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Direct single electron detection with a CMOS detector for electron microscopy

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Abstract

We report the results of an investigation into the use of a monolithic active pixel sensor (MAPS) for electron microscopy. MAPS, designed originally for astronomers at the Rutherford Appleton Laboratories, was installed in a 120 kV electron microscope (Philips CM12) at the MRC Laboratory in Cambridge for tests which included recording single electrons at 40 and 120 keV, and measuring signal-to-noise ratio (SNR), spatial resolution and radiation sensitivity. Our results show that, due to the excellent SNR and resolution, it is possible to register single electrons. The radiation damage to the detector is apparent with low doses and gets progressively greater so that its lifetime is limited to 600,000–900,000 electrons/pixel (very approximately 10–15 krad). Provided this detector can be radiation hardened to reduce its radiation sensitivity several hundred fold and increased in size, it will provide excellent performance for all types of electron microscopy.

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1. Introduction

Electron microscopy is used as a tool for obtaining high-resolution structural information in a broad range of disciplines, including physical, material, medical and biological sciences. Our primary interest as structural biologists is in using it to obtain near-atomic resolution structural information from large biological molecules and macro-molecular complexes. Protein crystallography, using X-ray diffraction, is the more commonly used technique for structure determination when good three-dimensional (3D) crystals, which diffract to high resolution, are available. However, many molecules can either not be crystallized or do not yield satisfactory data to high resolution. In

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some favourable cases large molecules can form, either naturally or with further biochemical processing, 2D crystalline arrays to which electron crystallographic methods can be applied to obtain near-atomic resolution results [1]. In the majority of structural investigations, however, 2D crystals are not available and the alternative method of single particle analysis is employed. Single particle analysis is somewhat similar to tomography in that a large number of isolated single particles are imaged, in random orientations, followed by sophisticated algorithms for averaging resulting finally in the model. The resolution attainable with single particle analysis is so far lower than for electron crystallography.

Due to the high sensitivity of biological specimen to radiation damage it is important to optimize the data collection strategy and detection techniques so that the maximum amount of information is obtained from the images. A detection technique, which offers very high quantum efficiency, very good resolution and minimal or no noise is consequently very desirable.

There are several key requirements for such a detector. Firstly, every electron should be detected, preferably with every electron having the same contribution to the image, such as would be the case in an electron counter. The next best thing to an electron counter would be a detector with the least variation in signal from each electron, and therefore highest detective quantum efficiency (DQE). Secondly, the point spread function (PSF) should be as small as possible so that the detection of electrons is not spread out over several pixels. A narrow PSF gives rise to the highest modulation transfer function (MTF) at the resolution limit given by the Nyquist sampling limit. Lastly, it is important to have minimal or no noise so that the image is limited only by the electron statistics. Thus a zero-noise pixellated electron counter would be ideal, but the next best approach would be a very low noise detector with high sensitivity and small PSF. This paper describes the properties of such a detector.

2. Electronic detectors : a recent history

The ability to read out images in electronic format is a very desirable feature for electron microscopy as discussed in a recent review [2]. The main advantages of electronic methods over the more traditional film methods could be summarized as

(i) developing or densitometry of film is not required, providing
(ii) access to data immediately, with
(iii) data in digital format, and
(iv) much improved signal-to-noise as film suffers from fog and dust.

The two main types of electronic detection technologies currently being pursued are indirect detection using light-emitting phosphors with cooled CCDs [3] and direct detection in hybrid pixel detectors, HPDs [4,5]. The former, viz. indirect CCD technology is relatively mature and well established but suffers from poor spatial resolution due to multiple light scattering within the phosphor and fibre optics. The second technology, viz. HPDs provides very high efficiency and, due to the ability to set high thresholds, no noise. However, HPDs utilize a difficult technology for large area sensors, viz. bump-bonding between the detector and readout ASICs; this makes it difficult to build sufficiently large area detectors without introducing some dead space between the sensitive areas.

With the advent of low-noise scientific-grade CCDs, developed originally for applications in optical astronomy, electronic methods of detection became more widely applied, at least in electron diffraction, for reasons discussed below. The main reasons why CCDs have not been used for direct detection of electrons were high levels of radiation damage and limited dynamic range due to the large amount of charge deposited by an incident electron. The usual method employed to circumvent this drawback was to use an indirect method of recording electrons, by conversion into a visible light image in a phosphor followed by a transfer of the image onto a cooled CCD, which acts as an integrating detector. The optical transfer is effected either with a lens or fibre optics [2]. The latter have been successfully used in our laboratory mainly for recording electron diffraction data as part of fairly extensive studies of different