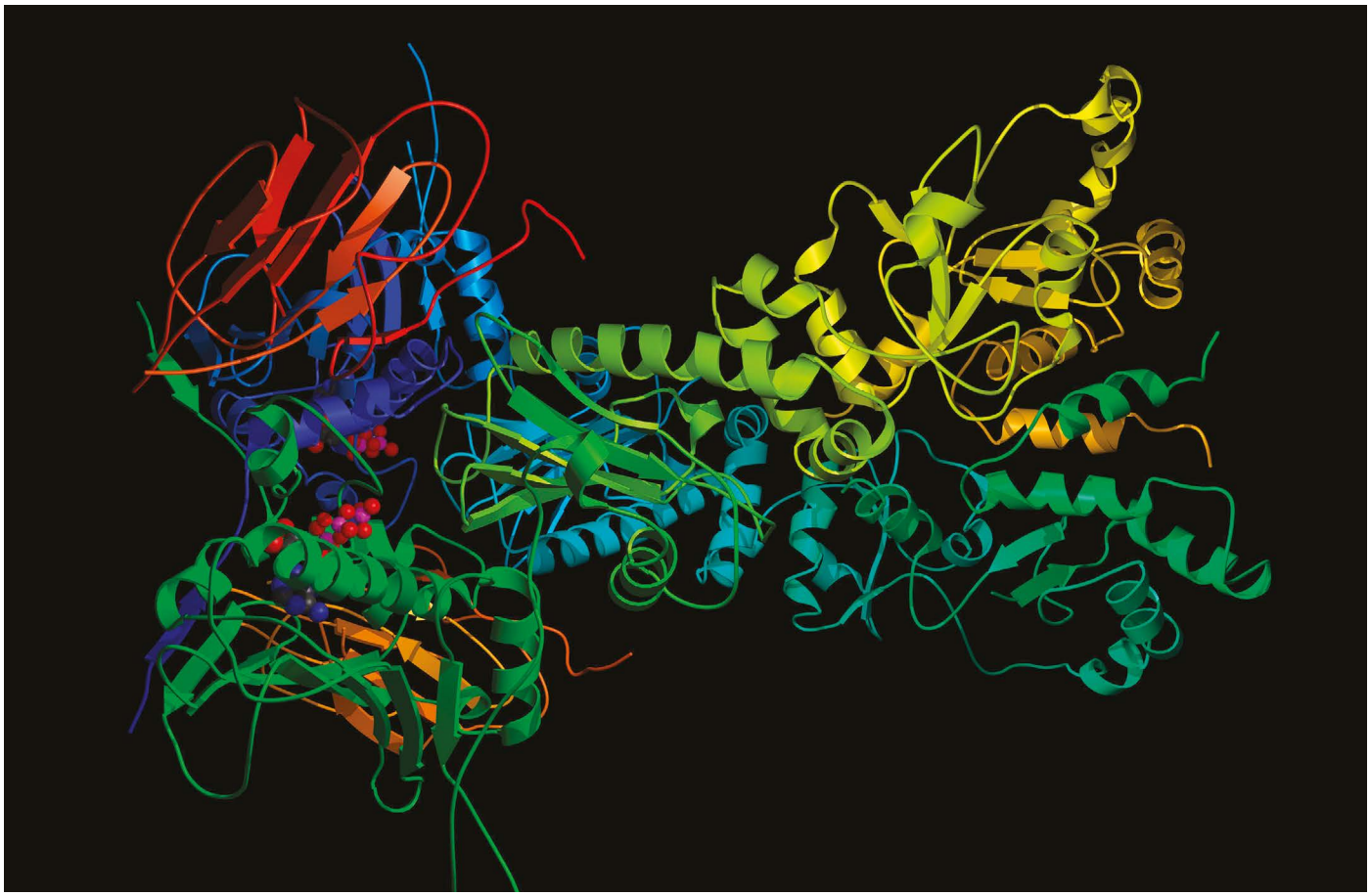
News in focus



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

'IT WILL CHANGE EVERYTHING': AI MAKES GIGANTIC LEAP IN SOLVING PROTEIN STRUCTURES

DeepMind's program for determining the 3D shapes of proteins stands to transform biology, say scientists.

By Ewen Callaway

An artificial intelligence (AI) network developed by Google AI offshoot DeepMind has made a gargantuan leap in solving one of biology's grandest challenges — determining a protein's 3D shape from its amino-acid sequence.

DeepMind's program, called AlphaFold, outperformed around 100 other teams in a biennial protein-structure prediction challenge called CASP, short for Critical Assessment of Structure Prediction. The results were announced on 30 November, at the start of the conference — held virtually this year — that takes stock of the exercise.

"This is a big deal," says John Moult, a computational biologist at the University of Maryland in College Park, who co-founded CASP in 1994 to improve computational methods for accurately predicting protein structures. "In some sense the problem is solved."

The ability to accurately predict proteins' structures from their amino-acid sequences would be a huge boon to life sciences and medicine. It would vastly accelerate efforts to understand the building blocks of cells and aid more advanced drug discovery.

AlphaFold came top of the table at the last CASP — in 2018, the first year that London-based DeepMind participated. But, this year, the outfit's deep-learning network was head-and-shoulders above other teams and, say scientists, performed so mind-bogglingly well that it could herald a revolution in biology.

"It's a game changer," says Andrei Lupas, an evolutionary biologist at the Max Planck Institute for Developmental Biology in Tübingen,

Germany, who assessed the performance of different teams in CASP. AlphaFold has helped him to find the structure of a protein that has vexed his laboratory for a decade. "This will change medicine. It will change research. It will change bioengineering. It will change everything," Lupas adds.

In some cases, AlphaFold's structure predictions were indistinguishable from those determined using 'gold standard' experimental methods such as X-ray crystallography and, in recent years, cryo-electron microscopy (cryo-EM). AlphaFold might not obviate the need for these laborious and expensive methods — yet — say scientists, but the AI will make it possible to study living things in new ways.

The structure problem

Proteins are the building blocks of life, responsible for most of what happens inside cells. How a protein works and what it does is determined by its 3D shape. Proteins tend to adopt their shape without help, guided only by the laws of physics.

For decades, laboratory experiments have been the main way to obtain good protein structures. The first complete structures of proteins were determined, starting in the 1950s, using a technique in which X-ray beams are fired at crystallized proteins and the diffracted light translated into a protein's atomic coordinates. X-ray crystallography has produced the lion's share of protein structures. But, over the past decade, cryo-EM has become the favoured tool of many structural-biology labs.

Scientists have long wondered how a protein's constituent amino acids map out the twists and folds of its eventual shape. Early attempts to use computers to predict protein structures in the 1980s and 1990s performed poorly. Lofty claims for methods in published papers tended to disintegrate when other scientists applied them to other proteins.

Moult started CASP to bring rigour to these efforts. The event challenges teams to predict the structures of proteins that have been solved using experimental methods, but for which the structures are not public.

DeepMind's 2018 performance at CASP13 startled many scientists in the field, which has long been the bastion of small academic groups. But its approach was broadly similar to those of other teams that were applying AI, says Jinbo Xu, a computational biologist at the University of Chicago, Illinois.

The first iteration of AlphaFold applied the AI method known as deep learning to structural and genetic data to predict the distance between pairs of amino acids in a protein. In a second step, which does not invoke AI, AlphaFold uses this information to come up with a 'consensus' model of what the protein should look like, says John Jumper at DeepMind, who is leading the project.

> **"This is going to empower a new generation of molecular biologists to ask more advanced questions."**

The team tried to build on that approach but eventually hit the wall. So it changed tack, says Jumper, and developed an AI network that incorporated additional information about the physical and geometric constraints that determine how a protein folds. The team also set it a more difficult task: instead of predicting relationships between amino acids, the network predicts the final structure of a target protein sequence. "It's a more complex system by quite a bit," Jumper says.

Startling accuracy

CASP takes place over several months. Target proteins or portions of proteins called domains — about 100 in total — are released on a regular basis, and teams have several weeks to submit their structure predictions. A team of independent scientists assesses the predictions using metrics that gauge how similar a predicted protein is to the experimentally determined structure. The assessors don't know who is making a prediction.

AlphaFold's predictions arrived under the name 'group 427', but the startling accuracy of many of its entries made them stand out, says Lupas. "I had guessed it was AlphaFold. Most people had," he says.

Some predictions were better than others, but nearly two-thirds were comparable in quality to experimental structures. In some cases, says Moult, it was not clear whether the discrepancy between AlphaFold's predictions and the experimental results was a prediction error or an artefact of the experiment. AlphaFold also struggled to model individual structures in protein complexes.

Faster structures

An AlphaFold prediction helped to determine the structure of a bacterial protein that Lupas's lab has been trying to crack for years. Lupas's team had previously collected raw X-ray diffraction data, but transforming these patterns into a structure requires some information about the shape of the protein. Tricks for getting this information, as well as other prediction tools, had failed. "The model from group 427 gave us our structure in half an hour," Lupas says.

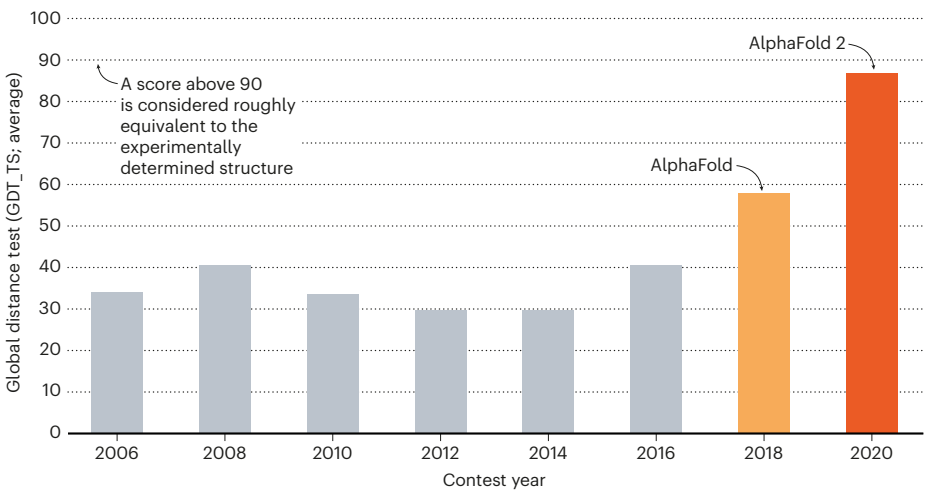
Demis Hassabis, DeepMind's co-founder and chief executive, says that the company plans to make AlphaFold useful to other scientists. (It previously published enough details about the first version of AlphaFold for other researchers to replicate the approach.) It can take AlphaFold days to come up with a predicted structure, which includes estimates on the reliability of different regions of the protein. "We're just starting to understand what biologists would want," adds Hassabis.

In early 2020, the company released predictions for a handful of SARS-CoV-2 protein structures that hadn't been determined experimentally. DeepMind's predictions for a protein called Orf3a ended up being similar to one later determined through cryo-EM, says Stephen Brohawn, a molecular neurobiologist at the University of California, Berkeley, whose team released the structure in June. "What they have been able to do is very impressive," he adds.

AlphaFold is unlikely to remove the need for labs, such as Brohawn's, that use experimental methods to solve protein structures. But it could mean that lower-quality experimental data would be all that's needed to get a good structure. Some applications, such as the evolutionary analysis of proteins, are set to flourish. "This is going to empower a new generation of molecular biologists to ask more advanced questions," says Lupas. "It's going to require more thinking and less pipetting."

STRUCTURE SOLVER

DeepMind's AlphaFold 2 algorithm significantly outperformed other teams at the CASP14 protein-folding contest — and its previous version's performance at the last CASP.



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