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PRESS RELEASE

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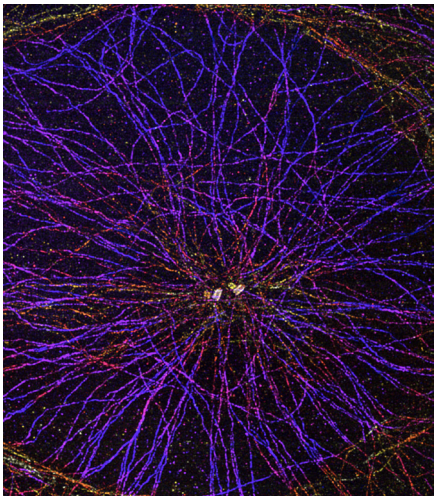
Inflate cells to observe their inner life

UNIGE researchers have developed a technique to visualize cellular elements with a resolution unequalled in optical microscopy

Cells are made up of tiny compartments, organelles, which have precise structures and roles. Being able to observe these structures represents an enormous challenge and would allow a better understanding of cellular functioning. However, until now, fluorescence microscopy did not offer sufficient resolution to obtain a detailed visualization of the ultrastructure of organelles. Today, researchers at the University of Geneva (UNIGE), Switzerland, have succeeded in enlarging biological samples without deforming them and revealing details at a nanometric scale, that is to say a millionth of a millimeter, an unsurpassed resolution in optical microscopy. This new technique, described in the journal *Nature Methods*, makes it possible to visualize the architecture and composition of organelles, as well as those of protein complexes of various types. The magnifying glass effect obtained even allows to detect biochemical modifications on components of these complexes, which can be used for mapping purposes.



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Human cell, whose microtubules forming the cytoskeleton radiate from the centrosome, their organizing center constituted of 4 centrioles (the 4 cylinders).

High definition pictures

It all started with baby diapers. Edouard Boyden, a professor at the Massachusetts Institute of Technology (MIT), had the idea to divert the properties of their component, sodium acrylate, for research purposes. “Three years ago, Edouard Boyden developed a method to embed cell structures with a mixture of sodium acrylate and acrylamide, a chemical substance that is formed during the browning of French fries. He then marked the targets to be observed with fluorescent molecules before swelling the whole biological sample with water. The targets had to be destroyed, but it was possible to visualize their fluorescent borders with a good resolution, thanks to the expansion obtained”, explains Paul Guichard, Professor at the Department of Cell Biology of the UNIGE Faculty of Science.

Preserve the architecture of the cell

The Geneva biologist is interested in the formation and functioning of organelles, cellular structures that perform specific tasks. Mitochondria, the cell’s power plants, and the centrosome, from which the cell skeleton is formed, are part of them. “We investigated whether it was possible to adapt this technique to observe organelles without having to destroy them, and enlarge them without deforming them”, notes Virginie Hamel, a researcher at the Department of Cell Biology and co-responsible for the study.

In collaboration with researchers from the University of Würzburg in Germany, the biologists modified the method, tested new conditions and analyzed the images obtained with different techniques. They finally found the right recipe, which allows the biological sample to be

inflated while maintaining it in its native state, without prior chemical fixation that could denature it. “Cells gradually expand and their components separate from each other while enlarging. The architecture of the various elements is preserved and it becomes possible to observe them with a resolution hitherto unattained in optical microscopy”, says Davide Gambarotto, researcher in the Geneva group and first author of the study.

Locate the proteins that make up the organelle

Named Ultrastructure Expansion Microscopy (U-ExM), their technique reveals cellular details at the nanoscale, which were only visible with electron microscopy. “However, electron microscopy does not allow to locate the proteins that constitute the observed elements. Our method combines the advantage of fluorescence microscopy to detect molecules, and high resolution to visualize the fine structure of organelles or of macromolecules”, explains Virginie Hamel.

The images of centrosomes obtained in three dimensions surpass those derived from techniques distinguished by the 2014 Nobel Prize, and even make it possible to detect biochemical modifications on the molecules that compose the organelles. “It is now becoming possible to map large intracellular molecular complexes. This method could also be used to reveal signatures of pathological processes at the very heart of the cell”, concludes Paul Guichard.

*A video showing the cytoskeleton of the unicellular alga Chlamydomonas is available **here**.*

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