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Accurate event localisation for pixelated direct electron detection using a convolutional neural network

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Modern pixelated electron counting detectors provided a giant leap in the use of cryogenic electron microscopy (cryo-EM) by structural biologists to study the structures of macromolecules and complexes thereof. Ideally, a detector for cryo-EM would give a list of position, time and energy of each individual electron that arrives at the detector surface with infinite accuracy. The ultimate direct-electron detector will have an ideal curve for both the detective quantum efficiency (DQE) and modulation transfer function (MTF), a large field of view, a large dynamic range and will be fast enough to record data at time scales during which stage drift is not an issue. The current range of commercially available direct electron detectors, while being a huge improvement over traditional film based or CCD solutions have a limited dynamic range, require long exposure times and do not reach ideal DQE and MTF figures. Moreover, their best results have only been obtained at 300 kV and require exposure times up to a minute. There is a need for detectors that can be operated at a broader range of energies and at higher throughput.
The Timepix3 ASIC, in quad configuration, has a maximum output of 120 Mhit/s in a noise-less, data-driven readout mode and provides position, time and energy data for each hit with a time resolution down to 1.6 ns. In the past, Medipix ASICs were reported to be unsuitable for electron imaging at energies above 80 kV as those electrons would affect too many pixels. Here we show that the Timepix3 ASIC using a 300-500 µm silicon sensor layer can be used for EM applications both at low and at higher energies. Detectors have been mounted under a 200 kV FEI Tecnai Arctica microscope and 300 kV FEI Tecnai G2 Polara microscope. A per-pixel response calibration method was developed to correct for per-pixel differences in both the Time-over-Threshold and Time-of-Arrival output. Using the simulation package GEANT4Medipix the output of the Timepix3 ASIC was simulated for individual electron events. Global statistical characteristics of the simulated detector response are shown to be in good agreement with experimental results. Series of simulated digitised pixel output have been used to train a convolutional neural network (CNN) to predict the incident position of the electron within a pixel cluster. A second series has been used to evaluate the performance of the CNN: it is able to predict the point of impact of individual electrons with, on average, 0.39 pixel and 0.42 pixel accuracy for 200 keV and 300 keV electrons respectively.
By applying the CNN on experimental data the MTF of the detector at half Nyquist is improved from 0.30 and 0.05 to 0.65 and 0.70 for 200 kV and 300 kV respectively. We show that the entire dose-lifetime of a protein can be measured within a 1 second exposure. Preliminary data will be shown on how the Timepix3 can be used for cryo-EM single particle data acquisition.

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