New 3-D microscope visualises fast biological processes better than ever

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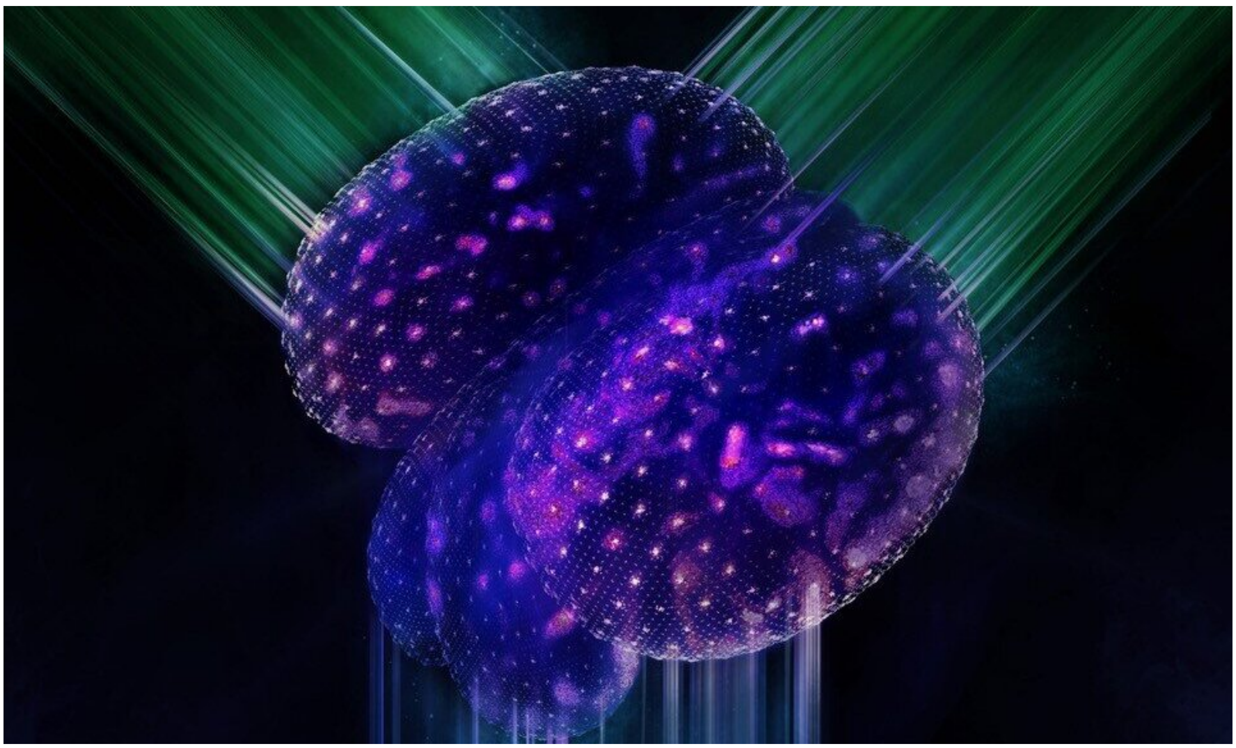

This illustration, based on real data shows the heart of a Japanese rice fish. The green and blue laser beams demonstrate how the newly developed 3D imaging microscope by researchers from EMBL is scanning the heart. Credit: Tobias Wüstenfeld

Researchers from the European Molecular Biology Laboratory (EMBL) in Heidelberg have combined their expertise to develop a new type of microscope. The revolutionary new light-field microscopy system makes it possible to study fast biological processes, creating up to 200 3-D images per second. Initial tests have already delivered new insights into the movement of blood cells in a heart.

"Many important biological processes occur in three dimensions and on millisecond timescales," says Lars Hufnagel on the rationale for developing the new microscope. Capturing these fast processes is a big challenge in biology. And showing them not only in 2-D but in 3-D is—next to the needed high resolution—the second main aspect of modern microscopy.

The research results are published in *Nature Methods*.

The new light-field microscopy system developed by EMBL group leaders Lars Hufnagel, Robert Prevedel and their teams overcomes both hurdles at once. "Our new method allows us to study processes both in 3-D and on timescales of 200 images per second," says Robert Prevedel. Lars Hufnagel adds: "On top of that, it delivers up to ten times better, namely truly isotropic, resolution than classic light field microscopy."

Previously developed microscopes, mostly based on light-sheet approaches, have also attempted to image fast biological processes but have only achieved much slower speeds than the new technique. As such, they were too slow to see dynamic processes within hearts and neuronal cells.

To demonstrate the capabilities of the new technique, the team studied the beating heart and blood flow in medaka—also known as Japanese rice fish—in real time. The medaka was used as it is a well understood model organism. In addition, blood cells move fast—up to one millimetre per second—which was a challenge for any existing microscope.

The images delivered by this test showed for the first time how individual blood cells move through the two heart chambers. "This opens up completely new possibilities," says co-author Joachim Wittbrodt from the Centre for Organismal Studies at Heidelberg University. "In showing how genetic backgrounds or mutations have an effect on the dynamics of heartbeats, the new technology can be used to research heart defects."

Constructing the new microscope was an interdisciplinary effort. The researchers within the two EMBL groups have backgrounds in various scientific fields: the multidisciplinary team comprised physicists, engineers, computer scientists and, of course, biologists.

"This new microscope demonstrates that EMBL is not only at the forefront of molecular biology research but also an important place to research and develop new technologies needed within the field," says Hufnagel.

The study on the medaka heart was only the first test for the new microscope. Robert Prevedel is looking forward to using the microscope to study the activity and dynamics of neuronal cell populations in these animals. "Future camera developments can further increase the imaging speed. This would make our new microscope technique an attractive tool to study the dynamics within small neuronal networks on millisecond time scales in 3-D," concludes Prevedel.

More information: Instantaneous isotropic volumetric imaging of fast biological processes, *Nature Methods*, DOI: 10.1038/s41592-019-0393-z , www.nature.com/articles/s41592-019-0393-z

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