

Electron detectors for cryoEM

Greg McMullan

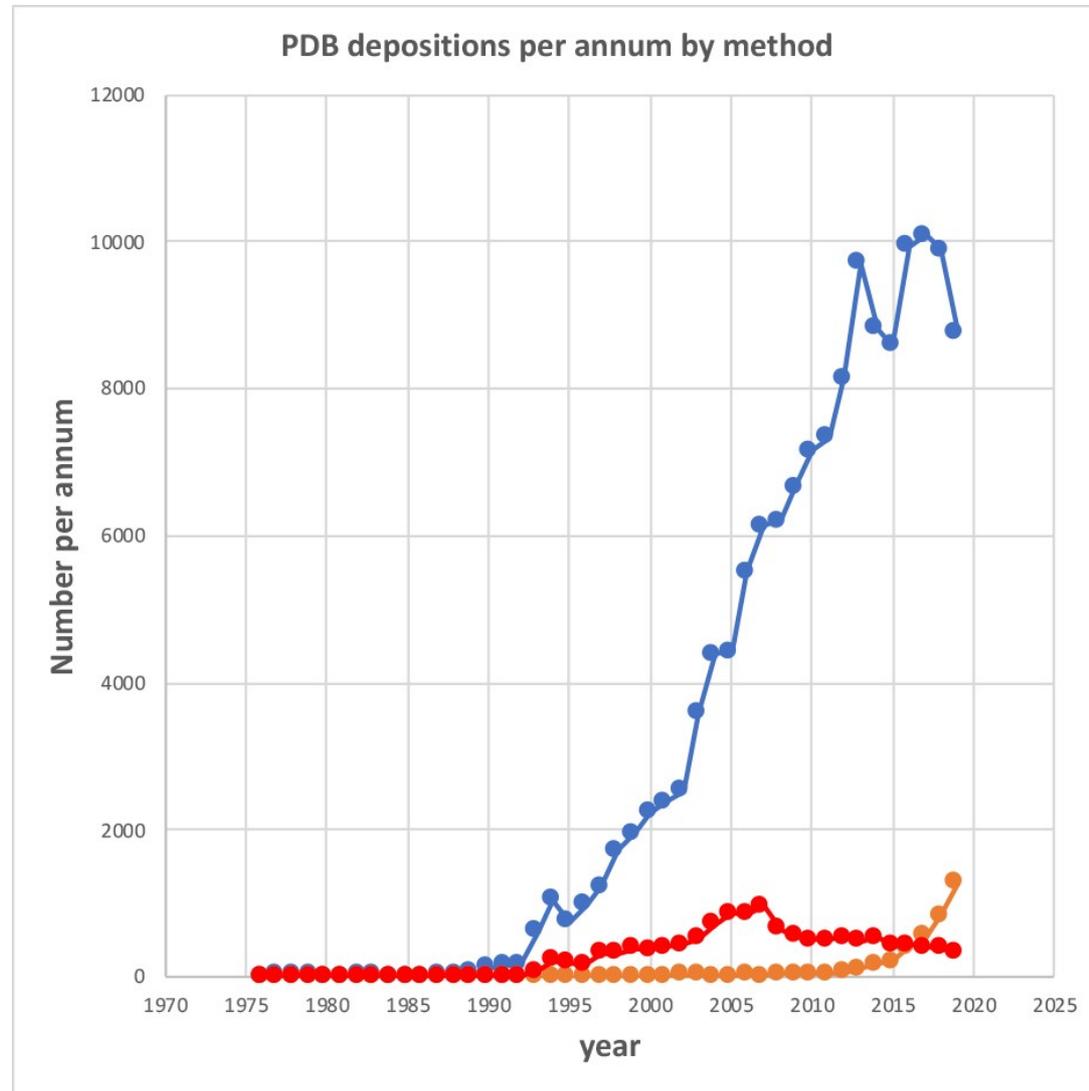
MRC-LMB

LGSPD 25th Nov 2019

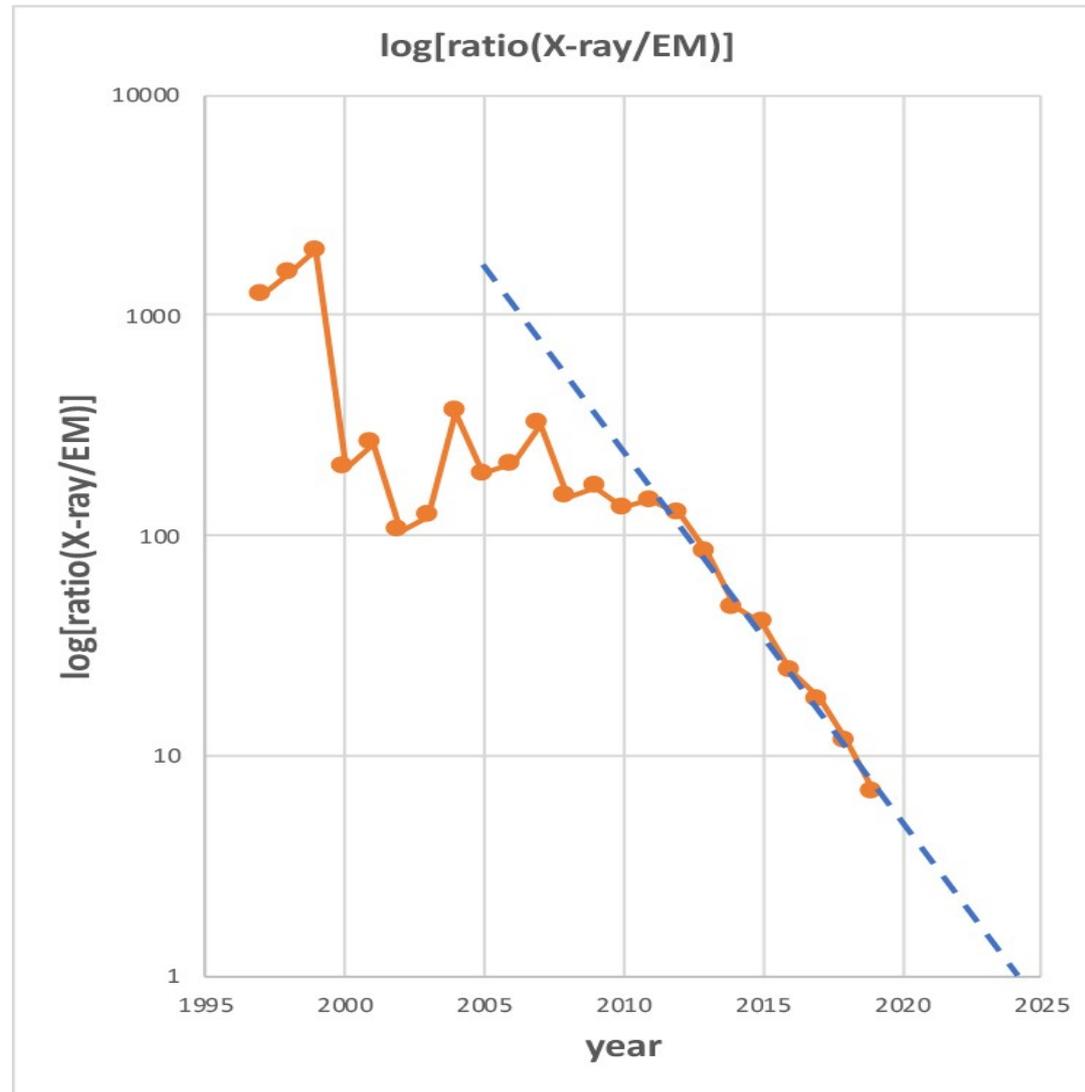
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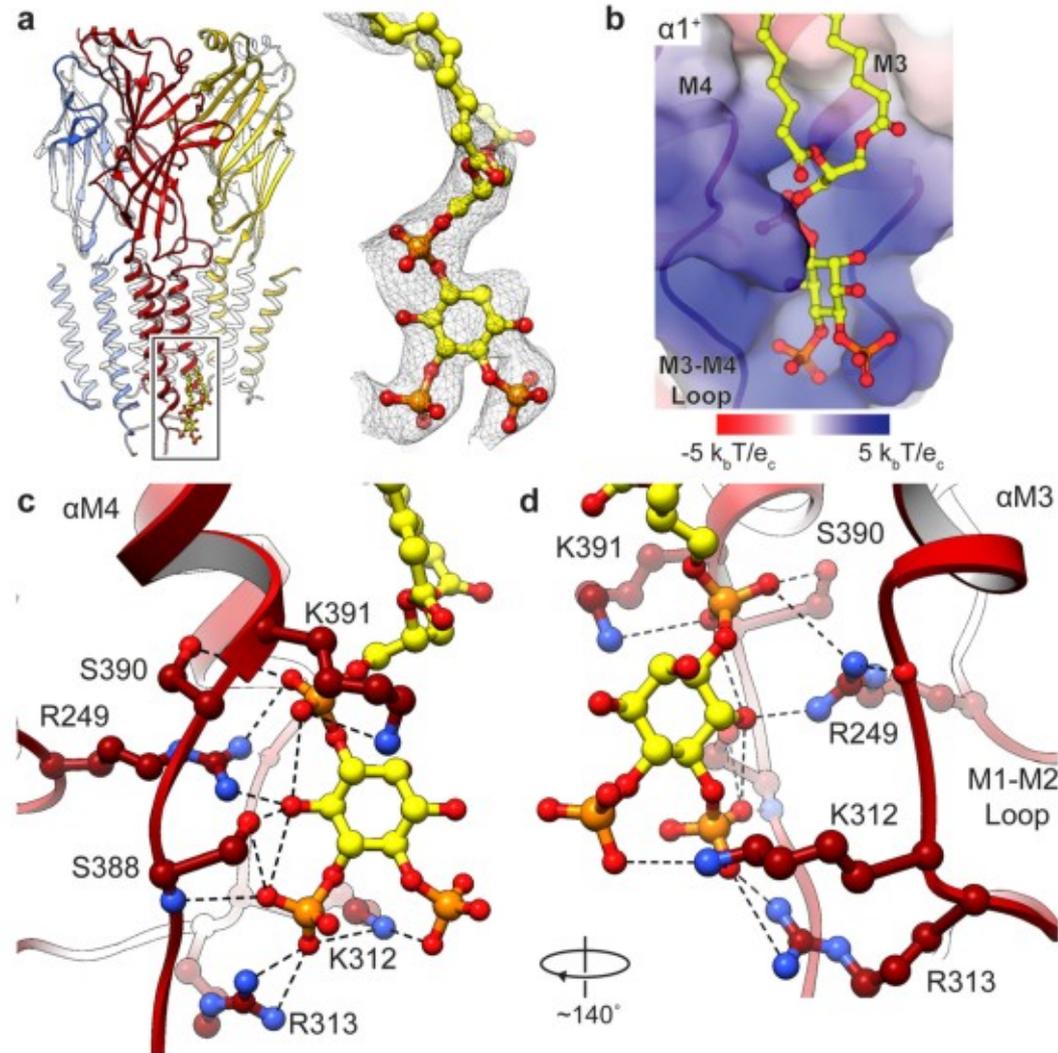
Impact of new detectors



Impact of new detectors



How do you get to:



From: Cryo-EM structure of human $\alpha 1\beta 3\gamma 2$ GABA_A receptor in a lipid bilayer, Lavertry et al *Nature* **565**, 515-520 (2019).

CryoEM growth not just detectors

- Computer programs / algorithms
- Faster computers (GPU)
- Microscope improvements
- Sample improvements (gold grids)
- More data (50 → 5000 images a day)
- Automation (24/7 data acquisition)
- Higher expectations
- More investment (people and money)

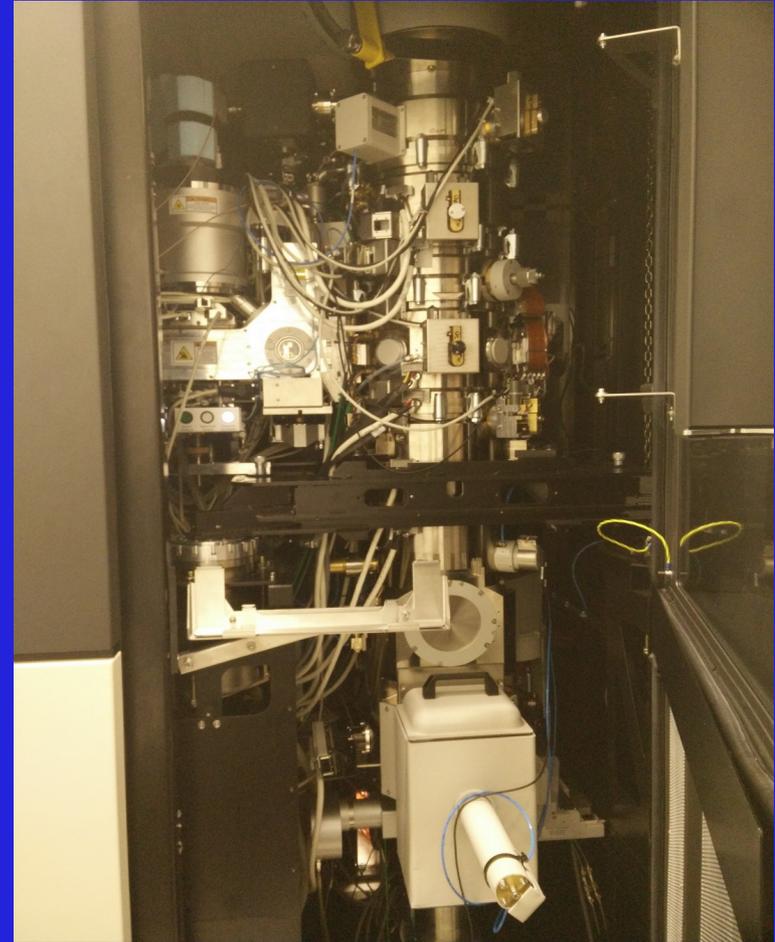
Detectors were the key enabler:

- Radiation damage necessitates low contrast images
- Every electron must be counted while retaining the maximum spatial information:

=> High DQE

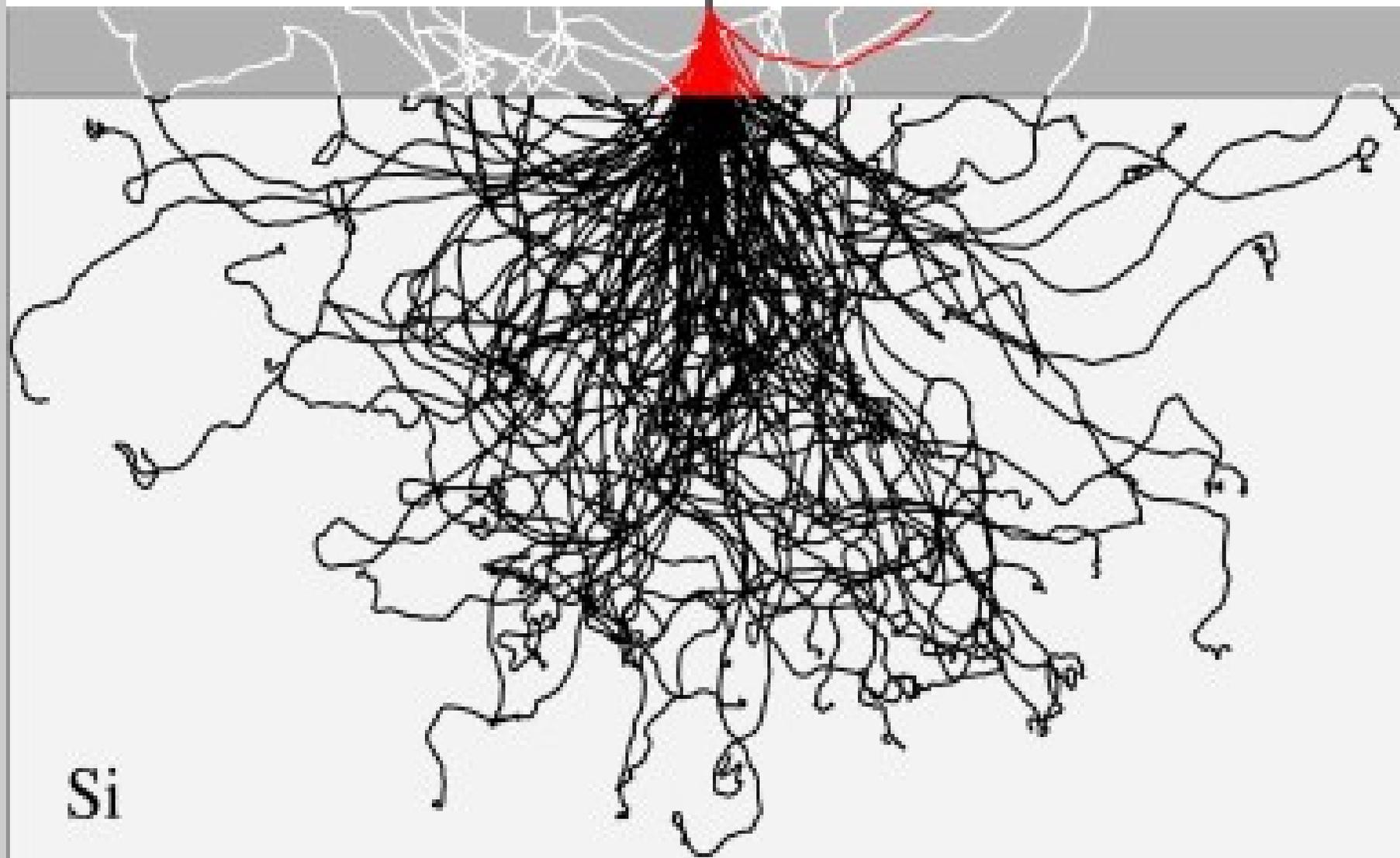
- Detector must be as large as possible
- Detector must be as fast as possible
- Must be rad-hard

Current high-end electron cryo microscope

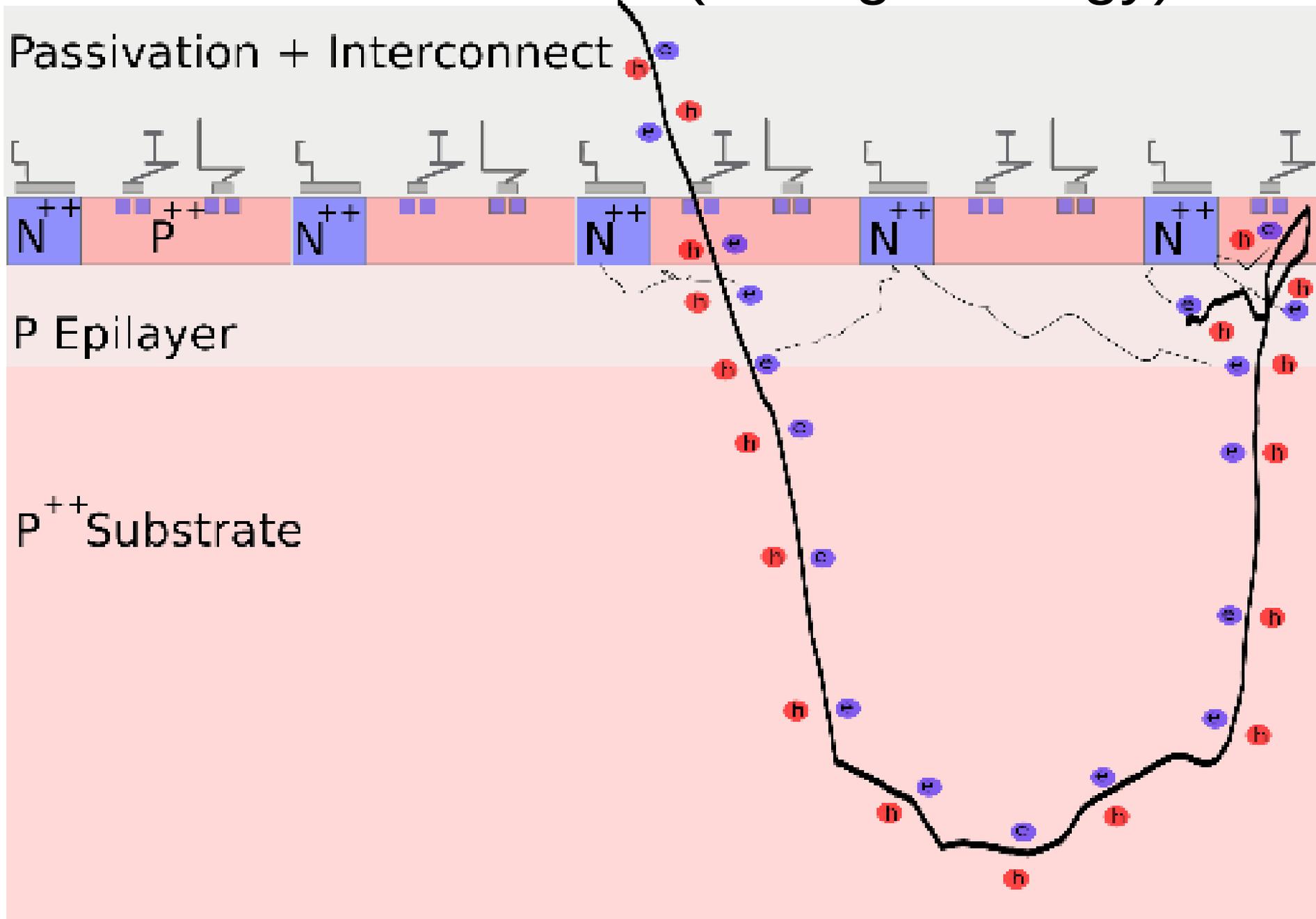


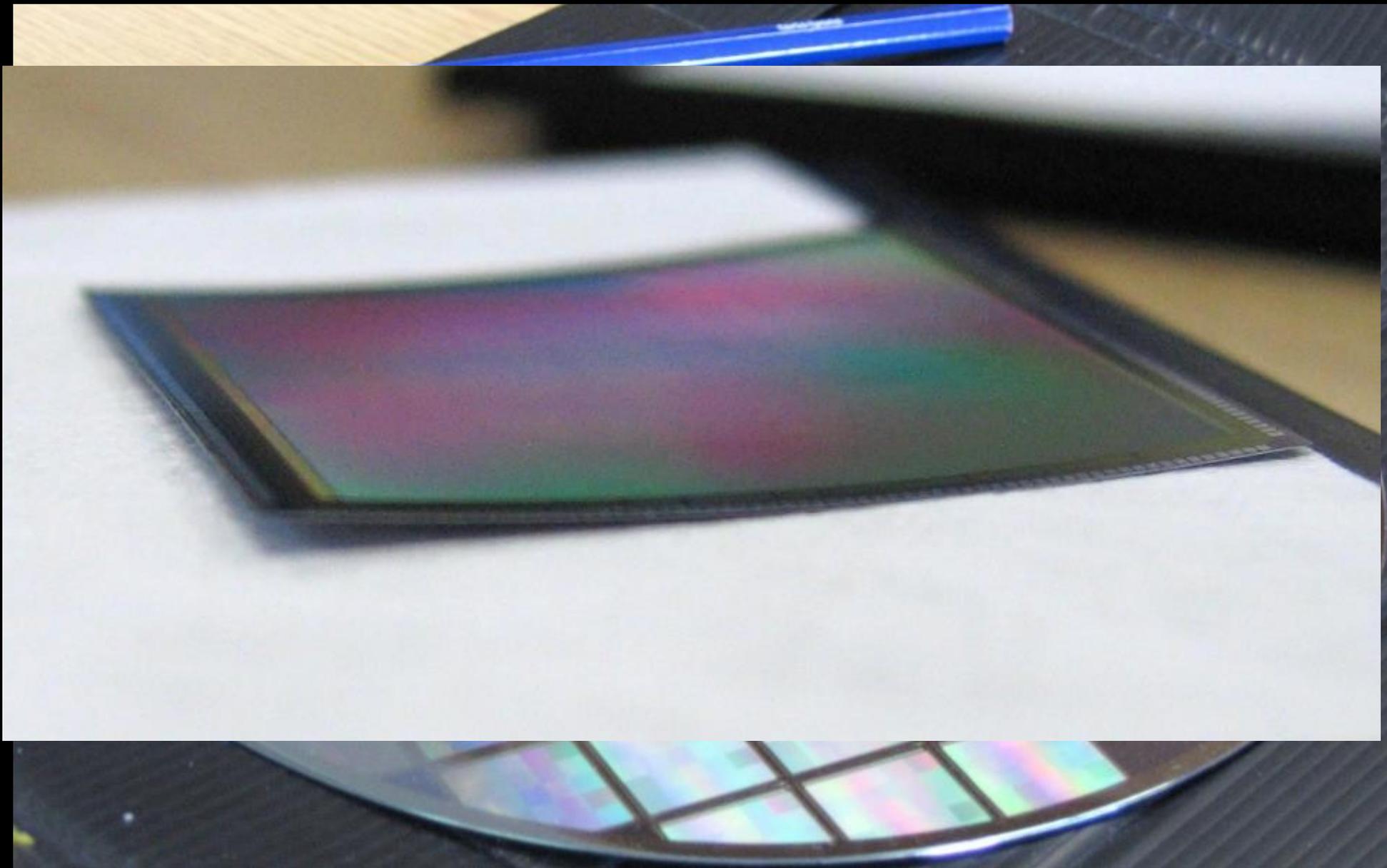
Operates at 300 keV
Costs ~50000000

300 keV electrons



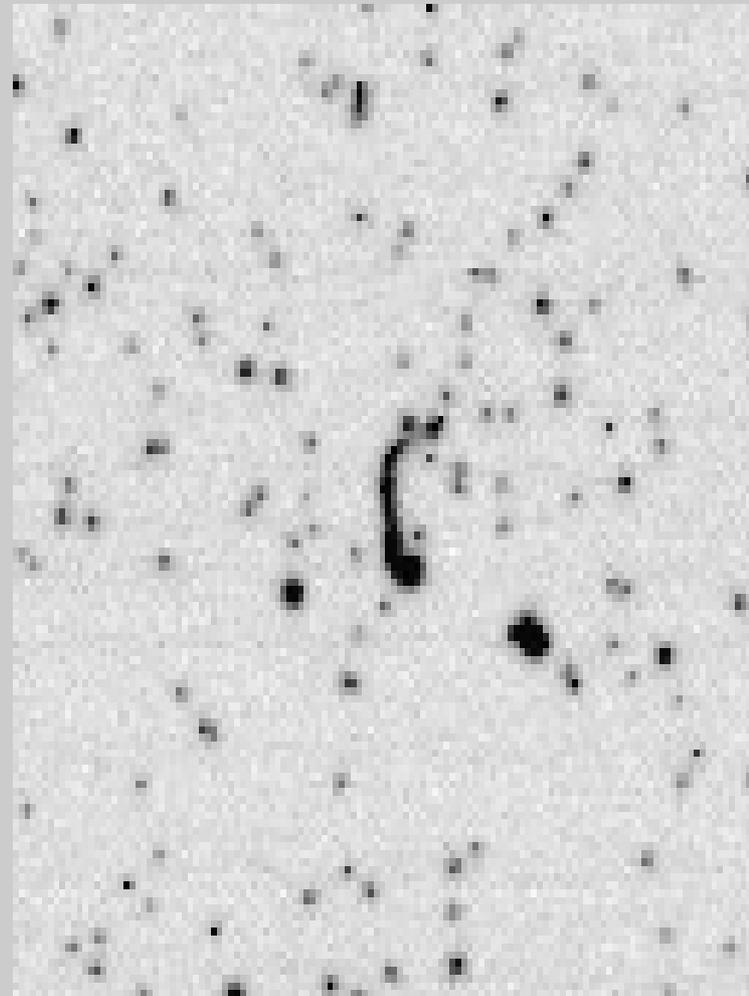
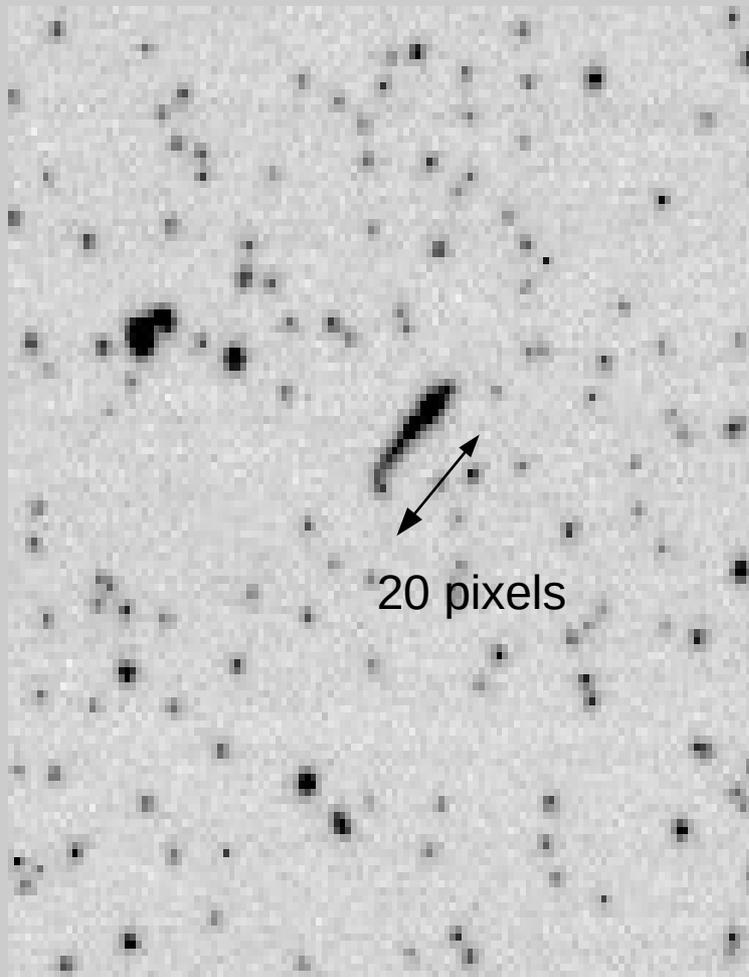
CMOS MAPS Detector (for high energy)





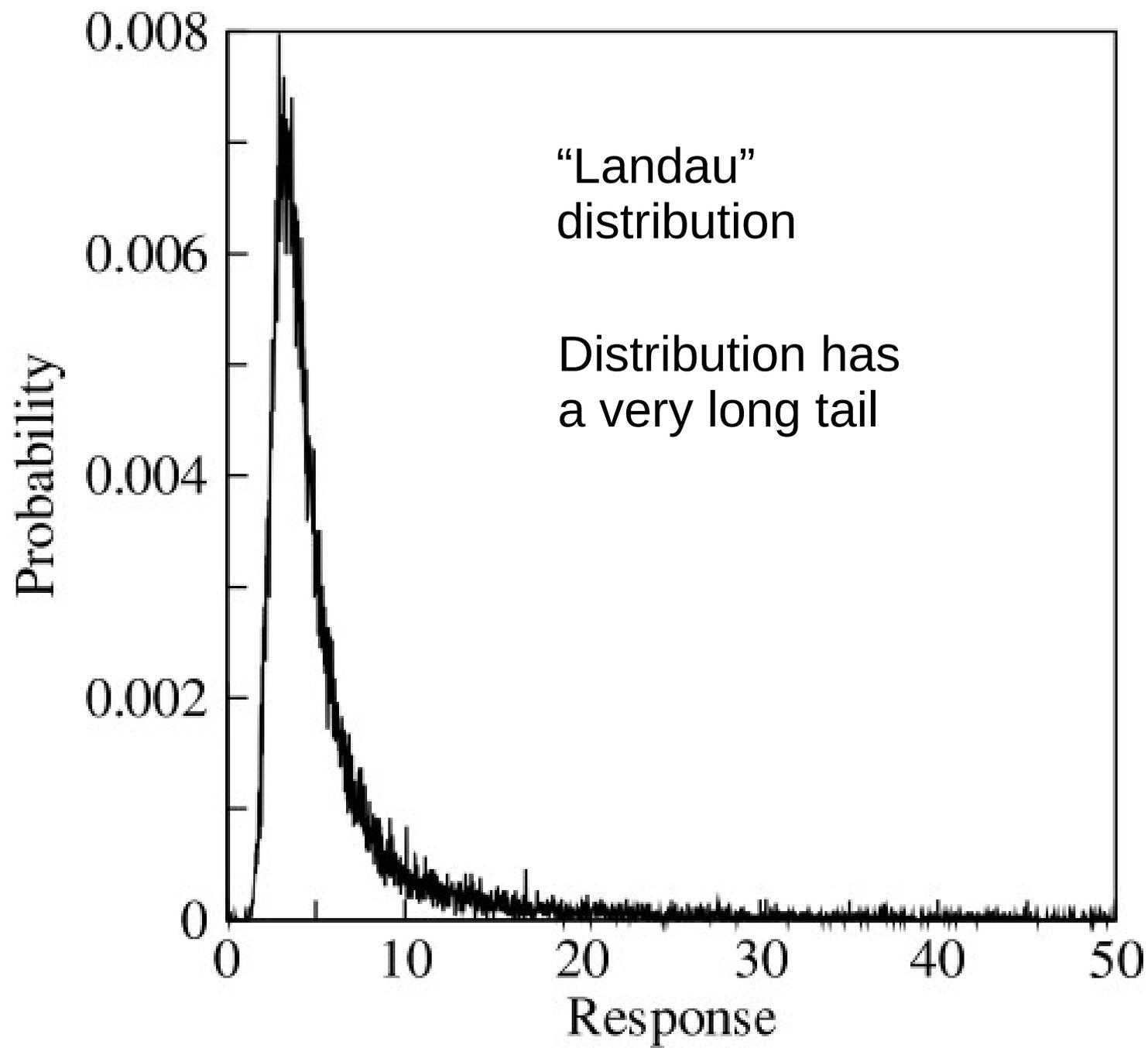
MAPS Electron Event Images

Backthinned 14 μm pixel

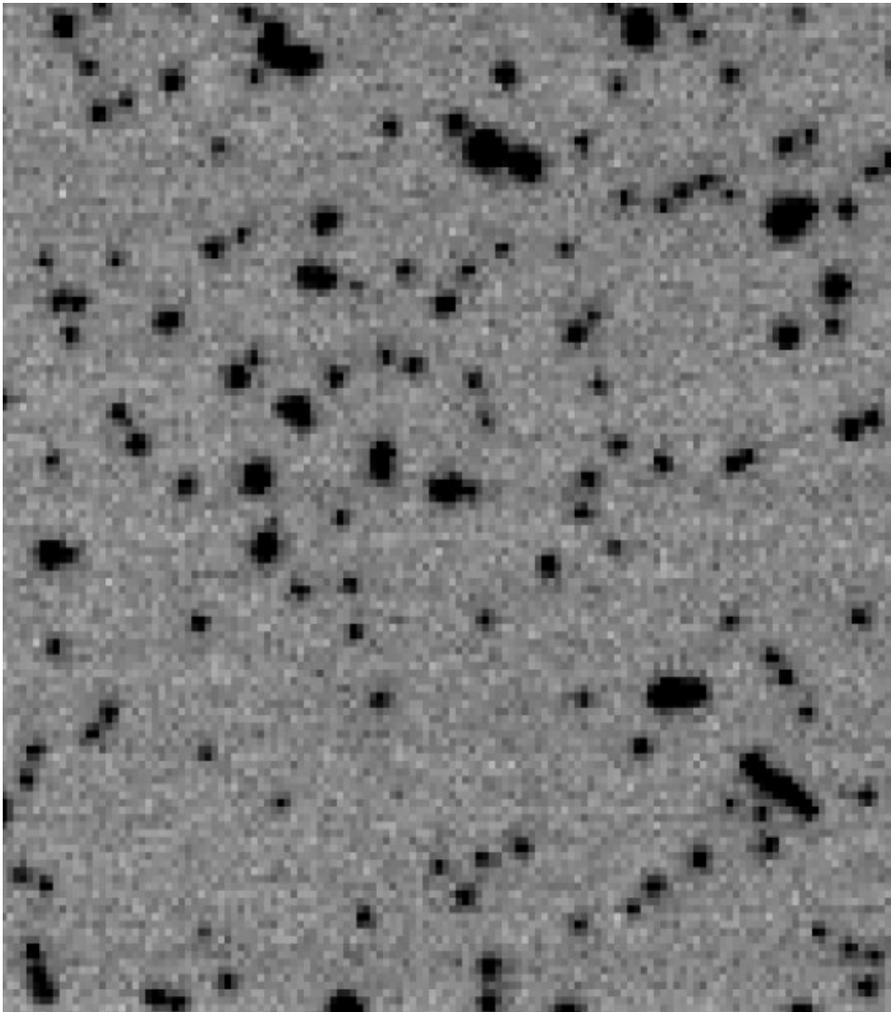


128 pixels

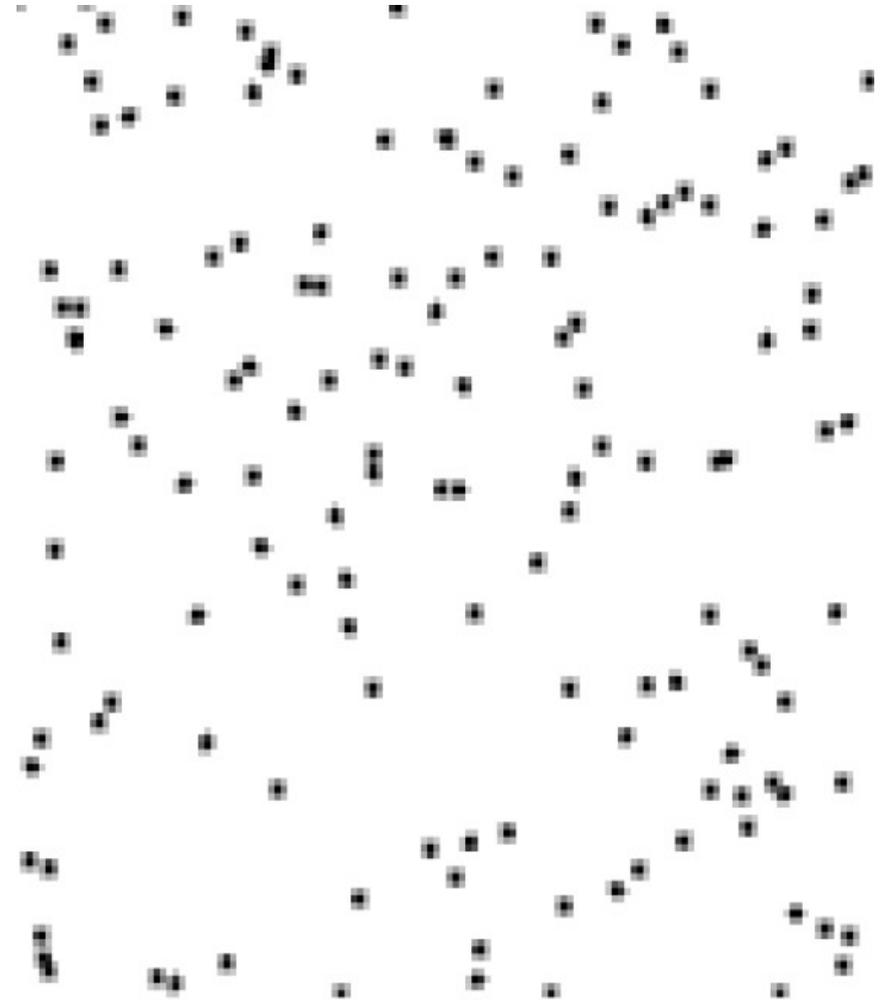




For highest DQE: Remove variable response by processing images of individual electron events



Raw output of camera



Electron counted output

FEI Falcon3

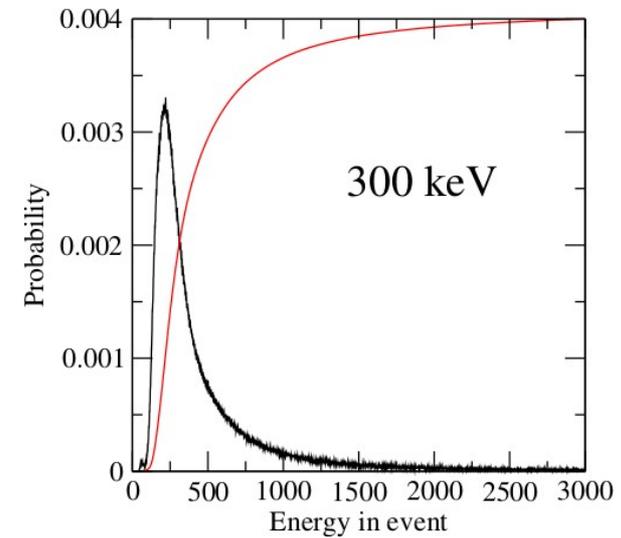
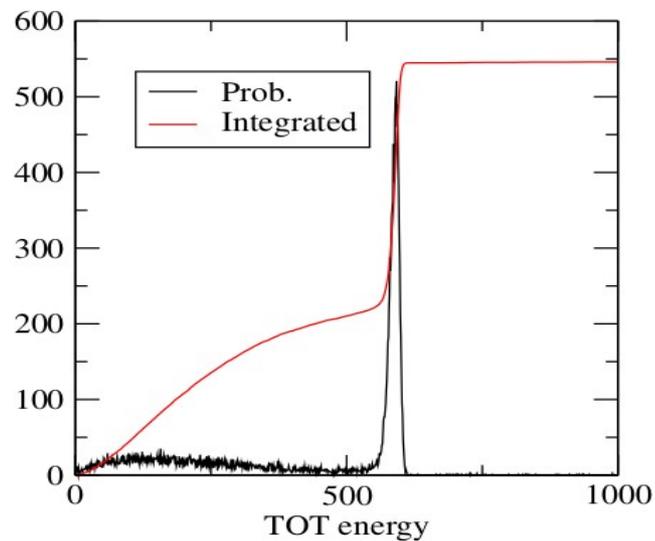
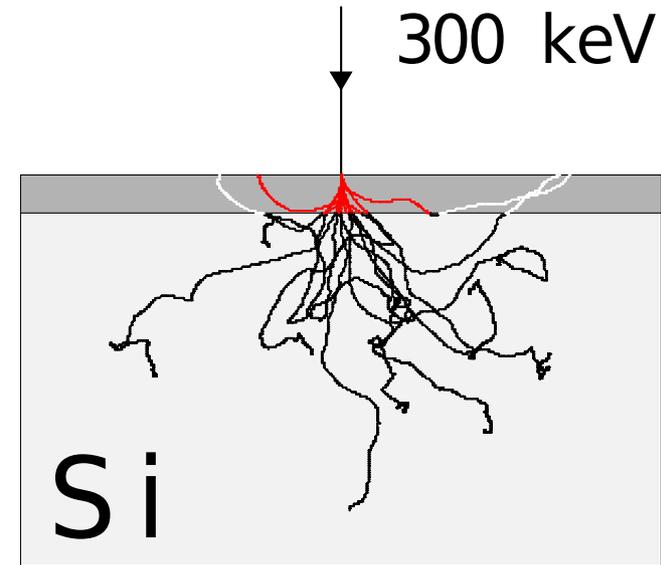
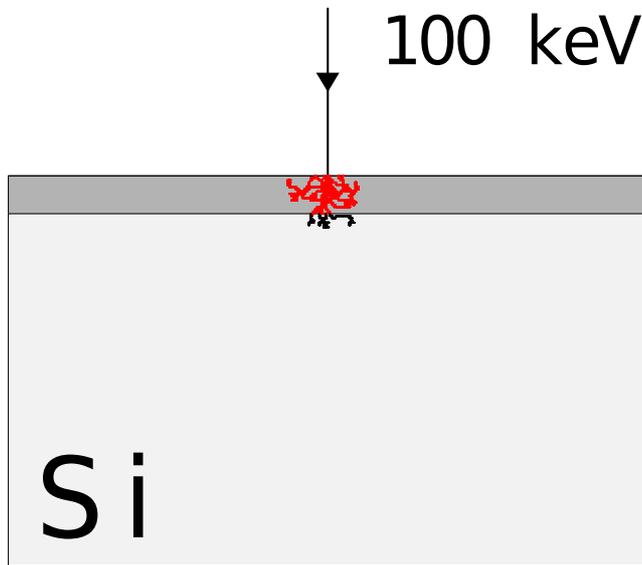
For 300 keV electron microscopes CMOS based MAPS detectors win.

- $DQE(0) > 90\%$
- Larger than 4k x4k
- ~ 1000 fps
- Pixel pitch 6 μ m-14 μ m
- Nyquist frequency DQE from 30 to 60%
- Rad-hard.

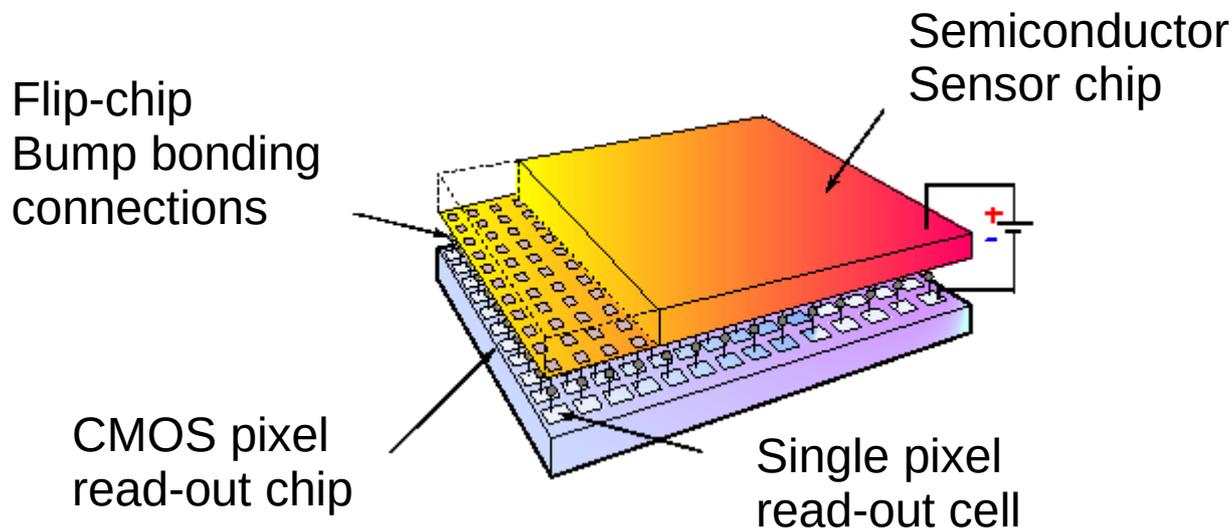
Interest in using lower energy: 100 keV rather than 300 keV

- 100 keV is cheaper (500,000 versus 5,000,000)
- Potentially better due to higher ratio for elastic to inelastic scattering
- Current detectors don't work well.
 - Need $> 50 \mu\text{m}$ pixel pitch
 - As big as possible (2k x 2k)
 - As fast as possible (2000 fps)
 - Rad-hard.

Option 1 : Detecting 100 keV electrons with CMOS/MAPS

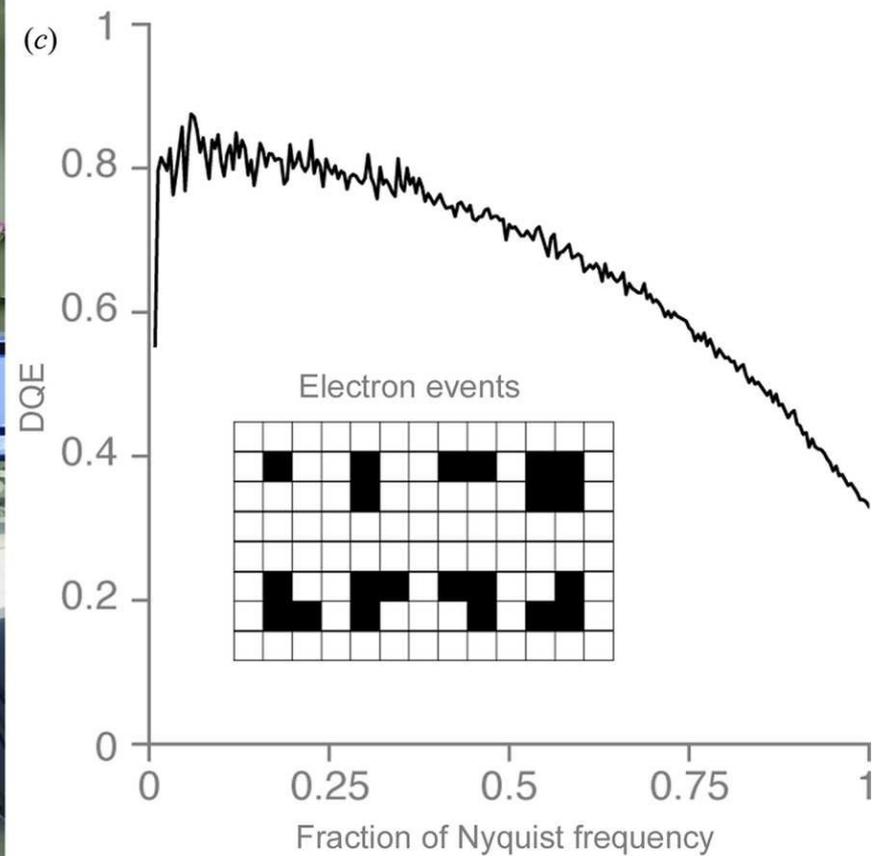


Option 2: Hybrid pixel Detector

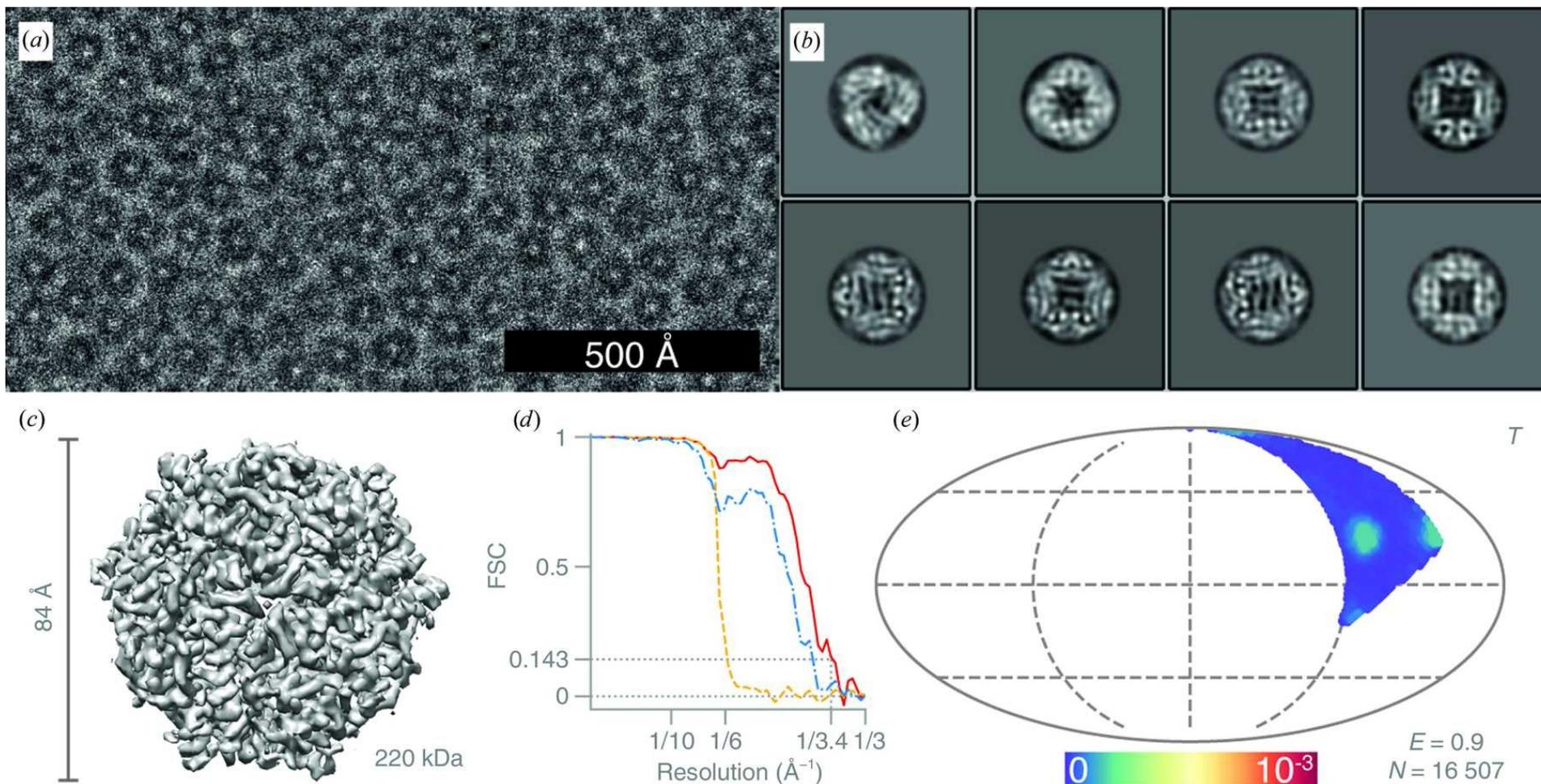


- **Quantum Detectors (Merlin based on Medipix III) (CERN)**
- **Dectris (Pilatus/Eiger) (Paul Scherrer Institute)**

Dectris 500K Hybrid pixel Detector (proof of principle)



Structure of DPS determined at 100 keV. (a) Typical micrograph of DPS after motion correction. Contrast is adjusted to $\pm 3\sigma$ from the mean intensity. (b) 2D class averages. (c) Sharpened masked 3D ...



Summary

- 300 keV – difficult to do better than what can be done with CMOS/MAPS
- 100 keV is still open but there is investment in both CMOS/MAPS and hybrid pixel options
- What is needed at 100 keV:
 - Need $> 50 \mu\text{m}$ pixel pitch
 - As big as possible (2k x 2k)
 - As fast as possible (2000 fps)
 - Rad-hard.

Thanks to...

Richard Henderson

Wasi Faruqi

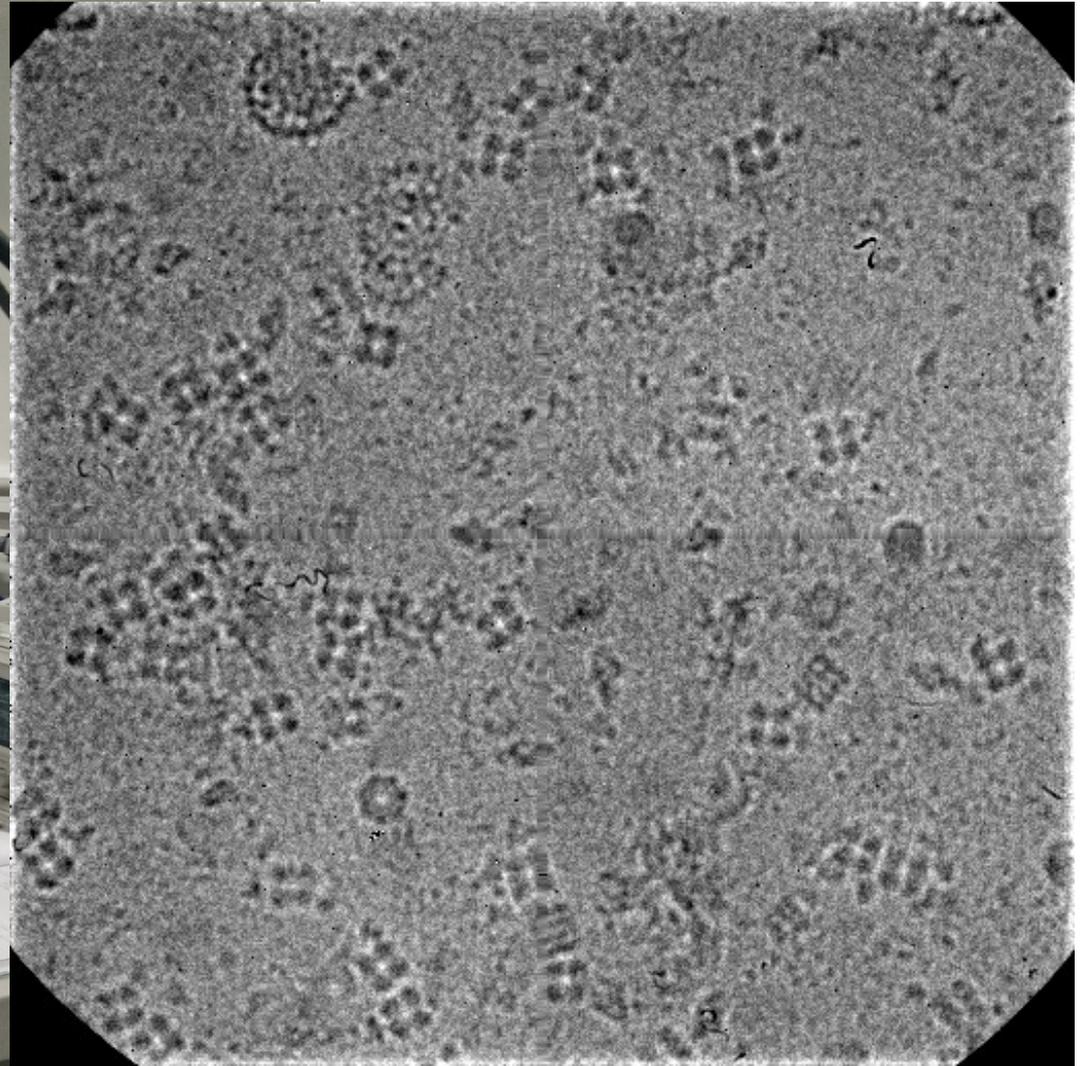
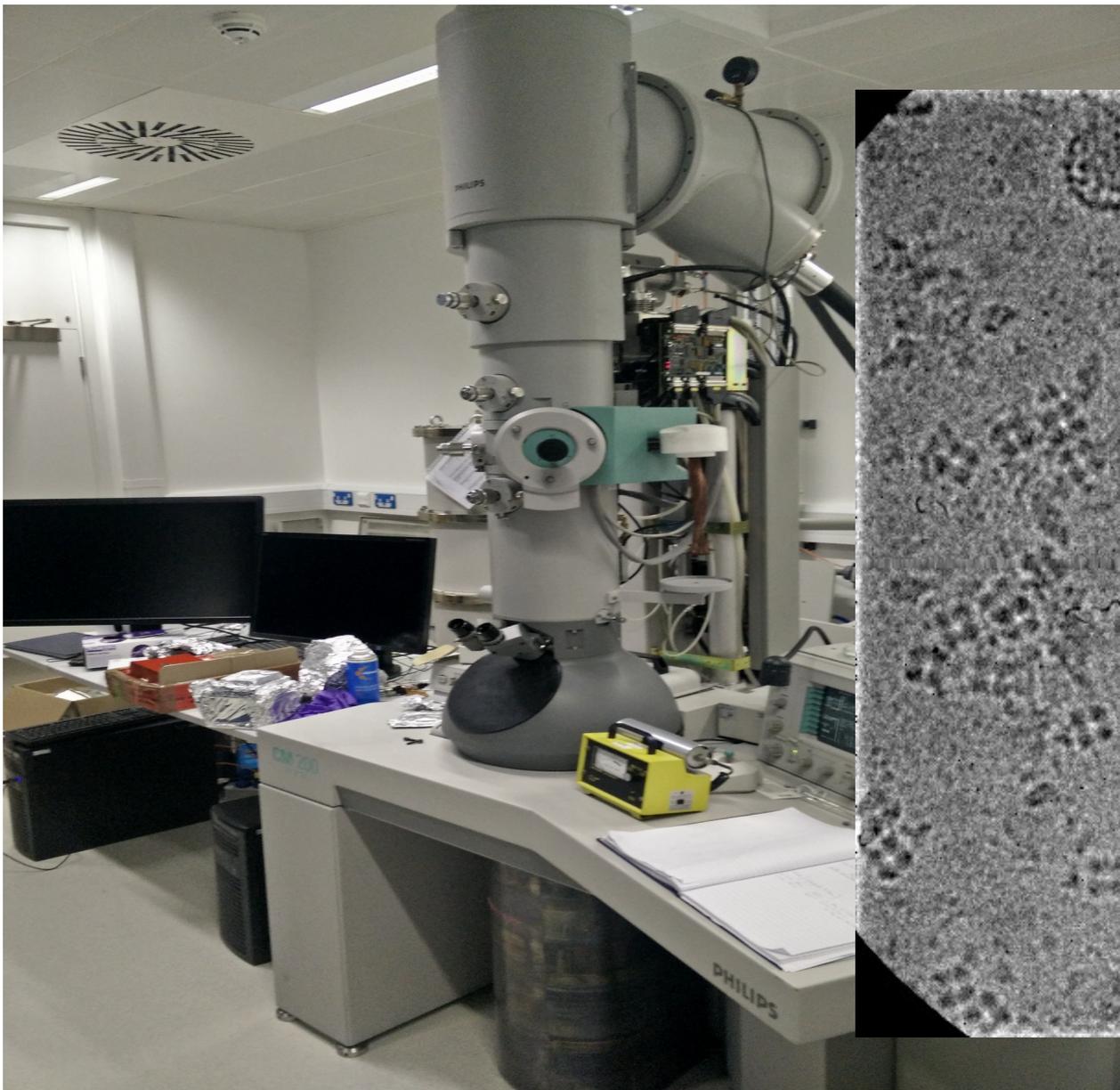
Chris Russo

Etc...

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Merlin detector (Medipix3)

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