Lab technology brings Nobel-winning cryo-EM into sharper focus

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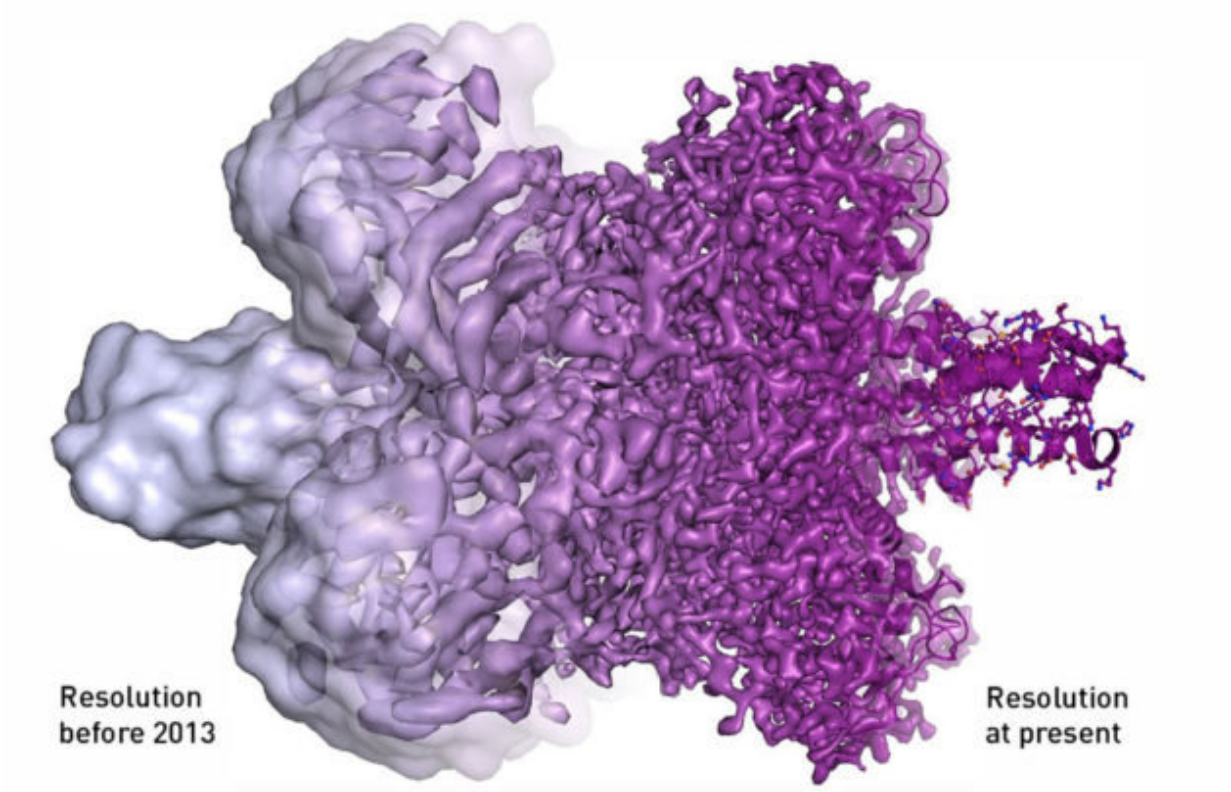

Credit: Martin Hogborn/The Royal Swedish Academy of Sciences

Pioneering work by scientists at the Department of Energy's Lawrence Berkeley National Laboratory (Berkeley Lab) played a key role in the 2017 Nobel Prize in chemistry, awarded today, honoring the development of cryo-electron microscopy, or cryo-EM, an imaging

technique that has launched the fields of structural biology and biochemistry into an exciting new era of discovery.

Jacques Dubochet, Joachim Frank and Richard Henderson were awarded the Nobel for their foundational work in cryo-electron microscopy, which uses electrons to image samples that have been frozen mid-motion, expanding a technique that had previously been used for dead or inanimate matter to proteins and other biomolecules.

In the scientific background detailing the development of cryo-EM, the Nobel committee highlighted a "series of critical developments" that has made it possible to take full advantage of the Nobel laureates' achievements. They cited multiple papers co-authored by Berkeley Lab scientists Robert Glaeser, Ken Downing, and Peter Denes.

Glaeser, who is also a UC Berkeley professor emeritus of biochemistry, was part of cryo-EM's formative years. (Notably, Glaeser was an advisor for Nobel winner Joachim Frank when he was a postdoctoral researcher at UC Berkeley in the early 1970s. Frank was also a principal investigator at Berkeley Lab's National Energy Research Scientific Computing Center, or NERSC, from 2004-2006.).

Glaeser and colleagues were among the first to show the importance of freezing samples to liquid nitrogen temperatures to protect them from the damage of intense electron beams. The Nobel committee noted Glaeser's research on quantifying electron-induced radiation damage and providing guidance for the use of low-electron doses averaged over multiple samples.

Robert Glaeser in front of his electron microscope equipped with a special cold stage. Credit: Roy Kaltschmidt/Berkeley Lab

To minimize damage to the sample, only a few electrons are used to image biological macromolecules, creating "noisy" images. The use of averaging is meant to deal with that "noise," but it requires the samples to be precisely aligned. That created a serious bottleneck when managing tens to hundreds of thousands of images.

Enter the revolution enabled by new direct detector technology, particularly the kind developed by Peter Denes, a senior staff scientist at Berkeley Lab. Rather than take a single picture for each sample, the direct detector camera shoots multiple frames that are then put together to create a high-resolution image. The technology has been compared to the process of recording a movie, and it effectively eliminates the problem of blur or noise when the sample moves.

Denes had been developing detectors based on complementary metal

oxide semiconductors (CMOS) technology for applications in materials science. The work allowed for direct detection of electrons, which directly hit pixel sensors in a thin layer of silicon. The state-of-the-art approach allowed for the direct "counting" of electrons and essentially eliminated the problem of noise.

His first prototype was developed for the Transmission Electron Aberration-corrected Microscope (TEAM), a DOE-funded project at the National Center for Electron Microscopy (NCEM), based at Berkeley Lab's Molecular Foundry. Denes pointed out that because the technology was initially designed for applications in materials science, it had to be fast to catch the movement of atoms and reveal how defects spread.

The Nobel committee specifically noted the advantage in speed as well as the improved signal-to-noise ratio and spatial resolution in this new generation of detectors.

A version of the Berkeley Lab camera has since been commercialized by Gatan, Inc., based in Pleasanton, California, and used in research labs, including that of Eva Nogales, faculty scientist at Berkeley Lab's Molecular Biophysics and Integrated Bioimaging Division.

Berkeley Lab's work on improving electron microscopy technology is ongoing. Both Glaeser and Denes credited the collaborative ecosystem at Berkeley Lab for fostering innovation in electron microscopy.

This collaborative environment was highlighted at a recent workshop on the "Future of Electron Microscopy," organized last year at Berkeley Lab by Denes; Andy Minor, NCEM director, and Paul Adams, director of the Molecular Biophysics and Integrated Bioimaging Division.

"I can't think of any other place in the United States that has the combination of expertise and resources we have here in Berkeley," said

Denes. "The experience in electron microscopy, the strong background in biological and materials science research, the high-performance computing resources, the track record of developing innovative technology, are all here under one roof."

In 2015, Denes, Downing and Uli Dahmen, former director of NCEM, were given Lab Lifetime Achievement Awards for their electron microscopy work at Berkeley Lab.

Provided by Lawrence Berkeley National Laboratory