



A protein's function is determined by its 3D shape.

# PROTEIN-FOLDING CONTEST SEEKS NEXT BIG BREAKTHROUGH

Scientists are building on the success of DeepMind's AI AlphaFold, after it swept a structure competition.

By Ewen Callaway

**“**In some sense the problem is solved,” computational biologist John Moult declared in late 2020. The London-based company DeepMind had just swept to victory at a biennial contest co-founded by Moult that tests teams' abilities to predict protein structures – one of biology's grandest challenges – with its revolutionary artificial-intelligence (AI) tool AlphaFold.

Two years later, Moult's competition, the Critical Assessment of Structure Prediction (CASP), is still walking in AlphaFold's long shadow. Results from the 2022 edition (CASP15) – which were unveiled in December at a conference in Antalya, Turkey – show that the most successful approaches to predicting protein structures from their amino-acid sequences incorporated AlphaFold, which relies on an AI approach called deep learning. “Everyone is using AlphaFold,” says Yang Zhang, a computational biologist at the University of Michigan in Ann Arbor.

Yet AlphaFold's progress has opened the floodgates for new challenges in protein-structure prediction – some included in this year's CASP – that might require fresh approaches

and more time to tackle fully. “The low-hanging fruit has been picked,” says Mohammed AlQuraishi, a computational biologist at Columbia University in New York City. “Some of the next problems are going to be harder.”

## Matchmaking

CASP started in 1994, aiming to bring rigour to the field of protein-structure prediction – progress on which would accelerate efforts to understand the building blocks of cells and

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advance drug discovery. During the year of a contest, teams are tasked with using computational tools to predict the structures of proteins that have been determined using experimental methods such as X-ray crystallography and cryo-electron microscopy, but not yet released.

Entries are assessed according to how well predictions for entire proteins, or independently folding subunits called domains,

match the experimental structures. Some of AlphaFold's predictions at CASP14 were more or less indistinguishable from the experimental models – the first time such accuracy had been achieved.

Since its unveiling at CASP14, AlphaFold has become omnipresent in life-sciences research. DeepMind released the software's underlying code in 2021 so that anyone could run the program, and an AlphaFold database updated last year holds predicted structures – of varying quality – for almost every protein from all organisms represented in genome databases, a total of more than 200 million proteins.

AlphaFold's success and new-found ubiquity presented a challenge to Moult, who is at the University of Maryland, Rockville, and his colleagues as they planned this year's CASP. “People say, ‘Oh, we don't need CASP anymore, the problem was solved.’ And I think that's exactly the wrong way round.”

At CASP15, the most successful teams were those that had adapted and built on AlphaFold in various ways, leading to modest gains in predicting the shape of individual proteins and domains. “The accuracy is already so high that it's hard to get much better,” says Moult.

## Protein complexes

To make the competition more relevant in a post-AlphaFold world, Moult and his team added challenges and tweaked existing ones. New tests include determining how proteins interact with other molecules such as drugs and predicting the multiple shapes that some proteins can assume. For the past decade, CASP has included ‘complexes’ of multiple interacting proteins, says Moult, but accurately predicting the structure of such molecules has taken on added emphasis this year.

“That is the right thing to do,” says Zhang, because predicting the structures of single proteins or domains – the bread and butter of past CASPs – has largely been solved by AlphaFold. Determining the shape of protein complexes, in particular, represents an important new challenge for the field, because there is a lot of room for improvement, says Arne Elofsson, a protein bioinformatician at Stockholm University.

AlphaFold was initially designed to predict the shape of individual proteins. But, within days of its public release, other scientists showed that the software could be ‘hacked’ to model how multiple proteins interact. In the months since then, researchers have come up with myriad approaches to improve AlphaFold's ability to tackle complexes. DeepMind even released an update called AlphaFold-Multimer, with that goal in mind.

Such efforts seem to have paid off, because CASP15 saw a marked increase in the number of accurate complexes, compared with previous contests, mainly due to methods that adapted AlphaFold. “It's a new game for us to be close to

## News in focus

experimental accuracy with complexes,” says Moulton. “We’ve got some failures, too.”

For instance, teams made stunningly accurate predictions of a viral molecule of unknown function that is made up of two identical intertwined proteins. This kind of shape bamboozled pre-AlphaFold tools, says Ezgi Karaca, a computational structural biologist at the Izmir Biomedicine and Genome Center in Turkey, who assessed the complex predictions. The standard version of AlphaFold failed to accurately model the shape of a giant, 20-chain bacterial enzyme, but some teams predicted the protein’s structure by applying extra hacks to the network, Karaca adds.

Meanwhile, teams struggled to predict complexes involving immune molecules called antibodies – including several attached to a SARS-CoV-2 protein – and related molecules called nanobodies. But there were glimpses of success in some teams’ predictions, says Karaca, suggesting that hacks to AlphaFold will be useful for predicting the shape of these medically important molecules.

### Time out

The 2022 CASP was also notable for the absence of DeepMind. The company did not say why it did not participate, but released a short statement during CASP15 congratulating

the teams that did. (At the same time, it rolled out an update to AlphaFold to help researchers benchmark their progress against the network.)

Other researchers say the competition is a considerable time commitment, which DeepMind might have felt was better spent on other challenges. “It would have been nice for us if they had participated,” Moulton says. But he adds that “because the methods are so good, they couldn’t do another big leap”.

Making big improvements to AlphaFold will take time, say researchers, and will probably require innovations in machine learning and protein-structure prediction. One area under development is the application of ‘language models’, such as those used in predictive-text tools, to the prediction of protein structures. But these methods – including one developed by the social-networking giant Meta – did not perform nearly as well at CASP15 as did tools based on AlphaFold.

Such tools might, however, be useful for predicting how mutations alter a protein’s structure – one of several key challenges in protein-structure prediction that has emerged as a result of AlphaFold’s success. Thanks to this, the field is no longer focused on a single goal, AlQuraishi says. “There’s a whole slew of these problems.”

physically define stages of Earth’s geological timescale – that is, if it’s approved. Even if the AWG agrees on a final candidate, several other committees of geologists must vote on the selection before it is made official. And not all scientists agree that it should be.

Here, *Nature* examines what it will take to formally define the Anthropocene epoch.

### Why do some geologists want an Anthropocene marker?

Scientists coined the term Anthropocene in 2000, and researchers from several fields now use it informally to refer to the current geological time interval, in which human activity is driving Earth’s conditions and processes. Formalizing the Anthropocene would unite efforts to study people’s influence on Earth’s systems, in fields including climatology and geology, researchers say. Transitioning to a new epoch might also coax policymakers to take into account the impact of humans on the environment during decision-making.

“It’s a label,” says Colin Waters, who chairs the AWG and is a geologist at the University of Leicester, UK. “It’s a great way of summarizing a lot of concepts into one word.”

Mentioning the Jurassic period (200 million to 146 million years ago), for instance, helps scientists to picture plants and animals that were alive during that time, he says. “The Anthropocene represents an umbrella for all of these different changes that humans have made to the planet,” he adds.

### How do scientists choose sites that define the geological timeline?

Typically, researchers will agree that a specific change in Earth’s geology must be captured in the official timeline. The ICS will then determine which set of rock layers, called strata, best illustrates that change, and will choose which layer marks the lower boundary. This is called the Global Stratotype Section and Point (GSSP), and it is defined by a signal, such as the first appearance of a fossil species, trapped in the rock, mud or other material. One location is selected to represent the boundary, and researchers mark this site physically with a golden spike, to commemorate it.

But the Anthropocene has posed problems. Geologists want to capture it in the timeline, but its beginning isn’t obvious in Earth’s strata, and signs of human activity have never before been part of the defining process. The AWG was established in 2009 to explore whether the Anthropocene should enter the geological timescale and, if so, how to define its start.

“We were starting from scratch,” says Jan Zalasiewicz, a geologist at the University of Leicester who formerly chaired the AWG and remains a voting member. “We had a vague idea about what it might be, [but] we didn’t know what kind of hard evidence would go into it.”

# GEOLOGISTS SEEK TO DEFINE THE ANTHROPOCENE

Researchers have identified nine sites that could denote a geological time marked by human activity.

By McKenzie Prillaman

**G**eologists could soon decide which spot on Earth marks the first clear evidence of the Anthropocene – which many of them think is a new geological epoch that began when humans started altering the planet with various forms of industrial and radioactive materials in the 1950s. They have so far whittled their choices down to nine candidate sites worldwide (see ‘Defining the Anthropocene’), each being considered for how reliably its layers of mud, ice or other matter tell the story of people’s influence on a timeline that extends billions of years into the past.

If the nearly two dozen voting members of the Anthropocene Working Group (AWG), a committee of scientists formed by the International Commission on Stratigraphy (ICS),

agree on a site, the decision could usher in the end of the roughly 12,000-year-old Holocene epoch. And it would officially acknowledge that humans have had a profound influence on Earth.

“We’re pointing to something in the rock record that shows we’ve changed the planet,” says Kristine DeLong, a palaeoclimatologist at Louisiana State University in Baton Rouge who studies the West Flower Garden Bank, a candidate site in the Gulf of Mexico.

The Anthropocene site will join 79 others that

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