Chemistry Nobel honors protein design and modeling

The prizewinning research enhances understanding of nature's molecular toolkit and enables the construction of novel proteins.

David Baker, Demis Hassabis, and John Jumper are the recipients of the 2024 Nobel Prize in Chemistry for their work on protein design and structure. Baker, of the University of Washington in Seattle, receives half the prize for using computational methods to design proteins. Hassabis and Jumper, at Google DeepMind in London, share the other half for predicting protein structures with neural network–based AI, the method that earned its developers this year's Nobel Prize in Physics (see page 12 of this issue).

To design amino acid sequences that would fold into desired structures, the earliest computational approaches searched through a vast number of sequences for a few that, when combined together, could yield new 3D structures. To make the process more efficient, Baker and his research group developed the Rosetta computer program in the 1990s. It takes structural-fragment data from various existing proteins and uses an energy-optimization procedure to assemble them together into a new form.[1,2] With Rosetta, Baker and colleagues created an entirely new and large protein known as Top7: Its sequencing and structure were significantly different from the proteins found in the research community's databases.

When Rosetta was developed, computational resources were meager enough that Baker founded a citizen science project called Rosetta@home. It's still in use today, and people can donate computational power from their personal computers to help complete Rosetta's calculations. Before the work by Baker's team, protein engineers had relied mostly on the modification of naturally occurring proteins—the achievement behind the 2018 chemistry Nobel (see Physics Today, December 2018, page 22). The *de novo* design capabilities ushered in by Rosetta have allowed biochemists to build proteins from scratch.[3] Such engineered proteins can be used for various functions, such as performing logic operations inside human cells (see Physics Today, June 2020, page 17).

So much of a protein's function depends on its 3D structure. Starting in the 1950s, researchers have used methods such as x-ray crystallography to empirically identify protein structure. But even today, x-ray crystallography is time-consuming, and not all proteins can be crystallized for the measurements. Since 1994, protein researchers have held a biennial challenge—the Critical Assessment of Structure Prediction (CASP) experiment—to improve theoretical structure predictions by testing them against experimental observations. The prediction accuracy, graded on a scale of 0 to 100, has been steadily improving for years, in part because AI models are adept at pattern recognition.

From 2016 to 2020 at DeepMind, an interdisciplinary team led by Hassabis and Jumper reworked its neural network algorithm to dramatically improve the prediction of protein structures.[4,5] The transformative work was published in 2021—unusually recent for a Nobel Prize.[6] For the 2018 CASP experiment, DeepMind's original AlphaFold model predicted protein targets better than any other model, receiving a grade of almost 70 for the most difficult targets. (In the previous CASP experiment, the best model in that category scored around 40.) DeepMind overhauled the AI algorithm for the 2020 CASP assessment, and AlphaFold2 leaped ahead of the competition and for the most difficult targets scored near 90—that's a grade equivalent to that of an experimentally determined structure. The prizewinning research was covered in detail in Physics Today in October 2021 (page 14).

The accurate design of proteins and the prediction of their structure have far-reaching implications in medicine and many other fields—the vitellogenin protein on page 18, for example, is important for the immunity of honeybees. Earlier this year, Hassabis, Jumper, and colleagues reported the development of AlphaFold3, an upgraded model that also predicts the structures of biochemical complexes that contain nucleic acids, small molecules, and other components.[7]

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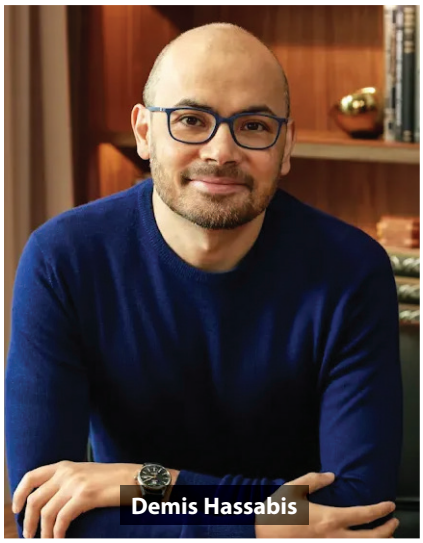

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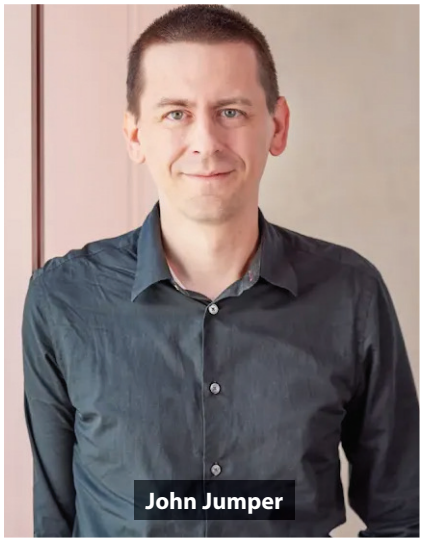

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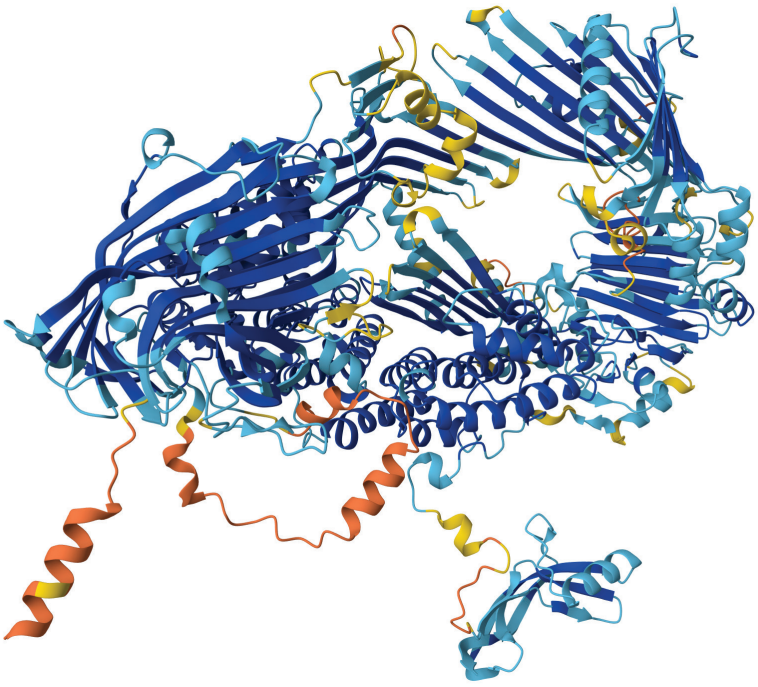

ALPHAFOLD2'S PREDICTED STRUCTURE of the vitellogenin protein, which contributes to immunity in honeybees. The colors represent regions of the protein predicted with high (blue) through low (yellow and orange) confidence. (AlphaFold Protein Structure Database/CC BY 4.0.)

Hassabis has a background in computer science and video game design. Before studying proteins and AI, Jumper majored in physics and mathematics. Only after dropping out of a physics PhD program did he become interested in biology. "I think of myself as a physicist who likes to work on these really complex, really interesting systems of biology," says Jumper. When asked what led him to join DeepMind, he recalls thinking that "machine learning and AI were exciting, and they were possibly going to solve some really important problems, and DeepMind was the most exciting place to do it."

Alex Lopatka

References

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UPDATES

Carbonate rocks may release more carbon dioxide as climate warms

An analysis of 60 years of water chemistry data from Arctic and subarctic Canadian rivers finds that some regions exhibit a major increase of dissolved sulfates, a product of weathering reactions that also release CO_2.

Rocks at Earth's surface experience natural weathering reactions that can both release carbon dioxide into the atmosphere and pull it out. Quantifying those exchanges is a challenge, and climate change throws another confounding factor into the mix: Temperature changes can alter the rates of weathering reactions. That may be especially important in the Arctic, where air temperatures are rising nearly four times as fast as the global average. In a new study, Ella Walsh (at the time at the University of Oxford) and colleagues show that warming temperatures in western Canada over the past six decades have driven increased rates of weathering reactions that release CO_2.

For their analysis, Walsh and colleagues used water chemistry data collected from rivers in the Mackenzie River basin in Canada between 1960 and 2020. The basin, which includes several smaller river watersheds, covers an area of about 1.8 million km^2, roughly 20% of Canada. A modeling study published over a decade ago had estimated that increased temperatures, rainfall, and vegetation, all associated with climate change, would produce weathering reactions in the basin that would draw more CO_2 from the atmosphere over time. The rocks' silicate and carbonate minerals react with CO_2 to form bicarbonate, which dissolves in river water and is ultimately delivered to the ocean.

But Walsh says that the contribution of sulfide weathering wasn't factored into those estimates. Oxidation of sulfide minerals, like pyrite, produces sulfuric acid. That acid reacts with carbonate minerals to release CO_2 and dissolved sulfate to river waters. The research team analyzed the sulfate flux for individual river basins, known as catchments, within the larger system. "By looking at this catchment scale, we were able to look at what some of the possible drivers are, why some catchments have greater increases than others," says Walsh.

The Mackenzie River, which is central to the basin, saw a 45% increase in sulfate flux with 2.3 °C of warming over the study period. One catchment had sulfate concentrations that rose by as much as 36% per decade. Others showed no significant changes in sulfate concentrations. Steeper