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Event driven Timepix3 hybrid pixel detector for cryo-EM at 200 keV

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The development of direct pixelated detectors has played a key role in the resolution revolution in which structures of macromolecular complexes are obtained at near-atomic resolution by cryo-EM [1]. Monolithic active pixel sensor (MAPS) detectors are currently widely applied for cryo-EM, however, they have their best performance at 300 keV and have relatively low readout speed. The Timepix3, a hybrid pixel detector (HPD), can operate at very broad energy range (2 - 400 keV) and has an extremely high time resolution (event-driven 1.56 ns).
Previously, we have shown that the incident position of the electron can be predicted at sub-pixel accuracy using convolutional neural networks (CNN), thereby boosting the modulation transfer funcion (MTF) of experimental knife-edge data both at 200 keV and 300 keV [2]. Here we present the Timepix3 fully integrated in a cryo-EM Single Particle Analysis workflow. We determined its detective quantum efficiency (DQE), an important factor for cryo-EM which is affected by both MTF and noise power spectrum (NPS). Our hard- and soft-ware integration allows for full control of all the factors important for the performance of a detector for a certain application. We studied the effect of deterministic blur to DQE and the final protein single particle analysis (SPA) reconstructions resolution. We could compare results obtained with our workflow with those obtained data collected from the same protein on the same microscope, using a commercial available camera. Our results show that our implementation of the Timepix3 for SPA applications can rival the data obtained with commercial MAPS detector. We discuss the versatility of our detector setup, which allows for a huge range of fluence settings, it could be used to study radiation-damage onset, it could be used both in imaging and diffraction mode, does not require dose-protection, and could be used at the widest possible energy range. Furthermore, we discuss its successor, the Timepix4, which we hope to use for liquid-cell applications as well as cryo-ptychography on biological samples.

[1] W. Kuhlbrandt, Biochemistry. Science 343, 1443–1444 (2014).
[2] J. P. van Schayck et al., Ultramicroscopy. 218, 113091 (2020).

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