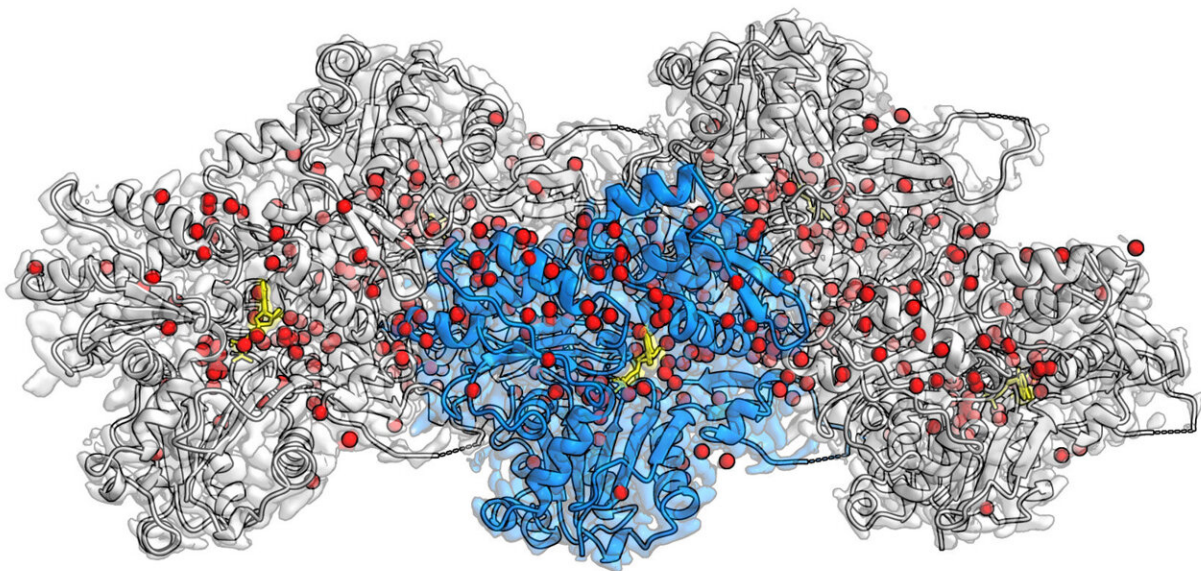


A pocket full of water molecules—how actin filaments drive the cell's motion

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Cryo-EM reconstruction of F-actin bound to Mg^{2+} -ADP-BeF₃ at 2.2 Å resolution. The central actin subunit is colored blue, the other four subunits are gray. Densities corresponding to water molecules are colored red and ADP in yellow. Credit: MPI of Molecular Physiology

Actin filaments are protein fibers that make up the internal skeleton of

the cell. As active elements of our cells, actin filaments support the cell's fusion, movement and are involved in many other cellular processes. Importantly, they are also a major constituent of muscle cells. The structural complexity of these filaments has fascinated scientists since its discovery in the 1940s—and has opened a sea of unanswered questions behind their ability to facilitate many processes of the cell.

For the first time, researchers at the Max Planck Institute of Molecular Physiology in Dortmund, Germany, have been successfully able to visualize hundreds of [water molecules](#) in the [actin](#) filament, representing a quantum leap in actin research.

Using the technique of electron cryo microscopy (cryo-EM), the group of Stefan Raunser reveals in unprecedented detail how actin proteins are arranged together in a filament, how ATP—the cell's energy source—sits in the protein pocket, and where individual water molecules position themselves and react with ATP.

"We are answering fundamental questions of life that scientists have been trying to answer for several decades," says Raunser. In [eukaryotic cells](#), actin proteins are abundant and tend to join together (polymerize) into filaments.

These filaments make up the network that constitutes the cytoskeleton of the cell and controls various cell processes through movement. Immune cells, for example, use [actin filaments](#) to move and hunt bacteria and viruses.

Researchers knew already that the filaments' dynamics is regulated by ATP hydrolysis—the reaction of ATP with water that cleaves a phosphate group and generates energy. What previously remained unanswered, however, was the exact molecular details behind this process.

Too flexible, too big?—not for cryo-EM

As actin filaments are too flexible or too big for X-ray crystallization and [nuclear magnetic resonance](#), cryo-EM has been the only technique viable for obtaining detailed images. In 2015, Raunser's team used cryo-EM to picture a novel three-dimensional atomic model of the filaments, with a resolution of 0.37 nanometers. In 2018, his group described the three different states that actin proteins acquire in the filament: bound to ATP, bound to ADP in the presence of the cleaved phosphate, bound to ADP after release of the phosphate.

How water molecules move

In their current study published in *Nature*, Raunser and his colleagues were able to set a new resolution record: they obtained all three actin-states with a resolution of about 0.2 nanometers, making previously invisible details visible. The three-dimensional maps not only display all amino-acid sidechains of the proteins but also reveal where hundreds of water molecules are placed.

Through comparison between these new structures and those of isolated actin, they were able to infer how water molecules move. Upon polymerization, water molecules relocate in the ATP pocket in such a way, that only a single water molecule remains in front of ATP, ready to attack one phosphate and initiate hydrolysis.

The accuracy obtained through this approach can help further research in the field: "Our high-resolution model can propel scientists in designing [small molecules](#) for light microscopy research on tissues, and ultimately in therapeutic applications," Raunser says.

A door opener?

The authors also cast light on the final fate of the phosphate. Previously, scientists believed there to be a back door in the ATP pocket that remains open after ATP hydrolysis to facilitate the exit of the phosphate. However, the new cryo-EM structures show no trace of open backdoors. Hence, the release mechanism remains a mystery.

"We believe there to be a door, but it likely opens momentarily," comments Raunser, who now wants to use mathematical simulations and time-resolved cryo-EM methods to demonstrate just how the [phosphate](#) exits. Evidently, these exciting discoveries have opened the door for scientists to dig deeper in the hopes of discovering even more details behind the processes by which actin [filaments](#) contribute to the cell's motion.

More information: Stefan Raunser, Structural basis of actin filament assembly and aging, *Nature* (2022). DOI: [10.1038/s41586-022-05241-8](https://doi.org/10.1038/s41586-022-05241-8). www.nature.com/articles/s41586-022-05241-8

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