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Update on Protein Folding

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Jagiellonian University

Agenda

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1. Protein Structure and Function
2. Introduction to the Protein Folding Problem
3. Classical Approach to Protein Modeling (Homology)
4. Deep Learning Protein Folding Models
    a. AlphaFold
    b. RoseTTAFold
    c. EigenFold
    d. QFold

Protein Structure

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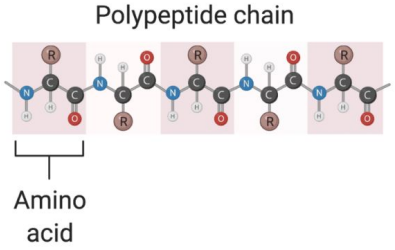
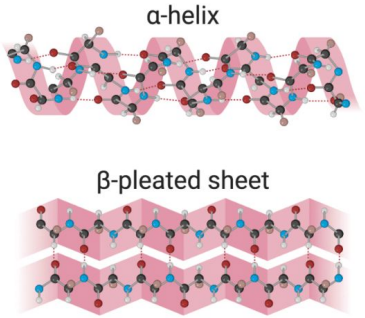
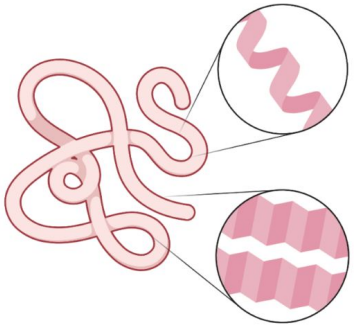
Primary structure



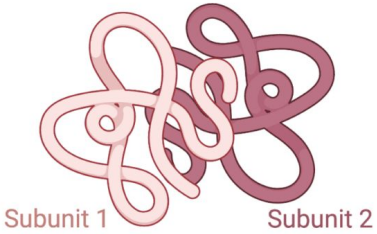
Secondary structure



Tertiary structure

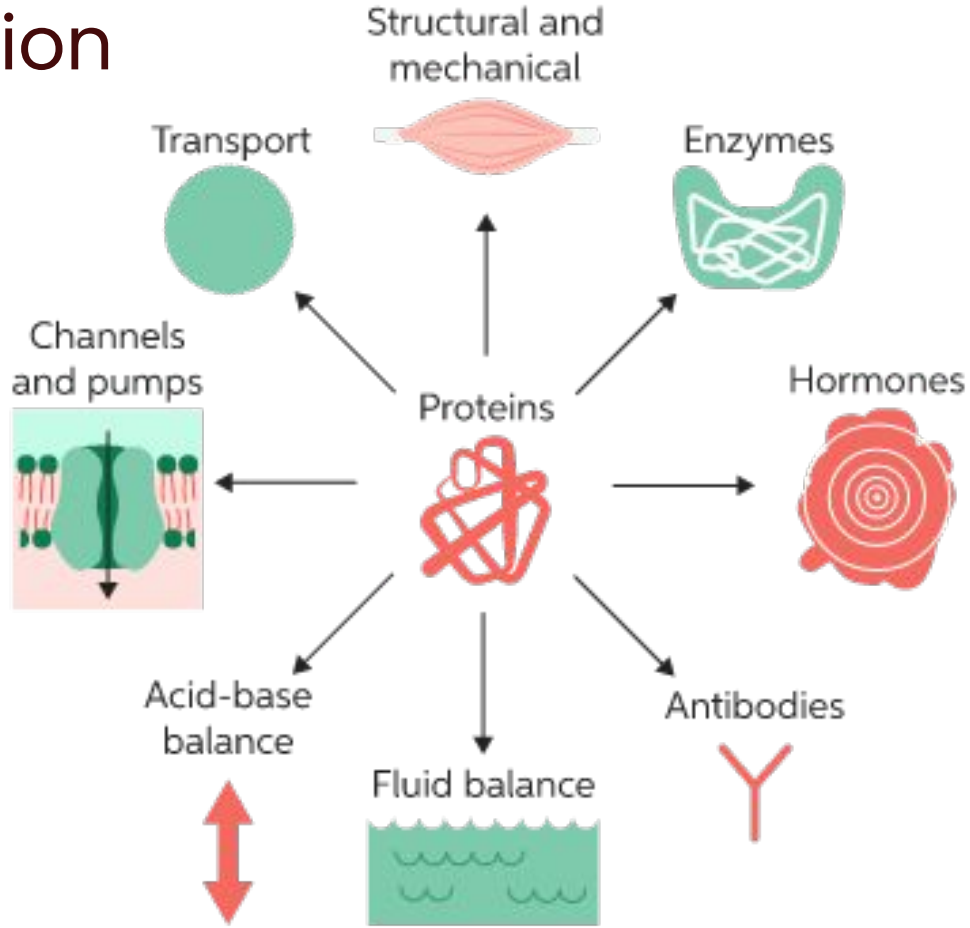


Quaternary structure

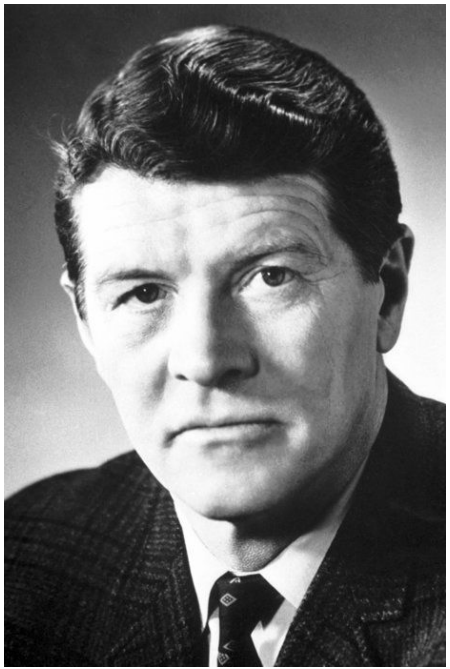


source: https://www.rapidnovor.com/

Protein Function



Genetic Code Defines Protein Structure

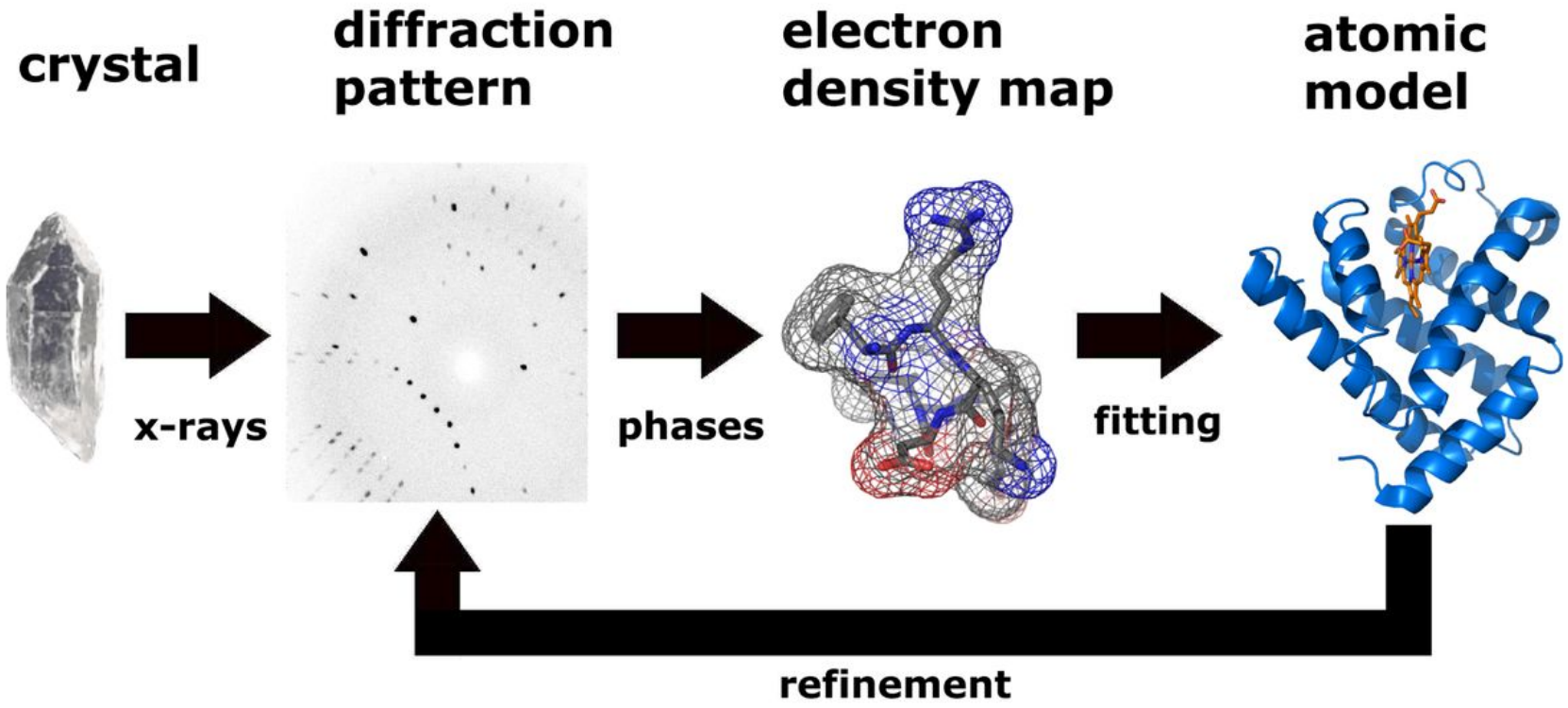


Christian B. Anfinsen

The Nobel Prize in Chemistry 1972

In 1961, Anfinsen proved that the sequence of amino acids, in itself, determines the way the chain folds itself and that no additional genetic information is required in this process.

Crystallography Methods: X-Ray



Crystallography Methods: X-Ray

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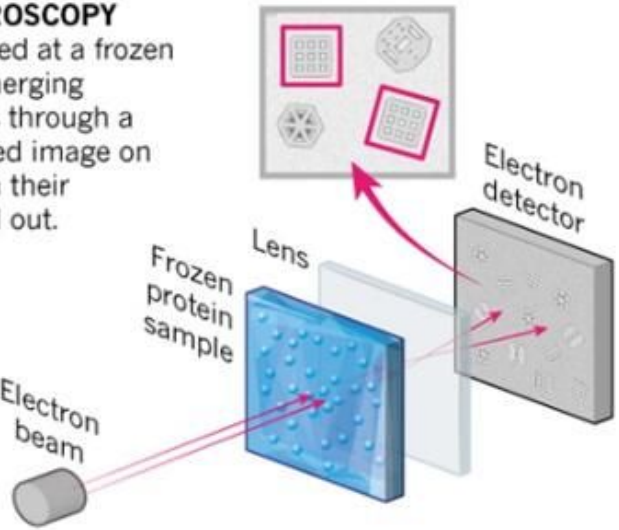
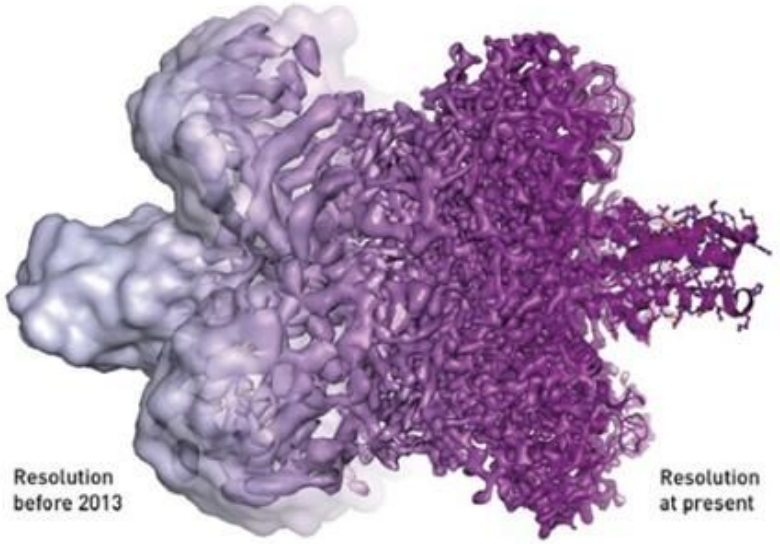
CRYO-ELECTRON MICROSCOPY
A beam of electron is fired at a frozen protein solution. The emerging scattered electrons pass through a lens to create a magnified image on the detector, from which their structure can be worked out.





source: https://www.creative-biostructure.com/

Protein Folding

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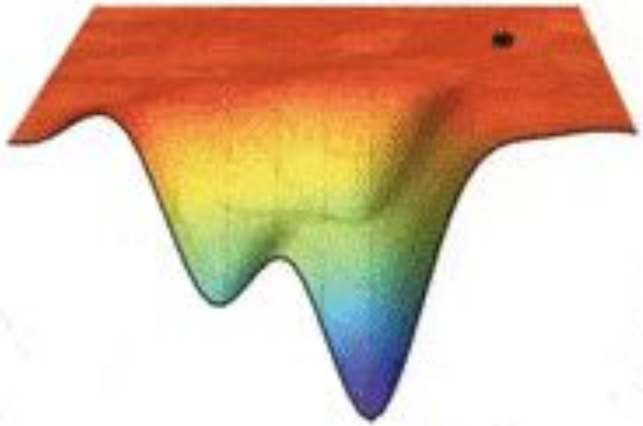
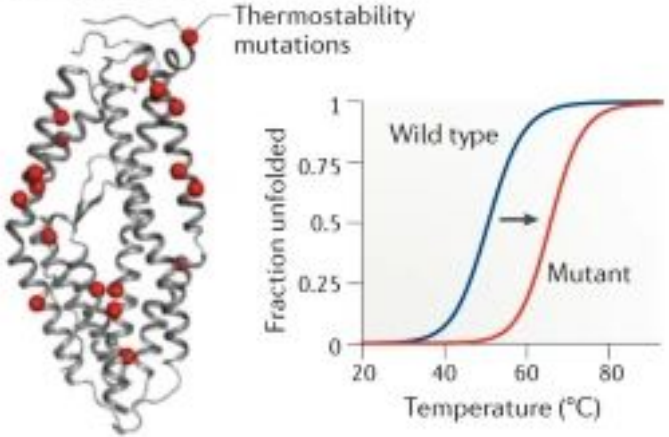
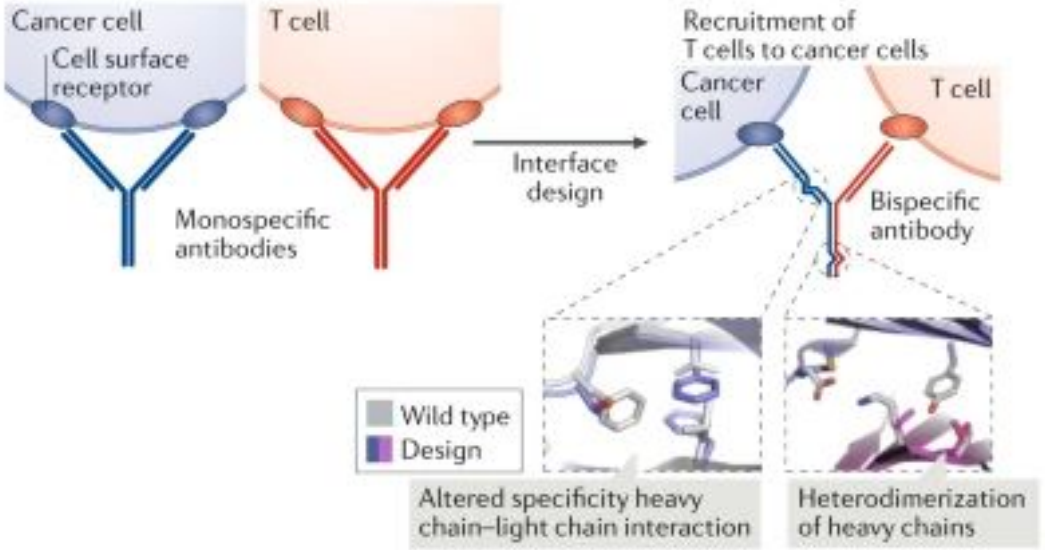


Inverse Protein Folding

a Stabilizing a malaria invasion protein for use as a vaccine antigen



b Orthogonal interface design to generate bispecific antibodies for cancer immunotherapy



Inverse Protein Folding

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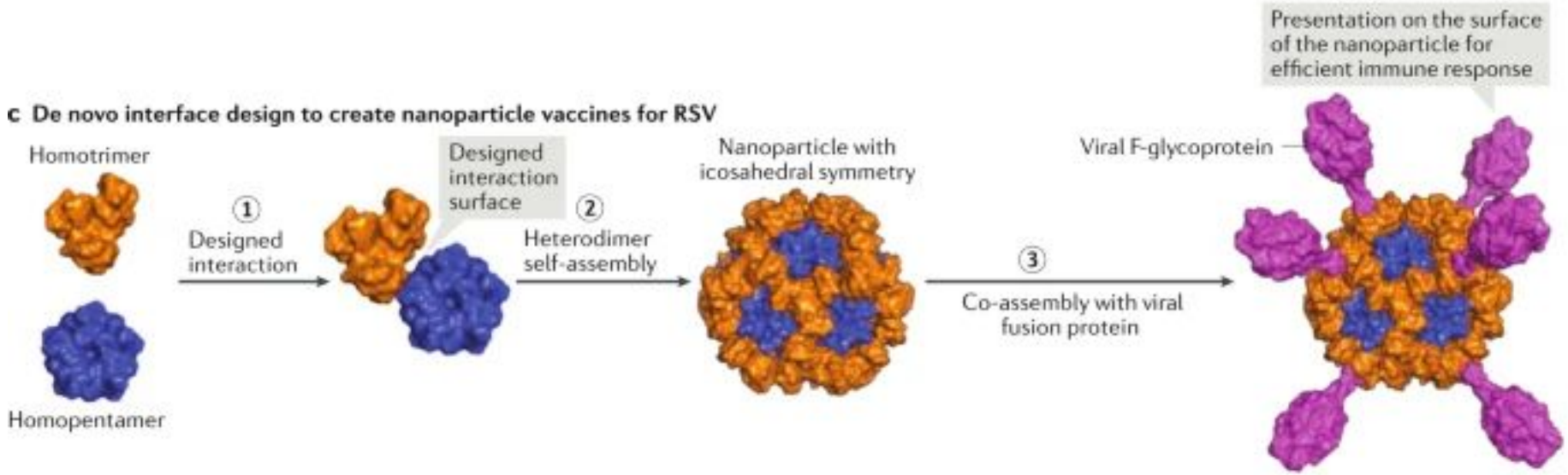

Inverse Protein Folding

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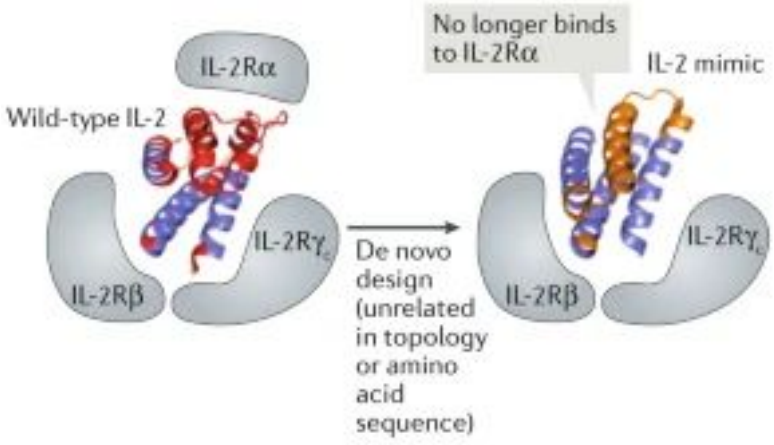
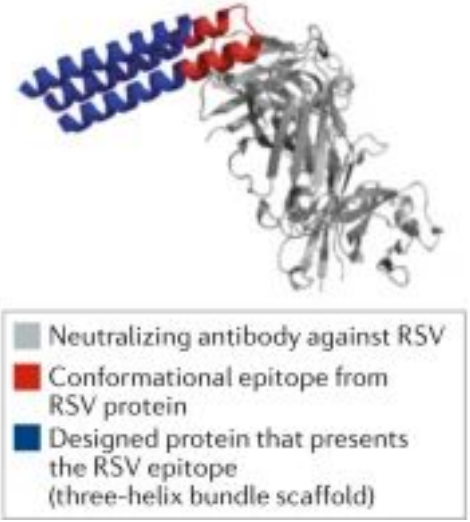
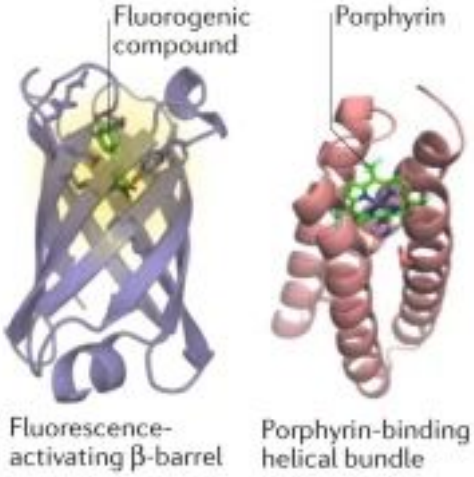
d De novo-designed mimic of IL-2 with receptor specificity altered to reduce toxicity in anti-cancer treatment



e Scaffolding of RSV epitope for vaccine design



f De novo design of ligand-binding proteins



Energy Minimization

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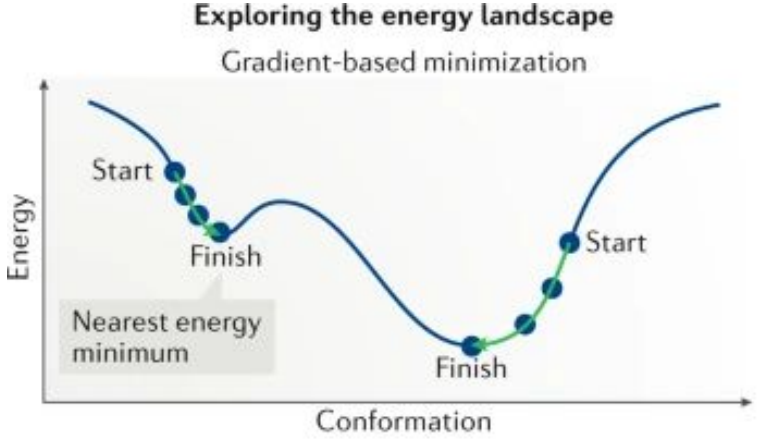
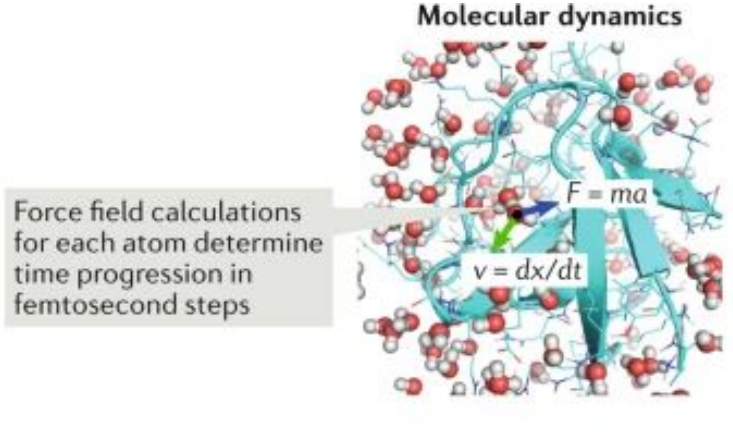
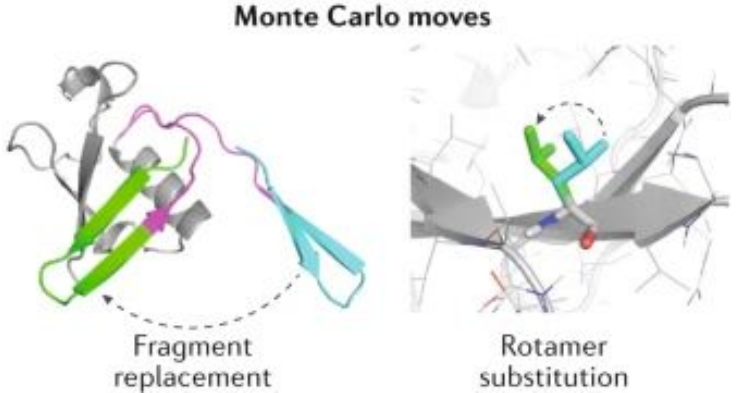
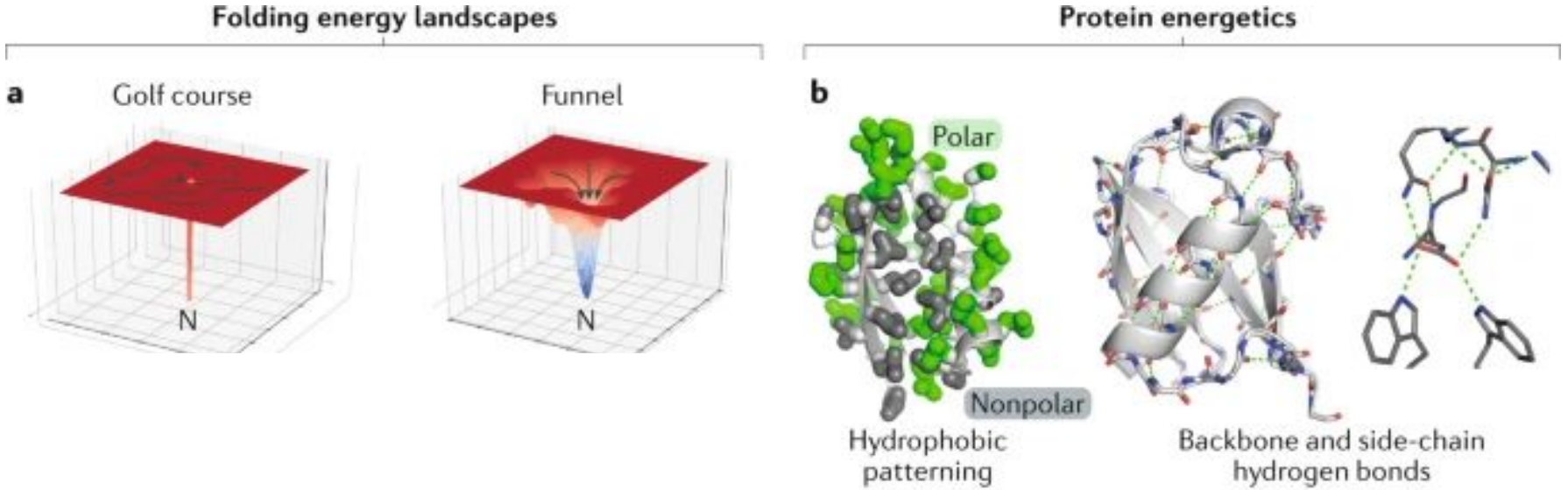






Energy Minimization



Homology Modeling

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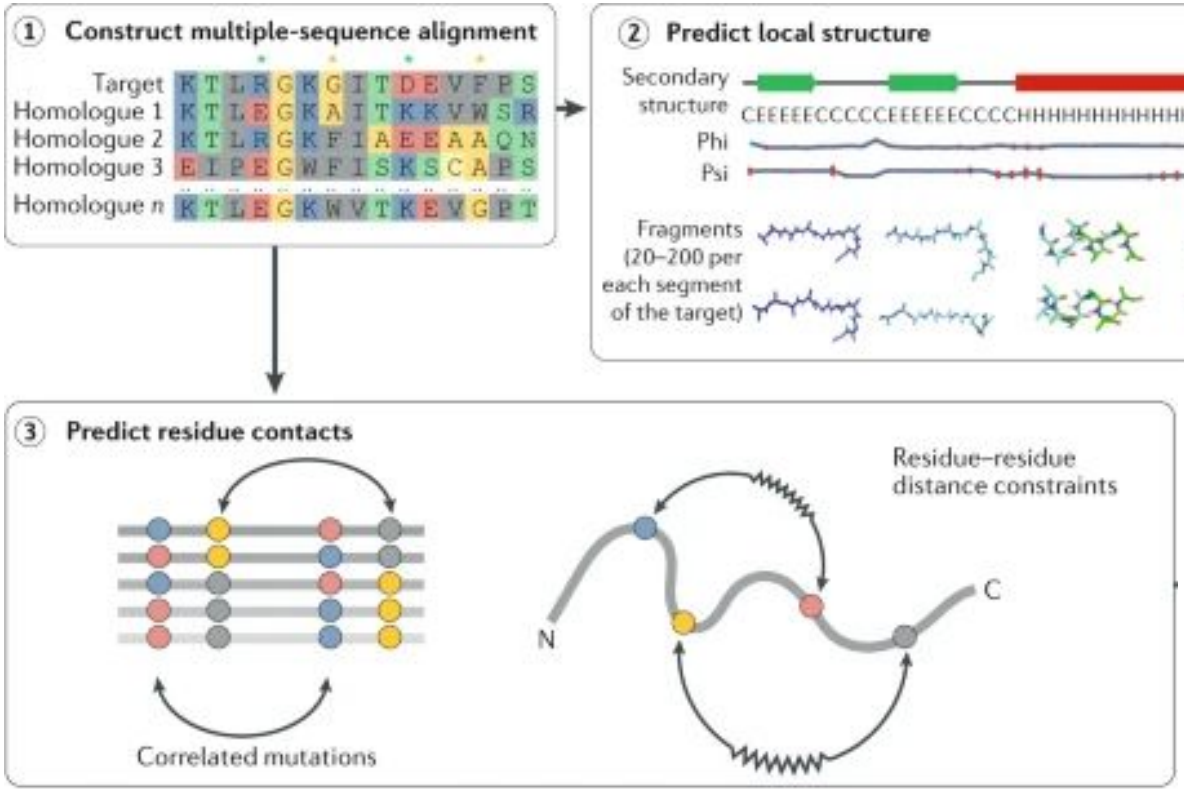

Homology Modeling

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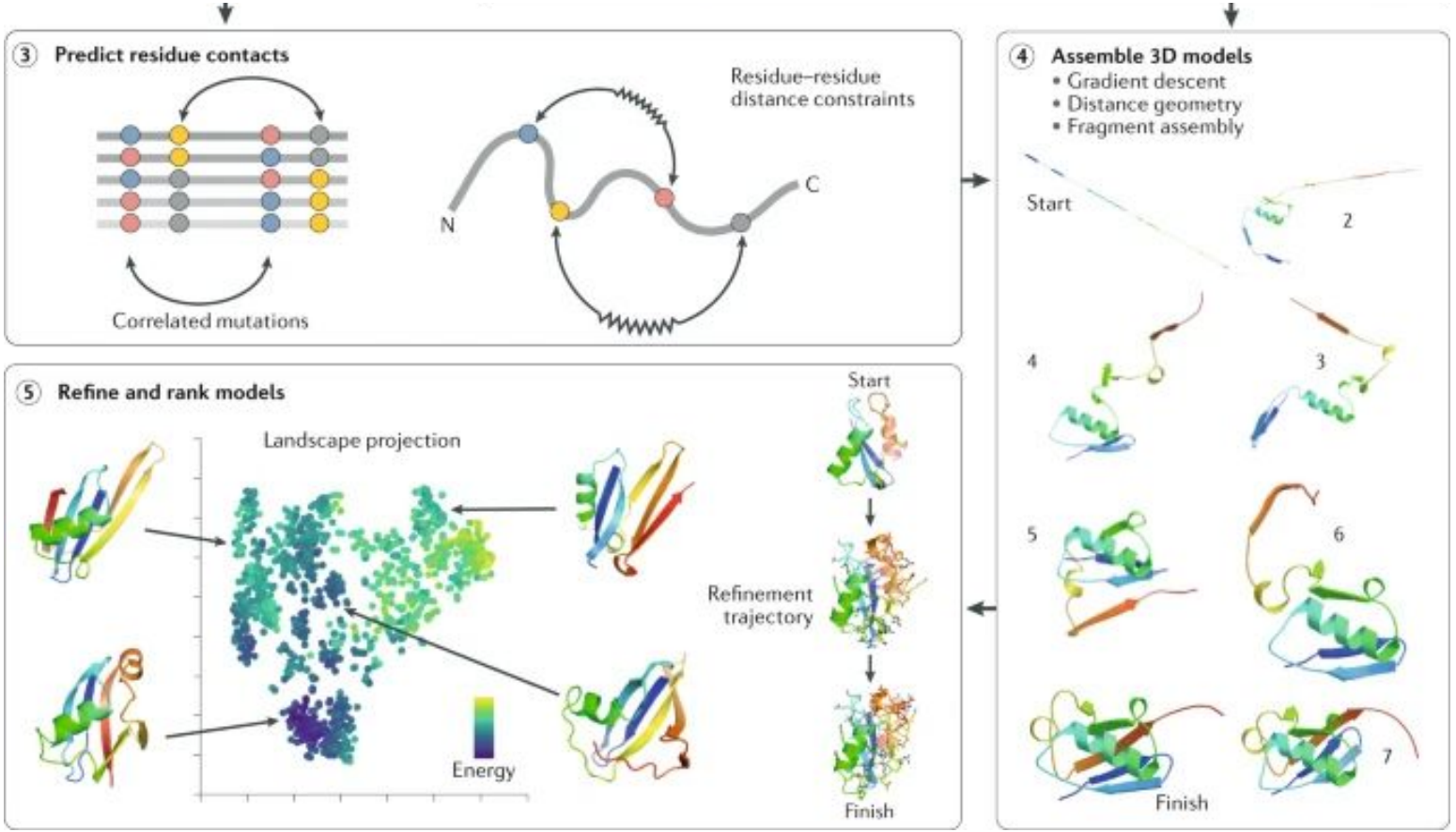

Protein Folding Challenge

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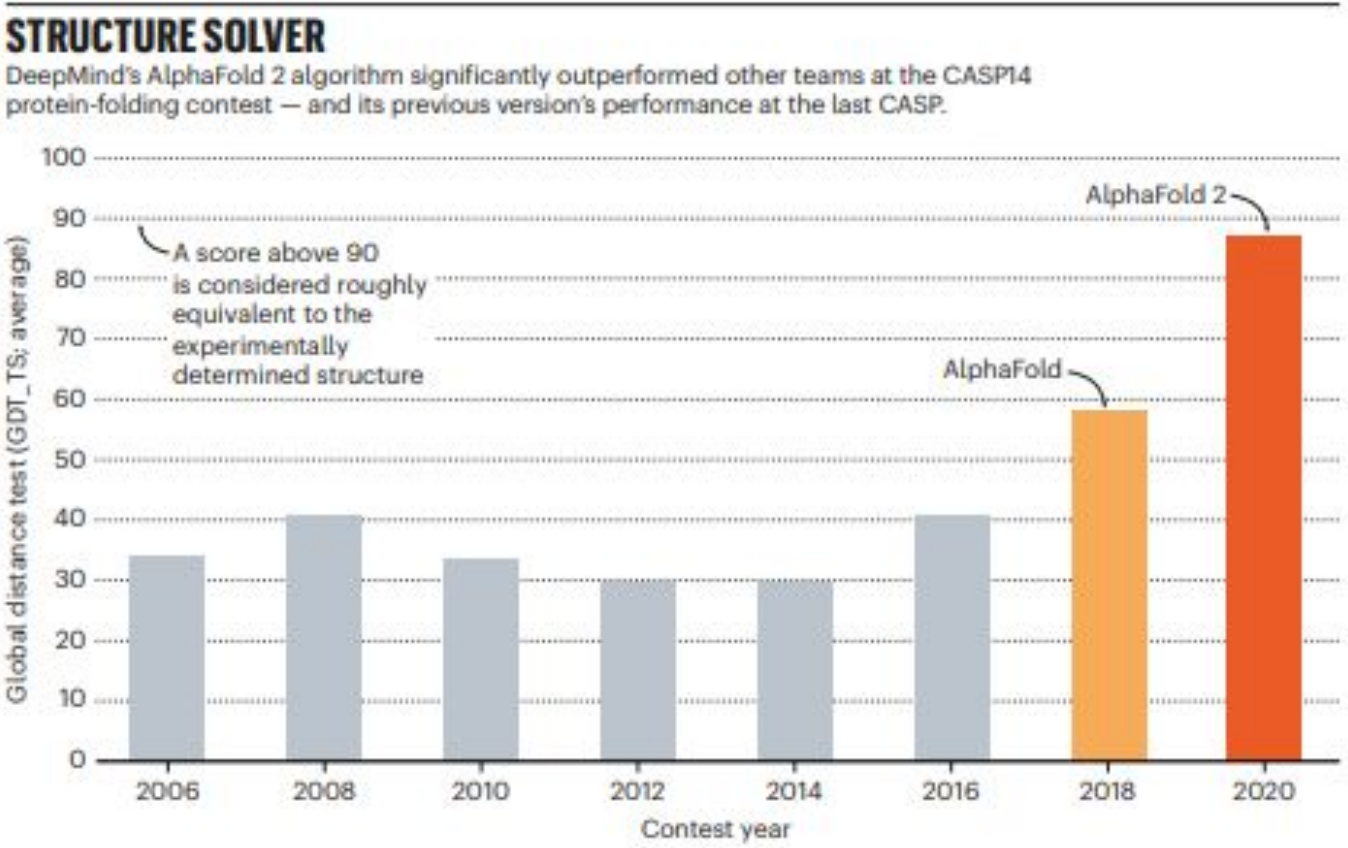

AlphaFold – Implications

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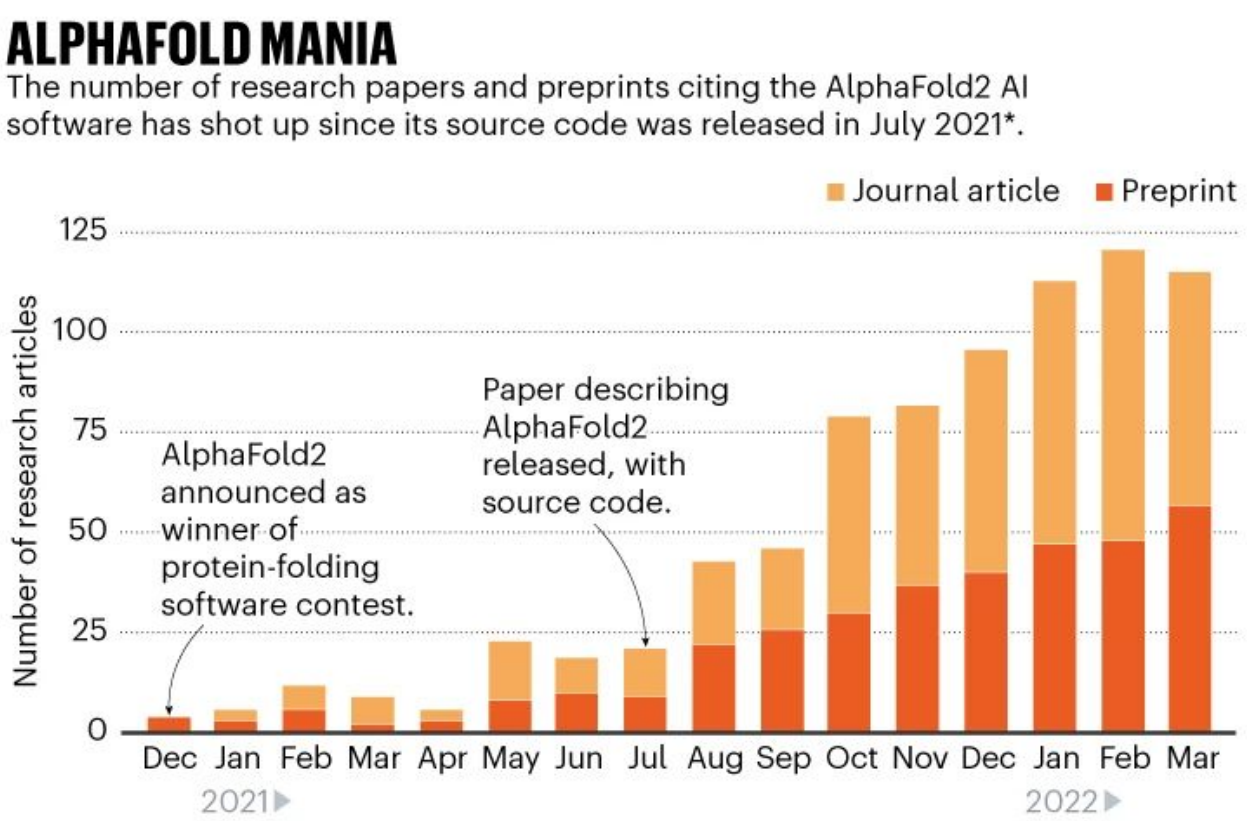

AlphaFold: CASP14 Winner

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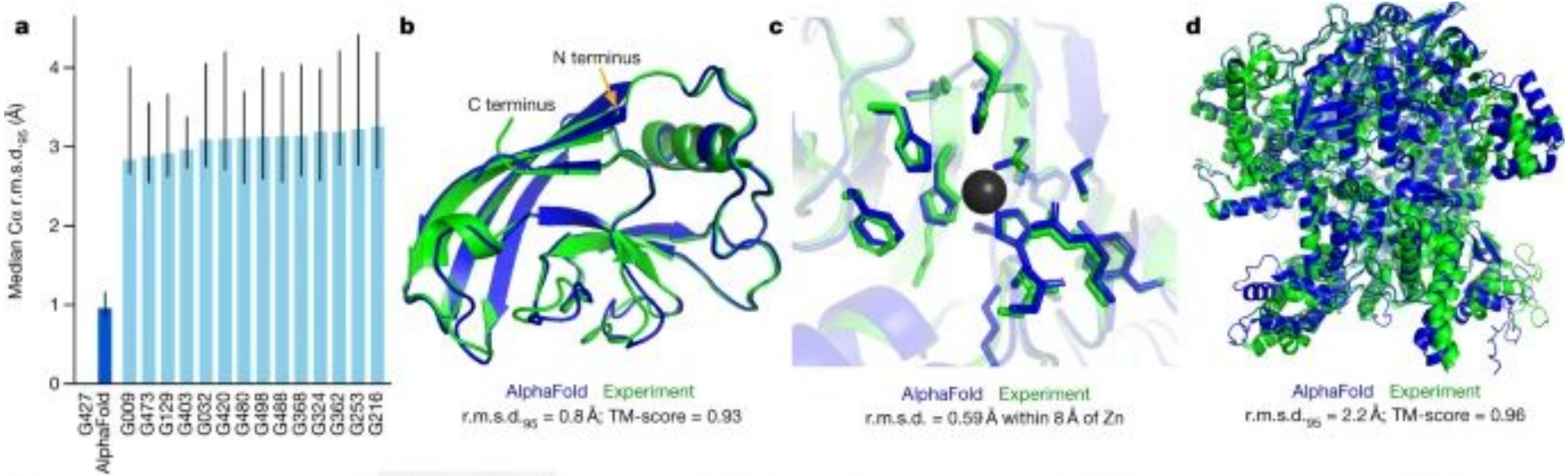

AlphaFold: Architecture

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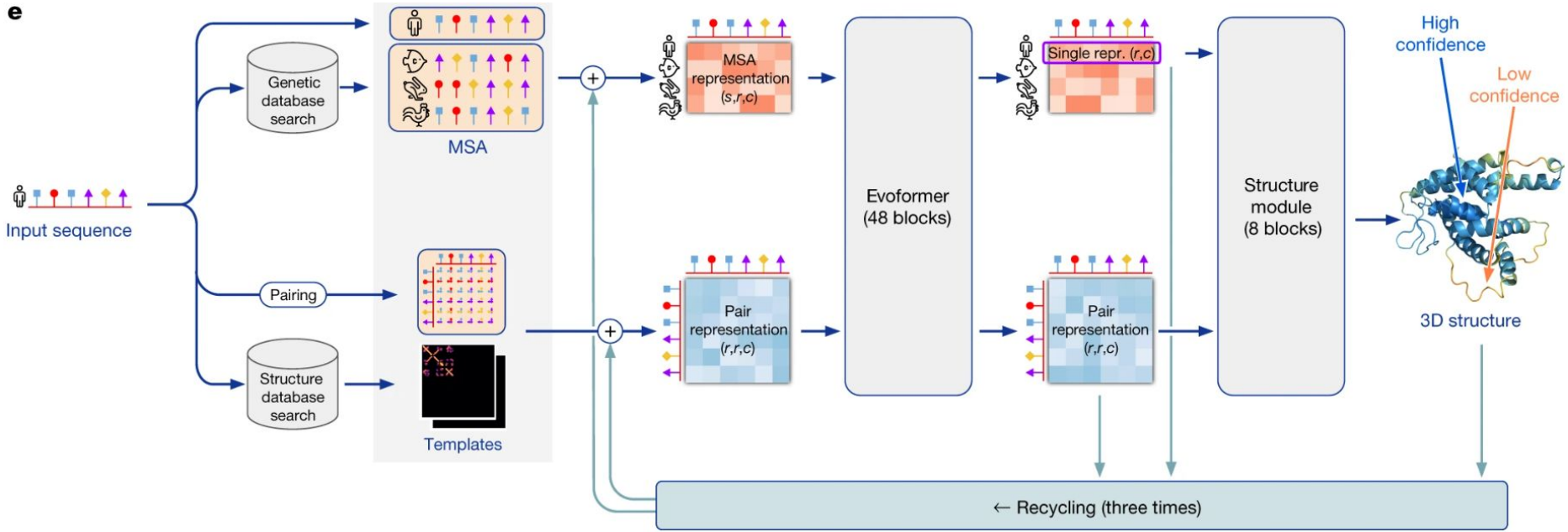

AlphaFold: Evoformer Block

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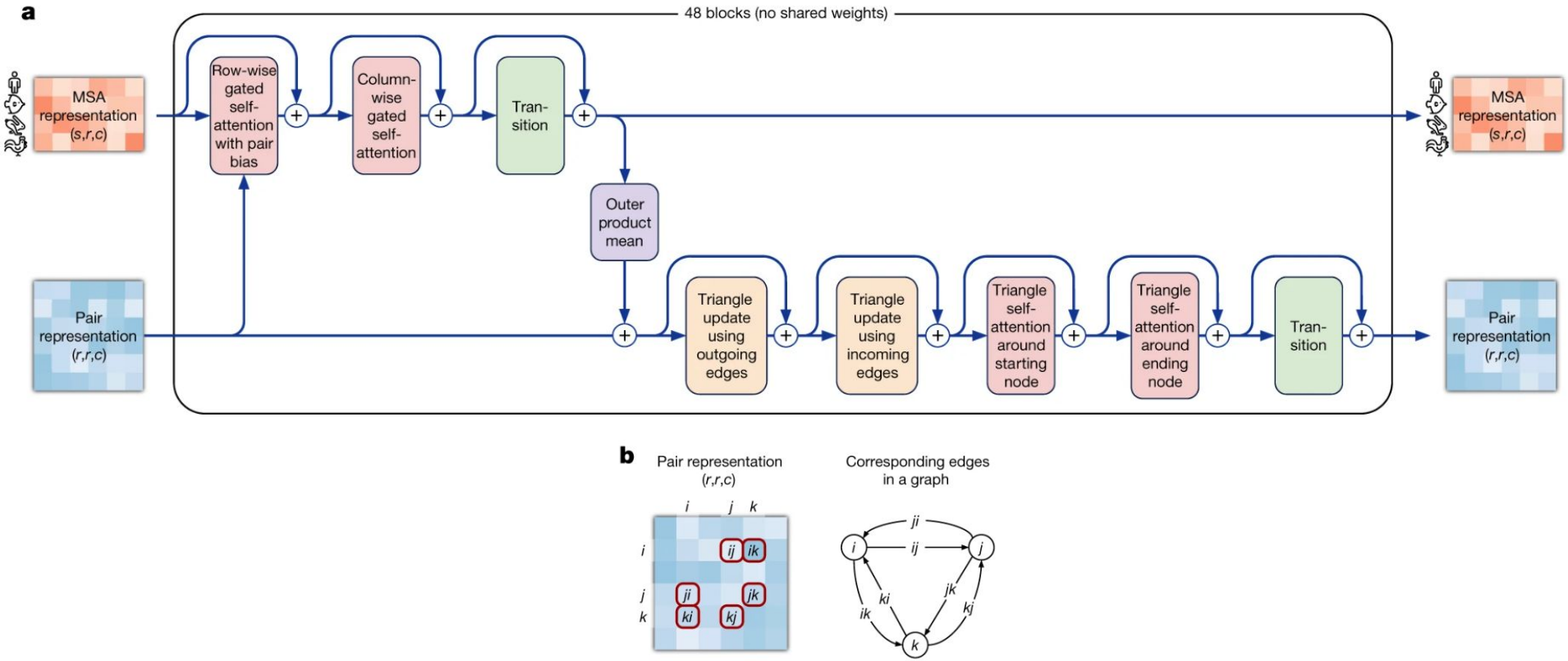

AlphaFold: Row-Wise Gated SA

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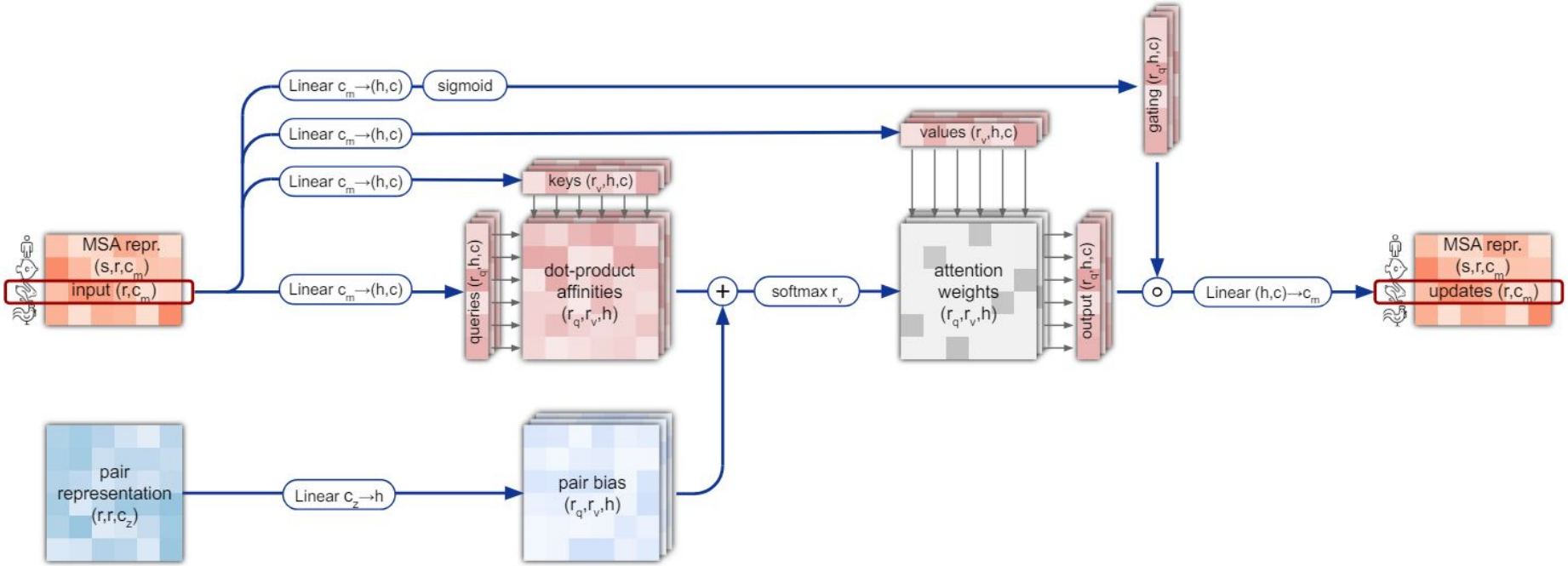
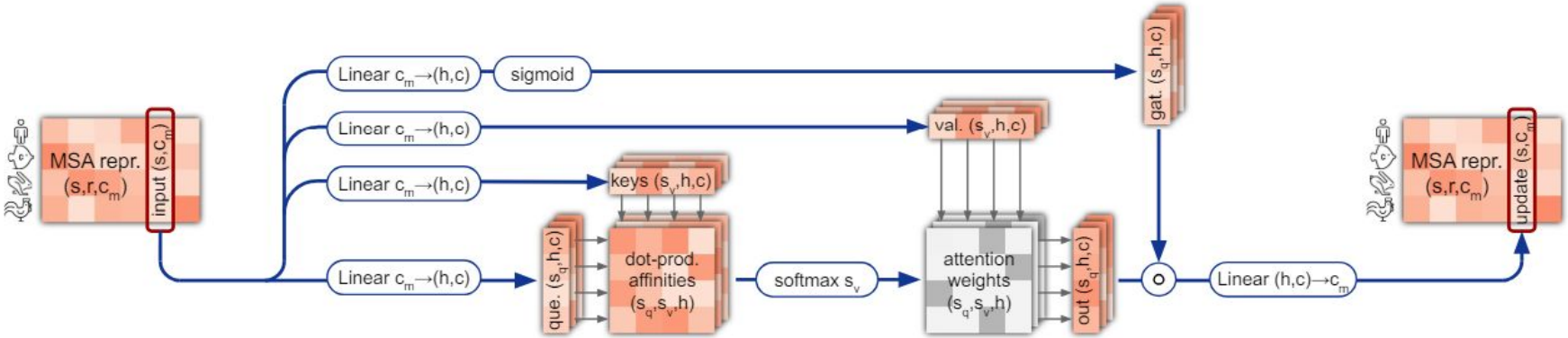
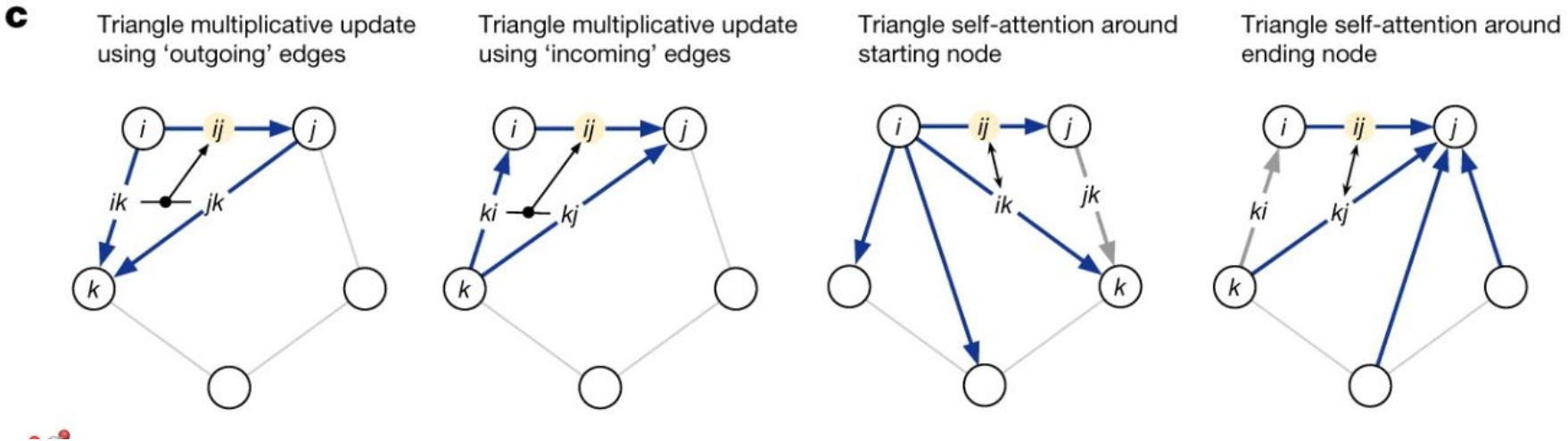


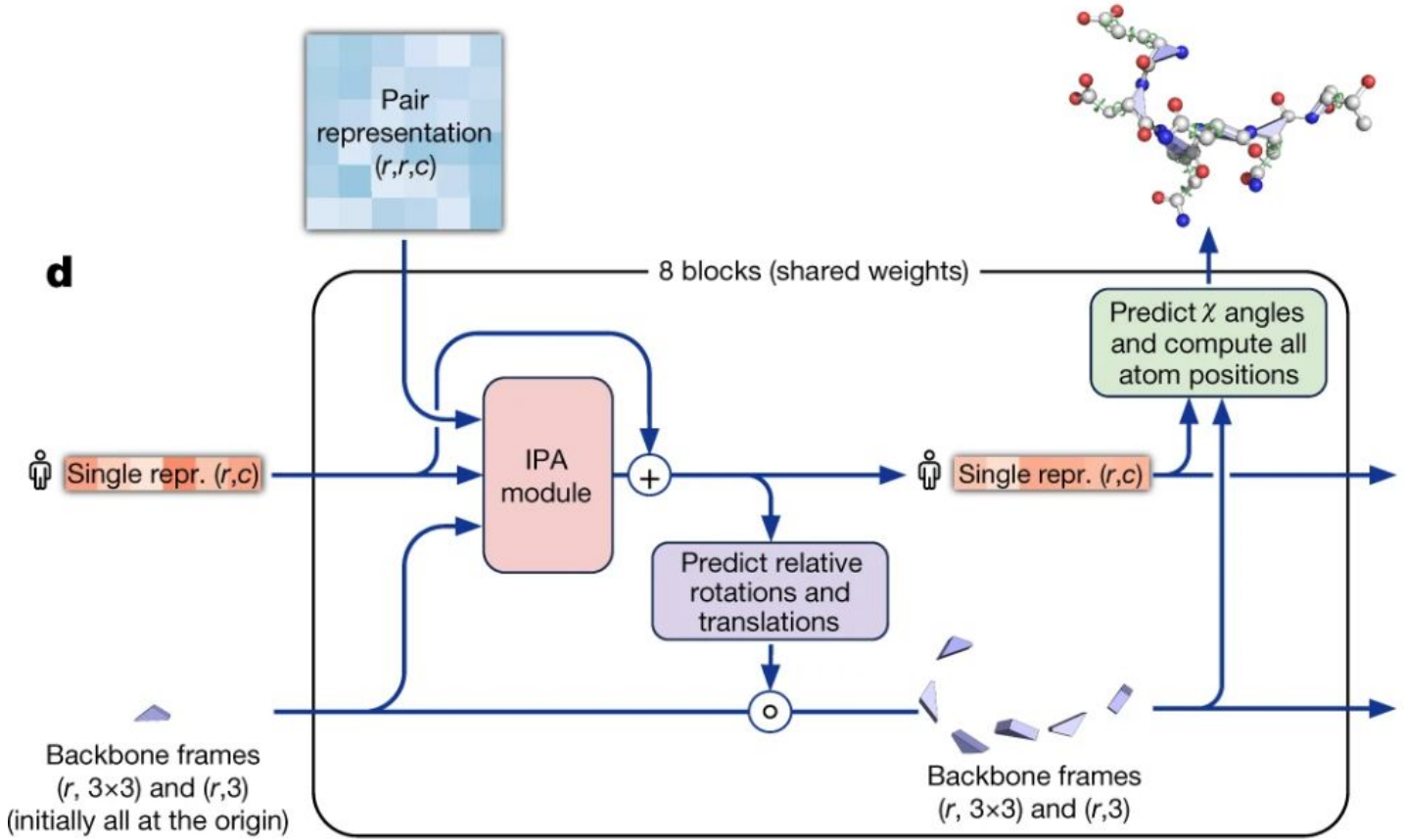
AlphaFold: Column-Wise Gated SA



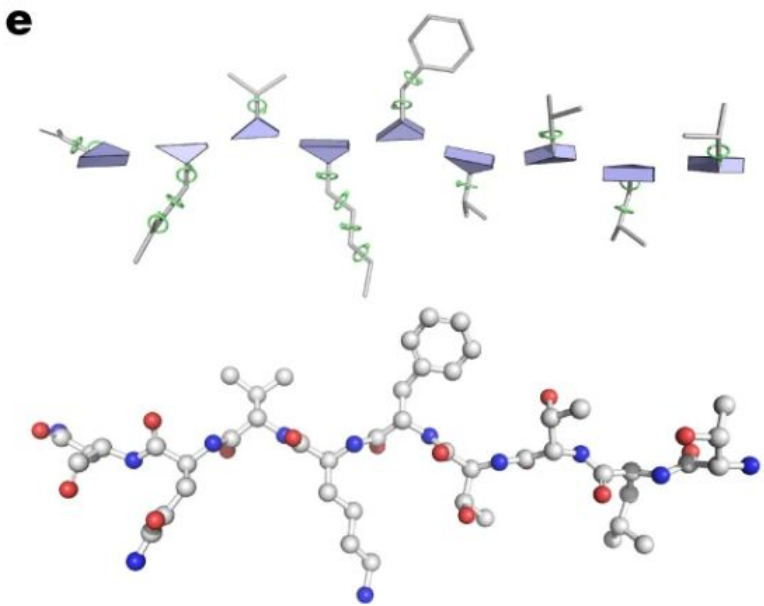
AlphaFold: Triangle Layers

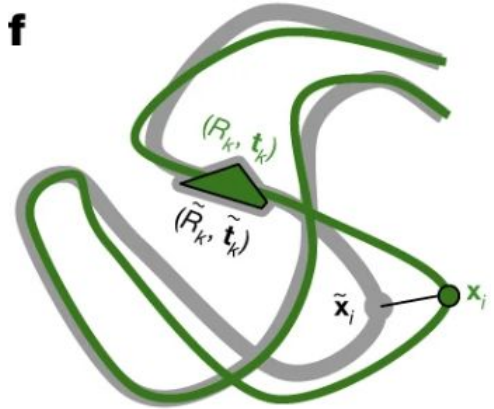


AlphaFold: Structure Module



AlphaFold: Frame Aligned Point Error





AlphaFold: Self-Distillation

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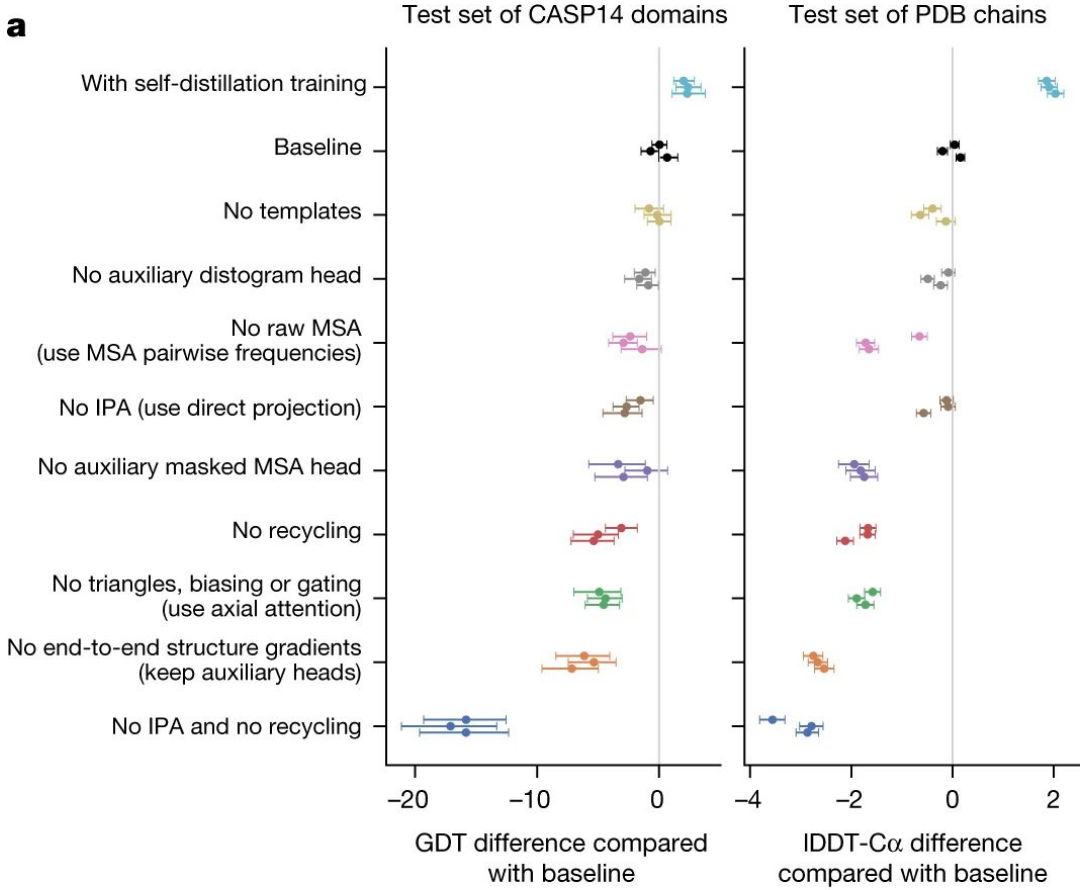

- 350,000 diverse sequences from Uniclust30
- predicted structures filtered to a high-confidence subset
- various training data augmentations such as cropping and MSA subsampling
- randomly mask out or mutate individual residues within the MSA

AlphaFold: Interpretation

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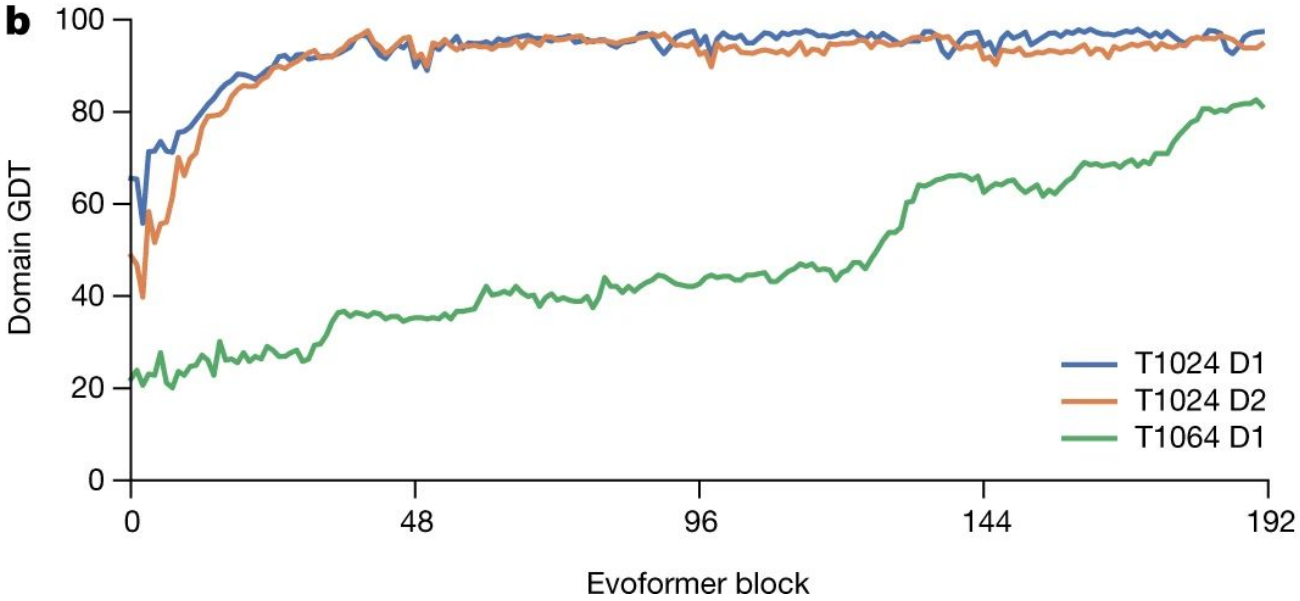

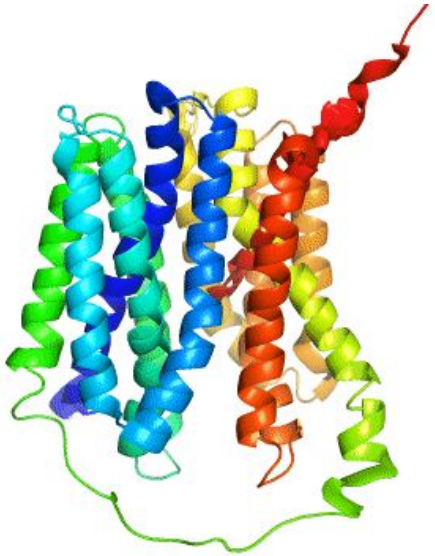

1

AlphaFold Protein Structure Database

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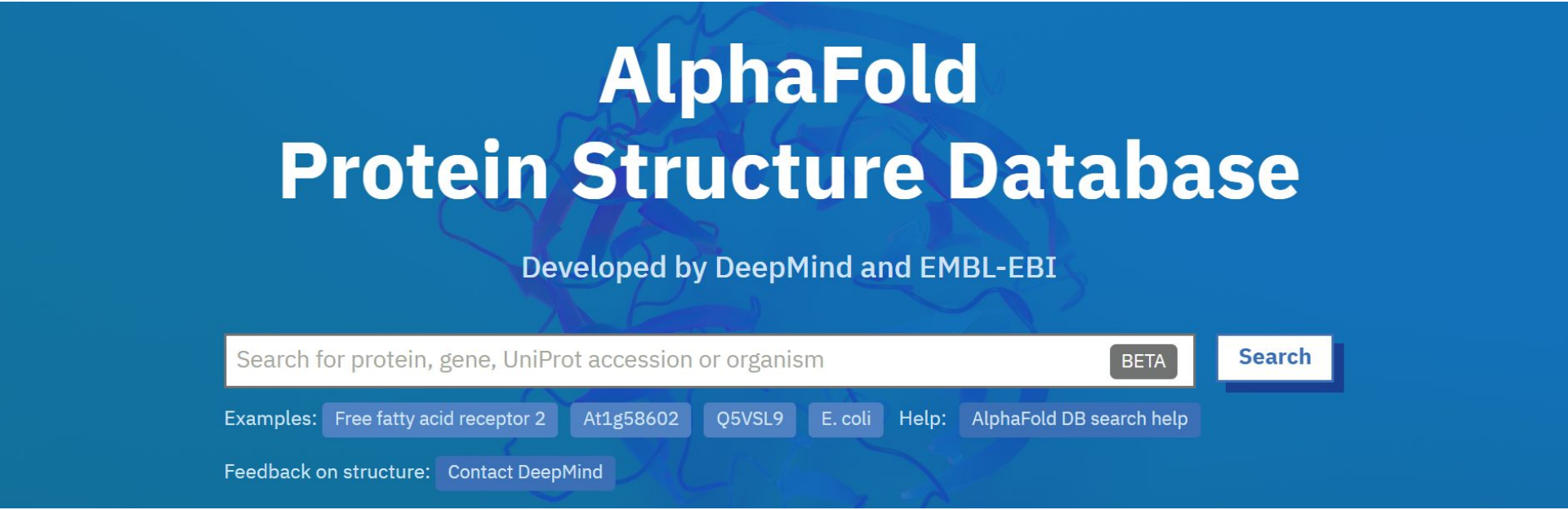

RoseTTAFold

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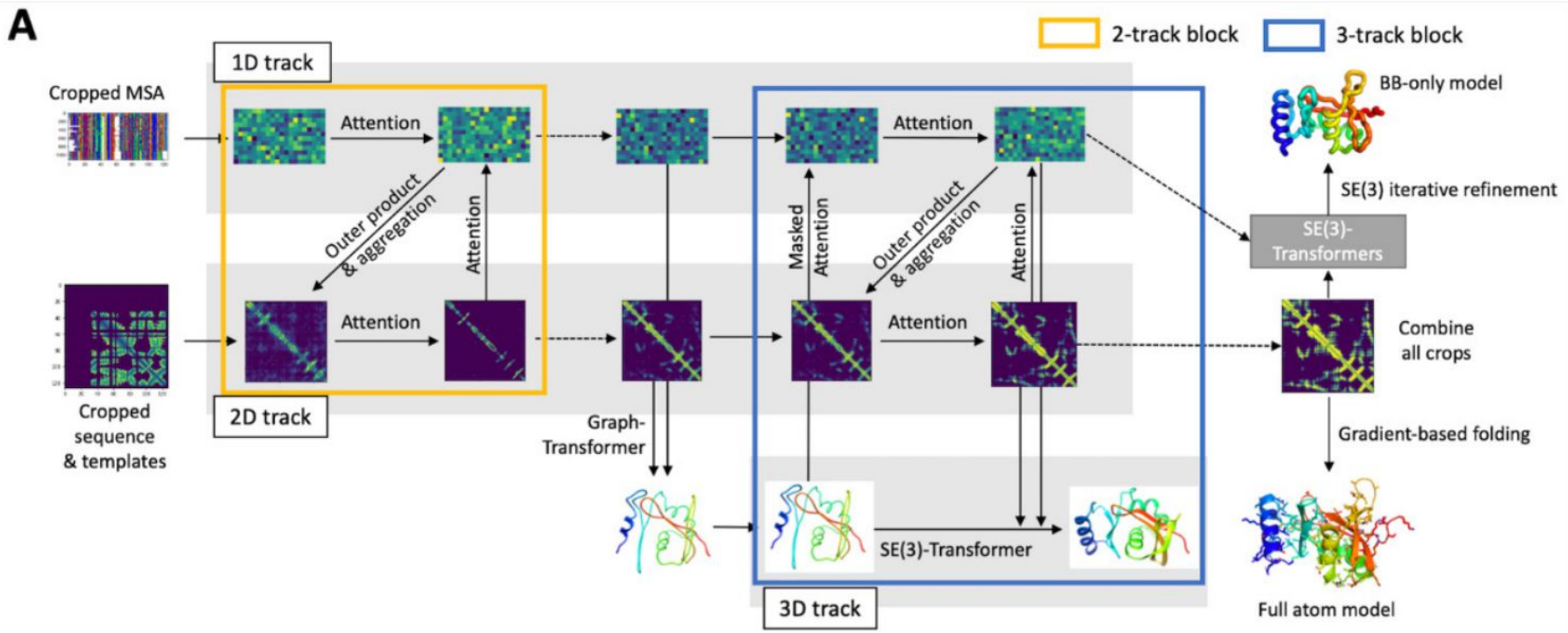
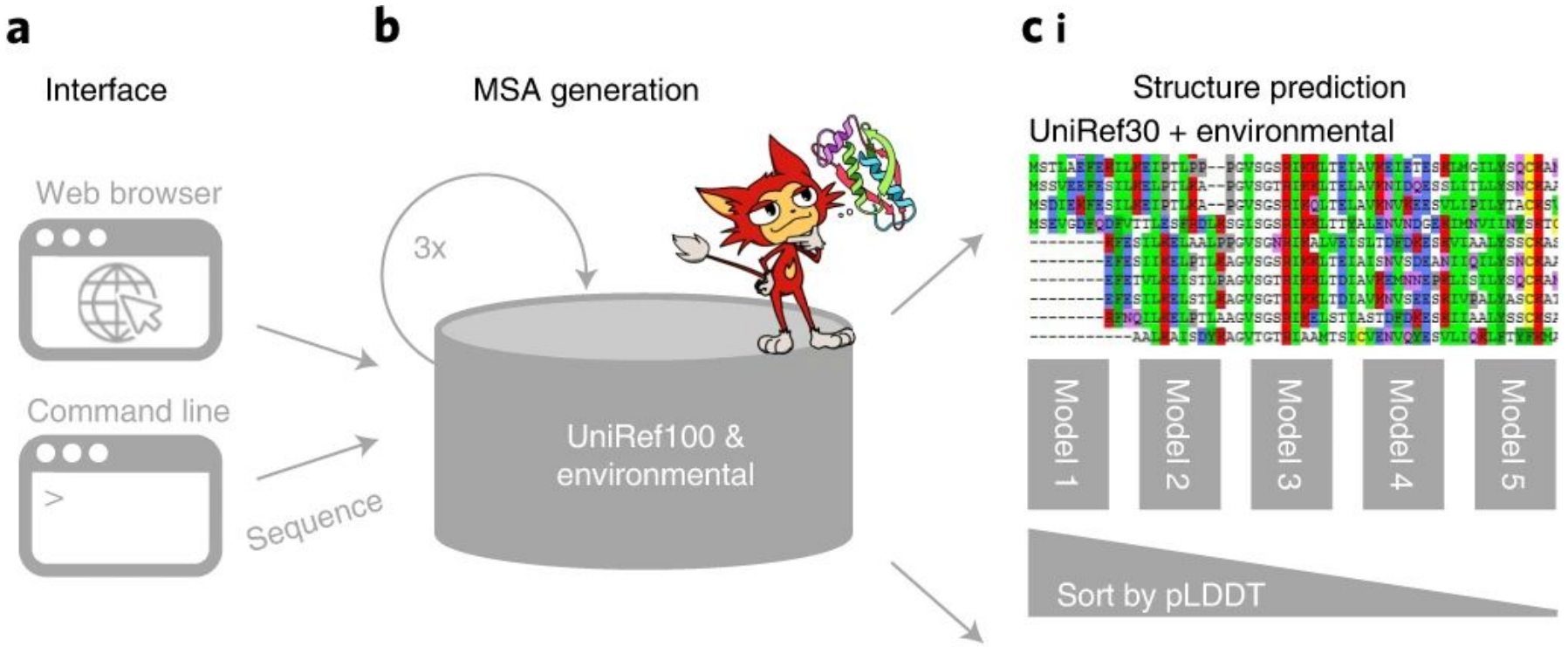
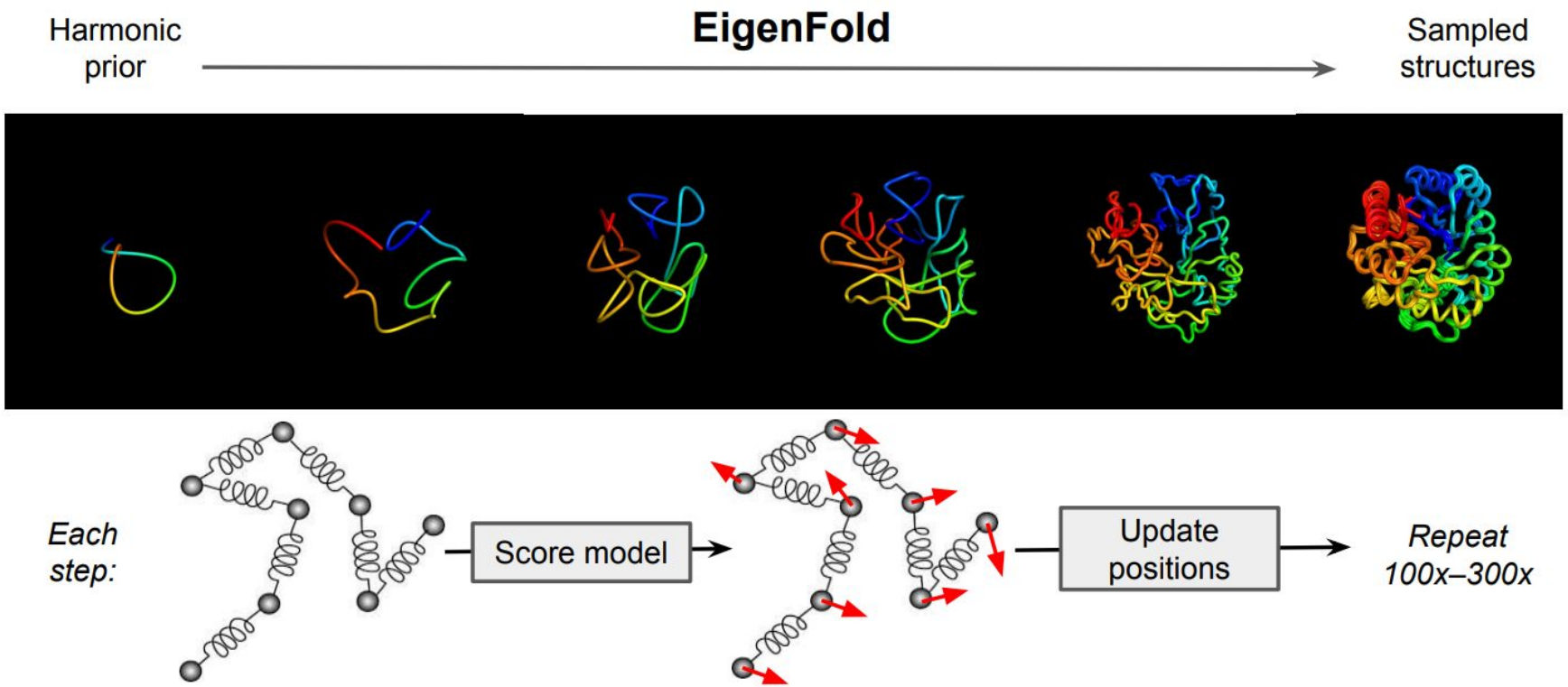


ColabFold


a
Interface
Web browser
Command line
>
Sequence
b
MSA generation
3x
UniRef100 &
environmental
c i
Structure prediction
UniRef30 + environmental
Model 1
Model 2
Model 3
Model 4
Model 5
Sort by pLDDT

EigenFold: Diffusion Protein Folding



EigenFold: Harmonic Diffusion

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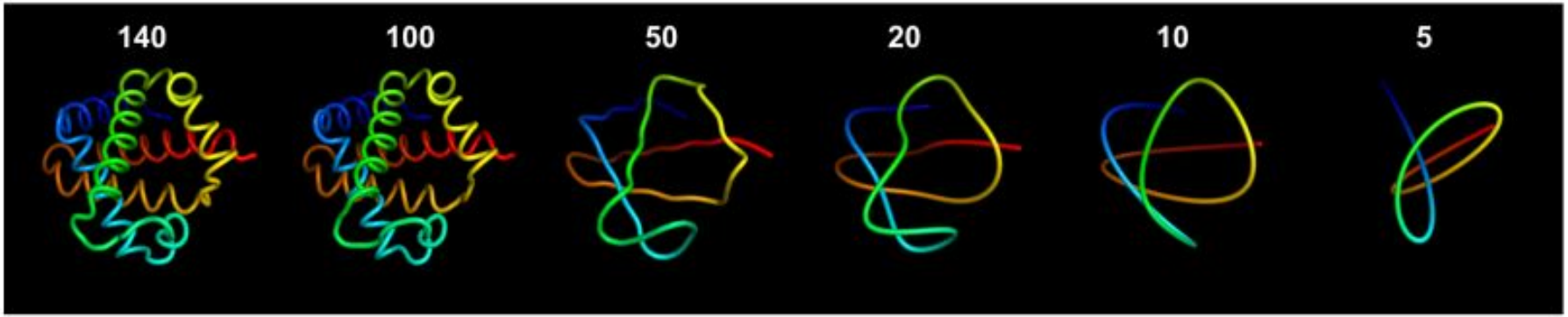

EigenFold: Results

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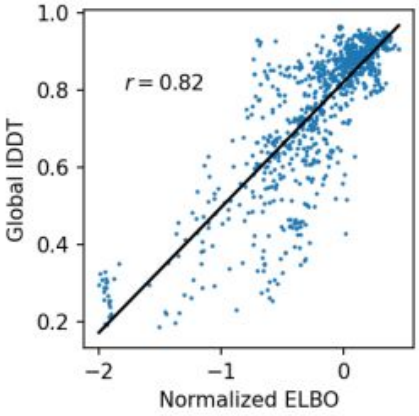
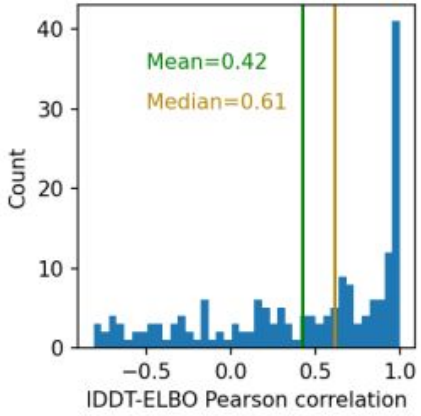
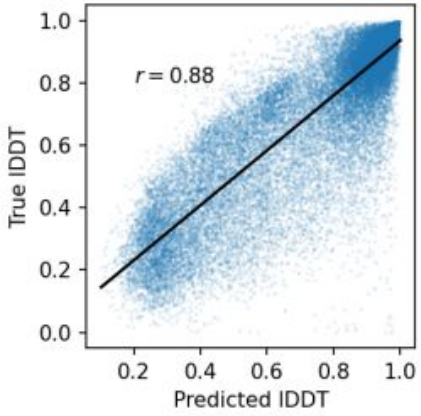
Table 1: Single-structure prediction accuracy of EIGENFOLD and baseline methods on CAMEO targets under 750 residues from Aug 1–Oct 31, 2022. All metrics are reported as mean / median.

	$RMSD_{C\alpha}$ ↓	TMScore ↑	GDT-TS ↑	$lDDT_{C\alpha}$ ↑
ALPHAFOLD2	3.30 / 1.64	0.87 / 0.95	0.86 / 0.91	0.90 / 0.93
ESMFOLD	3.99 / 2.03	0.85 / 0.93	0.83 / 0.88	0.87 / 0.90
OMEGAFOLD	5.26 / 2.62	0.80 / 0.89	0.77 / 0.84	0.83 / 0.89
ROSETTAFOLD	5.72 / 3.17	0.77 / 0.84	0.71 / 0.75	0.79 / 0.82
EIGENFOLD	7.37 / 3.50	0.75 / 0.84	0.71 / 0.79	0.78 / 0.85







Torsional Diffusion for Small Molecules

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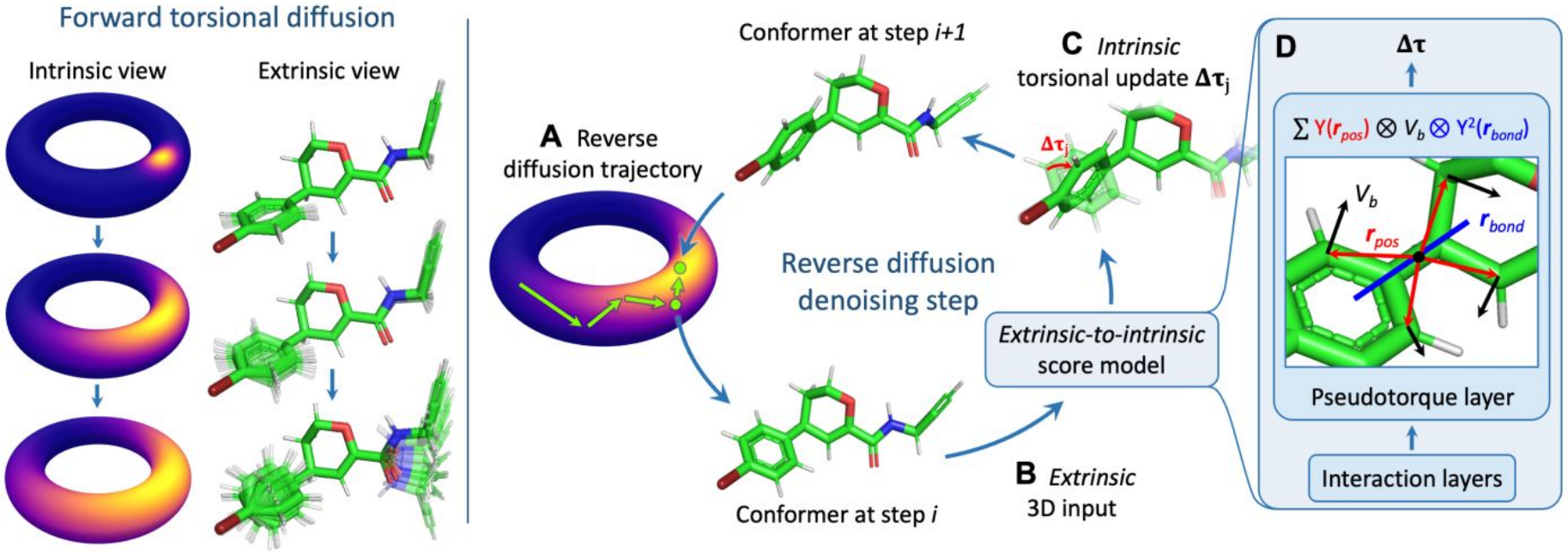

DiffDock: Docking with Deep Learning

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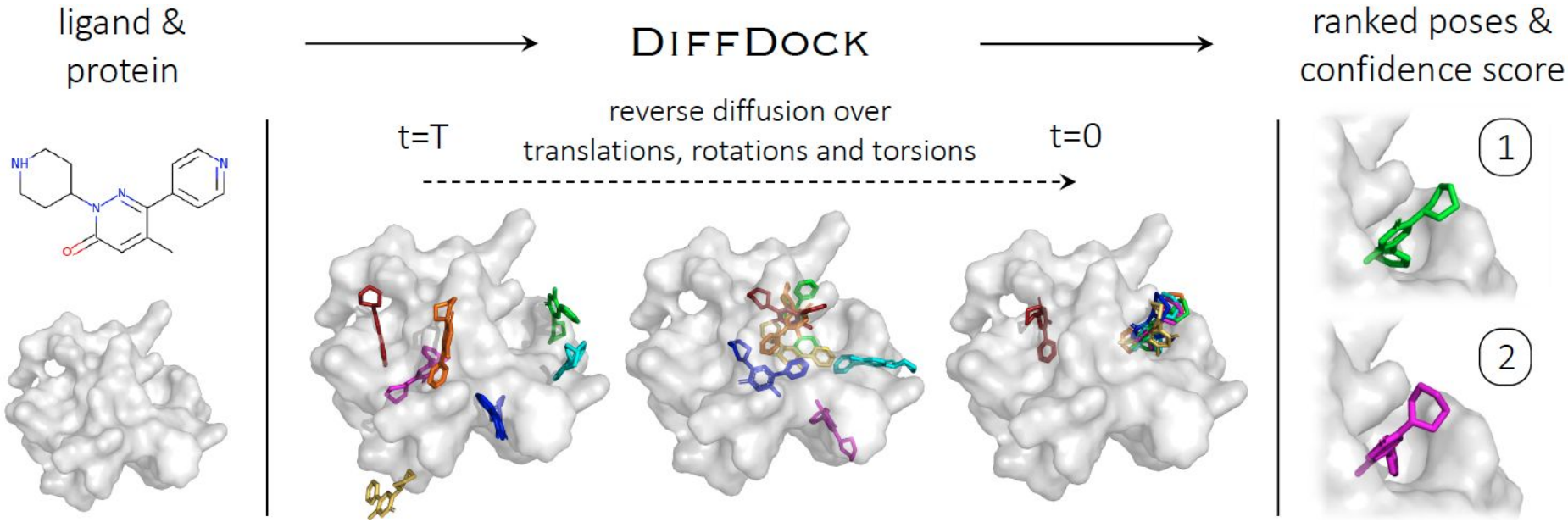

DiffDock: Motivation

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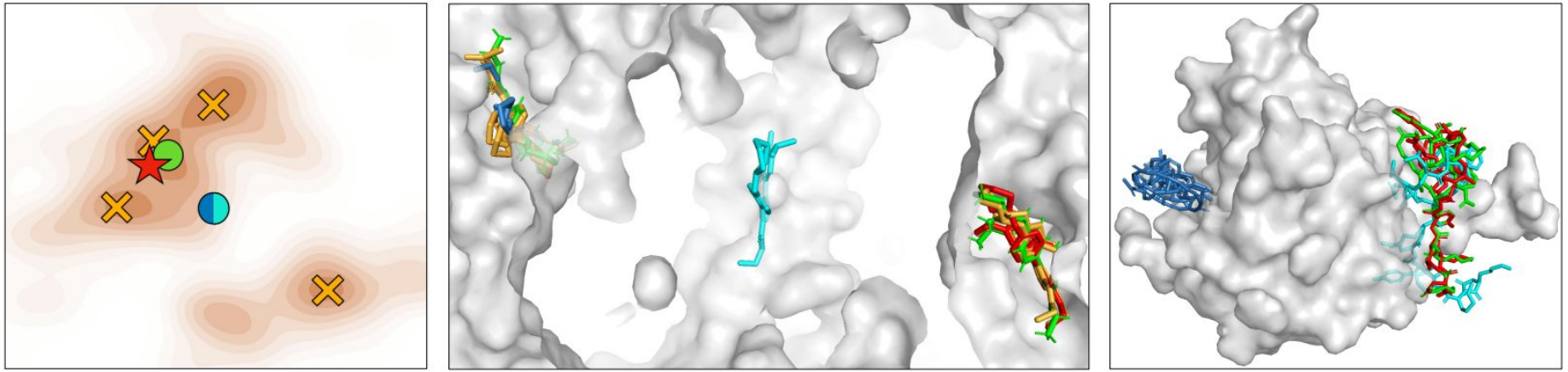

DiffDock: Results

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Method	Holo crystal proteins Top-1 RMSD %<2	Holo crystal proteins Top-1 RMSD Med.	Holo crystal proteins Top-5 RMSD %<2	Holo crystal proteins Top-5 RMSD Med.	Apo ESMFold proteins Top-1 RMSD %<2	Apo ESMFold proteins Top-1 RMSD Med.	Apo ESMFold proteins Top-5 RMSD %<2	Apo ESMFold proteins Top-5 RMSD Med.	Average Runtime (s)
GNINA	22.9	7.7	32.9	4.5	2.0	22.3	4.0	14.22	127
SMINA	18.7	7.1	29.3	4.6	3.4	15.4	6.9	10.0	126*
GLIDE	21.8	9.3							1405*
EQUIBIND	5.5	6.2	-	-	1.7	7.1	-	-	0.04
TANKBIND	20.4	4.0	24.5	3.4	10.4	5.4	14.7	4.3	0.7/2.5
P2RANK+SMINA	20.4	6.9	33.2	4.4	4.6	10.0	10.3	7.0	126*
P2RANK+GNINA	28.8	5.5	38.3	3.4	8.6	11.2	12.8	7.2	127
EQUIBIND+SMINA	23.2	6.5	38.6	3.4	4.3	8.3	11.7	5.8	126*
EQUIBIND+GNINA	28.8	4.9	39.1	3.1	10.2	8.8	18.6	5.6	127
DIFFDOCK (10)	35.0	3.6	40.7	2.65	**21.7**	**5.0**	**31.9**	**3.3**	10
DIFFDOCK (40)	**38.2**	**3.3**	**44.7**	**2.40**	20.3	5.1	31.3	**3.3**	40

QFold: Quantum Walks and DL

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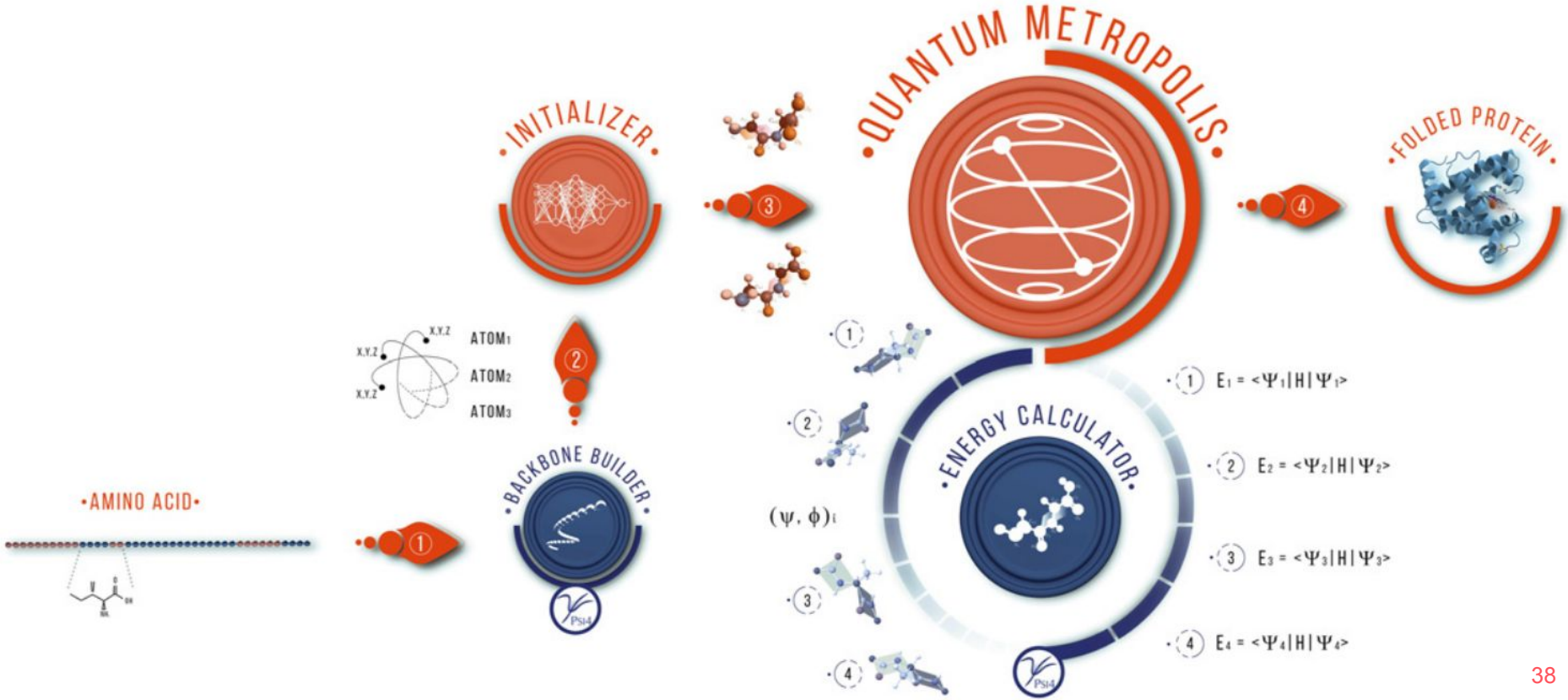

Literature

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