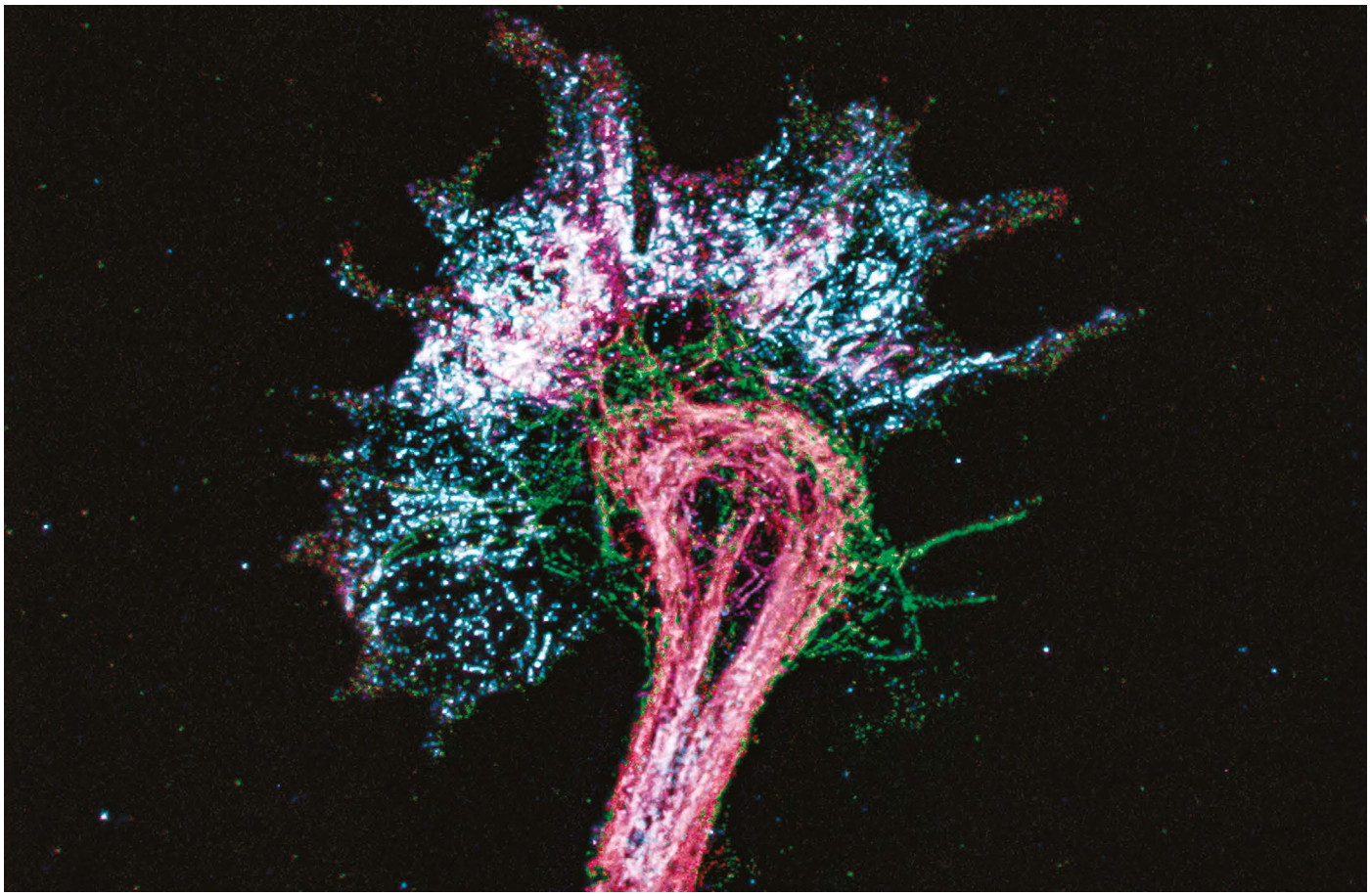
News in focus



ARTHUR CHIEN/SPL

High-resolution images can be produced by increasing the size of a nerve cell before fluorescence-microscopy imaging.

MAKING SAMPLES ONE BILLION TIMES BIGGER LETS SIMPLE MICROSCOPES PINPOINT AMINO ACIDS

Stretching protein samples in all directions pulls molecules farther apart, allowing them to be visualized using only light microscopy.

By Ewen Callaway

A technique that supersizes cells to reveal minute details has gone big — really big.

Using a polymer similar to those used in nappies to make them super-absorbent, scientists have expanded the volume of biological samples so they are one billion times bigger — 1,000-fold larger in each dimension. This level of expansion could inflate an individual cell to the size of a mouse brain and a US-dime-sized sample to the proportion of an Olympic swimming pool.

Researchers have used the technique to map the positions of amino acids (the building blocks of proteins) in proteins and small molecules called peptides using conventional light microscopes. The approach is outlined in a preprint posted on bioRxiv in June[1].

Previously, viewing molecules in such fine detail has typically been achieved by using costly and complicated techniques such as cryogenic electron microscopy (cryo-EM) and X-ray crystallography. "This is the democratization of structural biology," says study co-author Silvio Rizzoli, a neuroscientist and imaging specialist at the University Medical Center Göttingen (UMG) in Germany.

"It's really getting down to a ground-truth description of what a protein is," adds co-author Helena Hu, a bioengineer at the Massachusetts Institute of Technology (MIT) in Cambridge.

Expansion microscopy

The laws of physics limit the optical power of light microscopes: objects that are less than about 200 nanometres apart cannot

be distinguished. 'Super-resolution' light-microscopy techniques, which usually rely on optical tricks and costly kit, have cut this resolution limit to below 10 nm.

In 2015, MIT neuroengineer Edward Boyden, a co-author of the study, and his colleagues invented an alternative way to get extremely high resolution using ordinary fluorescent light microscopes[2]. Using a swelling hydrogel, the researchers expanded tissue samples about fourfold in each direction. This moved cellular components away from one another, improving resolution.

Researchers have since adapted Boyden's 'expansion microscopy' method to swell samples to greater volumes, but inflation has generally been limited to about a 20-fold increase in size.

To go bigger, the researchers developed a new hydrogel recipe in which samples were expanded multiple times. The team also used an expansion-microscopy approach called ONE microscopy[3] to map protein structures with a light microscope. Purified proteins were bonded to the hydrogel and then broken apart using enzymes or heat, enabling proteins to be stretched apart without compromising their 3D shape.

Gigantic proteins

Using their 1,000-fold expansion method, the researchers labelled several of the nine individual amino acids that make up a peptide called mCLING. They then imaged the relative locations of the building blocks using a fluorescent microscope. These measurements were consistent with structures of mCLING derived from computational simulations.

The method also revealed the structure of a protein called a nanobody (a small version of an antibody), as well as the locations of some of its amino acids. Furthermore, the researchers used the technique to map the previously determined structure of green fluorescent protein (GFP), a biotechnology workhorse used to label other proteins.

The researchers estimate that their model of GFP — reconstructed from thousands of snapshots — attained a resolution of around 1.2 nm, or 12 ångströms (Å). This is far from a 1.9-Å structure of GFP available in a public repository and determined using X-ray crystallography, or the level of detail that scientists routinely achieve using cryo-EM.

But co-author Ali Shaib, a nanoscale specialist at UMG, says that methodological improvements have driven resolution below 10 Å for purified proteins, in unpublished work. Rizzoli notes that the team is now able to determine the shapes of proteins that are still inside cells at around 10 Å. "We are trying to make cryo-EM like structures from affordable optical microscopes," Shaib says.

Still, Rizzoli argues that techniques such as 1,000-fold expansion microscopy should be judged on the biology that they can reveal. "I don't think it's about resolution. It's about what you can see."

We're gonna need a bigger microscope

Previous super-resolution light-microscopy techniques have achieved ångström-level resolution, says Lothar Schermelleh, a bioimaging specialist at the University of Oxford, UK, but the structural information that these methods provide is limited. "This paper changes everything," he says. "To see the GFP, this is just fantastic."

However, Kirti Prakash, a computational biologist at Anglia Ruskin University in Cambridge, UK, is sceptical that samples enlarged 1,000 times in each dimension still retain their original features and says that the structural details reported in the paper need to be validated using other methods as well. "It's very cool, sexy science. But, personally, I think there has been no new biology discovered."

Making biological samples one billion times bigger presents clear challenges. At that scale, even moderately sized proteins can occupy a microscope's entire field of view, says John Danial, an experimental photonics researcher at the University of St Andrews, UK. High-resolution structures make it necessary to 'average' numerous particles, so scientists might need to collect a large number of images to reconstruct a single protein structure, he explains.

Hu says that the technique could be used alongside automated imaging: the gels seem to retain their size for days without shrivelling. The technique can also image proteins that are too tiny for cryo-EM, she adds.

Still, Danial is hopeful that light-microscope techniques such as 1,000-fold expansion will deliver new structural insights into proteins and other biomolecules, and thinks that they could lower the economic barriers to structural biology. There is just one cryo-EM facility in Africa, for instance. "You could image a protein at a structural scale on a microscope that costs something like five to ten thousand pounds or dollars," Danial says. "That microscope exists where cryo-EM is not accessible."

1. Hu, H. *et al.* Preprint at bioRxiv https://doi.org/10.64898/2026.05.31.729018 (2026).
2. Chen, F., Tillberg, P. W. & Boyden, E. S. *Science* **347**, 543–548 (2015).
3. Shaib, A. H. *et al. Nature Biotechnol.* **43**, 1539–1547 (2025).

SHOULD NICOTINE BE REGULATED LIKE A NARCOTIC?

Palau asks United Nations to assess harms caused by the highly addictive substance.

By Rachel Fieldhouse

More than one billion people are dependent on nicotine globally. Now, a tiny archipelago in the Pacific Ocean known for its spectacular coral reefs wants to change that.

The Republic of Palau has asked the United Nations to review the harm caused by the highly addictive substance found in tobacco and vaping products. The nation wants nicotine to be added to a list of substances that the organization regulates, which include narcotics and psychotropic drugs such as amphetamines.

That would effectively make it illegal to sell products containing nicotine that are not considered medicinal, says Renee Bittoun, a nicotine-treatment specialist at the Woolcock Institute of Medical Research in Sydney, Australia. However, Bittoun thinks it is unlikely that nicotine will be added to the list, because tobacco companies will argue strongly against this.

Around 1.2 billion people use tobacco and at least 100 million people use electronic cigarettes, also known as vapes, according to the World Health Organization. The dangers of smoking are well known: it increases a person's risk of developing heart disease and stroke, as well as many cancers. Tobacco smoking kills more than 7 million people each year, including 1.6 million non-smokers who are exposed to second-hand smoke.

> **"Young people across the Pacific are being targeted by products that have never been critically reviewed."**

In the past decade, vapes have become more popular, particularly among young people, who are nine times more likely to vape than are adults. Vaping is highly addictive and can cause lung injuries; it might also increase