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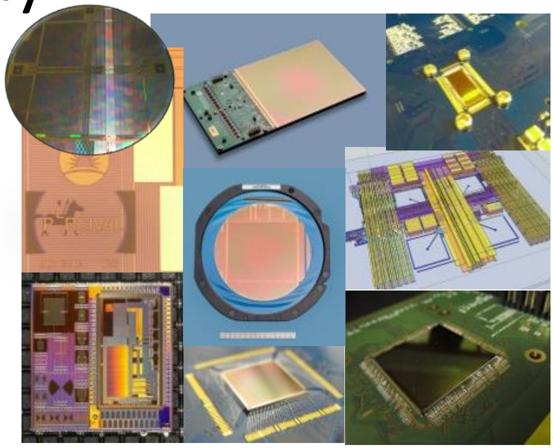
CMOS Sensors For Electron and X-Rays Detectors

Nicola Guerrini
CMOS Sensors Design Group
STFC – Rutherford Appleton Laboratory, UK

Outline

- Introduction
- CMOS sensors for X-Rays: Wafer Scale Sensor (LASSENA)
- CMOS sensors for X-Rays: Soft X-Rays (PERCIVAL)
- CMOS for EM: “the resolution revolution” in TEM
- CMOS for EM: cryo Electron Tomography
- CMOS for EM: 100keV, less is more?
- What’s next



Introduction

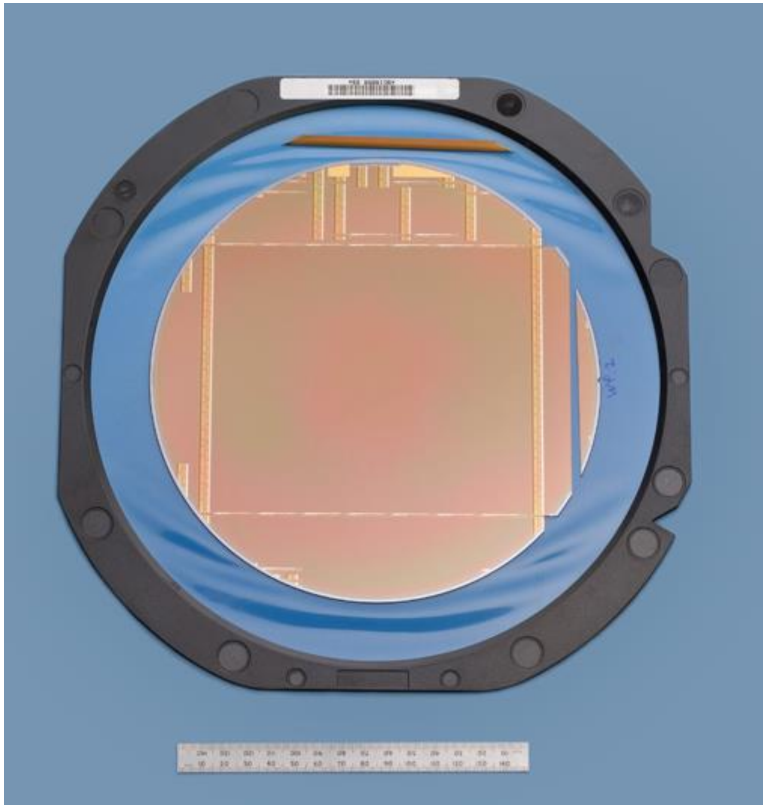
STFC (Science and Technology Facilities Council) is one of Europe's largest multidisciplinary research organisations supporting scientists and engineers world-wide providing access to lasers, accelerators, neutron sources, synchrotron light sources, scientific computing…..

Within STFC the Technology Department design and maintain the instruments needed for such large variety of experiments.

CMOS for X-RAYS

Wafer Scale

CMOS image sensors are nowadays widely used for medical X-Ray imaging as a replacement for amorphous silicon flat panels.



LASSENA wafer scale CMOS Sensor

No lens for CMOS-imaging-based X-ray application so the size of an image sensor has to match the size of the target area.

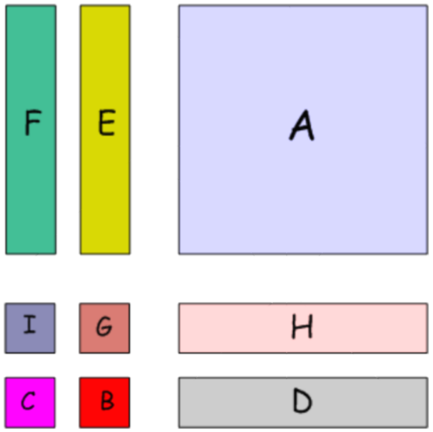
LASSENA:

- Focal plane of 139.2 x 120 mm
- 6.7-million (2800 x 2400) pixels
- 50-micron pixel pitch (3T)
- 32 analogue outputs
- Low noise and high dynamic range
- Programmable region-of-interest readout.
- Pixel binning (2X2 and 4X4)

CMOS for X-RAYS

Wafer Scale

When the sensor is well beyond the reticle size its fabrication it's made possible using a technique called **stitching**.

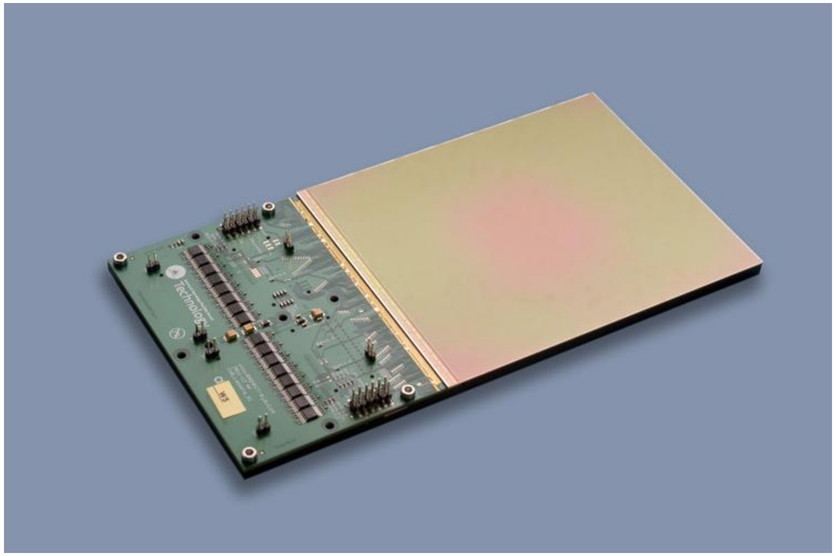


Above the reticle is shown and on the left the final result.

The fabricated sensor is obtained by stepping and repeating until the desired size is achieved.

CMOS for X-RAYS

Wafer Scale



LASSENA wafer scale CMOS Sensor

- Noise 60e-
- Gain 6.4uV/e-
- Linear full well 112,000 e-
- Linear dynamic range of 64.1 dB.
- QE 50.1%
- Frame rate of 30fps.

LASSENA tiled sensor would cover up to 280 mm in one direction and any multiple of 120mm in the other direction

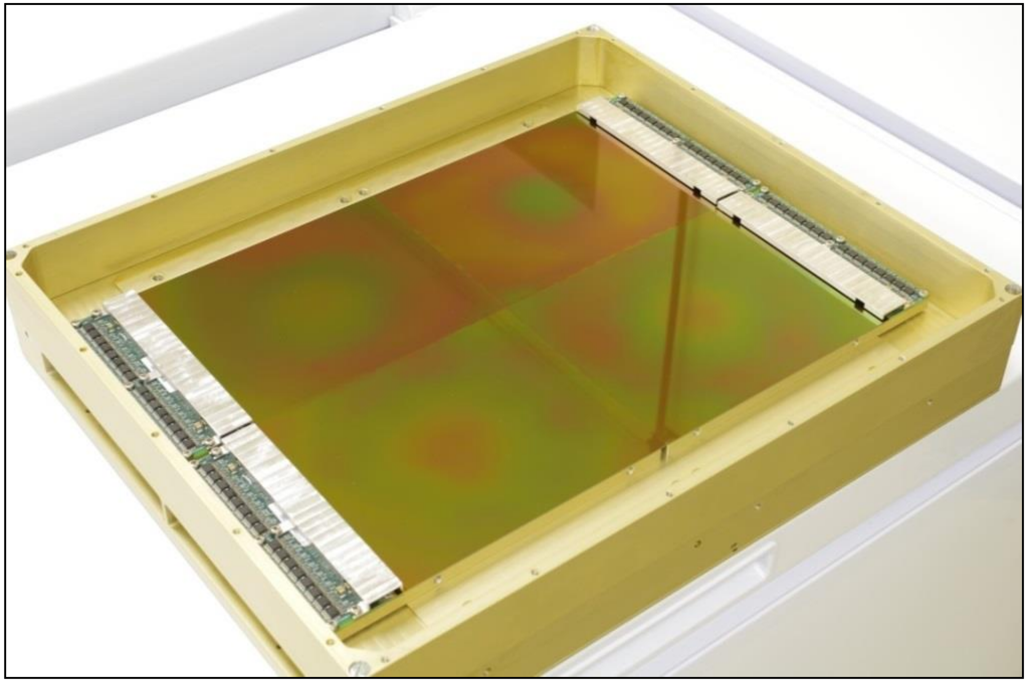
The readout electronics is just on one edge of the sensor, with extra circuitry embedded in the actual pixel array.

Wider than normal metal separation, increased transistor sizes, increased number of contacts and circuit redundancy have been adopted in order to maximise the yield.

CMOS for X-RAYS

Wafer Scale

STFC (RAL) setup in 2014 vivaMOS® a spin-out with the aim of commercialising the LASSENA image sensor.



A 2x2 array of LASSENA sensors has been successfully assembled and tested at STFC, paving the way to larger and larger X-rays detectors.

CMOS for X-RAYS

Wafer Scale

This X-ray video is taken using the Lassena Wafer Scale CMOS sensor developed by STFC. Four sensors were used here and combined into a single detector. The sensors are 12 cm x 14 cm, 6.7 MPixels and can operate at 30 frames per second. This results in the whole detector having 26.8 MPixels and an area of 24 cm x 28 cm. The detector can generate 1.5 GB of images per second. The image sensors are inefficient at detecting X-rays, therefore a Scintillator is used as the X-ray detection medium. The X-rays are converted into 550 nm light by the scintillator that is then detected by the image sensor. The scintillator used in this detector is Caesium Iodide doped with Thallium.

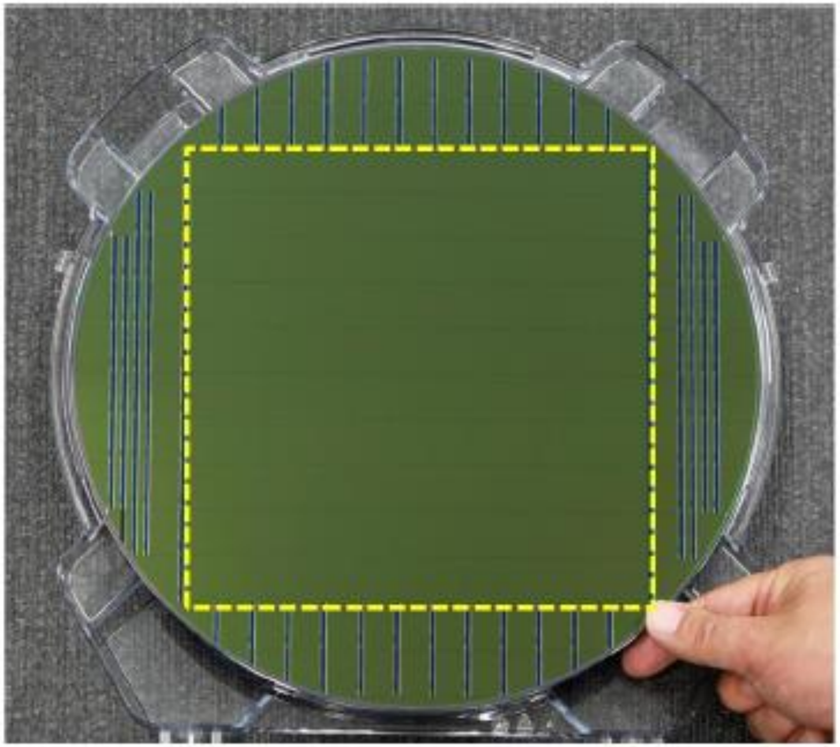
CMOS for X-RAYS

Wafer Scale

Wafer scale sensors have been proved with success also on larger wafers (12”).

In specific applications like nuclear waste inspection a large sensor capable of imaging the area of interest in one shot is a clear advantage.
HDR and low noise are obviously a plus.

On a more general note sensors for medical applications will benefit from higher frame rate for better images (after processing) and patient higher throughput.

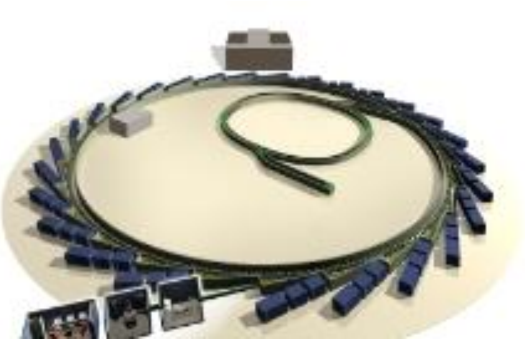


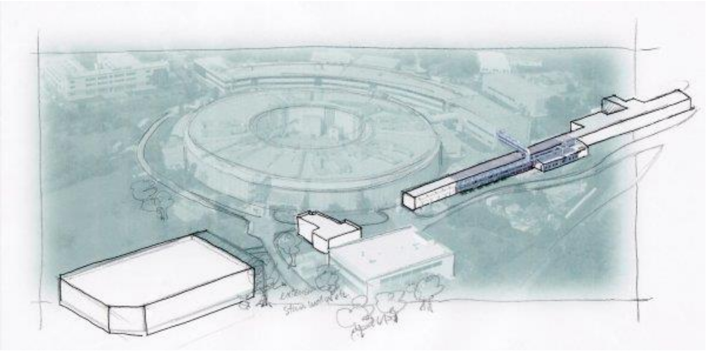
CANON 12” wafer scale CMOS Sensor
Picture from “R45: 300mm wafer scale sensor for low light level imaging”

CMOS for X-RAYS

PERCIVAL

- Large pixel count (up to limit of wafer)
- RMS Noise < 15e$^-$
- Full Well > 10Me$^-$
- Sensitive in the range 250eV – 1keV with >85% QE
- 12 bit ADC
- 120fps
- 27um pitch





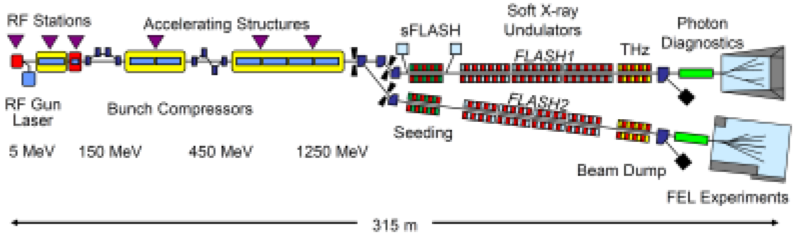


Image Credit: http://www.elettra.trieste.it/FERMI/

Image Credit: http://flash.desy.de/

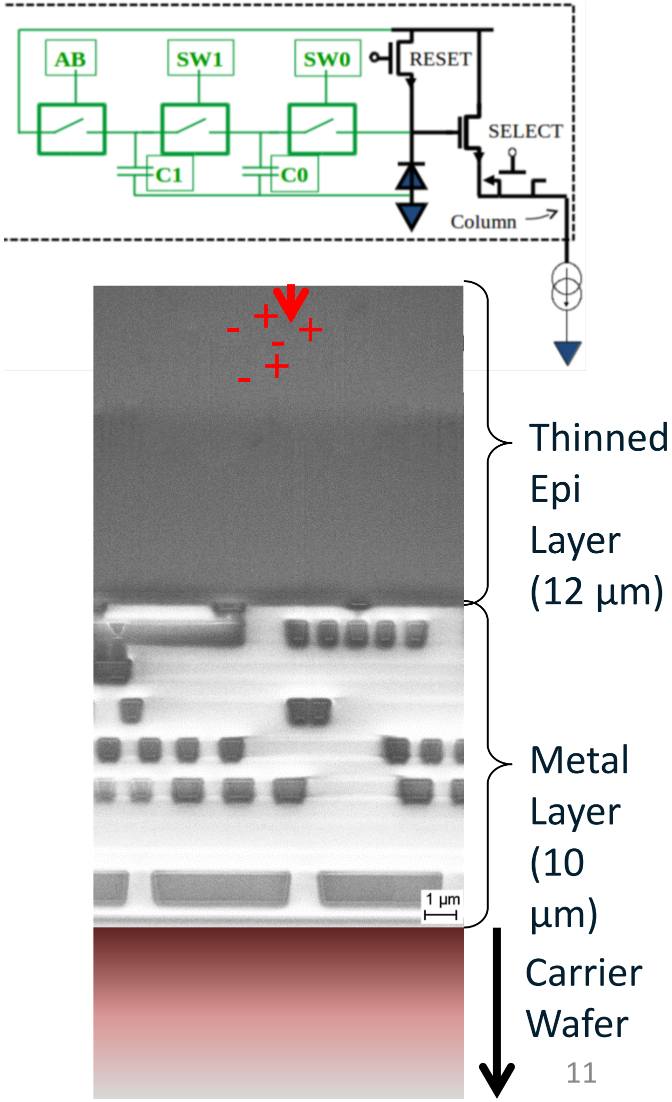
Image Credit: http://www.diamond.ac.uk/PressOffice/MediaResources.html

CMOS for X-RAYS

PERCIVAL

Compared to the LASSENA sensor a series of challenges arise:

- HDR pixel
- 250eV sensitivity
- Frame rate and data rate



More details on PERCIVAL please refer to the posters "*Quick turnaround ultrathin entrance window postprocessing of wafers and single dies*" C. Wunderer

"*Calibration and characterization software framework for the high data rate soft X-rays PERCIVAL imager*" B. Boitrelle

"*PERCIVAL: possible applications in X-ray micro-tomography*" G. Pinaroli

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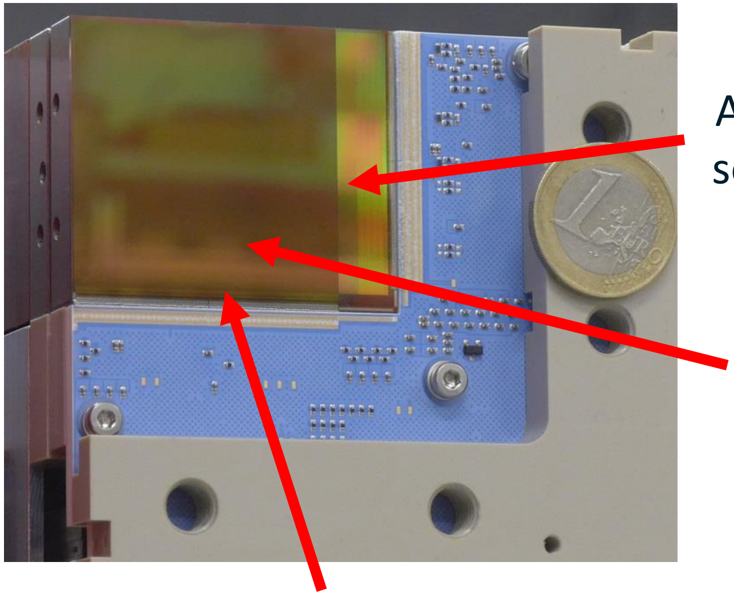
CMOS for X-RAYS

PERCIVAL

P2M


ADCs and serialisers

Pixel array

Row driving circuitry

- 1408 x 1484 pixels
- 4.18 x 4.97 cm^2
- 45 LVDS I/Os (@420Mbit/s)
- 18.9 Gbit/s output

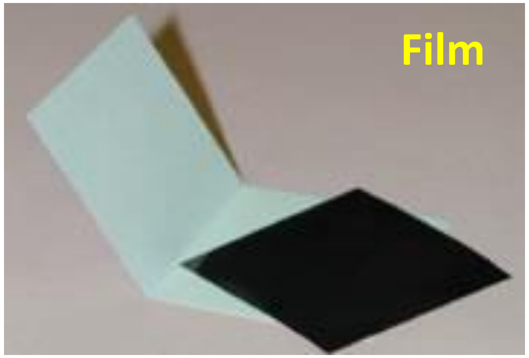
Next generation facilities will require considerably higher frame rates.

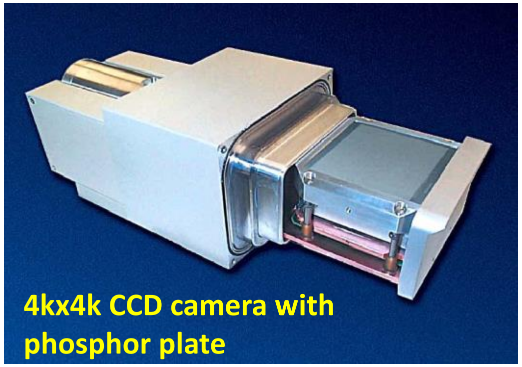
Should sensors like PERCIVAL require a even larger dynamic range extra in-pixel capacitors, so more readings, will needed.
Alternatively in-pixel processing will have to be considered.

CMOS for EM

In a similar way to what happened to flat panels for X-rays, CMOS sensors showed lots of potential when compared to alternatives like film or CCD sensors:

- Film: direct detection, very good resolution, non digital, needs time for development, poor S/N for weak exposure.
- CCD with phosphor: not direct detection (radiation hardness), phosphor ruins spatial resolution, good for tomography.
- CMOS: direct detection, good spatial resolution, good sensitivity (single electron detection).

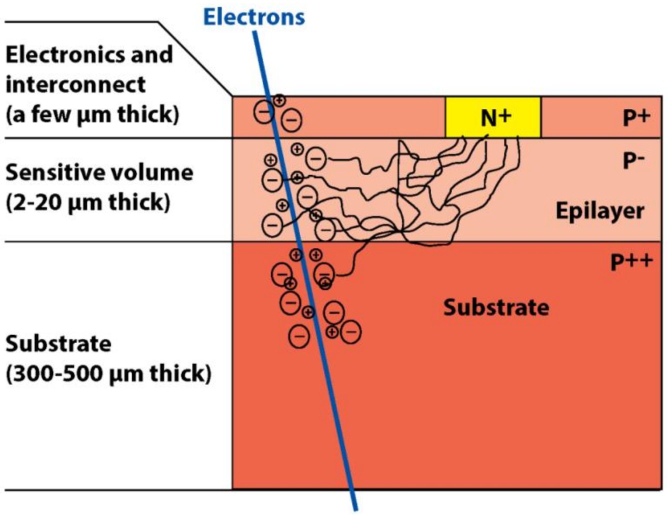

Film


4kx4k CCD camera with phosphor plate

CMOS for EM

In the TEM field CMOS sensors presents many advantages:

- Direct detection. No loss of resolution due the phosphor.
- Radiation hardness. Direct detection is possible only with radiation tolerant detector. CMOS circuits can be hardened by design.
- Images recorded digitally
- Possibility to have a lot functionality on-chip.
- Continuous process development



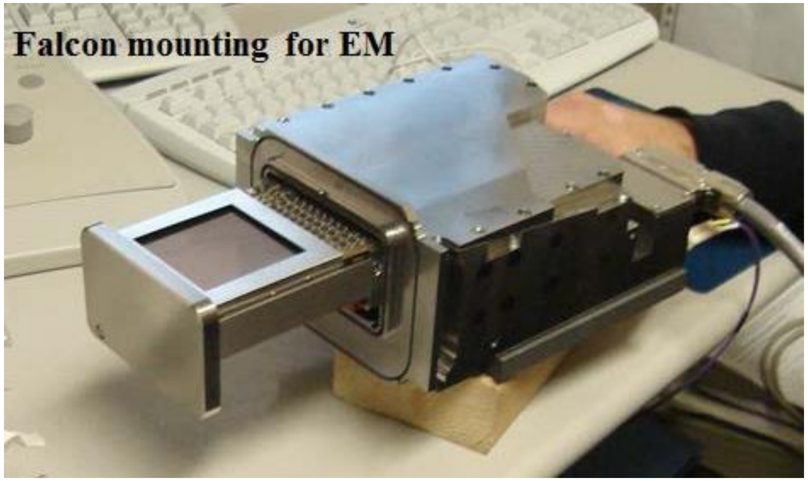
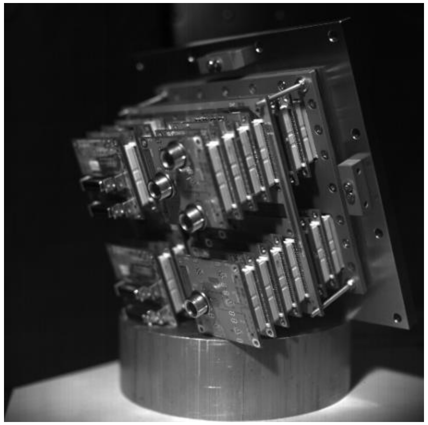


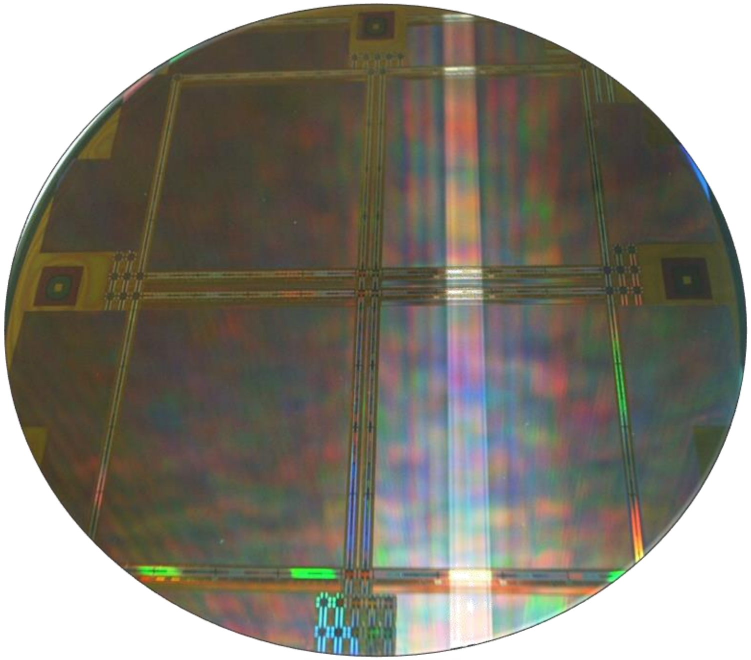
Image courtesy of LMB-Cambridge

CMOS for EM

CMOS sensor for TEM, used in the FEI Falcon© Direct Electron Detector and FEI CETA ©, developed by STFC in collaboration with LMB (R. Henderson Group), FEI and Max Planck Institute.



"Self-portrait"



- 61x63 mm^2 silicon area
- 16 million pixels
- 4Kx4K array
- Analogue outputs
- Frame rate in excess of video rate.
- Radiation hard characteristics.
- Pixel binning.
- Region Of Interest readout
- 0.35μm standard CMOS process
- High yield

CMOS for EM

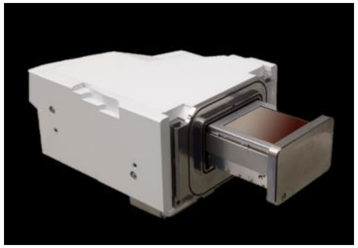
Electron detector development timeline

1950	Film (and earlier)
1990	Phosphor/fibre optics/CCD
1999	Medipix I silicon pixel detector - counting
2003	Medipix II silicon pixel detector -counting
2003	RAL StarTracker: CMOS camera-on-a-chip
2004	Medipix II Quad - counting
2006-08	TEMAPS : 1.5M pixels test structure with 25 different pixel types
2009-10	TEMAPS 2.0: 4k by 4k stitched CMOS sensor for TEM
2009	Electron counting papers using CMOS published
2010	DE-12
2012	FEI FALCON I : First TEM camera with a stitched CMOS image sensor
2013	FEI FALCON II: TEM camera with back-thinned CMOS sensor
2013	K2 – counting
2014	FEI CETA: TEM camera for indirect detection with a CMOS sensor
2014	DE-20
2017	K3 – 24 Mpixels, 1,500 fps CMOS camera

CMOS for EM

Gatan K3 – www.gatan.com

- 24 Mpixels (5,760 x 4,092)
- 1,500 full frames/second

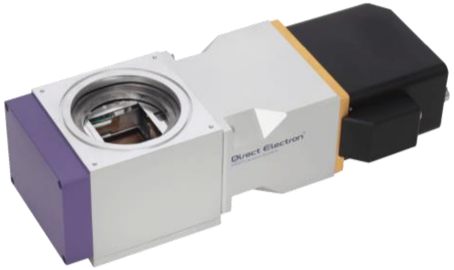


Thermofisher FALCON – www.fei.com

- 16 Mpixels (4k x 4k)
- 40 full frames/second

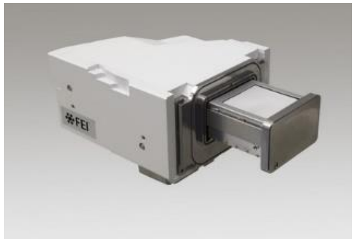
Gatan OneView – www.gatan.com

- 16 Mpixels (4k x 4k)
- 25 full frames/second



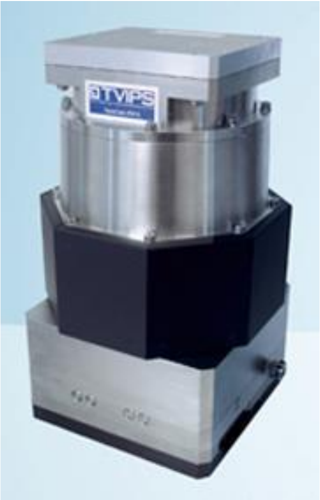
Direct Electron DE-64 – www.directelectron.com

- 64 Mpixels (8k x 8k)
- 42 full frames/second



Thermofisher CETA – www.fei.com

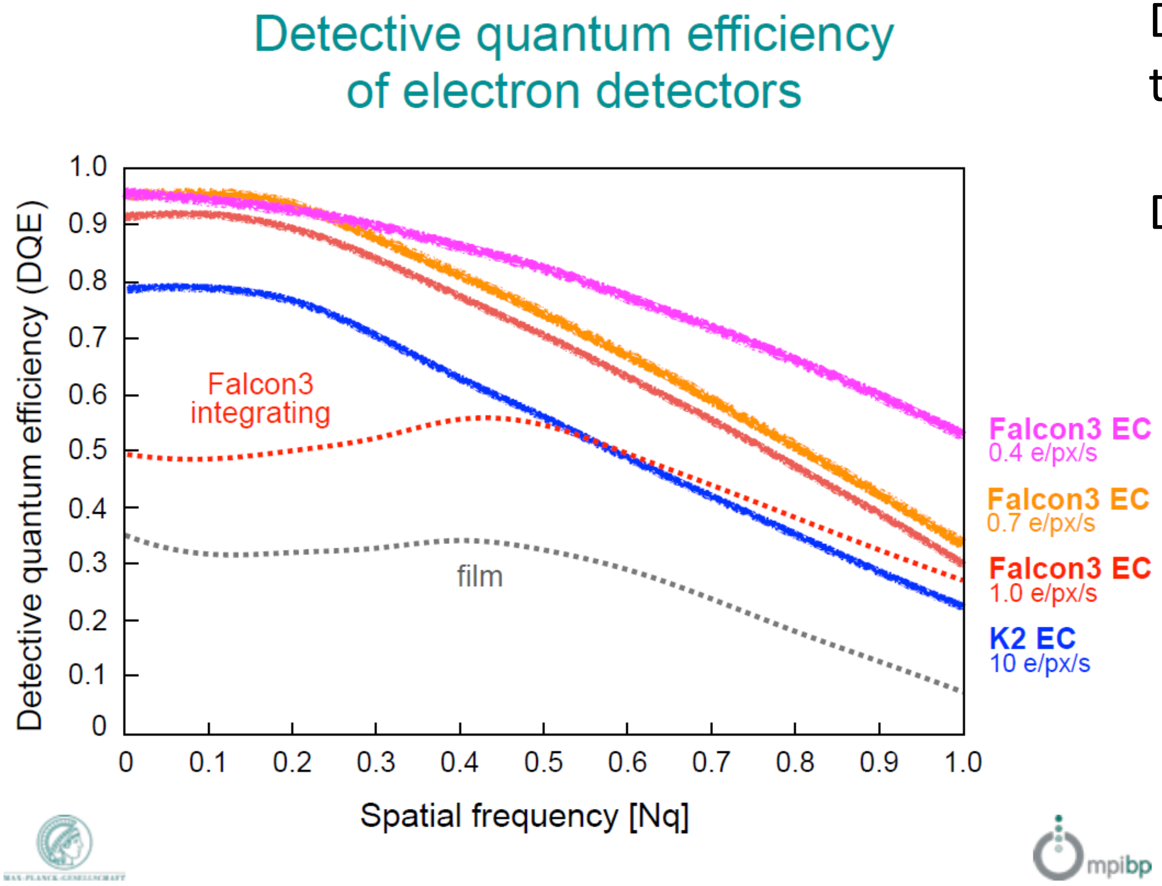
- 16 megapixels (4k x 4k)
- 40 full frames/second



- 64 Mpixels (8k x 8k, 128mm^2)
- 0.4 full frames/second

Tietz TemCam F816 – www.tvips.com

CMOS for EM



Picture from "Introduction to electron cryo-microscopy (cryoEM)"
Werner Kuhlbrandt, Max Planck Institute

DQE is defined as the ratio of the signal-to-noise-ratios.

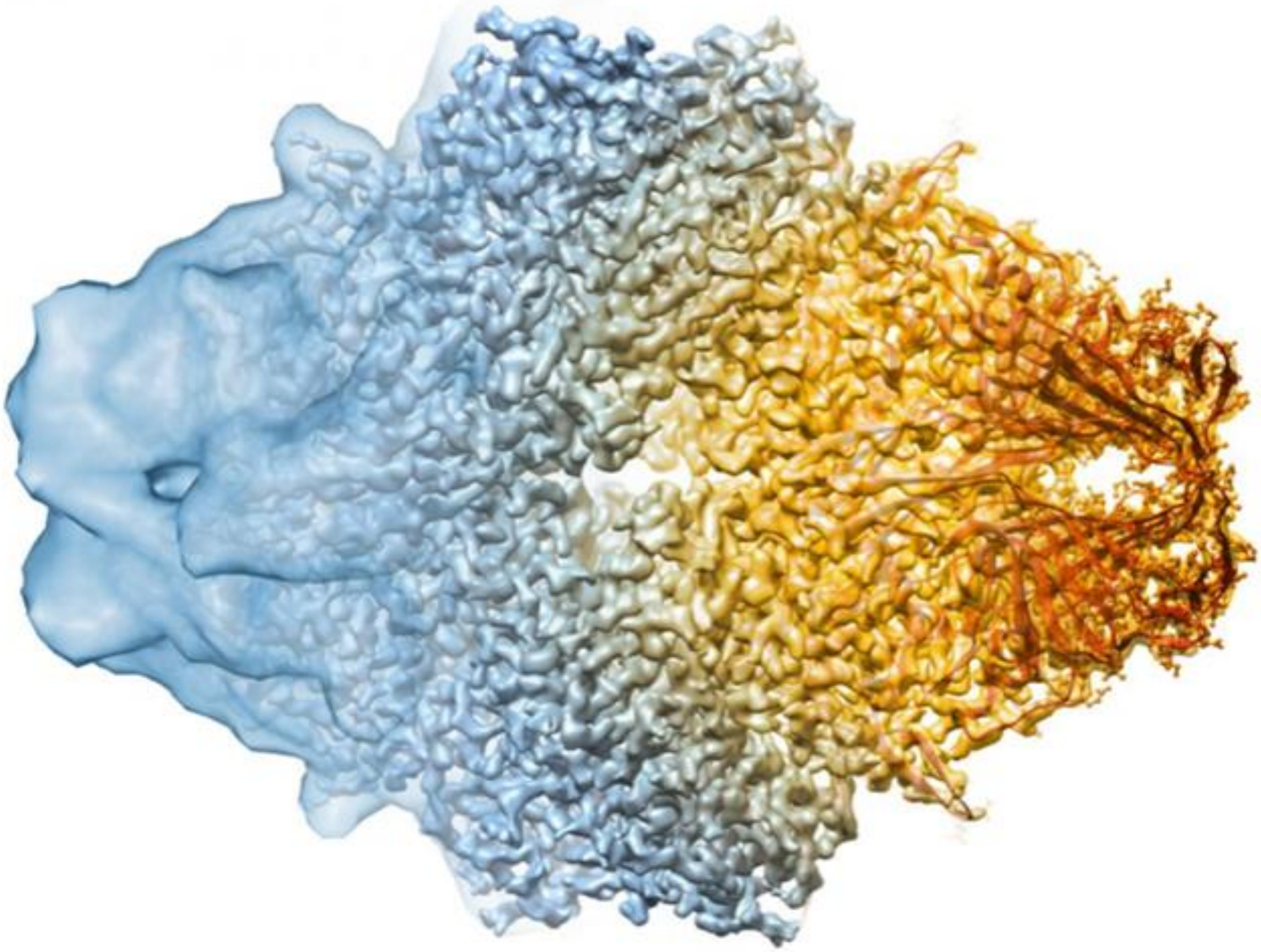
$$DQE = (S/N)_{out}^2/(S/N)_{in}^2$$

Switching from integration mode to electron counting the DQE is dramatically improved.

Electron counting requires high readout speeds in terms of frames per second.

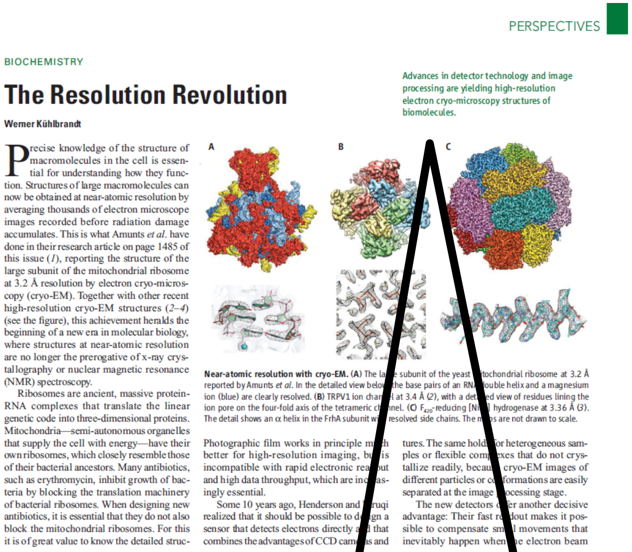
CMOS for EM

12 Å



2.2 Å

CMOS for EM



PERSPECTIVES

BIOCHEMISTRY

The Resolution Revolution

Werner Kühlbrandt

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

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. Mitochondria—semi-autonomous organelles that supply the cell with energy—have their own ribosomes, which closely resemble those of their bacterial ancestors. Many antibiotics, such as erythromycin, inhibit growth of bacteria by blocking the translation machinery of bacterial ribosomes. When designing new antibiotics, it is essential that they do not also block the mitochondrial ribosomes. For this it is of great value to know the detailed struc-

Near-atomic resolution with cryo-EM. (**A**) The la e subunit of the yeast itochondrial ribosome at 3.2 Å reported by Amunts *et al*. In the detailed view belo the base pairs of an RN ouble helix and a magnesium ion (blue) are clearly resolved. (**B**) TRPV1 ion char el at 3.4 Å (*2*), with a deta ed view of residues lining the ion pore on the four-fold axis of the tetrameric ch nnel. (**C**) F_{420}-reducing [Ni] hydrogenase at 3.36 Å (*3*). The detail shows an α helix in the FrhA subunit wi resolved side chains. The m ps are not drawn to scale.

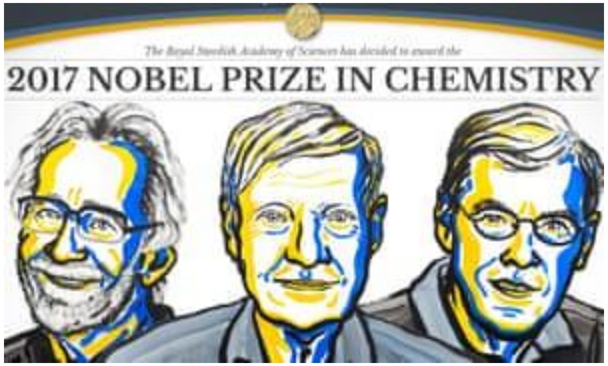
Photographic film works in principle m ch better for high-resolution imaging, bu is incompatible with rapid electronic rea out and high data throughput, which are inc easingly essential.

Some 10 years ago, Henderson and ruqi realized that it should be possible to de ign a sensor that detects electrons directly a d that combines the advantages of CCD cam as and

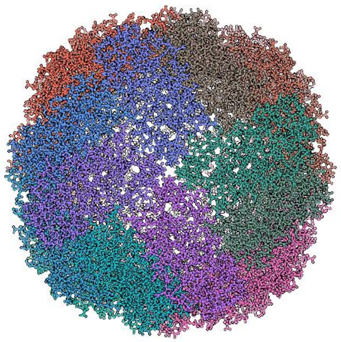
tures. The same hold for heterogeneous samples or flexible comp exes that do not crystallize readily, becau cryo-EM images of different particles or co formations are easily separated at the image p ocessing stage.

The new detectors o fer another decisive advantage: Their fast re dout makes it possible to compensate sm l movements that inevitably happen when e electron beam

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

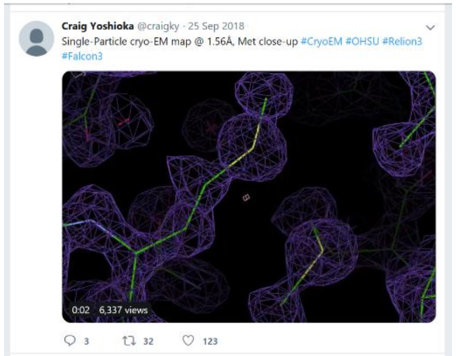


J. Dubochet, J. Frank, R. Henderson



1.54 Å resolution cryo-EM structure of apoferritin. Data courtesy of Kato T, Makino F, Nakane T, Terahara N, Namba K. Osaka University.

1.54Å structure with Gatan K3



Craig Yoshioka @craigky · 25 Sep 2018

Single-Particle cryo-EM map @ 1.56Å, Met close-up #CryoEM #OHSU #Relion3 #Falcon3

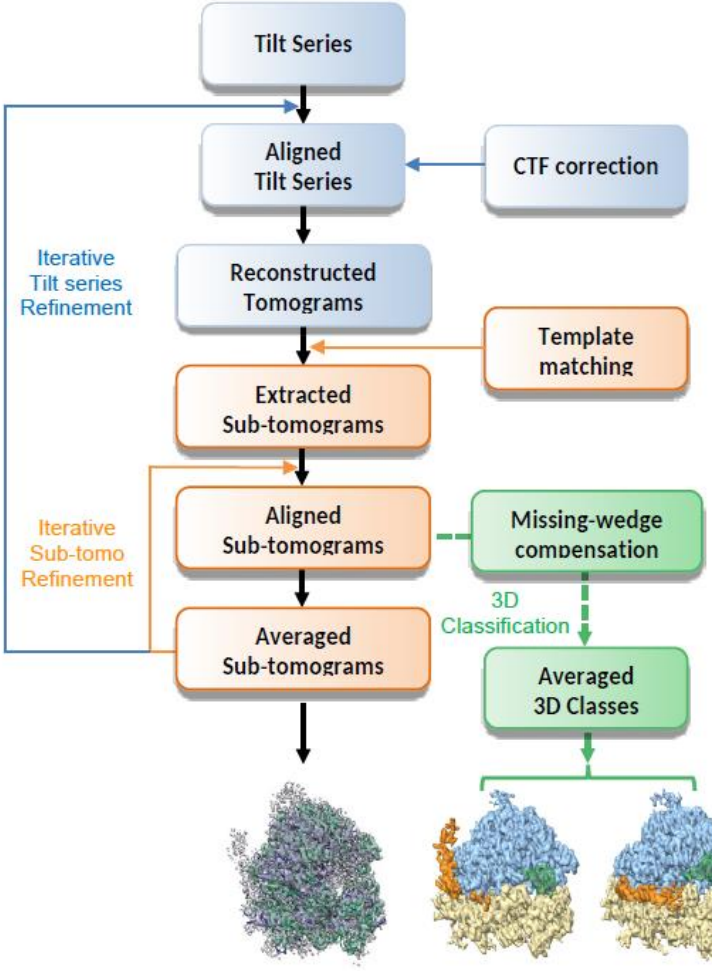
1.56Å structure announced in September 2018 with Falcon 3

CMOS for EM

Cryo Electron Tomography

Sophisticated machines like electron microscopes are also used for other applications such as cryo-electron tomography (cryo-ET), where the sample under investigation is rotated to collect a series of "tilted" images, used to reconstruct the three-dimensional tomographic volume.

Cryo-ET has emerged as a powerful method for visualizing the molecular organization within a native cell in functional states, potentially achieving near-atomic resolutions through sub-tomogram averaging.



Workflow for cryo-ET sub tomogram, averaging and classification (cryoSTAC)
Courtesy of Peijun Zhang, eBIC

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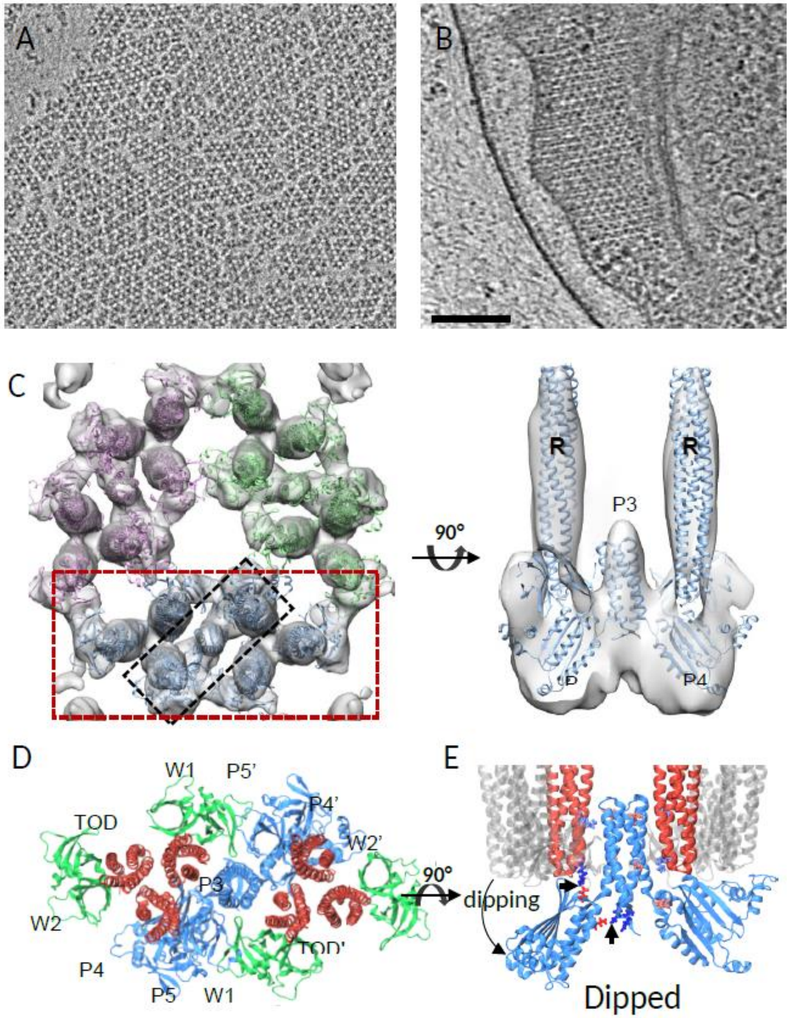
CMOS for EM

Cryo Electron Tomography

The number of images required for this technique is relatively large and so is the sensor area. Currently images for a complete tomographic tilt series require ~1 hour to record and this represents a serious limitation in terms of throughput, as such collecting 100 tilt-series which corresponds to 4000 total images requires over 4 days.

Commercially available cameras like Gatan K series, that deliver 1,000 to 1,500 frames per second, have helped considerably the technique, while cameras like the ThermoFisher Falcon series have the very large area needed to guarantee meaningful images at each rotation.



CryoSTAC of reconstituted bacterial chemotaxis signaling array
Courtesy of Peijun Zhang, eBIC

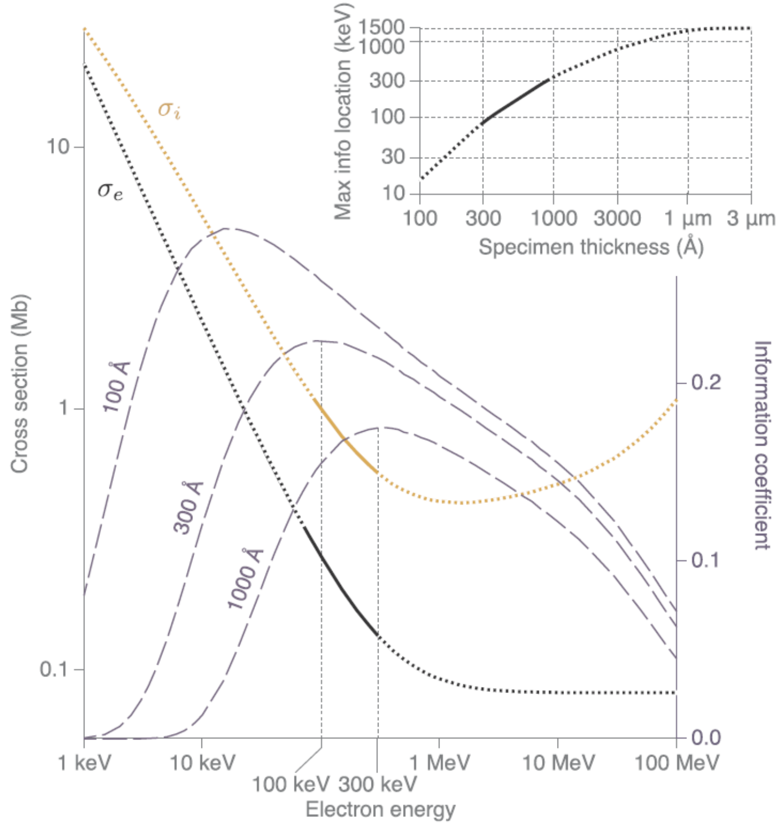
CMOS for EM

100 keV detectors. Less is more?

It is not new that the theoretical expectation is that the ratio of elastic to inelastic cross-sections gets better as the electron energy is lowered from 300keV to 100keV.

Recently the elastic σe and inelastic σi cross-sections, as well as radiation damage to organic and biological specimens as a function of electron energy has been measured [*Peet, Henderson,Russo, Ultramiscroscopy 203 (2019) 125-131*]

This latest results show that there is a 25% improvement in the ratio σe/σi between 300 keV and 100 keV, and a 25% improvement in the image contrast for a given amount of radiation damage.



Scaling of cross-sections and information vs energy. The theoretical relationship between the elastic (σ_e) and inelastic (σ_i) scattering cross-sections for carbon are plotted vs. energy.

CMOS for EM

100 keV detectors. Less is more?

Based on the latest measurements, it is possible to conclude that with all other considerations being equal, most single-particle cryoEM investigations would benefit from changing the electron energy from 300 to 100 keV instead.

The present limitation to low dose imaging at 100keV is the detector.

Currently available direct detectors are either optimised for higher energies (300 keV and above) or lack the combined features required for cryoEM (DQE, number of pixels and frame rate).

From M. Peet, R. Henderson,C. Russo, «The energy dependance of contrast and damage in electron cryomicroscopy of biological molecules»
Ultramiscroscopy 203 (2019) 125-131

The commercial production of a relatively low-cost 100 keV platform will enable many academic laboratories and pharmaceutical companies to join the cryoEM revolution in structural biology.

From D. Krukauskas, "C100 – CMOS Sensor for 100 keV EM"
Rosalind Franklin Institute annual meeting 2019

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CMOS for EM

100 keV detectors. Less is more?

STFC Tech Department is now working in collaboration with RFI (Rosalind Franklin Institute) and LMB-MRC to develop **C100**, a fast, large area CMOS sensor optimized for cryo-EM and 100keV.

"Our aim is to increase, by an order of magnitude, the number of biological specimens that can prepared for analysis by structural biology."
Professor James Naismith, Structural Biology Theme Leader

The Rosalind Franklin Institute

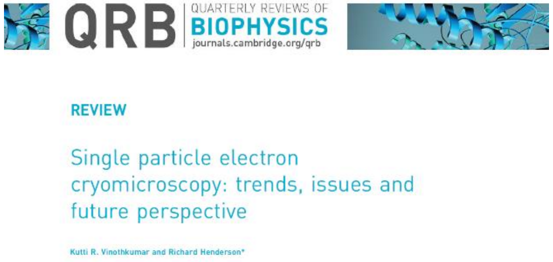
Specification	Target	
Sensor format	2048 x 2048	
Pixel pitch	50 x 50 µm	
Frame rate	2000 fps	2500 fps
Bit depth	12 bits	10 bits
Operation mode	Rolling shutter	
Readout mode	Continuous	
Readout type	Analogue CML lines	
Sensor size	200 mm wafer-scale sensor	
Manufacturing process	TowerJazz 180 nm CIS process	
Sensitive area	104 cm^2	
Radiation hardness	YES	
Back-thining	NO	
Dark pixels	Only on left and right sides of the pixel array	

From D. Krukauskas, "C100 – CMOS Sensor for 100 keV EM"
Rosalind Franklin Institute annual meeting 2019

What’s Next

We can identify two main causes limiting the resolution in cryo-EM:

- electron beam induced sample movements
- efficiency of the detectors used to record the images



QRB | QUARTERLY REVIEWS OF BIOPHYSICS
journals.cambridge.org/qrb

REVIEW

Single particle electron cryomicroscopy: trends, issues and future perspective

Kutti R. Vinothkumar and Richard Henderson*

With higher frame rates in fact, the time for image acquisition is reduced (higher throughput), better radiation tolerance is achieved and immunity from sample movements also improves.

This is also applicable to cryo-Tomography and lower energy (100keV) electron detectors.

Larger and faster imagers are also more and more on demand for X-Rays applications.

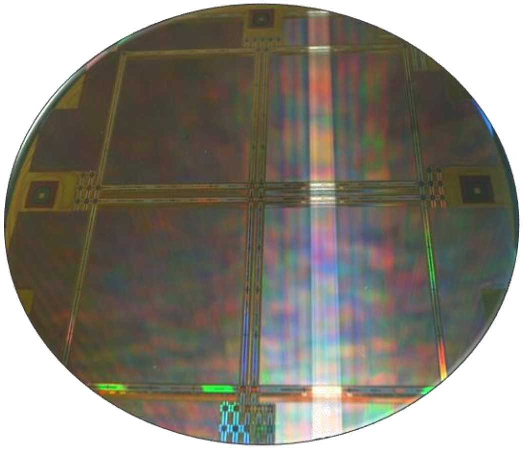
What’s Next

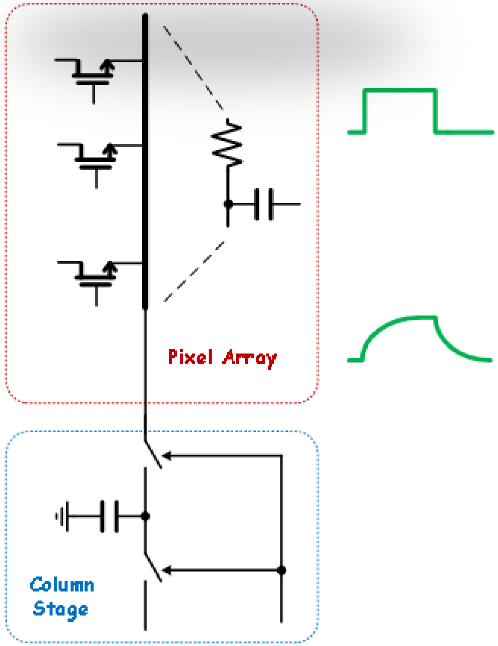
Increasing the readout speed (in terms of frames per second) on large sensors with several million pixels is not easy.

Because of the RC constant of columns there is a limit to the time needed to sample the values stored in the pixels.
In other words there is a limit to the time needed to move the data from the pixel array to the readout electronics.

A possible solution is to reduce the “distance” between pixels and readout electronics:

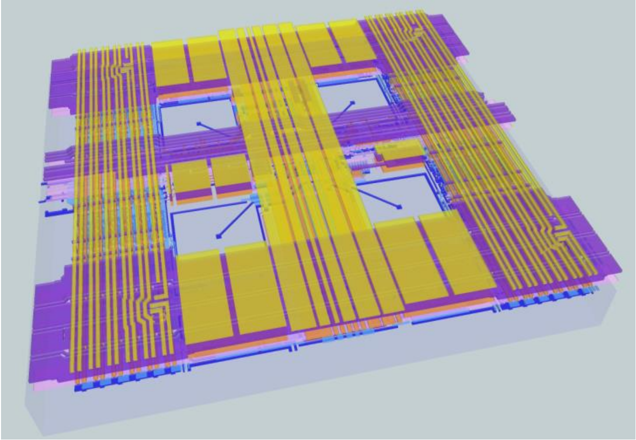
- In-pixel electronics
- 3D approach



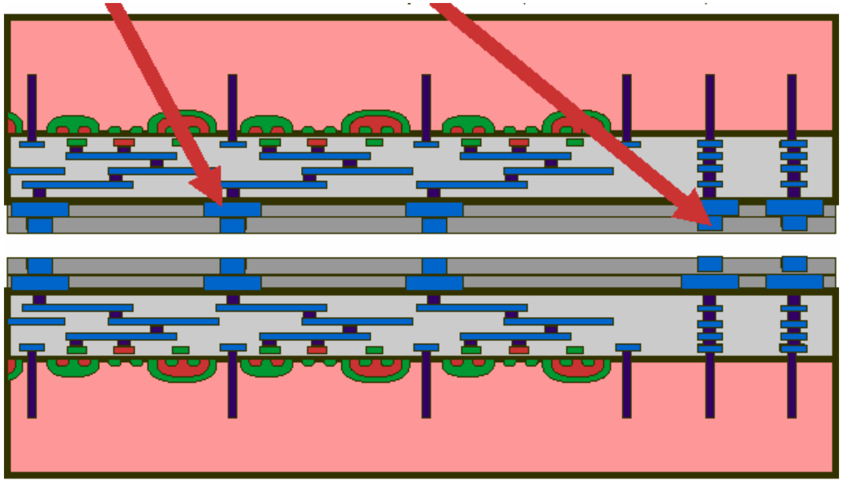


What's Next

- In-pixel electronics: signal can be processed in the pixel array adding analogue amplifiers or A-to-D converters. In this case the pixel layout becomes very dense.



3D representation of the PImMS pixel for ToF-MS (~700 transistors)



Picture from "MAPS are for amateurs, professionals do 3D" - G. Deptuch, Fermilab, CPIX 2014

- 3D approach: instead of moving the signal from the pixels in the X and Y directions we can go in the Z one, making the readout much faster.

Radiation hardness becomes very demanding.

What’s Next

Conclusions

When considering possible future developments for X-rays and EM we cannot ignore:

Technology scale-down Possibility of more complex electronic in the same area, improved radiation hardness, lower power consumption

Larger sensors: beyond 4k x 4k pixels (up to wafer scale devices) → More pixel for better resolution and larger areas

Fully digital sensor: simpler electronic interface and better noise immunity

Frame rate and data rate: there is a clear need for faster and faster detectors, which will generate high data volumes

Sensitivity: the operating range can be extended by post-processing (BSI)

Power consumption: faster and larger sensors are likely to be power hungry, hence quite tricky to cool in vacuum (especially if thinned)

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Thanks for your attention!