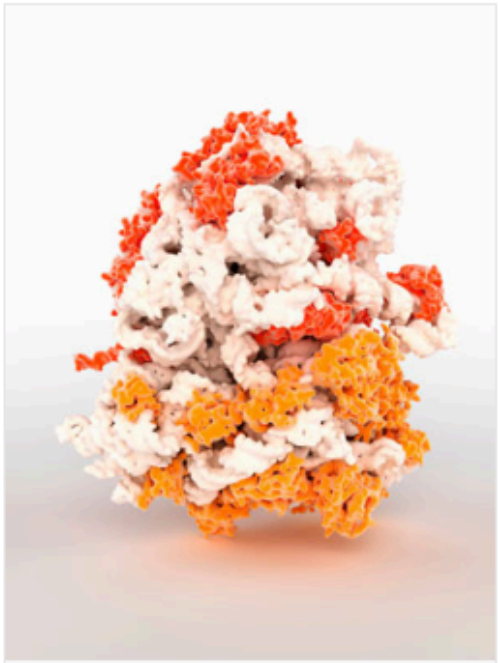
Watching proteins get into shape

21 December 2017

Proteins are the machinery of our cells, complex molecules with specific functions and capabilities determined by their shape. By investigating how proteins fold into a shape — and how that can go wrong — researchers hope to learn how to manipulate the process to our advantage.



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An international team led by Martin Hegner of Ireland's Trinity College Dublin observed protein folding in unprecedented detail, tracking the behaviour of individual protein molecules as they were being synthesized and folded in a ribosome, the part of a cell where proteins are assembled. The team attached a microscopic bead to one end of the protein and another to the ribosome and then used lasers to push and pull the beads, enabling them to measure and manipulate the nascent protein to determine its length in real-time and to tug on it to see how folding was affected.

The team used this technique to study how three different proteins folded. "By comparing the three, we could gain more insight than from just one of them," says Hegner.

One of the proteins folds into a compact barrel, and no amount of tugging could make it relax into an unfolded state. The second protein was more flexible, folding into different shapes as the team pulled on it with varying levels of force. The final protein, known as hTau40, is normally unfolded, but folded forms which clump together have been implicated in Alzheimer's disease and other neurodegenerative diseases.

Using precise, real-time measurements, the team also shed light on what factors affect protein folding during synthesis. One type of amino acid, proline, had a particularly pronounced effect. Prolines introduce a kink into the forming protein, and the chain of kinks introduced by successive prolines significantly slowed synthesis.

These delays are counterbalanced by the free end of the protein folding as it leaves the ribosome and pulling on the other end, where amino acids are still being added. When a stretch of hydrophobic amino acids leave the ribosome, they immediately fold into a compact structure, and the folding process tugs on the remainder of the protein.

Hegner hopes that understanding how synthesis and folding are coupled will open the door to chemical manipulations that can prevent hTau40 from folding and aggregating or even to impair the folding of crucial proteins in viruses. "At the moment, we're working on interfering with the translational process," says Hegner. "We're trying to find the mechanical difference between healthy and non-healthy proteins and how small chemicals can interfere to slow down the translational process."

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1. *PNAS* **114,** E4399-E4407 (2017). doi: **10.1073/pnas.1617873114**