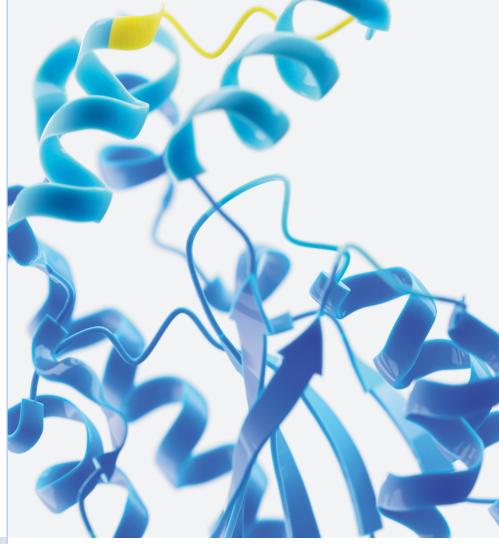
AlphaFold





How AlphaFold uncovered one of nature's toughest proteins

Structural biologist Dr. Danny Hsu and his lab largely explore 3D structures of a molecule, with a focus on its protein components. The team is especially interested in what happens when a gene mutates, or misfolds, given that how it knots and folds determines which disease might occur, such as Alzheimer's, Parkinson's or cancer.

To understand more about gene mutations and knots, Dr. Hsu, Research Fellow and Deputy Director at the Institute of Biological Chemistry, Academia Sinica in Taiwan, and Principal Investigator at the International Institute for Sustainability with Knotted Chiral Meta Matter (WPI-SKCM2), Hiroshima University, Japan, studies lesser known proteins with the goal of uncovering more knowledge about them. A major puzzle is the Q9PR55 protein, a molecule with an exceptionally complex and mysterious structure. Dr. Hsu and his team had been using traditional methods to solve the riddle for years without much luck. Rather than continue sifting through a database of 200 million possible mutation knots in hope of finding one that could fit the mutation structure of the Q9PR55, they decided to put Google DeepMind AlphaFold's predictive abilities to the test.



Knowing they were standing in front of a goldmine of mutations and knots, the team hoped AlphaFold would shed some light on the unfamiliar. And that's exactly what AlphaFold delivered: a model that had never been heard of or seen before, the unprecedented 7₁-torus knot topology. Dr. Hsu says, "We were uncertain if AlphaFold's prediction could be trusted because we thought that you had to train the tool using pre-existing data. Protein folds can be extremely hard to predict because of how complex they are. So if the tool proposes a new fold, especially one this intricate, could it even be real?"

As it turns out, AlphaFold had accurately modelled the most complex protein structure known to date – and it didn't draw from existing information or data about the protein.



Predicting the unknown and filling in the gaps

Dr. Hsu's team set out to verify AlphaFold's radical prediction. Using standard methods of X-ray crystallography and NMR spectroscopy to map the protein's true form, a near-perfect match confirmed the 7₁-torus knot – otherwise known as the smallest and most complex protein knot known to date. Dr. Hsu states, "This shows us that not only can AlphaFold predict something that has never been seen before, its predictions are reliable. The tool can help fill in gaps that we haven't been able to solve otherwise – that's pretty important."



Filing in a piece of the puzzle

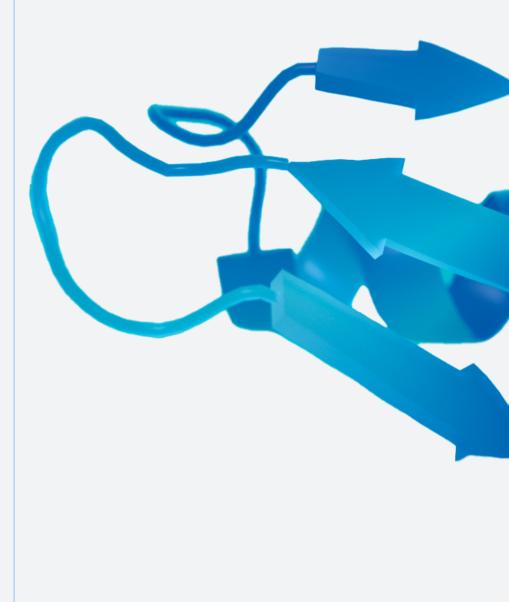
A study of this size usually takes months to solve. Sometimes, it can take years and the team might still come out empty handed. Various technical bottle necks could stand in the way, including how long it takes to identify the protein – a critical first step in the research. Before AI, this likely involved conducting a protein crystallography, a process that was more art than science. One of Dr. Hsu's research, for example, set out to identify the crystal in a cancer mutation. Ten years later, they still hadn't found it.

AlphaFold's prediction of the 7₁-torus knot topology has shifted the starting point of the journey forward significantly. Dr. Hsu shares, "In less than six months, we launched the research from scratch, identified the sequence, and the structure came soon after. Once the structure is determined, the rest is quite straightforward."

Significance of 7,-Torus Knot

What makes the 7₁-torus knot especially interesting is the formation of the knot. Every bit of the protein chain is involved in the knot formation, creating what is known as a 'tight knot'. Exactly how the 7₁-torus knot became so knotted remains a mystery, but it clearly went through a highly intricate folding process to reach its current state. Dr. Hsu's unexpected discovery offers the biology community a springboard into many other areas of research, including the 7₁-torus knot's behaviours and knotting patterns, and what it might mean for diseases.

The biological function of the 7₁-torus knot is yet to be discovered, but the significance of its sudden existence is game-changing. Dr. Hsu says, "Going forward, we can leverage AlphaFold to give us a very close guess of the protein structure - this gives us a very good starting point. The confidence score, in particular, is not commonly used in the community but it is very useful because it lets us know how confident it is of its prediction in one area versus another. This helps guide our analysis as we interpret the prediction."



From 7,-Torus Knot to ancestral sequences

AlphaFold's ability to accurately predict never-seen-before protein structures like the 7₁-torus knot fundamentally changes the game for structural biology. It proves that AI is not merely a tool for interpolation or a fancy database search, but a deep learning engine that has grasped the very principles of protein folding. This breakthrough opens a world of new possibilities that were once pure science fiction. The tool's audacious prediction of a structure no one had ever seen sparked Dr. Hsu and his lab to pursue what seemed impossible, leading to the discovery of the most complex protein knot ever documented.

For Dr. Hsu, this newfound power allows researchers to tackle previous long-standing unsolved genetic conundrums by looking backward in time. "Given the power of AlphaFold, we can explore ancestral sequence reconstruction," he says. "We can go back in time to see what a protein might have looked like, predict missing structures, and even give insights on how a protein might have evolved."

In this way, AlphaFold has become the ultimate bridge between the theoretical world of computational biology and the tangible, real-world of laboratory science. It transforms what was once a laborious, hit-or-miss process into a targeted and efficient journey toward groundbreaking discoveries.