Brain-chip-interfaces (BCHIs) are hybrid entities where chips and nerve cells establish a close physical interaction allowing the transfer of information in one or both directions. Typical examples are represented by multi-site-recording chips interfaced to cultured neurons or implanted in the brain to record or stimulate neuronal excitation. We provide an overview on recent achievements in the field of BCHIs leading to enhancement of signals transmission from nerve cells to chip or from chip to nerve cells, either in terms of signal-to-noise ratio or of spatiotemporal resolution. Micro-nail shaped microelectrodes engulfed by neurons in culture establish a tight electrical coupling with the cells and allow for high signal-to-noise ratio recording. Oxide-insulated chips, featuring large-scale and high-resolution arrays of stimulation and recording elements, represent a promising technology for high spatiotemporal resolution interfacing, as recently demonstrated by recordings obtained from hippocampal slices and brain cortex in implanted animals. Although most BCHIs deal with electrical signals, chemical signaling has also to be considered and some new advances in this direction are reported. Finally, we present and discuss important challenges for design and fabrication of new generations of BCHIs.

Keywords: Brain-Chip interface; Multi-transistor array; Electrolyte-oxide-semiconductor field effect transistor; Electrolyte-oxide-semiconductor capacitor; Local field potentials

1. Brain-chip interfacing

1.1. Towards a definition of Brain-Chip-Interface (BCHI)

The use of on-chip microelectromechanical systems (MEMS) in the biomedical field has gained increasing attention in recent years. The continuous improvement of micromachining and microelectronics technologies and simultaneous deepening of knowledge about cellular and molecular mechanisms in life sciences are driving development of new generations of MEMS serving as scientific, diagnostic and therapeutic tools. Microchips for multi-site recording of neuronal activity were among the first to be introduced [1] and now represent an expanding technology [2,3] with great potential for novel applications. From its infancy, the technology has undergone a progressive development and it is now widely adopted by neuroscientists for recording living neurons “in vitro”. More recently, we have assisted to the increasing usage of implantable microchips as neuronal probes for investigating brain circuits “in vivo” while, in parallel, their potential for neuroprosthetics applications has been successfully demonstrated in non-human primates [4] and assessed in clinical trials in paralyzed patients [5].
**Brain-Chip Interface** (BCHI) “Hybrid system where brain cells and chip-based MEMS establish a close physical interaction allowing the transfer of information in one or both directions”.

The multiplication of approaches and examples of applications that are based on chip-to-brain interaction and communication has led us to attempt the formulation of a comprehensive definition for this class of hybrid devices. Brain-Chip-Interfaces (BCHIs) is proposed as the term to identify hybrid systems in which chip-based MEMS establish communication pathways through close physical interaction with brain cells, either “in vitro” or “in vivo” (Figure 1).

Despite the fact the most BCHIs are based on electrical signaling between neurons and microelectronics sensors, the definition is wide and comprehensive of other technological approaches. It includes, for example, other physical means of information exchange, such as those based on chemical or optical signals. In addition, the definition takes into account that interfacing can occur at different levels, either of individual cells or ensembles, and that communication can be uni- or bi-directional.

### 1.2. Levels of brain-chip interfacing

At least three basic levels of brain-chip interfacing are identified on the basis of the dimensional scale of the biological entities involved: neurons, tissue and brain [2]. At present, neurons are most frequently interfaced to metal microelectrodes [1,6] or oxide-insulated electrical microtransducers (e.g. EOSFETs or Electrolyte-Oxide-Semiconductor-Capacitors) to record or stimulate their electrical activity in dissociated cultures [2,7]. This first-level of interfacing implies that single cells are contacting and signaling to cell-sized microdevices. A recent and original example of such a BCHI was proposed within the Brain Storm project (http://www.bio-ict.org/index.php/projects/brainstorm) where a tight electrical coupling between neurons and chip was achieved through gold micro-nail shaped microelectrodes that were engulfed by neurons through a phagocytosis-like mechanism [8]. Large-scale high-resolution recordings from individual neurons in a network can be obtained, instead, thanks to a chip featuring a large Multi-Transistor-Array (MTA), as demonstrated with neuronal networks “in vitro” [9]. A second level of interfacing implements the concept of establishing an interaction with the brain tissue. This is achieved, usually, by placing a tissue slice a several hundred micrometers thick in contact with the chip. We report, as an example, the MTA recording of slices from the rat hippocampus [10]. In these cases, individual microdevices sample the activity of a population of cells rather than of single neurons. Signals are in the form of Local-Field-Potentials (LFPs), multi-unit or single-unit activity. In general, even if single-units can be detected and identified, they originate from the activity of several neurons distributed in the proximity of the sensor and can be reduced, therefore, to a population recording scheme. Finally, the third level of interfacing is represented by chip implants in the brain or other parts of the nervous system, such as the spinal cord, peripheral nerves or sensory organs. To this respect, recent results from the CyberRat project (http://www.cyberrat.eu) show that high-resolution recording from the rat brain somatosensory cortex can be performed using MTAs [11].

### 2. CMOS Chips for Neural Tissue Interfacing

Extracellular recording and stimulation techniques have been developed with the aim of interfacing (in vitro) neural tissue simultaneously at a number of sites distributed in space [12]. With this type of approach, the tissue is located in
Fig. 2. Schematic description of extracellular nerve cell interfacing approaches. Left: Nobel metal electrode based interfacing, right: EOSFET based interfacing.

an electrolyte above the surface of a solid-state chip with the surface of the chip providing voltage-sensitive sites in a regular spatial arrangement. Moreover, between the tissue and the surface a cleft of the order of 50 nm thickness is formed. In Fig. 2 depicts two different approaches to form the voltage-sensitive device: On the left, the site is made by means of a noble metal electrode, which is connected to further signal-processing circuitry. Commercially available Multi-Electrodes-Arrays (MEAs) use this approach and separate a number of such noble metal electrodes arranged within a 2D array from each other in the lateral direction by an insulating substrate material. Ideally, noble metal electrode and electrolyte form a capacitor with a very thin so-called Helmholtz double layer capacitance. Whereas in this case the capacitance per area is very high, so that cleft-voltage coupling to the electrode is very efficient, the entire surface consists of a chemically non-homogeneous surface, as electrodes and the insulating material between the electrodes periodically alternate.

EOSFETs (Fig. 2, right) represent the second approach in this context [13]. In this case, the gate of the well-known Metal-Oxide-Semiconductor-Field-Effect-Transistor (MOSFET) is replaced by the electrolyte above the transistor’s gate dielectric, and cleft voltages induced by a firing nerve cell translate into a modulation of the transistor’s drain current. This approach provides a homogeneous dielectric surface within the entire active neural tissue interfacing area. Also in this case, a number of 2D arrays have been published.

In both cases, however, realization of large high-density 2D arrays is restricted by interconnect(ion?) issues: Only one interconnect(ion?) layer is available in the bulk material which is used to make a connection between the active sites in the center of the chips and the pads at the chip borders. Thus, to circumvent such interconnect(ion) problems (extended) Complementary-Metal-Oxide-Semiconductor (CMOS) technology and chips with related circuitry have been proposed in recent years with the aim of significantly increasing spatiotemporal resolution. Moreover, such chips allow provision of signal processing circuitry in close proximity to the related recording/stimulation sites. CMOS-based noble metal electrode arrays have been published with up to 11k sites, and extended EOSFET arrays have been reported with up to 16 k and, very recently, 32 k sites [14–17]. Depending on the respective application, different design goals have been targeted: in [15], the 11 k chips provide 126 signal channels which can be selected from the entire array using a sophisticated signal routing algorithm. The chips presented in [16,17], on the other hand, always record entire frames or entire sub-frames so that a neural tissue imaging mode is obtained.

A number of recent developments also aim at “in vivo” interfacing (e.g. http://www.cyberrat.eu). Whereas extracellular recording and stimulation principles as described in the preceding paragraph can be adopted, the chips developed in that context cannot simply be transfered as such. The main concern being power: if the power is transferred wirelessly, the amount of available power is limited; if that is not the case (and power is provided through a cable), the maximum power which can be consumed in live tissue is limited due to heat generation. Unfortunately, however, the number of sites and bandwidth of such a system increase the power consumption whereas the noise of a system shows an increase with decreasing power allowed per site. In conclusion, “in vivo” systems must always be carefully tailored depending on the related target application.

3. Perspectives of BCHIs in neuroprosthetics

Although preliminary evidence has been provided that BCHIs can be employed to drive neuroprosthetic devices in humans [5], there is a long way to go before the demonstration of reasonable advantages justifying an extensive use of this approach at the clinical level. As an example, BCHIs potentially offer the possibility of on-chip integration of neuromorphic substitutes of brain circuits. A recent report provides an example of a cerebellar microcircuit with a model based neuroprosthetic device [18–20]. In conclusion, BCHIs represent a transdisciplinary approach allowing the
investigation of brain function with unprecedented resolution and a communication link between the nervous system and neuroprostheses in bionics.

Acknowledgments

We thank Prof. R. Thewes, Prof. P. Verschure and Dr. R. Huygs for their contribution to the Brain Chip Interfaces: the Present and the Future session during the FET11 meeting and for their help with the preparation of the manuscript.

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