Journal Club

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Article

Highly accurate protein structure prediction with AlphaFold

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Proteins are essential to life, and understanding their structure can facilitate a mechanistic understanding of their function. Through an enormous experimental effort[1–4], the structures of around 100,000 unique proteins have been determined[5], but this represents a small fraction of the billions of known protein sequences[6,7]. Structural coverage is bottlenecked by the months to years of painstaking effort required to determine a single protein structure. Accurate computational approaches are needed to address this gap and to enable large-scale structural bioinformatics. Predicting the three-dimensional structure that a protein will adopt based solely on its amino acid sequence—the structure prediction component of the 'protein folding problem'[8]—has been an important open research problem for more than 50 years[9]. Despite recent progress[10–14], existing methods fall far short of atomic accuracy, especially when no homologous structure is available. Here we provide the first computational method that can regularly predict protein structures with atomic accuracy even in cases in which no similar structure is known. We validated an entirely redesigned version of our neural network-based model, AlphaFold, in the challenging 14th Critical Assessment of protein Structure Prediction (CASP14)[15], demonstrating accuracy competitive with experimental structures in a majority of cases and greatly outperforming other methods. Underpinning the latest version of AlphaFold is a novel machine learning approach that incorporates physical and biological knowledge about protein structure, leveraging multi-sequence alignments, into the design of the deep learning algorithm.

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

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DeepMind presented remarkably accurate predictions at the recent CASP14 protein structure prediction assessment conference. We explored network architectures incorporating related ideas and obtained the best performance with a three-track network in which information at the 1D sequence level, the 2D distance map level, and the 3D coordinate level is successively transformed and integrated. The three-track network produces structure predictions with accuracies approaching those of DeepMind in CASP14, enables the rapid solution of challenging X-ray crystallography and cryo-EM structure modeling problems, and provides insights into the functions of proteins of currently unknown structure. The network also enables rapid generation of accurate protein-protein complex models from sequence information alone, short circuiting traditional approaches which require modeling of individual subunits followed by docking. We make the method available to the scientific community to speed biological research.

Background Information

- The “protein folding problem” increases in complexity as the peptide chain grows.
- Current go-to methods include X-ray Crystallography, Fluorescence Spectroscopy, and Nuclear Magnetic Resonance Spectroscopy.
- CASP: Critical Assessment of Protein Structure, a biennial competition to test protein structure computation methods on newly decoded.

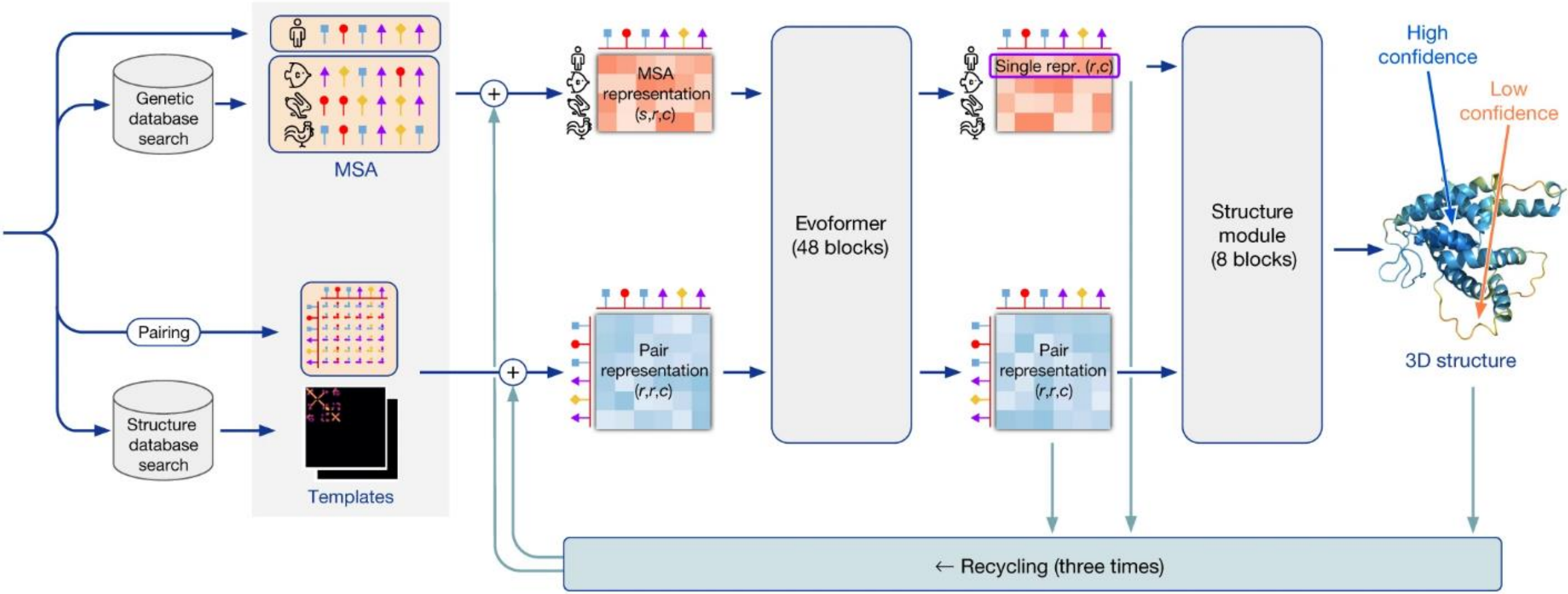
DeepMind and AlphaFold

- UK-based company purchased by Google.
- Developed AlphaGO which is famous for being the first AI to beat the world Go champion.
- Participated in CASP13 with the first Iteration of AlphaFold and met limited success.
- Participated in CASP14 with AlphaFold2 and outperformed all competing methods.
  - 0.96 Å r.m.s.d. backbone accuracy vs. 2.8 Å r.m.s.d. second best performer.
  - 1.5 Å r.m.s.d. all-atom accuracy vs. 3 Å r.m.s.d. second best performer.

AlphaFold2

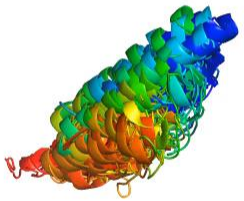
- Neural Net that treats the protein structure as a Graph Inference problem in 3D.
- Consisting of two main stages:
  - Trunk with “EvoFormer” blocks that have parallel channels:
    - (N_{res} x N_{seq}) which represents the Multiple Sequence Alignment (MSA)
    - (N_{res} x N_{res}) which represents the residues along the chain.
  - Structure Model that performs rotations and translations on the resulting chain in order to output 3D shape.
- Up to 48 EvoFormer blocks.
- End-to-end prediction of protein structure

AlphaFold2 Structure



AlphaFold in Action

RNA Polymerase of a crAss-like Phage



Recycling iteration 0, block 01
Secondary structure assigned from the final prediction

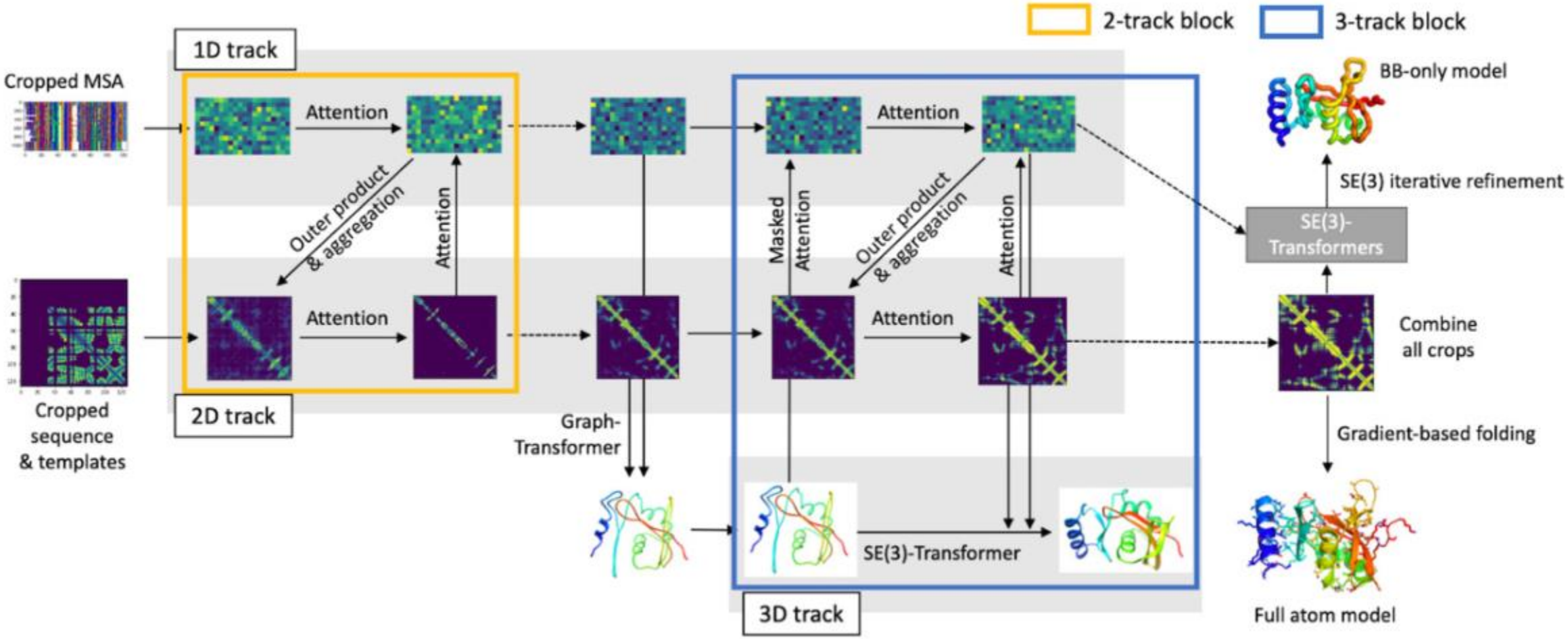
T1091

Recycling iteration 0, block 01
Secondary structure assigned from the final prediction

RoseTTAFold

- Developed by research group at University of Washington after CASP14.
- Tried two approaches and decided on a 3-Track approach:
  1. 1D sequence alignment.
  2. 2D distance matrix.
  3. 3D backbone coordinates.
- Constant back-and-forth communication between the 3 tracks.
- Simultaneously performs calculations on all 3 tracks instead of taking a hierarchical approach.

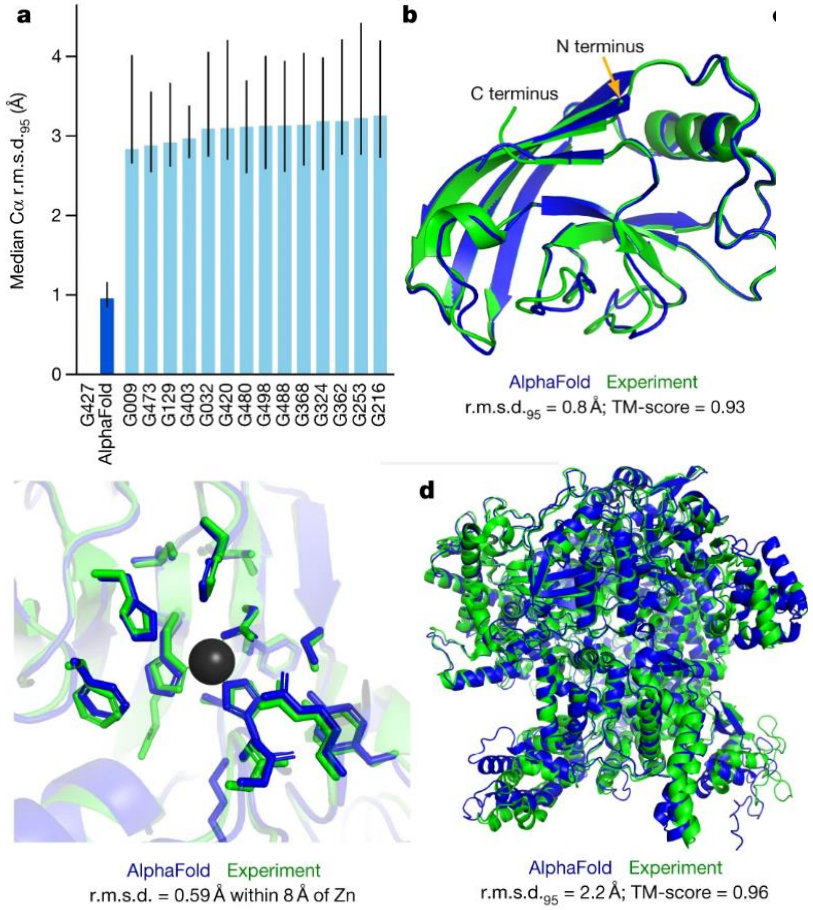
RoseTTAFold Structure

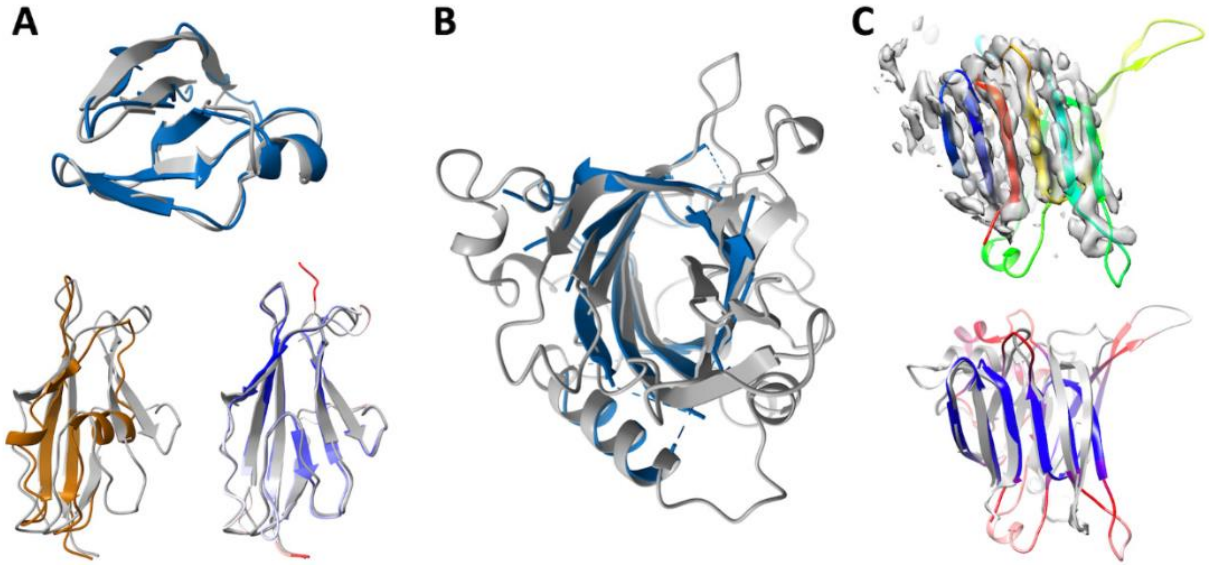


Why it’s worth mentioning RoseTTAFold

- Due to hardware limitations, the networks takes small snippets of the whole chain at a time.
  - Seems to produce better results than end-to-end
- Whole model trains more efficiently than the described training of AlphaFold2.
- Being able to deal with disconnected snippets has the side-effect of allowing RoseTTAFold to deal with protein-protein complexes.

Side by side of the results





Takeaways

- Sometimes trying to work around a problem yields some pleasant little surprises.
- Finding inspiration in the work of others, communicating, collaborating, and competing.
- And most importantly: open source.

generation of accurate protein-protein complex models from sequence information alone, short circuiting traditional approaches which require modeling of individual subunits followed by docking. We make the method available to the scientific community to speed biological research.

Code availability

Source code for the AlphaFold model, trained weights and inference script are available under an open-source license at https://github.com/deepmind/alphafold.

Thank you

Resources

- https://www.nature.com/articles/s41586-021-03819-2
- https://github.com/deepmind/alphafold
- https://www.science.org/doi/abs/10.1126/science.abj8754
- https://github.com/RosettaCommons/RoseTTAFold