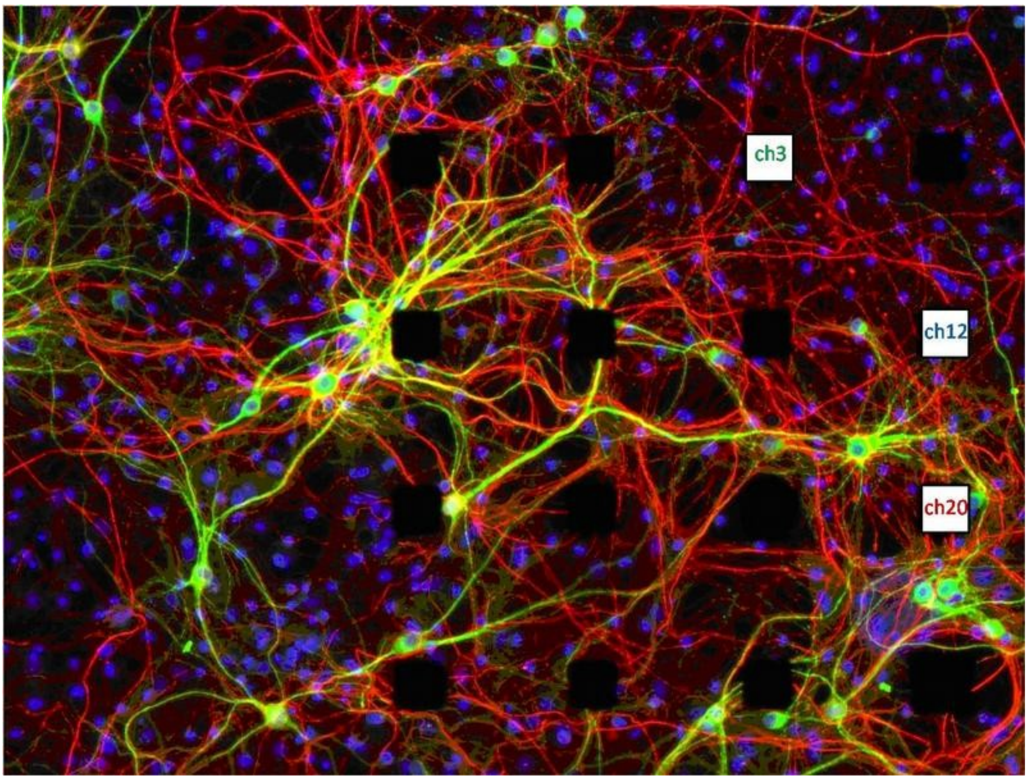
Healthcare industry BW

Health research with microsystems

The NMI Natural and Medical Sciences Institute in Reutlingen organised its biannual MEA conference from 8 to 11 July 2008. More than 200 developers and microelectrode array users from 18 countries came together in Reutlingen to present their latest developments and results from basic physiological and industrial drug research in a total of 147 papers.



Neural network on a microelectrode array (antibody staining) (Photo: University of Hokkaido)

The brain is a complex system for the processing of information. Billions of interlinked nerve cells process huge amounts of information within the fraction of a second. The nerve cells transmit information as electrical signals. The network of nerve cells leads to a highly complex, spatiotemporal electrical activity pattern in which our perceptions, thoughts, actions and emotions are encoded. However, little is known about what this code looks like and which codes the nerve cells use to communicate with each other. Numerous work groups are focusing on these issues.

A standard method for examining the function of smaller neural networks is the measurement and analysis of spatiotemporal activity patterns in brain slices and neural networks from hundreds or thousands of cultured nerve cells. Microelectrode array technology has become a standard technology for doing so and enables the simultaneous measurement of the samples and cultures at many sites.

Microelectrode arrays, MEAs for short, are small glass plates on which up to several hundred microscopically small electrodes are arranged. Nerve cells and tissue segments of brain samples can be cultivated on such glass plates for weeks and months. The cells can be stimulated electrically through the electrodes and their electrical activity can be measured. The model preparations are used in basic neurophysiological research as well as in industrial drug discovery processes focusing on diseases such as epilepsy, stroke, schizophrenia, Alzheimer’s and cardiovascular diseases.

Discussing state-of-the-art results and developments

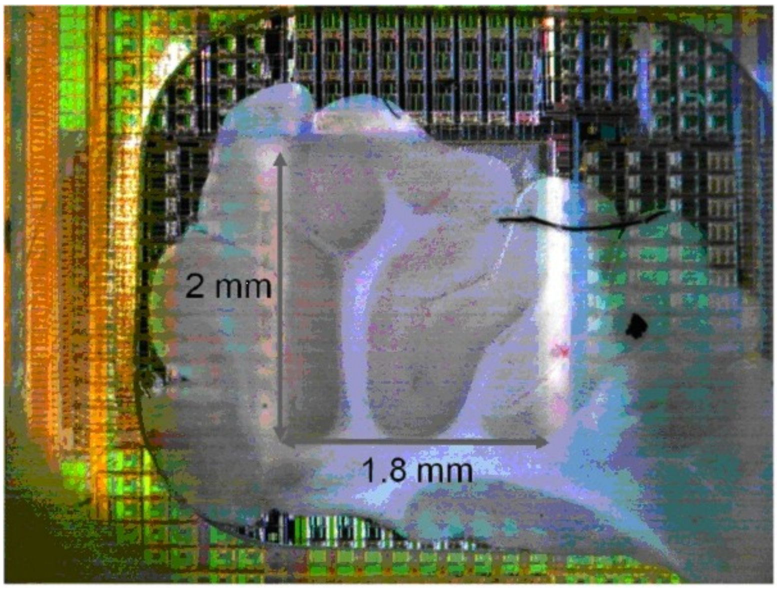
The developers and users of MEA technology meet in Reutlingen every two years. The meeting, organised by the NMI Natural and Medical Sciences Institute, is the most important international information and discussion forum for MEA technology. Experts, students and interested scientists use the opportunity to discuss state-of-the-art results and developments and initiate new partnerships. This year’s meeting focused on the structure, dynamics and plasticity of neuronal activity of neural networks, methods for the analysis of neuronal activity patterns, the use of the technology for pharmacological, toxicological and neurotechnological examinations as well as numerous technical developments.

The conference was opened by Shimon Marom from the Technion, the Israel Technology Institute in Haifa. Marom, who has made major contributions to the use of MEAs for the analysis of networks, reported on the order in which neurons of small networks react to localised stimuli. This order thus represents information through stimulation patterns. Apart from the question of how information is encoded by the neurons, the question of how certain genes affect human behaviour is a far greater challenge for the modern neurosciences. MEAs are used as screening tools for investigating a large number of brain slices of mutated animals, reported Arjen Brussaard from the University of Amsterdam. Tim Holy from the University of Washington in St. Louis, USA, also uses microelectrode arrays for screening purposes. He reported on the identification of pheromones on the basis of the effect substances isolated from mouse urine have on the activity of cultivated neurons from the olfactory system.

Lior Gebstein, also from the Technion in Haifa, reported on the application of MEAs in tissue engineering and presented the progress made in cell therapy in which stem cells are used to treat cardiac dysfunction. Transplanted stem cells take over the function of the defective heart muscle cells. Although the researchers were able to show in animal experiments that this approach works, at least in principle, clinical studies or even routine applications are still not in sight.

The continuous further development of MEA technology is driven by the wish for greater spatial resolution when scanning the activity patterns and for the improved possibility of analysis and reducing the huge amounts of data generated by laboratory experiments.

The NMI in Reutlingen is one of the pioneers of MEA technology



Brain slice on a CMOS-based microelectrode array (Photo: ETH Zurich)

While the majority of glass MEAs used contain sixty electrodes, the further development of the arrays also enables the measurement of cellular activity with up to 1024 electrodes. However, this is the best that can be achieved with simple conductor lines on the glass substrate. This also limits the spatial density of the electrodes. If detailed examinations of the activity of individual cells within a broad neural network need to be carried out, then this low spatial density is insufficient. Several papers highlighted the developments and applications of different arrays consisting of 4096 electrodes (Institute of Microtechnology, University of Neuchatel, CH), 11016 electrodes (ETH Zurich) and 16384 conductor sites on an area of 1 mm^2 (Max Panck Institute, Martinsried). Andreas Hierlemann from the ETH Zurich highlighted that the CMOS (complementary metal–oxide–semiconductor) technology can be used to achieve high electrode densities (3150 electrodes per mm^2) with a high signal-noise ratio through integrated circuits for on-chip signal filtering and processing.

The NMI in Reutlingen is one of the pioneers of MEA technology and has continuously developed, simplified and automated the technology over the last 20 years. Special electrode materials enable almost noise-free measurements. New material combinations and manufacturing methods result in MEAs that can be used for completely new applications. The MEAs are produced in the institute's cleanroom and provided to its partner, Multi Channel Systems MCS GmbH, which is also located in Reutlingen. Multi Channel Systems, established in 1996, develops electronic measurement systems and software for non-clinical electrophysiology.

As the major competitor, Japanese Panasonic, is gradually retreating from this market, the company has become the most important supplier of MEA technology around the world, with a market share of about 90 per cent.

MEAs have now become standard tools in many academic laboratories, which are the main users of this technology. Pharmaceutical and biotechnology companies are nowadays also showing a greater interest in this technology which they use to test specific substances for their effect and undesired side effects on ion channels and receptor systems in neural systems and the cardiovascular system. MEAs are also used to discover and test substances used for the therapy of neurological and psychiatric diseases.

New diagnostic and therapeutic approaches

"Micro- and nanotechnological innovations are an important basis for new test methods for drug development and for new diagnostic and therapeutic approaches in medical technology. We are developing microsystems and nanotechnologies that can be used for the manipulation and analysis of biomolecules, cells and tissues and combine microtechnological developments with biotechnological and cell biological method developments," said Dr. Alfred Stett, Vice Managing Director of the NMI, explaining the development of sensor arrays, lab-on-a-chip applications and microimplants at the NMI.

Electrophysiology is gaining in importance for the NMI's work, especially with regard to basic research, drug development and neurotechnology. In these fields of research, MEA technology is a particularly successful microsystem for life science applications and was also the technological basis for automated patch clamping that led to the foundation of the company Cytocentrics AG. This company, now relocated to Rostock, has turned the concept into application and is developing an automated system that enables the electrophysiological testing of effects and side effects of drugs on cell lines. MEA microsystems technologies have also been used to develop a miniature retinal implant that led to the establishment of Retina Implant AG in Reutlingen. The implant helps restore vision in blind people, at least partially.

BIOPRO Baden-Württemberg GmbH, co-organiser of the conference, has published conference proceedings that highlight the manifold aspects of the technology and potential applications. The first MEA conference proceedings issue was published in 2006.

MEA Meeting 2008 Proceedings (PDF, 16.22 MB)

Source: NMI Natural and Medical Sciences Institute at the University of Tübingen - 13 August 2008