University of Warsaw
Faculty of Mathematics, Informatics and Mechanics

Architecture of large projects in bioinformatics (ADP)

AlphaFold 3

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Warsaw, 2025

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Article

Accurate structure prediction of biomolecular interactions with AlphaFold 3

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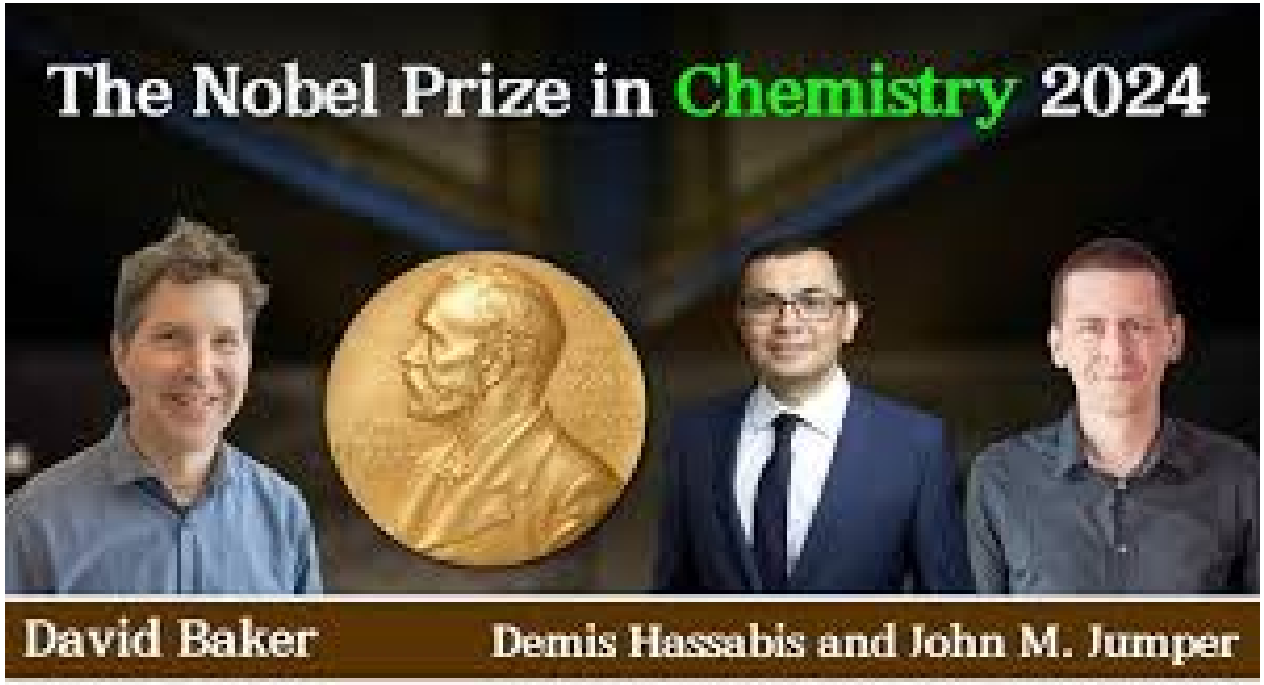

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cccaaccatt cccttatcca ggccttttga
caacgctatg ctccgcgccc atcgtctgca
ccagctggcc tttgacacct accaggagtt
tgaagaagcc tatatcccaa aggaacagaa
gtattcattc ctgcagaacc cccagacctc
```

DNA sequence

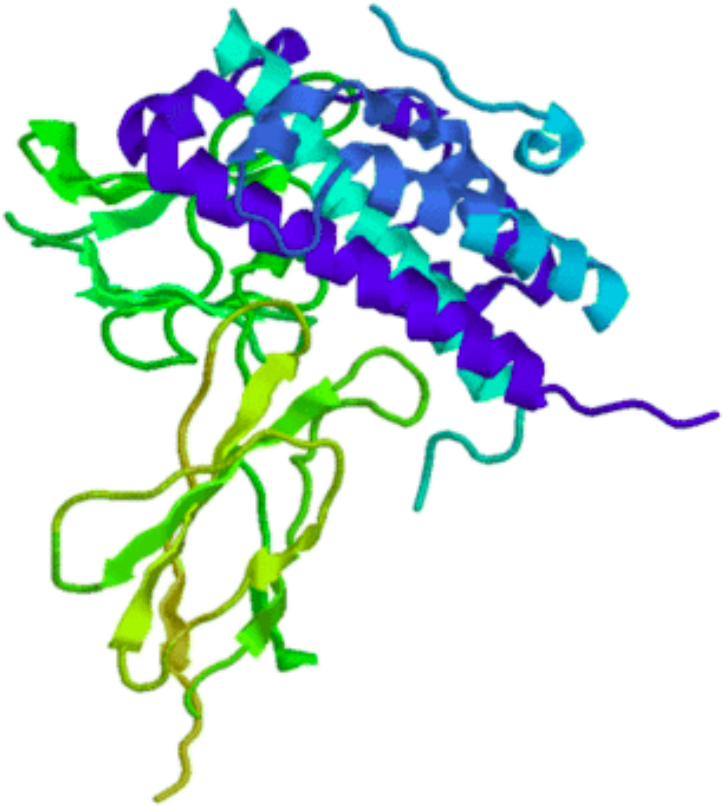
transcription & translation

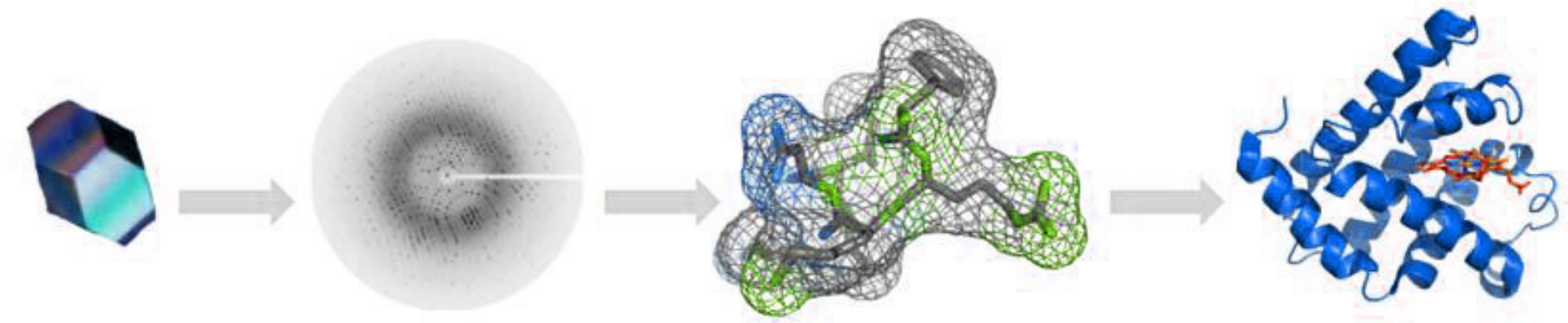
```
MATGSRTSLLLAFGLLCLPWLQEGSAFPTIPL
SRPFDNAMLRAHRLHQLAFDTYQEFEEAYIPK
EQKYSFLQNPQTSLCFSESIPTPSNREETQQK
SNLELLRISLLLIQSWLEPVQFLRSVFANSLV
YGASDSNVYDLLKDLEEGIQTLMGRLEDGSPR
TGQIFKQTYSKFDTNSHNDDALLKNYGLLYCF
RKDMDKVETFLRIVQCRSVEGSCGF
```

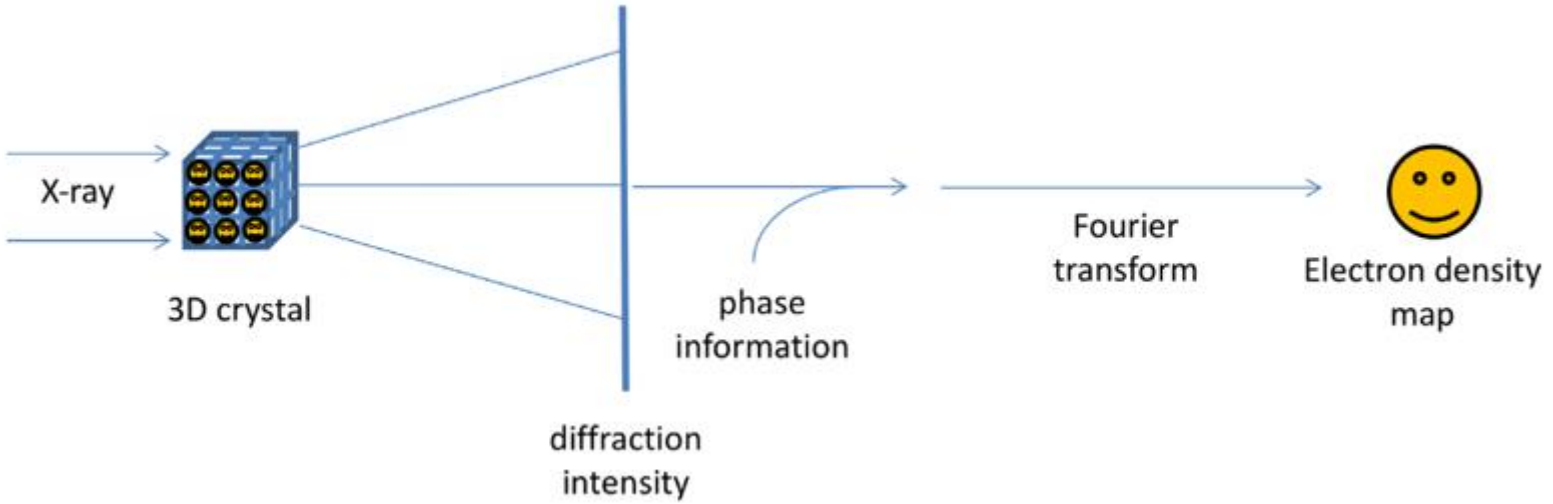
protein amino acid sequence

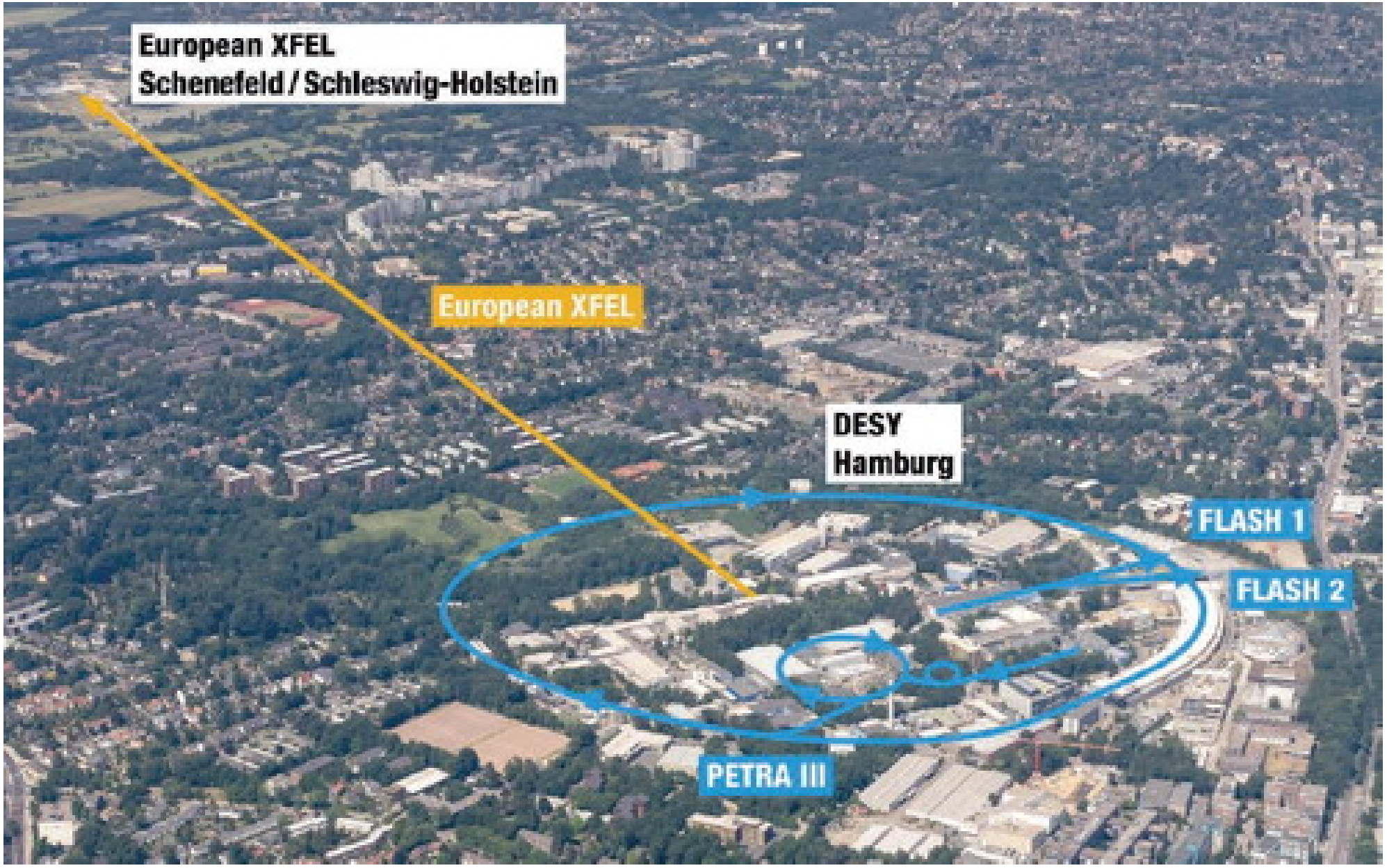
folding

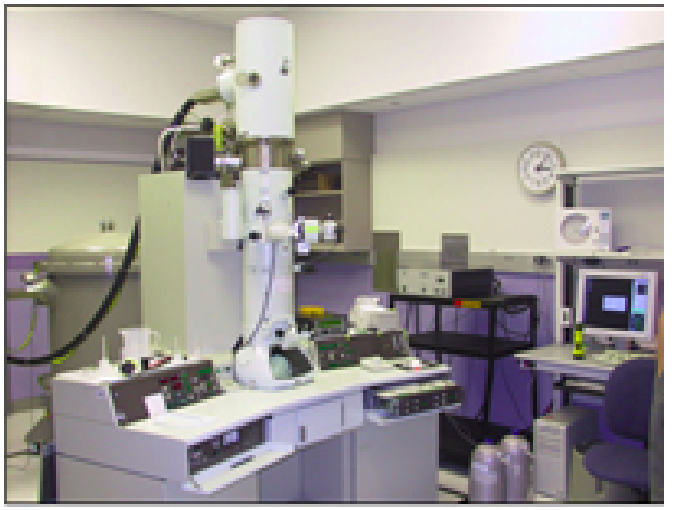
3D protein structure



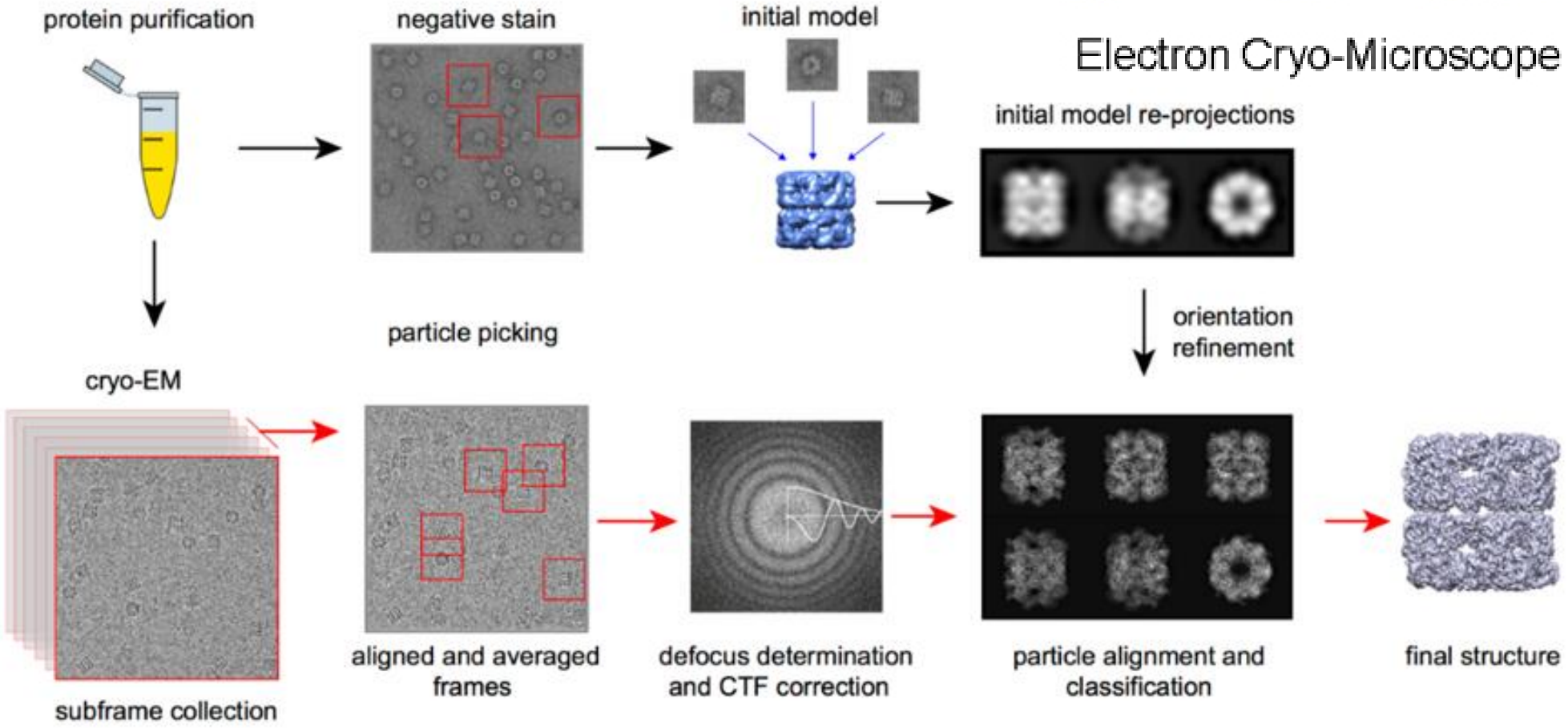

Single crystal
Diffraction pattern
Electron density map
Protein model


X-ray
3D crystal
diffraction intensity
phase information
Fourier transform
Electron density map


European XFEL
Schenefeld / Schleswig-Holstein
European XFEL
DESY
Hamburg
FLASH 1
FLASH 2
PETRA III

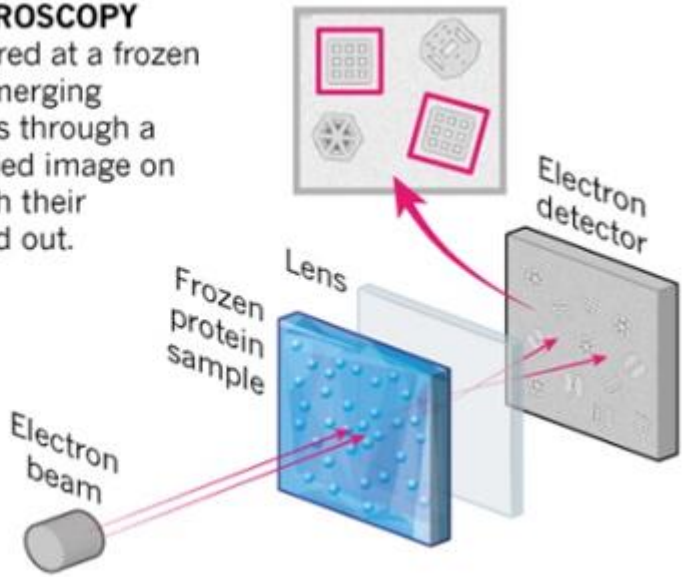


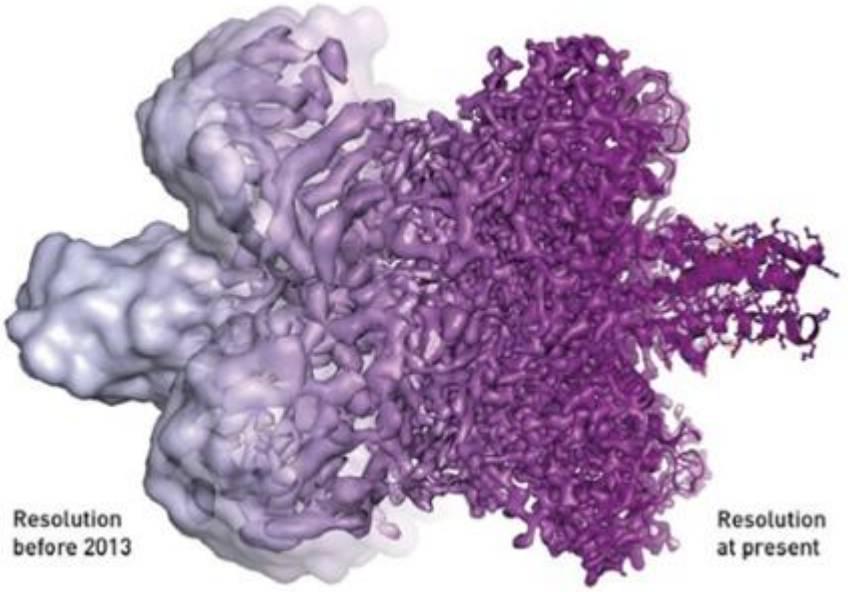
Electron Cryo-Microscope

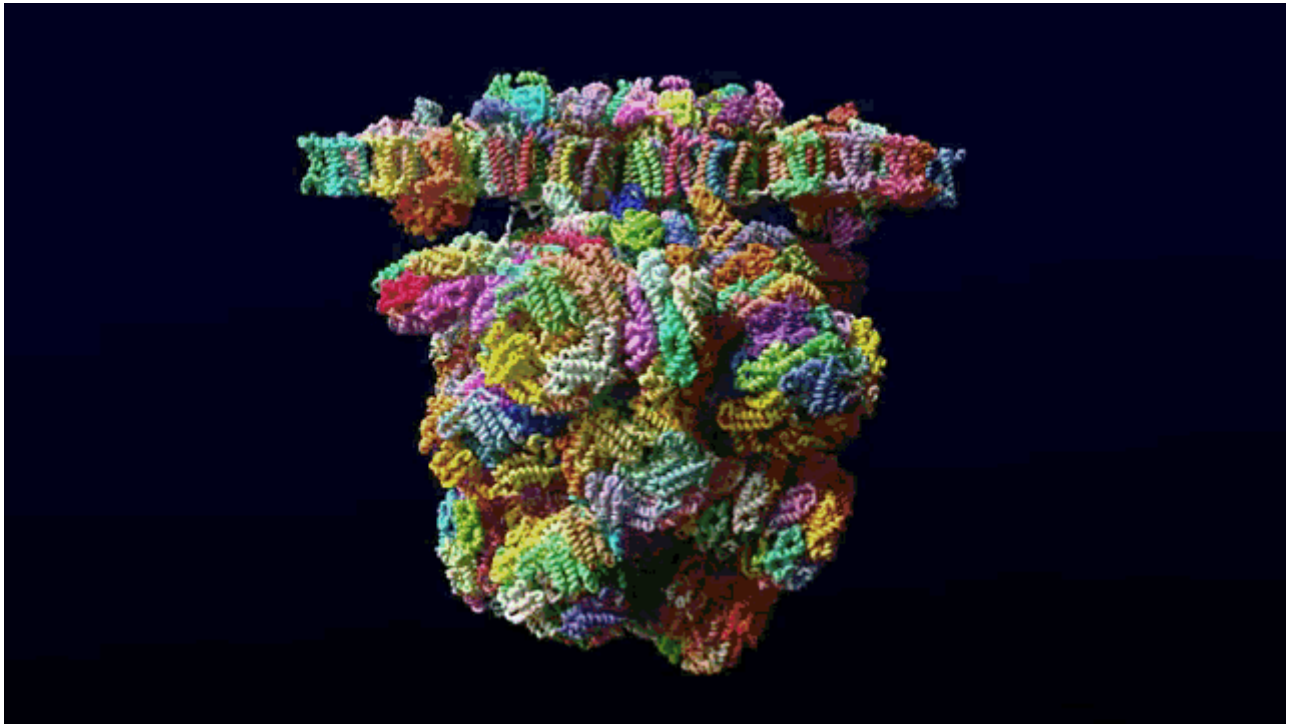


https://www.creative-biostructure.com/comparison-of-crystallography-nmr-and-em_6.htm

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.





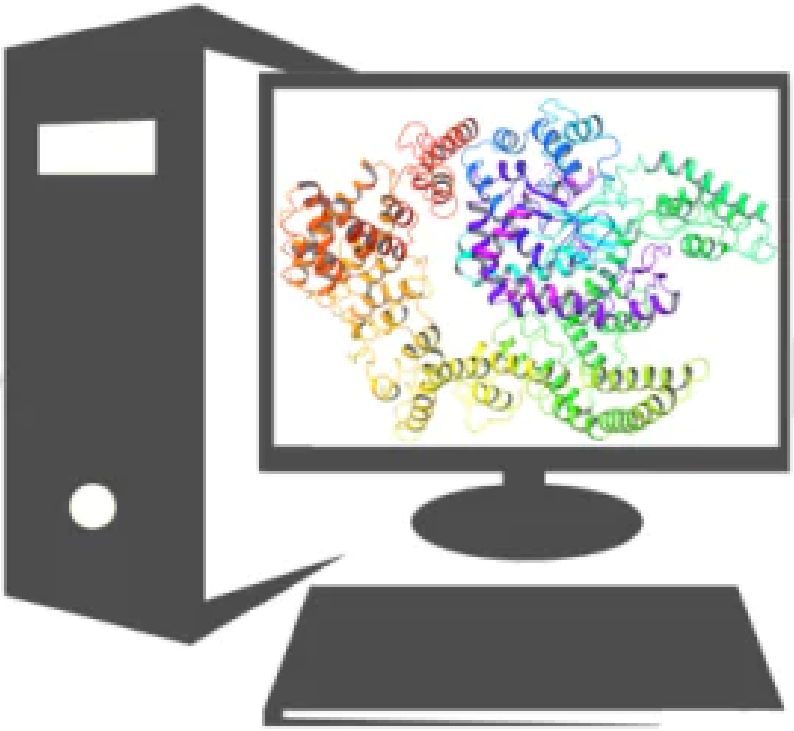


https://www.creative-biostructure.com/comparison-of-crystallography-nmr-and-em_6.htm

AI-based **3D** protein structure prediction

Amino **A**cid **S**equence

AGGT**A**GCTGC**G**TGGCTA**A**C
GCTGCA**G**CCACC**G**CCGCGG
C**AG**CGGCTT**C**TGCGCTGGG
ATGCA**C**CCCTCCAG**AG**TGG



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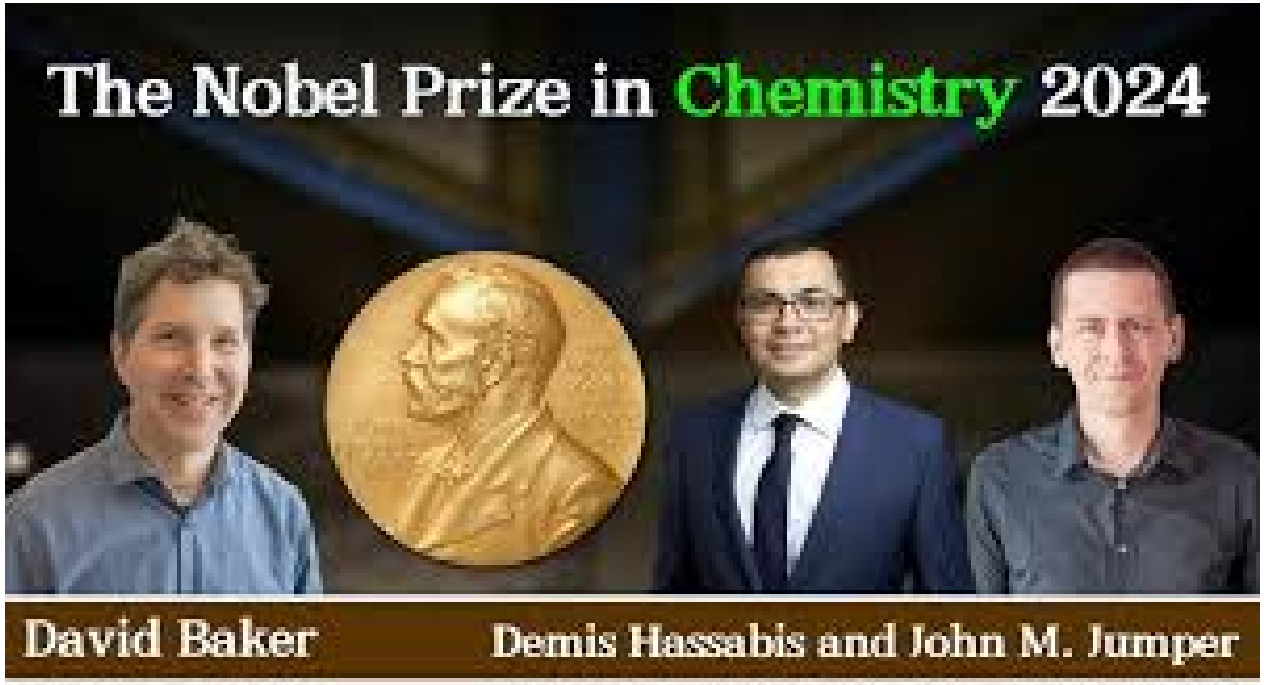
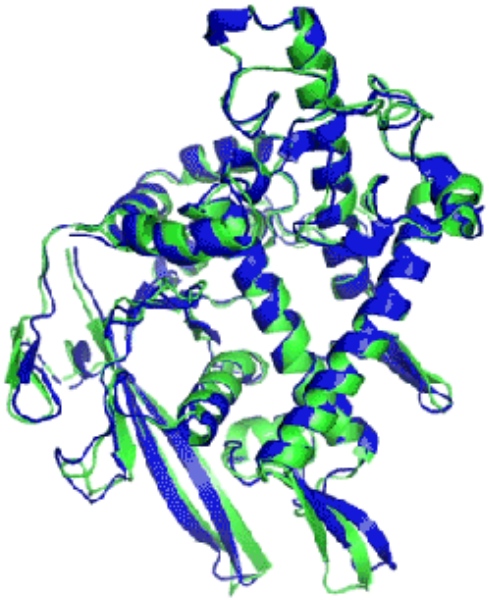
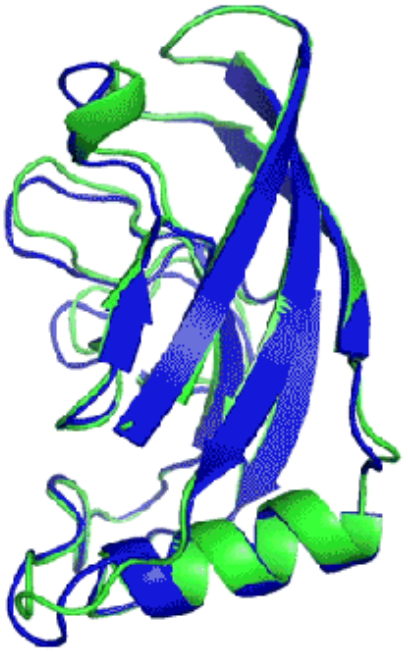




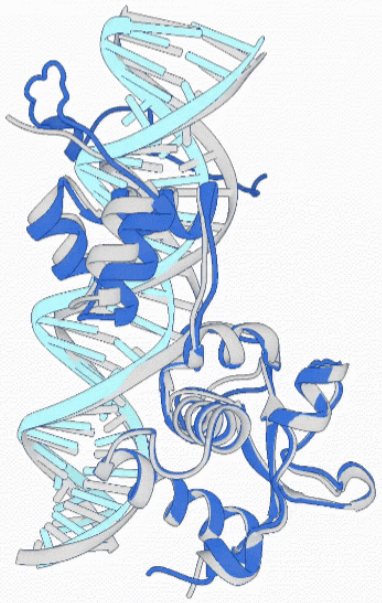
T1037 / 6vr4
90.7 GDT
(RNA polymerase domain)



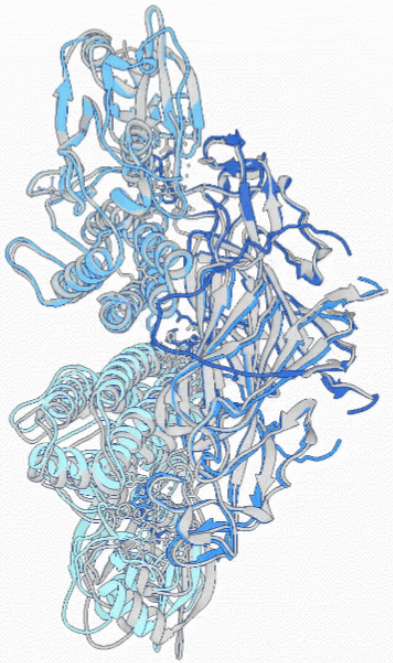
T1049 / 6y4f
93.3 GDT
(adhesin tip)

Experimental result

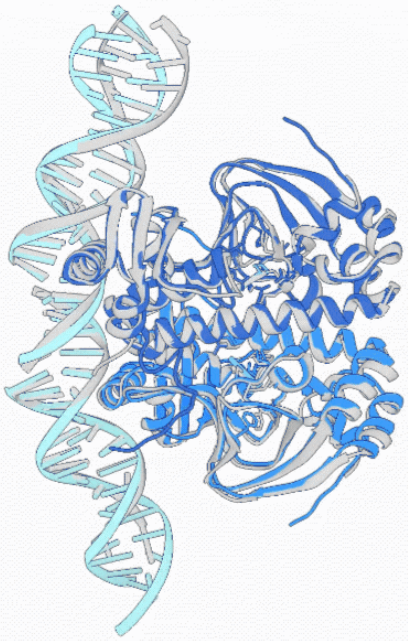
Computational prediction



PDB ID: 7r6r
(mycobacteriophage immunity repressor-DNA complex)

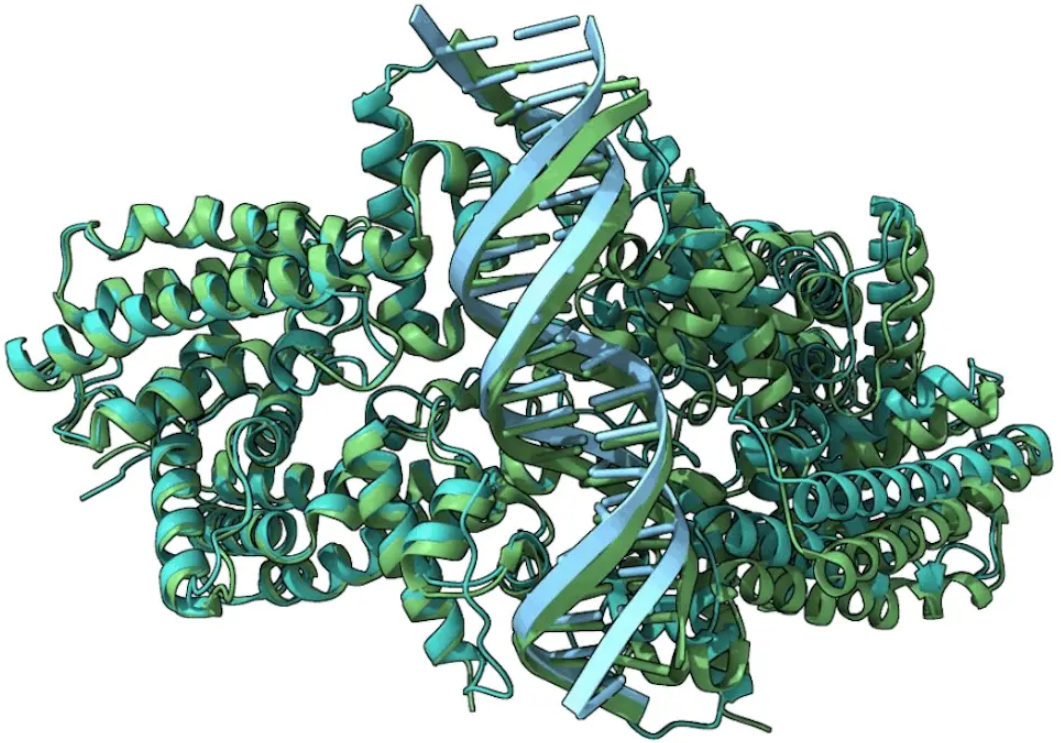


PDB ID: 7wux
(AziU3/U2 complexed with (5S,6S)-O7-sulfo DADH)

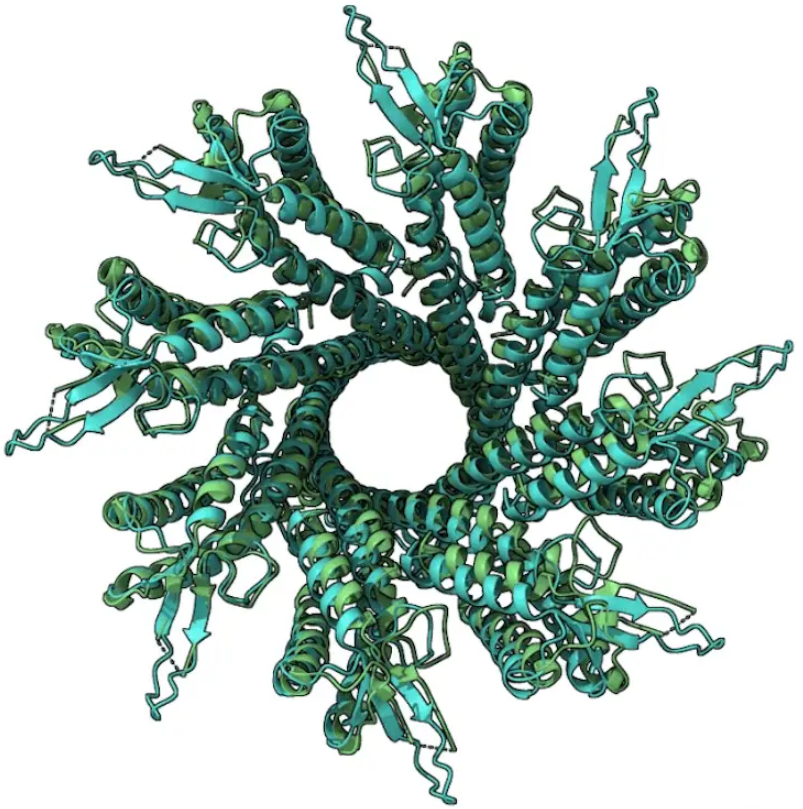


PDB ID: 7pzb
(Clr-cAMP-DNA complex)

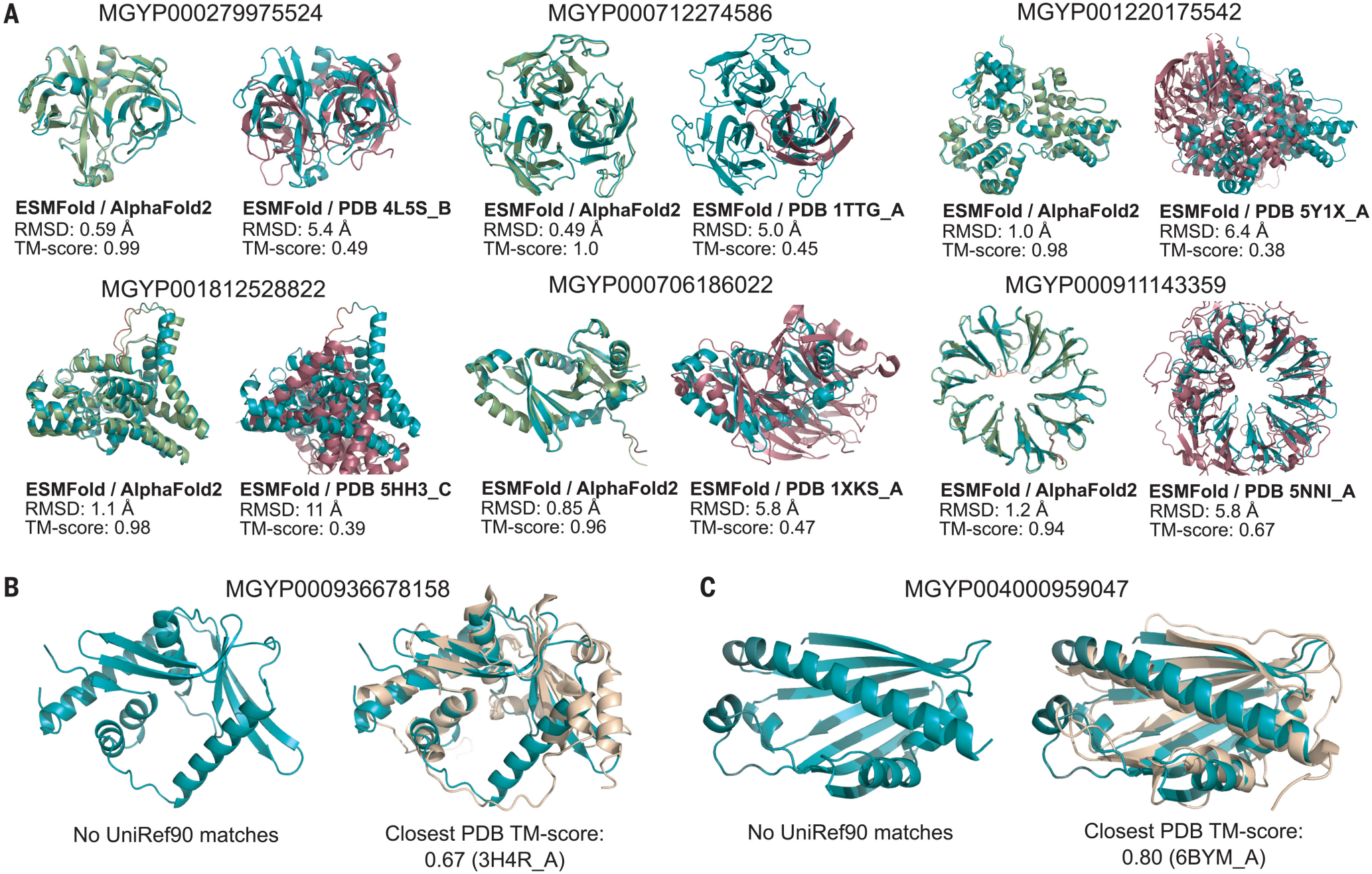
Protenix prediction **Experimental result**



BOLTZ-1 prediction on PDB structure 8SVA
TM-score: 0.95



BOLTZ-1 prediction on PDB structure 8IG1
TM-score: 0.95


A
MGYP000279975524
ESMFold / AlphaFold2
RMSD: 0.59 Å
TM-score: 0.99
ESMFold / PDB 4L5S_B
RMSD: 5.4 Å
TM-score: 0.49
MGYP000712274586
ESMFold / AlphaFold2
RMSD: 0.49 Å
TM-score: 1.0
ESMFold / PDB 1TTG_A
RMSD: 5.0 Å
TM-score: 0.45
MGYP001220175542
ESMFold / AlphaFold2
RMSD: 1.0 Å
TM-score: 0.98
ESMFold / PDB 5Y1X_A
RMSD: 6.4 Å
TM-score: 0.38
MGYP001812528822
ESMFold / AlphaFold2
RMSD: 1.1 Å
TM-score: 0.98
ESMFold / PDB 5HH3_C
RMSD: 11 Å
TM-score: 0.39
MGYP000706186022
ESMFold / AlphaFold2
RMSD: 0.85 Å
TM-score: 0.96
ESMFold / PDB 1XKS_A
RMSD: 5.8 Å
TM-score: 0.47
MGYP000911143359
ESMFold / AlphaFold2
RMSD: 1.2 Å
TM-score: 0.94
ESMFold / PDB 5NNI_A
RMSD: 5.8 Å
TM-score: 0.67
B
MGYP000936678158
No UniRef90 matches
Closest PDB TM-score:
0.67 (3H4R_A)
C
MGYP004000959047
No UniRef90 matches
Closest PDB TM-score:
0.80 (6BYM_A)

nature

Article | Published: 08 May 2024

Accurate structure prediction of biomolecular interactions with AlphaFold 3

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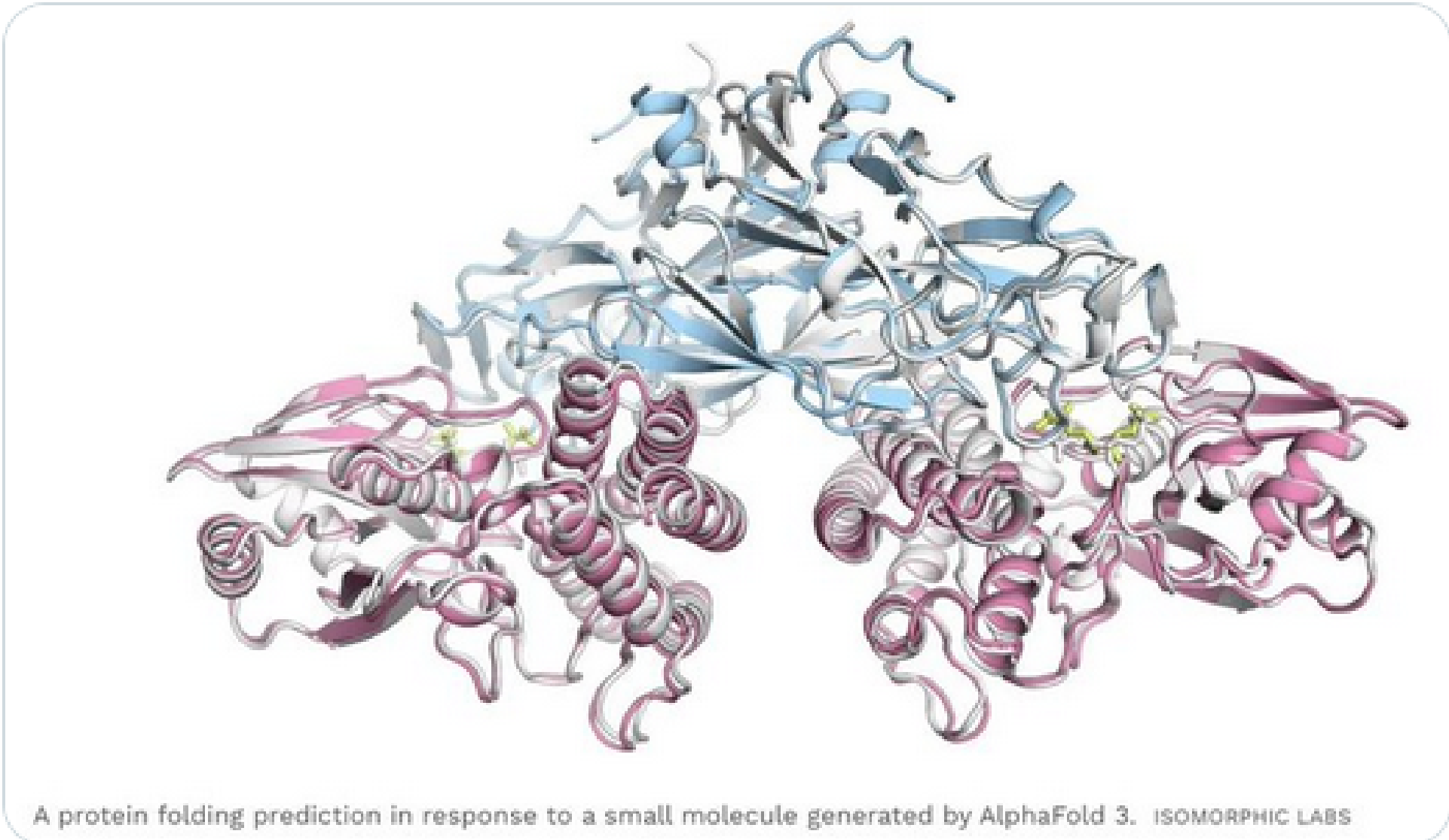
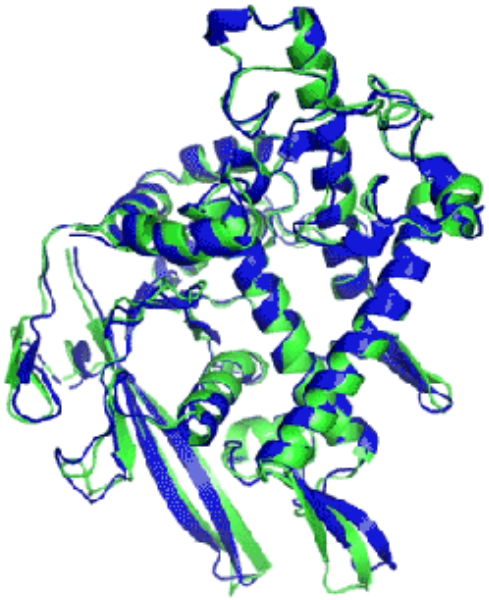
Unlike AF2, which focused on individual proteins, **AF3** embraces complexity of biomolecular interactions. It models diverse entities within a unified framework, highlighting interactions that are crucial for understanding cellular functions, moving toward realistic simulations.



A protein folding prediction in response to a small molecule generated by AlphaFold 3. ISOMORPHIC LABS



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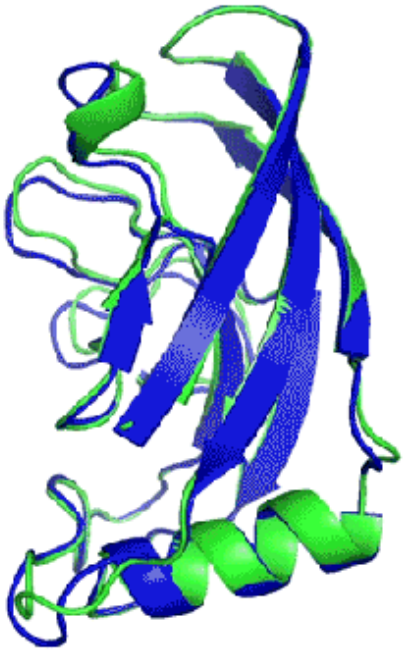

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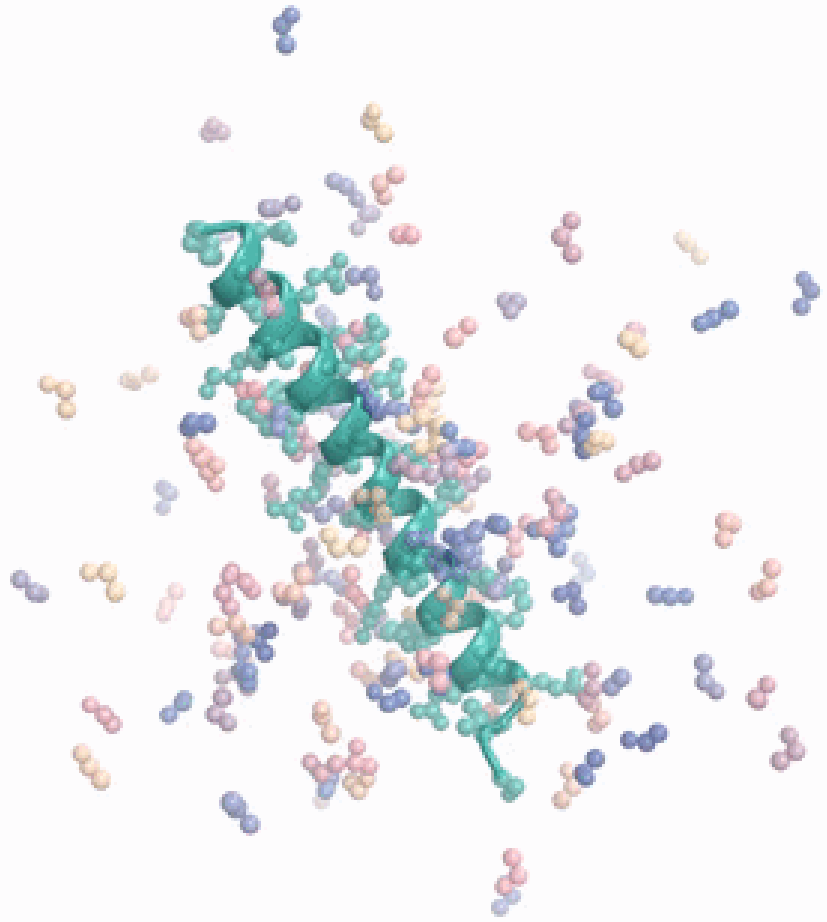


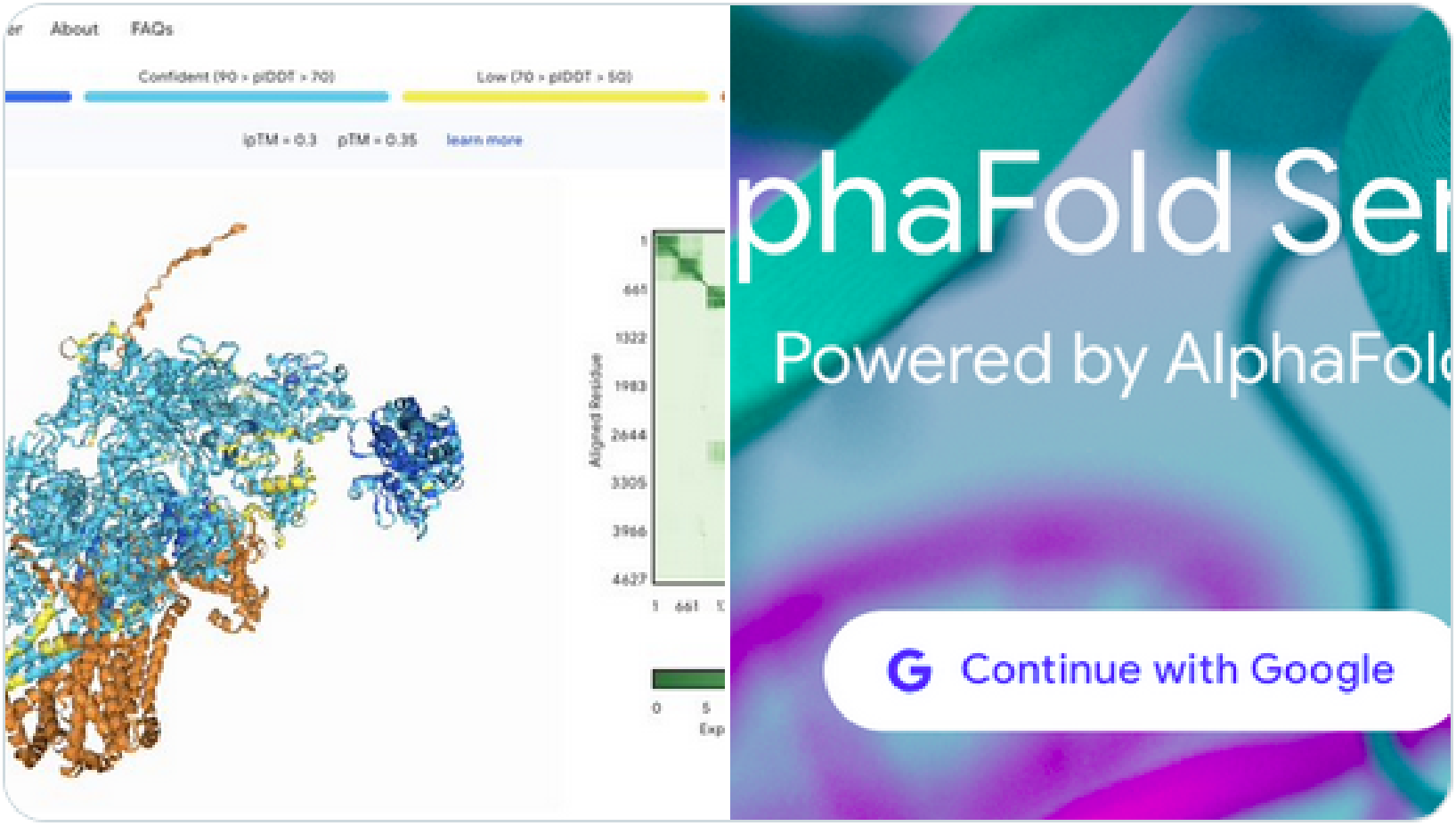
https://alphafoldserver.com

ADP

Sergey Ovchinnikov @sokrypton · 16 g.

AF3 server is LIVE! Just tried predicting complex with almost 5K amino acids.

TIP: you need to click "continue with google" to access the server (otherwise the "server" is grayed out). alphafoldserver.com



7 77 324 23 tys.

https://alphafoldserver.com

Use of AlphaFold Server is subject to the Google Terms of Service; and AlphaFold Server Additional Terms of Service

Key things to know

1. AlphaFold Server is **only** available for non-commercial use by individuals and non-commercial organizations (universities, non-profit organizations and research institutes, educational and government bodies), or for journalism.
2. You **must not** use AlphaFold Server or its outputs:
    a. in connection with **any commercial activities, including research on behalf of commercial organizations;**
    b. in **any automated system that predicts the binding or interaction of the protein with ligands or peptides**, such as Glide or AutoDock; or
    c. to **train machine learning models** or related technology for **biomolecular structure prediction** similar to AlphaFold Server.
3. You **can publish, share and adapt** AlphaFold Server output in accordance with our terms, including the requirement to provide clear notice that ongoing use is subject to AlphaFold Server Output Terms of Use and of any modifications you make.

Ajasja @AjasjaLjubetic · 18 g.

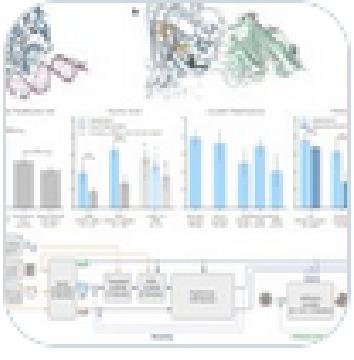
This is super exciting! Although it's a bit sad to see that the source code and weights are not available, even for academic use.

Time will tell if **AF3** will be as widely used and universal as AF2 currently is. Can't wait for this year's CASP :)

Code availability

AlphaFold 3 will be available as a non-commercial usage only server at https://www.alphafoldserver.com, with restrictions on allowed ligands and covalent modifications. Pseudocode describing the algorithms is available in the Supplementary Information. Code is not provided.

Max Jaderberg @maxjaderberg · 19 g.

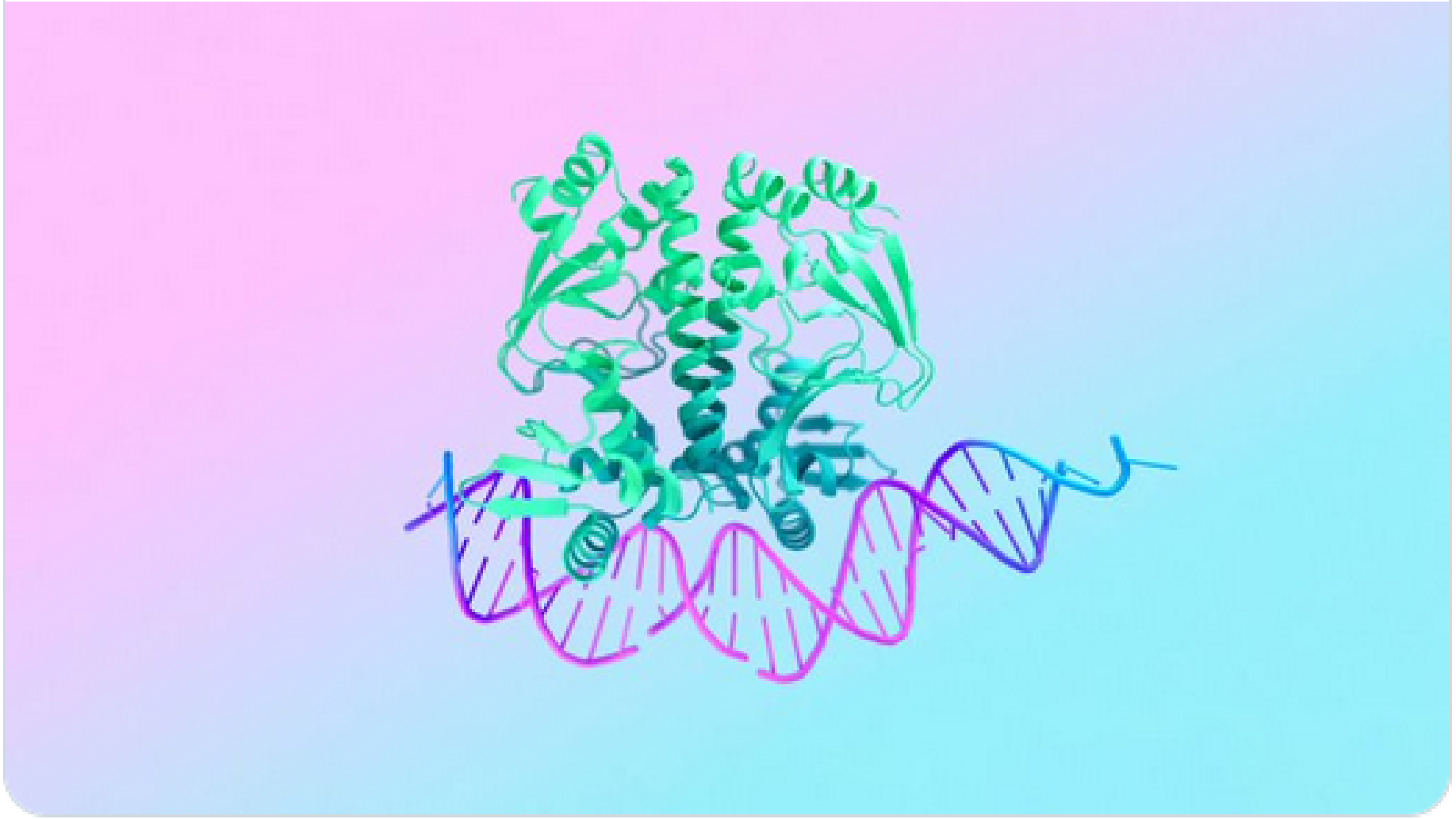


Super excited to be releasing AlphaFold 3 today, developed by @IsomorphicLabs and @GoogleDeepMind: our next generation AI model for predicting the biomolecular structures and interactions of proteins, DNA, RNA, small molecules, and more: bit.ly/44yfaCw...

13 1 tys.

Demis Hassabis @demishassabis · 18 g.

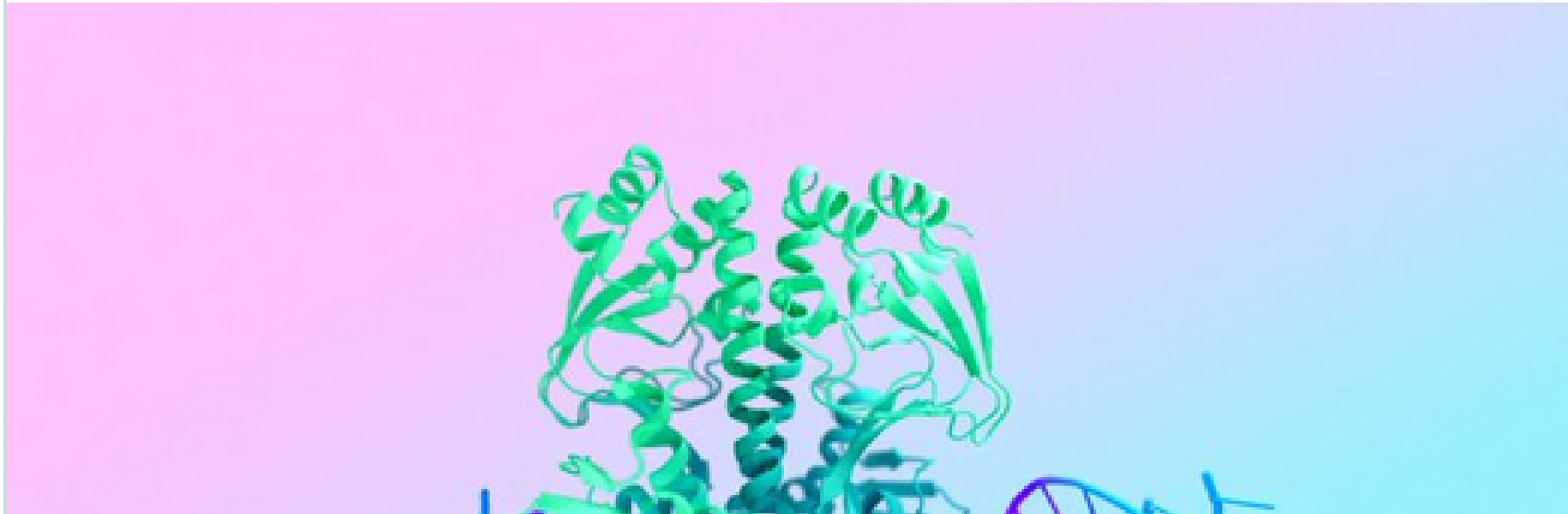
Thrilled to announce AlphaFold 3 which can predict the structures and interactions of nearly all of life's molecules with state-of-the-art accuracy including proteins, DNA and RNA. Biology is a complex dynamical system so modeling interactions is crucial blog.google/technology/ai/...



21 312 1 tys. 371 tys.

Roland Dunbrack 🏳️‍🌈 **@rolanddunbrack.bsky.socia** @RolandDunbrack · 16 g. ⋯

Demis -- I think AlphaFold3 is really exciting. As Reviewer #3, I got great results from the server. I tried hard to get @Nature to urge you to release the code but was unsuccessful. I did not get it for re-review so I don't know if you responded. So why no code? @GoogleDeepMind

>  **Demis Hassabis** ✓ @demishassabis · 18 g.
>
> Thrilled to announce AlphaFold 3 which can predict the structures and interactions of nearly all of life's molecules with state-of-the-art accuracy including proteins, DNA and RNA. Biology is a complex dynamical system so modeling interactions is crucial blog.google/technology/ai/...
>
> 

Roland Dunbrack 🏳️‍🌈 **@rolanddunbrack.bsky.socia** @RolandDunbrack · 4 g. ···

Neither @Magda_Skipper (editor of @Nature) nor the handling editor would answer my emails about my concerns. I was not allowed to see any response to the reviews by the AlphaFold3 authors, so I don't know what they think either. Extremely unusual and very disappointing

>  **Stephen Curry** @Stephen_Curry · 5 g.
>
> I'd be interested to hear @Nature's and @GoogleDeepMind's responses to this. x.com/rolanddunbrack...

12 79 7 tys.

Roland Dunbrack 🏳️‍🌈 **@rolanddunbrack.bsky.socia** @RolandDunbrack · 4 g. ···

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>
> I'd be interested to hear @Nature's and @GoogleDeepMind's responses to this. x.com/rolanddunbrack...

Altuna Akalin @AltunaAkalin · 1 g. ···

Reviewer asked @Nature and authors to release **alphafold3** code with no success. Dangerous trend for journals acting as marketing avenues for new tech without reproducibility or code review

>  **Roland Dunbrack** 🏳️‍🌈 **@rolanddunbrack.bsky.so** @RolandDunbrac · 17 g.
>
> Demis -- I think AlphaFold3 is really exciting. As Reviewer #3, I got great results from the server. I tried hard to get @Nature to urge you to release the code but was unsuccessful. I did not get it for re-review so I don't know if you responded. So why no code? @GoogleDeepMind x.com/demishassabis/...

Pratyush Tiwary
@tiwarylab

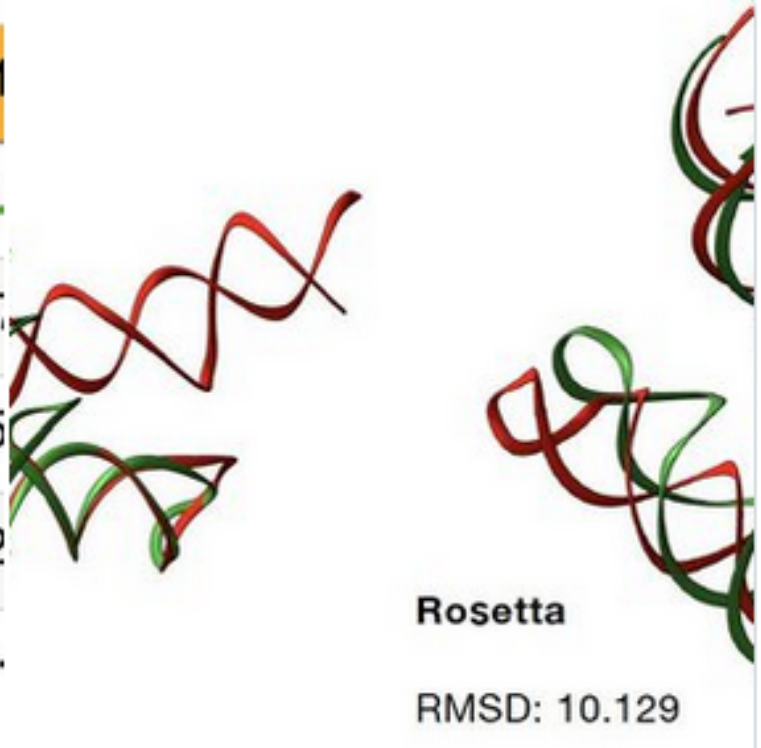
It seems rather convenient that two of the structures* left out in the @Nature paper for AlphaFold3 on RNA by @GoogleDeepMind are ones where it does not well (multiple trials on web server)

* R1149 and R1156 predictioncenter.org/casp15/results...

Przetłumacz wpis

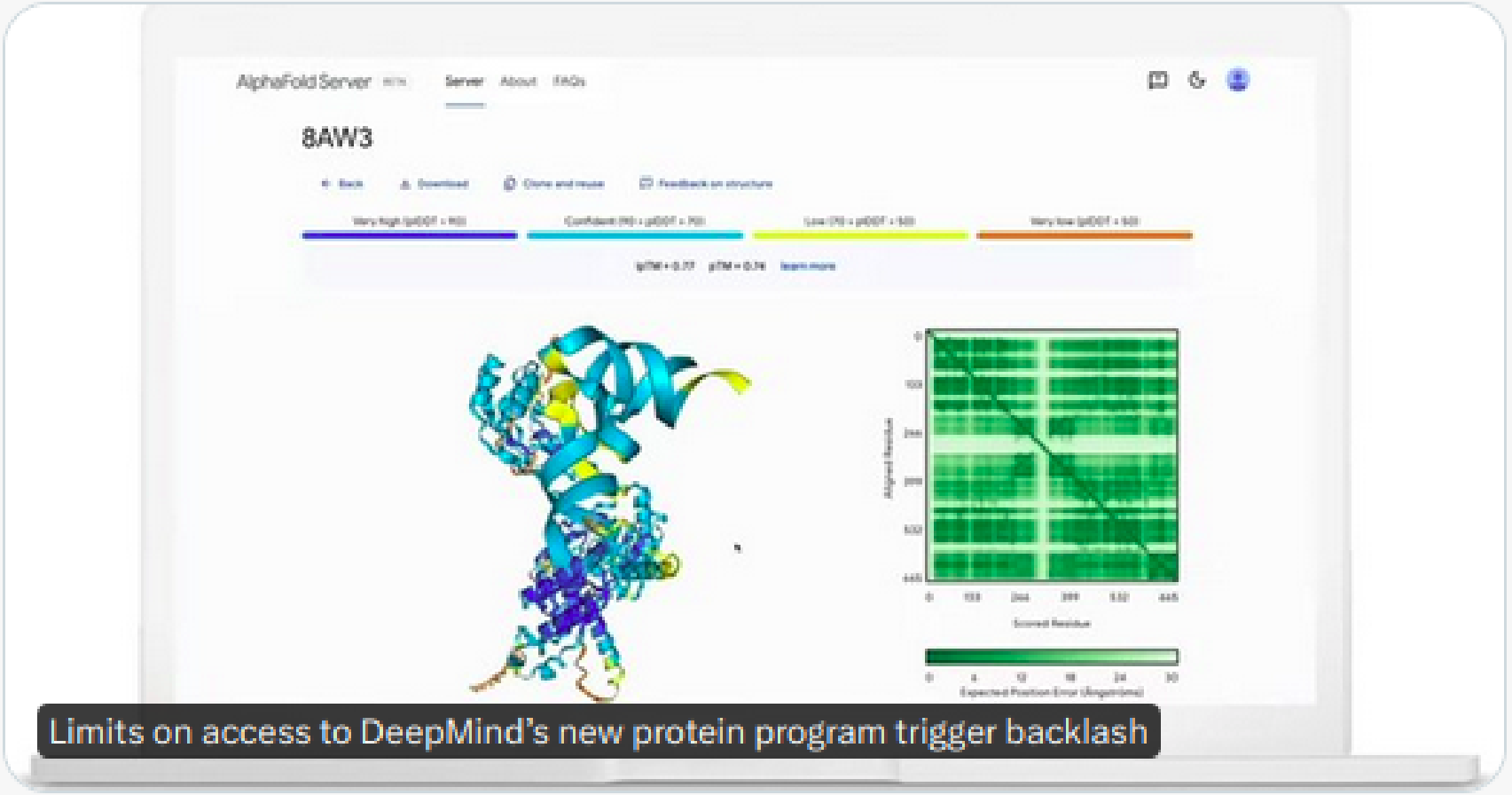
R1107*	R1117	R111
6.513	2.645	15.
9.762	5.102	1
-	0.2225	0.5
-	0.1351	0.2

er form and bound to a protein.



Roland Dunbrack 🏳️‍🌈 **@rolanddunbrack.bsky.socia** @RolandDunbrack · 19 g. •••

Got interviewed for this article in Science on the release of alphafoldserver.com.



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Limits on access to DeepMind's new protein program trigger backlash

Critics accuse *Nature*, which published the research, of failing to meet its own transparency standards

Limits on access to DeepMind's new protein program trigger backlash

Critics accuse *Nature*, which published the research, of failing to meet its own transparency standards

AlphaFold 3's code wasn't available during the review process for the *Nature* paper, either. Roland Dunbrack, a computational structural biologist at the Fox Chase Cancer Center and letter co-author, says he received the manuscript without any way to test the program. After contacting the journal, he got access to an early version of the web server, but repeated requests for code in the leadup to publication went unanswered, he says. "I don't understand why [*Nature*'s editors] sent it out for review under those conditions."

The paper doesn't provide a justification, simply noting, "Code is not provided"—an omission that appears to "flagrantly violate" *Nature*'s policies, says James Fraser, a structural biologist at the University of California San Francisco (UCSF) and one of the letter's organizers. *Nature*'s submission guidelines state that custom code supporting a paper's main claims must be made available to referees upon request, and its editorial policies specify that "authors are required to make [code] promptly available to readers without undue qualifications."

Limits on access to DeepMind's new protein program trigger backlash

Critics accuse *Nature*, which published the research, of failing to meet its own transparency standards

Regardless, since the open letter was posted, DeepMind researchers have indicated that more information on AlphaFold 3 is on the way. A DeepMind media representative pointed *Science* to a 13 May social media post in which Kohli, another co-author, announced the increase in the web server's daily request limit to 20. The team is also "working on releasing the AF3 model" for academic use within 6 months, Kohli wrote, a move welcomed by researchers who spoke to *Science*.

Stephanie Wankowicz, a computational structural biologist at UCSF and another of the letter's organizers, says she hopes the episode will encourage the computational biology community to set concrete standards for research communication, particularly given the increasing influence of for-profit companies in this field.

It's also an opportunity for journals to reflect on their role in upholding scientific standards, Fraser says. If they apply standards selectively, "it's like they're the traffic cops that are letting some people speed and pulling other people over for rolling through a stop sign. And that's not fair."

Article

Accurate structure prediction of biomolecular interactions with AlphaFold 3

https://doi.org/10.1038/s41586-024-07487-w

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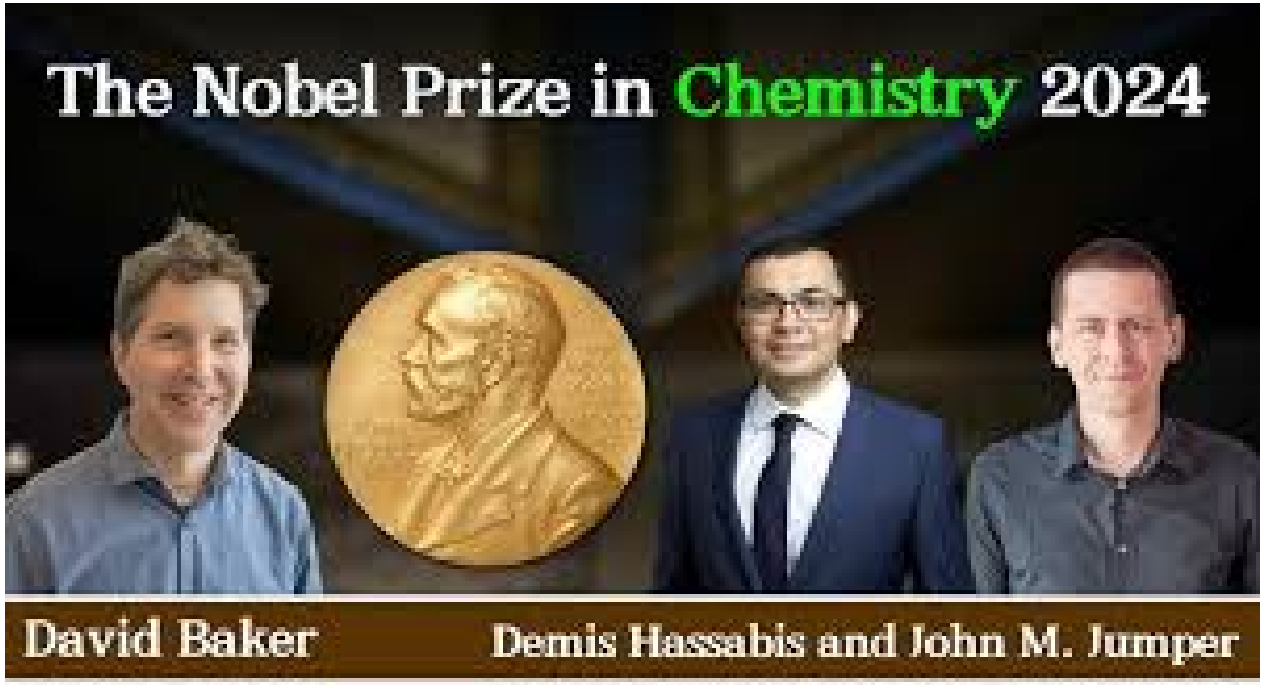
Open access

Check for updates

Josh Abramson[1,7], Jonas Adler[1,7], Jack Dunger[1,7], Richard Evans[1,7], Tim Green[1,7], Alexander Pritzel[1,7], Olaf Ronneberger[1,7], Lindsay Willmore[1,7], Andrew J. Ballard[1], Joshua Bambrick[2], Sebastian W. Bodenstein[1], David A. Evans[1], Chia-Chun Hung[2], Michael O'Neill[1], David Reiman[1], Kathryn Tunyasuvunakool[1], Zachary Wu[1], Akvilė Žemgulytė[1], Eirini Arvaniti[3], Charles Beattie[3], Ottavia Bertolli[3], Alex Bridgland[3], Alexey Cherepanov[4], Miles Congreve[4], Alexander I. Cowen-Rivers[3], Andrew Cowie[3], Michael Figurnov[3], Fabian B. Fuchs[3], Hannah Gladman[3], Rishub Jain[3], Yousuf A. Khan[3,5], Caroline M. R. Low[4], Kuba Perlin[3], Anna Potapenko[3], Pascal Savy[4], Sukhdeep Singh[3], Adrian Stecula[4], Ashok Thillaisundaram[3], Catherine Tong[4], Sergei Yakneen[4], Ellen D. Zhong[3,6], Michal Zielinski[3], Augustin Žídek[3], Victor Bapst[1,8], Pushmeet Kohli[1,8], Max Jaderberg[2,8]✉, Demis Hassabis[1,2,8]✉ & John M. Jumper[1,8]✉



David Konerding • 3rd+
Principal Engineer at Genentech
1d •

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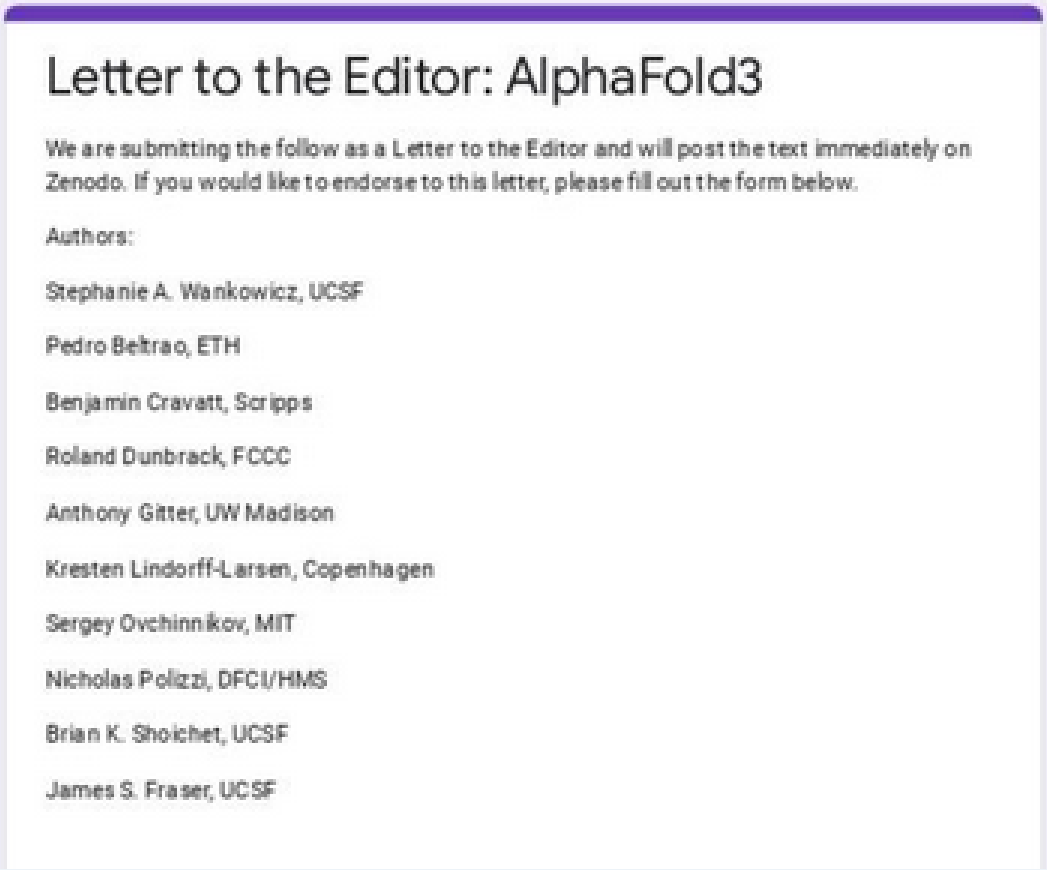
There is a minor controversy over AlphaFold3, DeepMind's latest protein structure prediction model: the paper was published in Nature with insufficient supplementary info to reproduce the results. Even the reviewer was …see more



Letter to the Editor: AlphaFold3

We are submitting the follow as a Letter to the Editor and will post the text immediately on Zenodo. If you would like to endorse to this letter, please fill out the form below.

Authors:

Stephanie A. Wankowicz, UCSF

Pedro Beltrao, ETH

Benjamin Cravatt, Scripps

Roland Dunbrack, FCCC

Anthony Gitter, UW Madison

Kresten Lindorff-Larsen, Copenhagen

Sergey Ovchinnikov, MIT

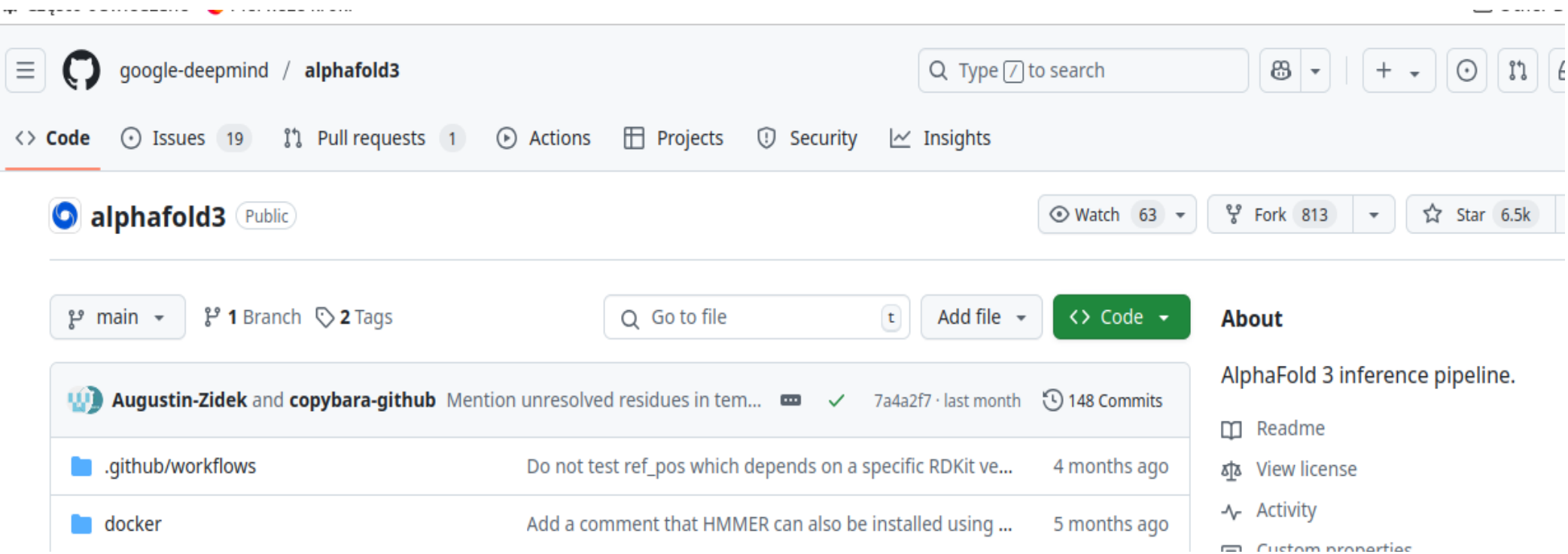
Nicholas Polizzi, DFCI/HMS

Brian K. Shoichet, UCSF

James S. Fraser, UCSF

Letter to the Editor: AlphaFold3

https://github.com/google-deepmind/alphafold3



Obtaining Model Parameters

This repository contains all necessary code for AlphaFold 3 inference. To request access to the AlphaFold 3 model parameters, please complete this form. Access will be granted at Google DeepMind's sole discretion. We will aim to respond to requests within 2–3 business days. You may only use AlphaFold 3 model parameters if received directly from Google. Use is subject to these terms of use.

https://github.com/google-deepmind/alphafold3

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Key things to know when using the AlphaFold 3 model parameters and output

1. The AlphaFold 3 model parameters and output are **only** available for non-commercial use by, or on behalf of, non-commercial organizations (*i.e.*, universities, non-profit organizations and research institutes, educational, journalism and government bodies). If you are a researcher affiliated with a non-commercial organization, provided **you are not a commercial organisation or acting on behalf of a commercial organisation,** this means you can use these for your non-commercial affiliated research.
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   ii. AlphaFold 3 output to **train machine learning models** or related technology for **biomolecular structure prediction** similar to AlphaFold 3.
3. You ***must not*** **publish or share AlphaFold 3 model parameters**, except sharing these within your organization in accordance with these Terms.
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Article | Published: 08 May 2024

Accurate structure prediction of biomolecular interactions with AlphaFold 3

Josh Abramson, Jonas Adler, Jack Dunger, Richard Evans, Tim Green, Alexander Pritzel, Olaf Ronneberger, Lindsay Willmore, Andrew J. Ballard, Joshua Bambrick, Sebastian W. Bodenstein, David A. Evans, Chia-Chun Hung, Michael O'Neill, David Reiman, Kathryn Tunyasuvunakool, Zachary Wu, Akvilė Žemgulytė, Eirini Arvaniti, Charles Beattie, Ottavia Bertolli, Alex Bridgland, Alexey Cherepanov, Miles Congreve, … John M. Jumper ✉ + Show authors

Nature (2024) | Cite this article

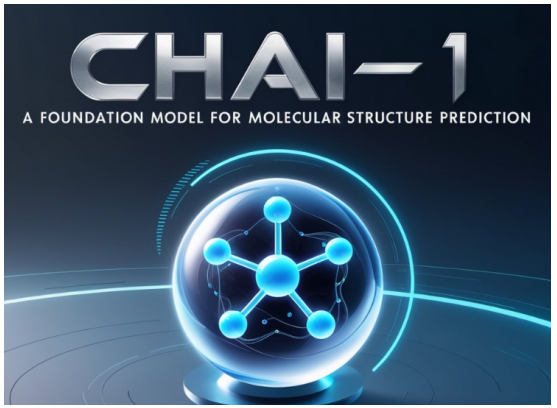
[HERE PAPER]


AlphaFold


AlphaFold


ESM3

HelixFold3



ANKH

AlphaFold

RoseTTAFold

ESM3

Fold proteins with Boltz-1

HeliXonProtein/
OmegaFold

Protenix: Protein + X

README Apache-2.0 license

Chai-1

Chai-1 is a multi-modal foundation model for molecular structure p
art across a variety of benchmarks. Chai-1 enables unified predictic
glycosylations, and more.

jwohlwend / boltz

Code Issues 97 Pull requests 16 Actions Projects

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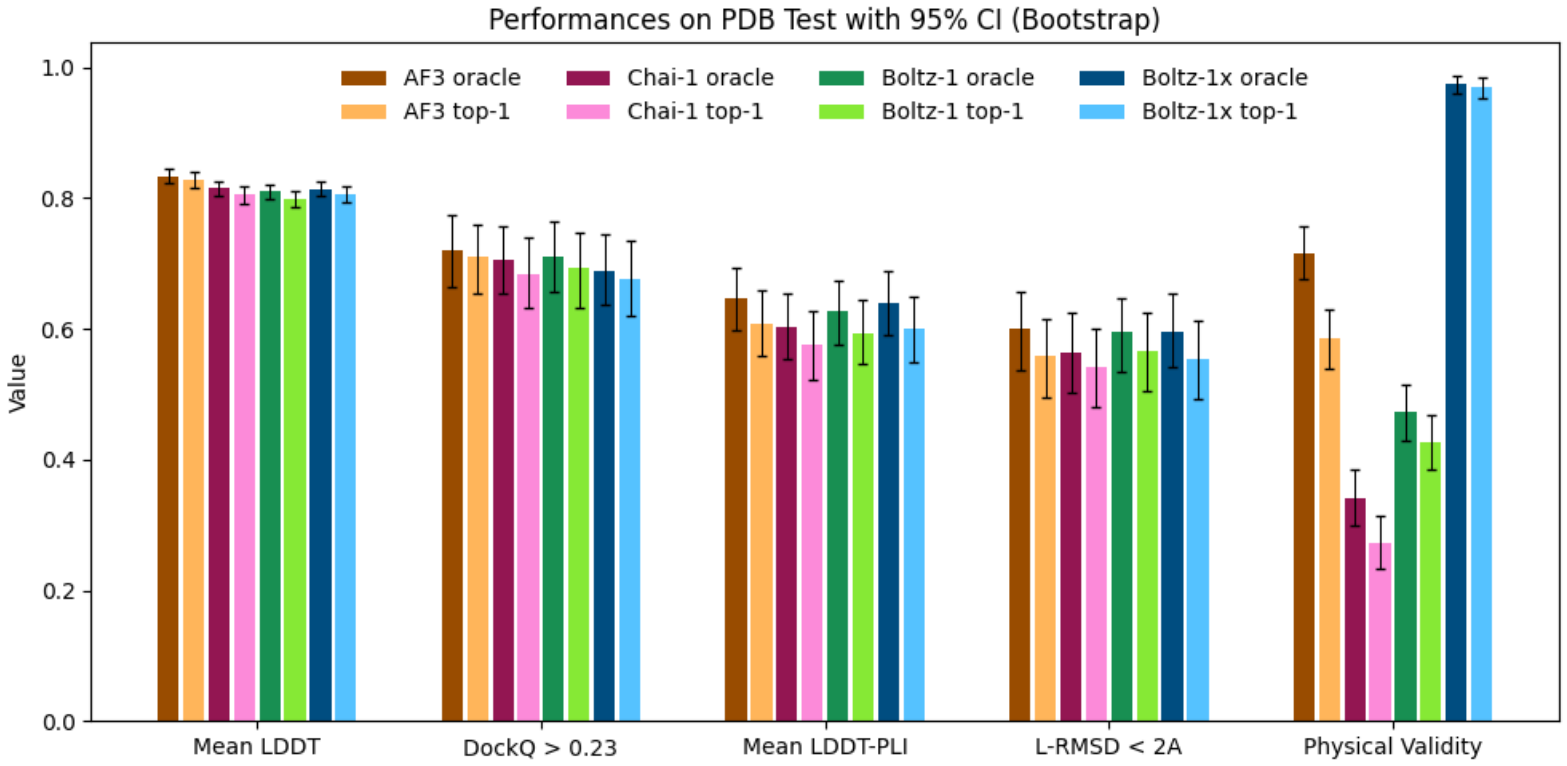

nature biotechnology

Article

https://doi.org/10.1038/s41587-025-02654-4

Deep-learning-based single-domain and multidomain protein structure prediction with D-I-TASSER

Received: 13 April 2024

Accepted: 26 March 2025

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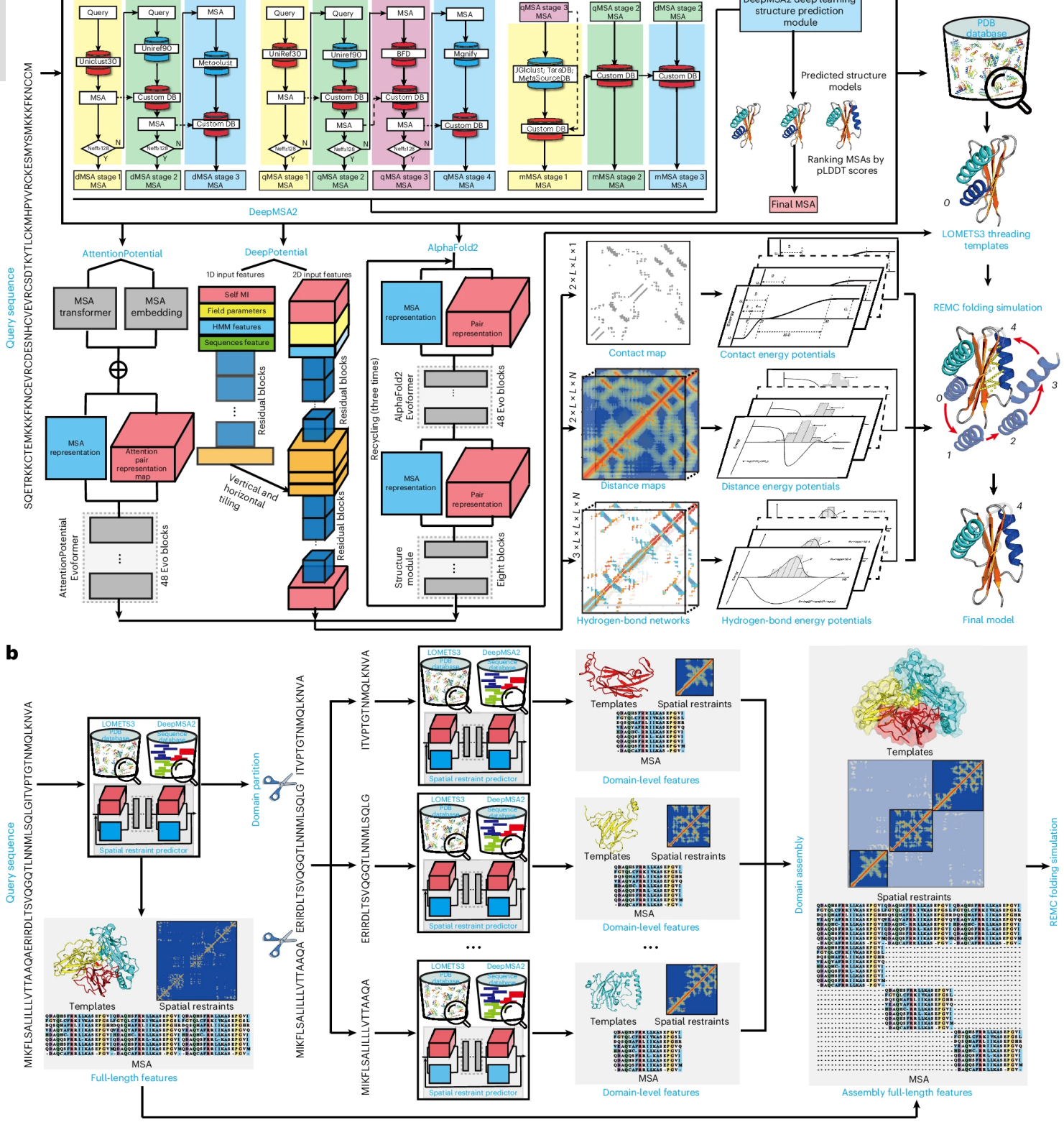
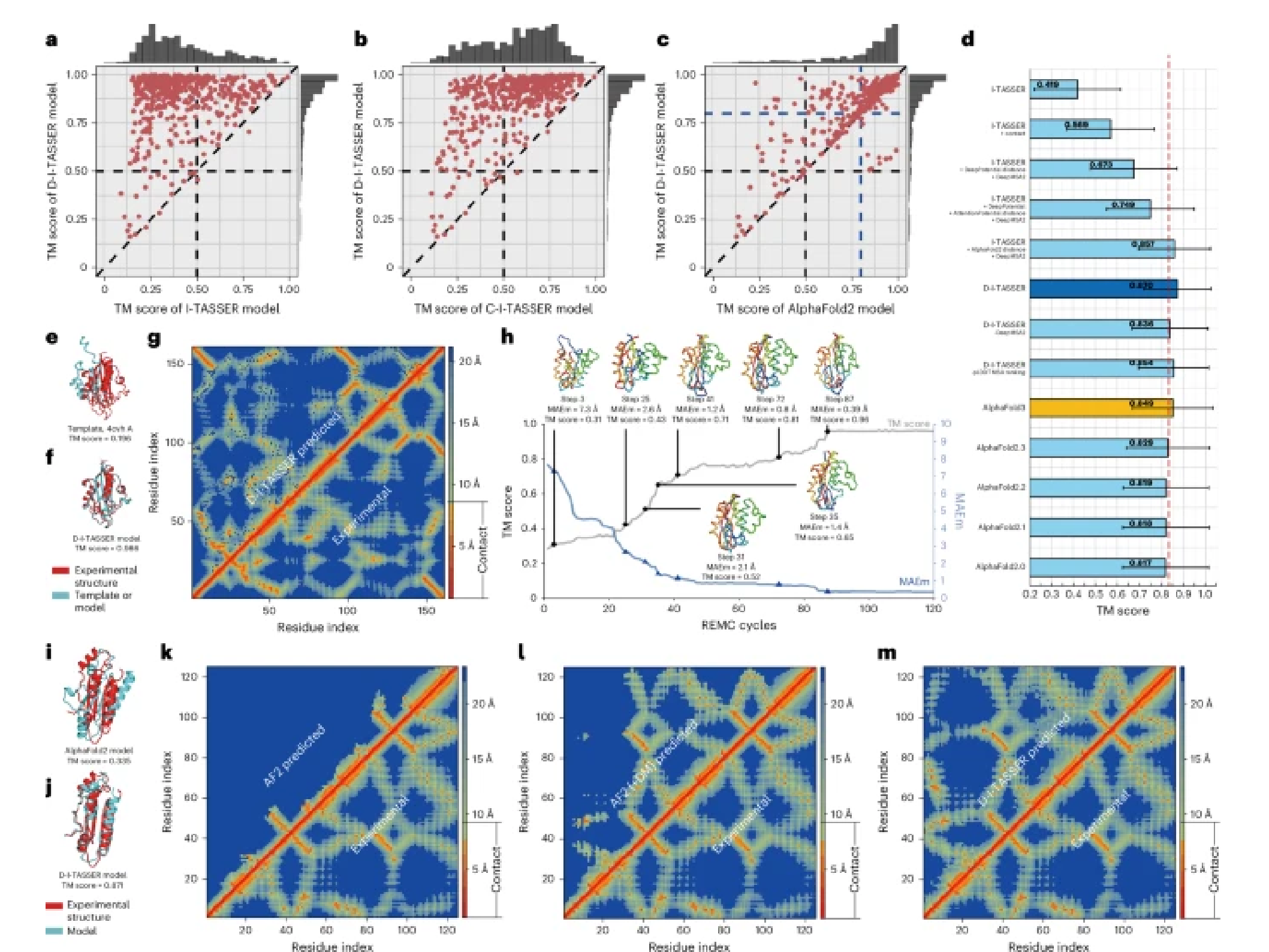
Check for updates

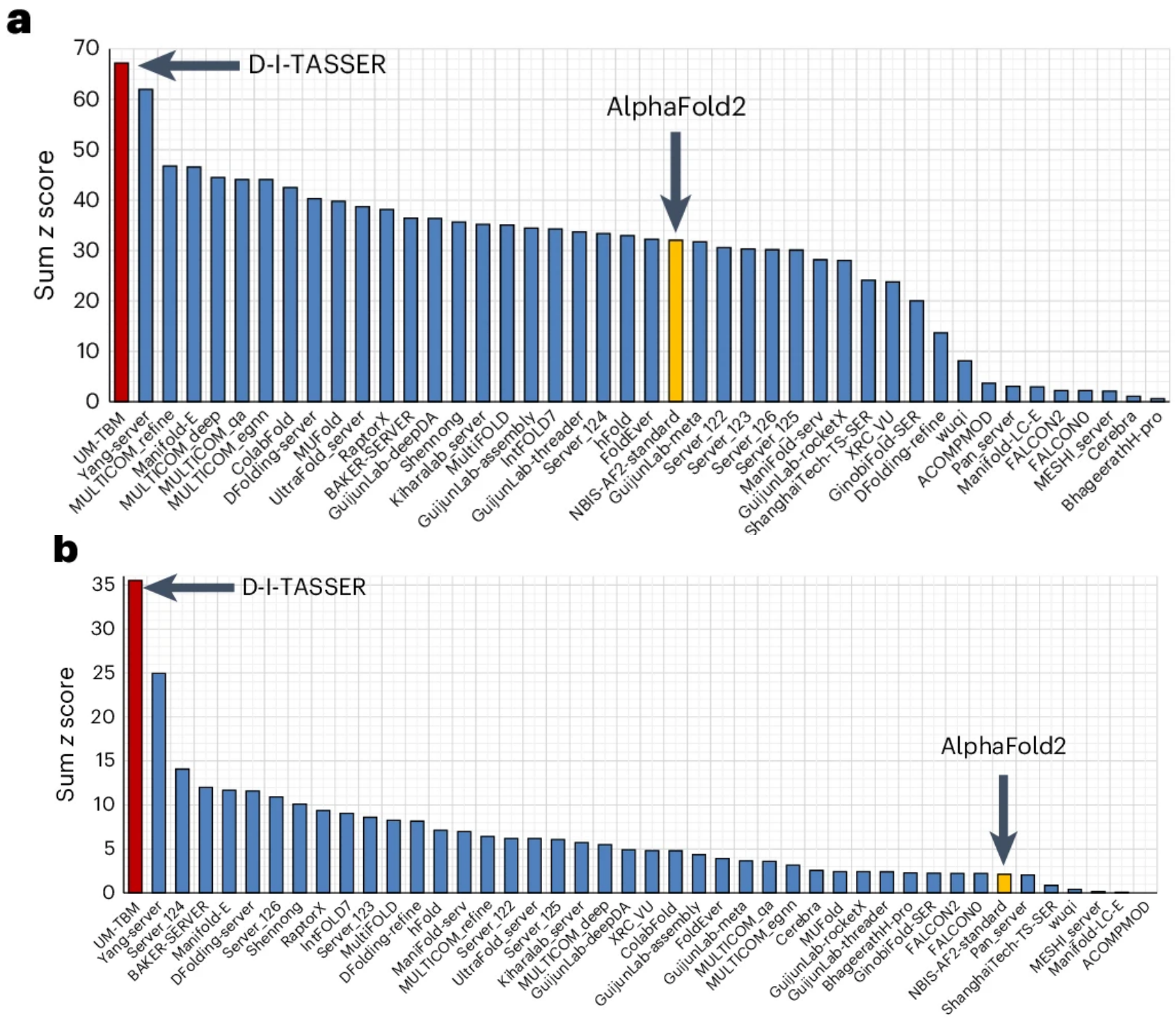
Wei Zheng[1,2,8], Qiqige Wuyun[3,8], Yang Li[4,8], Quancheng Liu[2], Xiaogen Zhou[2], Chunxiang Peng[2,5], Yiheng Zhu[2], Lydia Freddolino[2,5] & Yang Zhang[4,6,7]

The dominant success of deep learning techniques on protein structure prediction has challenged the necessity and usefulness of traditional force field-based folding simulations. We proposed a hybrid approach, deep-learning-based iterative threading assembly refinement (D-I-TASSER),


Query sequence
SQETRKKCTEMKKKFKNCEVRCDESNHCVEVRCSDTKYTLCKMHPYVRCKESMYSMKKKFKNCCM
DeepMSA2
AttentionPotential
DeepPotential
AlphaFold2
MSA transformer
MSA embedding
MSA representation
Attention pair representation map
AttentionPotential Evoformer
48 Evo blocks
1D input features
2D input features
Self MI
Field parameters
HMM features
Sequences feature
Residual blocks
Vertical and horizontal tiling
Recycling (three times)
AlphaFold2 Evoformer
48 Evo blocks
Pair representation
Structure module
Eight blocks
DeepMSA2 deep learning structure prediction module
Predicted structure models
Ranking MSAs by pLDDT scores
Final MSA
PDB database
LOMETS3 threading templates
REMC folding simulation
Final model
Contact map
Contact energy potentials
Distance maps
Distance energy potentials
Hydrogen-bond networks
Hydrogen-bond energy potentials

b
Query sequence
MIKFLSALILLLVTTAAQAERIRDLTSVQGQTLNNMLSQLGITVPTGTNMQLKNVA
Domain partition
ITVPTGTNMQLKNVA
ERIRDLTSVQGQTLNNMLSQLG
MIKFLSALILLLVTTAAQA
LOMETS3
DeepMSA2
Spatial restraint predictor
Templates
Spatial restraints
MSA
Full-length features
Domain-level features
Domain assembly
Assembly full-length features
REMC folding simulation


a
b
c
d
TM score of D-I-TASSER model
TM score of I-TASSER model
TM score of C-I-TASSER model
TM score of AlphaFold2 model
I-TASSER
D-I-TASSER
AlphaFold3
AlphaFold3.3
AlphaFold3.2
AlphaFold3.1
AlphaFold2.0
TM score
e
Template, 4cvh A
TM score = 0.795
f
D-I-TASSER model
TM score = 0.988
Experimental structure
Template or model
g
D-I-TASSER predicted
Experimental
Residue index
20 Å
15 Å
10 Å
5 Å
Contact
h
Step 3
MAEm = 7.3 Å
TM score = 0.31
Step 25
MAEm = 2.6 Å
TM score = 0.43
Step 61
MAEm = 1.2 Å
TM score = 0.71
Step 72
MAEm = 0.8 Å
TM score = 0.81
Step 87
MAEm = 0.39 Å
TM score = 0.98
Step 35
MAEm = 1.4 Å
TM score = 0.65
Step 31
MAEm = 2.1 Å
TM score = 0.52
TM score
MAEm
REMC cycles
i
AlphaFold2 model
TM score = 0.305
j
D-I-TASSER model
TM score = 0.871
Experimental structure
Model
k
AF2 predicted
Experimental
l
AF2-I-DM3 predicted
Experimental
m
D-I-TASSER predicted
Experimental



‘regular modeling’ (a) and ‘interdomain modeling’ (b)

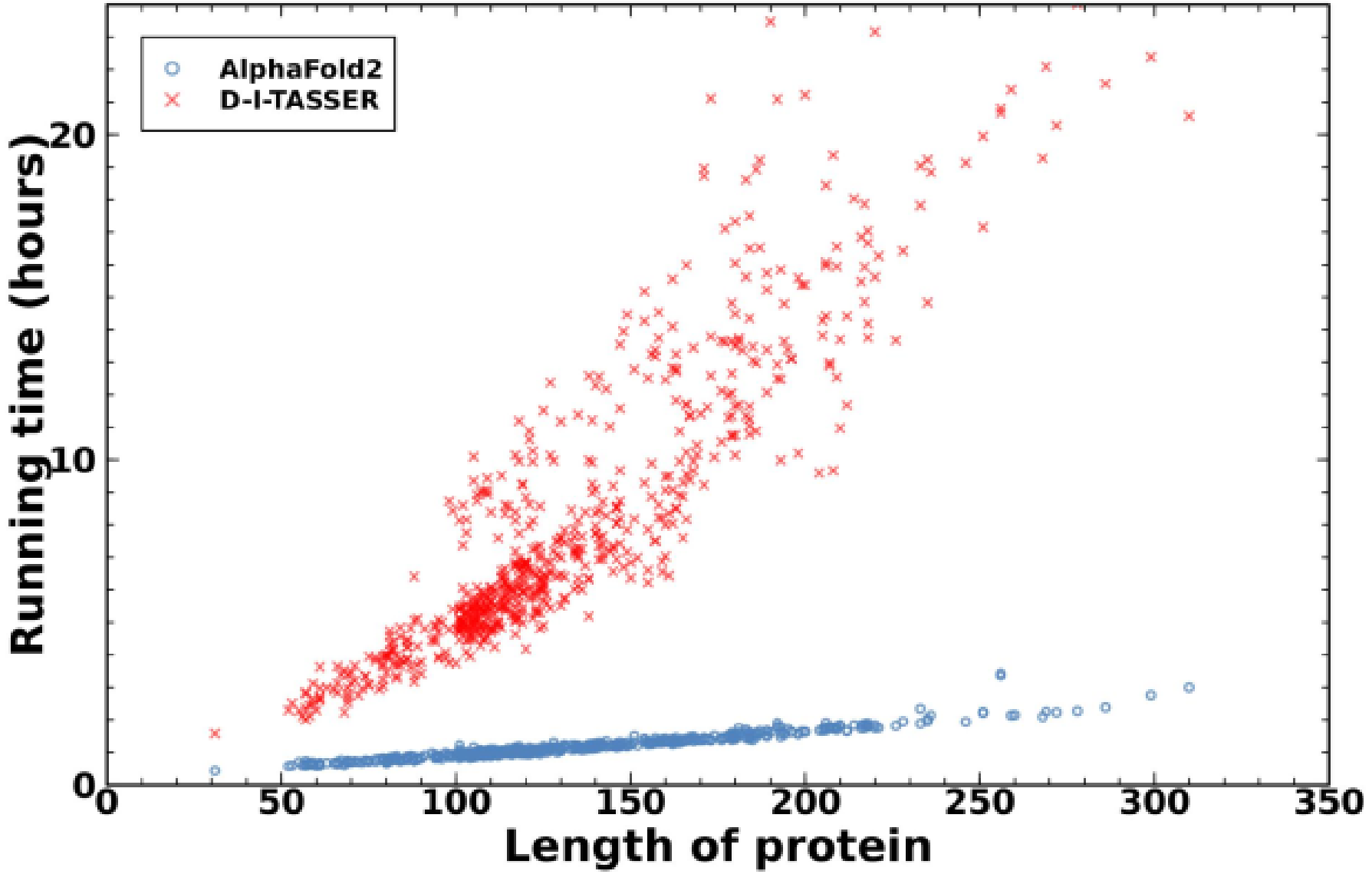
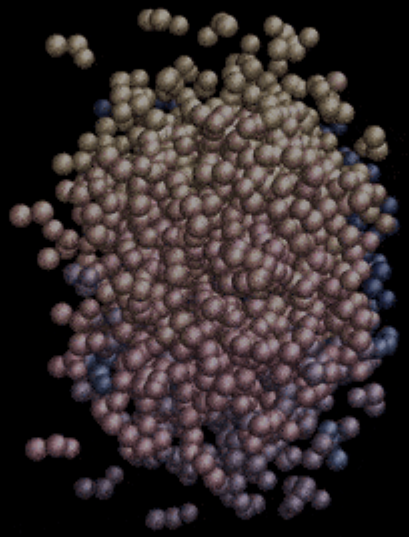
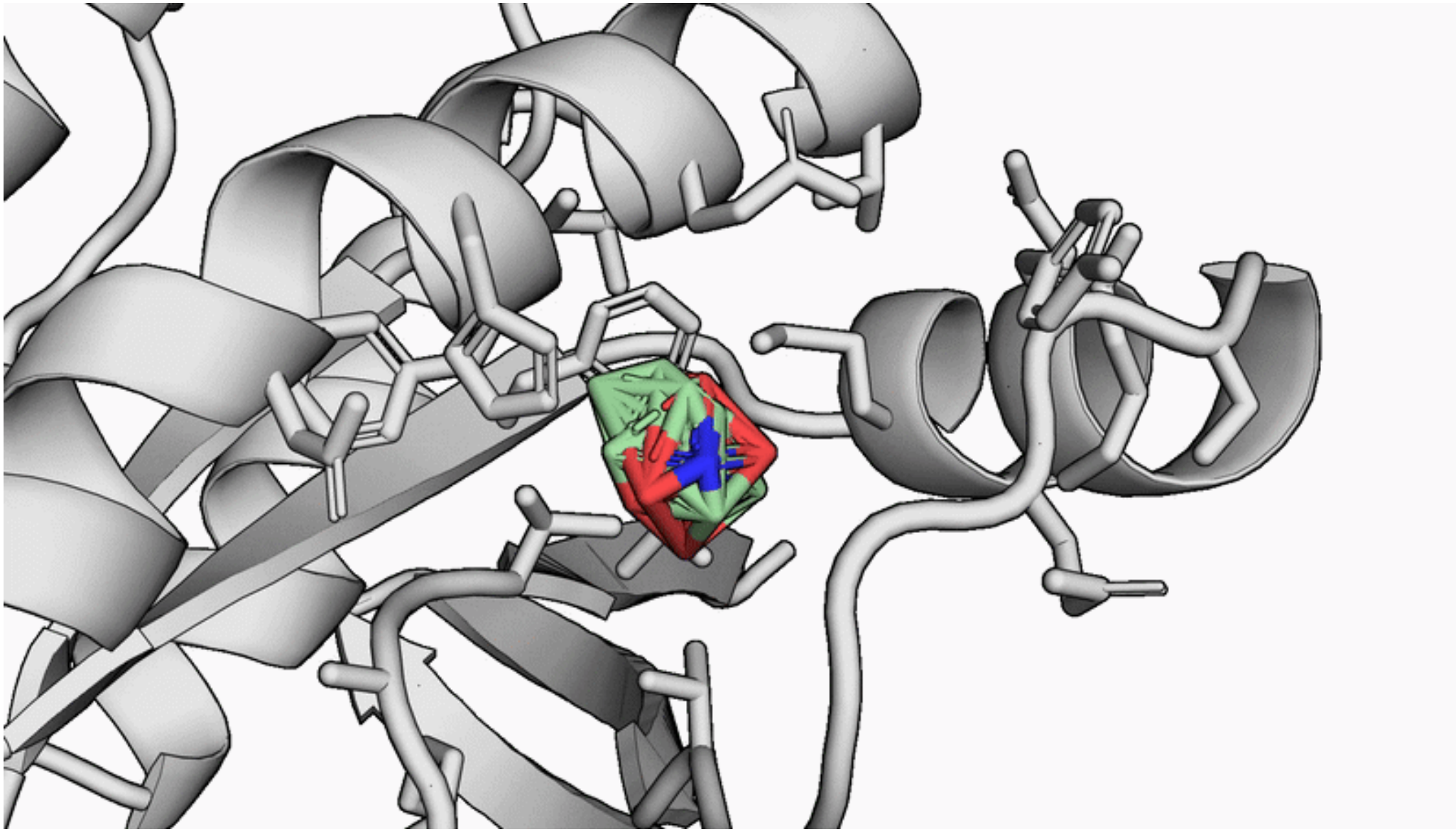


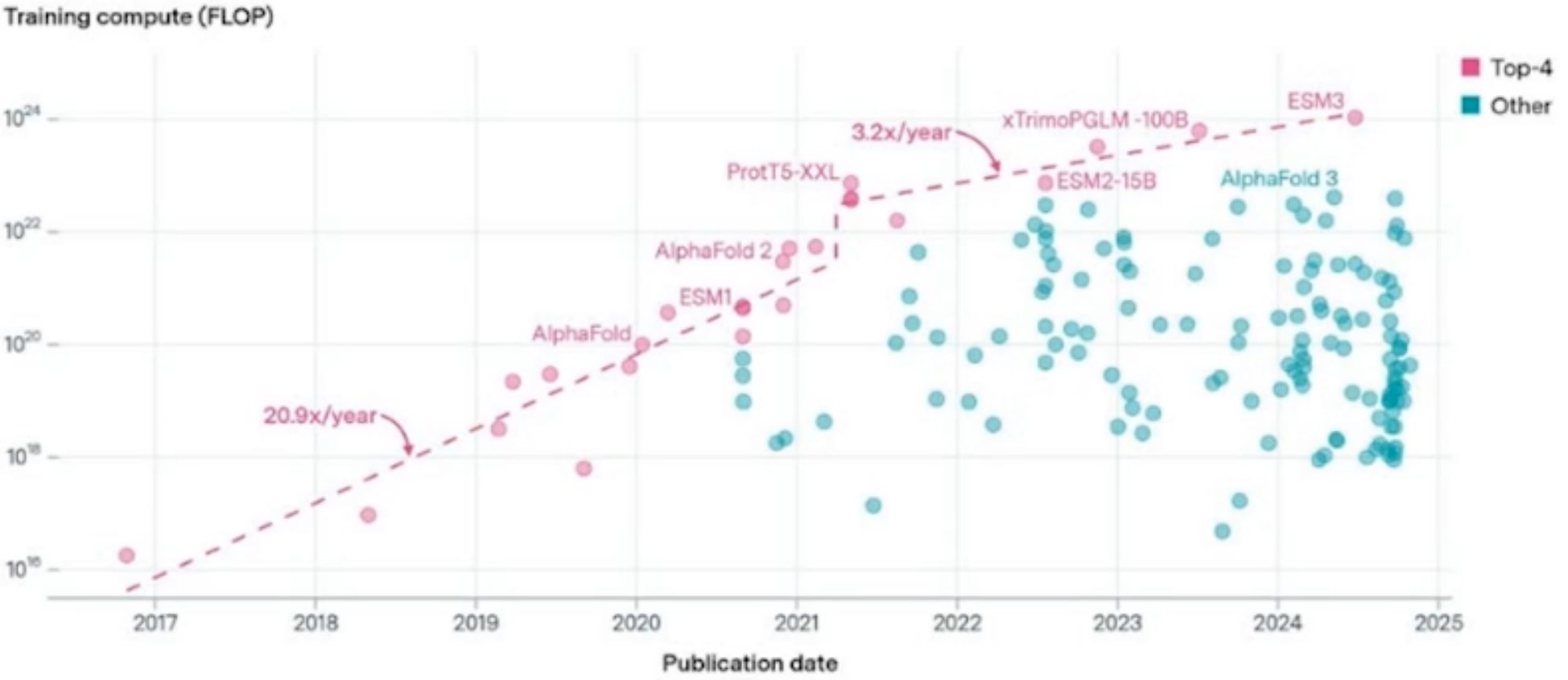
Fig. S13. Comparison of time requirements for D-I-TASSER and AlphaFold2 on different size proteins on a dataset of 645 proteins. Both programs were run using 10 CPUs with parallel processing, generating 5 models each. The AlphaFold2 program was executed with default settings, including 1 ensemble, full_dbs and monomer pipeline as implemented in AlphaFold version 2.2.0. The running time reported excludes the DeepMSA2 search time, as the speed of large database searches is largely influenced by I/O performance. For instance, storing databases on SSD or NVMe drives can significantly reduce search time.





Training compute of biological models

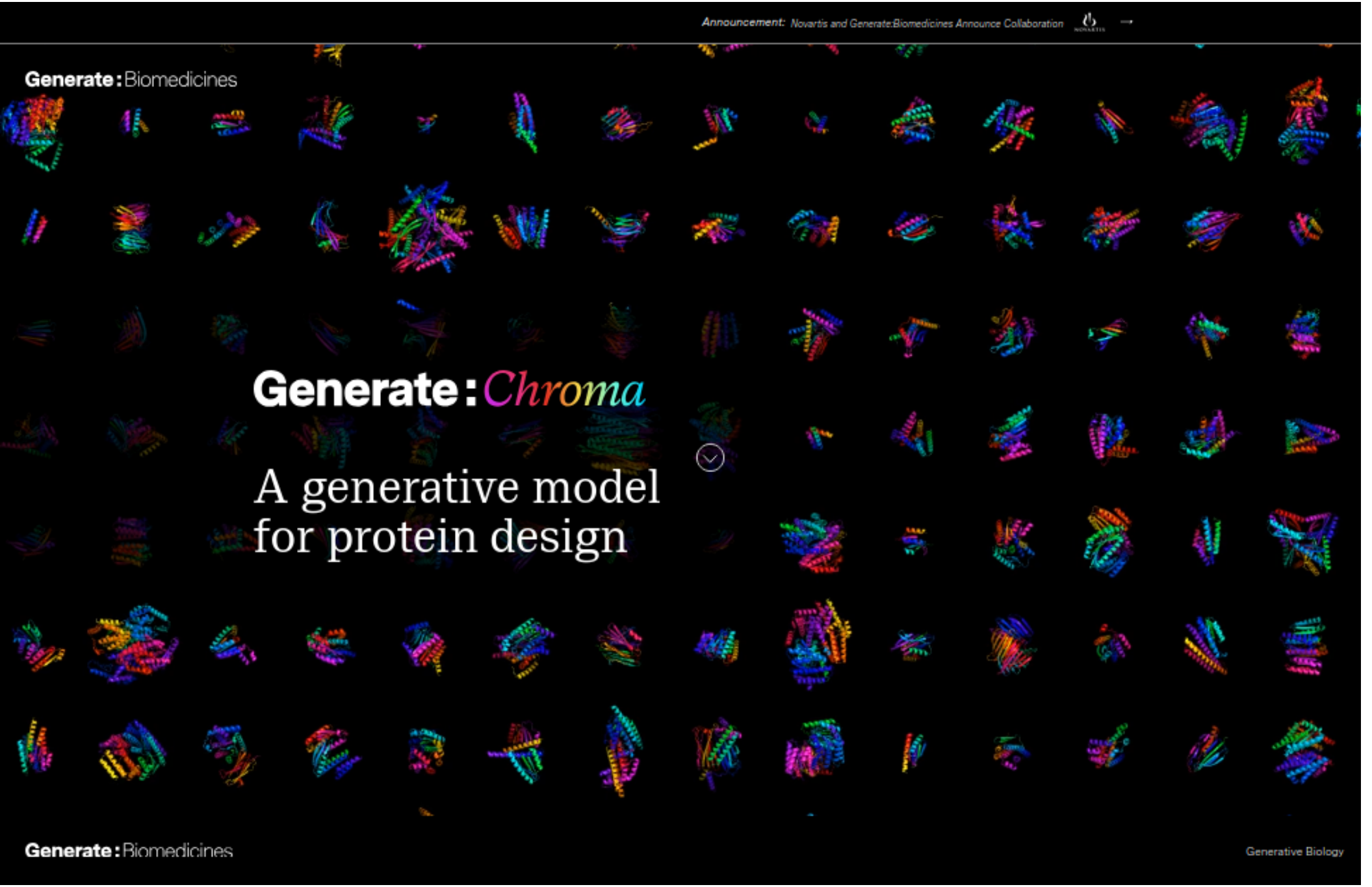
EPOCH AI



epoch.ai

Generative models

Model	Paradigm	Output	Training Data Sources					Postprocessing Required for All-Atom Designs			Ability for TEV protease conditional design
			RCSB PDB	SCOPe	CATH	UniRef	BFD	Backbone Refinement (RosettaMinMover)	Sequence Design (ProteinMPNN)	Structure Prediction (OmegaFold)	
RFdiffusion [11]	D(Str)	BC	✓						✓	✓	✓
Genie [12]	D(Str)	BC (C□)		✓					✓	✓	
ProteinSGM [13]	D(Str)	BC			✓			✓	✓	✓	
FoldingDiff [14]	D(Str)	BC			✓				✓	✓	
FrameDiff [15]	D(Str)	BC	✓						✓	✓	
Chroma [16]	D(Str)	FTS	✓								✓
Protpardelle [17]	D(Str)	FTS			✓				*		✓
ProteinGenerator [18]	D(Seq)	FTS	✓							**	✓
EvoDiff [6]	D(Seq)	Sequences				✓				✓	✓
RITA [7]	APLM	Sequences				✓				✓	
ProGen2 [8]	APLM	Sequences				✓	✓			✓	
ProtGPT2 [9]	APLM	Sequences				✓				✓	
ESM-Design [10]	MTPLM	Sequences				✓				✓	



https://generatebiomedicines.com/chroma

Thank you for your time
and
See you at the next lecture

Any other
questions & comments

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