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Future requirements for detectors in Electron Cryo-microscopy

Detectors have played a central role in the structure determination of biological macromolecules to near-atomic resolution using electron cryo-microscopy. Over the past two or three years progress has been so rapid that it has been called a 'revolution'by a leading structural biologist [1]. Further progress in detector technology is essential for obtaining near-perfect detectors with a faster readout and to have a higher time resolution in imaging mode. It has been established that the highest DQE can only be obtained in the 'counting' mode with electron sub-pixel impact localization [2].
Advances have been possible due to developments of detectors based on backthinned CMOS technology; these detectors have a high detective quantum efficiency for 300 keV electrons at all spatial frequencies and can read out at a sufficiently high speed to enable movie-mode imaging [3]. The detector development can be divided into two related parts: the detector and the readout and processing electronics. Our present detectors use 180 nm lithography, which have been superseded by 65 nm or finer lithography, with superior performance. We also need larger detectors with 8k x 8k pixels and faster readout to collect data at 2000 frames/second. Since the detectors are exposed to the direct beam of 100 –300 keV electrons in the microscope they need to be sufficiently resistant to radiation damage over several years operation. Data readout, pre-processing and storage are challenging issues. During image recording data output will be several hundreds of GBytes/second, which needs pre-processing for event localisation and disk storage.
We think that a detector with the proposed parameters would transform the field of electron cryo-microscopy by allowing considerably more macro-molecular structures to be solved, which are not accessible with present day detectors. For example, such structures could include many lower molecular weight membrane proteins, whose detailed structure is vital for intelligent drug design.

[1] W. Kühlbrandt, The Resolution Revolution, Science, 343 (2014) 1443-1444.
[2] G. McMullan, A.T. Clark, R. Turchetta, A.R. Faruqi, Enhanced imaging in low dose electron microscopy using electron counting, Ultramicroscopy, 109 (2009) 1411-1416.
[3] G. McMullan, A.R. Faruqi, D. Clare, R. Henderson, Comparison of optimal performance at 300 keV of three direct electron detectors for use in low dose electron microscopy, Ultramicroscopy, 147 (2014) 156-163.

Summary

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