IISW 2021

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

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Motivation

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BIOCHEMISTRY

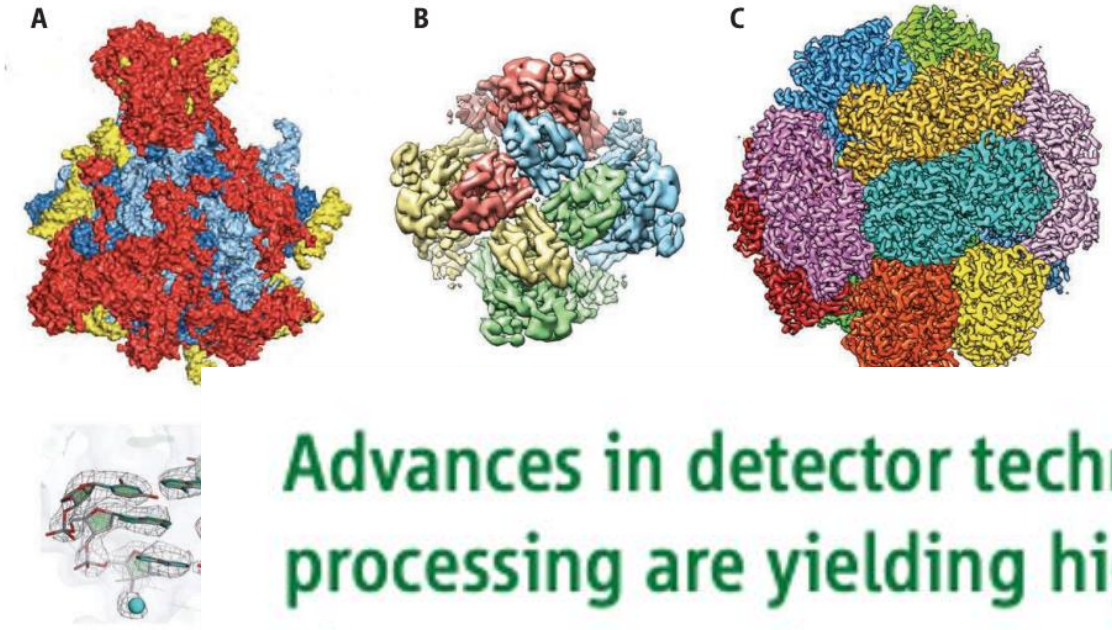
The Resolution Revolution

Werner Kühlbrandt

Precise knowledge of the structure of macromolecules in the cell is essential for understanding how they function. Structures of large macromolecules can now be obtained at near-atomic resolution by averaging thousands of electron microscope images recorded before radiation damage accumulates. This is what Amunts *et al.* have done in their research article on page 1485 of this issue (*1*), reporting the structure of the large subunit of the mitochondrial ribosome at 3.2 Å resolution by electron cryo-microscopy (cryo-EM). Together with other recent high-resolution cryo-EM structures (*2*–*4*) (see the figure), this achievement heralds the beginning of a new era in molecular biology, where structures at near-atomic resolution are no longer the prerogative of x-ray crystallography or nuclear magnetic resonance (NMR) spectroscopy.

Ribosomes are ancient, massive protein-RNA complexes that translate the linear genetic code into three-dimensional proteins.

Advances in detector technology and image processing are yielding high-resolution electron cryo-microscopy structures of biomolecules.



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Advances in detector technology and image processing are yielding high-resolution electron cryo-microscopy structures of biomolecules.

Outline

- Introduction
- Signal chain overview
- Measurement results
- Take home message

Introduction

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- **Wanted detector for cryo-EM**
  - Direct detection
  - Single electron counting
  - High frame rate: desired > 8000fps
  - High resolution: > 4k x 4k
  - …

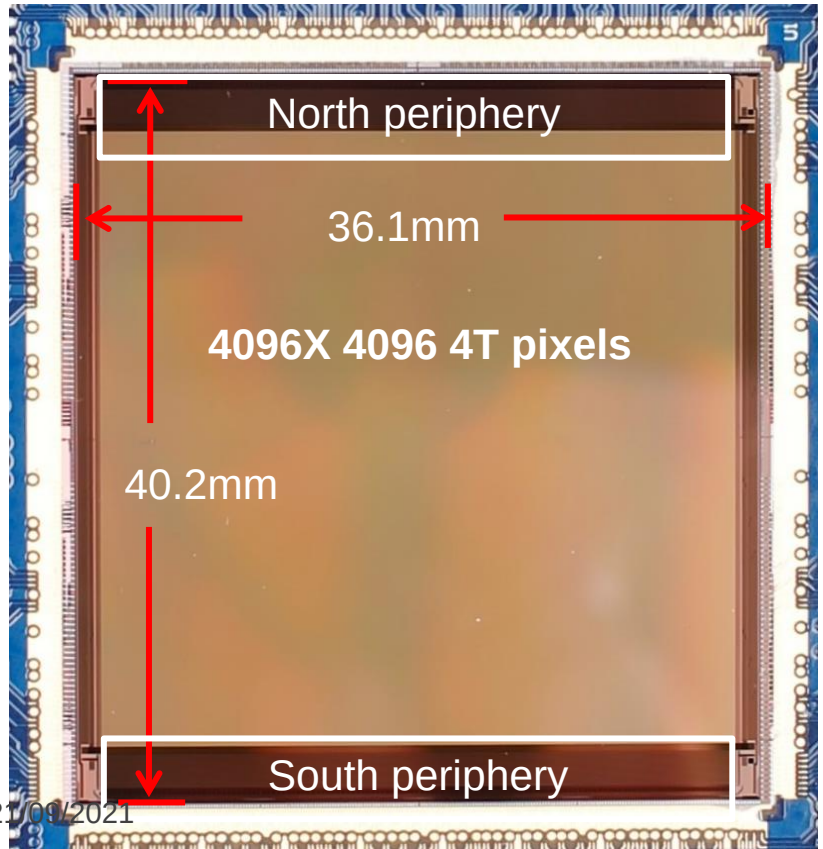
All 4k by 4k pixels would be read at 8000fps:
➔ 134 Gpixel/s
Data rate **> 1 Tbit/s (8bit)**

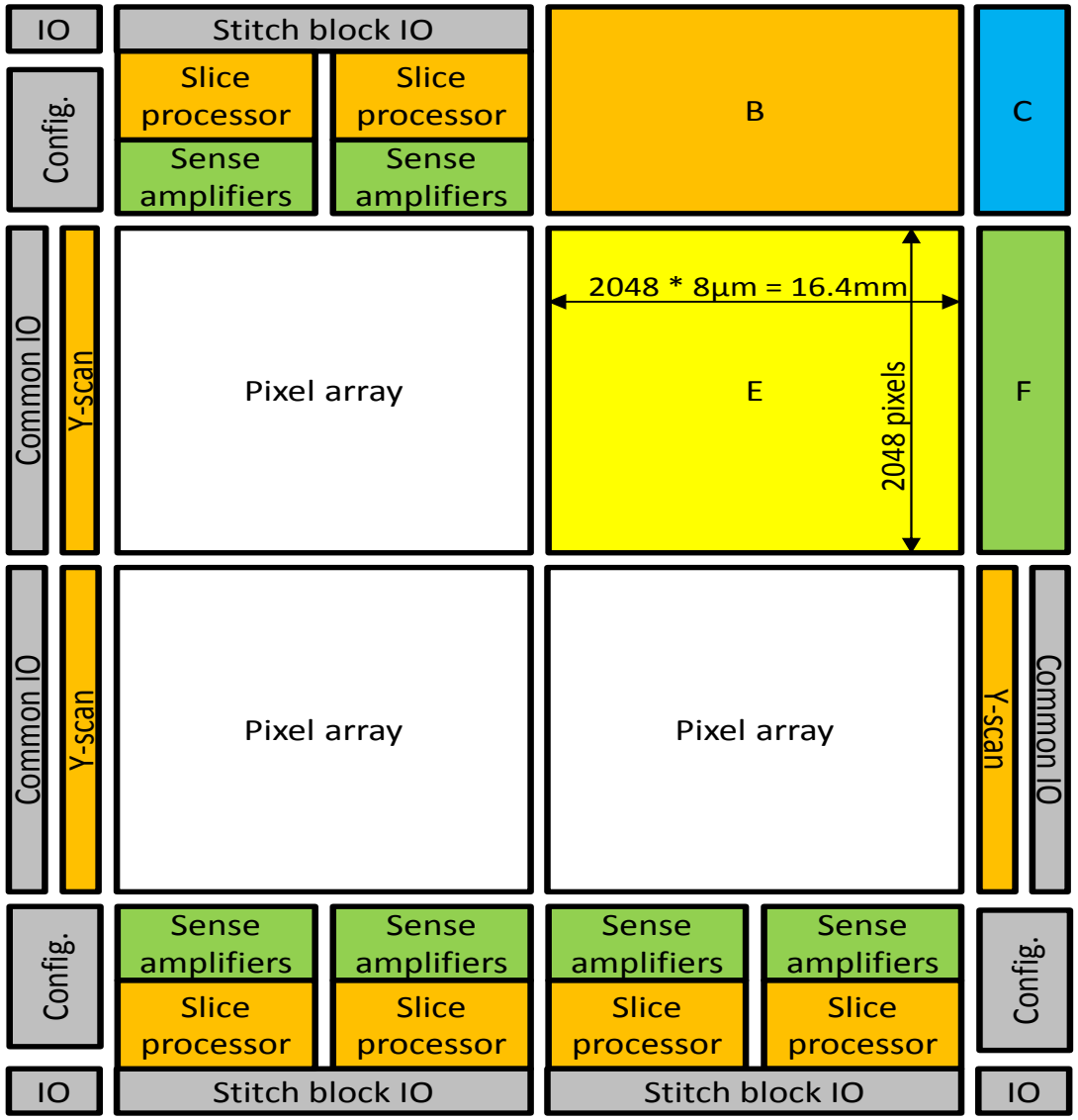
- **Proposed techniques**
  - Single electron detection
    - On chip event detection: as early as possible in signal chain
  - High frame rate
    - Current mode circuity
    - Event based sparse readout

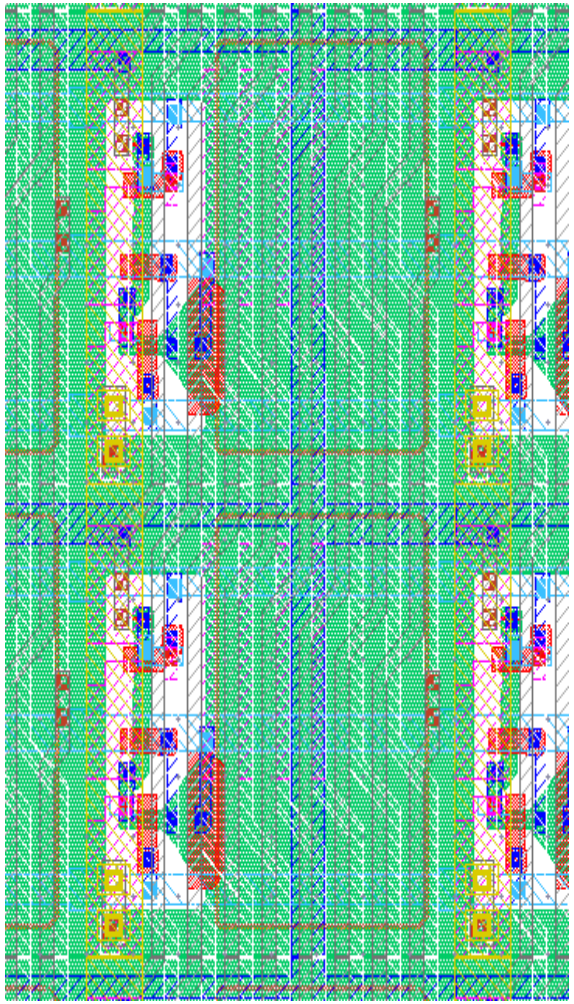
Follow the proposed methods, 4k resolution and 8000fps can be reached in sparse mode readout:
Date rate: 48 Gbit/s
Data reduction: 20 X

Architecture

- 2 by 2 stitching
- 2 side readout
- Simultaneously 16 rows readout at each side
- Segmentation: 4 X 1024 columns







Signal chain of single pixel

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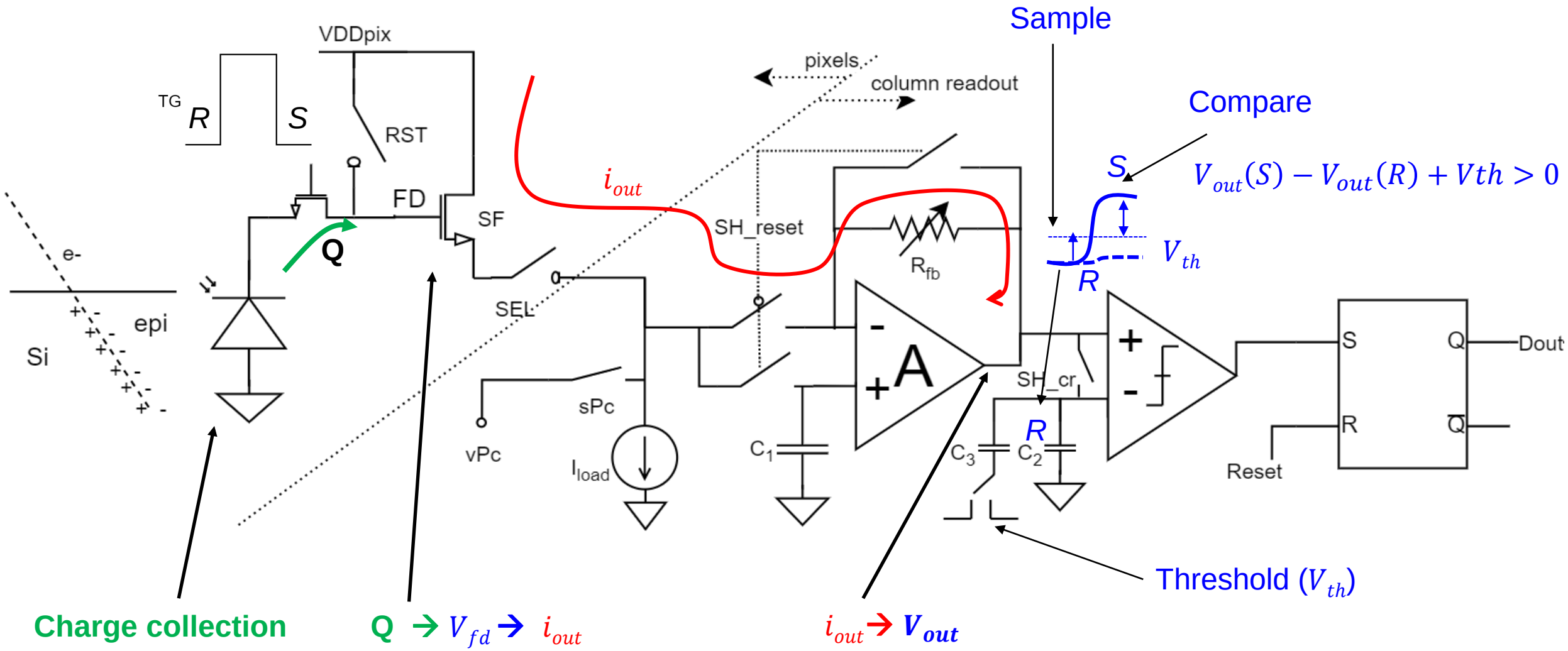
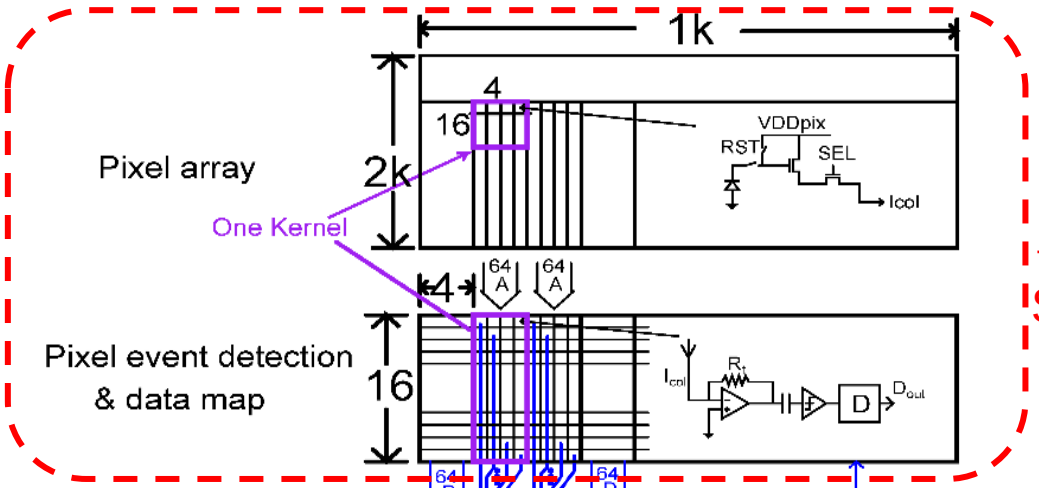


$$V_{fd} = \frac{Q}{C_{fd}}$$

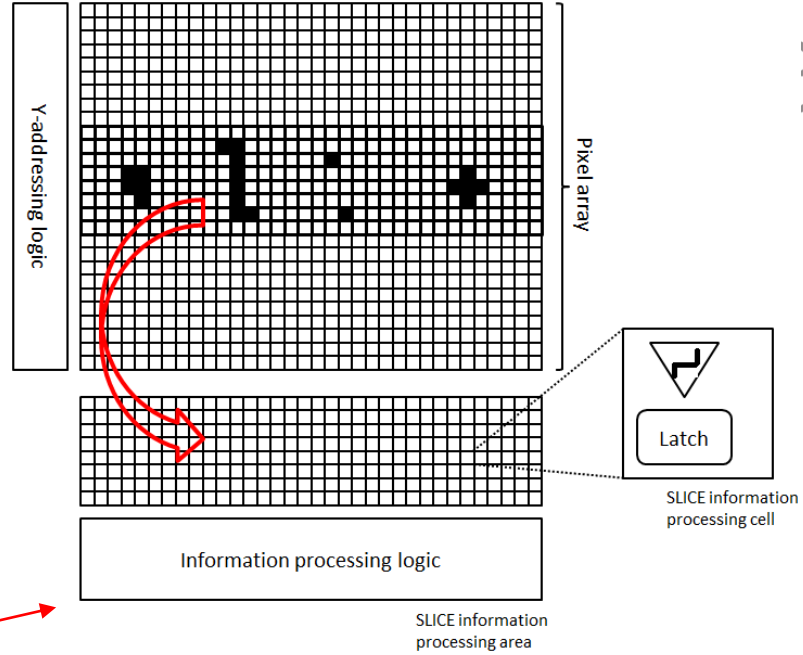
$$i_{out} = V_{fd} * gm$$

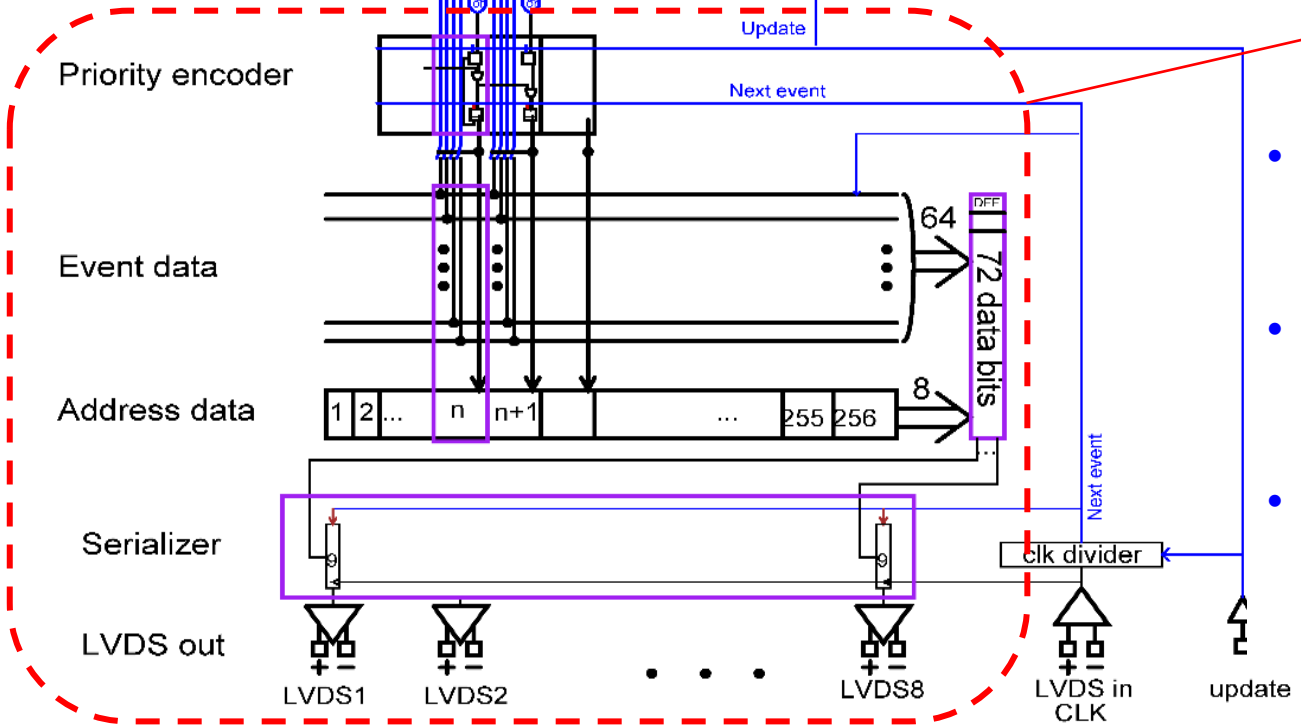
$$V_{out} = i_{out} * R_{fb} = \frac{Q}{C_{fd}} * gm * Rfb$$

Signal chain with sparse readout



Slice (16 rows) copied





- Kernel based (4x16 pixels) event analysis in slice processor
- Flag as event when one or more ‘1’ appear in the kernel.
- During subsequent readout, only output the event kernels and send out its 8-bit kernel address and 64-bit kernel data.

Patent: US10616521

P. Gao, et al."16.7Mpixel 8000fps sparse binarized scientific image sensor ", IISW 2019

Full camera system

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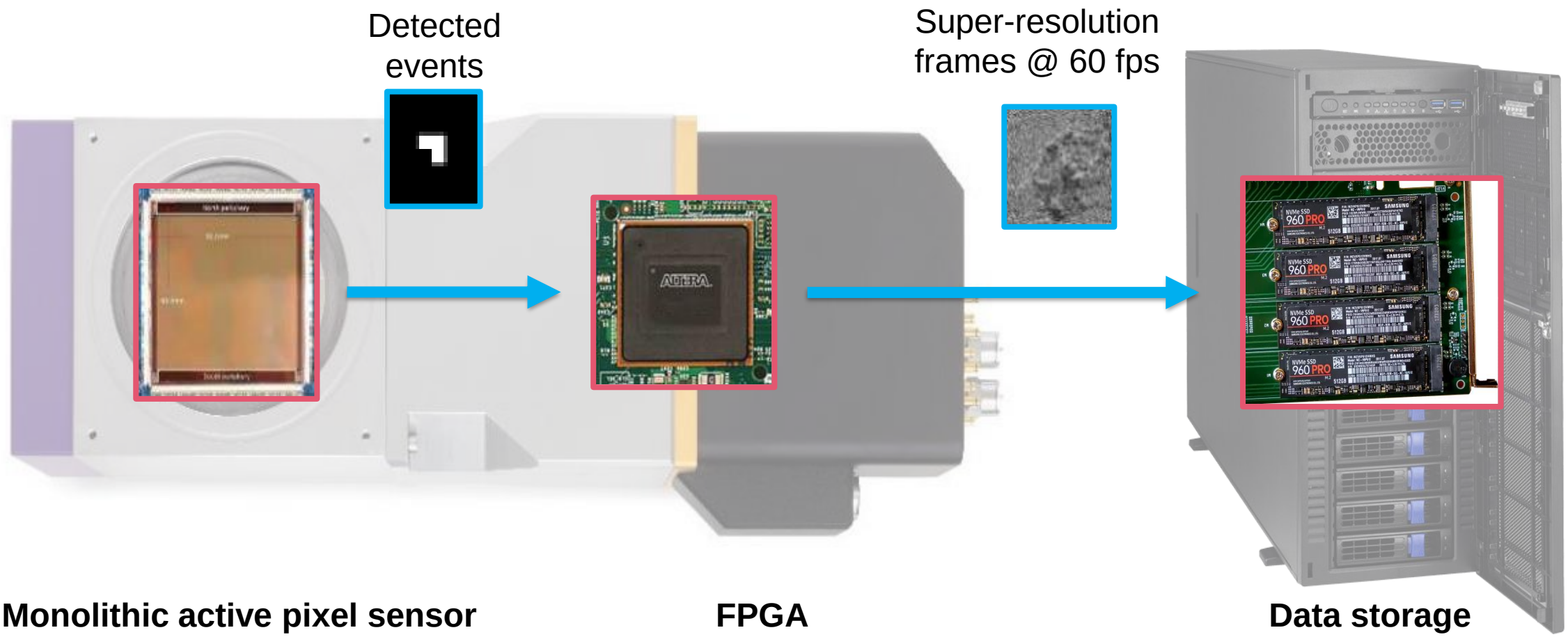

Monolithic active pixel sensor

8µm pixel

4096 x 4096 array

On-chip event detection

Event address encoding

FPGA

Sensor control

Super-resolution centroiding

Generation of output frames

Data storage

User interface

TEM automation

Post-processing or network transfer

True & False Positive Rates

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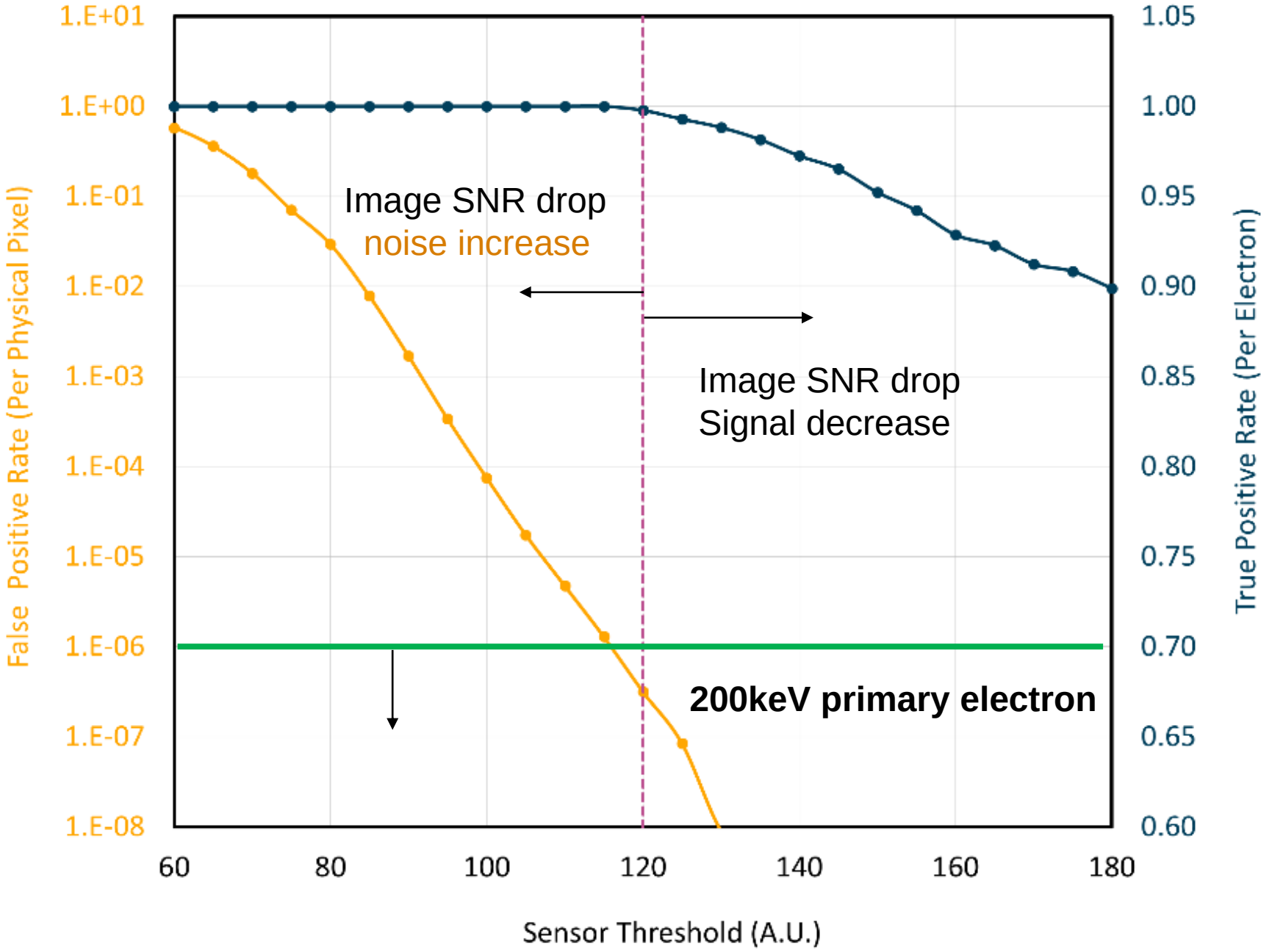
High quality scientific image

- **High detection efficient**

  → 100%

- **Low noise**

  False positives rates < **1E-6**



Detection linearity as function of does rate

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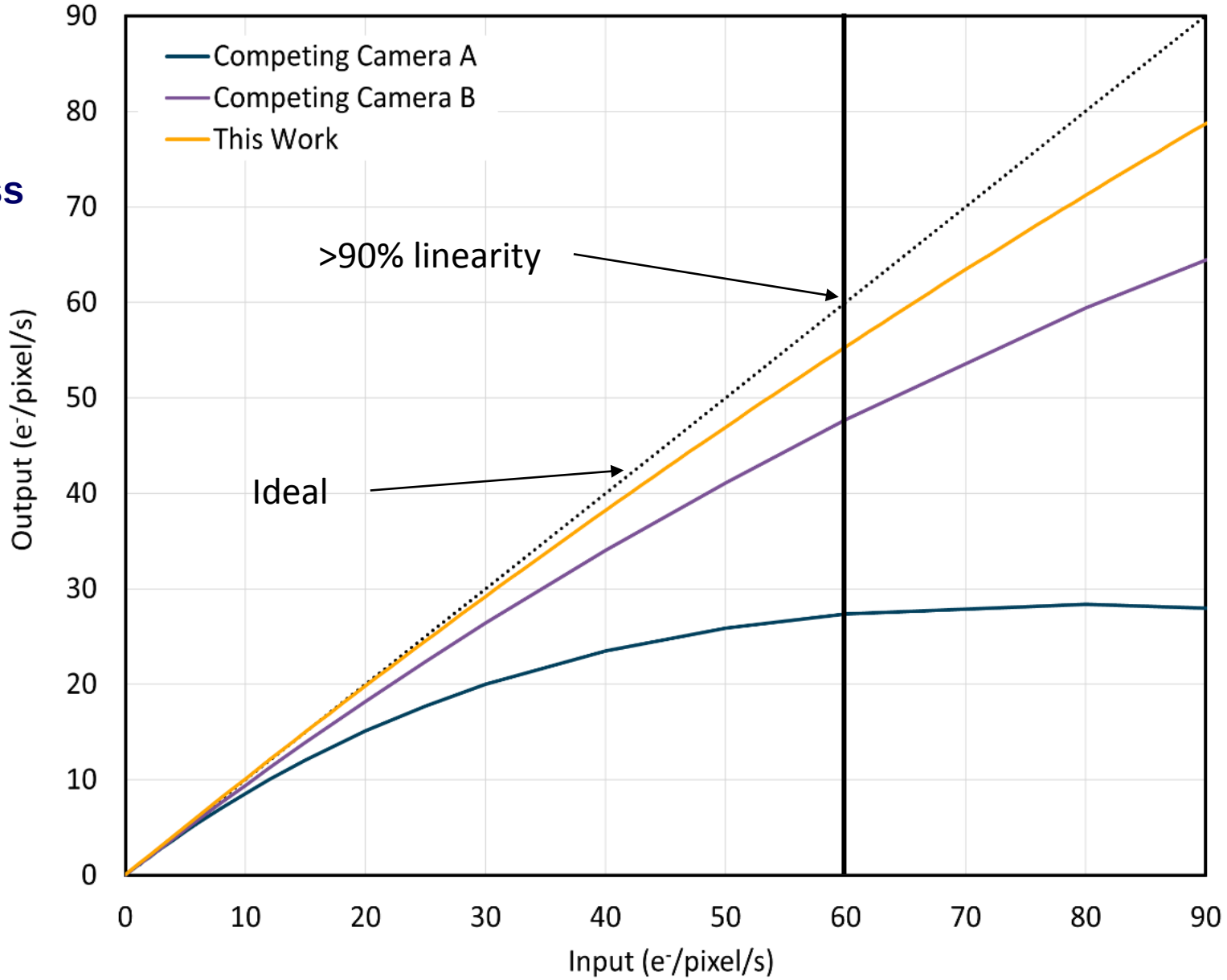
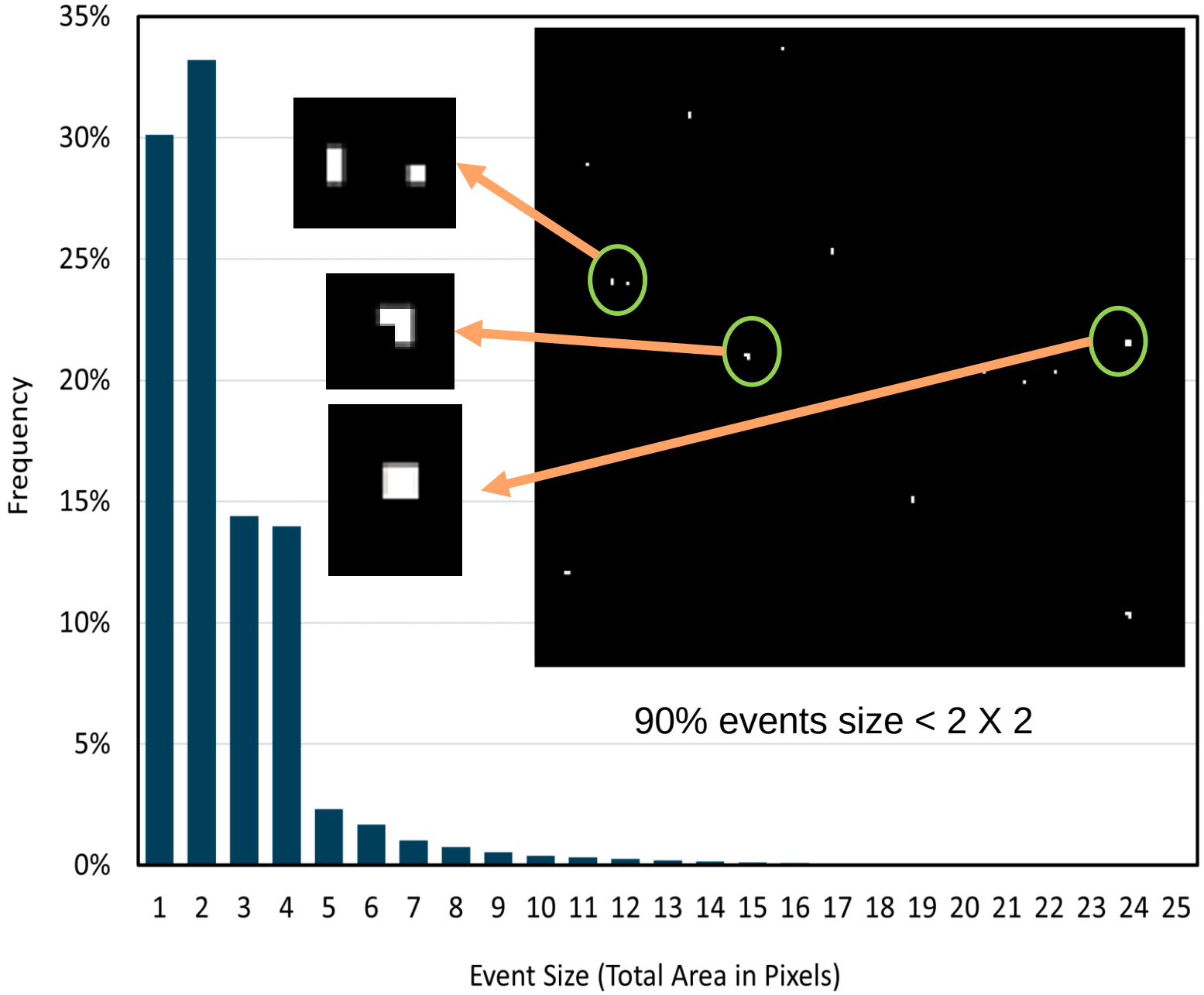
Linearly drops due to co-incidence loss

i.e. Multiple electrons hit the same pixel and the output is saturated to only 1.

Tolerate higher dose rate



Histogram of event size



Event size histogram of detected primary electron at 200 keV.

Summary of sensor performance

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Pixel Array	8µm 4T 4096 x 4096
Frame rate	2500 fps (brute force), 8000 fps (sparse)
Output interface	48 Gbit/s (64channels*750Mbit/s)
Data compression	> 20X
Shutter type	Rolling readout
Bit error rate	< 1E-6 (200/300kV primary electrons)
Sensor Power	<5W @ 3.3V & 1.8V
Technology	CIS 0.18µm

Example image

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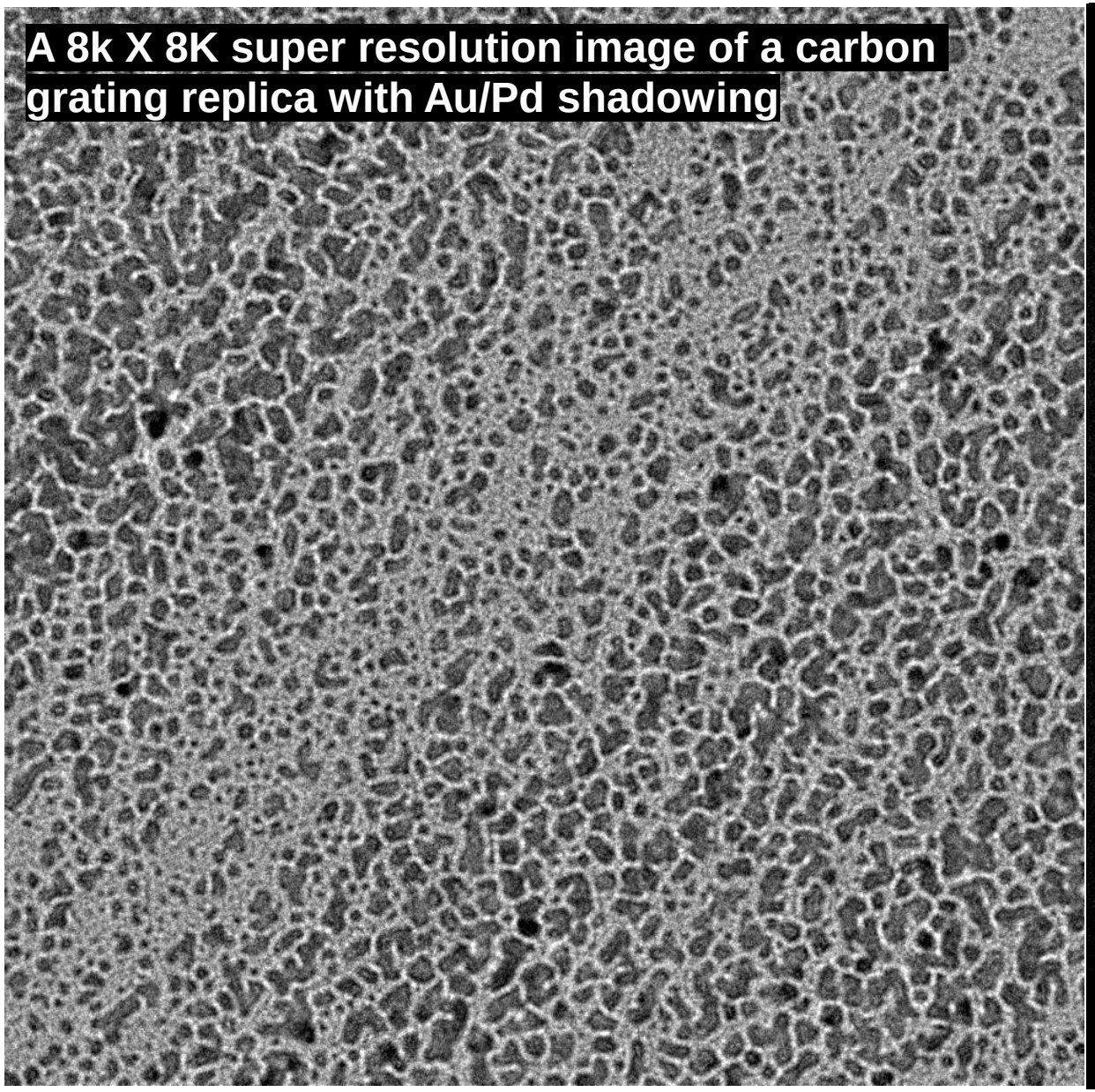

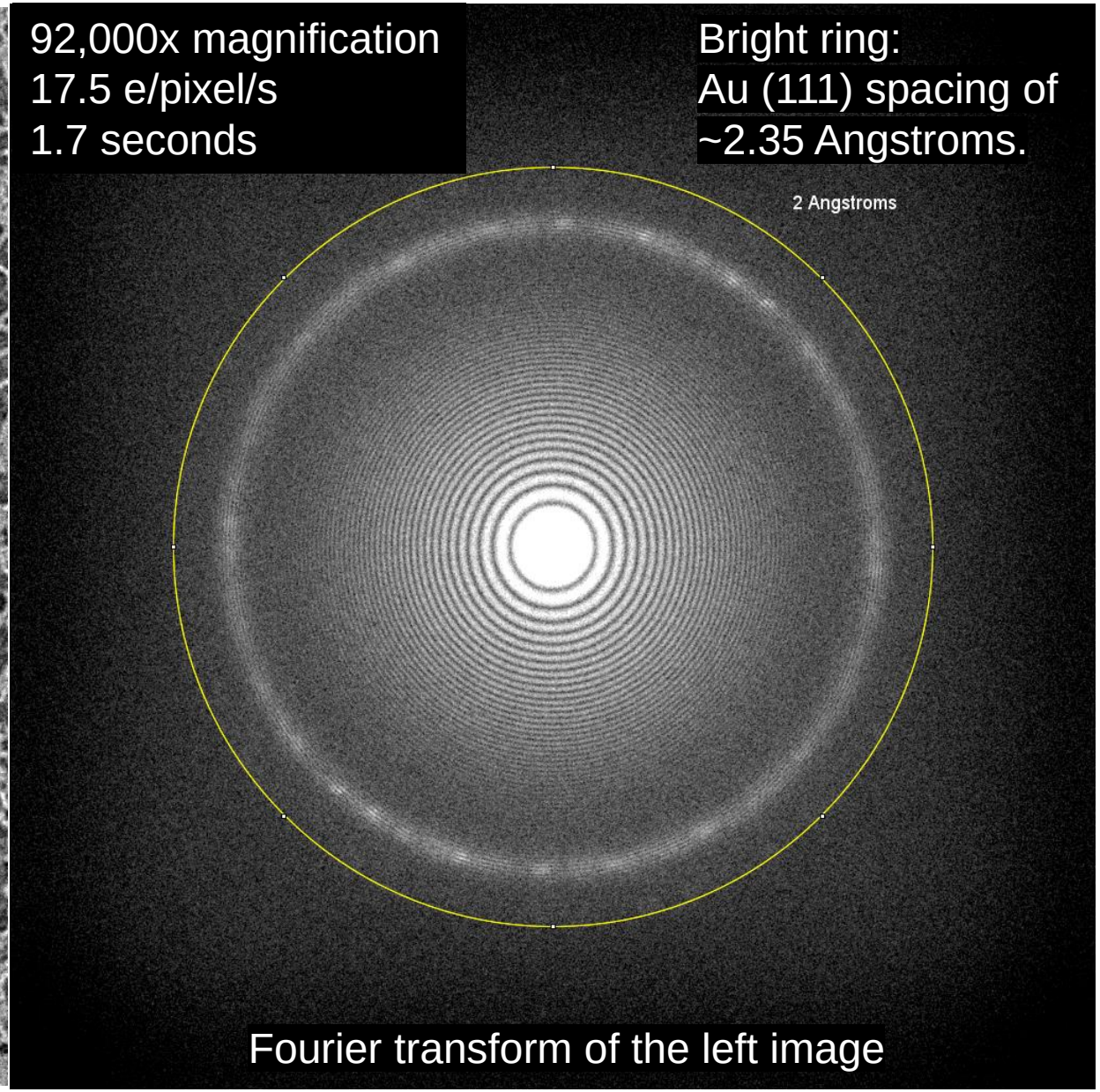

Continuous-Rotation Electron Tomography

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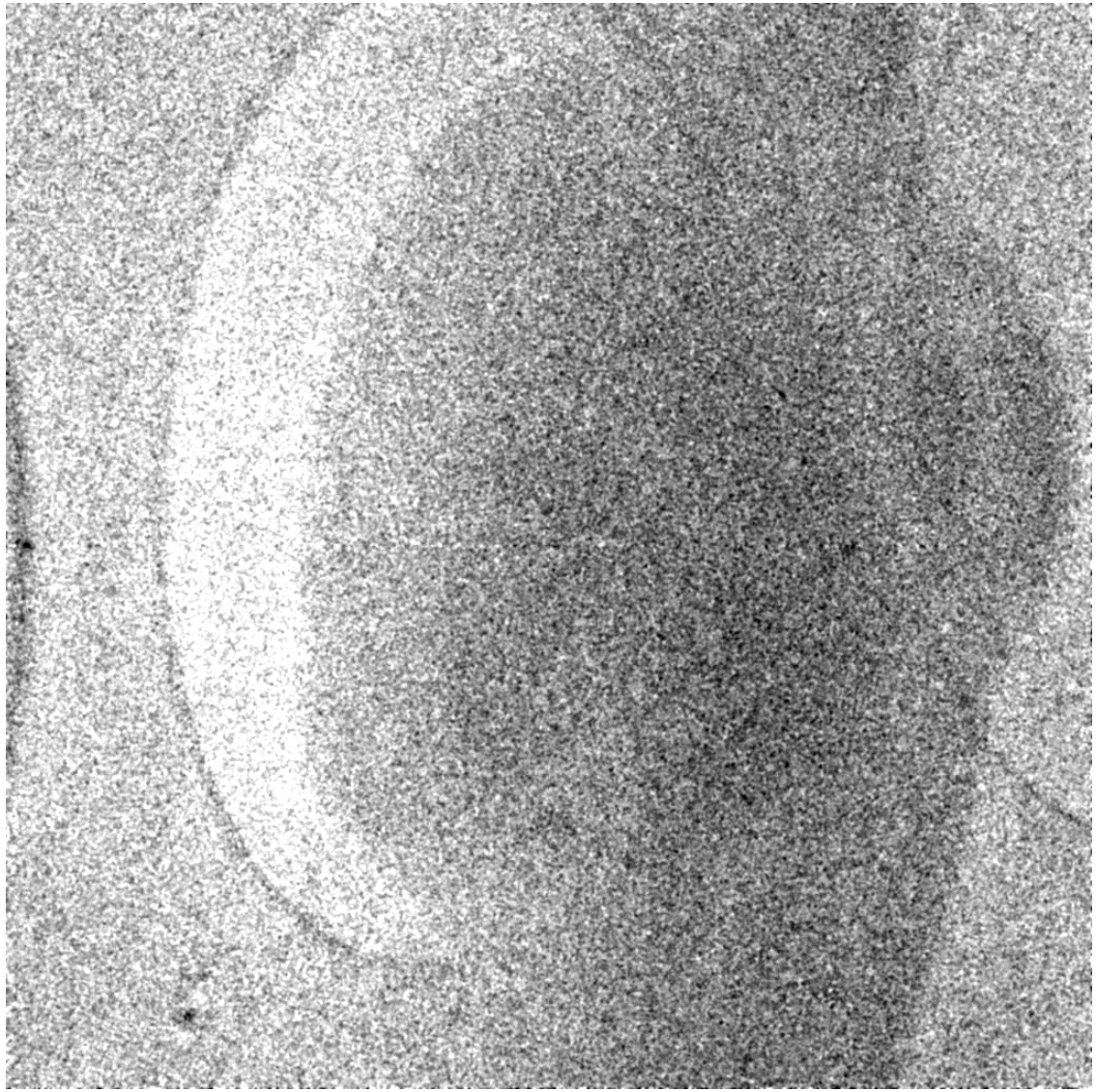
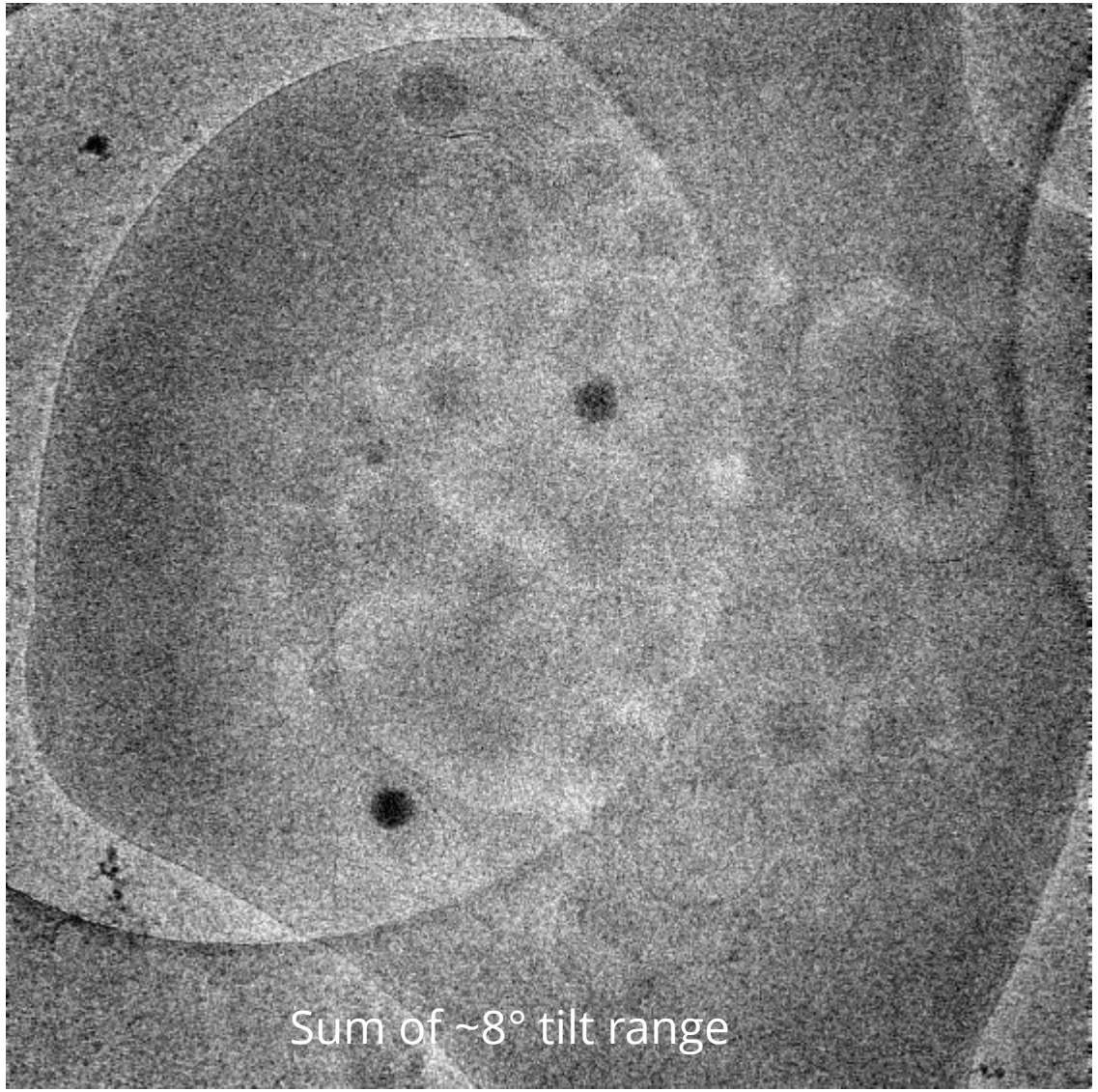
Realtime movie





Courtesy of Zhili Yu & Zhao Wang (Baylor College of Medicine, USA).

Take home messages

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- **A 4k by 4k, 8000fps sensor, thanks to**
  - Fast row time by current mode circuit
  - Event based sparse readout, exploiting the properties of the electron radiation

- **Realizing ~10X higher linear dose rate than competing sensors**

- **High SNR by**
  - High detection efficiency
  - Low false positive rate (<1.E-6)

Thank you

For questions or more information, please contact:

Peng Gao at peng.gao@caeleste.be

Or scan the QR-code to visit our website: www.caeleste.be

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