CMOS Sensors For Electron and X-Rays Detectors

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

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)
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

- 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 24.8 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.
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.
• 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
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 microtomography" G. Pinaroli
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.

- 1408 x 1484 pixels
- 4.18 x 4.97 cm²
- 45 LVDS I/Os (@420Mbit/s)
- 18.9 Gbit/s output
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).
In the TEM field CMOS sensors present many advantages:

- Direct detection. No loss of resolution due to 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 of functionality on-chip.
- Continuous process development
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.

- 61x63 mm² 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
<table>
<thead>
<tr>
<th>Year</th>
<th>Event</th>
</tr>
</thead>
<tbody>
<tr>
<td>1950</td>
<td>Film (and earlier)</td>
</tr>
<tr>
<td>1990</td>
<td>Phosphor/fibre optics/CCD</td>
</tr>
<tr>
<td>1999</td>
<td>Medipix I silicon pixel detector - counting</td>
</tr>
<tr>
<td>2003</td>
<td>Medipix II silicon pixel detector - counting</td>
</tr>
<tr>
<td>2003</td>
<td>RAL StarTracker: CMOS camera-on-a-chip</td>
</tr>
<tr>
<td>2004</td>
<td>Medipix II Quad - counting</td>
</tr>
<tr>
<td>2006-08</td>
<td>TEMAPS: 1.5M pixels test structure with 25 different pixel types</td>
</tr>
<tr>
<td>2009-10</td>
<td>TEMAPS 2.0: 4k by 4k stitched CMOS sensor for TEM</td>
</tr>
<tr>
<td>2009</td>
<td>Electron counting papers using CMOS published</td>
</tr>
<tr>
<td>2010</td>
<td>DE-12</td>
</tr>
<tr>
<td>2012</td>
<td>FEI FALCON I: First TEM camera with a stitched CMOS image sensor</td>
</tr>
<tr>
<td>2013</td>
<td>FEI FALCON II: TEM camera with back-thinned CMOS sensor</td>
</tr>
<tr>
<td>2013</td>
<td>K2 – counting</td>
</tr>
<tr>
<td>2014</td>
<td>FEI CETA: TEM camera for indirect detection with a CMOS sensor</td>
</tr>
<tr>
<td>2014</td>
<td>DE-20</td>
</tr>
<tr>
<td>2017</td>
<td>K3 – 24 Mpixels, 1,500 fps CMOS camera</td>
</tr>
</tbody>
</table>
Gatan K3 – www.gatan.com
- 24 Mpixels (5,760 x 4,092)
- 1,500 full frames/second

Thermofisher FALCON – www.fei.com
- 16 Mixels (4k x 4k)
- 40 full frames/second

Direct Electron DE-64 – www.directelectron.com
- 64 Mixels (8k x 8k)
- 42 full frames/second

Tietz TemCam F816 – www.tvips.com
- 64 Mixels (8k x 8k, 128mm²)
- 0.4 full frames/second

Gatan OneView – www.gatan.com
- 16 Mixels (4k x 4k)
- 25 full frames/second

Thermofisher CETA – www.fei.com
- 16 megapixels (4k x 4k)
- 40 full frames/second
Switching from integration mode to electron counting the DQE is dramatically improved.

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

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

\[
\text{DQE} = \frac{(S/N)^2}{(S/N)^2}
\]
CMOS for EM

12 Å  2.2 Å
Advances in detector technology and image processing are yielding high-resolution electron cryo-microscopy structures of biomolecules.

1.54Å structure with Gatan K3

1.56Å structure announced in September 2018 with Falcon 3
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
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
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 300 keV to 100 keV. Recently the elastic $\sigma_e$ and inelastic $\sigma_i$ cross-sections, as well as radiation damage to organic and biological specimens as a function of electron energy has been measured [Peet, Henderson, Russo, Ultramicroscopy 203 (2019) 125-131].

This latest results show that there is a 25% improvement in the ratio $\sigma_e/\sigma_i$ 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 ($\sigma_e$) and inelastic ($\sigma_i$) scattering cross-sections for carbon are plotted vs. energy.
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» Ultramicroscopy 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
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

### CMOS for EM

**100 keV detectors. Less is more?**

<table>
<thead>
<tr>
<th>Specification</th>
<th>Target</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sensor format</td>
<td>2048 x 2048</td>
</tr>
<tr>
<td>Pixel pitch</td>
<td>50 x 50 µm</td>
</tr>
<tr>
<td>Frame rate</td>
<td>2000 fps</td>
</tr>
<tr>
<td>Bit depth</td>
<td>12 bits</td>
</tr>
<tr>
<td>Operation mode</td>
<td>Rolling shutter</td>
</tr>
<tr>
<td>Readout mode</td>
<td>Continuous</td>
</tr>
<tr>
<td>Readout type</td>
<td>Analogue CML lines</td>
</tr>
<tr>
<td>Sensor size</td>
<td>200 mm wafer-scale sensor</td>
</tr>
<tr>
<td>Manufacturing process</td>
<td>TowerJazz 180 nm CIS process</td>
</tr>
<tr>
<td>Sensitive area</td>
<td>104 cm²</td>
</tr>
<tr>
<td>Radiation hardness</td>
<td>YES</td>
</tr>
<tr>
<td>Back-thining</td>
<td>NO</td>
</tr>
<tr>
<td>Dark pixels</td>
<td>Only on left and right sides of the pixel array</td>
</tr>
</tbody>
</table>

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

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.
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
• 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 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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