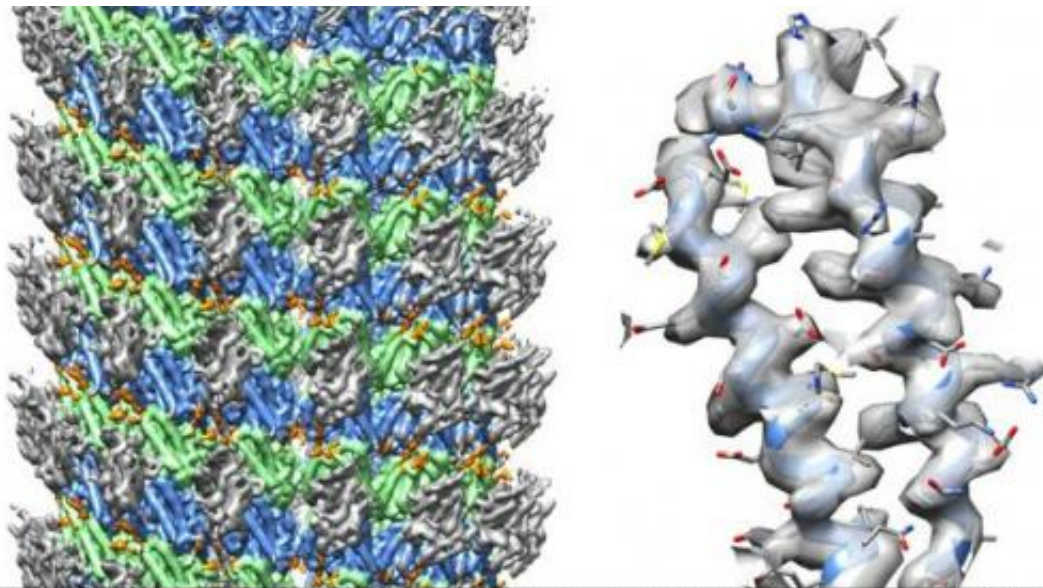


New player emerges in mapping protein structures

September 20 2013, by Dan Krotz



The left image is a cryo-EM reconstruction of a microtubule made of repeating $\alpha\beta$ -tubulin subunits (α -tubulin green, β -tubulin blue) bound to the motor protein kinesin (grey). It was obtained from microtubule images containing about 150,000 tubulin subunits recorded on a direct electron detection camera. The estimated resolution is approximately 3.8 Å. The right panel shows a segment of the density map for an alpha helical segment of the protein depicting clear density for side chains. (Credit: Rui Zhang and Eva Nogales, Berkeley Lab and UC Berkeley)

(Phys.org) —If you keep up with biology, you've probably seen those colorful images in which the atom-by-atom structure of a protein is portrayed by a tangle of ribbons. For the past couple of decades, scientists have been hard at work deriving these structures, which provide clues as to what proteins do.

It's critical research. Proteins are workhorse compounds that sustain all living things. The next drug breakthrough, or insight into how life works at the molecular scale, could originate from one of these images.

Most protein structures are obtained via x-ray crystallography. Scientists also use [nuclear magnetic resonance imaging](#) to solve structures. And coming in at a distant third is a technique called single-particle cryoelectron microscopy (cryo-EM), in which a macromolecule is immobilized in a thin film of vitrified buffer and inserted into the vacuum of an [electron microscope](#).

Cryo-EM's back-of-the-pack status is changing, however, thanks in part to technology developed at Berkeley Lab.

The shift is due to advances in the camera, or detector. Traditional high-performance [electron microscopy](#) cameras record the image indirectly. Electrons hit a scintillator, and the resulting light is sent to a CCD chip, where it is converted to an electronic image and read-out.

But a new generation of cameras offers a more direct approach. With these cameras, electrons hit the silicon pixels directly, and the resulting events are collected by microfabricated electronics that render an image.

One such direct-conversion [electron detector](#) owes its origins to a camera developed for one of the world's most powerful electron microscopes, TEAM, which is located at Berkeley Lab's National Center for Electron Microscopy. The camera was engineered by Berkeley Lab's Peter Denes and colleagues, and began its service when TEAM started operating in 2009.

A version of the Berkeley Lab camera has since been commercialized by the Pleasanton, California-based Gatan, Inc. Its 16 million pixels capture events at 400 frames per second. Several are now in use at UC San

Francisco, Caltech, and in the UC Berkeley lab of Eva Nogales, who is also a scientist in Berkeley Lab's Life Sciences Division.

This camera, along with two other commercially available direct-conversion electron cameras, are making cryo-EM a real player when it comes to mapping protein structures.

For example, scientists from the United Kingdom used the method to [derive a 4.5-angstrom resolution image of the yeast ribosome](#), and did so using only two percent of the data than was necessary for earlier efforts that produced lower-resolution results. Previously, scientists had to merge data from as many as a couple of million single particles in order to improve the signal-to-noise ratio, and even then they were not able see ribosomal structures such as side chains. Now, only 35,000 particles are needed.

"That's a huge and sudden improvement," says Robert Glaeser, a scientist in Berkeley Lab's Life Sciences Division and a pioneer in using cryo-EM to determine the structure of proteins. Glaeser outlined the impacts of direct-conversion cameras in a recent News and Views [article](#) for *Nature Methods*.

In addition, as Glaeser outlines in the *Nature Methods* article, the new, direct-conversion camera makes it possible to record a 'stroboscopic movie' while exposing a protein to electrons. Such movies are important because the cryo-EM specimen constantly moves while an image is being recorded, probably because of stresses caused by radiation damage.

Improvements like these put many important proteins within reach for the first time. Recently, scientists from UC San Francisco used cryo-EM to [solve the structure](#) of a much smaller protein complex than previously possible with the technique: the 20S proteasome. And Nogales is using

the technique to derive high-resolution structures of a microtubule, a protein that helps to maintain the structure of a cell among other functions.

There are several advantages to using cryo-EM for deriving protein structures. Unlike [x-ray crystallography](#), a protein doesn't have to be crystallized in order to map it, which is a time consuming process. And a protein's structure can be determined in its biochemically native solution.

So, the next time you see an image of a near atomic-scale structure of a [protein](#), be sure to read the caption. Don't be surprised if it's derived from single-particle cryo-EM.

Provided by Lawrence Berkeley National Laboratory

Citation: New player emerges in mapping protein structures (2013, September 20) retrieved 26 April 2024 from <https://phys.org/news/2013-09-player-emerges-protein.html>

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