

# Scientists Unlock Protein Structures from a Single Cell

## A new method brings structural biology closer to real cellular life

Press Release, 13 May 2026

**An international research team, with a leading contribution from Dominik Pinkas from the Institute of Molecular Genetics of the Czech Academy of Sciences (IMG), has developed a method that makes it possible to determine the near-atomic structure of proteins from a single microscopic crystal inside a single cell. The study, published in Nature Communications, combines intracellular protein crystallization with electron diffraction, overcoming one of the major bottlenecks of structural biology: the need for vast amounts of material. By reducing the required sample volume by several orders of magnitude, the approach enables high-resolution structural studies of proteins that are difficult to purify or crystallize in large quantities, bringing molecular structure determination closer to the level of individual cells.**

## From a truckload of material to a single crystal

Understanding the shape of proteins—the molecular machines that drive nearly all processes in living organisms—is essential for modern biology and medicine. Traditionally, this has required large protein crystals, tens of thousands of microscopic ones, or lots of very concentrated purified protein solution to collect enough data for a single structure. In practice, this meant that many proteins simply remained inaccessible to structural analysis.

The new method, called IncelluloED, changes this paradigm. Instead of pooling data from enormous numbers of microcrystals, researchers can now determine a structure from one intracellular microcrystal. In the study, a protein structure obtained from a crystal volume of about 1.6 cubic micrometers provided comparable detail to a structure previously derived from a total volume exceeding 11 million cubic micrometers using serial X-ray crystallography.

Put simply, it is the difference between needing an entire swimming pool of material and working with a single drop—while still recovering the same essential information.

## Seeing matter at the scale of atoms

IncelluloED achieves a resolution of around 1.9 angstroms, allowing scientists to resolve individual atoms within a protein. To put this into perspective: if the width of a human hair were scaled up to the size of the Czech Republic, one angstrom would correspond roughly to the size of a small coin in

the center of Prague. This is the level of detail that can now be reached from a single crystal inside a cell.

*“What we demonstrate is a fundamental change in how much material is needed for high-resolution structural biology,”* says Dominik Pinkas from the Institute of Molecular Genetics of the Czech Academy of Sciences (IMG). *“Instead of averaging over tens of thousands of crystals, we can extract comparable structural information from a single crystal inside a single cell. That removes a major barrier for studying proteins that are difficult to obtain in large quantities.”*

## Proteins studied inside cells, not test tubes

A key advantage of the approach is that protein crystals are grown inside living cells, avoiding many of the purification steps that can alter or damage sensitive proteins. While the final measurements are performed on frozen, thinned cellular sections, the structures originate from proteins formed in a cellular context, preserving features that may be lost during conventional sample preparation.

The method builds on widely used cryo-electron microscopy tools, making it accessible to many laboratories without the need for large international X-ray facilities. In the long term, the authors envision this as a step toward a “single-cell structural laboratory”—where detailed molecular structures can be determined from minimal biological material.

By dramatically lowering the material requirements for structure determination, IncelluloED opens new opportunities for studying proteins that were previously beyond reach, advancing our understanding of molecular biology at its most fundamental scale.

**Publication:** <https://www.nature.com/articles/s41467-026-69205-6>

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