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Announcement

Paper of the Year Award

Beam-induced motion of vitrified specimen on holey carbon film, by A.F. Brilot, J.Z. Chen, A. Cheng, J. Pan, S.C. Harrison, C.S. Potter, B. Carragher, R. Henderson, N. Grigorieff [J. Struct. Biol. 177 (2012) 630–637]

Brilot

Beam-induced motion, first described by Henderson and Glaeser in 1985, is a well-known problem that has plagued users of electron cryo-microscopy (cryo-EM) for decades. The motion occurs while the electron beam irradiates the sample and leads to significant blurring of the image and, ultimately, to loss of resolution in three-dimensional reconstructions of the visualized molecules. The cause of beam-induced motion is still not fully understood, but likely results from the radiation damage suffered by the sample under the beam, as well as specimen charging due to ejected electrons. The goal of the work reported by Brilot et al. was to better understand beam-induced motion. The project began with images of rotavirus double-layered particles (DLPs) to demonstrate the application of the so-called tilt pair test originally described by Henderson & Rosenthal. DLPs were kindly provided by Junhua Pan and Stephen Harrison and images were initially recorded by James Chen. When analyzing the images, Richard Henderson noticed systematic deviations in the measured DLP rotations that he ascribed to beam-induced motion. Additional

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experiments by James and Axel Brilot confirmed Henderson's hypothesis and led to a more extensive study, carried out by Axel. The study included a more thorough statistical analysis of particle rotations and translations observed in exposure series under different experimental conditions. While this study did not lead to a solution for stopping beam-induced motion, it showed that the motion is more extensive in the beginning of the exposure and then slows down, a result that has been reproduced since then by several other groups.

While these experiments were ongoing, a new type of detector, called a direct electron detector, became available. The potential advantages of direct detection were first described by Faruqi in 2001. This was followed by the development of viable cameras as real alternatives to older detectors (film, scintillator-based cameras). The development occurred in parallel by Faruqi and co-workers at the MRC Laboratory of Molecular Biology (Cambridge, UK) and a team led by Ellisman, Xuong and co-workers at the University of California, San Diego. The latter effort produced the first commercially available device (the DE-12 camera, Direct Electron), and the first of these cameras was installed at the National Resource for Automated Molecular Microscopy (NRAMM) at The Scripps Research Institute, run by Bridget Carragher and Clint Potter. In addition to the higher sensitivity (DQE) compared to older detectors, the CMOS technology underlying the DE-12 camera is also able to record movies at a rate of 40 frames/second, ideal for the study of motion under the beam. The recording of movies was not a new idea: in 1984 Kunath et al. used a TV camera to record movies of glutamine synthetase embedded in negative stain to study beam damage and to reduce blurring due to sample stage drift. The correction of stage drift was also accomplished in movies collected by McMullan and Faruqi (2008) and Glaeser et al. (2011) who used an early type of a direct detector. Jointly with the Carragher/Potter lab, Axel and Anchi Cheng continued the study of beam-induced motion of DLPs using the DE-12 camera. They were the first to demonstrate that image blurring produced by beam-induced motion on ice-embedded specimens can be significantly reduced by aligning movie frames. This post-processing of electron micrographs thus overcomes one of the major obstacles limiting the resolution of cryo-EM structures. Movies have since transformed the field of cryo-EM and are now in common use. Several groups, including those of Cheng at the University of California, Scheres at the MRC-LMB and Rubinstein at the University of Toronto have implemented their own movie processing algorithms, building upon the pioneering work by Brilot et al. Together with the improved sensitivity of direct detectors, movie mode has made single particle cryo-EM a high-resolution technique on par with X-ray crystallography, without the need for crystals.

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