fast-em

Fast Imaging by Delmic

Ultra-fast automated multibeam scanning electron microscope

delmic

Current state of electron microscopy

In life sciences, electron microscopy (EM) is an essential technique that allows the biologists to examine cells, cellular processes, and organelle architecture at nanometer resolution. Even with the ongoing improvements in automation and stability, most EM workflows still have issues that limit their power as a biological investigation tool. The most impactful issues are the low throughput and the hands-on nature of electron microscopes.

Due to the limited throughput of EM, microscope operators are forced to strike a compromise between the size and number of samples, the resolution used for imaging, and the time available for imaging. In addition, operators are often required to constantly supervise the system to ensure consistent imaging quality throughout the project.

Sander den Hoedt, Delmic CEO:

" If you look at the current state of microscopy, there is always somebody who needs to be at the machine, so you are extremely limited in how many samples you can image in a day. We think that it's really important that there is a new kind of microscope, that is automated and fast, allowing people to use electron microscopy in a whole new way. "

High throughput imaging is the solution

What would you be able to achieve if EM throughput was not a bottleneck anymore? What if you could acquire EM images 100 times faster? What if you were able to image 3D EM volumes of unprecedented scale? Or finally make statistically significant conclusions from your EM data, whether that is in pathology, connectomics, toxicology, or cell biology?

Rat kidney in Durcupan ACM, OTO stained. 4 nm pixel size

Samples courtesy of Cell Microscopy Core, UMC Utrecht

Meet Delmic's **Fast Imaging Solutions**

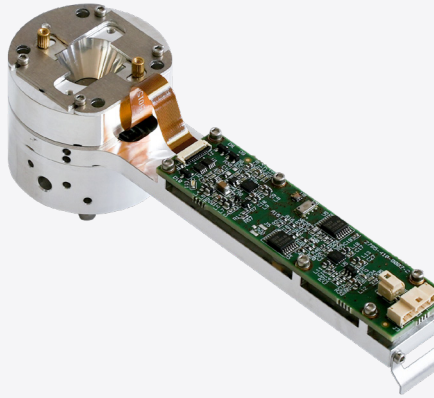
We believe that faster imaging of large biological samples transforms electron microscopy into a powerful tool that provides quantitative answers to scientific questions rather than simply qualitative indications.

FAST-EM is a multibeam Scanning Electron Microscope.

- With its 64 parallel beams and dedicated data-management architecture, it acquires images 100 times faster compared to standard SEM microscopes, consistently, at 4 nm resolution
- With its high level of automation, FAST-EM offers up to 3 days of unattended imaging
- Its innovative sample stage allows you to work on multiple samples from different sources and different preparation techniques in a single run

SNEL is a fast STEM detector for your SEM system.

- Large uninterrupted area available for section deposition, enabling users to operate the SEM system for long periods of time, unattended, as well as catering to large biological sample sets.
- Faster acquisition time compared to other retrofit SEM detectors, for a given image quality/contrast



Introducing **FAST-EM**

FAST-EM is an ultra-fast automated multibeam scanning electron microscope. Reliable and extremely fast, the system allows imaging of biological samples in complete autonomy. The system was created by a consortium, consisting of Delmic, Thermo Fisher Scientific, Technolution and Delft University of Technology.

Image 100x faster *

Acquire larger sample sets faster with 64 parallel electron beams, short dwell times, and optimized data-management infrastructure.

Rigid uniform substrate for your samples

Samples are placed on a rigid and stable support for imaging, preventing distortions in your images. The imaging area is unobstructed due to the uniformity of composition across the substrate.

Get the details and the big picture

Collect nanoscale detail while retaining larger context of the sample.

Boost productivity and focus on data analysis

Achieve high, sustained, throughput and image hundreds of sections with high levels of autonomy.

Easily achieve statistical impact with EM data

Faster imaging enables collection of data from more samples, conditions or time points.

* *The comparison is against the average acquisition speed of a standard single beam SEM system of 1 Mpix/s.*

How can FAST-EM be beneficial for you?

Having worked with researchers for many years, we understand how difficult-to-use and slow equipment can stop your research or work from moving further. Most of the time all you need are the right devices, that are able to provide you reliable insights fast and easily. Therefore, Delmic is determined to deliver innovative world-leading solutions which are designed not only to offer you outstanding quality but also simplify your workflows.

How can FAST-EM help you?

Principal investigators in an ambitious team

- Get results faster than anyone else
- Focus on research instead of imaging: don't waste time on system supervision
- Start answering fundamental research questions and make more impactful publications
- Achieve more with reliable automation
- Make statistically significant conclusions from your data easily, whether that is in pathology, connectomics, toxicology, or cell biology

Facility managers

- Drastically decrease your cost-per-pixel
- Increase your capacity to help more clients
- Allow you clients to have access to the full sample at high resolution and identify ROIs and structures at their own leisure
- Boost productivity of your facility while saving costs

Workflow advantages

Scintillator preparation

Supports various sectioning and section collecting methods, to host small or large samples on scintillators that allow an unobstructed view of your samples.

Load in FAST-EM

With ease, secure up to nine scintillators in the sample holder and load it into the system. With a fully loaded sample holder, observe an area up to 1700 mm^2 in the microscope.

Prepare for imaging

Proceed with three automated calibrations with minimal user input. Next select your regions of interest, identified through quick localization via single beam imaging.

Imaging

Ultra-fast imaging 64 parallel beams, fully automated by beam monitoring, which helps to correct calibrations whenever necessary. This ensures the best image quality throughout the entire acquisition.

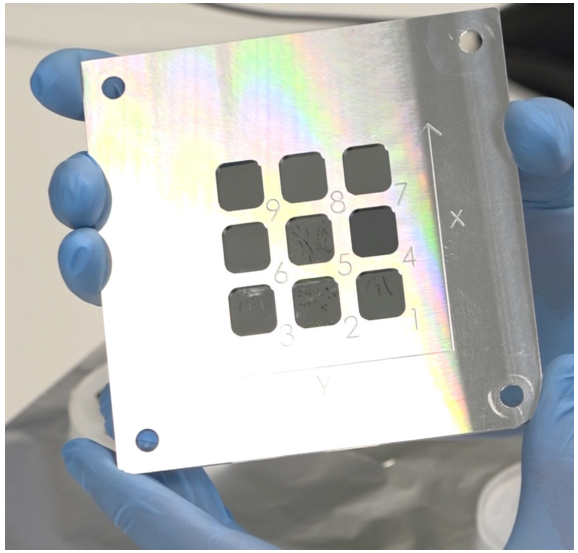
Image and data management

Your images are automatically saved on the local storage platform. The data management system allows for streaming your data directly on compatible software tools, e.g. on CATMAID for 2D visualization, or on your own image processing algorithm to perform segmentation, registration, features counting, etc.

Image stitching and visualization with CATMAID

Pre-installed Python API provides you with data streaming functionalities to connect FAST-EM output with your image analysis and visualization tools and algorithms.

Build and use your own applications for image and data analysis, seamlessly.



Prepare and load the samples

FAST-EM uses scintillators as rigid sample support. They are compatible with a wide range of automated and fast sample collection techniques. For example, multiple ribbons can be collected on scintillators after sectioning by draining the water of the ultramicrotome knife boat, e.g., Leica Artos 3D approach. Alternatively, single sections can be collected using the MagC extension (from Collectome) to your ultramicrotome. The standard carrier plate holds nine substrates sized at 14 x 14 mm^2. Carrier plates can be customized to meet specific requirements for different substrate sizes and applications.

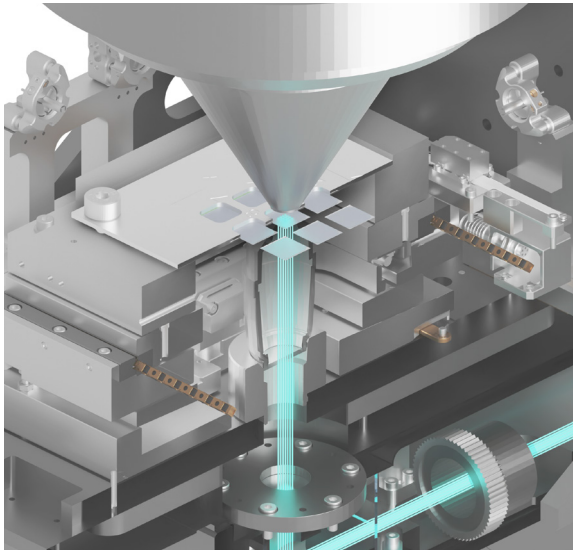
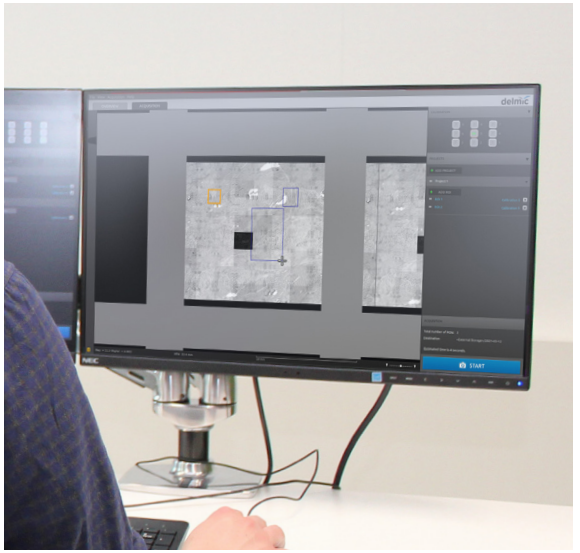


Image with 64 beams and shorter dwell times

FAST-EM uses 64 electron beams that scanned over your sample in parallel. The signal from each individual beam is recorded using a fast and highly sensitive Silicon Photo Multiplier (SiPM) array.

FAST-EM uses Scanning Electron Transmission Microscopy (STEM) for image formation. Scintillators, that are carrying the samples, produce localized cathodoluminescence when struck by electrons. Light is then captured using an electro-optical acquisition path by means of a Silicon Photo Multiplier array, and processed to form the final image. Due to this unique detection setup you can obtain excellent signal to noise ratios even at dwell times as short as 400 ns.



Acquire and analyse images with minimal user interaction

The reliability of the microscope and the software allow the operator to leave the system running without constant supervision. Delmic's easy-to use and robust automation software (Odemis) allows you to easily create and manage projects which are handled automatically. Finally, an optimized storage solution enables easy access to your projects after acquisition for visualization, analysis and collaboration purposes.

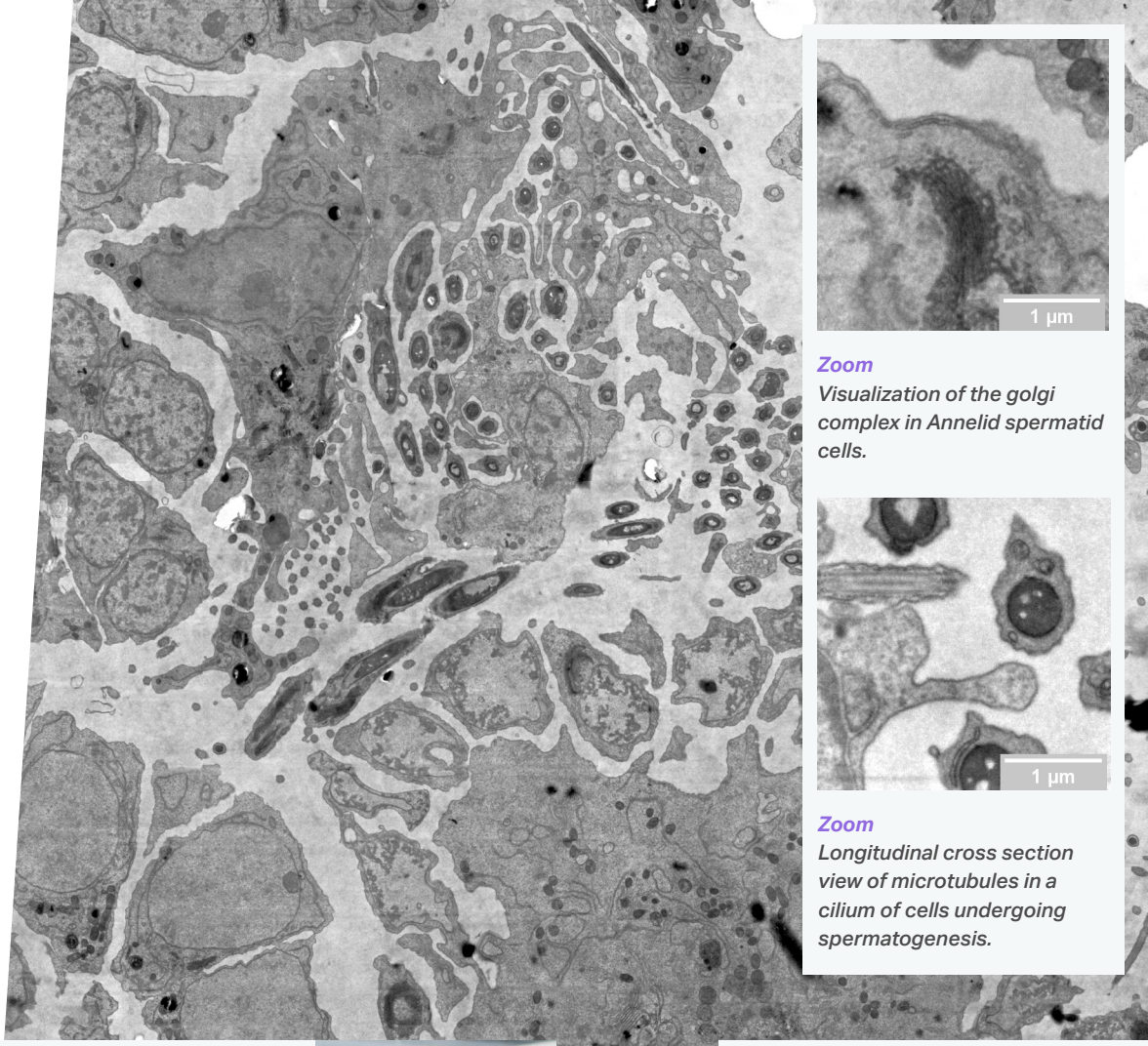
Application areas

Large area imaging

FAST-EM is highly beneficial for large-scale electron microscopy, where high-resolution imaging is performed on large samples ranging from tissues or organs. Large-scale imaging provides both nanoscale information to analyze subcellular types and also the context needed to understand the distribution of cell types within tissues or organs.

The elevated throughput enables quantitative analysis of larger sample sets, comparisons between healthy and diseased material, and screening of drug treatments or mutants, all while retaining nanometer-range resolution. The system can be used to image model organisms in their entirety, such as zebrafish, C. elegans or Drosophila.

Application: digital pathology, analysis of tissues, cells, biomaterials, soft matter, developmental biology.



Zoom
Visualization of the golgi complex in Annelid spermatid cells.

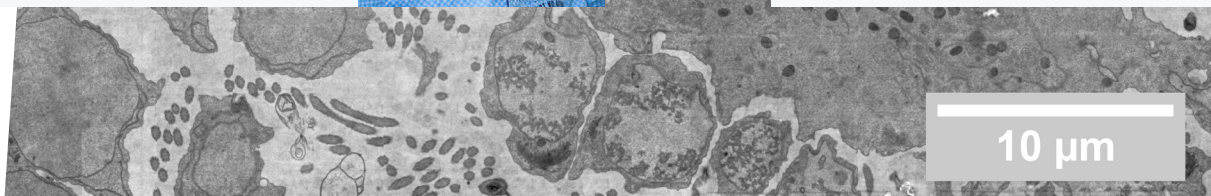
Zoom
Longitudinal cross section view of microtubules in a cilium of cells undergoing spermatogenesis.

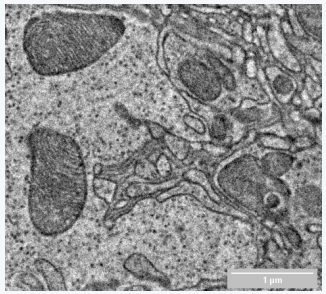
Jacob Hoogenboom, Associate Professor at TU Delft:

"At present, throughput is one of the major limitations in electron microscopy, especially in imaging facilities. A user typically receives images of parts of the sample that have been selected for recording. With FAST-EM, each user can receive the data from the full section or multiple sections and virtually browse and analyze these later. Besides practical reasons, this will also allow to span larger areas and volumes and analyze the structural layout of biological systems from the molecular scale to the level of an entire organ."

Annelid worm tissue – 80 nm sections of OTO stained samples FOV 102.4 x 76.8 µm², 16 seconds acquisition time

Sample courtesy of Karol Malota, University of Silesia





Zoom
Close up view of complex cell-cell interfaces.

Drosophila brain – 60 nm
rOTO stained samples
4 nm pixel size

Samples courtesy of Thomas Templier

5 µm

Volume electron microscopy

Processes in life rarely occur in two dimensions, so three-dimensional EM or volume EM is especially helpful to understand the architecture of tissues or organisms. Most volume EM techniques can produce 3D data by imaging many subsequent sections of a sample, which are then reconstructed into a 3D representation for analysis.

Researchers in cell biology and neurobiology rely heavily on volume EM to answer their research questions. Its high resolution is indispensable to visualize the nanoscale details that define individual cells. This also makes it a useful technique in the connectomics field, where the ability to resolve the intricate structures of neurons at nanometer-range resolution is indispensable to map the interactions between neurons in the brain.

The high throughput of FAST-EM is highly beneficial for volume EM, as larger volumes can be imaged within a shorter amount of time. This opens the way to ever larger projects, like imaging an entire hemisphere or even entire brains for connectomics. At the same time, high-throughput imaging enables comparative studies, which were previously too time-consuming to be feasible.

Application: neurobiology, cell biology, histology, plant biology, biofilm analysis, developmental biology.

Elizabeth Carroll, Assistant Professor at TU Delft:

" EM remains the gold standard method to resolve the structure of the synapse. In connectomics, we need to image tens of thousands of thin sections to reconstruct all the connections in a neural network. FAST-EM will make it possible to image more brains so we can start to compare individual animals. "

High-throughput imaging in facilities

Imaging facilities often handle material from many different researchers, each with a different research question. This presents logistical and biological challenges. Researchers face a high turnaround time of data since data collection is a time-consuming process. At the same time, the slow speed of EM means that there is a limit to the sample size that can be imaged for a given time or for a given cost. Therefore, there is a limit to the type of conclusions that can be drawn.

FAST-EM enables a fundamental shift in EM. The extremely high throughput of the system enables the imaging of the entire portion of the biological material available for analysis and then the selection of regions of interest at a later stage, off line, away from the microscope, directly by the biologists. This prevents tedious iterations between microscopists and biologists, and simplifies the workflow of the imaging facility.

Guido Ridolfi, Delmic Chief Operations Officer:

" With a much faster throughput, FAST-EM drastically reduces cost-per-pixel and allows facilities to provide quicker turnaround and enormously increases their EM capacity. "

Cells infected with SARS-CoV-2 Delta variant. Heavy metal staining.

Sample courtesy of University College London - Burgoyne, Thomas.

Customer story

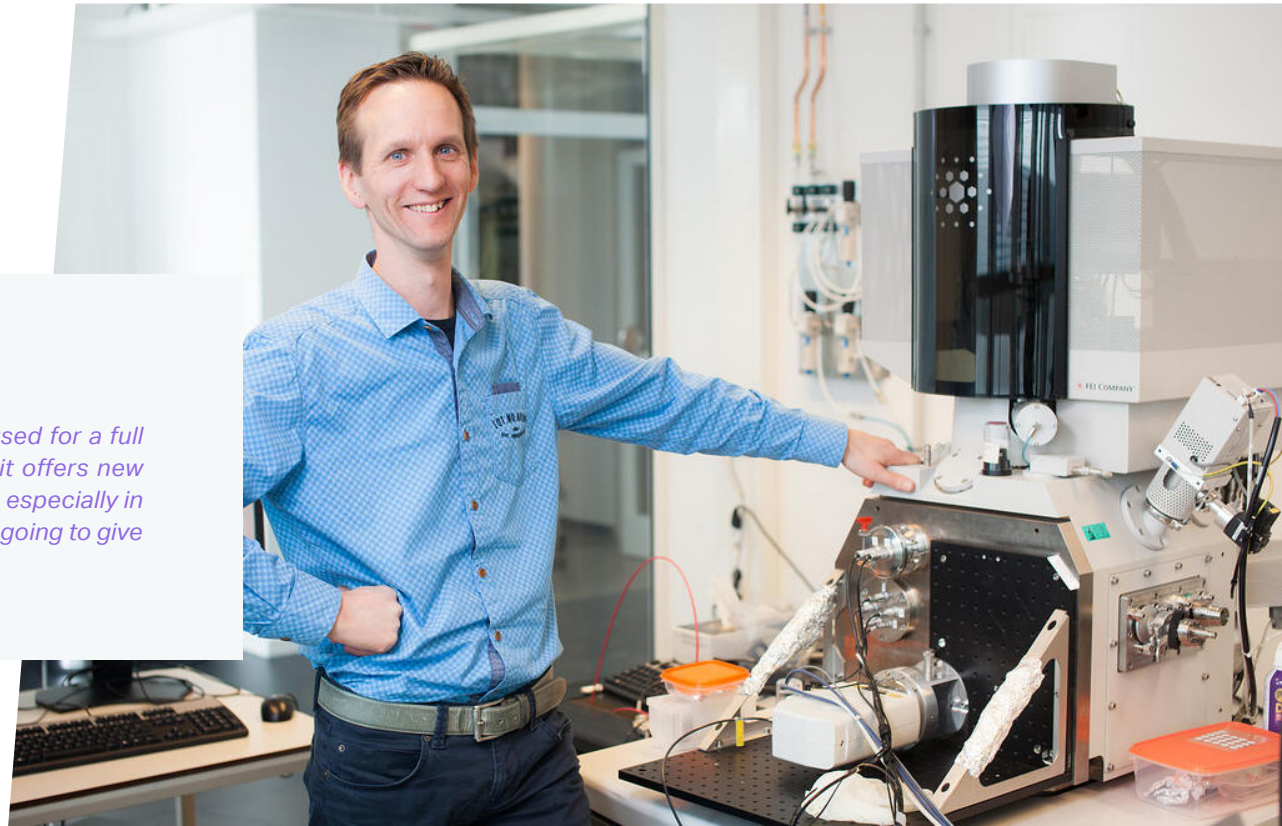
Advancing Scanning Electron Microscopy with FAST-EM

Dr. Jacob P. Hoogenboom is leading one of the ImPhys research groups at the Faculty of Applied Sciences at the TU Delft. The focus of his research group lies in the development of and research with new tools and techniques bridging the gap between light and electron microscopy.

The department of Imaging Physics integrates the fields of life sciences, healthcare and hightech industry. The group of Dr. Hoogenboom mainly focuses on developing innovative imaging technologies and instruments. These imaging systems are then put to use in groundbreaking research fields such as connectomics or cancer research. This dual function Dr. Hoogenboom facilitates creates collaboration and interaction between both the development and the application side of these techniques.

As early adopters, as well as the initiators of the FAST-EM system, Dr. Hoogenboom's research team contributes to the new opportunities for the research that is being done on the application side. According to Dr. Hoogenboom, the field of life sciences will benefit the most from the FAST-EM system. One of the hardest research field in life sciences is large volume imaging of biological samples. With FAST-EM, the acquisition time is reduced from months to a few days, meaning that researchers have more time to image multiple specimens, multiple model systems, multiple animal brains, and at the end start comparative analysis earlier.

The possibility to correlate these two modalities on larger scale length will bring in many research questions and requests for new technology, specifically for combining that data. The system installed at the TU Delft will attract users with biological life science-related questions and this, in turn, will bring the team into contact with their feedback and further requests.



Jacob Hoogenboom, Associate Professor at TU Delft:

" With FAST-EM, we can go to larger volumes. For instance, it could be used for a full model animal brain to map out all the neurons' connections. Moreover, it offers new possibilities for my field of research - correlative light electron microscopy, especially in terms of neurons or system development. The electron microscope is now going to give volumes and areas that used to be the domain of light microscopy only. "

System specifications

Dimensions

System base		800 mm (height) x 900 mm (width) x 1400 mm (depth)
Entire system		1900 mm (height) x 900 mm (width) x 1400 mm (depth)

Electron optics

System base		Thermo Fisher Scientific Apreo 2
Emitter		Schottky field emission source
Beam stability		< 3% beamlet intensity variation
Voltage range		2.5 kV -10 kV
Beamlet current		400 pA -1000 pA
Total current		25 nA - 64 nA
Nominal working distance		5 mm
Single beam mode:		Yes

Scanning and detection

Multiprobe arrangement		Square, 8 x 8 array
Beamlets		64
Dwell time		400 ns minimum, adjustable
Pixel size	During field acquisition	4 nm
Beamlet pitch		3.2 µm
Field of view (single field)		25.6 x 25.6 μm^2
Detectors	Multibeam	Transmission detector with 64 silicon photomultiplier cells
	Single-beam	Segmented in-lens backscattered electron detector
		Upper in-lens secondary electron detector

Sample and stage

Type		3-axes motorized (XYZ)
Stage position readout		Laser interferometry for nanometer-level positioning accuracy
Travel range XY		50 × 50 mm^2
Typical substrate size		14 x 14 mm^2 *
Max simultaneous substrates		9 substrates with current substrate size

* *Other sizes can be available*

System specifications

Sample substrates

Usable samples	Directly on scintillators	Sections (maximum thickness < 200 nm), nanoparticles, vesicles, viruses
Unattended run-time		Up to 72 hours **
Use cases	Routine data collection	Automated imaging of user-defined Regions of Interest and section arrays
Data format		One 16-bit TIFF per field image, stored per project.
Sustained throughput	During megafield acquisition at 400 ns dwell time	100 megapixels/second

Software

	64-bit GUI with Windows
Microscope control	Linux-based acquisition control
Acquisition support	User guidance for basic operations
System health monitoring	Continuous logging of crucial system features
Automatic calibrations	Detector gain, detector alignment, autostigmation, autofocus, global alignment of components

Vacuum and support hardware

System hardware	≥ 4 core CPU, ≥ 8Gb RAM, ≥ 1 Tb HDD, 1Gbps Ethernet
I/O	2 Monitors, 1920 x 1200 pixels (24"), keyboard, optical mouse
Vacuum pumps	1x Scroll pump
	1x 240 l/s turbomolecular drag pump
Operational vacuum	≤ 3×10^{-4} mbar
Network storage connection	10 Gbit Ethernet (10 GBASE-SR using LC Duplex OM3 MM fiber)

Optional components

High performance storage module	Scalable high-speed storage for data analysis and data sharing
Support Infrastructure	Standalone water chiller
	Acoustic enclosure for backing pump
Consumables	Sample substrates

** *Provided that the available sampling area is not the limiting factor.*

Interested?

For more information on this topic visit www.delmic.com

About

Delmic is a passionate high-tech company based in Delft, the Netherlands that develops powerful and user-friendly solutions for light and electron microscopy. Our systems are used by researchers and companies all over the world in fields ranging from life sciences, geology, material sciences to nanophotonics.

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