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How dense is it inside living cells?

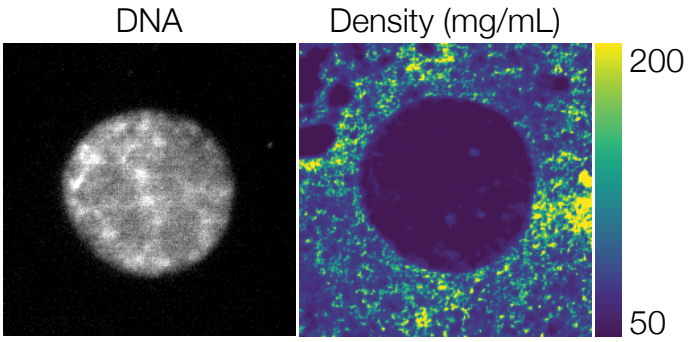
Just as life pulsates in big vibrant cities, it also prospers in crowded environments inside cells. The interior of cells is densely packed with biomolecules like proteins and nucleic acids. How is all this material distributed within a cell and what regulates its distribution? In a recent study published in "Nature Communications" researchers measure subcellular densities across a wide range of organisms. Their aim is to better understand biomolecular processes ranging from yeast cells to human cells.

Not what most scientists would think

Conventional scientific textbooks describe the cell nucleus as a compartment packed with an impressive amount of DNA wrapped around histone proteins. Now, an international team of researchers with the participation of the Max-Planck-Zentrum für Physik und Medizin, Erlangen (MPZPM), the Max Planck Institutes for Infection Biology, Berlin (MPIIB) and the Science of Light, Erlangen (MPL) has discovered that – contrary to expectations – the nucleus is less dense than the surrounding cytoplasm. Despite their rich biomolecular composition, nuclei contain less dry mass than the same volume of the surrounding cytoplasm.

Prof. Simone Reber, MPIIB and University of Applied Sciences, Berlin explains why it is important to understand how crowded cellular environments are: "It is essential to understand the 'real' environment inside cells as it affects biomolecular structure, dynamics, and function. The main discovery of our study is that although different species broadly vary in their absolute intracellular density, they maintain the same nuclear-to-cytoplasmic (NC) density ratio."

"While every organism is unique in its biomolecular composition, it is likely that the fundamental physical principles of pressure balance set the density and the volume of the nucleus," explains Prof. Vasily Zaburdaev, MPZPM and Friedrich-Alexander-Universität Erlangen-Nürnberg.



A cell nucleus reconstituted *in vitro* in *Xenopus laevis* (African clawed frog) egg extract. Left image shows a fluorescence image where DNA has been stained and right image shows a density map of the same nucleus aquired using Optical Diffraction Tomography (ODT).

Using light to probe density at microscales

How can density be measured in microscopic objects such as individual cell compartments? Scientists use light for this purpose. Not only does light allow cells to be examined, it also enables them to be manipulated. Light can exert forces, enabling laser beams to "pull" on cells and measure their mechanical properties using an "optical stretcher". "We had previously tried to use our optical stretcher on nuclei, but were not successful. The physically plausible – but back then biologically counterintuitive – explanation was that the nucleus had a lower density than its surrounding material," adds

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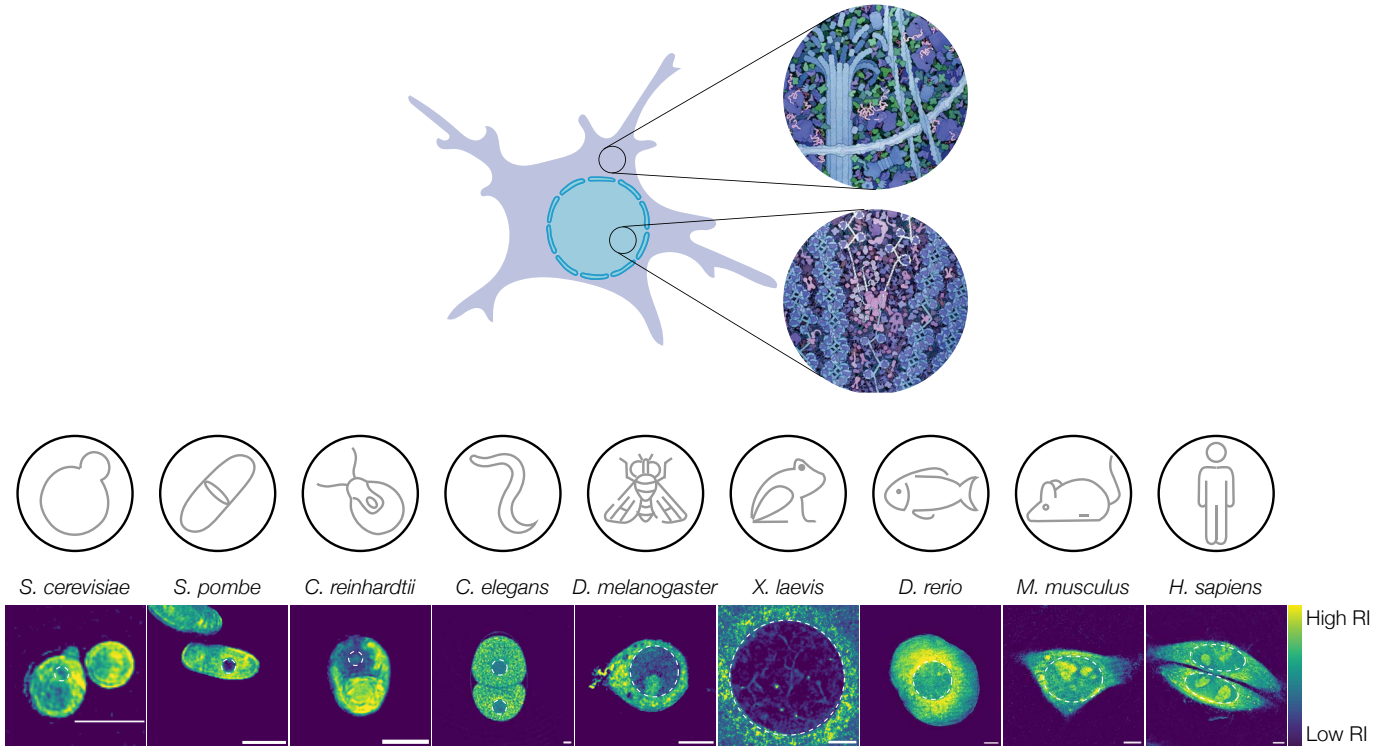
Prof. Jochen Guck, MPZPM and Director at MPL, Erlangen. Therefore, the researchers developed an optical setup which allowed them to obtain three-dimensional density distributions inside cells at high resolution by combining optical diffraction tomography and confocal fluorescence microscopy.

Density as a fundamental property and diagnostic indicator

"While NC density ratios are maintained from yeast to human cells, we do start seeing deviations in disease. During stressed cellular states such as ageing, the so-called senescence, cell nuclei become denser than the cytoplasm. Thus, the study points to the fundamental importance of density as a variable that determines healthy cellular processes," says Reber. The scientists now want to understand how cells establish and maintain a specific intracellular density distribution in order to decipher further biophysical mechanisms that regulate cell function in both healthy and pathological states.

An international and interdisciplinary effort

"Apart from being an exciting question to tackle, what stood out for me was how we were able to synergize the expertise of scientists at different locations to achieve a common goal," says Abin Biswas, postdoc at MPZPM and MPIIB and first author. Indeed, this work was the result of close collaborative cooperation with international colleagues from the MPI for Molecular Genetics, MPI for Cell Biology and the Albert Einstein College of Medicine in New York.



Scale bar: 5 µm

Nuclei from different organisms have a lower density than the surrounding cytoplasm. Top: Illustration of the complex interior within the nucleus and cytoplasm (Illustration by David Goodsell). Representative images of nuclei from each organism. Color gradient shows the density distribution from low (blue) to high (yellow).

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*The **Max-Planck-Zentrum für Physik und Medizin** is conceived as a joint effort between the Max-Planck-Institute for the Science of Light (MPL), the Friedrich-Alexander-Universität Erlangen-Nürnberg (FAU) and the Universitätsklinikum Erlangen (UKER). The new scientific center aims to apply advanced methods from experimental physics and mathematics to basic biomedical research with an emphasis on the intercellular microenvironment. Learn more at mpzpm.mpg.de.*

***Max Planck Institute for Infection Biology (MPIIB):** Founded in 1992, the MPIIB is located on the historic campus of Berlin's Charité hospital. Here, researchers investigate how pathogens cause disease and how their hosts respond. In order to find answers to fundamental questions in infection biology, the research spans various levels: from atoms, molecules, cells, tissues, and organisms to clinical aspects and social contexts.*

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