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Large-Format Direct Detection Camera for Cryo-EM at 100 keV

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Imaging vitrified biological samples at 100 keV has been shown to provide more signal-to-noise per unit damage as compared to 200 or 300 keV[1-2]. In addition to a better image per unit damage, screening samples at lower keV offers an economical solution due to the higher accessibility of 100 keV transmission electron microscopes (TEMs). Direct detection sensors provide the highest DQE and have been a key contributor to the resolution revolution in cryo electron microscopy (cryoEM). Unfortunately to date, direct detection cameras have been primarily optimized to work at high accelerating voltages (200 - 300 kV) and low accelerating voltages (5 – 80 kV) so there remains a gap in direct detection technologies targeting 100 kV[1-2]. Through a major shift in detector design, we have for the first time realized a sensor that performs optimally at 100 kV. The performance of this sensor at 100 kV is comparable to the best performance of existing monolithic active pixel and hybrid pixel arrays working in their respective optimal energy ranges, and it simultaneously provides a large number of pixels (2304 x 3240). This new direct detection sensor optimized for imaging at 100keV is expected to have significant implications for the field of cryo-electron microscopy (cryo-EM) in the push for a low-cost cryo-EM microscope.

Recent efforts in using cryo-EM at 100 keV have demonstrated the feasibility of achieving high-resolution protein structures using single particle reconstruction[1]. These studies have also noted the lack of a suitable detector that could take advantage of the expected increase in SNR per unit damage offered by the acceleration voltage of 100 keV as compared to 200 or 300 keV[1]. Electrons with an acceleration voltage of 100 keV are challenging to detect because of competing constraints in sensor design: the pixel size needed to contain the electron interaction volume is quite large, but the sensor thickness required to detect only the incoming electron and not the sideways-scattered and back-scattered electrons must be very thin. When these parameters are not simultaneously optimized, the detective quantum efficiency of the sensor drops significantly at 100 keV (Fig 1).

For the new sensor presented here, the design was optimized such that the electron event detection occurs closer to the entry point resulting in a better detection of 100 keV electron events. This optimization results in a 4-fold increase in DQE at the Nyquist frequency as compared to K3 at 100 keV (Fig 2).

The exponentially rising demand for cryo-EM and the need to drive down costs of data screening requires a high DQE, large-format detector optimized for lower accelerating voltages. The camera presented here fills this need and will pave a path toward better imaging with more information gained per unit damage to a biological sample while making cryo-EM a default tool in every laboratory to study protein biochemistry.

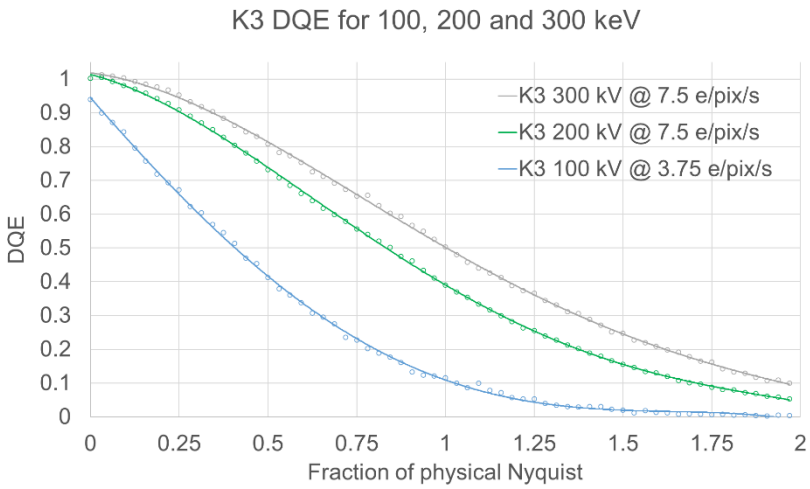

Figure 1. The DQE of the K3 camera at 100, 200, and 300 keV in correlated double sampling mode. The 200 and 300 keV curves were measured at an electron dose of 7.5 e^-/pix/s, while the 100 keV curve was taken at 3.75 e^-/pix/s. The effect of different dose rates does not affect results appreciably (data not shown).

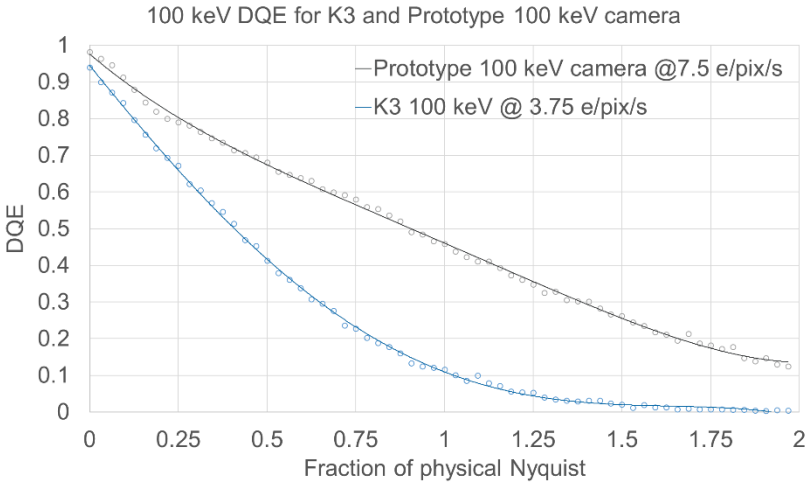

Figure 2. The DQE comparison between the K3 camera and the new 100 keV camera at 100 keV. The measurements were performed at 7.5 e^-/pix/s for the new 100 keV camera and at 3.75 e^-/pix/s for the K3 camera. The DQE(Nyq) of the new 100 keV camera is 4-fold higher than K3 at 100 keV.

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