscopy (cryo-EM)

- Today we learn about in silico approaches to predict structures:
  - Homology Modelling
  - Artificial Intelligence and AlphaFold
  - What AlphaFold can and can’t do (yet)

Experimental Structures in the PDB

- Enormous and growing number of structures that have been experimentally determined

- These are freely available in the online Protein Data Bank and listed in UniProt

- If an experimental structure exists – USE IT!

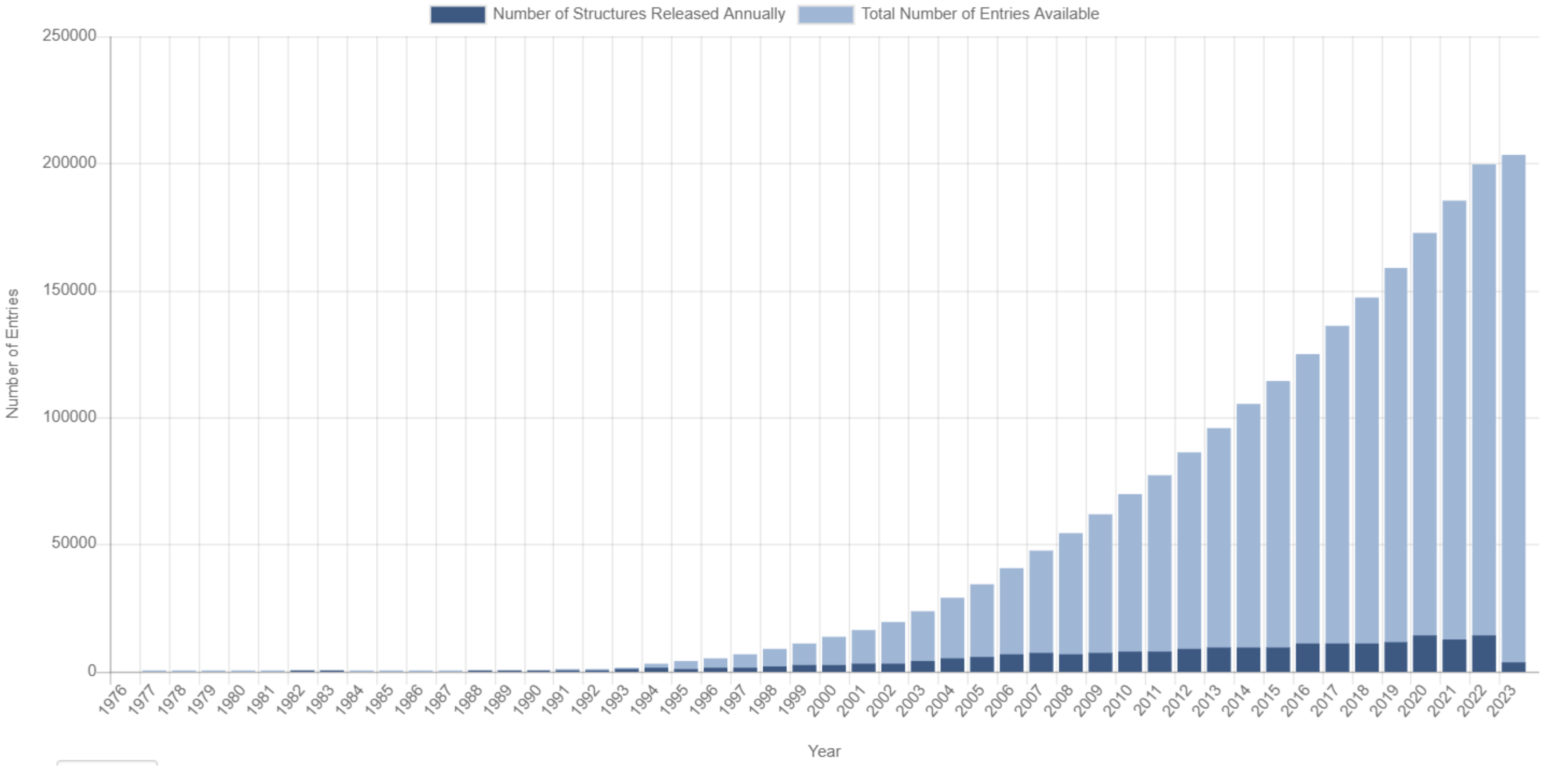
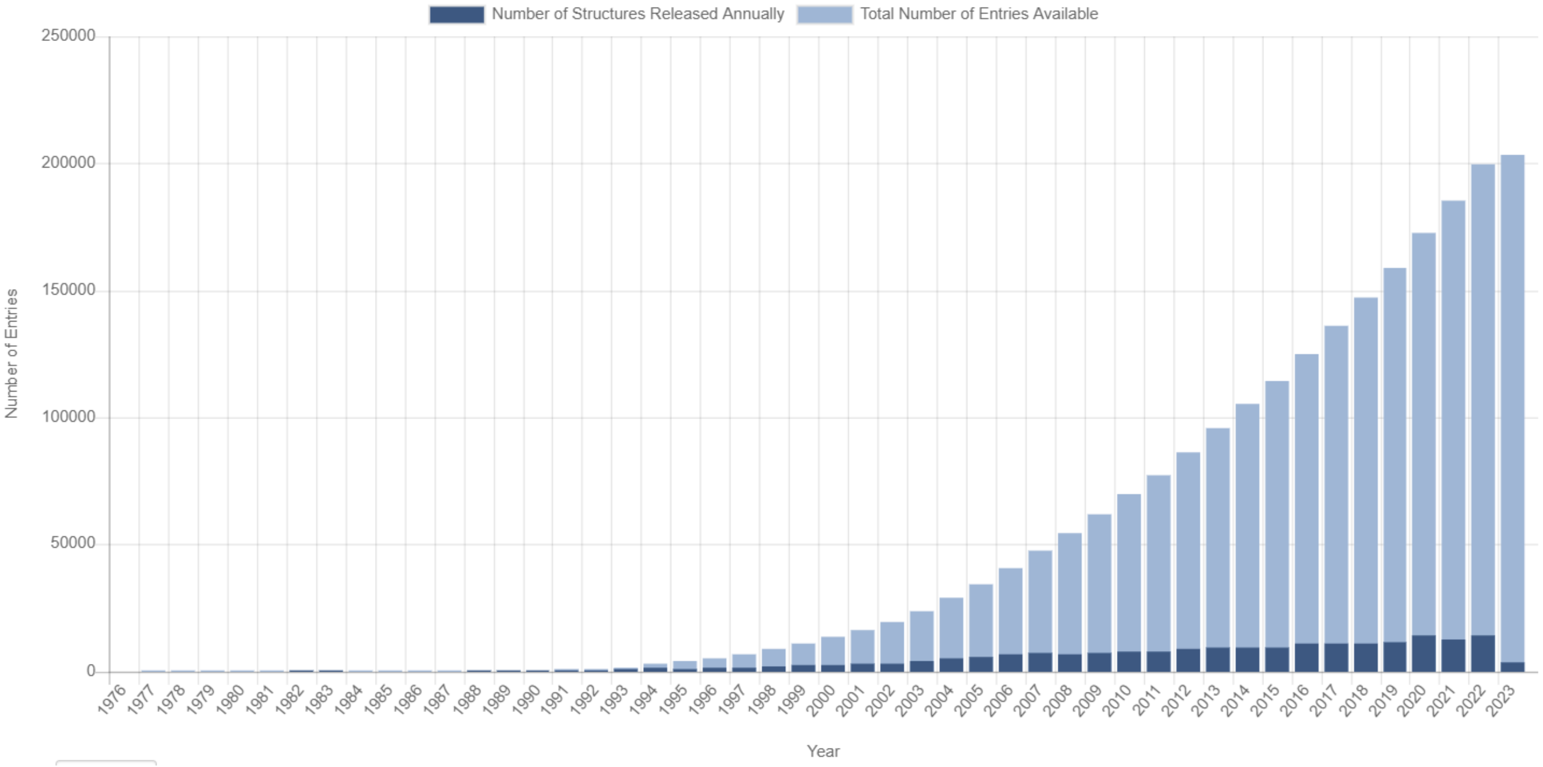


Image: www.rcsb.org/stats/growth/growth-released-structures

Experimental Structures in the PDB

- These experimental structures have been a very rich source of information for structure prediction for decades



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Experimental Structures in the PDB

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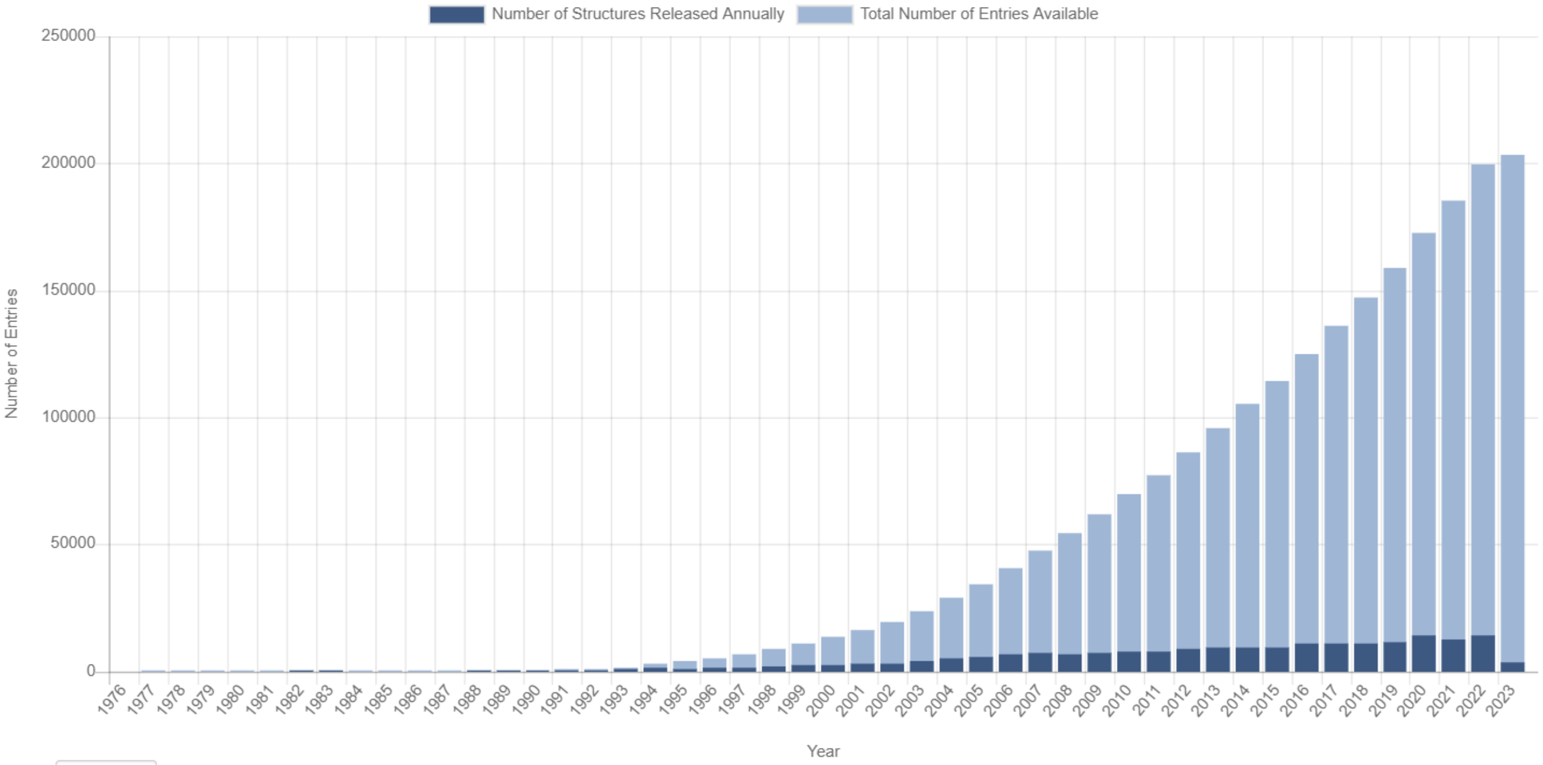
- This approach is called Homology Modelling



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Predicting a 3D structure

- Homology modelling has existed for a long time – use a closely related known structure to predict a new one
  - Modeller
  - SwissModel
  - HHPred
  - FFAS
  - SCWRL

Predicting a 3D structure

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- Ab initio modelling has been a huge challenge and actually stimulated an open competition called CASP

Critical Assessment of protein Structure Prediction (CASP)

- Experiment initiated by John Moult started in 1994
- Independent benchmark of ability to predict novel protein structures
- Targets ranked based on 'difficulty'
- Scored on accuracy and coverage of backbone prediction (GDT_TS)

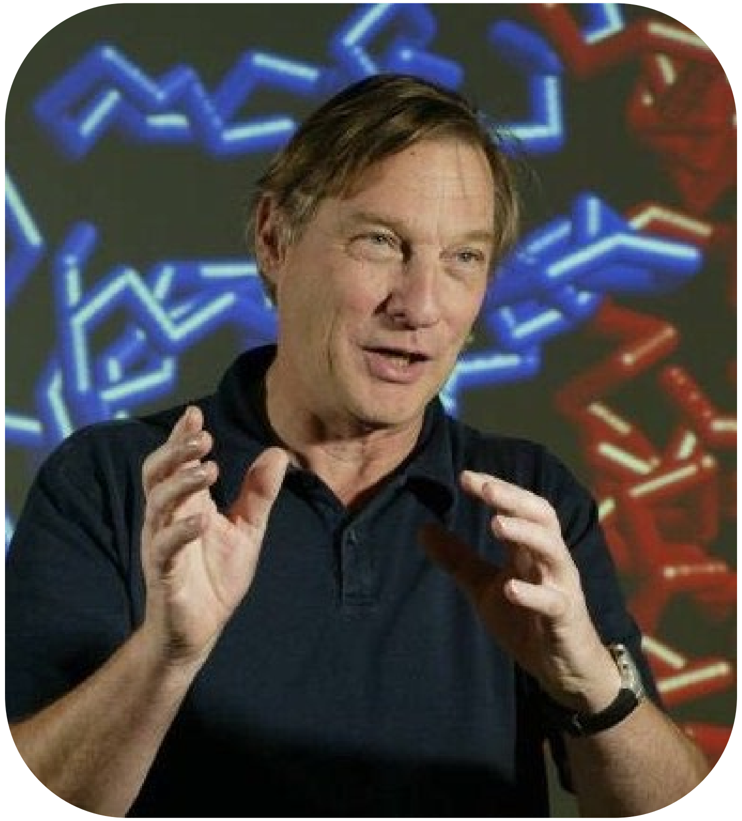
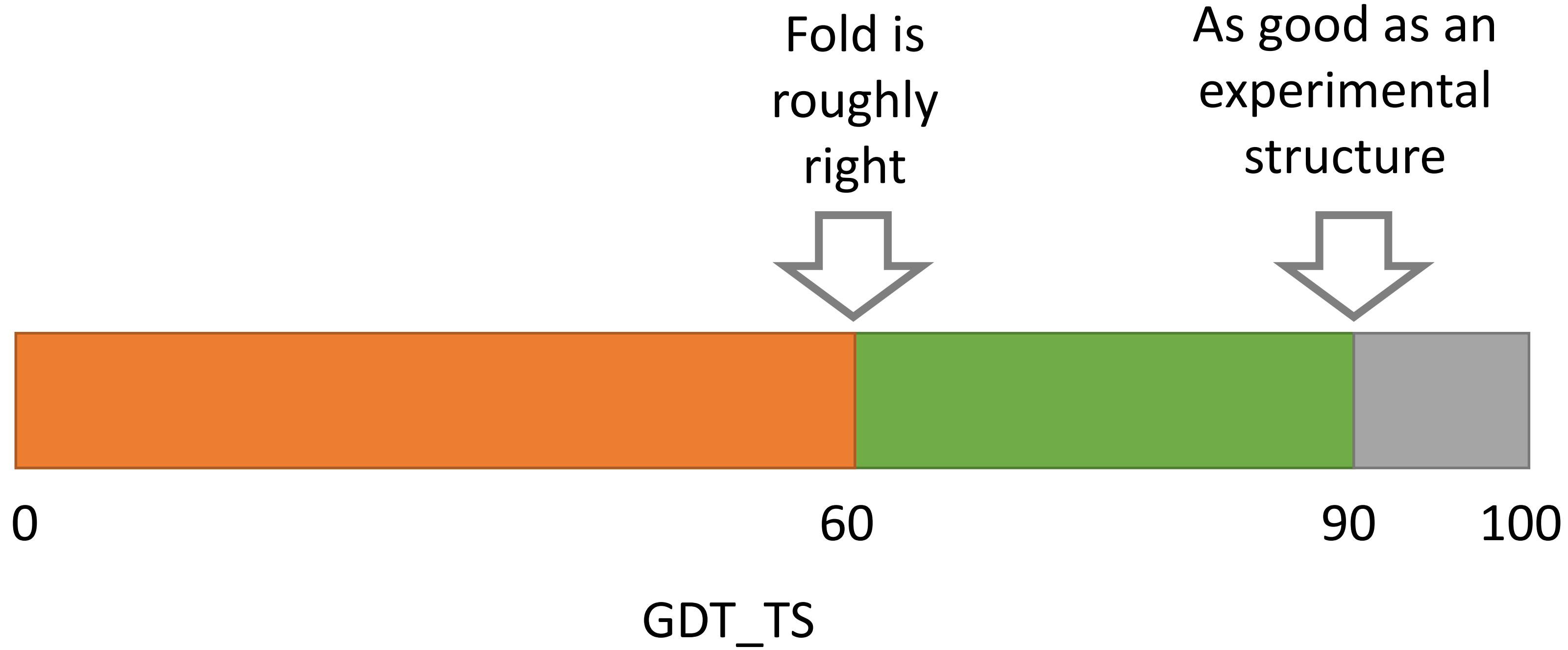


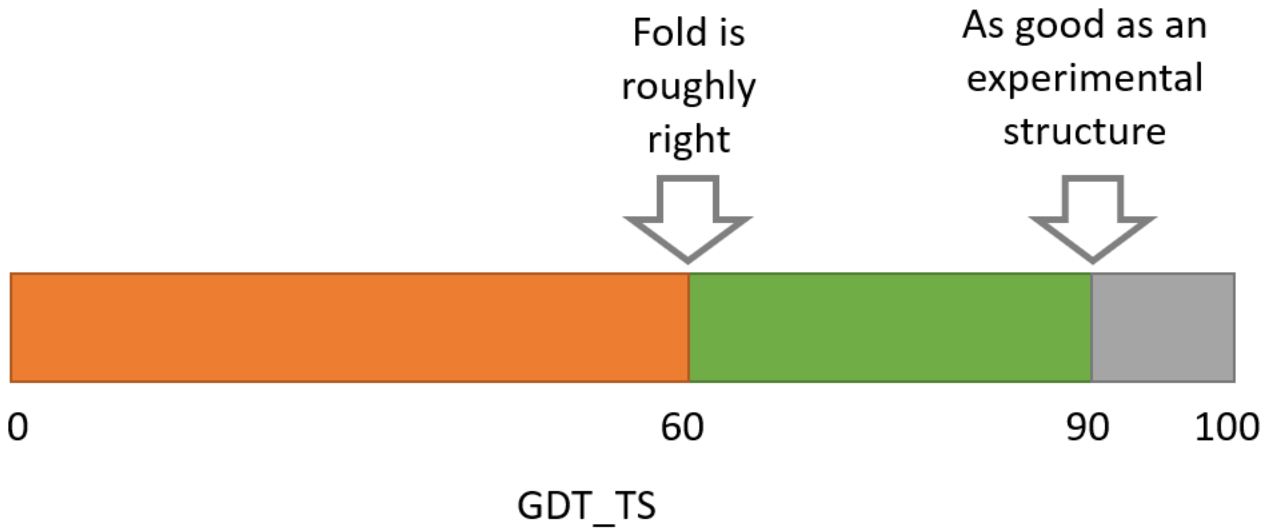
Image: https://predictioncenter.org/ CASP Organisers

How good is the prediction?



Predicting structures

- CASP outcomes and scoring



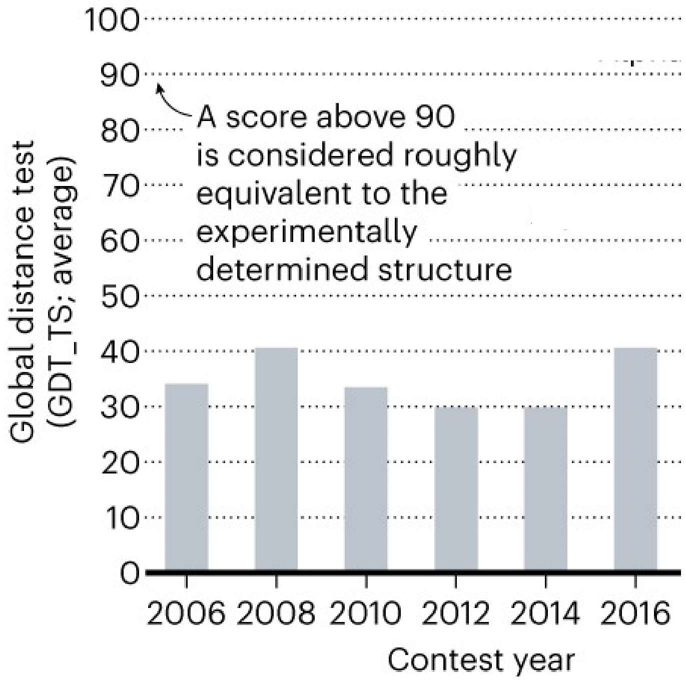
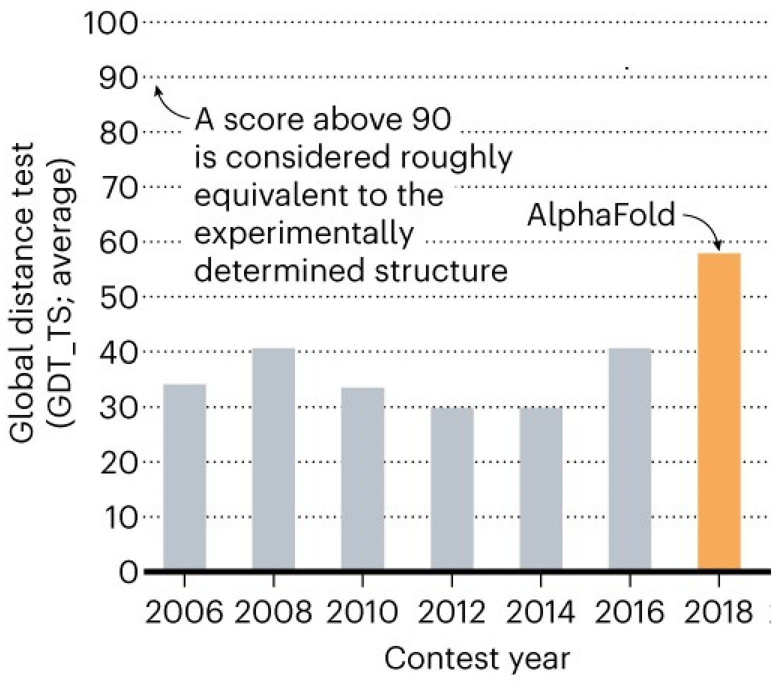


Image: Callaway (2020) Nature, 588: 203-204

AlphaFold was a huge step forward

- DeepMind developed a deep learning approach to structure prediction for CASP13 (2016)

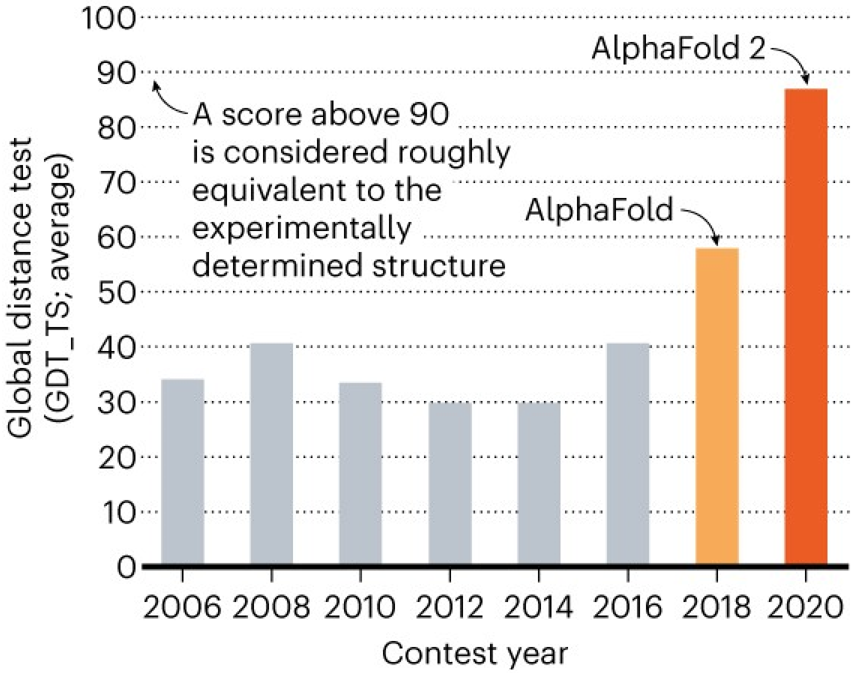
- Step-change in quality



Right image: Callaway (2020) Nature, 588: 203-204

CASP14 and AlphaFold2

- DeepMind completely redesigned their prediction pipeline
- Unparalleled accuracy
- Quality of the prediction was largely decoupled from sequence identity to homologues



Right image: Callaway (2020) Nature, 588: 203-204

How does AlphaFold2 do this?

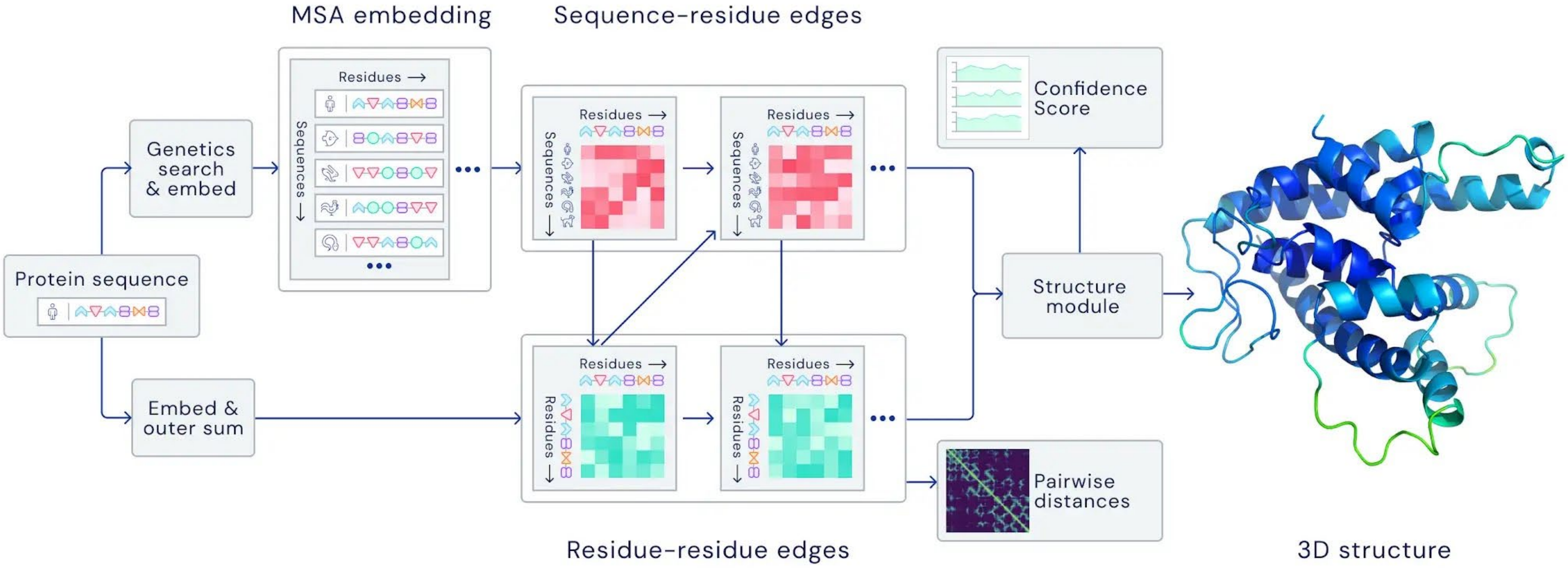
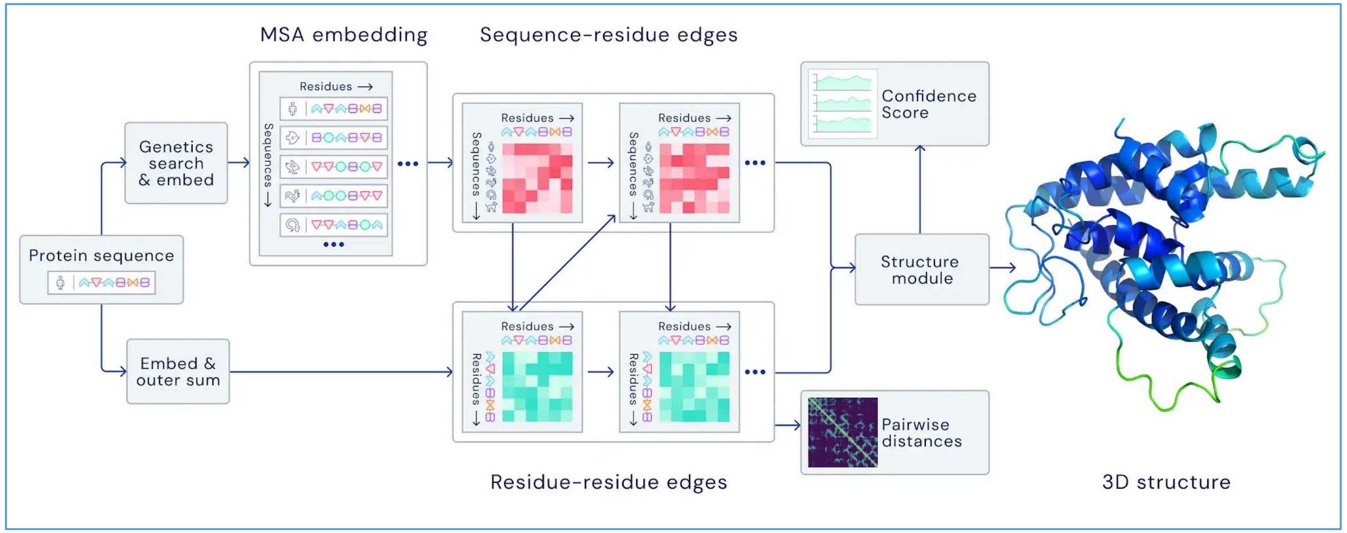


Image: www.deepmind.com

How does AlphaFold2 do this?

- The only input needed is a sequence!



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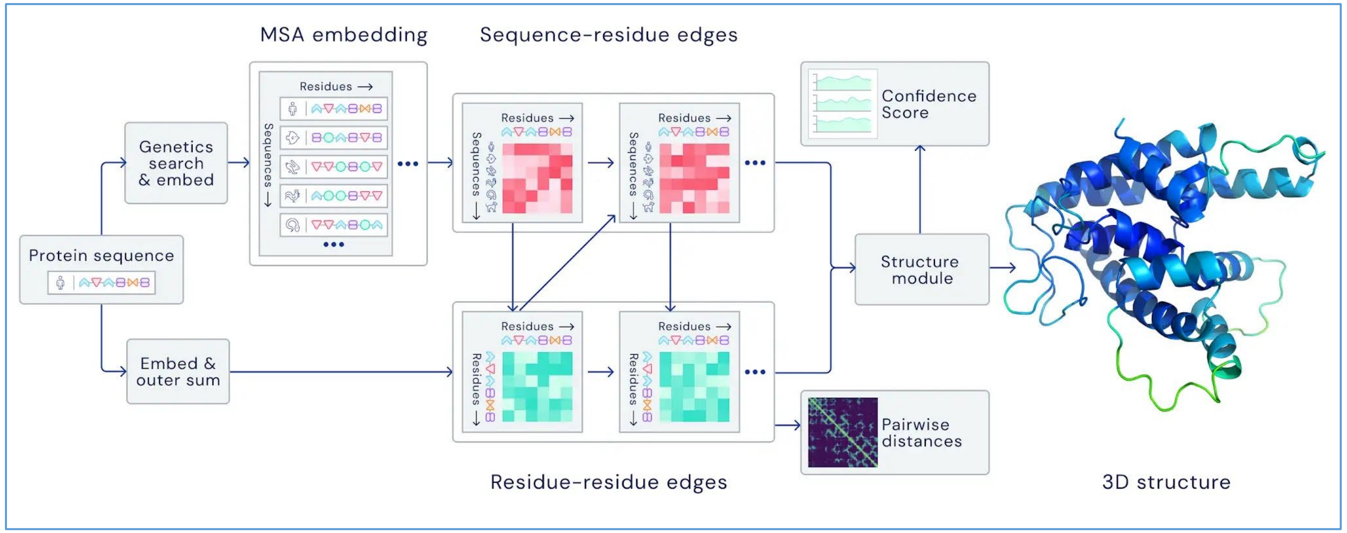
How does AlphaFold2 do this?

- Powerful neural networks
    - Attention-based neural networks



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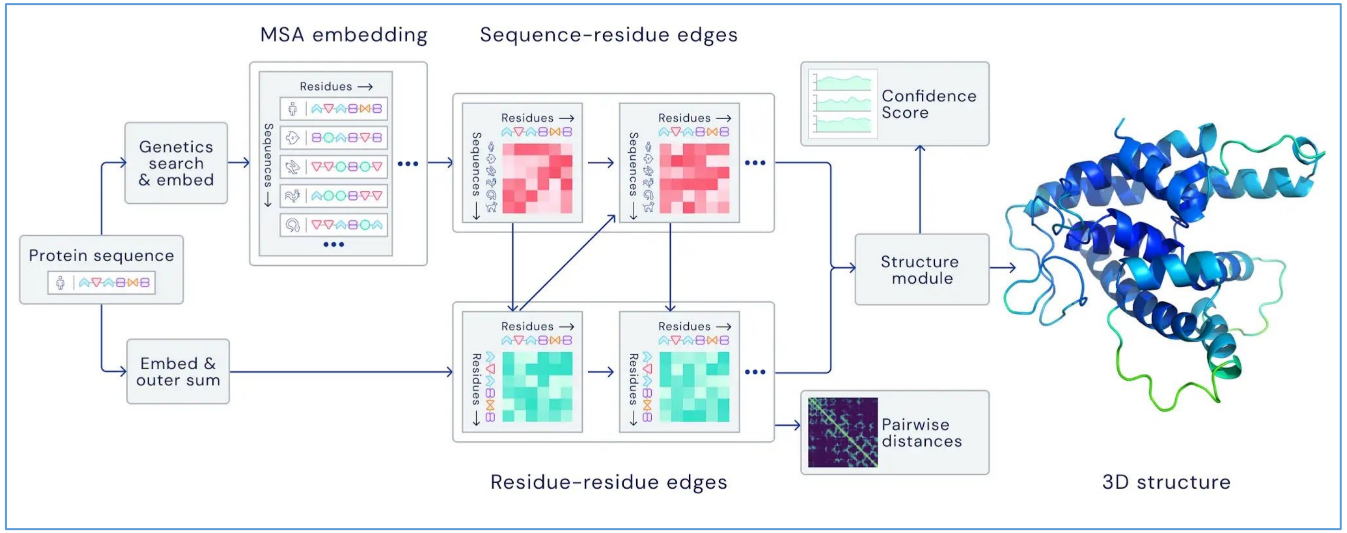

- Protein sequences
  - Multiple sequence alignments
  - Interrogate co-evolution of residues

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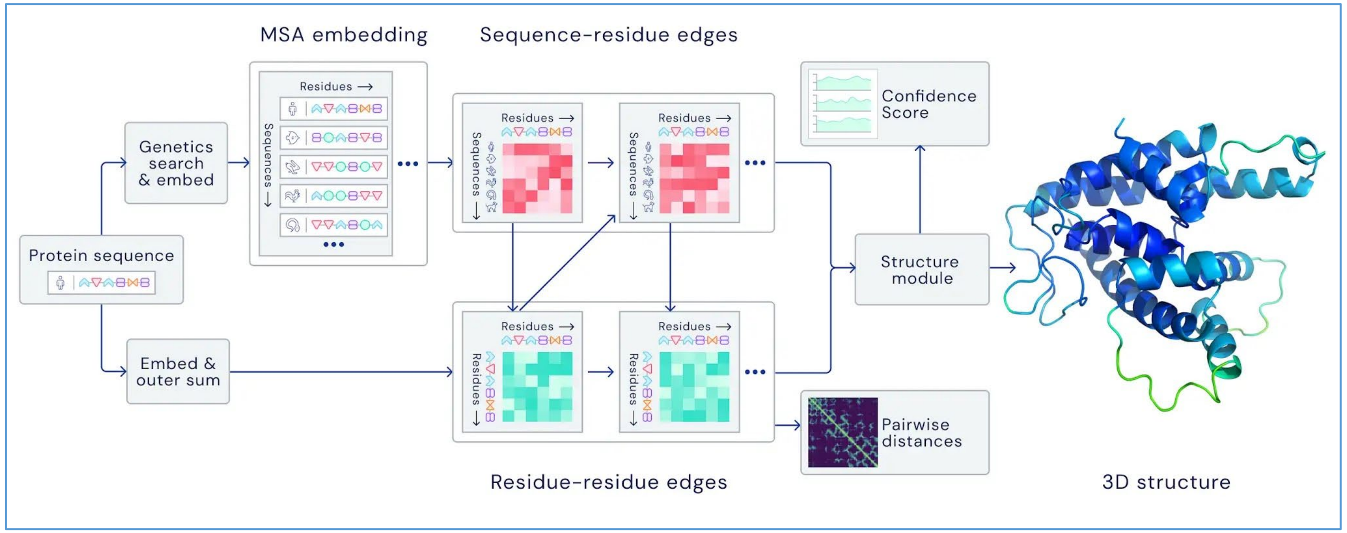

- Protein sequences
  - Multiple sequence alignments
  - Interrogate co-evolution of residues

- Protein structures
  - Identifying residue pairs that should be close to each other
  - Experience of what folded proteins 'look like'

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How does AlphaFold2 do this?

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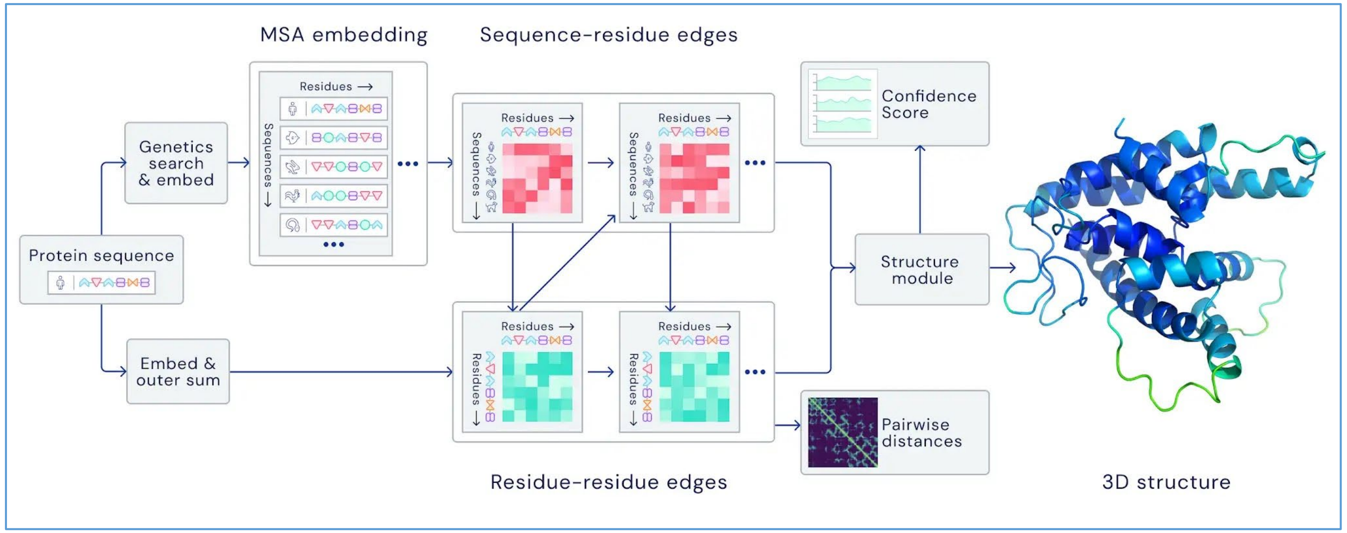

- Very powerful computers

- Protein sequences
  - Multiple sequence alignments
  - Interrogate co-evolution of residues

- Protein structures
  - Identifying residue pairs that should be close to each other
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Image: www.deepmind.com

Did Quake make AlphaFold happen?

Image: ID software

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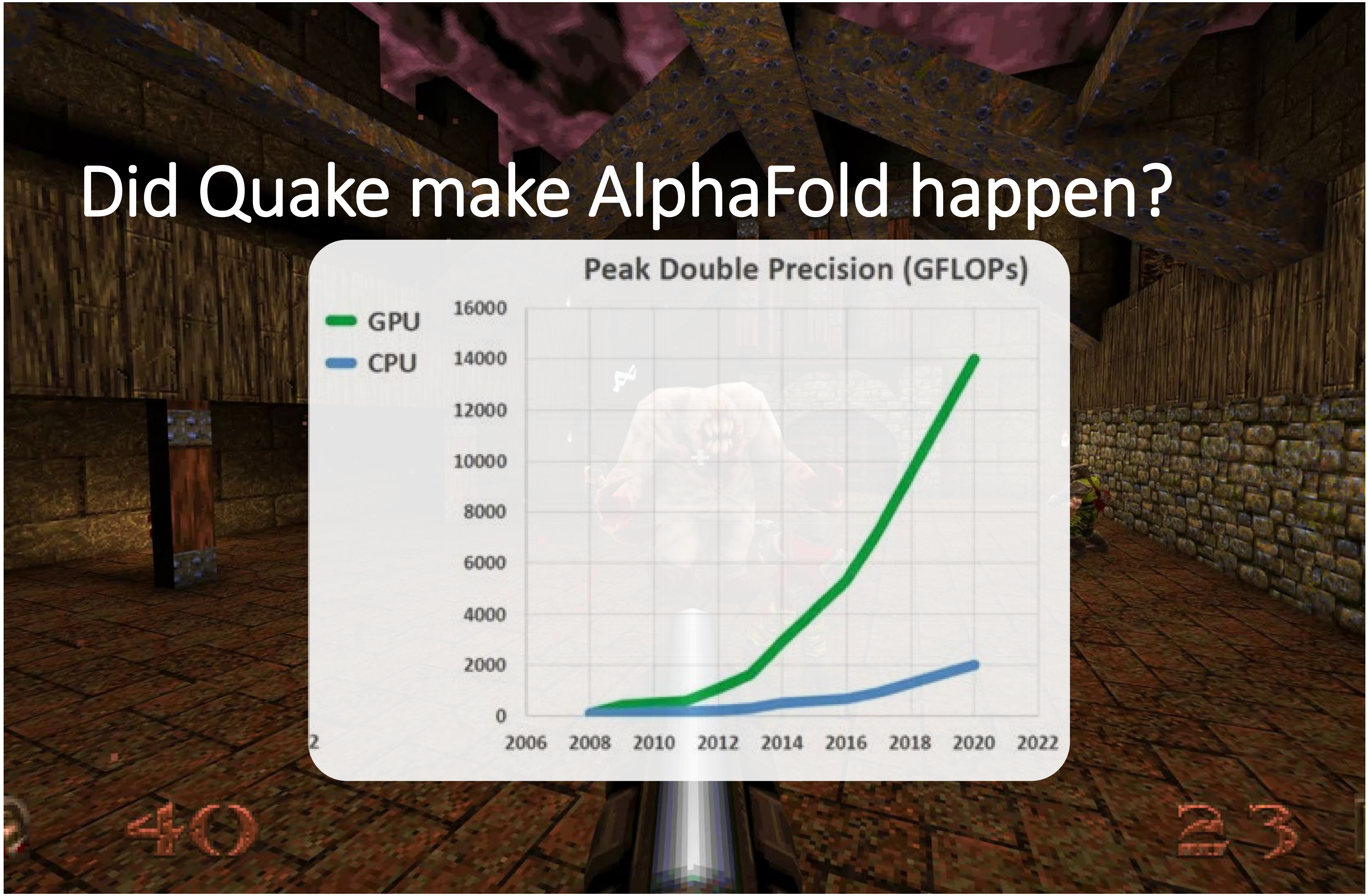

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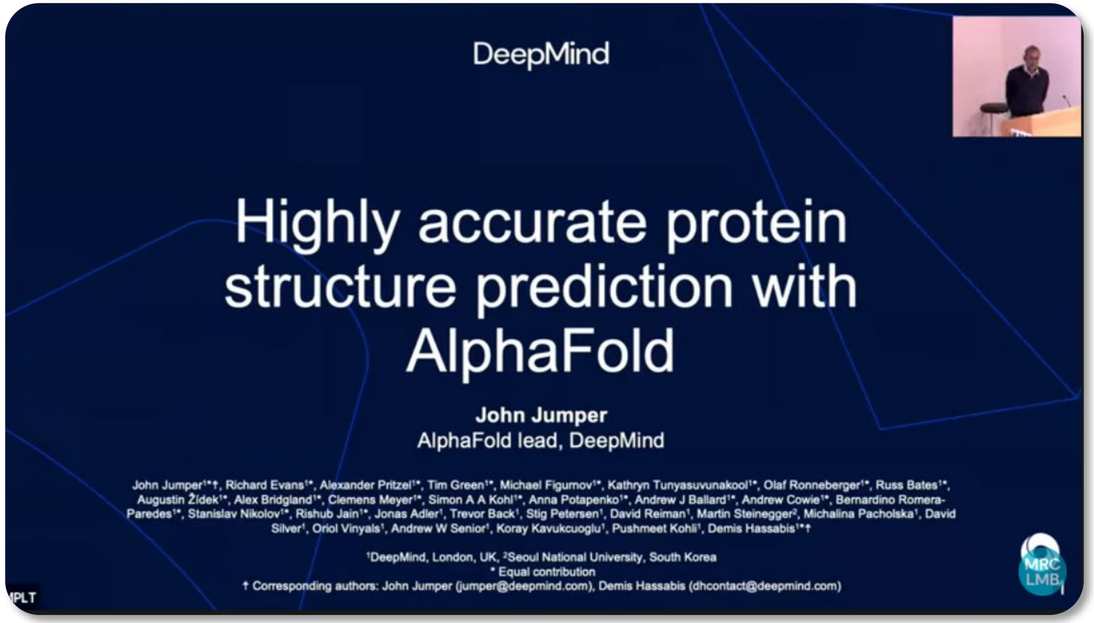
Image: ID software

Image:www.nextplatform.com

AlphaFold2 in a nutshell



DeepMind

Highly accurate protein structure prediction with AlphaFold

John Jumper
AlphaFold lead, DeepMind

John Jumper[1*†], Richard Evans[1*], Alexander Pritzel[1*], Tim Green[1*], Michael Figurnov[1*], Kathryn Tunyasuvunakool[1*], Olaf Ronneberger[1*], Russ Bates[1*], Augustin Žídek[1*], Alex Bridgland[1*], Clemens Meyer[1*], Simon A A Kohl[1*], Anna Potapenko[1*], Andrew J Ballard[1*], Andrew Cowie[1*], Bernardino Romera-Paredes[1*], Stanislav Nikolov[1*], Rishub Jain[1*], Jonas Adler[1], Trevor Back[1], Stig Petersen[1], David Reiman[1], Martin Steinegger[2], Michalina Pacholska[1], David Silver[1], Oriol Vinyals[1], Andrew W Senior[1], Koray Kavukcuoglu[1], Pushmeet Kohli[1], Demis Hassabis[1*†]

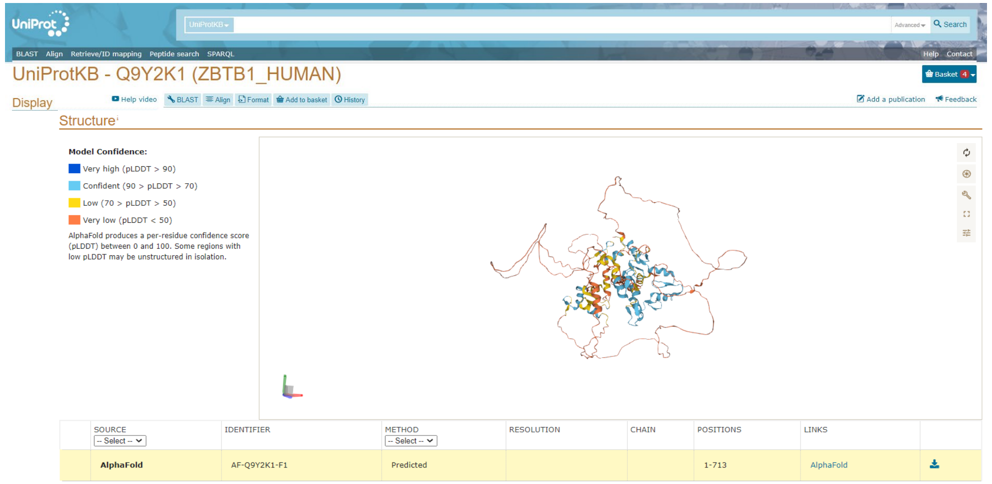
[1] DeepMind, London, UK, [2] Seoul National University, South Korea
* Equal contribution
† Corresponding authors: John Jumper (jumper@deepmind.com), Demis Hassabis (dhcontact@deepmind.com)

- Kendrew Lecture 2021: https://www.youtube.com/watch?v=jTO6odQNp90

AF2 predictions of all proteins

- Teamed up with EBI to predict representative set of all known proteins (still ongoing…)

- Results for human and model organisms available already from Uniprot website



UniProtKB - Q9Y2K1 (ZBTB1_HUMAN)

Display

Structure

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 with low pLDDT may be unstructured in isolation.

	SOURCE -- Select --	IDENTIFIER	METHOD -- Select --	RESOLUTION	CHAIN	POSITIONS	LINKS	
	AlphaFold	AF-Q9Y2K1-F1	Predicted			1-713	AlphaFold	

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Image: UniProt

How reliable is your AF2 model?

- AF2 will always give you a structure
- But that doesn’t mean it is right

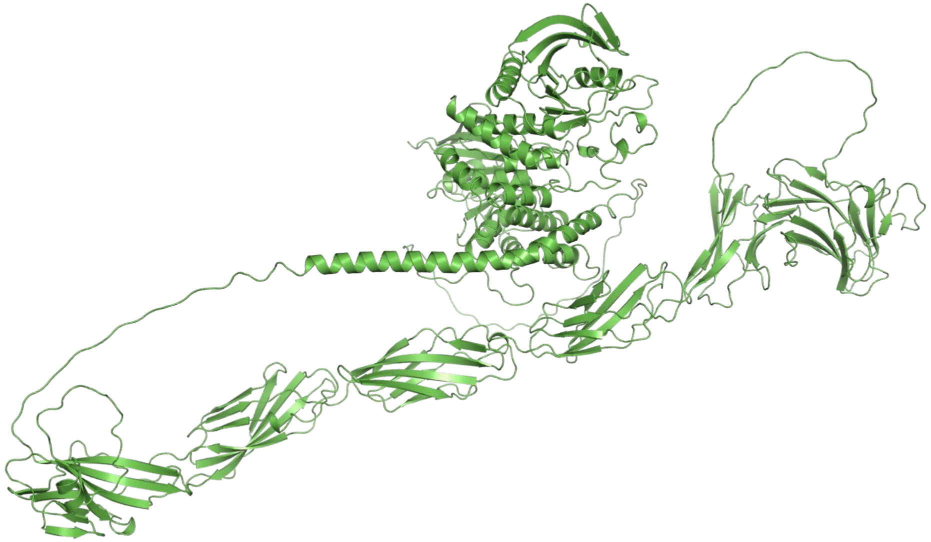

Image: Janet Deane CCBY 4.0

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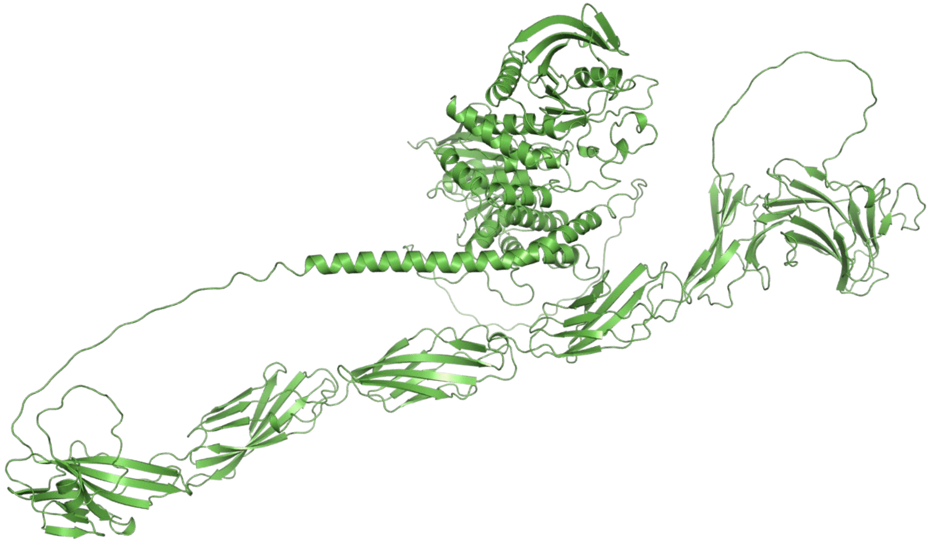
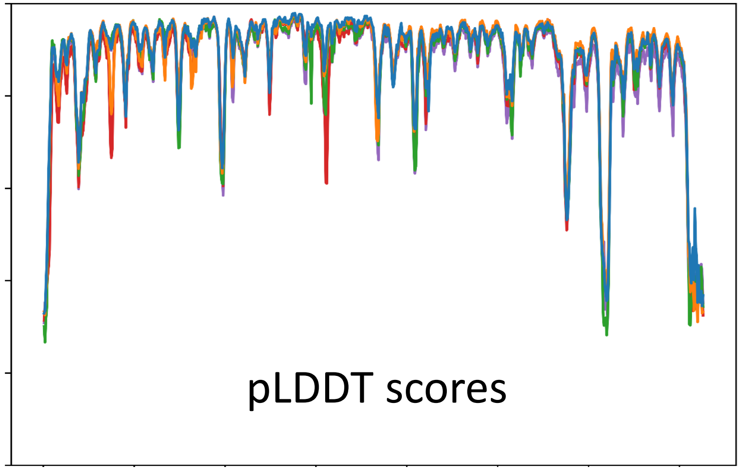
- But that doesn't mean it is right

- **You have to check** the statistical plots and scores that are also generated





PAE plot

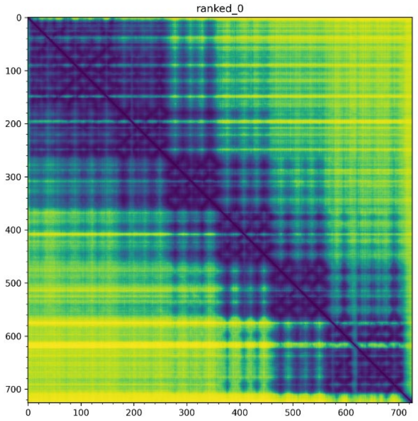


Image: Janet Deane CCBY 4.0

pLDDT Scores and Plot

- This is a per residue score on scale of 0 to 100
- Score above 70 is a confident prediction

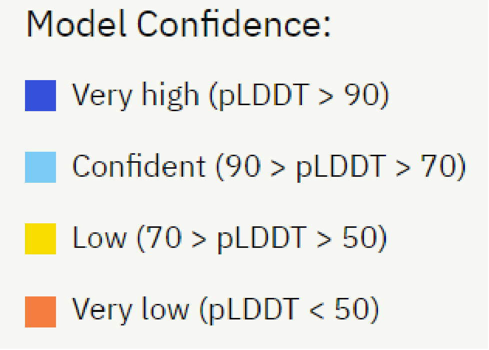


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Image: UniProt

pLDDT Scores and Plot

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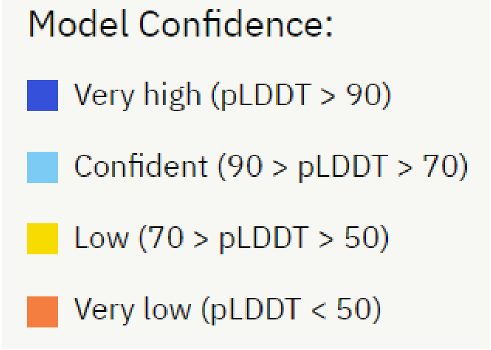
- Score above 70 is a confident prediction
- Displayed as a coloured structure



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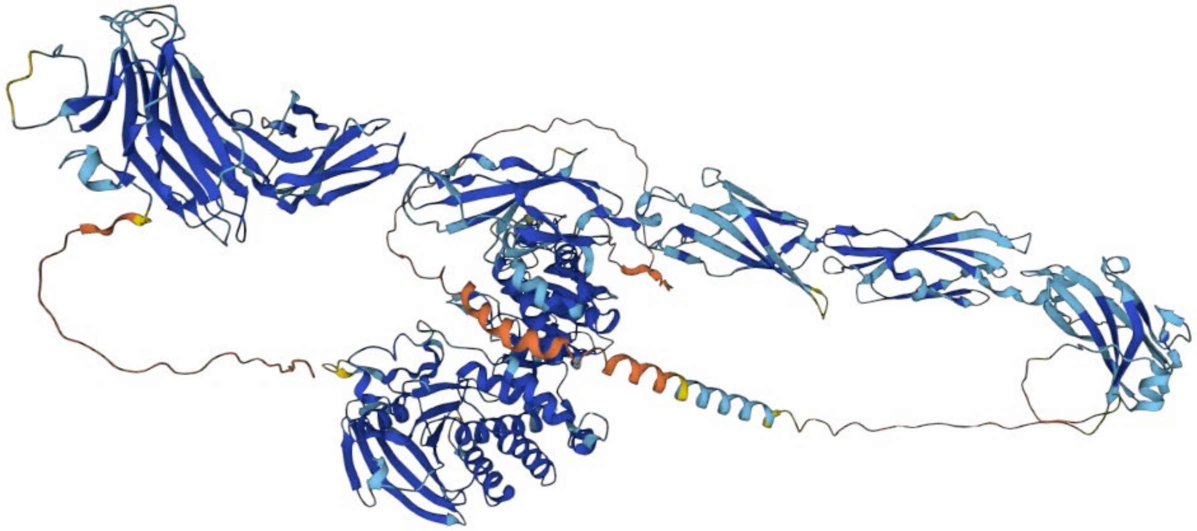

Image: UniProt

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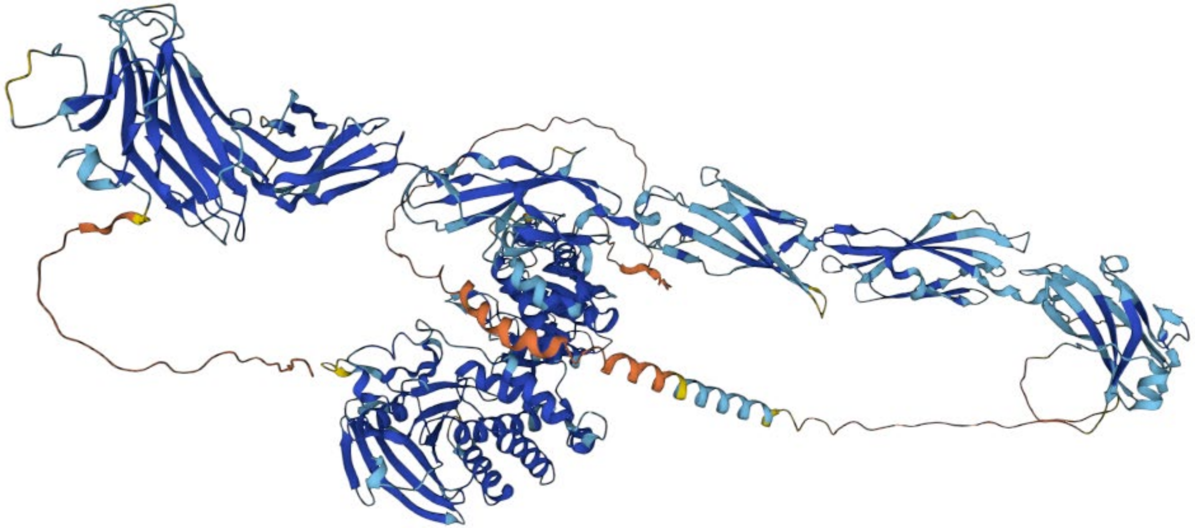


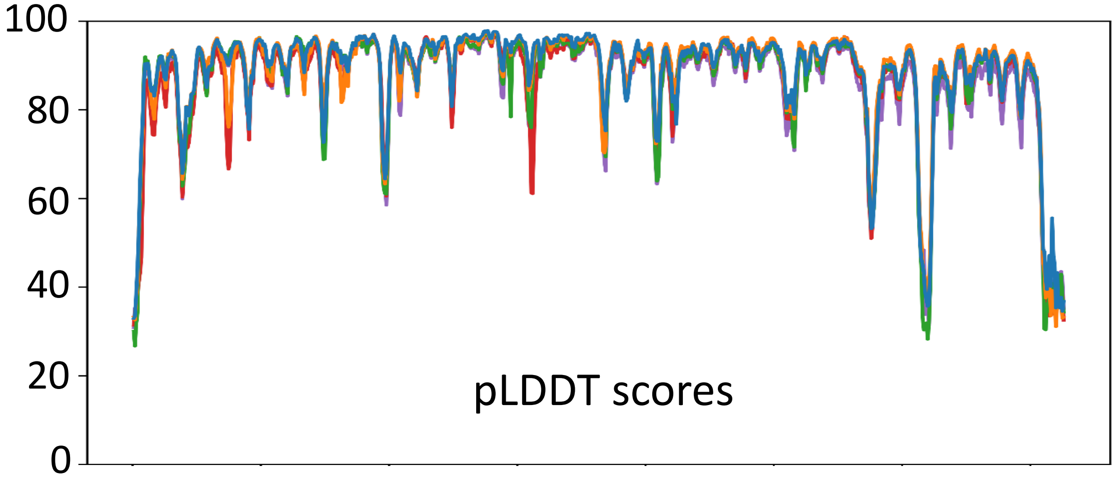
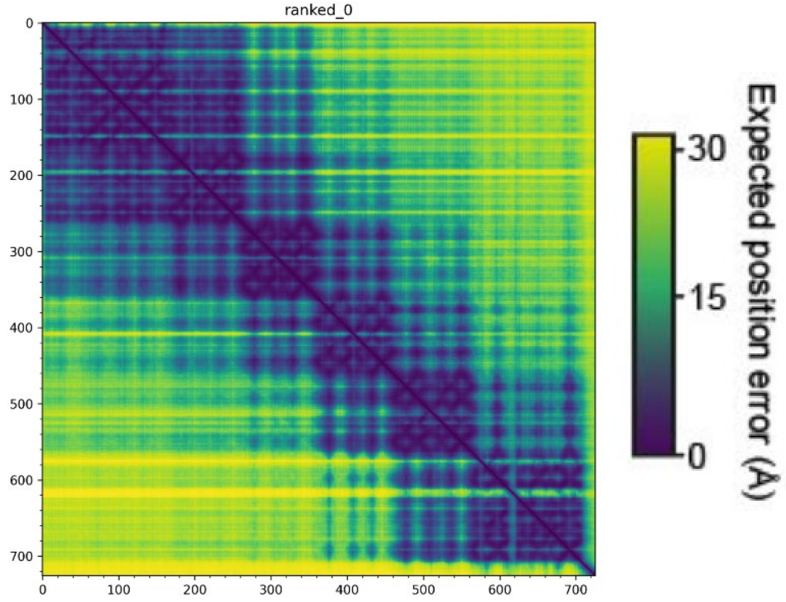


Image: UniProt

PAE plots – Predicted Aligned Error

- This is a measure of confidence relative to other regions of the structure
- Low error is high confidence (blue)
- High error is low confidence (yellow)



PAE plots – Predicted Aligned Error

- This is a measure of confidence relative to other regions of the structure
- Low error is high confidence (blue)
- High error is low confidence (yellow)
- In this example:
  - Domains 1 and 2 confident relative to each other
  - Domains 1 and 2 not confident relative to domains 4 and 5

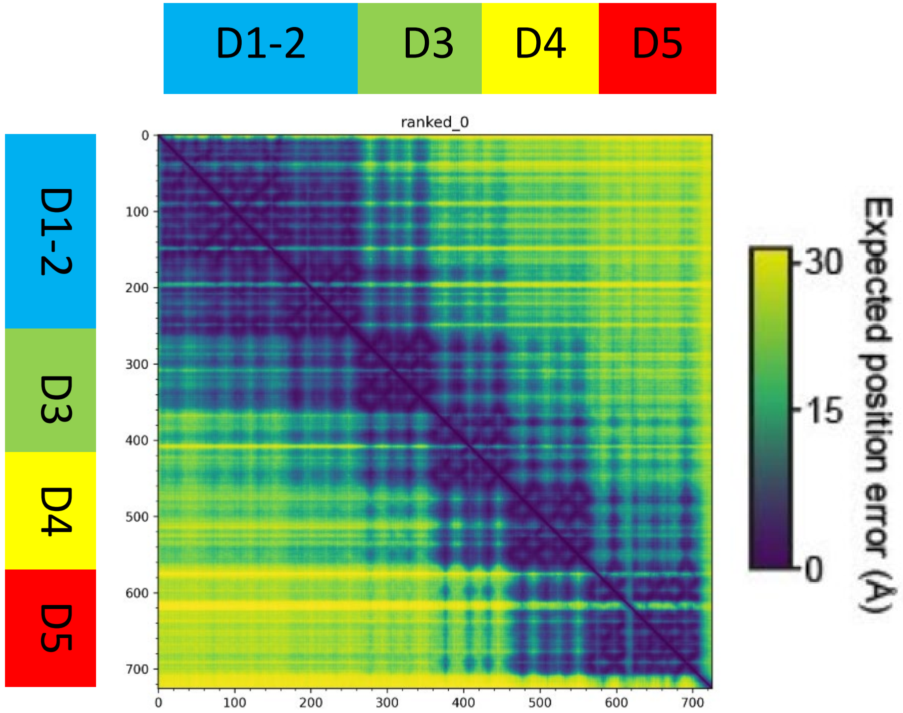
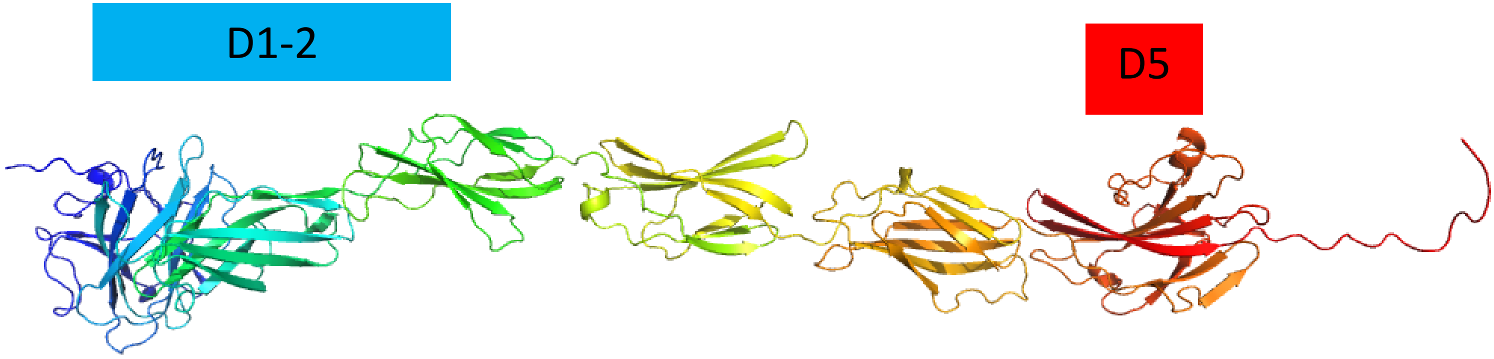


Image: Janet Deane CCBY 4.0

PAE plots – Predicted Aligned Error



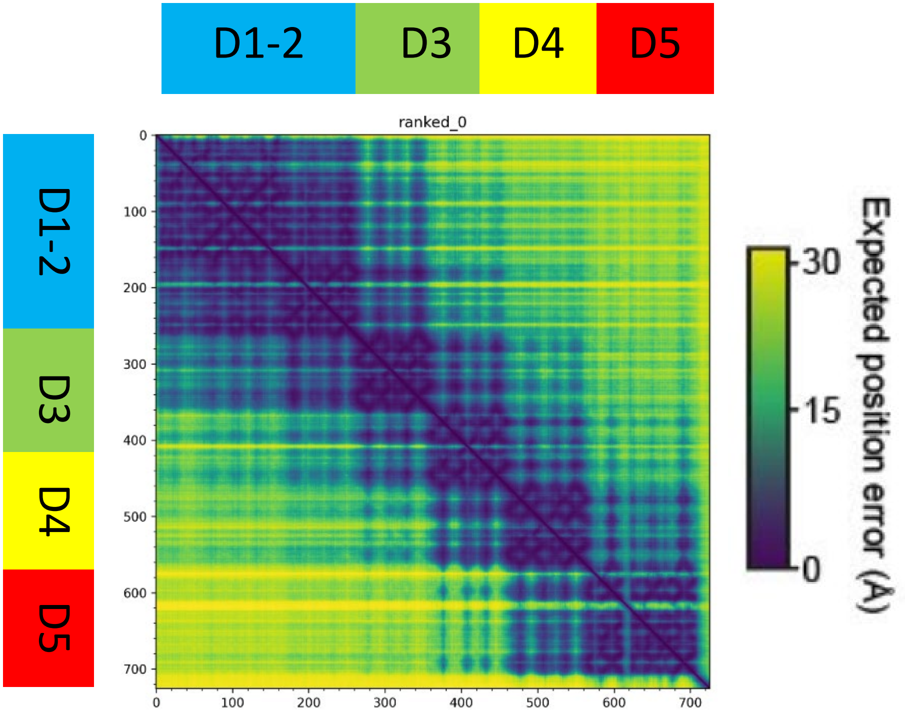


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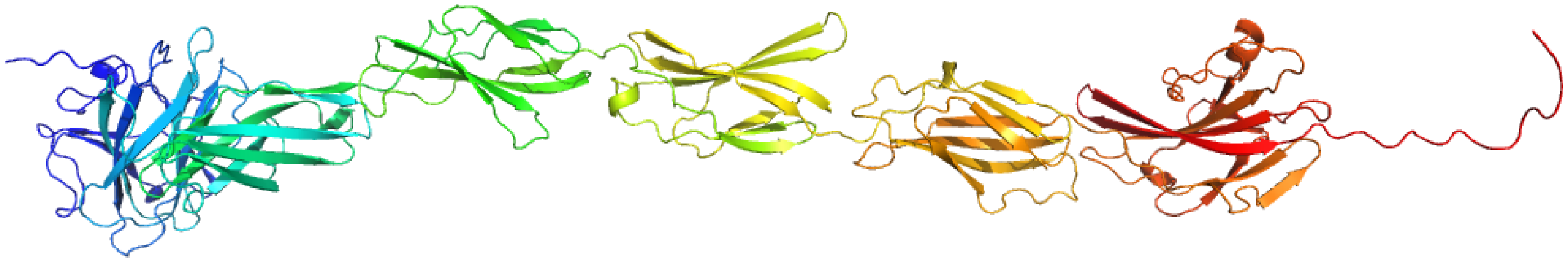
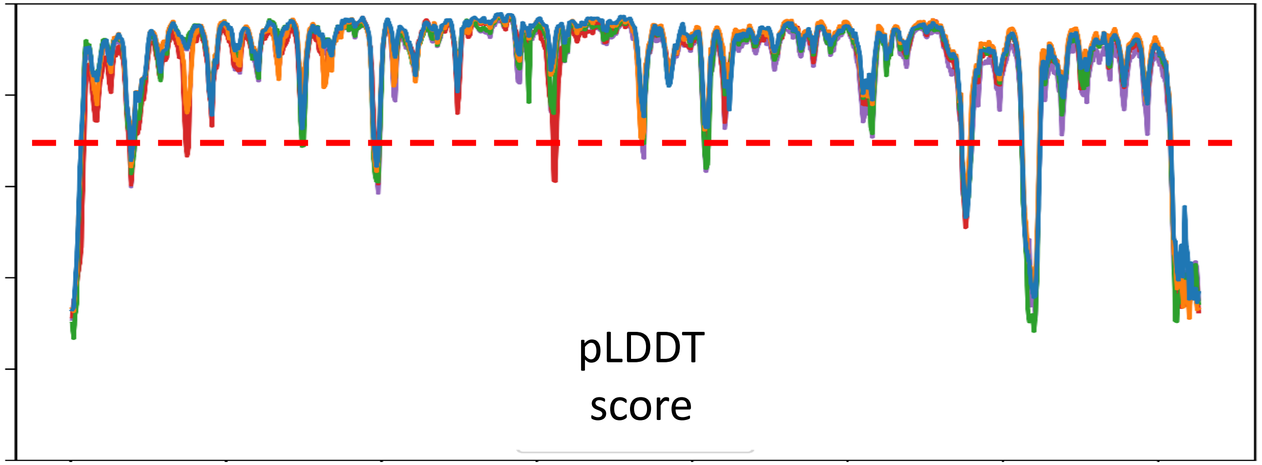
Image: Janet Deane CCBY 4.0

How to judge an AF2 model

- To summarise, a high-confidence per-residue model can be low-confidence overall





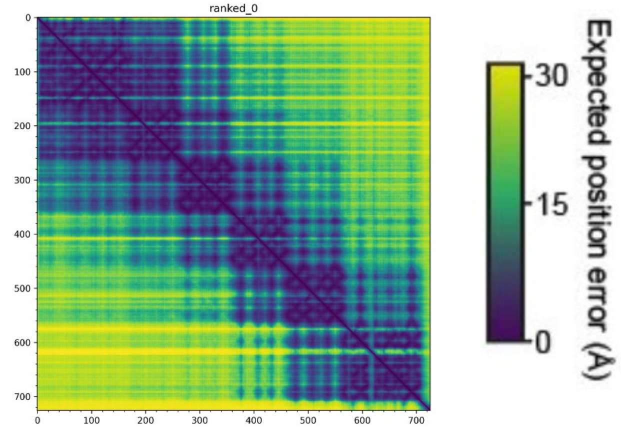
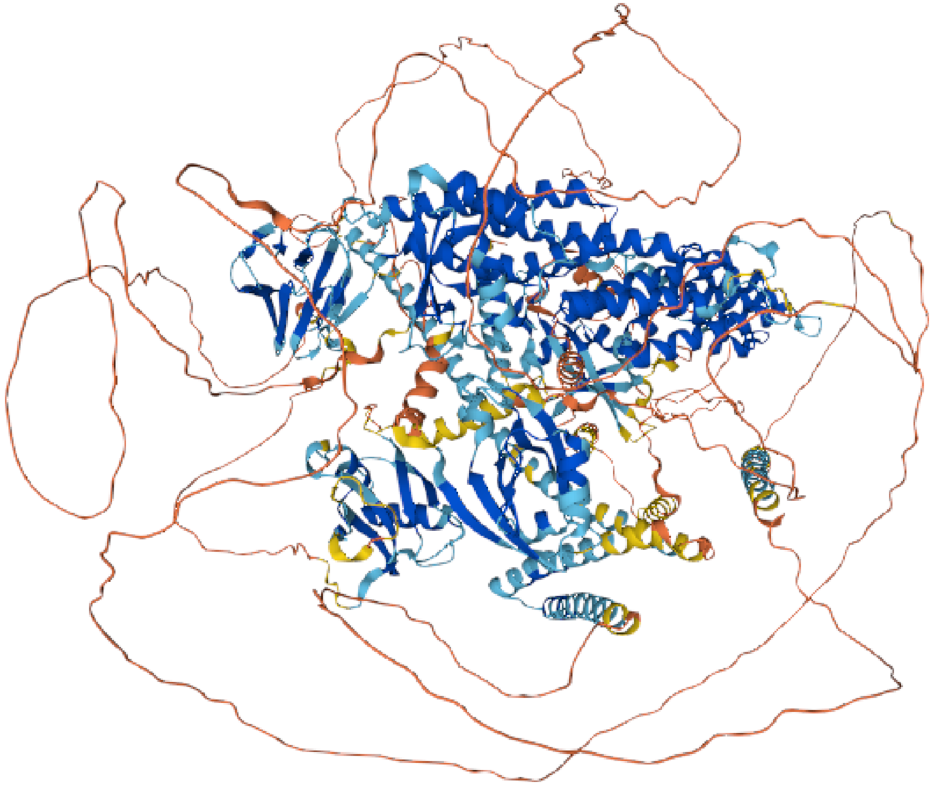


Image: Janet Deane CCBY 4.0

What about proteins like this?

Human Afadin



Predicted accuracy

High → Low

- If you see something like this, can you learn anything at all?

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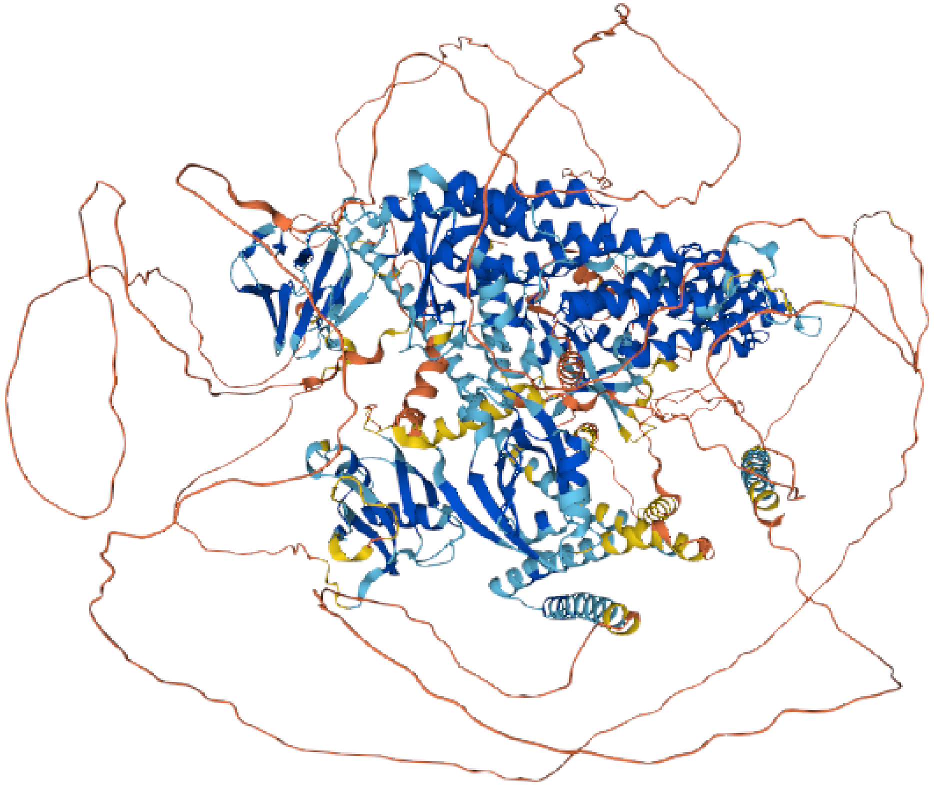
Image: UniProt

What about proteins like this?

Human Afadin



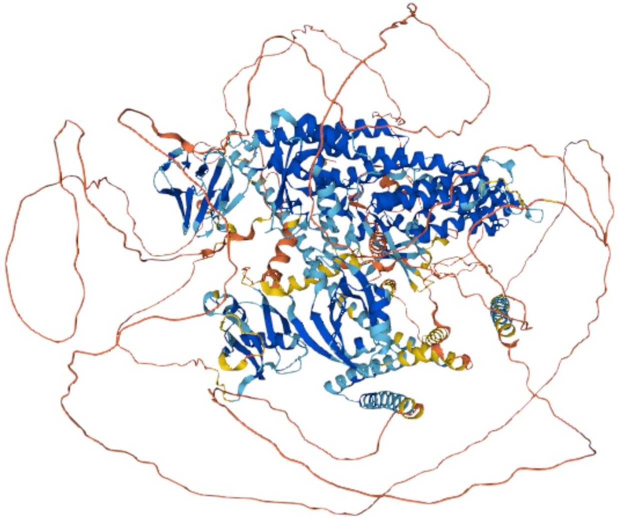
Predicted accuracy

High → Low

Actually quite high confidence these regions are unstructured

Image: UniProt

Look at the pLDDT plot

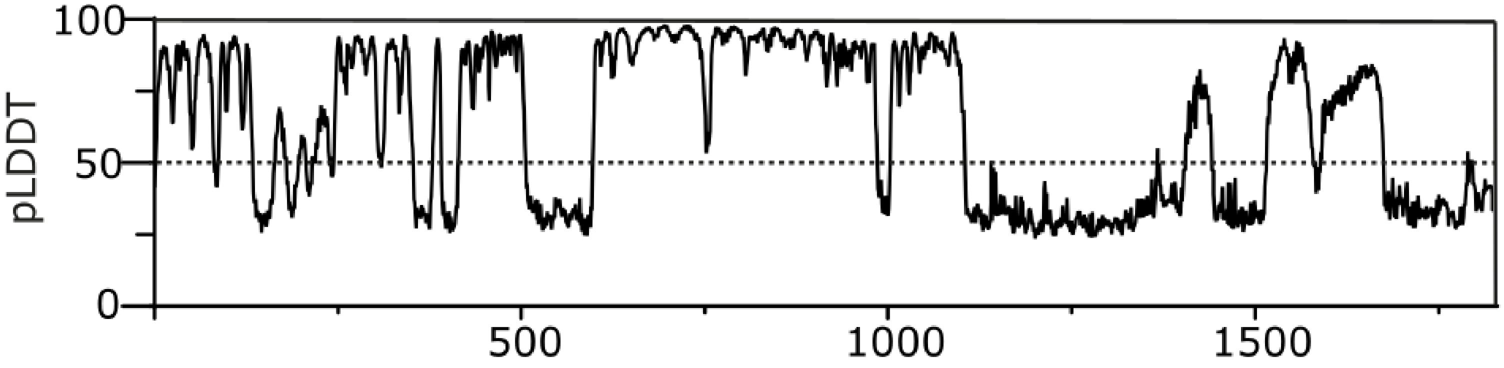


Predicted accuracy

High

↑

Low

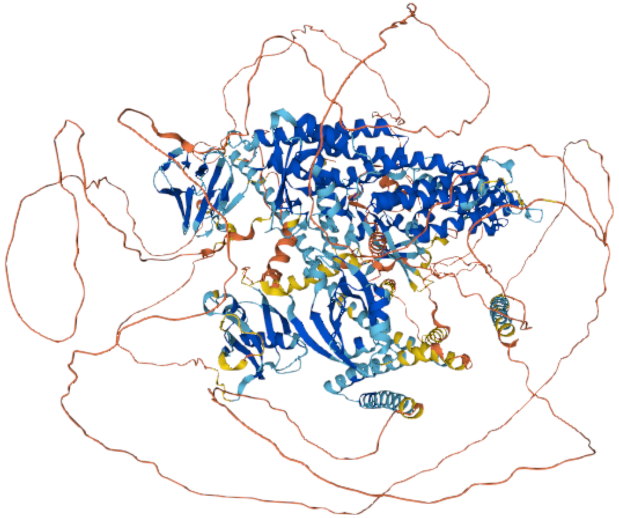


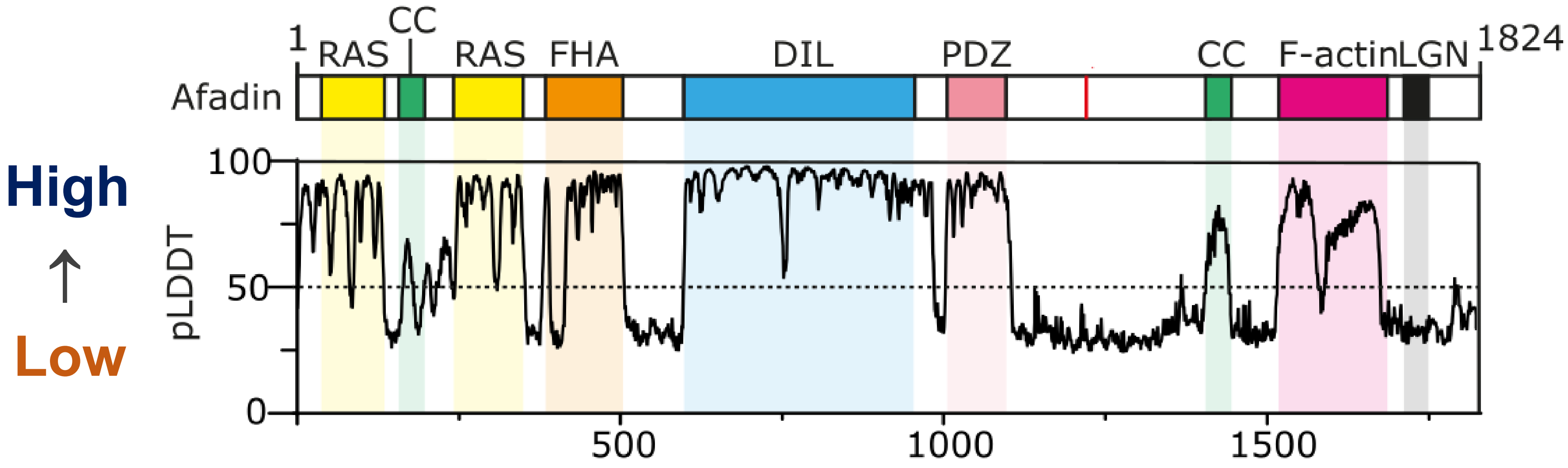
Top Image: UniProt

Bottom image: Hay et al (2022) eLife, 11:e79855

Look at the pLDDT plot

- Clearly determine domain boundaries





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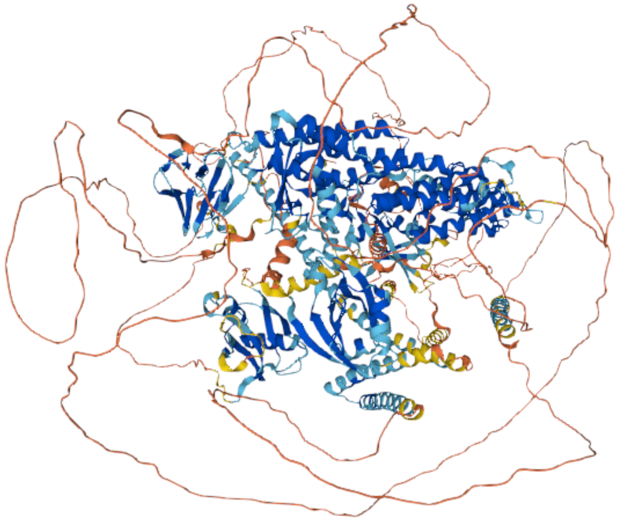
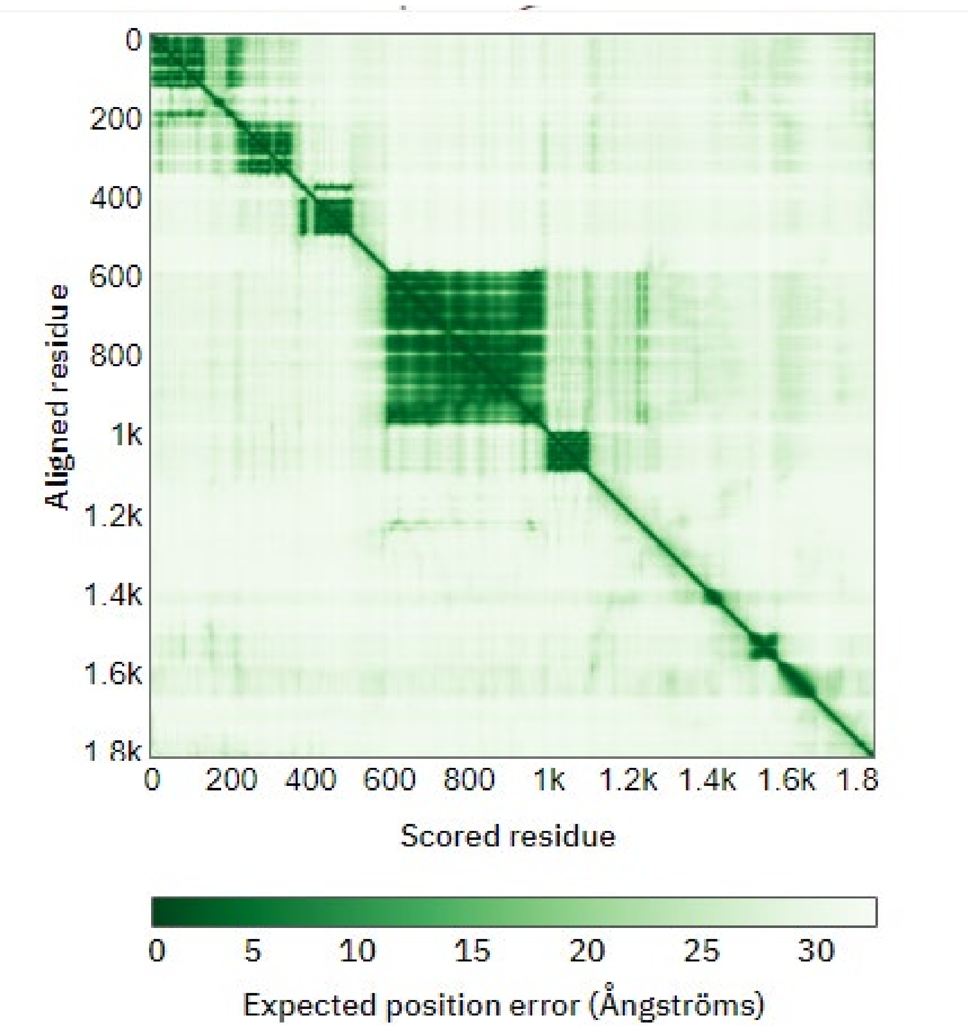
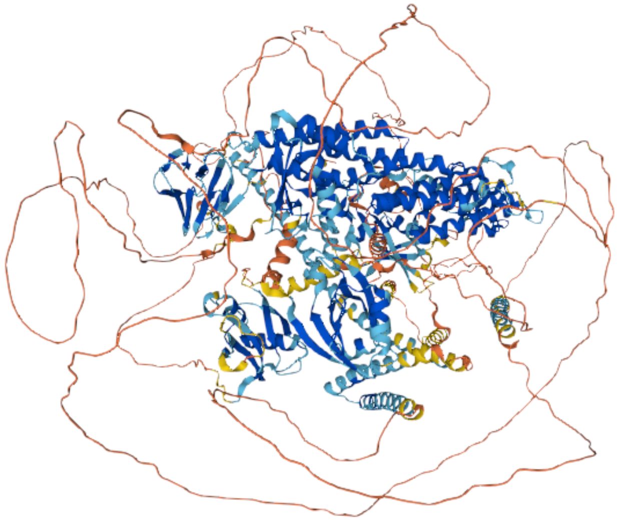




Images: DeepMind

Look at the PAE plot



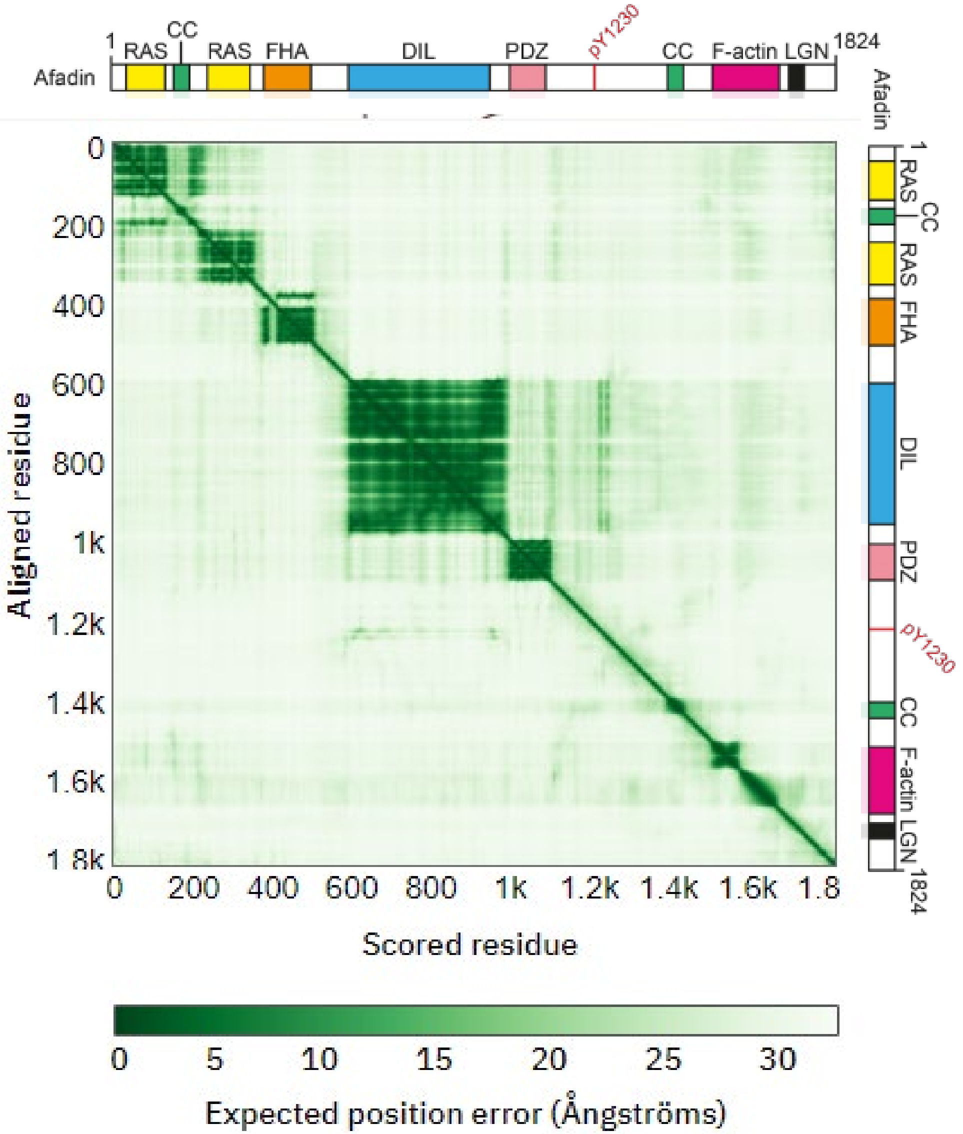


Image: Janet Deane CC-BY 4.0

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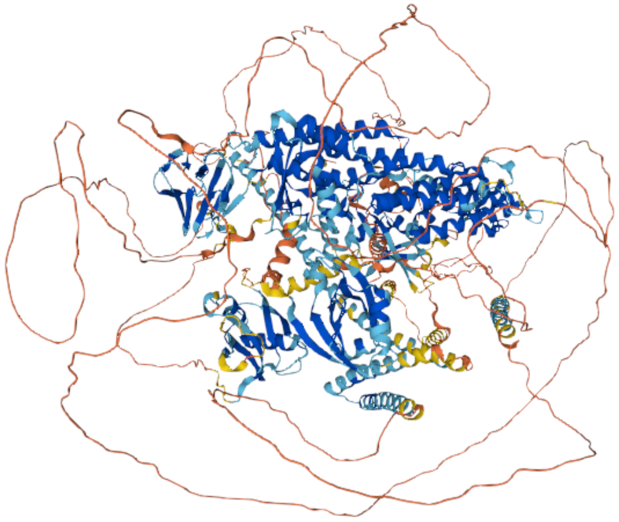


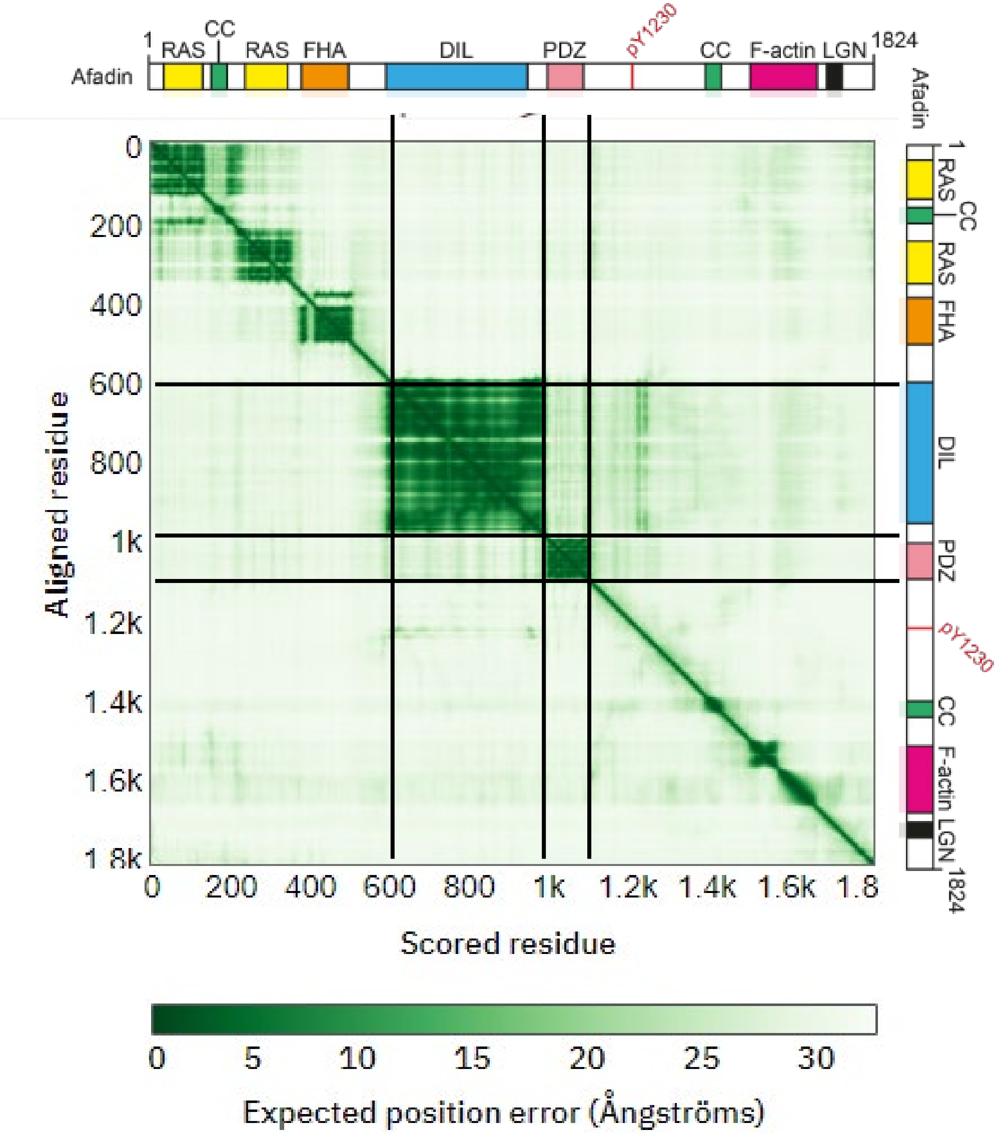


Image: Janet Deane CC-BY 4.0

Look at the PAE plot

- The predictions are only confident within domains NOT BETWEEN

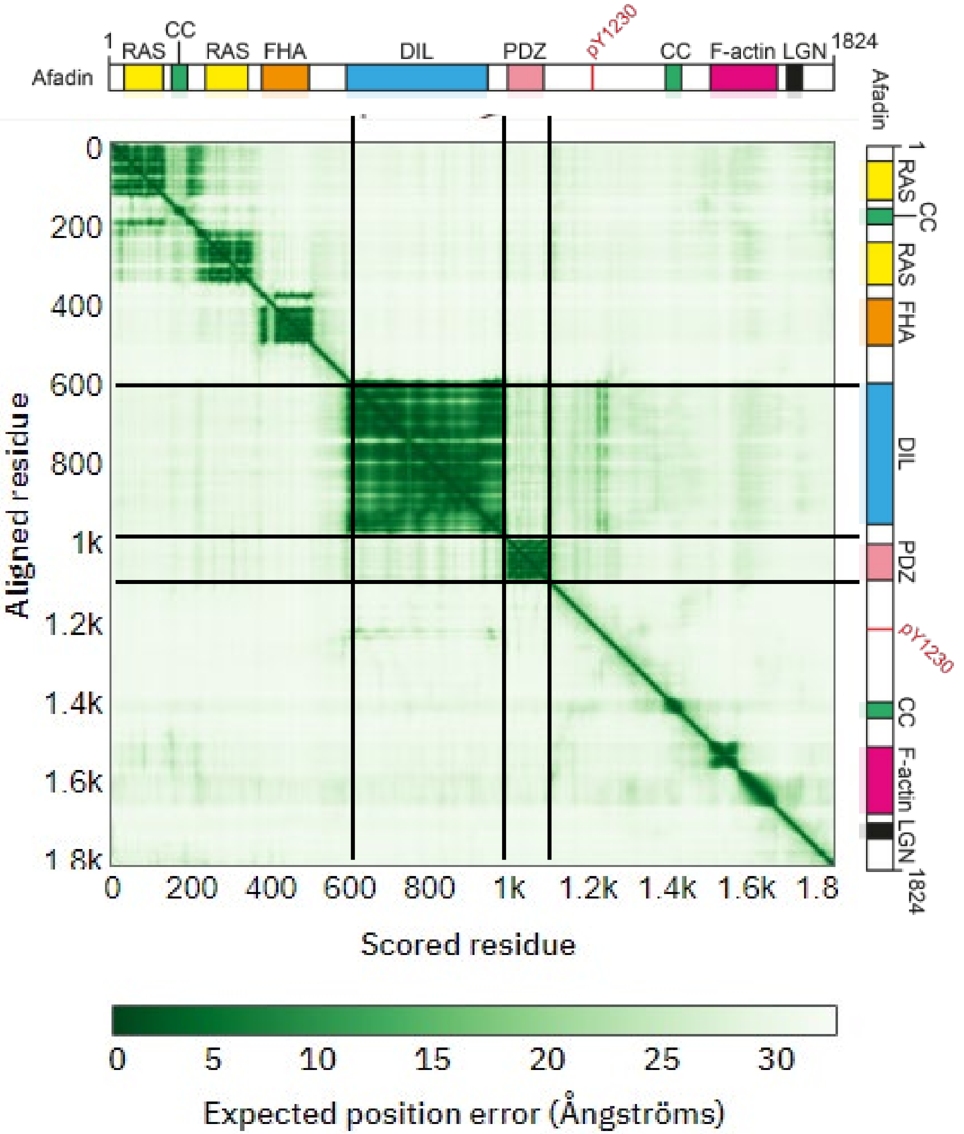
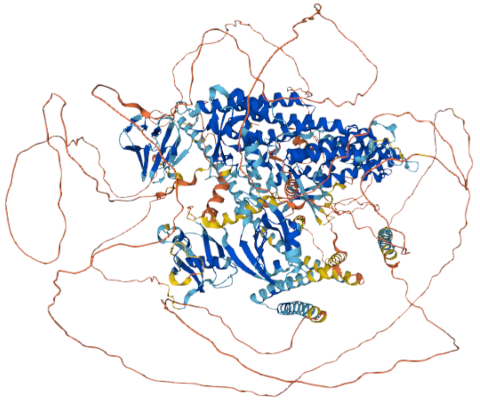
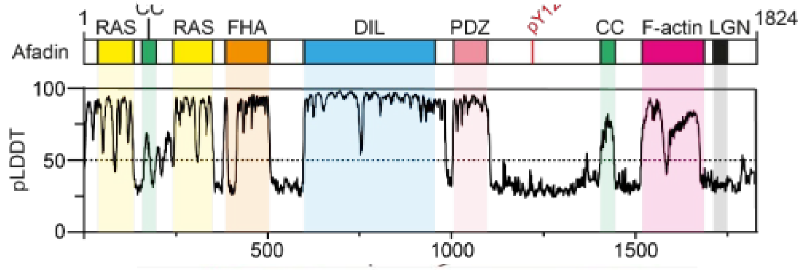


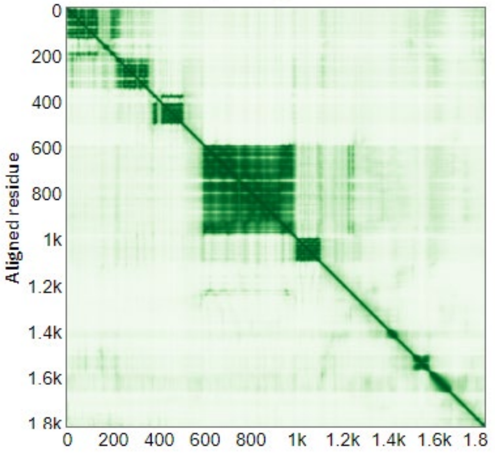
Image: Janet Deane CC-BY 4.0

In this case:

- This AF2 model is useful for:
  - Determining domain boundaries
  - Fold of individual domains

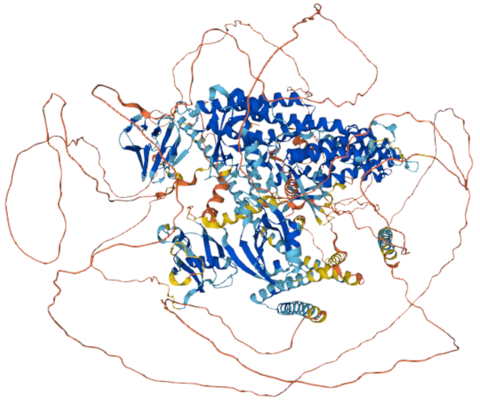


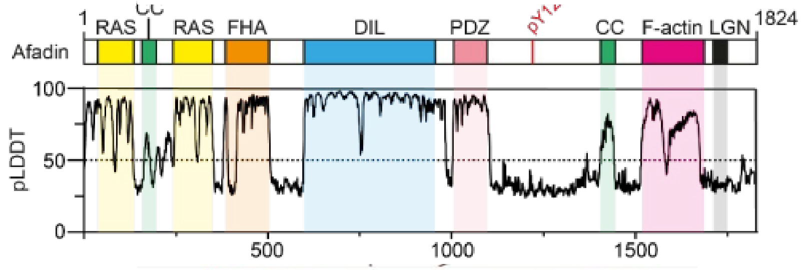


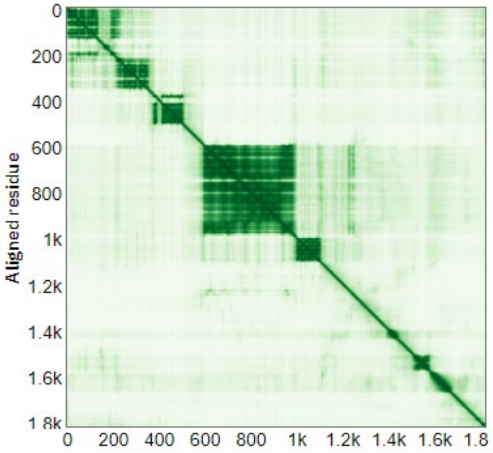


In this case:

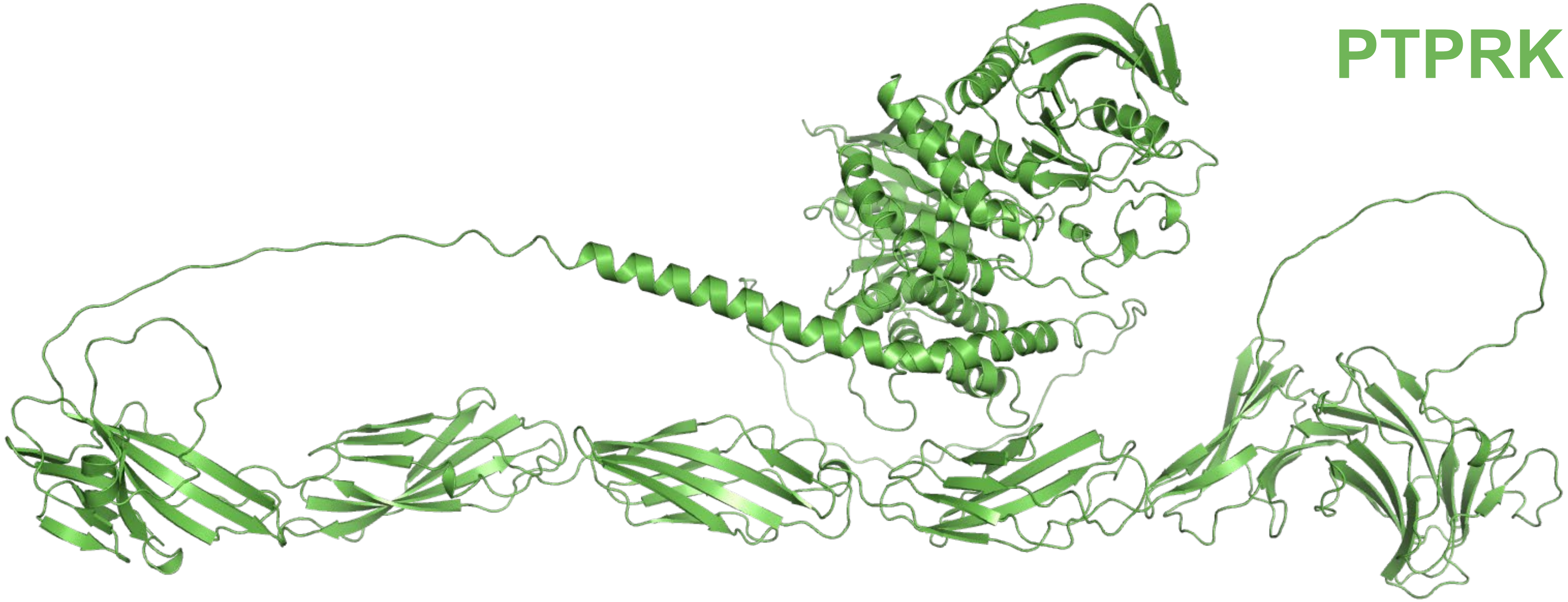
- This AF2 model is useful for:
  - Determining domain boundaries
  - Fold of individual domains
  - You could then use these individual domains to search using DALI or FoldSeek to find structural homologues that may inform function







AF2 doesn't know about topology



Human PTPRK

Image: Janet Deane CC-BY 4.0

AF2 doesn't know about topology

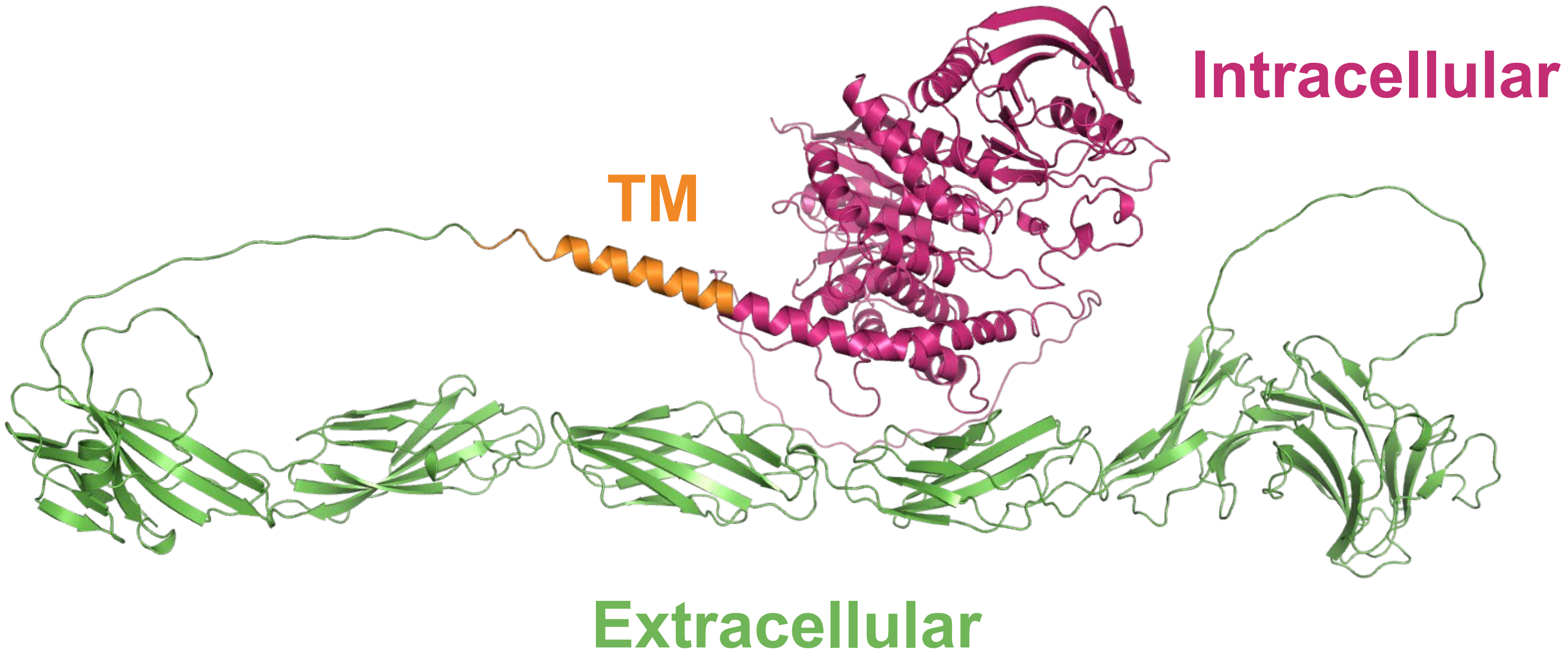
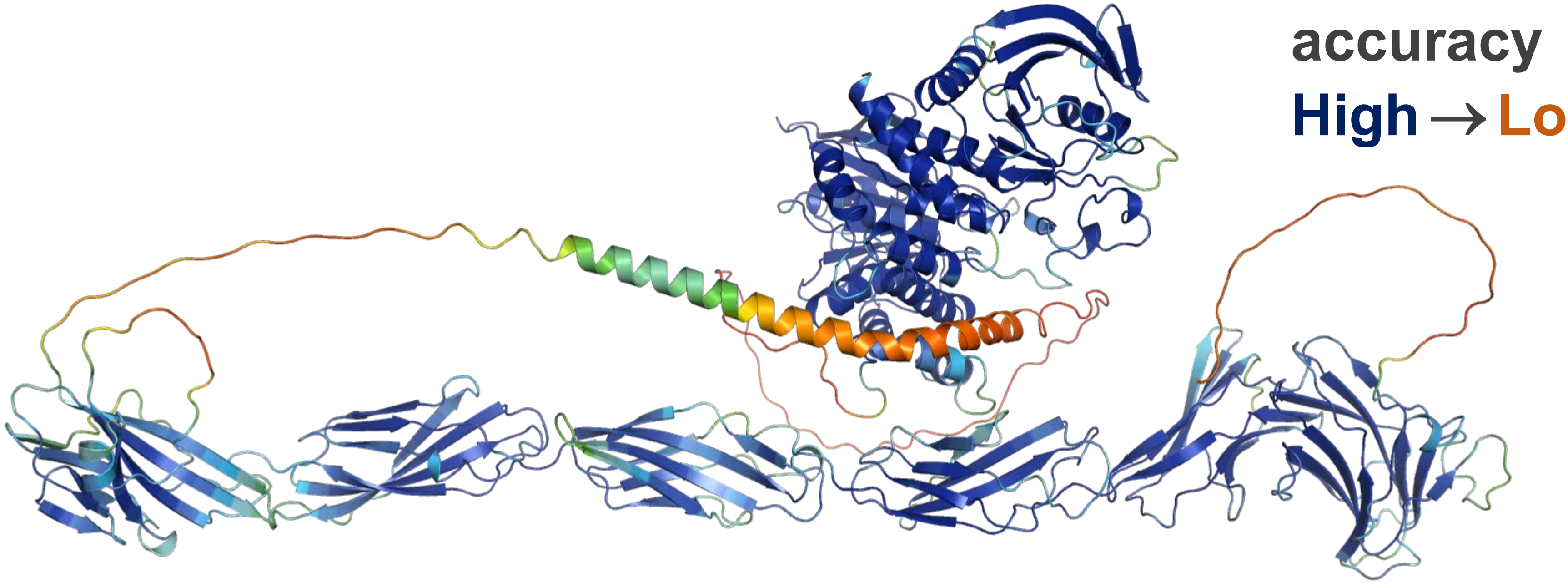


Image: Janet Deane CC-BY 4.0

AF2 doesn't know about topology



Predicted accuracy
High → Low

- Treat membrane-spanning models with caution…

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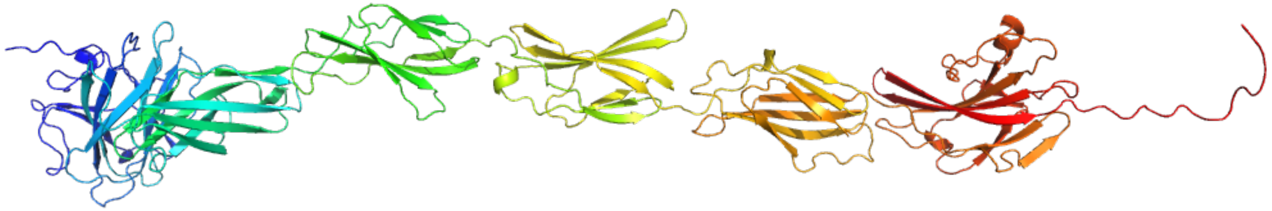
Image: DeepMind

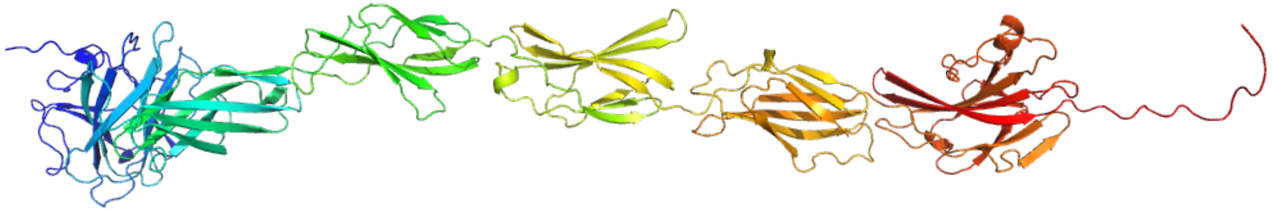
Validate using experimental techniques

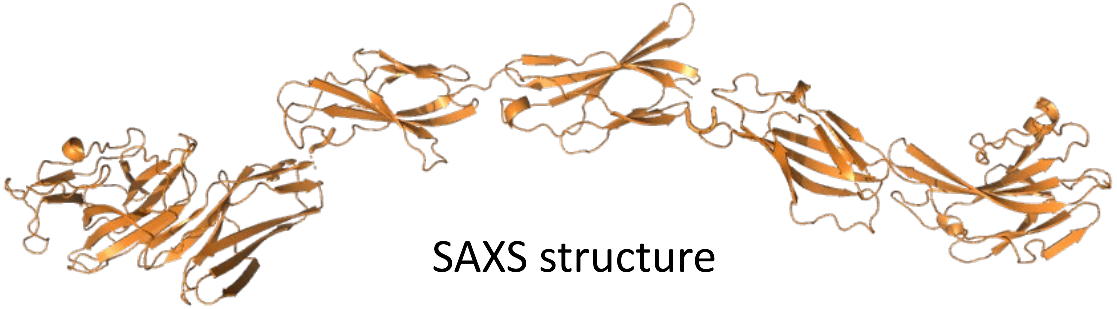
AlphaFold Prediction



Validate using experimental techniques

AlphaFold Prediction



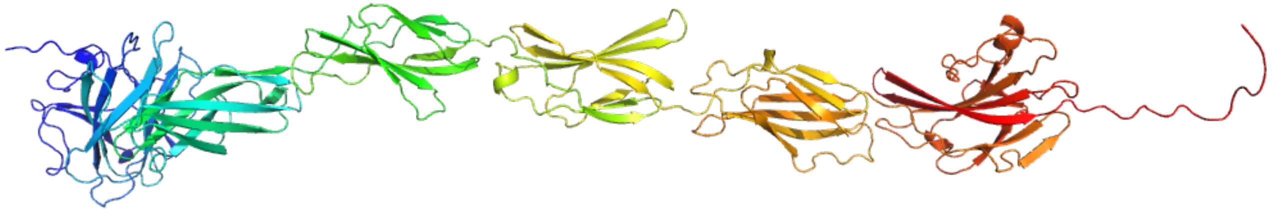


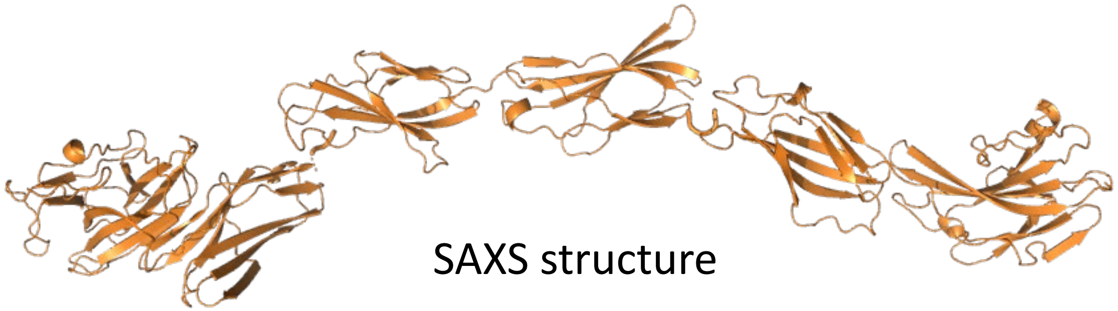
SAXS structure

Image: Hay et al (2023) J. Biol. Chem. 299:102750

Validate using experimental techniques

AlphaFold Prediction





SAXS structure

AlphaFold
Prediction

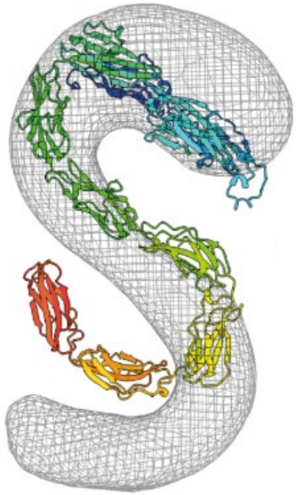
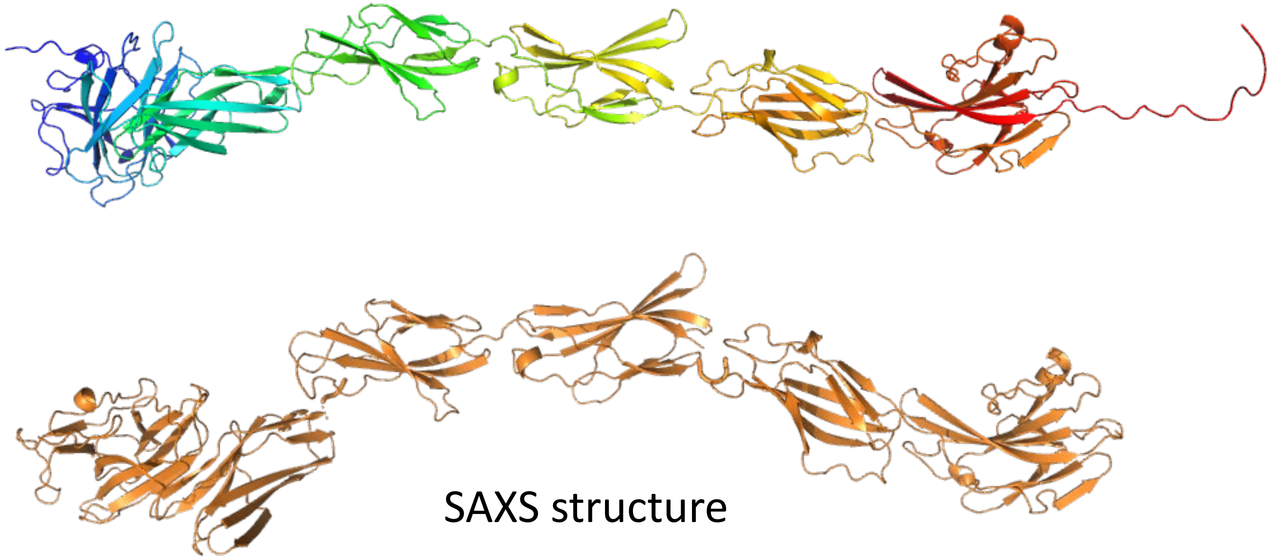


Image: Hay et al (2023) J. Biol. Chem. 299:102750

Right image: McKie et al (2023) PNAS In press

Validate using experimental techniques

AlphaFold Prediction



SAXS structure

AlphaFold Prediction

EM structure

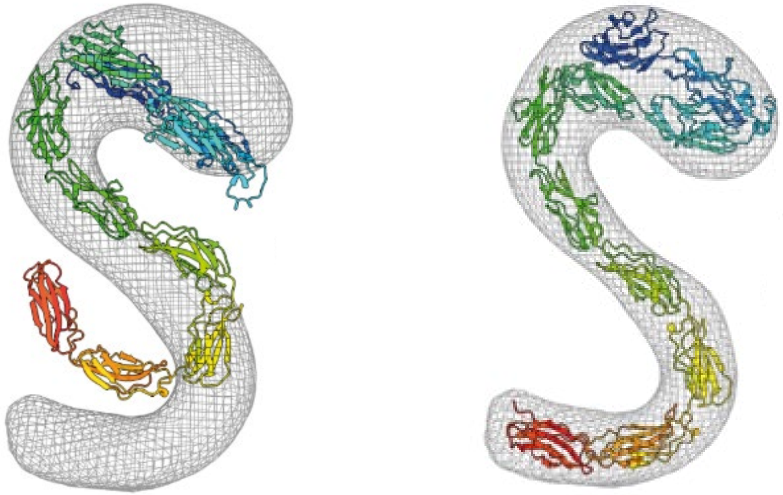
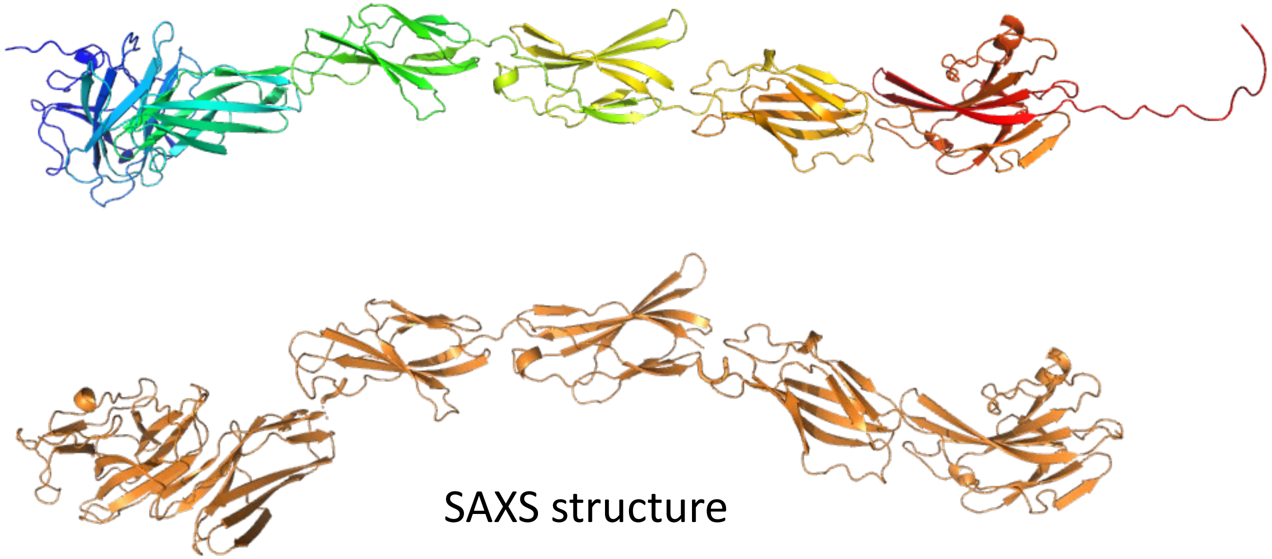


Image: Hay et al (2023) J. Biol. Chem. 299:102750

Right image: McKie et al (2023) PNAS In press

Validate using experimental techniques

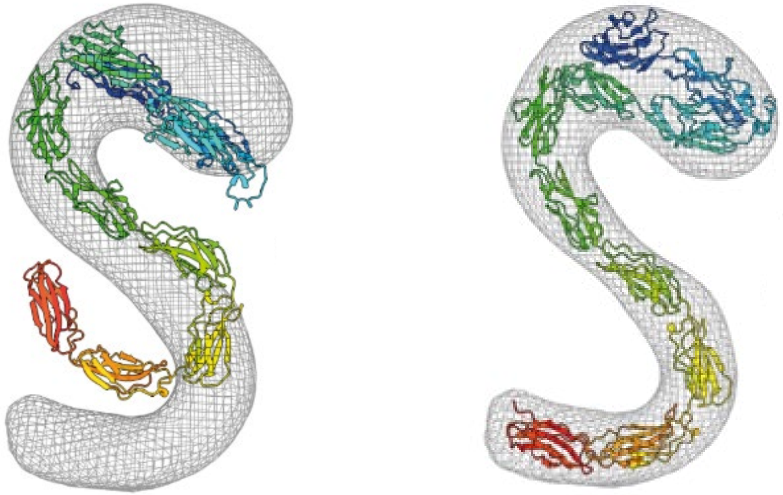
AlphaFold Prediction



SAXS structure

AlphaFold Prediction

EM structure



- Importantly, AF2 provided excellent starting models for these experimental approaches

Image: Hay et al (2023) J. Biol. Chem. 299:102750

Right image: McKie et al (2023) PNAS In press

AF2 is pretty good at single proteins…what about complexes?

- AF2 Multimer was developed to try and address this question

- Answer is mixed, again you have to know how to interpret the statistics of the models produced

- Two examples: CD1d-LIMP2

  PTPRK-Afadin

CD1d-LIMP2

- Lipid binding proteins: CD1d is like MHC-I, LIMP-2 has a lipid tunnel

- From literature they’re predicted to interact

- AF2 predicts a consistent complex (all models agree)

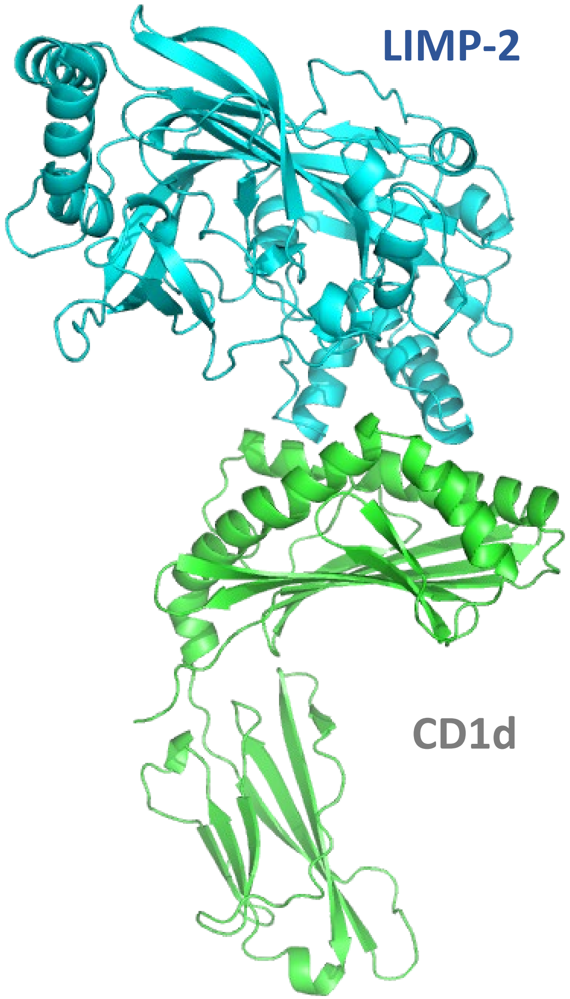


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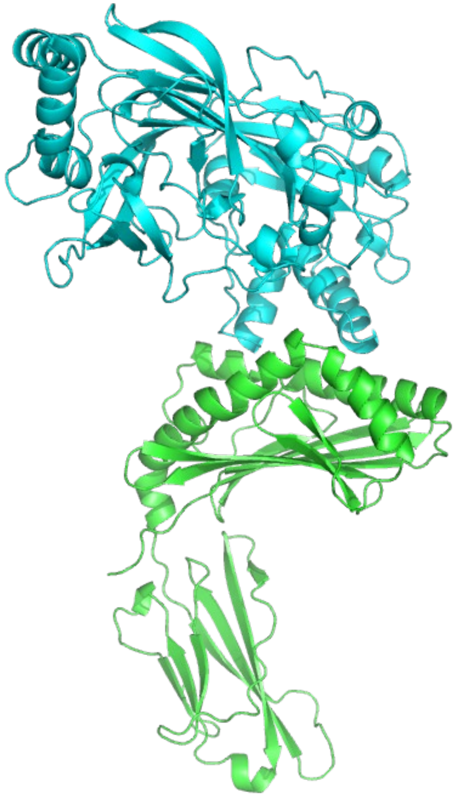
Image: Janet Deane CC-BY 4.0

CD1d-LIMP2

- pLDDT plot



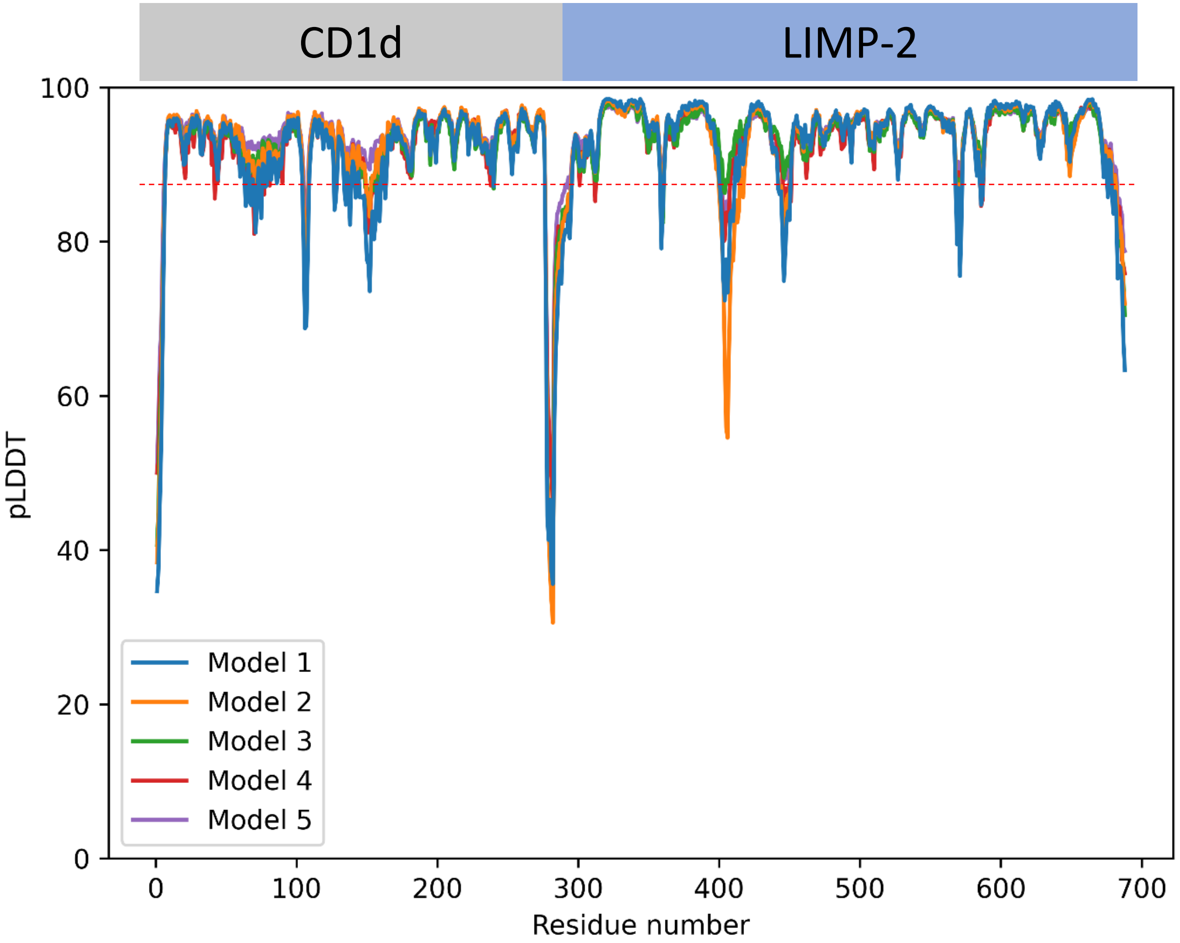
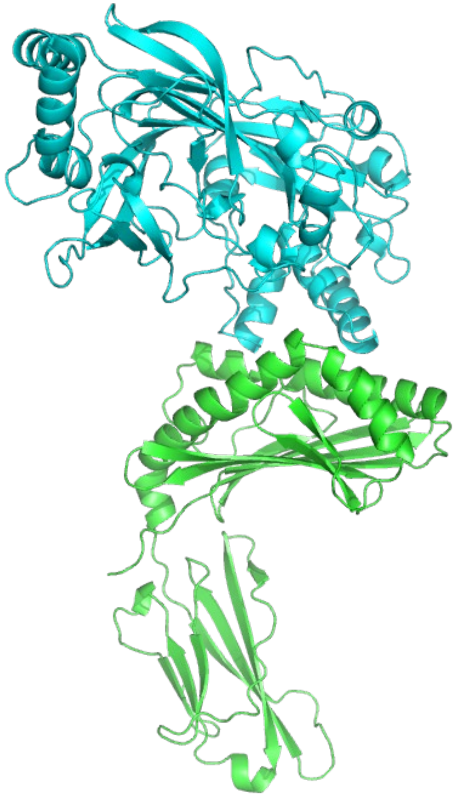


Image: Janet Deane CC-BY 4.0

CD1d-LIMP2

- PAE plot



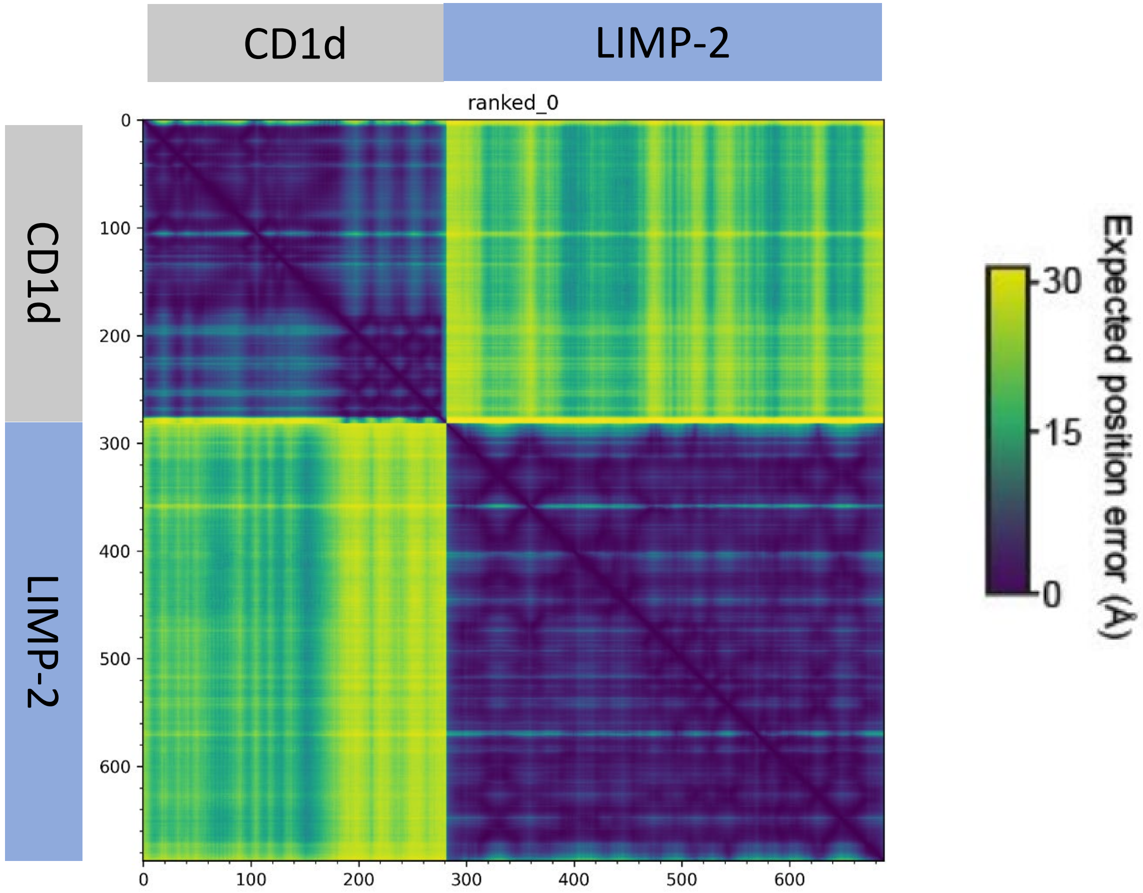
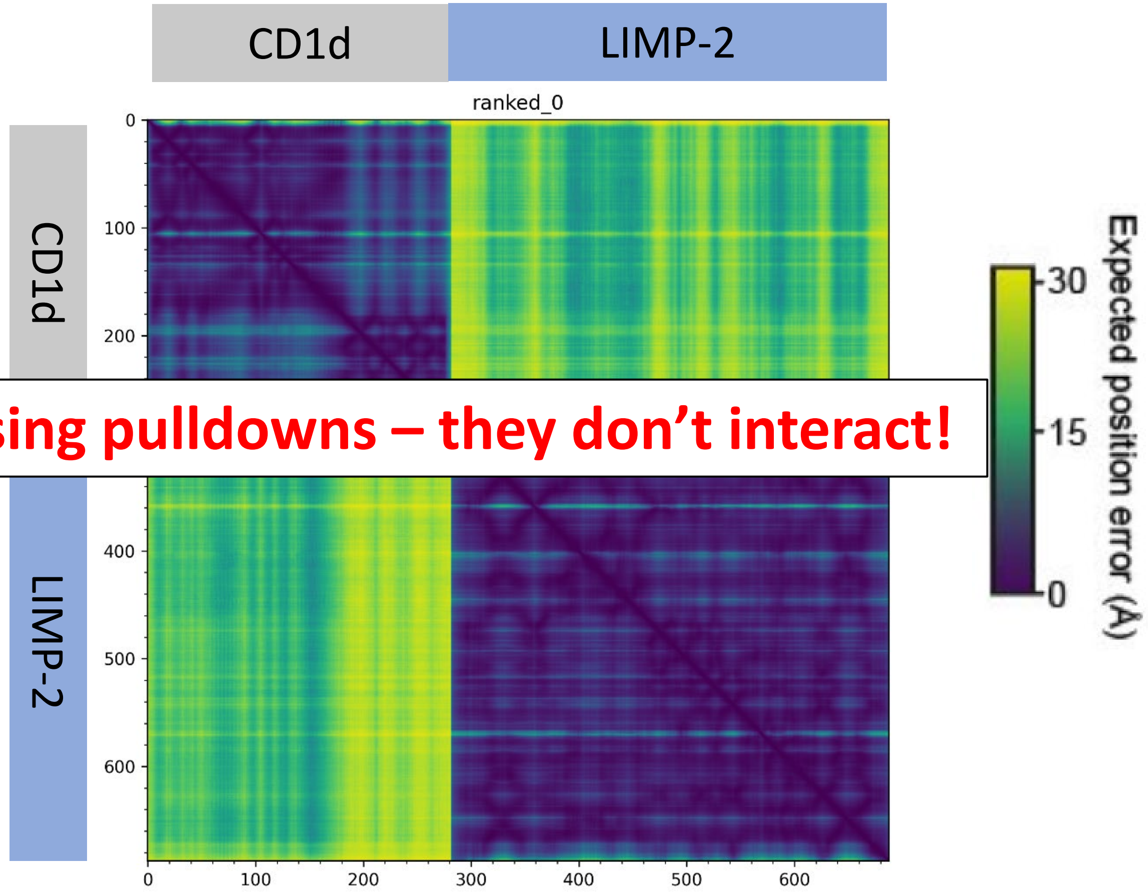


Image: Janet Deane CC-BY 4.0

CD1d-LIMP2

- PAE plot

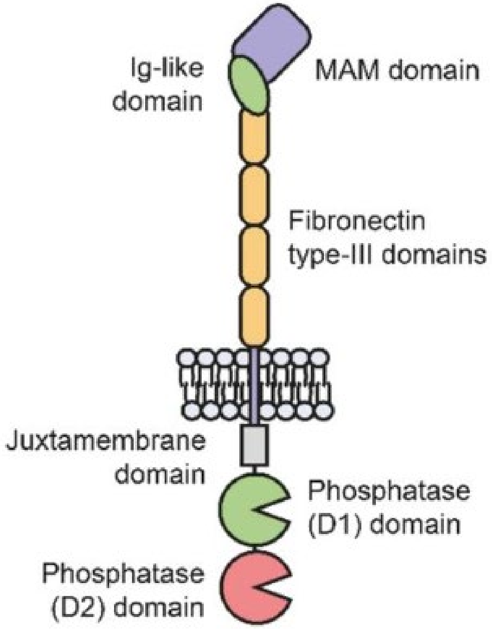


We tested this using pulldowns – they don’t interact!

Image: Janet Deane CC-BY 4.0

PTPRK-Afadin

- We knew that PTPRK binds Afadin but these are both BIG proteins



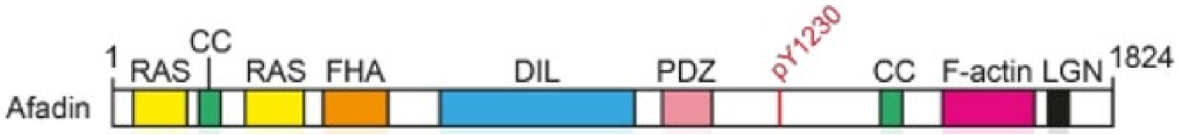


Image: Janet Deane CC-BY 4.0

PTPRK-Afadin

- In the lab, mapped this down to much smaller domains

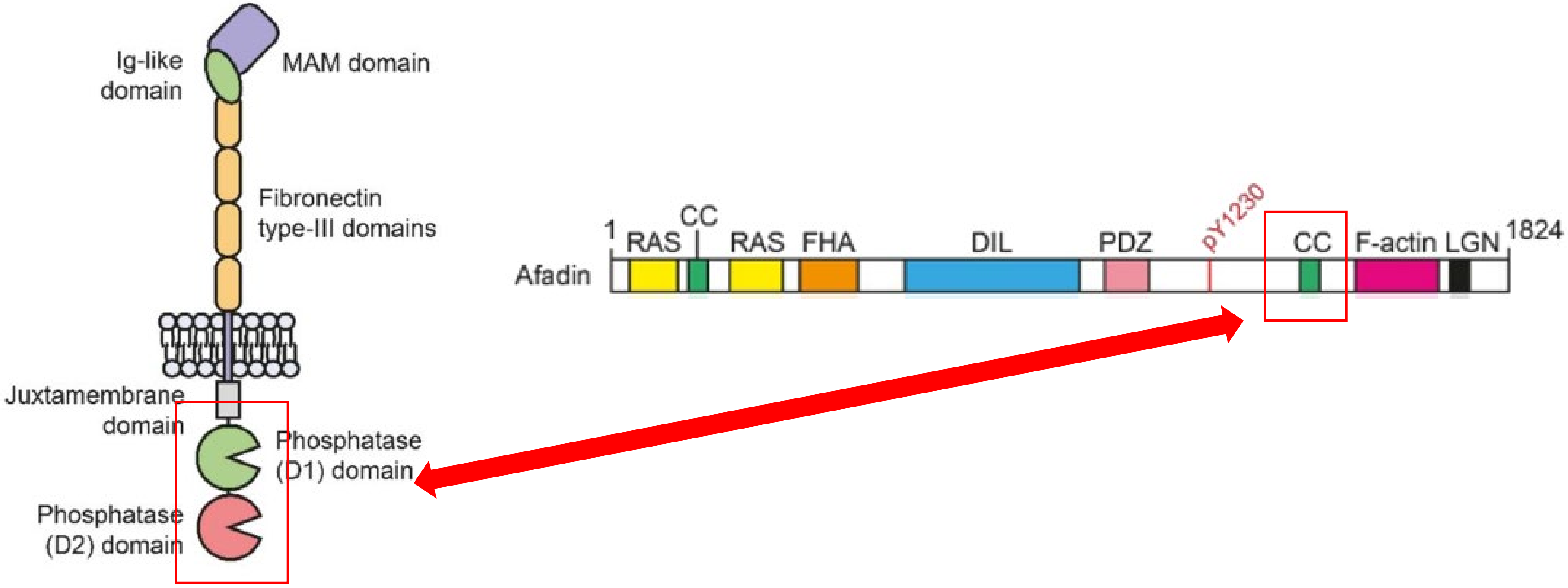
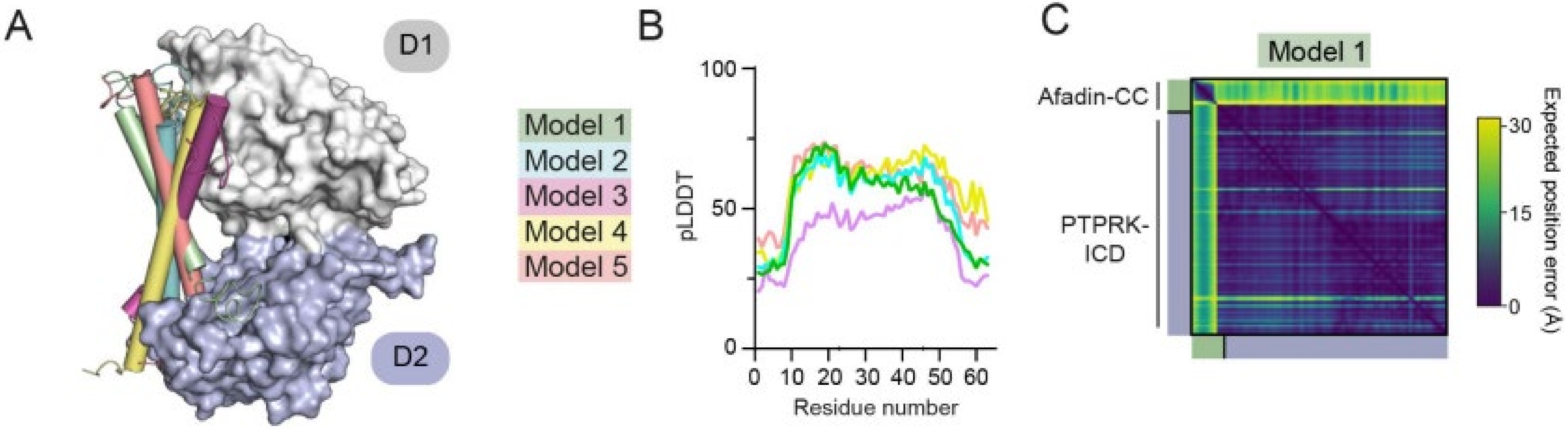


Image: Janet Deane CC-BY 4.0

PTPRK-Afadin

- But AF2 Multimer models weren’t good



Images from: Hay et al (2022) eLife 11:e79855

PTPRK-Afadin

- Experimentally mapped it down to smaller pieces

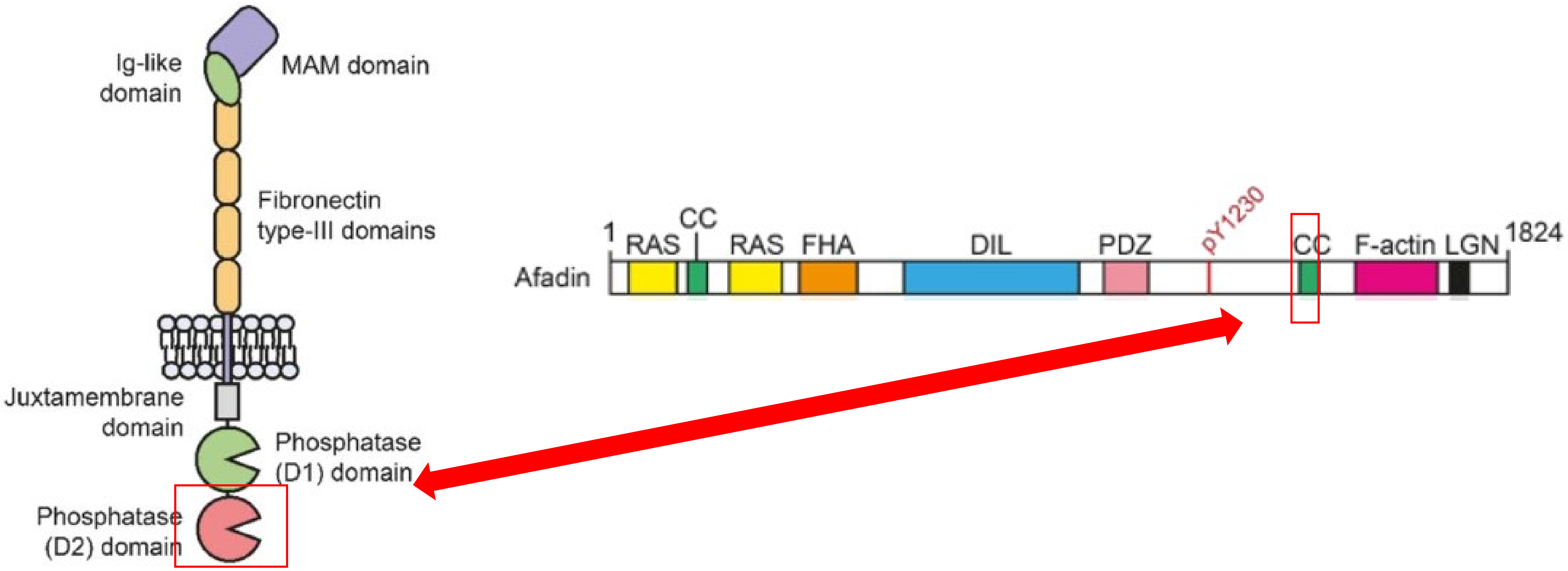
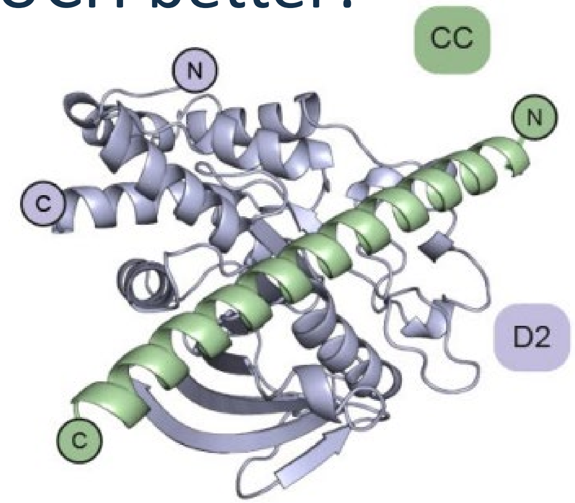
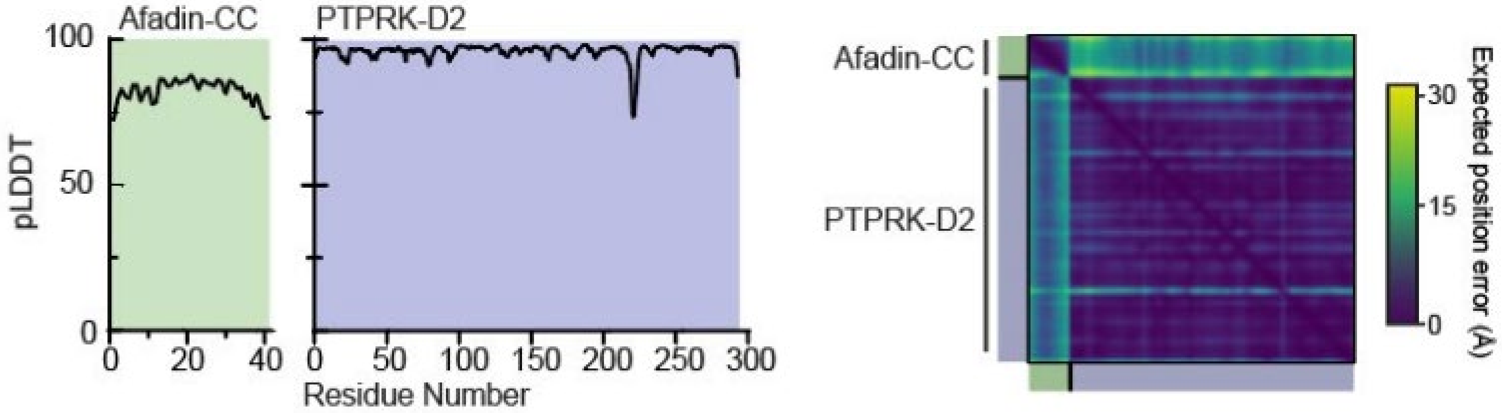


Image: Janet Deane CC-BY 4.0

PTPRK-Afadin

- AF2 Multimer models MUCH better!

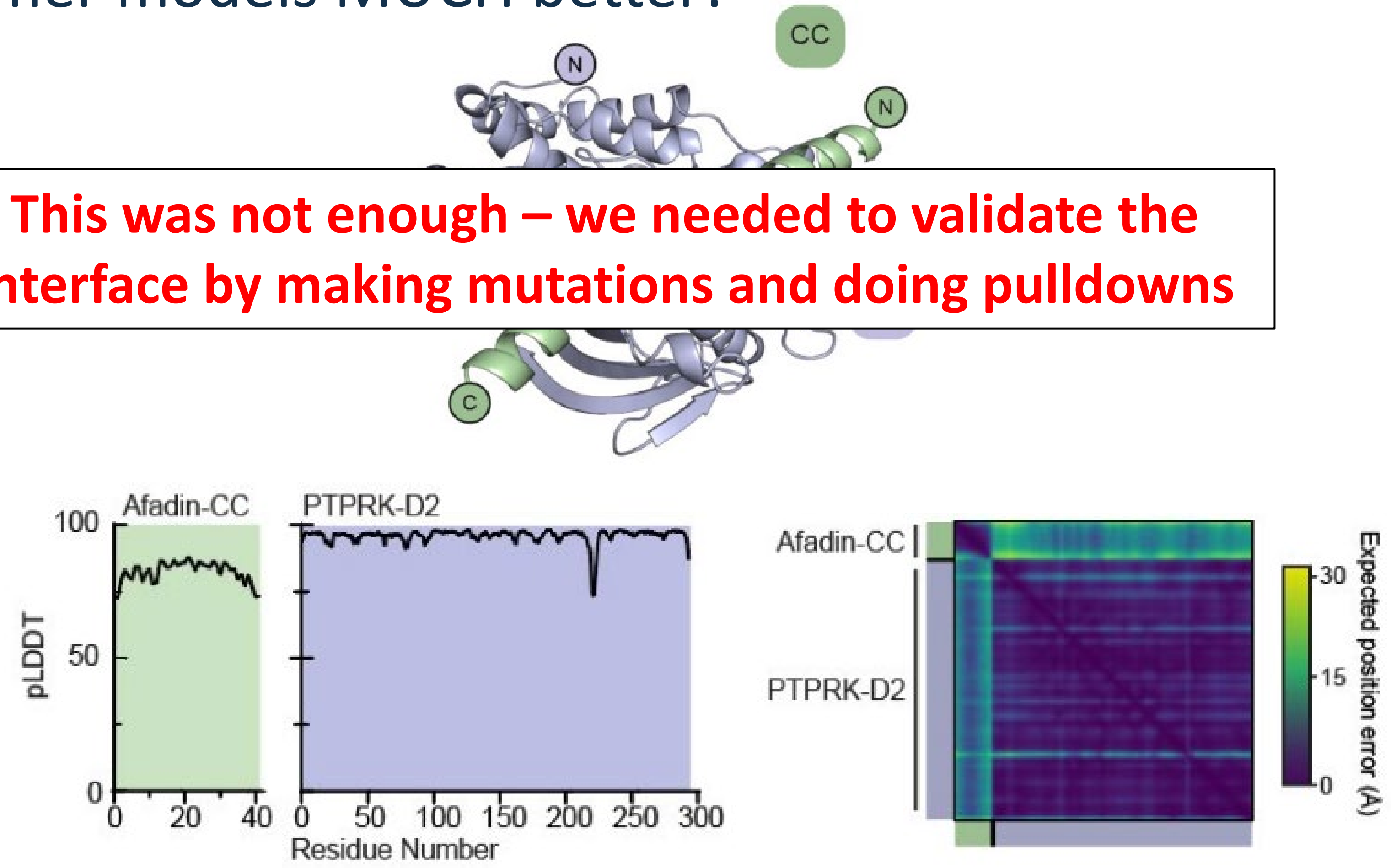




Images from: Hay et al (2022) eLife 11:e79855

PTPRK-Afadin

- AF2 Multimer models MUCH better!

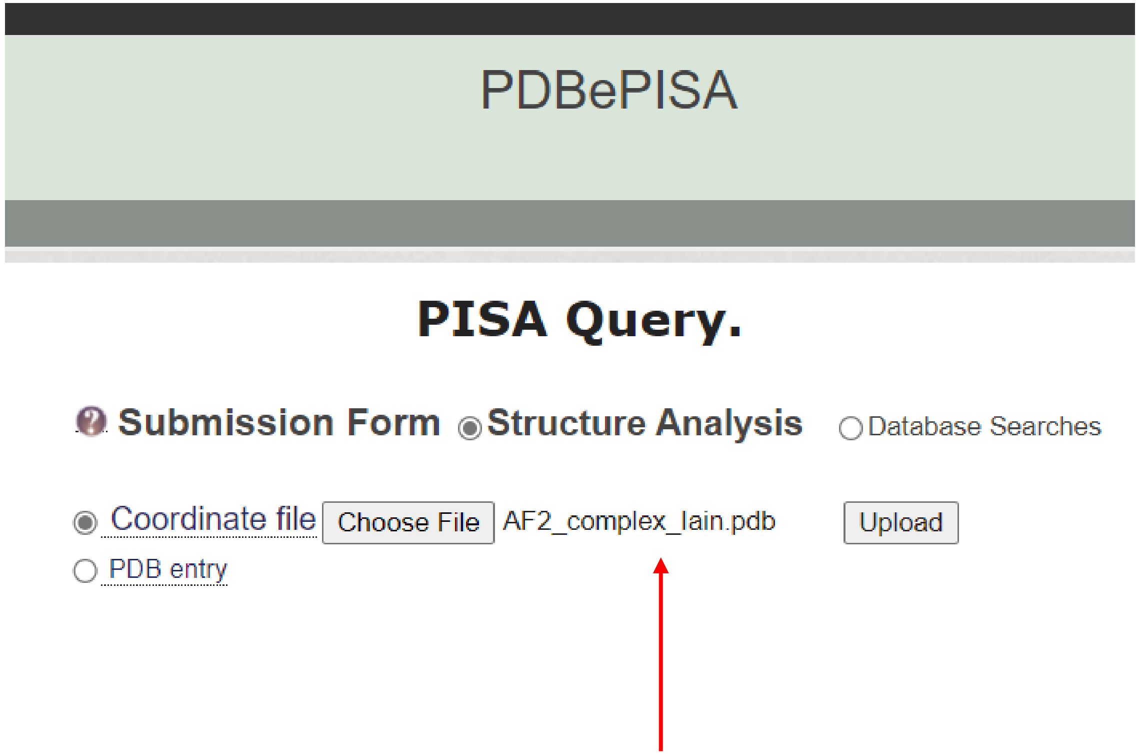


This was not enough – we needed to validate the interface by making mutations and doing pulldowns

Images from: Hay et al (2022) eLife 11:e79855

Using PDBePISA with AlphaFold Models

- Upload AF2 model of complex to PDBePISA



PDBePISA

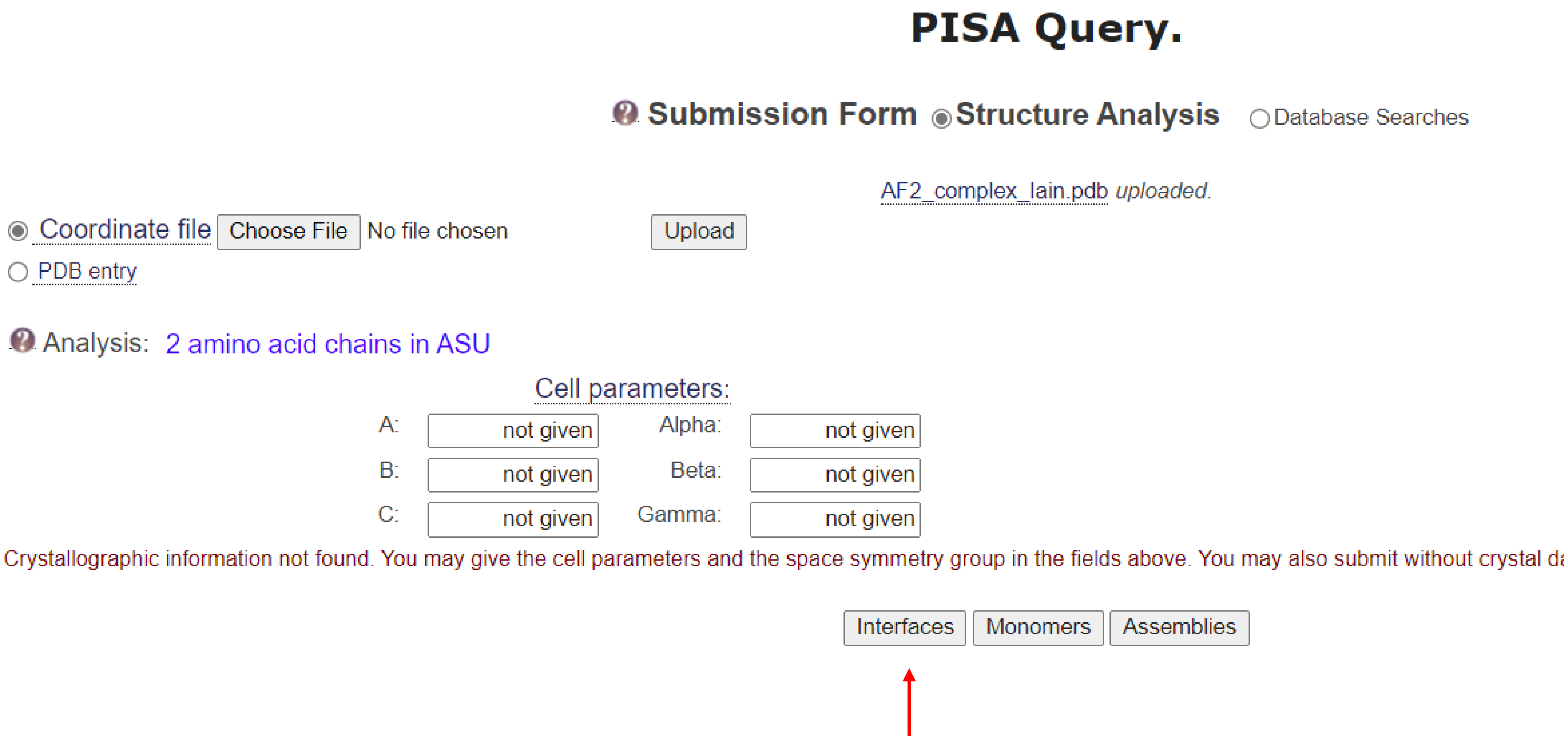
PISA Query.

Submission Form ● **Structure Analysis** ○ Database Searches

● Coordinate file Choose File AF2_complex_Iain.pdb Upload

○ PDB entry

Using PDBePISA with AlphaFold Models



PISA Query.

Submission Form ● Structure Analysis ○ Database Searches

AF2_complex_lain.pdb *uploaded.*

● Coordinate file Choose File No file chosen Upload

○ PDB entry

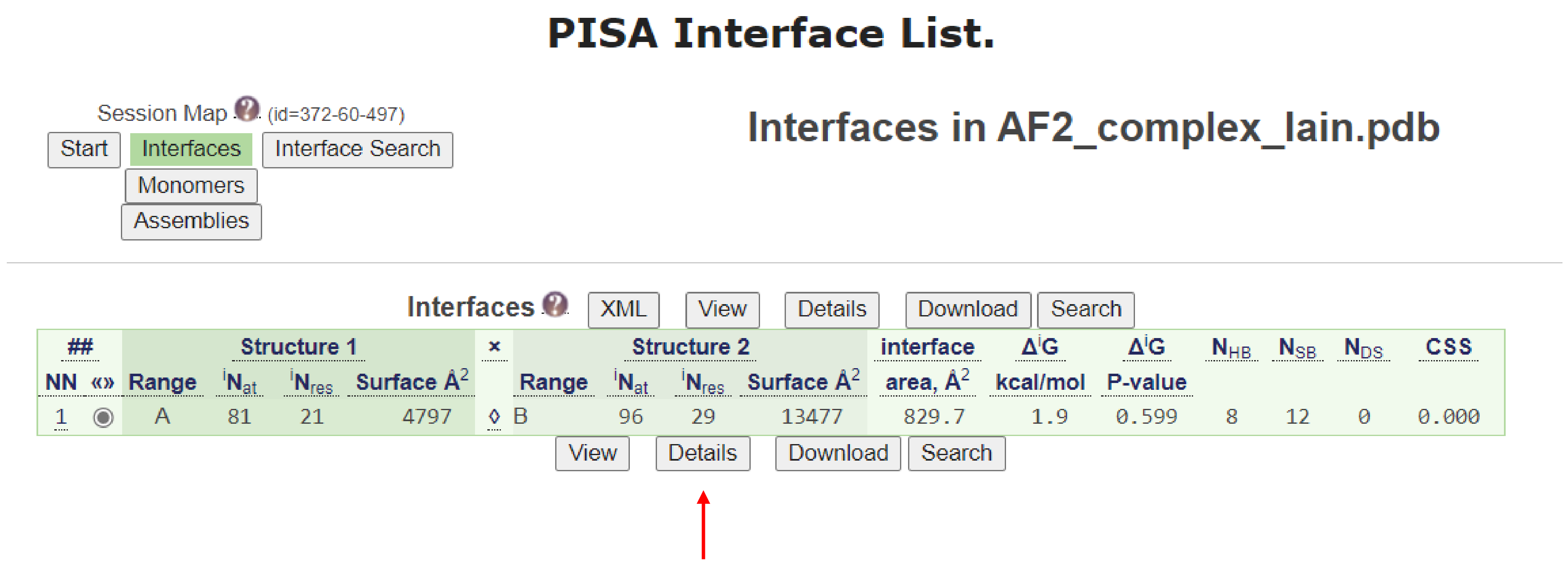
Analysis: 2 amino acid chains in ASU

Cell parameters:

A:	not given	Alpha:	not given
B:	not given	Beta:	not given
C:	not given	Gamma:	not given

Crystallographic information not found. You may give the cell parameters and the space symmetry group in the fields above. You may also submit without crystal d

Using PDBePISA with AlphaFold Models



PISA Interface List.

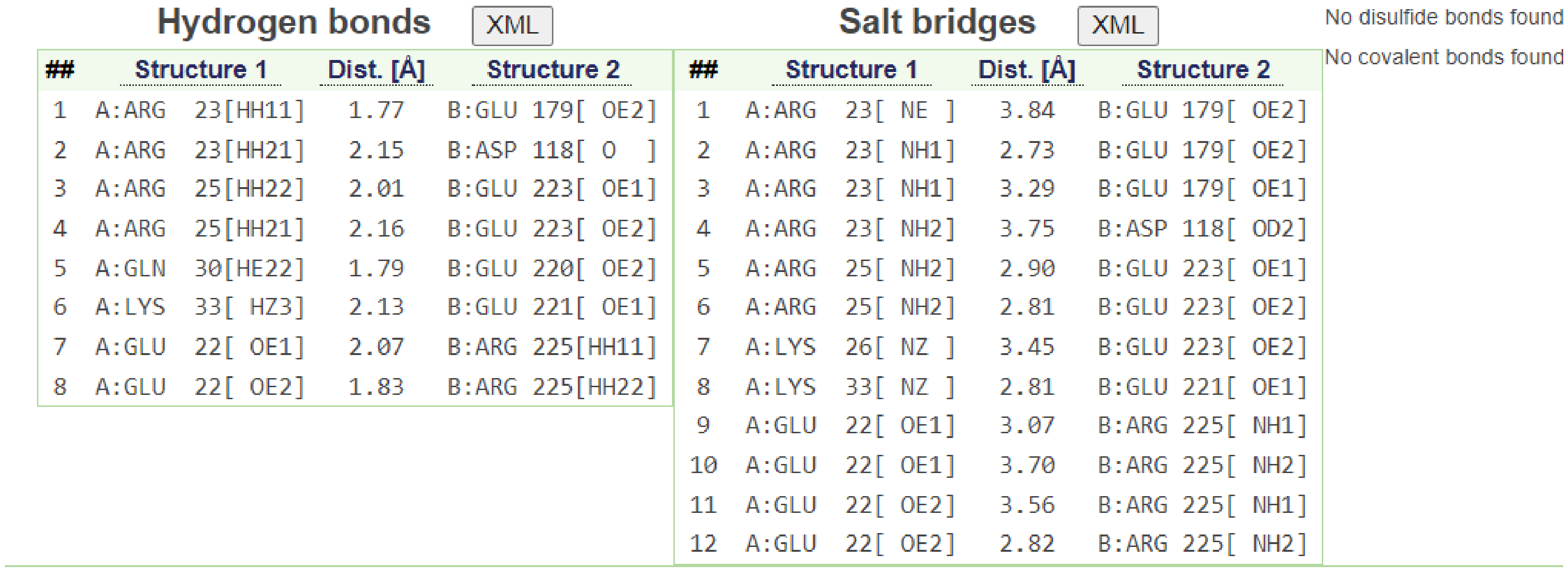
Session Map (id=372-60-497)

Interfaces in AF2_complex_lain.pdb

Interfaces

##		Structure 1				×	Structure 2				interface	$\Delta^{i}G$	$\Delta^{i}G$	N_{HB}	N_{SB}	N_{DS}	CSS
NN	«»	Range	$^{i}N_{at}$	$^{i}N_{res}$	Surface Å^2		Range	$^{i}N_{at}$	$^{i}N_{res}$	Surface Å^2	area, Å^2	kcal/mol	P-value				
1	◉	A	81	21	4797	◊	B	96	29	13477	829.7	1.9	0.599	8	12	0	0.000

Using PDBePISA with AlphaFold Models



Hydrogen bonds

##	Structure 1	Dist. [Å]	Structure 2
1	A:ARG 23[HH11]	1.77	B:GLU 179[OE2]
2	A:ARG 23[HH21]	2.15	B:ASP 118[O]
3	A:ARG 25[HH22]	2.01	B:GLU 223[OE1]
4	A:ARG 25[HH21]	2.16	B:GLU 223[OE2]
5	A:GLN 30[HE22]	1.79	B:GLU 220[OE2]
6	A:LYS 33[HZ3]	2.13	B:GLU 221[OE1]
7	A:GLU 22[OE1]	2.07	B:ARG 225[HH11]
8	A:GLU 22[OE2]	1.83	B:ARG 225[HH22]

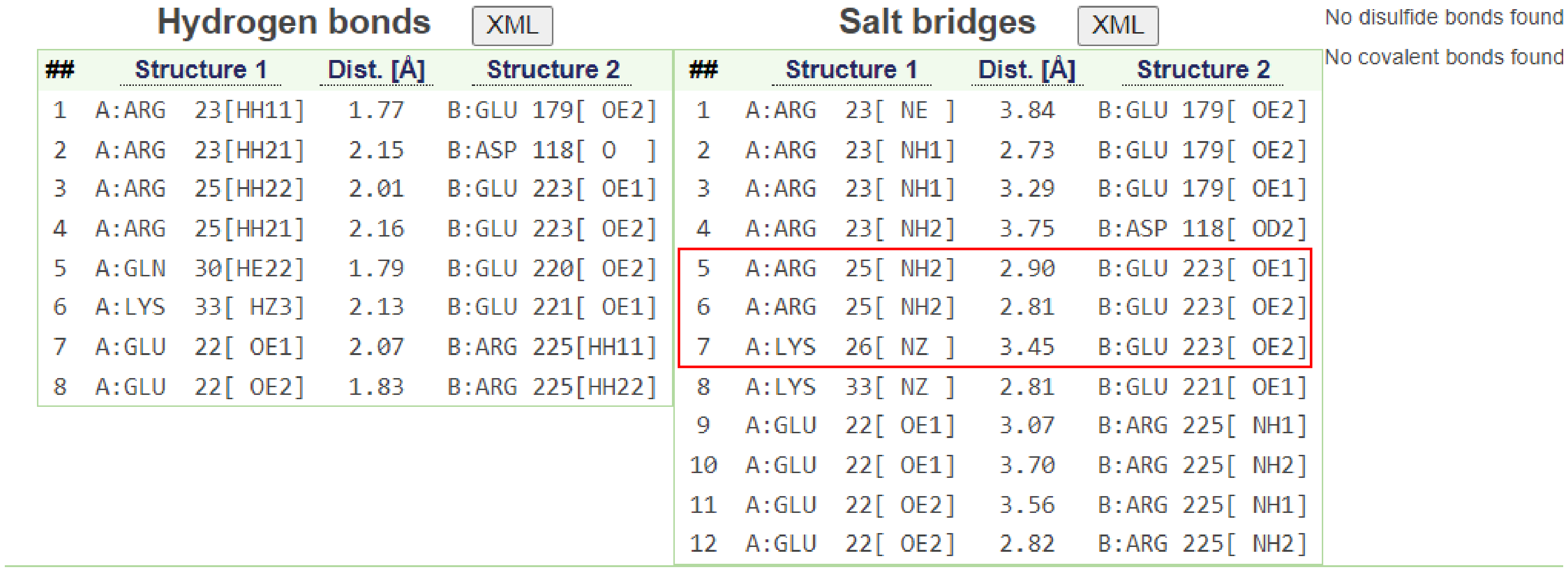
Salt bridges

##	Structure 1	Dist. [Å]	Structure 2
1	A:ARG 23[NE]	3.84	B:GLU 179[OE2]
2	A:ARG 23[NH1]	2.73	B:GLU 179[OE2]
3	A:ARG 23[NH1]	3.29	B:GLU 179[OE1]
4	A:ARG 23[NH2]	3.75	B:ASP 118[OD2]
5	A:ARG 25[NH2]	2.90	B:GLU 223[OE1]
6	A:ARG 25[NH2]	2.81	B:GLU 223[OE2]
7	A:LYS 26[NZ]	3.45	B:GLU 223[OE2]
8	A:LYS 33[NZ]	2.81	B:GLU 221[OE1]
9	A:GLU 22[OE1]	3.07	B:ARG 225[NH1]
10	A:GLU 22[OE1]	3.70	B:ARG 225[NH2]
11	A:GLU 22[OE2]	3.56	B:ARG 225[NH1]
12	A:GLU 22[OE2]	2.82	B:ARG 225[NH2]

No disulfide bonds found

No covalent bonds found

Using PDBePISA with AlphaFold Models



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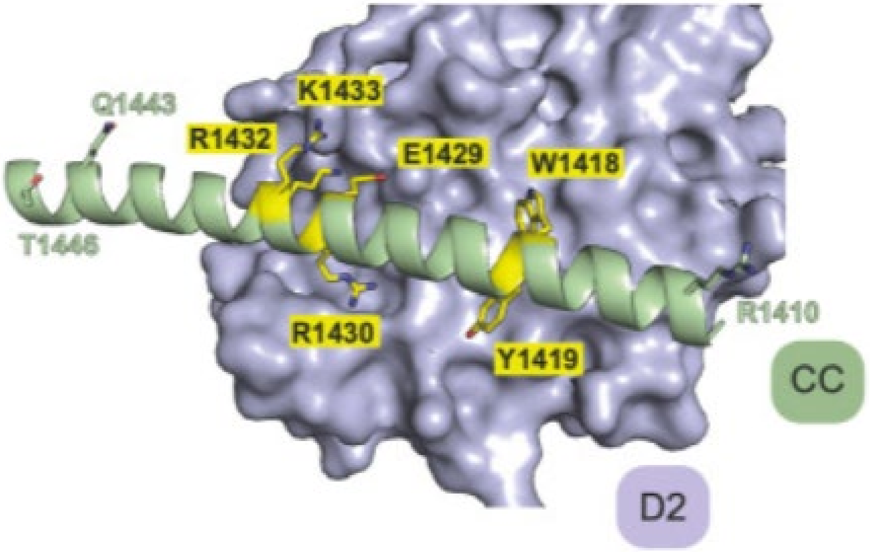
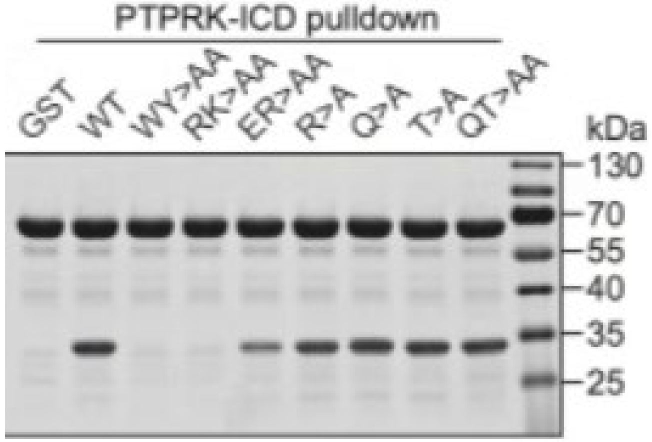
No disulfide bonds found

No covalent bonds found

PTPRK-Afadin

- Our pulldowns using mutations based on the AF2 model validated the interface experimentally





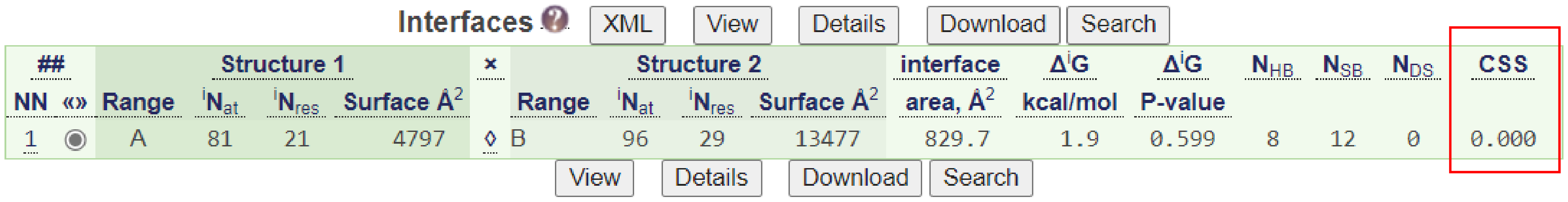
In the interface

Not in the interface

Images from: Hay et al (2022) eLife 11:e79855

A few caveats

- PDBePISA didn't predict this interface to be significant - but it was!



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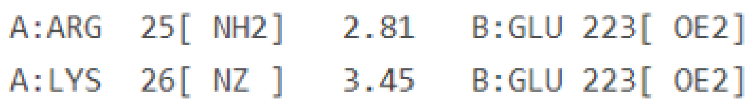
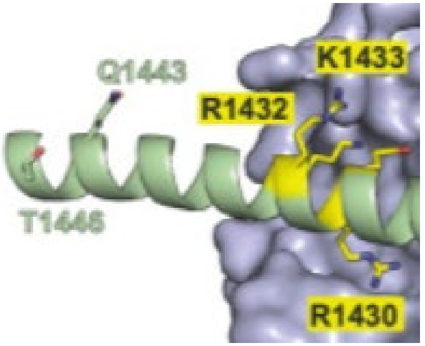
1	◉	A	81	21	4797	◊	B	96	29	13477	829.7	1.9	0.599	8	12	0	0.000

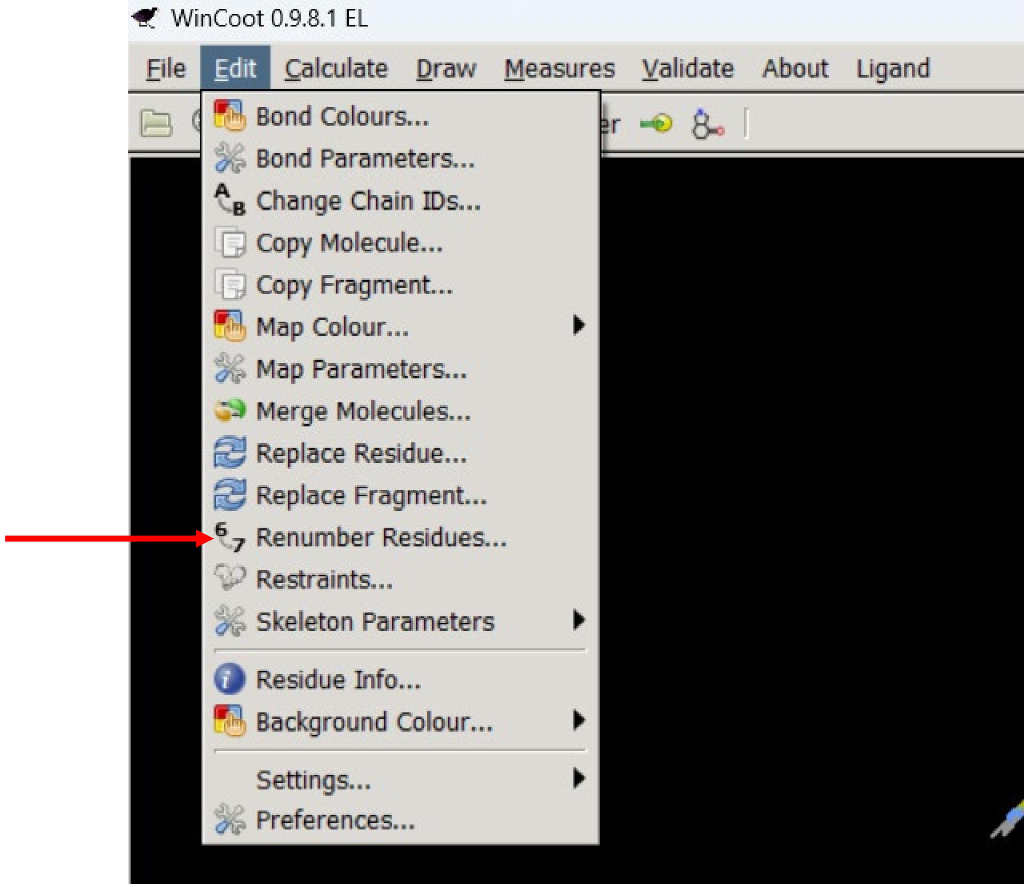
- AF2 renumbers your residues so they might no longer match the Uniprot entry – you can renumber your model using Coot



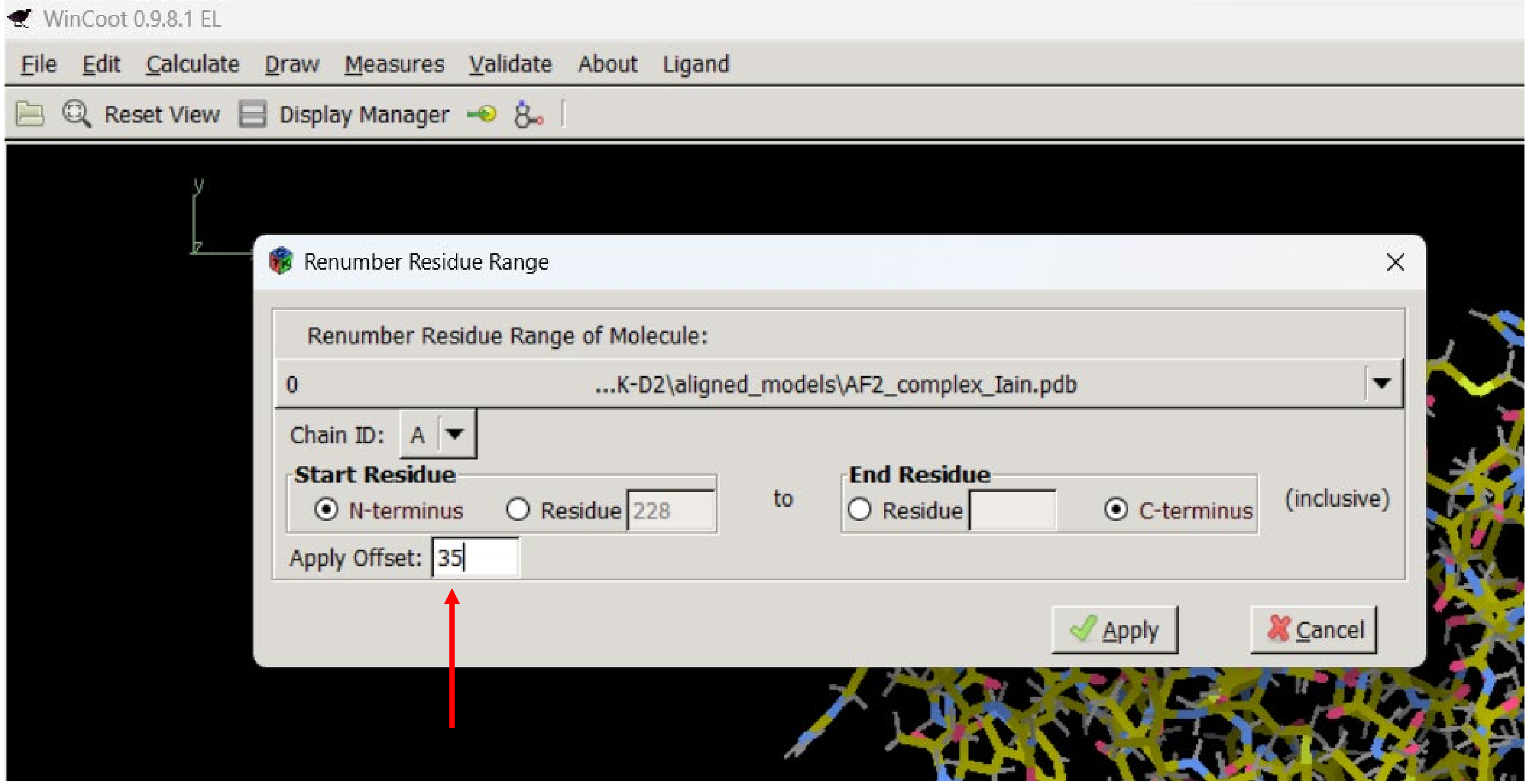
```
A:ARG   25[ NH2]    2.81    B:GLU 223[ OE2]
A:LYS   26[ NZ ]    3.45    B:GLU 223[ OE2]
```



Renumber residues in Coot



Renumber residues in Coot



Renumber Residue Range of Molecule:

0 ...K-D2\aligned_models\AF2_complex_Iain.pdb

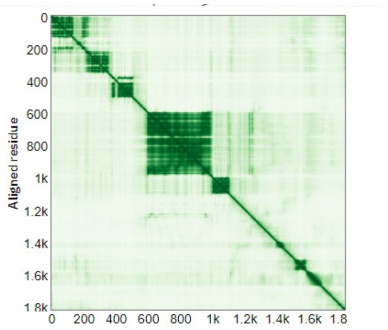
Chain ID: A

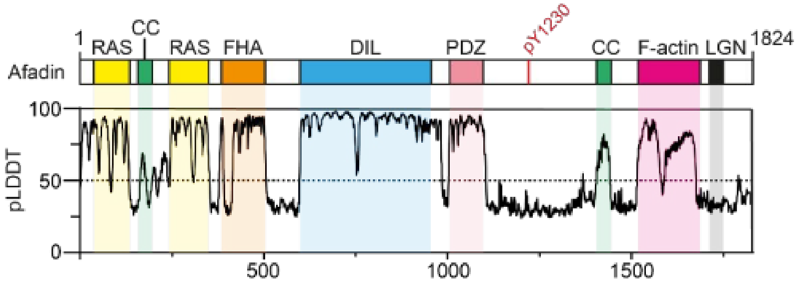
Start Residue ● N-terminus ○ Residue 228 to **End Residue** ○ Residue ● C-terminus (inclusive)

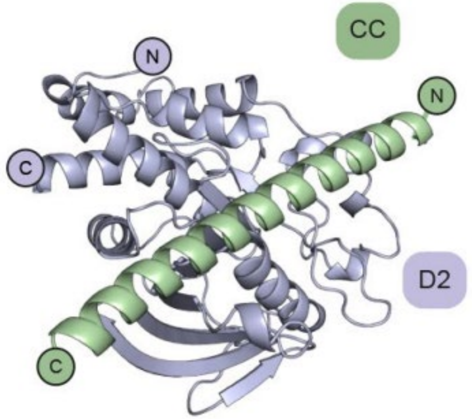
Apply Offset: 35

So, what is AlphaFold2 good for?

- Determining the fold of protein domain(s)
  - Identify potential functional homology
- Determining domain boundaries
  - Clone sensible constructs
- Protein:peptide complexes
  - And some protein:protein complexes



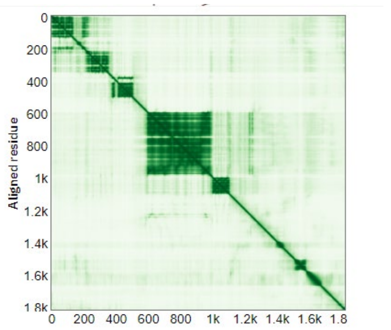


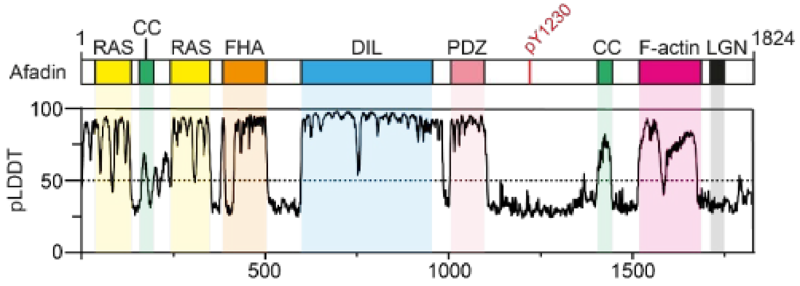


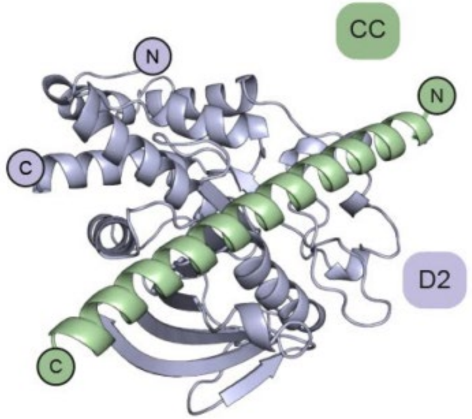
So, what is AlphaFold2 good for?

- Determining the fold of protein domain(s)
  - Identify potential functional homology
- Determining domain boundaries
  - Clone sensible constructs
- Protein:peptide complexes
  - And some protein:protein complexes

- AF2 models should always be:
  - Shown with their statistical plot
  - Tested experimentally







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AlphaFold is being constantly developed and expanded
It is likely several of these limitations will be overcome eventually

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Try it yourself

- You can access all the pre-calculated AlphaFold structures by DeepMind/EMBL-EBI:
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- NOTE: if you want to run locally on your computer you need a very powerful computer (GPU with lots of RAM) and we recommend installing ColabFold not AlphaFold