CMOS APS for TEM

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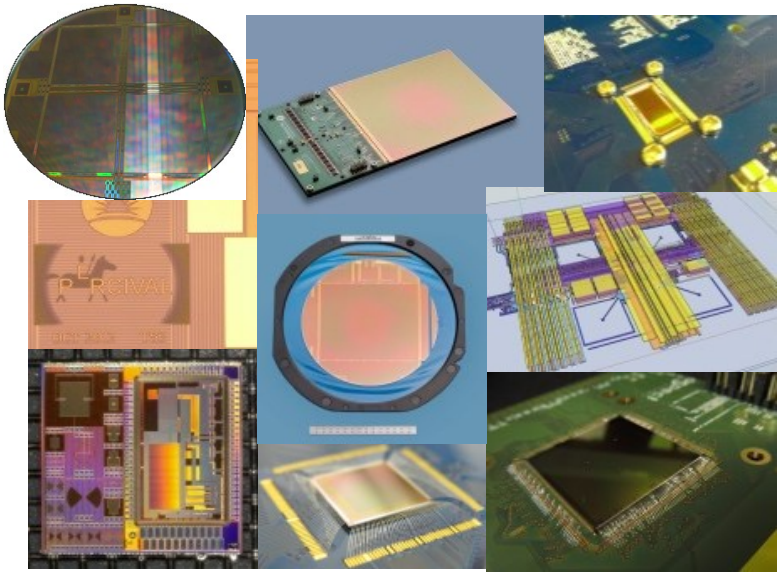
Workshop on CMOS Active Pixel Sensors for Particle Tracking (CPIX14)

15th September 2014

OUTLINE

- Introduction
- CMOS Sensors for TEM
- Results
- What's next?
- Conclusions



INTRODUCTION

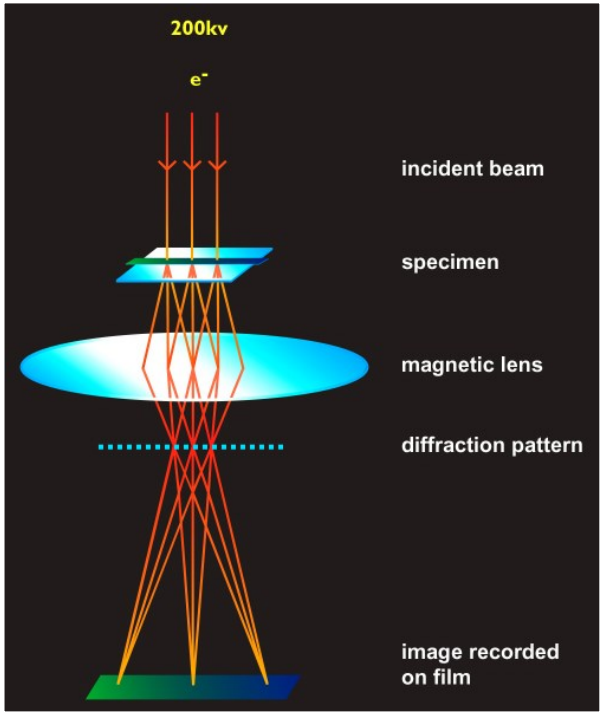


Image courtesy of LMB-Cambridge

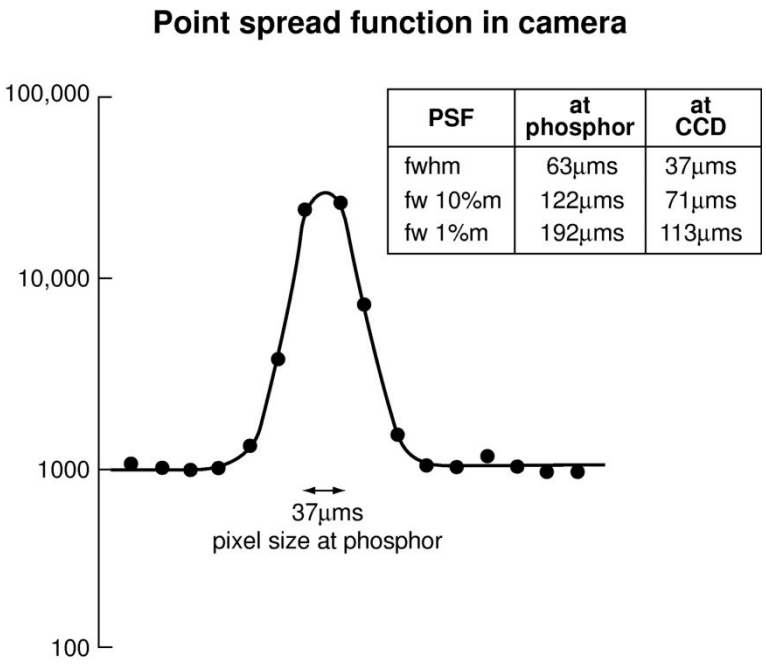
With visible light it is impossible to resolve points that are closer together than a few hundred nanometres.

Electron and ion microscopes use a beam of charged particles instead of light, and electromagnetic or electrostatic lenses to focus the particles.

The resulting image used to be recorded on film or with a CCD camera with phosphor and a fibre optics.

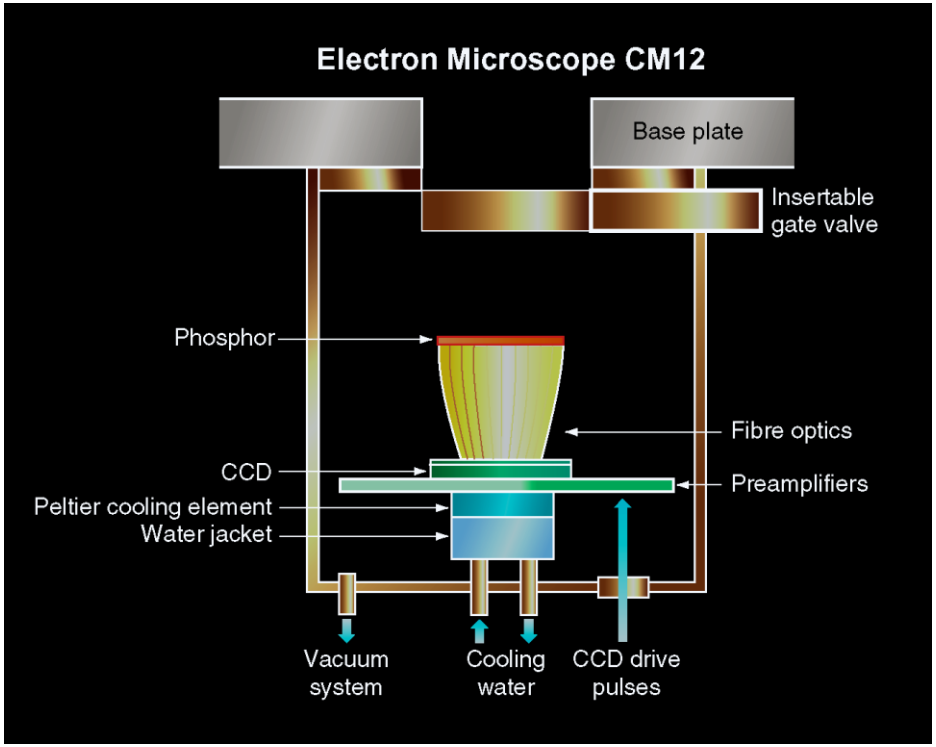
INTRODUCTION

CCD indirect detection suffers from poor spatial resolution.



PSF	at phosphor	at CCD
fwhm	63µms	37µms
fw 10%m	122µms	71µms
fw 1%m	192µms	113µms

Faruqi & Andrews NIM A392,233-236 (1997)

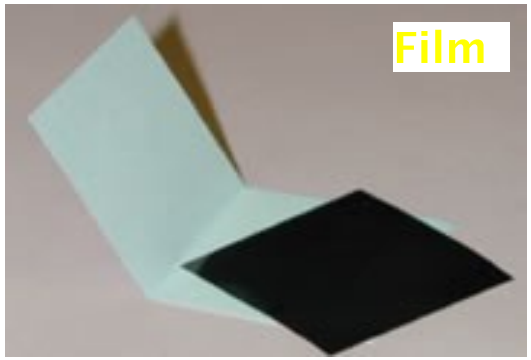


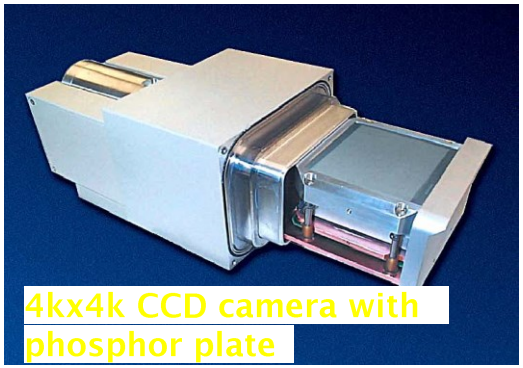
Images courtesy of LMB-Cambridge

INTRODUCTION

- Film: 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 sensors allow direct detection, digital, have good spatial resolution and good sensitivity (single electron).

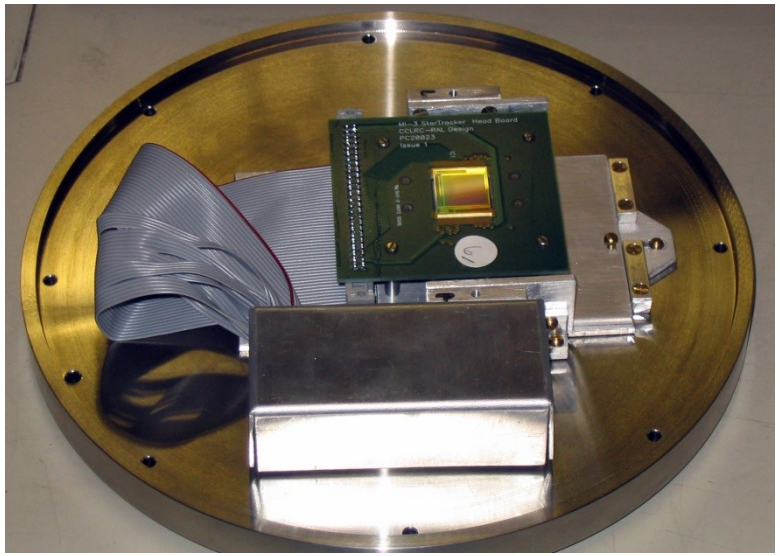
CMOS MAPS FOR TEM

Development of CMOS sensors for TEM at STFC-RAL (UK).

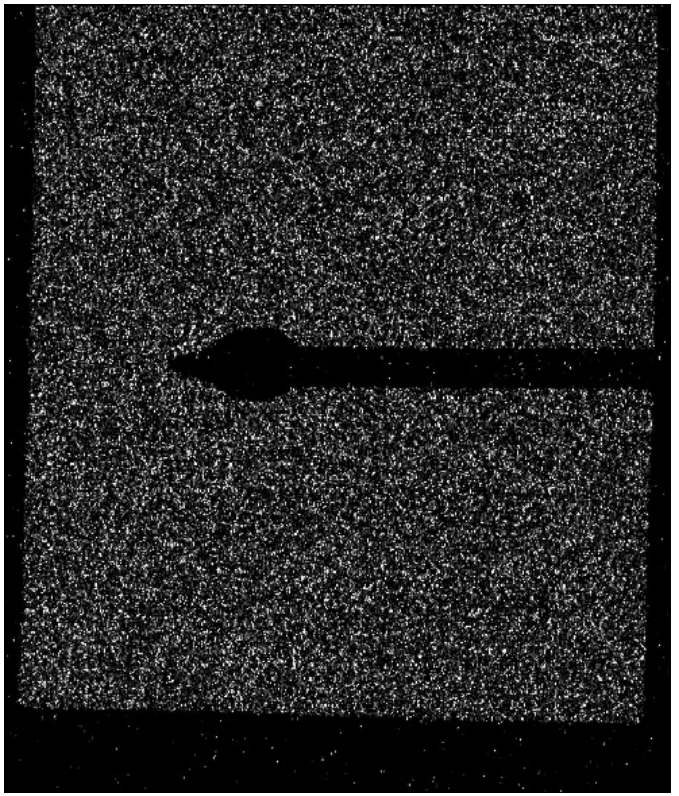
- 2003-4 StarTracker : CMOS camera-on-a-chip.
- 2006-8 TEMAPS : 1.5M pixels test structure with 25 different pixel types.
- 2009-10 TEMAPS 2.0: 4k by 4k stitched CMOS sensor for TEM .
- 2012 FEI FALCON I : First camera in the TEM market with a CMOS image sensor.
- 2013 FEI FALCON II: TEM camera with back-thinned CMOS sensor for improved performance.
- 2014 FEI CETA: TEM camera for indirect detection with a CMOS sensor.

CMOS MAPS FOR TEM

CMOS detector can be used as an imaging device for electron microscopy.



NIMA 546 (2005) 170–175

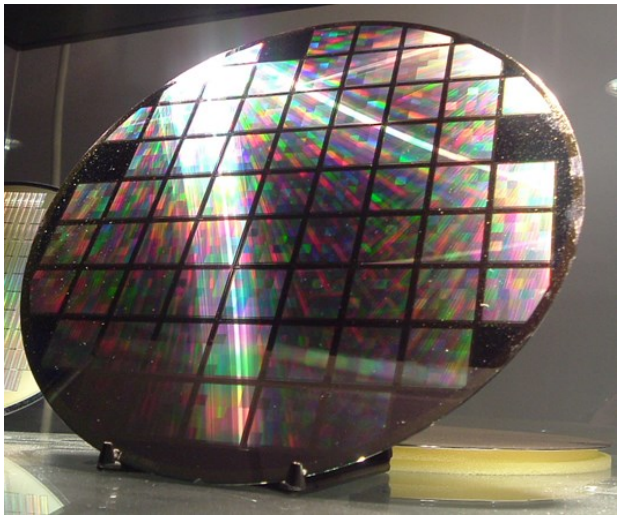


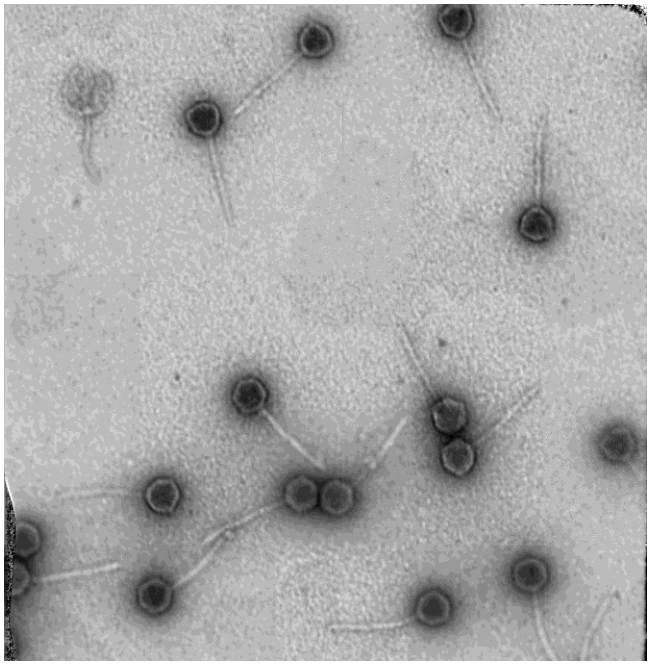
First images in an electron microscope, LMB-MRC Cambridge 19 February 2003

CMOS MAPS FOR TEM

TEMAPS Project:

- 23mm x 21mm sensor.
- 1.5 Mpixels
- 25 pixel topologies.
- Fast analogue outputs.
- Rad hard design.
- ROI addressing.



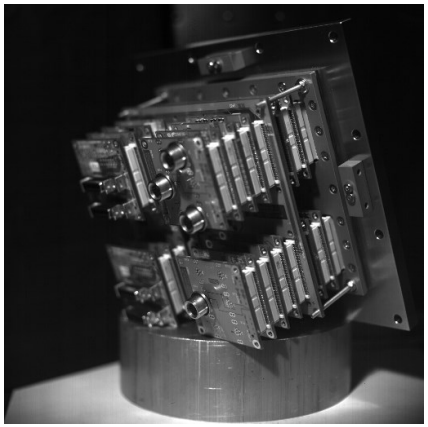


" Lambda bacteriophage" picture with a x17,000 magnification

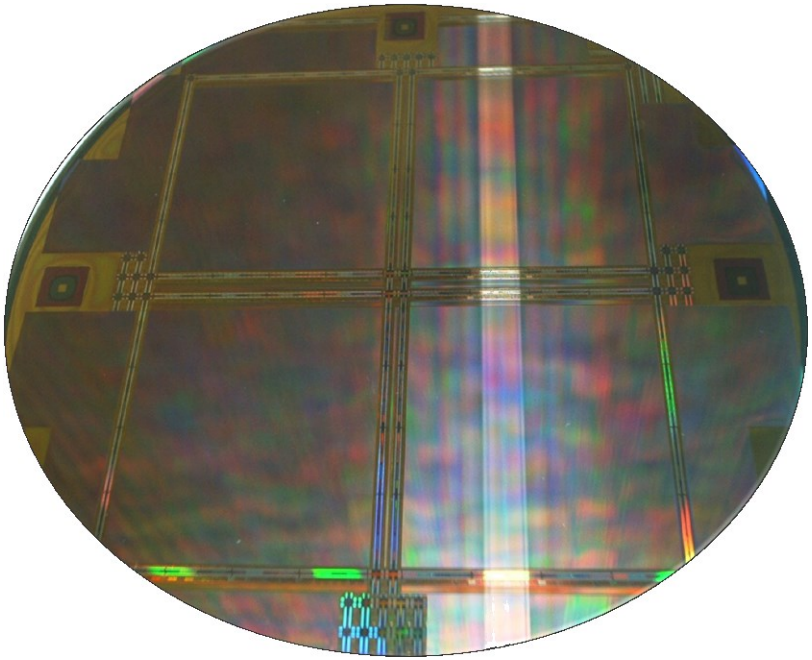
Courtesy of W. Faruqi and R. Henderson (LMB-MRC Cambridge)

CMOS MAPS FOR TEM

CMOS sensor for TEM, used in the
FEI Falcon© Direct Electron Detector.

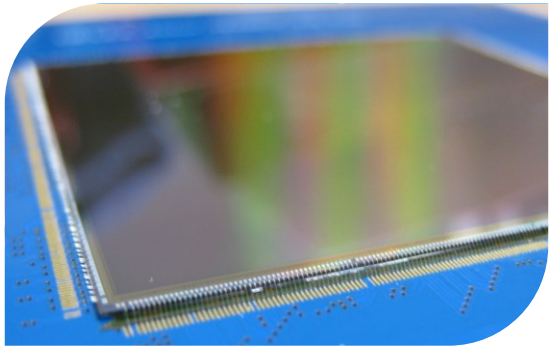


"Self-portrait"

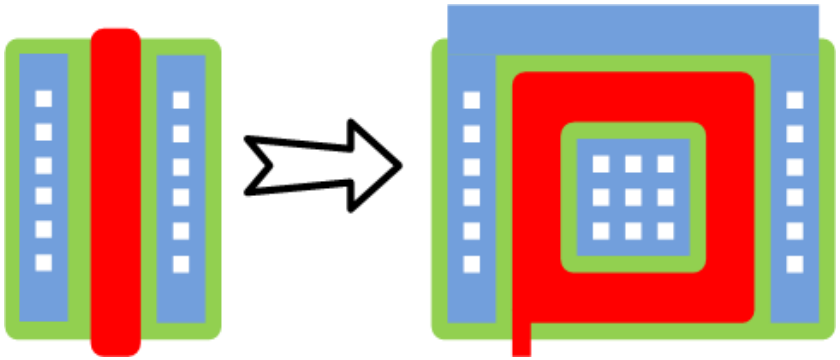


- 61x63 mm^2 silicon area
- 16 million pixels
- 4Kx4K array
- Analogue outputs
- Frame rate in excess of video rate.
- Radiation hard characteristics.
- Pixel binning.
- Region Of Interest readout
- 0.35μm standard CMOS process
- High yield.

SENSOR DETAILS



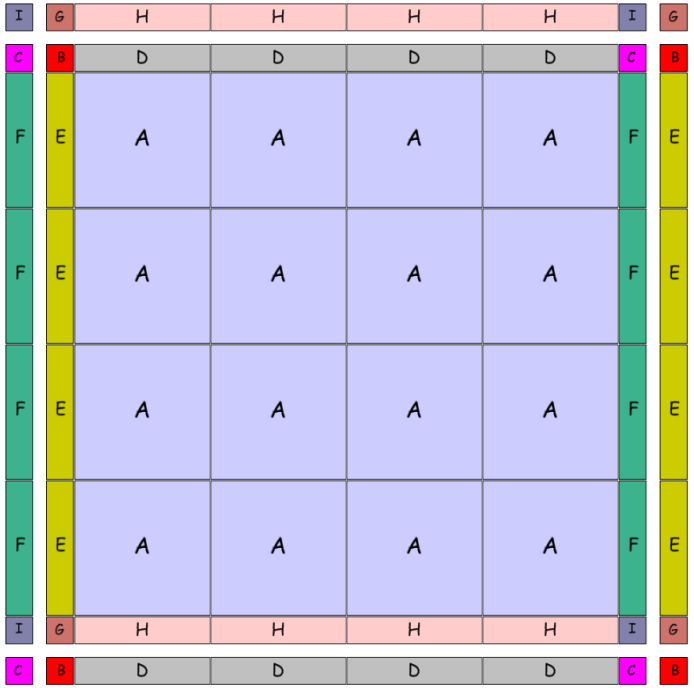
Radiation can create positive charge at the thin/thick oxide interface (bird's beak) that can short-circuit source and drain of the MOS transistors.

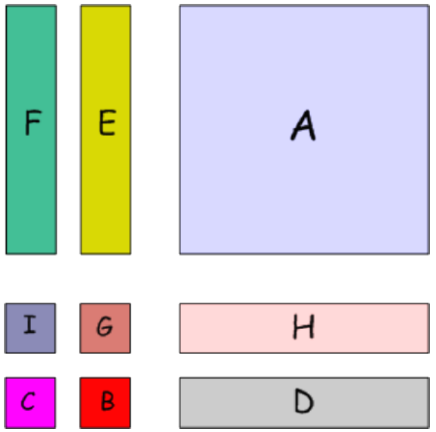


Radiation hardness improved by design techniques (ELT, substrate contacts and circuit redundancy) and technology progress.

SENSOR DETAILS

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



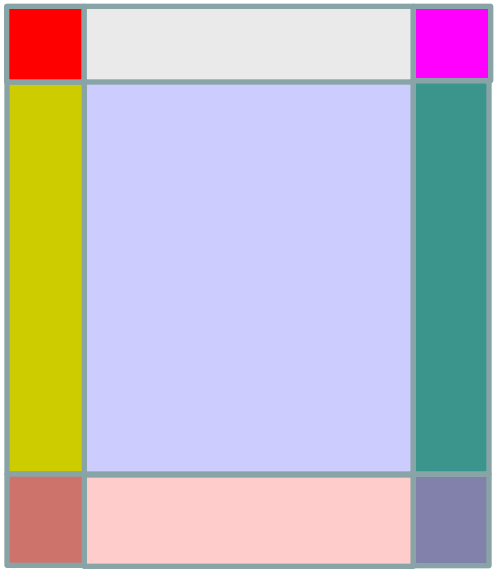


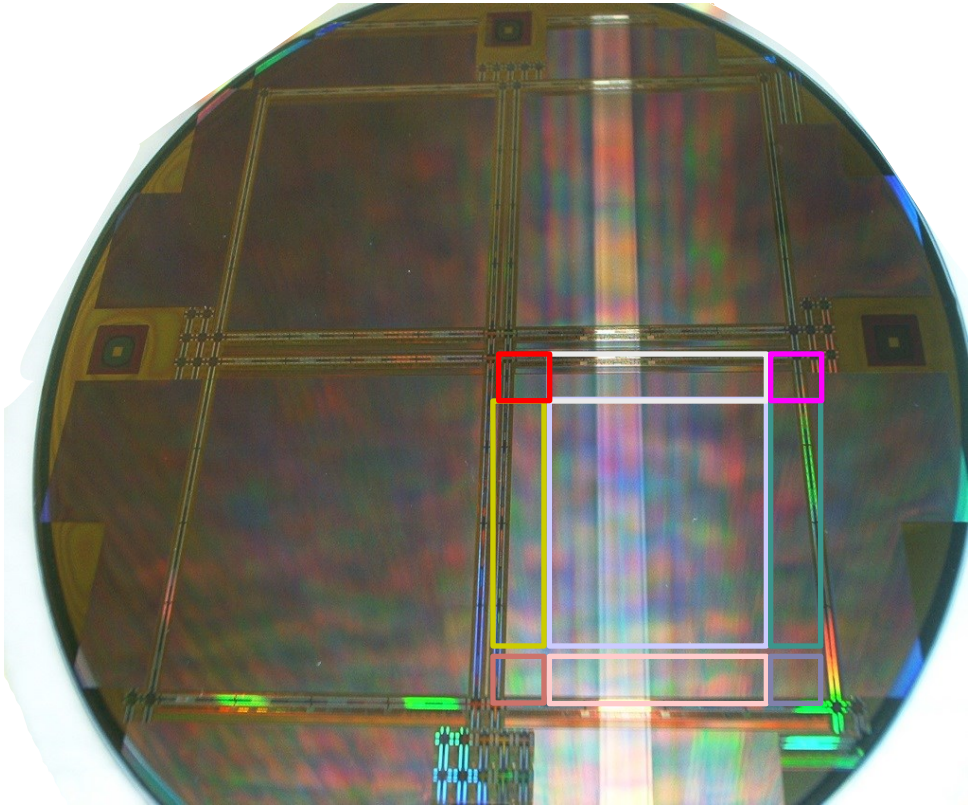
Above the reticle is shown and on the left the final result.

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

SENSOR DETAILS

Typical **CMOS** sensor architecture.





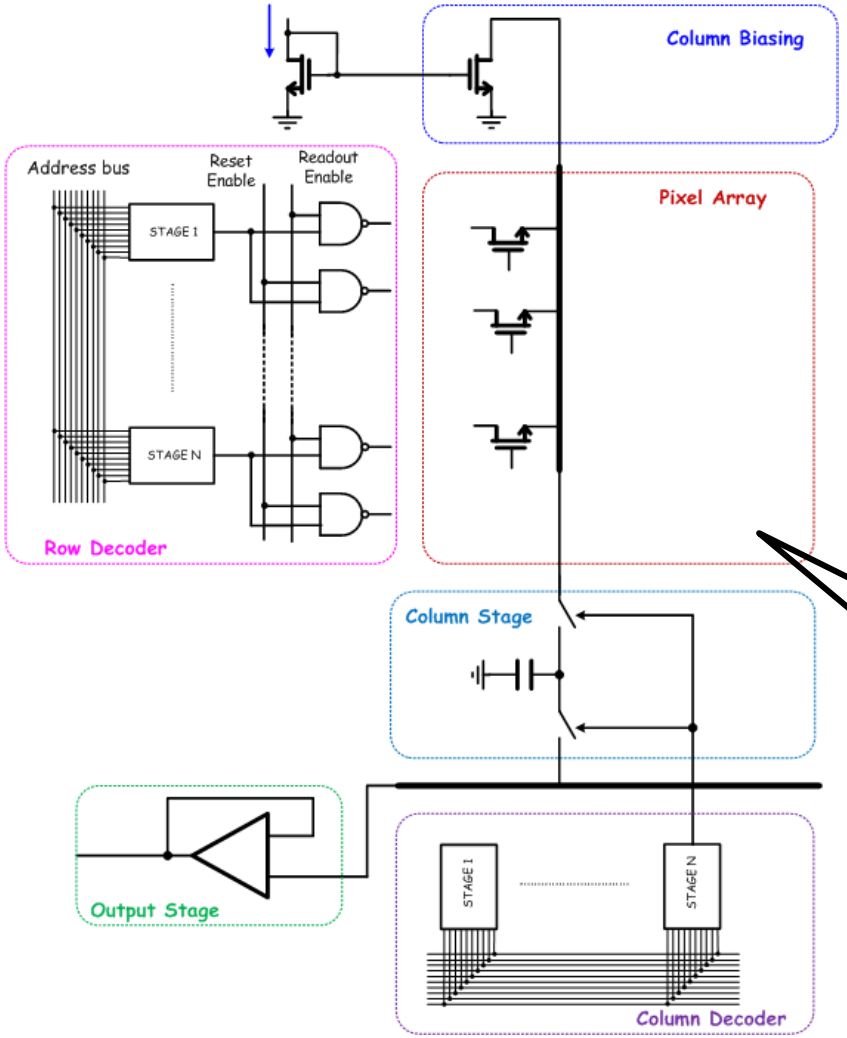
Horizontal (row) controls

Readout electronics and column controls

Auxiliary electronics

Pixel array

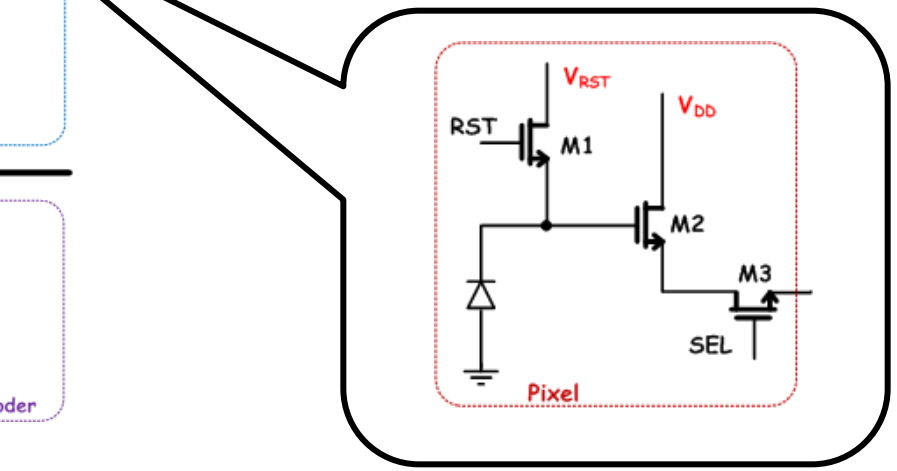
SENSOR DETAILS



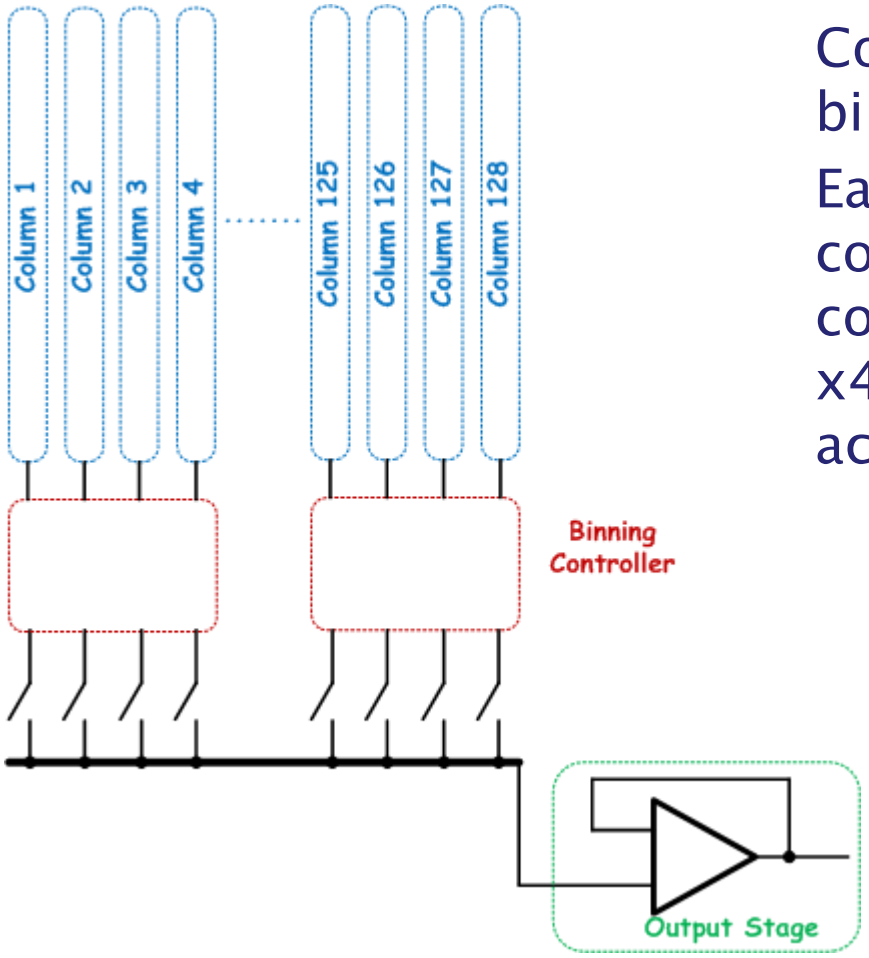
The sensor is based on a 3T pixel array fully addressable with the possibility of ROI readout.

Sensor architecture is based on a fully analogue readout chain.

This improves power consumption and the overall sensor yield.



SENSOR DETAILS



Column stages are connected to the binning controller.

Each binning block is common to 4 columns and can process the signal coming from 4 rows so that x2 and x4 binning in both directions is achieved independently.

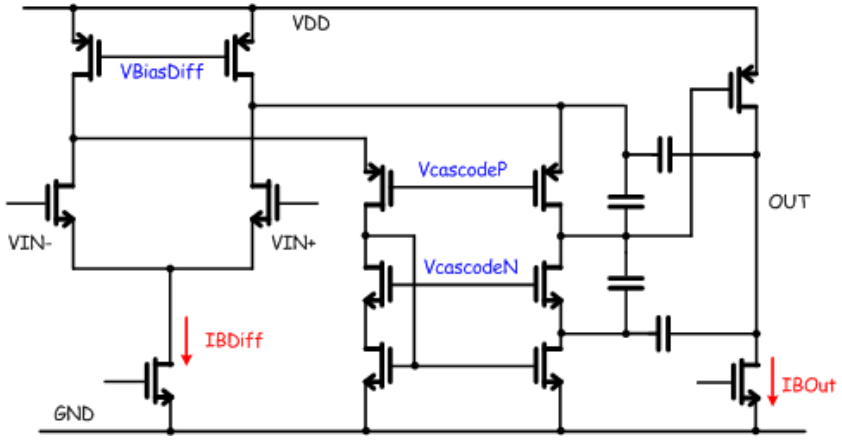
Having 4096 columns requires 32 parallel analogue outputs.

The sensor can operate with a maximum frame rate of 40fps.

SENSOR DETAILS

The very large silicon area of the sensor posed a challenge in terms of signal routing and signal delays.

Row and column selection circuits have been optimised in order to contain such delays and allow the fast readout targeted.



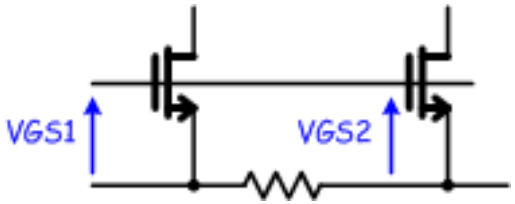
Particular attention has been also paid to the output stages, due to the demanding performance required.

- Input and output dynamic range larger than 2.0V.
- GBW in excess of 190MHz.
- Phase margin in excess of 60° .

SENSOR DETAILS

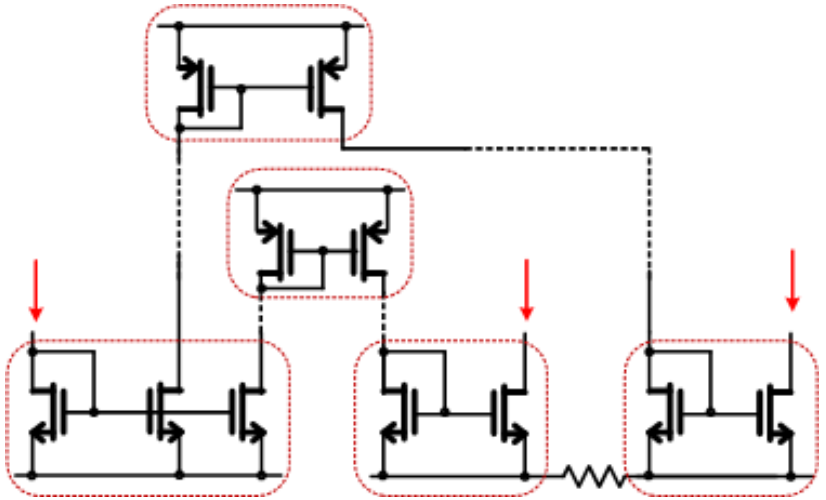
Routing of biasing currents to blocks placed at very large distance represents another challenge.

In these cases it is best practice to route the actual current and not a voltage.

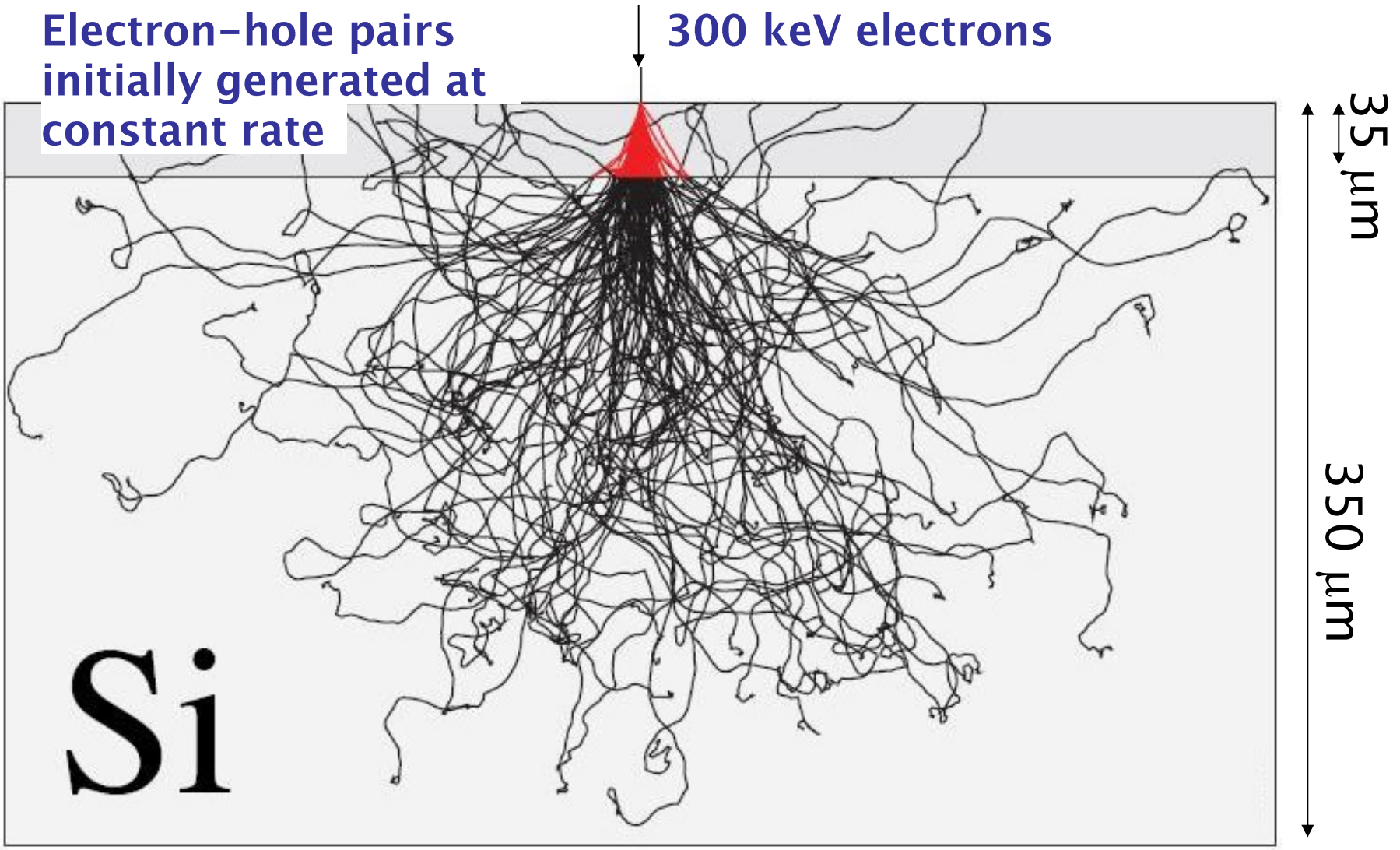


In case of very large distances the resistance of the substrate can play an important role.

Such approach has to be kept modular in order to be used in a stitching layout, where the same block is repeated more than once.

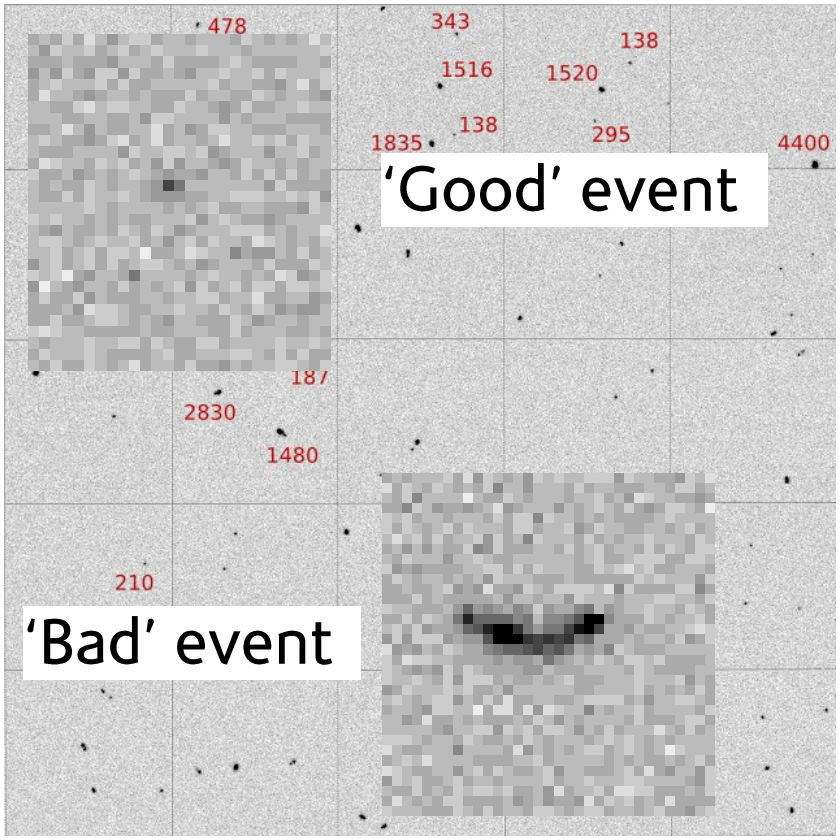


BACK SCATTERING



RESULTS

Single Electron Detection



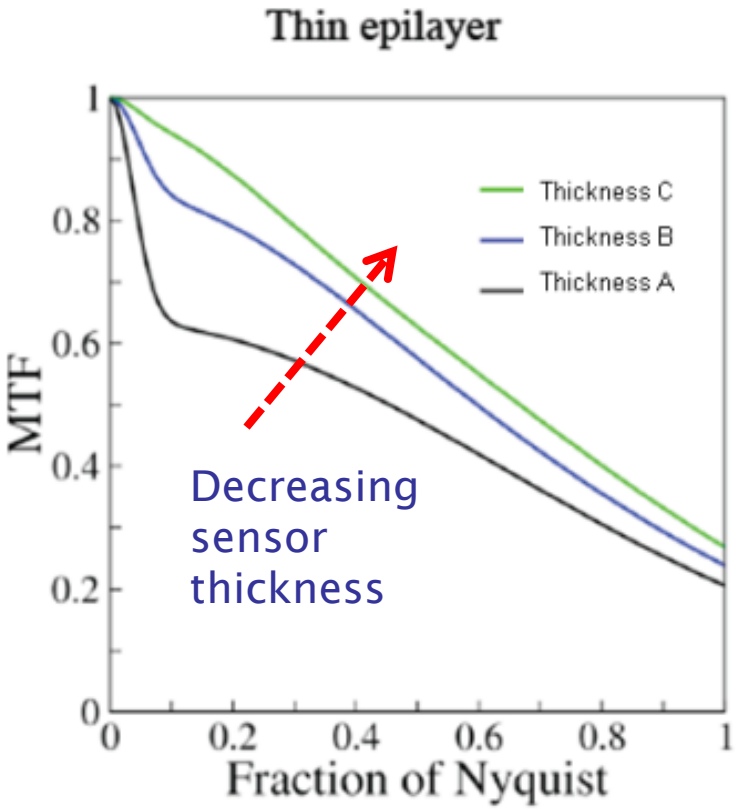
Picture from Ultramicroscopy 109 (2009) 1144–1147

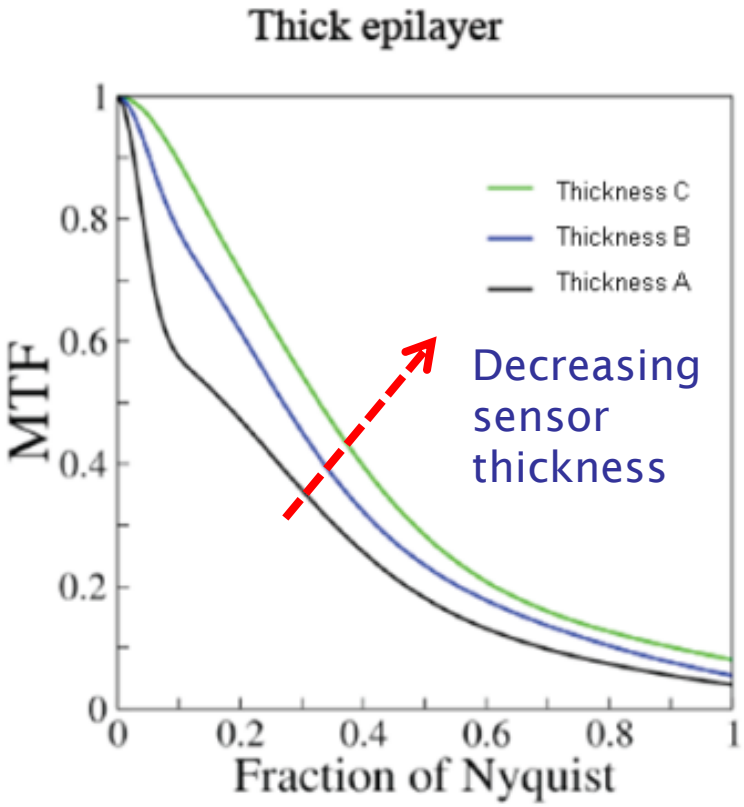
Many of the events consist of two adjacent energy deposits, one from the incident and one from the backscattered trajectories (in case of backscattering).

Electrons passing in only one direction (not suffering any backscattering) appear as single events, usually with a relatively small amount of energy deposited.

Electrons slow down due to their interactions in the substrate, hence the second traversal through the epilayer leads to a greater energy deposition.

RESULTS

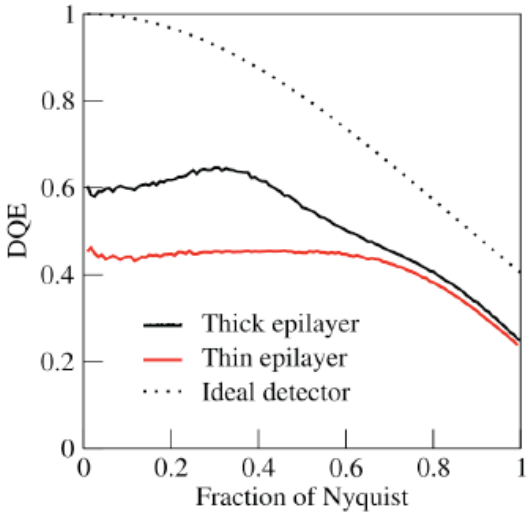




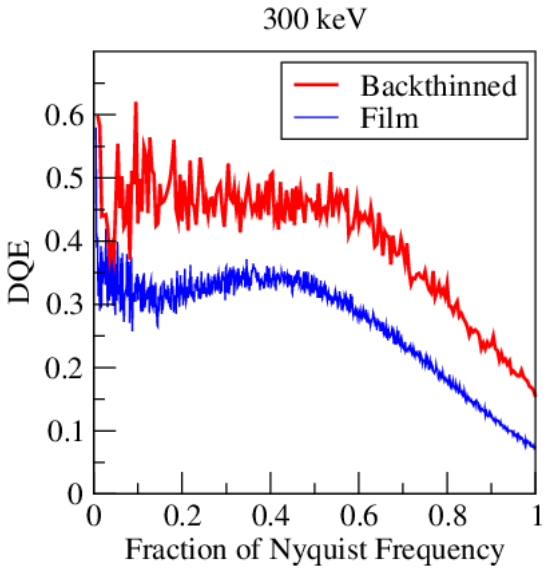
- Total thickness of CMOS sensor
- Thickness of epitaxial layer

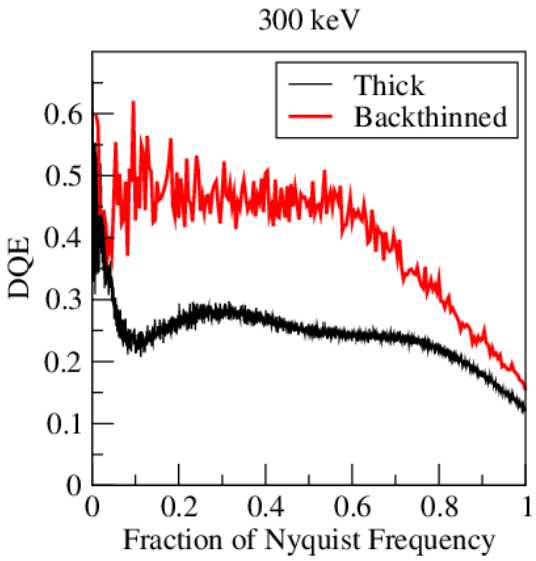
RESULTS

Charge generated , charge collection and crosstalk are related to the thickness of the epitaxial layer.



The thickness of the detector plays an important role in the MTF and in the DQE, hence there are some trade-off to be considered.





Pictures from Ultramicroscopy 109 (2009) 1144–1147

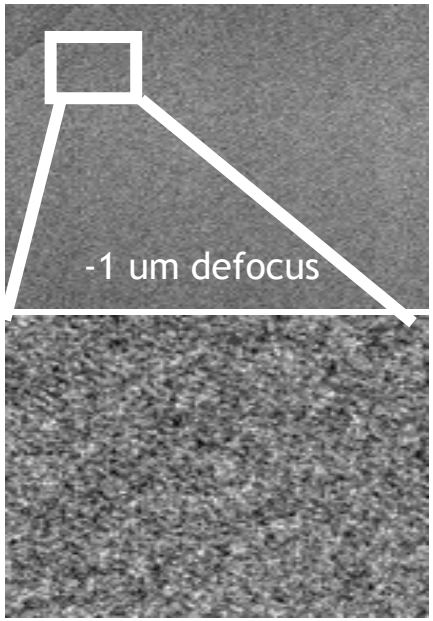
RESULTS

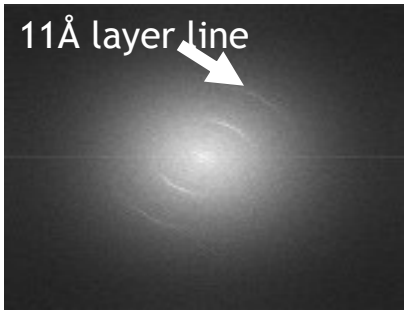
Cryo TEM of TMV

Electron Dose: **5e⁻/A²**

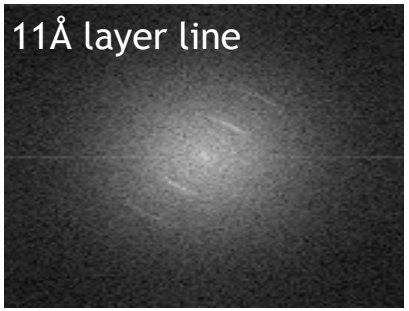
~2.7Å/pixel – TEM Mag 37kx

FEI Falcon™





2k x 2k



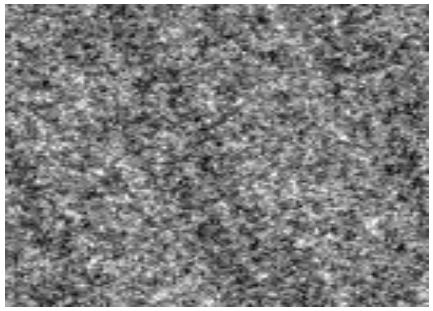
512 x 512

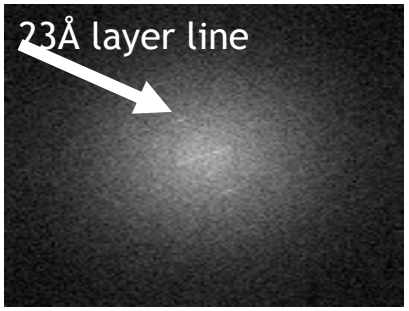
FEI™

Electron Dose: **5e⁻/A²**

~2.6Å/pixel – TEM Mag 39kx

4kx4k CCD

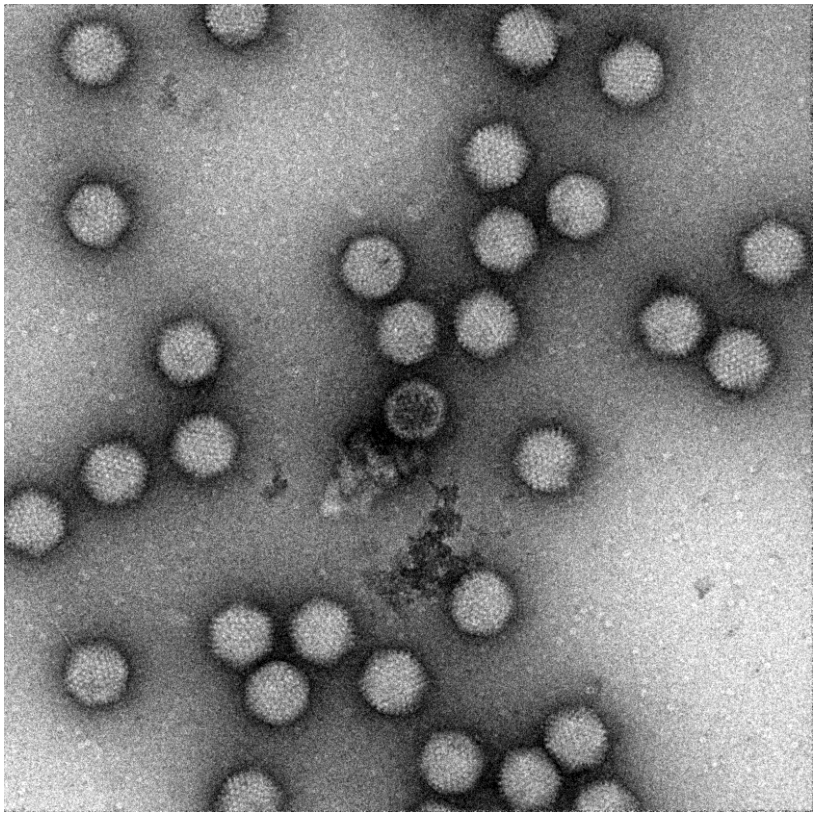




512 x 512

SUMMARY

- First CMOS image sensor for the TEM market in the FEI Falcon© Direct Electron Detector.



Courtesy of G. McMullan (LMB, Cambridge, UK)

- Direct detection of electrons → high MTF and DQE
- 16 Mpixel, 14 µm pitch
- 40 fps or 640 Mpixel/sec
- Radiation hard → >20 Mrad
- CMOS image sensors are replacing film / CCD

RESULTS

Direct detection enabled by CMOS sensors has led to a "resolution revolution".

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

BIOCHEMISTRY

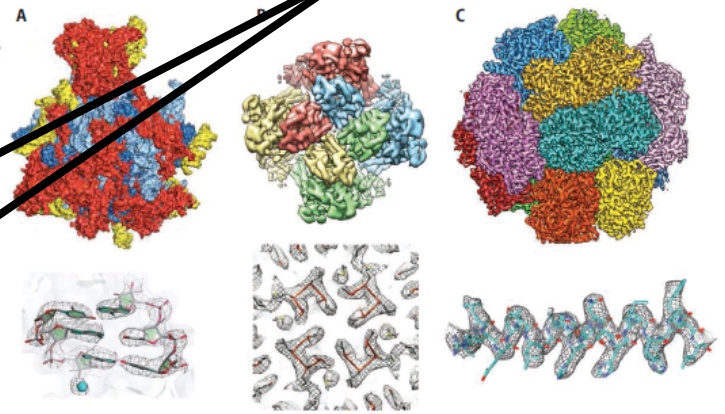
The Resolution Revolution

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 structures. The same holds for heterogeneous samples or flexible complexes that do not crystallize readily, because cryo-EM images of different particles or conformations are easily separated at the image processing stage.



Near-atomic resolution with cryo-EM. (**A**) The large subunit of the yeast mitochondrial ribosome at 3.2 Å reported by Amunts *et al.* In the detailed view below, the base pairs of an RNA double helix and a magnesium ion (blue) are clearly resolved. (**B**) TRPV1 ion channel at 3.4 Å (*2*), with a detailed view of residues lining the ion pore on the four-fold axis of the tetrameric channel. (**C**) F_{420}-reducing [NiFe] hydrogenase at 3.36 Å (*3*). The detail shows an α helix in the FrhA subunit with resolved side chains. The maps are not drawn to scale.

Photographic film works in principle much better for high-resolution imaging, but is incompatible with rapid electronic readout and high data throughput, which are increasingly essential.

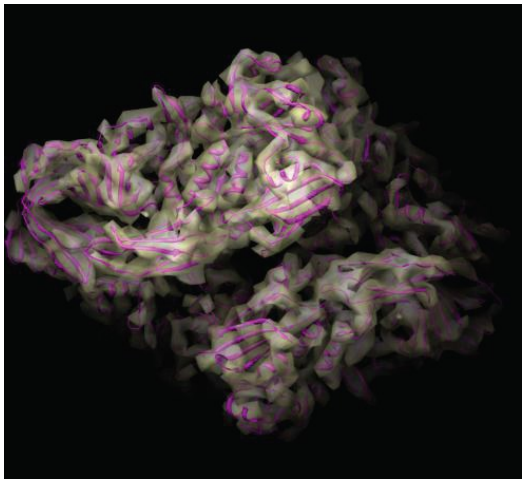
Some 10 years ago, Henderson and Faruqi realized that it should be possible to design a sensor that detects electrons directly and that combines the advantages of CCD cameras and

The new detectors offer another decisive advantage: Their fast readout makes it possible to compensate small movements that inevitably happen when the electron beam

W. Kühlbrandt, SCIENCE, vol. 343, 28 March 2014

RESULTS

Higher DQE of backthinned Falcon II allows higher resolution data.



Chen, et al Ultramicroscopy 135, 24–35, 2013

Falcon II vs. film:
Film: 11 Å resolution
Falcon II 3.8 Å resolution

STRUCTURAL BIOLOGY

Ion channel seen by electron microscopy

Structures of the heat-sensitive TRPV1 ion channel have been solved using single-particle electron cryo-microscopy, representing a landmark in the use of this technique for structural biology. SEE ARTICLES P.107 & P.113

RICHARD HENDERSON

Membrane proteins known as transient receptor potential (TRP) ion channels occur in species ranging from yeast to humans. Members of this receptor family are involved in the perception of an enormous range of stimuli[1], including vision (in invertebrates), taste, hot or cold temperatures, pH and physical forces. On page 107 of this issue, Liao *et al.*[2] report the first high-resolution structure of TRPV1, the ion channel responsible for sensing heat. And in a second paper from the same group, Cao *et al.*[3] (page 113) describe the sites at which three ligand molecules bind to TRPV1, and how this binding triggers the opening of the channel.

There are 27 members of the TRP receptor family in humans, each with their own functions and different tissue distribution. Most TRP channels, including TRPV1, are weakly selective for calcium ions. TRPV1 was first identified[4] as the receptor for capsaicin — the compound that makes chilli peppers seem hot — in 1997. The channel has four identical subunits, and the modified version used in the present studies has an overall molecular weight of about 300 kilodaltons (bigger than most ion channels). Not only is TRPV1 opened by capsaicin, it is also strongly activated by toxins, such as resiniferatoxin from *Euphorbia* plants, or 'cysteine-knot' toxins from tarantulas. These chemosensory stimuli are thought to have evolved as protective deterrents against predators, and elicit a burning sensation by usurping normal heat sensing through TRPV1 activation.

To solve the structure of TRPV1, Liao *et al.* used single-particle electron cryo-microscopy (cryo-EM), with no help from any of the more established methods of structural biology. The authors made full use of several technical advances: they used a slightly truncated rat TRPV1 construct that is biochemically stable; they transferred purified ion channels into a polymeric 'amphipol' framework[5] to maintain the channels' stability and solubility in water; and, most importantly, they used a camera that detects electrons directly (minimizing noise and allowing any image blurring during an exposure to be compensated for[6,7]) and a state-of-the-art computer program that

R. Henderson, NATURE, 504, 93–94 2013

…landmark in the evolution of single particle cryo-TEM…

WHAT'S NEXT

The exciting results presented show the impact that CMOS imaging technology can make in the TEM field.

Possible future developments can be:

- Technology scale-down → Possibility of more complex electronic in the same area, improved radiation hardness, power consumption.
- Larger sensors : 8k x 8k pixels (wafer scale devices) → More pixel for better resolution and larger areas
- Increased frame rate → Reduced time for image acquisition, better radiation tolerance.
- Lower noise
- Fully digital sensor

CONCLUSIONS

- CMOS technology has changed the TEM world replacing already exiting solutions like film and CCD.
- The 16 million pixels CMOS sensor for TEM designed at RAL is installed in high-end FEI Electron microscopes.
- Other players in the TEM field are embracing the CMOS revolution.
- Scientist all over the world are generating novel and outstanding results.
- CMOS is becoming the reference in TEM.

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