

A microscope that allows detail as small as individual protein molecules on the surface of living cells to be seen for the first time has been developed using BBSRC funding. Spin-out company Ionscope¹, established in 2004 to market these microscopes, has already sold more than 35 to researchers worldwide.

The new type of microscope, called a scanning ion conductance microscope (SICM)², has been developed by researchers at Imperial College London and the University of Cambridge. It can produce 3D images of the surface of live cells showing 50 times more detail than can be seen with a conventional microscope, without damaging the cells, and has so far been used to look at neurons³, heart muscle⁴, kidney⁵, sperm⁶ and stem cells⁷.

“When we started to produce results from our BBSRC grant and publish them, straight away people were interested in getting something similar for their labs,” says Professor Yuri Korchev from Imperial College London⁸ who pioneered this technique and co-founded Ionscope.

Fruits of BBSRC funding

Four three-year BBSRC responsive mode grants, jointly awarded to Professor Yuri Korchev at Imperial College and Professor David Klenerman at the University of Cambridge in the early 2000s, provided the majority of the funding needed to develop the SICM device. In 2004, Korchev and Klenerman formed Ionscope in response to an influx of requests from researchers for their microscopes.

Over 35 Ionscope SICMs are installed across the globe in leading life-science and materials-science laboratories. Ionscope now employs five full-time staff and sells its novel products in Asia, North America and Europe. Academic publications based on SICM data are increasing 30% year-on-year. Exports also continue to increase.

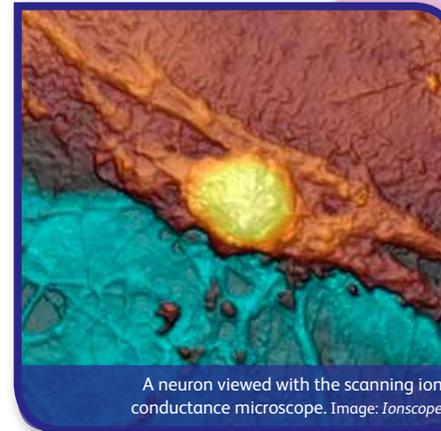
Opening up new areas of science

The SICM is unique because, unlike other types of microscope that can capture the same level of detail, such as high power electron microscopes and atomic force microscopes, SCIM can be used on live cells, without touching them or extracting the water from the sample, so they are not deformed or damaged. This allows researchers to observe living processes as they happen, on a scale smaller than a thousandth of a millimetre – previously impossible.

SICM devices have been employed in a wide range of research areas⁹, including cardiology and neuroscience.

Professor Mario Delmar from New York University Medical School, who uses a SCIM from Ionscope, explains, “We are interested in understanding the causes of sudden, unexpected cardiac death in a particular group of young people, especially athletes, affected with a disease called arrhythmogenic cardiomyopathy. We look at specific molecules of the cardiac cells, and how their exact position on the cell surface determines proper or improper electrical cardiac function.”

“We have hypothesized that if a molecule is distant from another by only a few millionths of an inch, the cell will not work properly and arrhythmias could eventually ensue. Having a tool that defines the precise relation between location and function on a nanometre scale is critical for this research. SICM is allowing us to move our research forward to a new level of understanding.”



IMPACT SUMMARY

Spin-out company Ionscope has been established to market a new type of microscope, the scanning ion conductance microscope (SICM), which has been developed by researchers at Imperial College London and the University of Cambridge.

Ionscope has sold over 35 SICM devices to leading life-science and materials-science researchers world-wide. Exports continue to rise as applications expand.

The scanning ion conductance microscope is opening up new areas of science by making it possible to study complex biological systems at a new level of detail.

Dr Guy Moss from the Department of Neuroscience, Physiology and Pharmacology at University College London says, “Supported by Ionscope, we are developing SICM technology to allow new experimental approaches for studying cell behaviour with amazing precision.”

“For example, as part of a team, we have used the precise positioning afforded by SICM to record directly from presynaptic boutons. These boutons form a tiny part of each nerve cell that plays a critical role in controlling the lines of communication to neighbouring cells.”

“The minute size of presynaptic boutons has traditionally made it impossible to record directly from them. (They are about one millionth of a metre across.) By using SICM technology, these recordings have become possible for the very first time.”

Other applications of the SICM have included studies of how viruses enter cells¹⁰, and how cells are affected by the presence of nanomaterials, which are now widespread in the environment¹¹.

Although the SICM was developed for biomedical science, it has found wider use, including in materials science. For example, it has been exploited to study the inside of lithium batteries to help researchers understand how and why

they fail¹². It has even been used to print tiny nanoscale colour pictures using DNA, which could be used for security tagging¹³.

Funded through a BBSRC industrial CASE PhD studentship, Korchev and his colleagues are now working with GlaxoSmithKline to investigate the potential of the SICM for testing new drugs.

HOW DOES IT WORK?

The microscope scans the surface of a sample using a hollow glass tube (a nanopipette) with a pointed tip approximately one nanometre across (one millionth of a millimetre).

Before it can be scanned, the sample is placed in a liquid. The microscope has two electrodes, equivalent to the two ends of a battery. One sits in the liquid containing the sample and the other sits inside the nanopipette.

When the tip of the nanopipette is placed in the liquid, an electrical current flows between the electrode in the liquid and the electrode inside the pipette. As the tip of the pipette gets close to the sample, its opening becomes obscured, so it is harder for the current to flow to the electrode inside. By measuring how much current is flowing, the device can work out how close the tip of the pipette is to the sample surface and, from this, calculate the height of the surface.

To produce a 3D image of the sample, the nanopipette scans across the sample surface measuring the electrical current flowing at each point and uses this to build up a contour map. Because the pipette never touches the sample surface, it does no damage.

Many of the applications of the SCIM take advantage of the hollow nature of the nanopipette. For example, researchers have delivered chemicals through the pipette to individual receptors on the surface of cells to see how they respond⁴. The SICM can also be used for colour printing using a specially designed nanopipette with several barrels that contain different colours, like a miniature inkjet printer¹³.

The scanning ion conductance microscope.
Image: Ionscope



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