A 4k by 4k 8000fps large format event-based sparse readout direct electron image sensor

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Introduction

We describe the electron-to-image signal chain and performance of a high-speed, large format (4096 x 4096), 8µm pitch, event-based, direct electron CMOS imager for cryogenic electron microscopy (cryo-EM) applications. The distinguishing elements in this signal chain are: use of current-mode circuits instead of voltage-mode to avoid settling lag, and on-chip event detection combined with sparse readout to minimize the irrelevant information transferred per frame. This resulting image sensor can operate at an exposure rate approx. 8x the current nearest competing camera while maintaining high detection efficiency and low noise at high speed; specifically, the sensor exceeds 2500fps in "brute force" readout mode and 8000fps in "event-based sparse" readout mode, and is currently the fastest 4k sensor for cryo-EM application. The detailed sensor architecture, event based sparse algorithm and its implementations were previously discussed in [1,2,3]; its stitching configuration, the chip photograph, and the 4T radiation hard pixel layout are shown in Figure 1(a-c).

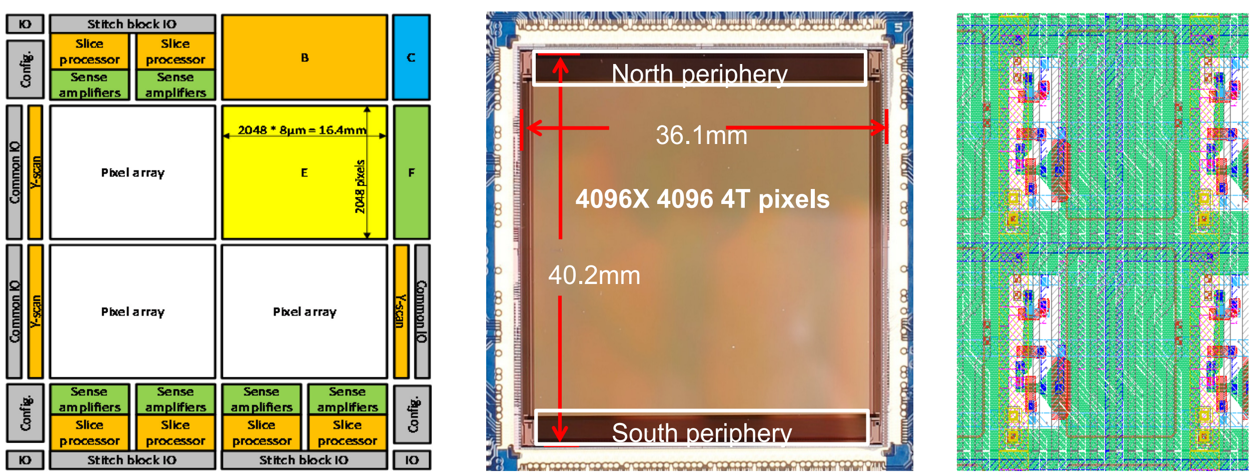

Figure 1 (a) The sensor architecture floor plan, (b) chip photo and, (c) pixel layout showing the 16 column wires.

Signal chain

In an electron microscope, the incident high-energy primary electrons are detected directly in a thin silicon layer; the quantity of free electron-hole pairs are induced along the trajectory being a function of the linear energy transfer (LET) for a given primary electron and the silicon thickness. As illustrated in Figure 2, the free electrons deposited in the lowly doped epi layer, and especially in the depletion region, are quickly collected by the nearby pixel PPD. When the pixel is accessed subsequently, the collected charges transfer to the floating diffusion (FD) node which drives the gate of the source follower (SF) and modulates its output current. Because this pixel outputs current, a programmable gain transimpedance amplifier (TIA) is needed to amplify this modulated SF current. The TIA output is quantized (sampled and digitized) by an on-chip programmable threshold comparator [2]. Correlated double sampling (CDS) based on reset value being sampled on capacitor C_2 and C_3, is used when performing the comparison, which cancels the KTC noise from FD and C1, as well as the voltage offset of SF and TIA. If the collected electrons are above the comparator trigger level, a digital signal '1' is stored in the SR register. At each side of the sensor, a slice of 16 rows will be selected at the same time, which generates 32x4096 bits simultaneously.

The digital signal readout can be configured to either 1) send out *all* pixel data in the "brute-force" readout mode or 2) only the events data in "event-based sparse" readout mode. An event is encoded as follows: when one or more pixel contains a '1' in a 16 by 4 pixel kernel, a flag is generated that will allow to output the kernel data and its corresponding kernel address. The slice is segmented into a unit of 256 kernels (1024 columns), where 8-bits is used to encode their addresses. During the sparse readout mode, the sensor control sequence will be adapted by the expected sparseness resulting in readout a predefined number of flagged kernels (on the order of 70 kernels instead of the original 256). Once the horizontal scanner selects a kernel, the 64-bit kernel data and 8-bit address data will be serialized and output by 64 (8 per segment) high-speed LVDS channels to the system FPGAs. In the FPGAs, sub-pixel precision centroiding is executed on each event and the resulting super-resolution (8192 × 8192 pixel) dose-fractionated frames are sent to the microscope's computer, where the image is stored, post processed and transferred.

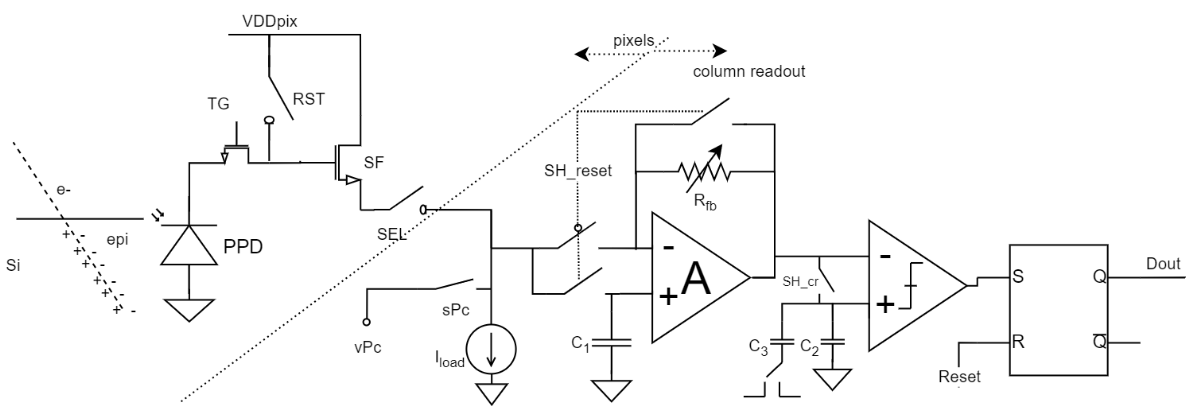

Figure 2 Single event detection. Electron hole pairs generated from an incident primary electron are processed through the signal chain resulting in a quantized digital bit.

Performance under cryo-EM

The input-referred read noise of this image sensor including gain, offset mismatch, device noise was analyzed from the false positive rate of the dark images with different the comparator threshold. Thanks to the on-chip CDS, programmable gain TIA and proper comparator thresholding 28e-$_{rms}$ was reported in [2], which is far below the indued charge package of a single primary electrons with 200 or 300 keV energy (in order of a few hundreds). The measured true- and false-positive rate as function of the threshold are shown in Figure 3(a). When using a low threshold, all primary electrons are detected, yet many "false" events due to noise are also registered. When using a higher threshold, primary electrons are missed because some pixels fail to trigger the comparator. Sufficiently low false positive (<1e-6) and high true positive (> 99%) rate can be observed around threshold of 120 (programmed value, A.U). Compared to the progenitor direct detection sensors with 5µm pitch[4], notwithstanding the larger 8µm pixel pitch, one can localize individual events within a pixel pitch or less (Figure 3(b)) thereby improving the modulation transfer function (MTF) (Figure 4(a)). This results in high detective quantum efficiency (DQE) for cryo-EM electron detection.

The final image is generated by accumulating a large number of frames from a sufficiently dim scene, composed of exclusively single insulated hits. A reasonably high sparsity within each frame is necessary to avoid coincidence and thus the inability to discriminate multiple coincident hits as separate events [5]. Operating outside of the sparse conditions has thus important performance consequences, mainly a loss of MTF and DQE. The method is particularly suitable for quantitative, low-dose applications such as cryo-EM. Therefore, at present, transmission electron microscopy (TEM) use is largely limited by the specific sensor exposure rate requirements of the electron counting camera.

With the high frame rate and low noise level, this sensor can detect and process incident electrons at an order of magnitude higher rate than brute force software-based counting sensors [4]. Measurement shows >90% linearity up to 60 electrons per pixel per second at both 200 and 300 kV, with high DQE (>90%) over at least three orders of magnitude of exposure rates (Figure 4(b)). An example EM image from this sensor is shown in Figure 5.

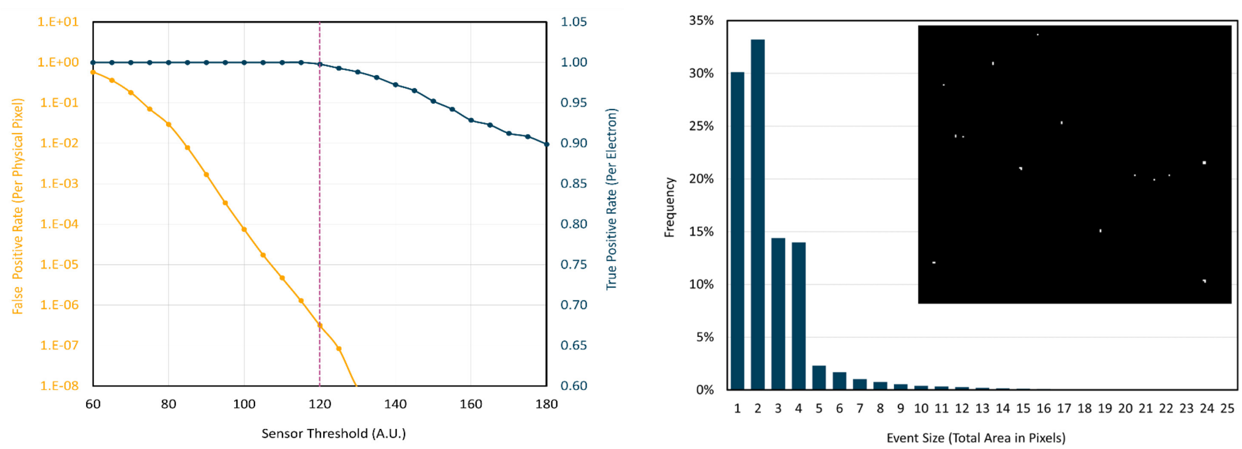

Figure 3 (a) True & False positive rates under 200keV electron beam. (b) Histogram of the number of adjacent pixels registering signal (event size) for each detected primary electron at 200 keV. The inset shows an example of a cropped region from a raw frame.

Conclusion

The single electron detection and counting promises to improve the productivity and throughput of cryo-EM, by enabling event-based high-speed acquisition of high-SNR datasets. Additionally, the simplicity of on-chip digitalization and sparse readout reduces the overall power consumption and cost of this camera, making high-resolution cryo-EM equipment more accessible.

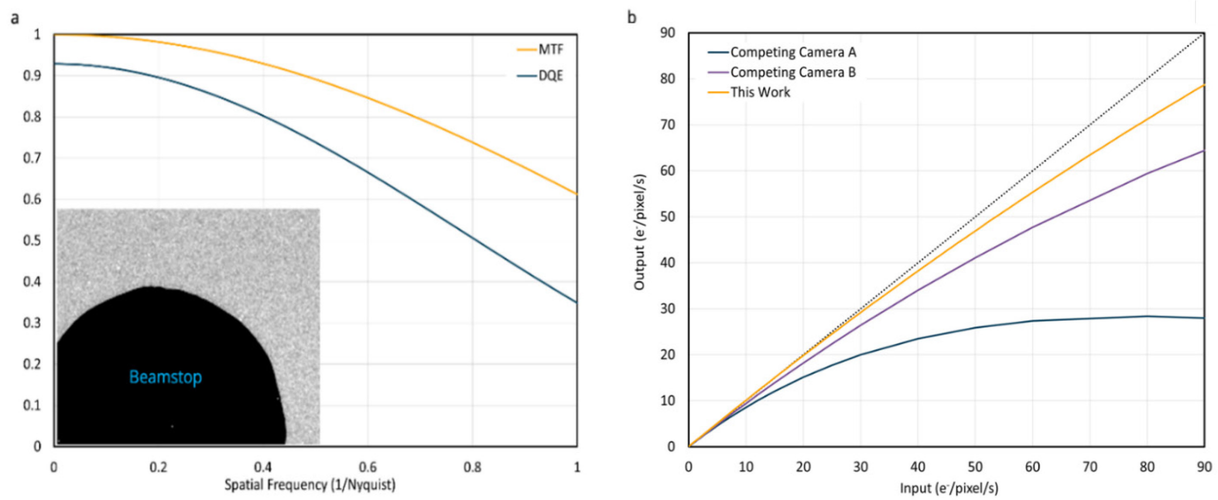

Figure 4 (a) The measured DQE and MTF for detection of 200 keV electrons. The inset shows a cropped region of an image of a microscope beamstop with ~50 electrons per pixel total exposure. (b) The linearity for detection of 200 keV electrons, compared to an ideal sensor and two other commercially-available competing cameras [4].

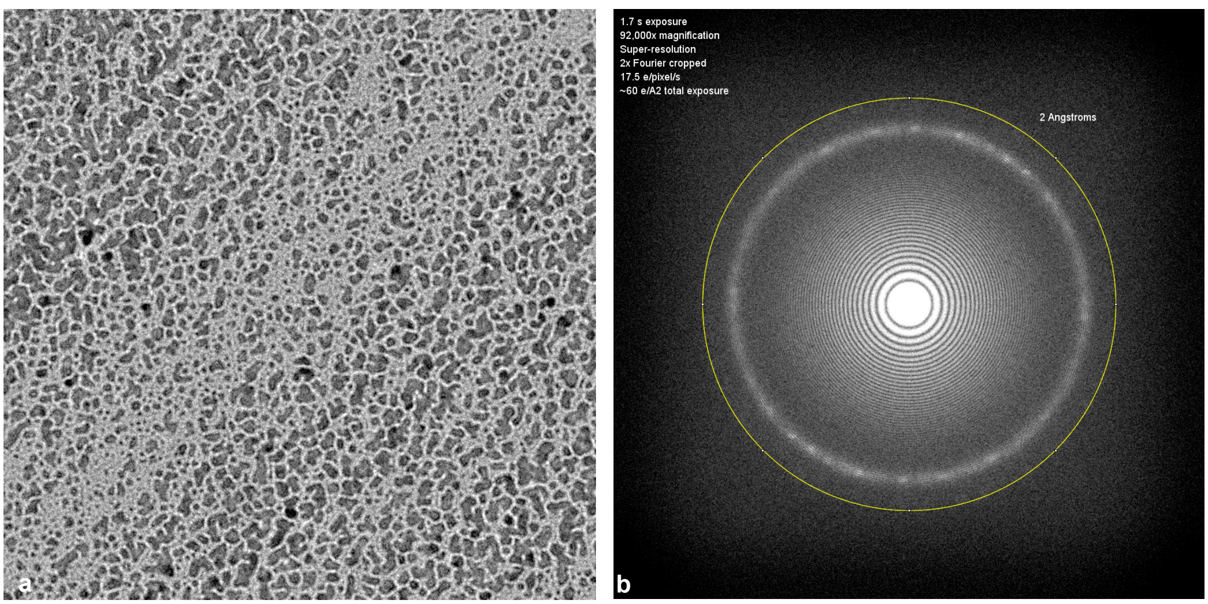

Figure 5 (a) An image of a carbon grating replica with Au/Pd shadowing collected at 92,000x magnification on a 200 kV TEM, with a total exposure of approx. 17.5 electrons per pixel over 1.7 seconds. (b) The Fourier transform of the image, showing a bright ring corresponding to the Au (111) spacing of ~2.35 Angstroms.

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