The impact of AlphaFold2 one year on

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The first and last authors of AlphaFold2

The Nobel Prize in Chemistry 2024

David Baker

"for computational protein design"

David Baker. Ill. Niklas Elmehed © Nobel Prize Outreach

Demis Hassabis

"for protein structure prediction"

Demis Hassabis. Ill. Niklas Elmehed © Nobel Prize Outreach

John Jumper

"for protein structure prediction"

John Jumper. Ill. Niklas Elmehed © Nobel Prize Outreach

Neural Networks

The Nobel Prize in Physics 2024

John Hopfield

"for foundational discoveries and inventions that enable machine learning with artificial neural networks"

John Hopfield. Ill. Niklas Elmehed © Nobel Prize Outreach

Geoffrey Hinton

"for foundational discoveries and inventions that enable machine learning with artificial neural networks"

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Alphafold2

Strength:

1. Best Accuracy (higher than RF)
2. Recycling (Global)
3. End to end

Weakness:

1. TPU
2. Frames were not intuitive

RoseTTAFold

Strength:

1. Obtainable GPU
2. Equivariant transformer
3. Intuitive

Weaknesses:

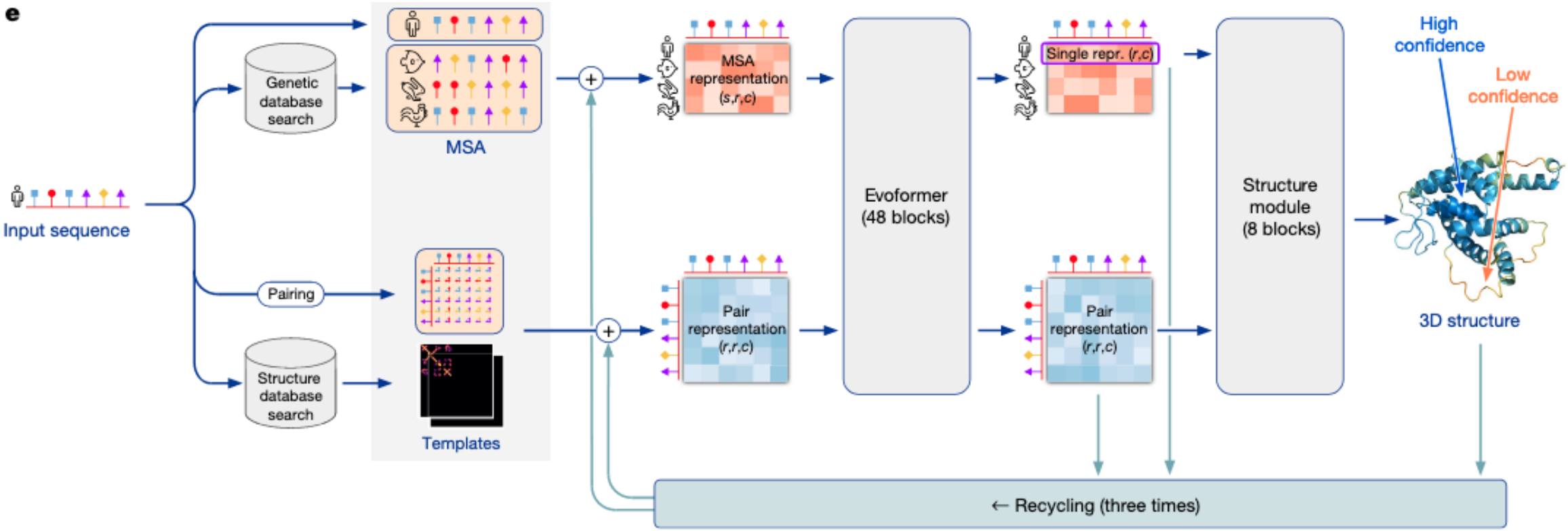
1. Overengineered
2. 3D track necessary
3. Local Recycling

IT'S DIFFICULT TO FIND AF2'S WEAKNESS!

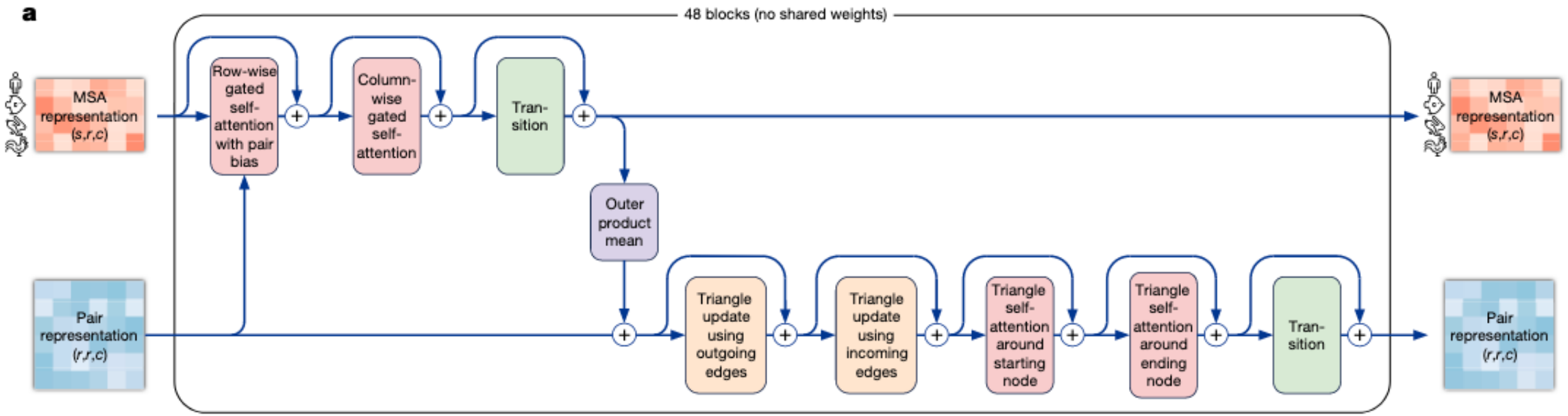
Outline

- Quick Review of AF2
- Strengths and weaknesses of the models
- What has and has not been achieved
- How this might evolve in the future

Review AlphaFold2



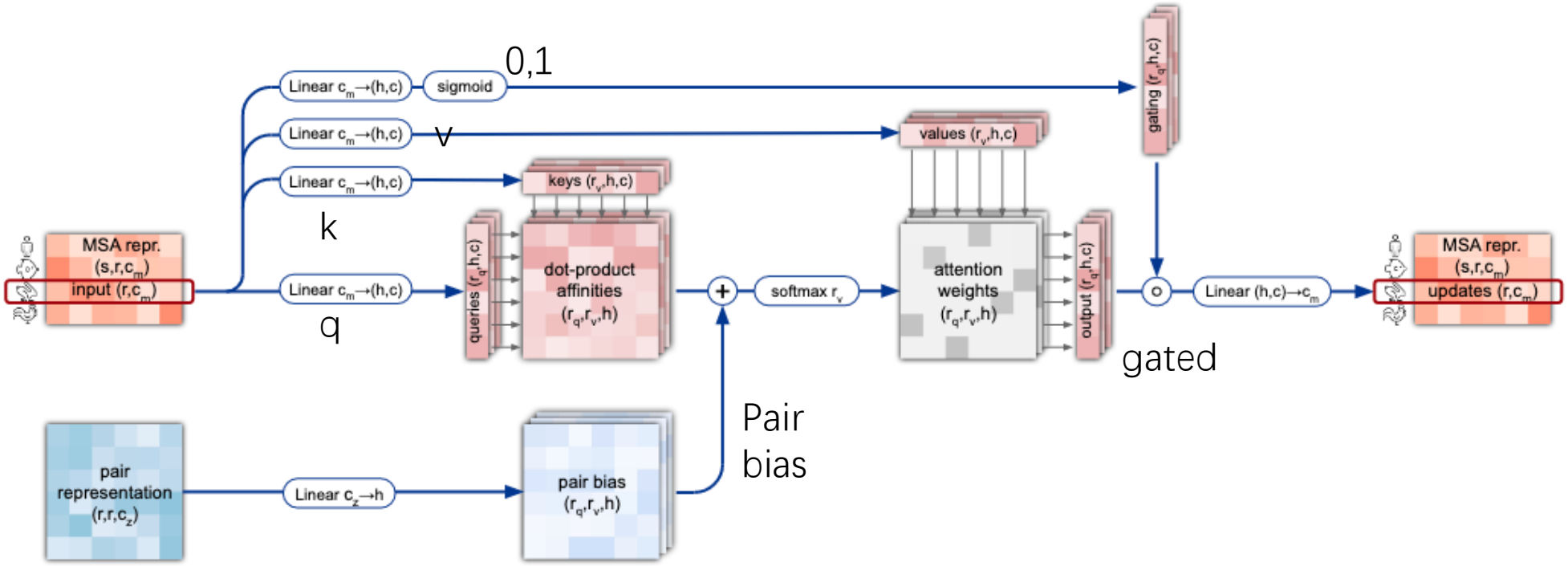
Encoder



Different from Transformer blocks:

- each block in this model allows MSA and pair information to interact with each other
- Row-wise self-attention and column-wise self-attention

Row-wise gated self-attention (pair bias)



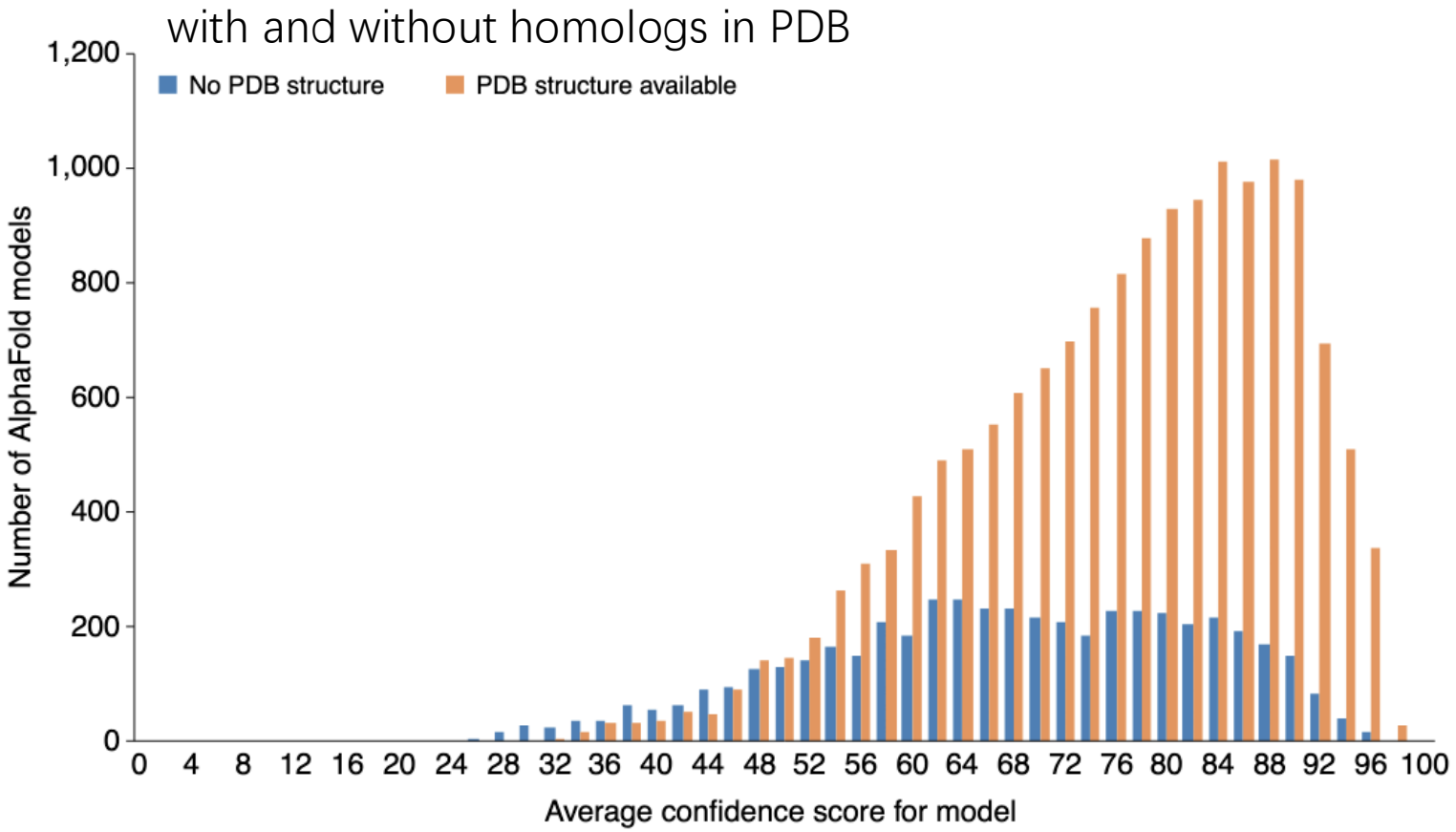
Open Questions

- no radical new biological insights that were essential to the method's success
- What makes AF2 so success?
- Does the interplay between two tracks important?
  - Remove MSA track->AF2's performance(casp14) drop slightly

2 Interpretations

- AlphaFold2 is currently over-engineered
  - simplify the model, remove the less important aspects and replacing them with new, better ideas.
- AlphaFold2 is just a collection of many individually small ideas
  - a Formula 1 racing car： remove any little things, final performance drop
  - Improvements: add little tricks

when benchmark AF2



AF2's confidence scores are correlated with **whether the target structure has homologs** in PDB or not.

- the explicit use of templates
  - Remove use
- AF2's training set (All PDB data before 2018/05)
  - Better options, fold classification databases like CATH, SCOP and ECOD

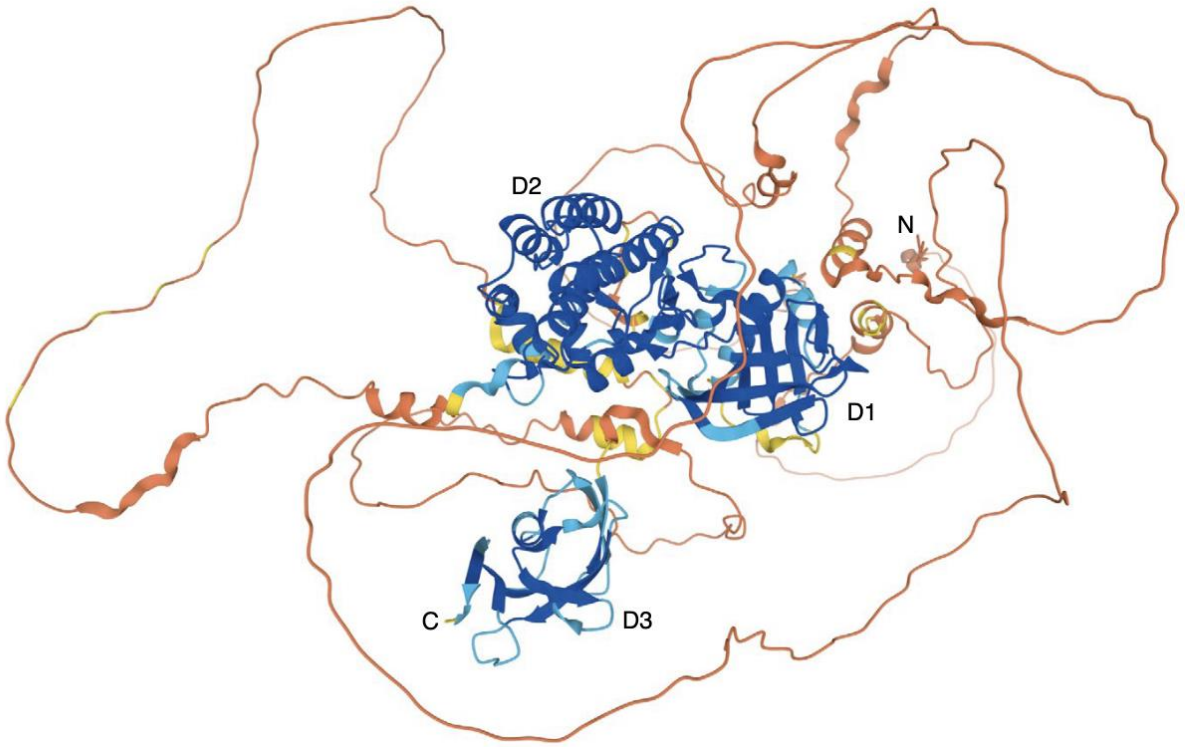
Quality of AF2 models

- two measures of confidence
  - predicted local-distance difference test, pLDDT
  - Reliability of pairwise interactions between different residues

- most AF2 models
  - good side-chain placement and very low RMSD
- without clear homologs
  - pLDDT scores are usually lower

a typical large human protein-MAP3K14

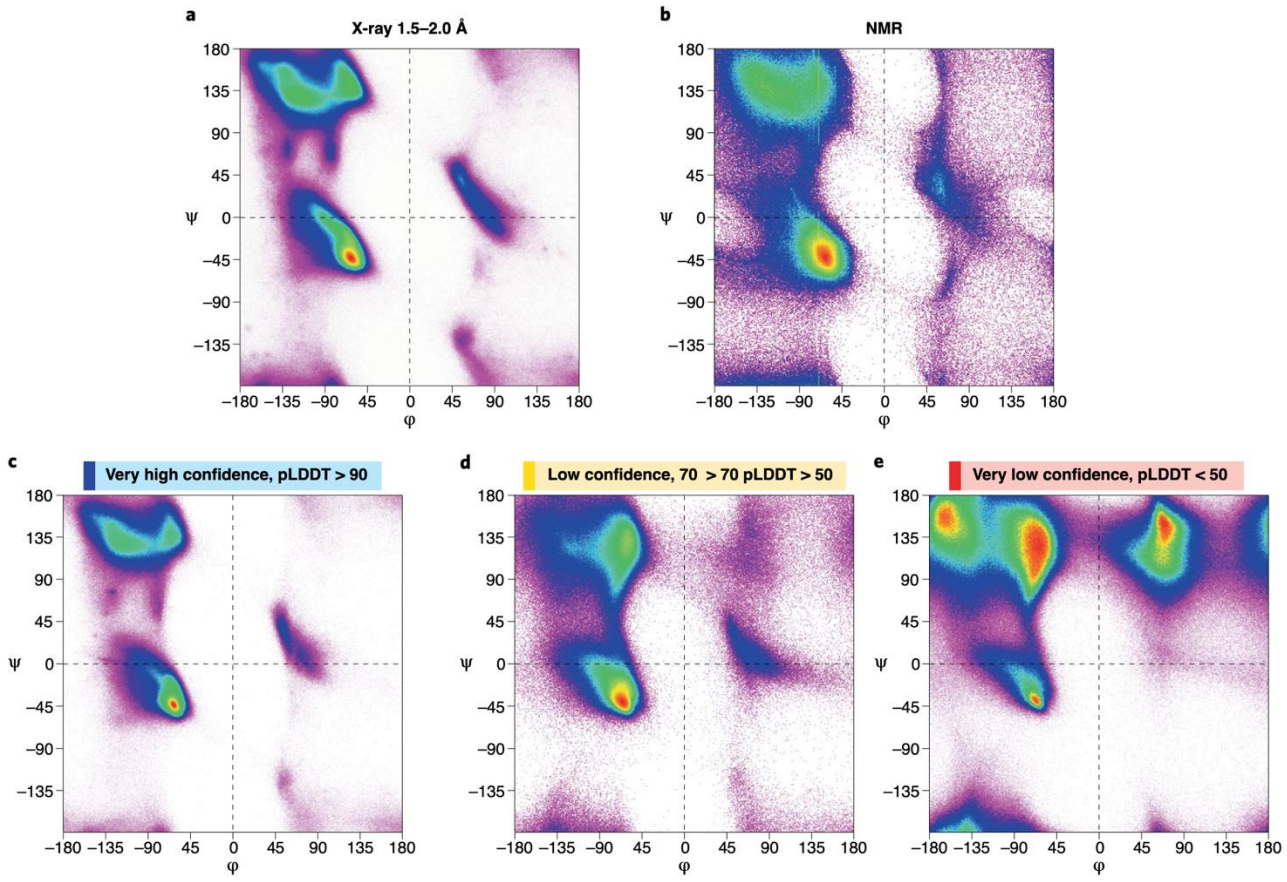
From EBI AlphaFold Database



Blue: greatest confidence
Orange: least confidence

- D1 and D2: experimentally determined
- D3: without any obvious homologs in PDB
  - domains are placed seemingly arbitrarily
- long loops that project from the structured core
  - Obey the stereochemical rules for polypeptides

φ,ψ （ Ramachandran ）



- below a pLDDT score of 70
  - the φ,ψ distributions of A2 models differ from those observed for experimental structures
- very low pLDDT scores
  - not at all physically realistic and will cause errors

tests on AlphaFold2

- a long sequence of **alanine residues**
  - a single long α-helix predicted with high confidence,
- a similar sequence of **isoleucine residues**
  - not a common feature in the training set
  - the same high-confidence α-helix prediction

Challenges

- AF2 models do not include any ligands
  - AlphaFold 3 (AF3) includes ligands, model protein-ligand interactions
- AF2 does not aim to elucidate the folding pathway, nor the dynamics of the structure
- AF2 models cannot be explained or externally validated
  - ‘asking’ why it predicted something in a particular conformation is not feasible

New work inspired by AF2

- Validate AF2 use various benchmark sets
  - proper cross-validation, be careful
  - some consider the regions that are not predicted with any accuracy
- AF2 application
  - inverse protein folding, or protein design

Use for?

- seed and solve the determination of experimental structures
  - large complexes or even tomograms of whole cells
- docking and energy calculations
- improve ability to design proteins with new functions
  - benefit of humankind

Thanks for Listening!