Biological light sensor filmed in action

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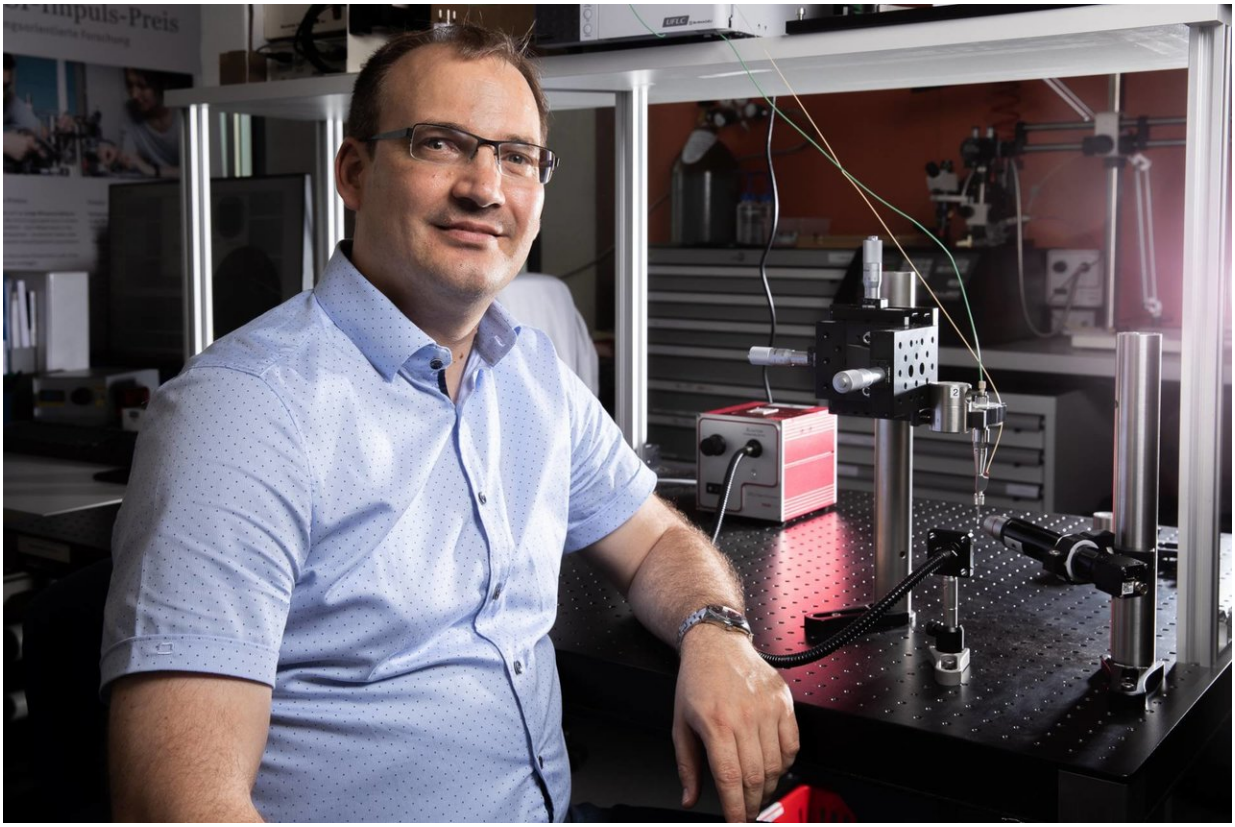

Jörg Standfuss at the injector with which protein crystals for the experiments at the Californian X-ray laser LCLS were tested. In the near future, this technology will also be available at PSI's X-ray laser SwissFEL, for scientists from all over the world. Credit: Paul Scherrer Institute/Mahir Dzambegovic

Using X-ray laser technology, a team led by researchers of the Paul Scherrer Institute PSI has recorded one of the fastest processes in

biology. In doing so, they produced a molecular movie that reveals how the light sensor retinal is activated in a protein molecule. Such reactions occur in numerous organisms that use the information or energy content of light – they enable certain bacteria to produce energy through photosynthesis, initiate the process of vision in humans and animals, and regulate adaptations to the circadian rhythm. The movie shows for the first time how a protein efficiently controls the reaction of the embedded light sensor. The images, now published in the journal *Science*, were captured at the free-electron X-ray laser LCLS at Stanford University in California. Further investigations are planned at SwissFEL, the new free-electron X-ray laser at PSI. Besides the scientists from Switzerland, researchers from Japan, the USA, Germany, Israel, and Sweden took part in this study.

The molecule retinal is a form of vitamin A and is of central importance to humans, animals, certain algae, and many bacteria. In the retina of the human eye, retinal triggers the process of vision when it changes its shape under the influence of light. In a similar form, certain bacteria also use this reaction to pump protons or ions through the cell membrane. Light energy can be stored in this way, as in the reservoir of an alpine hydropower plant, so that it is available on demand as biological fuel. To ensure efficient utilisation of light, the retinal molecule is embedded in proteins that play a critical role in regulating the process. The protein -regulated reaction of retinal is one of the fastest biological processes and occurs within 500 femtoseconds (a femtosecond is one-millionth of one-billionth of a second). That is roughly a trillion times faster than the blink of an eye, says Jörg Standfuss, who heads the group for time-resolved crystallography in the Division of Biology and Chemistry at PSI. What happens in the process on the atomic level has now been captured for the first time by PSI researchers, in 20 snapshots that they have assembled into a molecular movie. No one has previously measured a retinal protein at such high speed and with such precision. It's a world record, says Jörg Standfuss, who led the study.

The researchers studied the protein bacteriorhodopsin, which is found in simple microbes. When the retinal molecule embedded in the bacteriorhodopsin traps a light particle, it changes its original elongated shape into a curving form, like when a cat arches its back, explains the PSI researcher. Such changes can also be observed when retinal is examined in a solution without protein. There, though, different reactions, which are also less productive, take place. Proteins are like factories in which chemical reactions run especially efficiently, Jörg Standfuss explains. We wanted to look at how this interplay between the protein and the molecule functions.

A surprising observation

The researchers discovered that water molecules in the vicinity of the retinal play a critical role. They were able to observe how the water molecules moved aside and made room for the retinal molecule to do its cat-arching-its-back move – in the technical jargon, a trans-cis isomerisation. This detail, which no one had seen before, surprised Jörg Standfuss, as he explains with the help of the cat analogy: You expect that a cat might arch its back to scare another one away. But here the second cat runs away even before the first has arched its back. Computer simulations confirm the measurements, which could be explained by ultrafast quantum processes.

Besides the retinal reaction, the researchers were also able to detect protein quakes that had been predicted by theory. The arching of the cat's back does not require the entire energy of the light that falls on the protein. Excess energy is released, evidently, not in the form of heat but rather in vibrations of the protein.

New measurements planned at SwissFEL

For their images, the PSI researchers traveled to California, to the free-

electron X-ray laser LCLS at Stanford University. In the future, they will be able to realise such films right at PSI with the newly commissioned facility SwissFEL. For such studies, the sample is illuminated with extremely short and intense flashes of laser-quality X-ray light. The X-ray beams are diverted in different directions by the sample and generate diffraction patterns from which the original structure can be calculated.

As samples, the researchers use tiny crystals in which the bacteriorhodopsin is densely packed in an ordered state. The light sensor in the bacteriorhodopsin is excited by a short pulse from an optical laser. Afterwards, the X-ray flash hits the crystal and lights up the scene. The time between the optical signal and the X-ray flash determines how far the reaction will have progressed. Individual snapshots taken at different points in time can be spliced together into a movie.

After studying bacteriorhodopsin, the PSI researchers want to use SwissFEL to investigate the retinal in rhodopsin in our eyes. Similar retinal proteins can also be artificially incorporated into nerve cells, so it becomes possible to selectively activate nerve cells with light and study their function. With these retinal proteins, one can activate any region in the brain with the help of light, says Jörg Standfuss, explaining the goal of the new field called optogenetics. Measurements with SwissFEL are expected to contribute to the improvement of optogenetics applications.

More information: Przemyslaw Nogly et al. Retinal isomerization in bacteriorhodopsin captured by a femtosecond x-ray laser, *Science* (2018). DOI: 10.1126/science.aat0094

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