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On Micro-Electrode Array Revival: Its Development, Sophistication of Recording, and Stimulation

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Introduction

Network activity of electrically active cells such as neurons and heart cells underlies fundamental physiological and pathophysiological functions. Despite the well-known properties of single neurons, synapses, and ion channels to exhibit long-term changes upon electrical or chemical stimulation, it is believed that only a concerted effort of many cells make up what it is commonly experienced in humans as self-awareness. In particular, higher brain functions such as associative learning, memory acquisition and retrieval, and pattern and speech recognition depend on many neurons acting synchronically in space and time. Moreover, pathophysiological conditions such as epilepsy, Alzheimer's disease, or other psychological mental impairments have been shown to rely on many neurons to form one of the latter states.

Thus many researchers have been seeking a multi-channel approach to bridge the gap in understanding single-cell properties and population coding in cellular networks. Despite the pioneering work by Thomas et al. (1972), Wise and Angell (1975), and Gross (1979) a remarkable step forward in Micro-Electrode Array (MEA) applications has been achieved only over the last ten years or so, particularly due to the lack of affordable computing power and commercial MEA systems. In this chapter we describe the technology of the most common MEA chips manufactured by the NMI (Natural and Medical Sciences Institute, Reutlingen, Germany), its various design approaches, and current developments. Furthermore, the multi-channel recording and analysis system around the MEA chip developed by and available from MULTI CHANNEL SYSTEMS (MCS, Reutlingen, Germany) together with new developments for multi-site stimulation are described. Additionally, emphasis is given towards an in-depth understanding of the physical prerequisites for adequate extracellular stimulation and recording using MEA. This in turn has led to new approaches in MEA electrode and insulation material as well as new developments in artifact suppression by using digital electronic feedback circuits implemented in a 60-channel MEA amplifier.

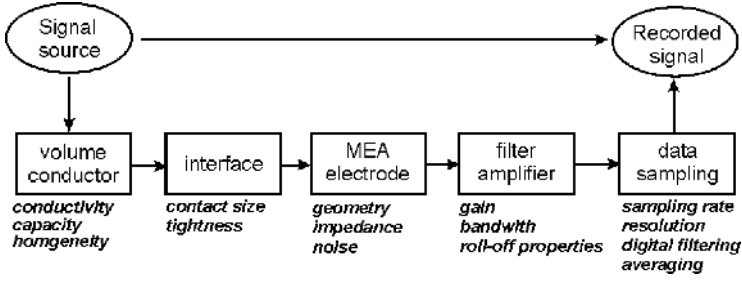


FIGURE 2.1. Pathway showing what parameters are involved in shaping the recorded signal coming from an original cellular signal source.

2.1 Theoretical Considerations of MEA Extracellular Stimulation and Recording

In principle, a MEA is a two-dimensional arrangement of voltage probes designed for extracellular stimulation and monitoring of electrical activity of electrogenic cells, either isolated or in neuronal, muscle, and cardiac tissue. If an analysis of the performance of these probes and its transfer properties is to be performed the electrical characteristics of the main components of the entire system have to be considered (Figure 2.1): (i) the cellular signal sources and the tissue allowing spread of ionic current; (ii) the contact between the cell and the tissue, respectively, and the electrodes; (iii) the substrate and the embedded microelectrodes; and (iv) the external hardware with stimulators and filter amplifiers connected to the electrodes.

2.1.1 Single-Cell Recording with Planar Electrodes

When recording from cells cultured on the MEA surface, individual cells may contact the planar electrodes as shown in Figure 2.2. The cell body is partially covering the electrode surface, and the free electrode area is in contact with the external saline and connected to ground. The amplifier connected to the conducting lane records the sum of the potentials at the surface of the free electrode and the surface of the electrode covered by the membrane. Neglecting the low resistance R_b of the bath solution above the free electrode, the relation between the voltage at the contact pad V_{pad} and in the cleft between cell membrane and the electrode V_J is given by the frequency-independent relation:

$$\frac{V_{pad}}{V_J} = \frac{C_{JE}}{C_E + C_{sh}} \approx \frac{a_{JE}}{a_E}$$

where C_{JE} is the capacity of the covered electrode area of size a_{JE} , C_E the capacity of the entire electrode area of size a_E , and C_{sh} is the shunt capacity of the connecting lane. Given that $C_{sh} \ll C_E$, the amplitude of the recorded signal depends linearly on the ratio of the covered electrode area and the entire electrode area.

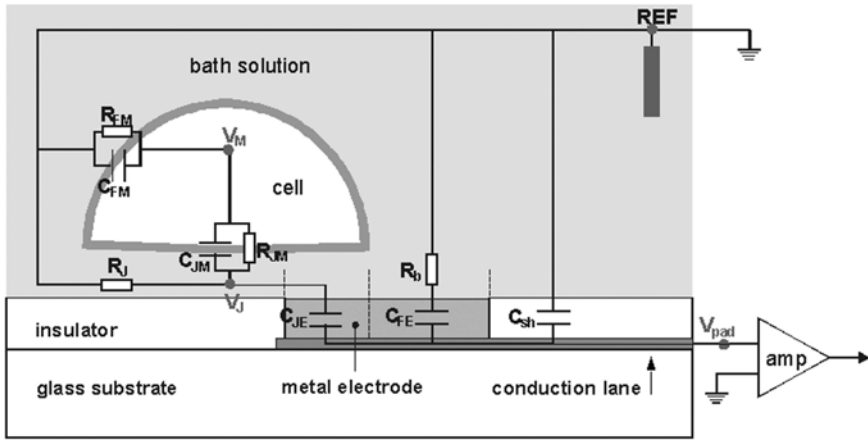


FIGURE 2.2. Extracellular recording of single-cell activity with planar electrodes. Given the electrical circuit the voltage picked up by the amplifier between the contact pads and the reference electrode can be calculated.

The lesson that can be learned from this simplified consideration is the following. In combination with an ideal insulation of the connecting lanes exhibiting neglecting shunt capacity and the use of ideal bandpass filters (infinite input impedance, low cut-off frequency of the highpass, high cut-off frequency of the lowpass), MEA electrodes can be operated as frequency-independent voltage-followers for the currentless monitoring of cellular signals. More advanced considerations on single-cell contacts are given by Buitengeweg et al., who used a geometry-based finite-element model for studying the electrical properties of the contact between a passive membrane (Buitengeweg et al., 2003), a membrane containing voltage-gated ion channels (Buitengeweg et al., 2002), and a planar electrode, respectively.

2.1.2 Tissue Recording with MEAs

The spatial distribution of the voltage in a thin layer of a conductive tissue sheet above the surface of the electrodes of the MEA is recorded with respect to the reference electrode located in the bath solution (Figure 2.3). The signal sources that generate the field potential are compartments of single cells, for example, dendrites or axon hillocks. The electrical activity, be it either spontaneous or evoked by chemical or physical stimulation, spreads within the cellular compartments and from cells to cells via synaptic connections. This spread of excitation within cells and the tissue is always accompanied by the flow of ionic current through the extracellular fluid. Related to the current is an extracellular voltage gradient that varies in time and space according to the time course of the temporal activity as well as the spatial distribution and orientation of the cells.

The recordings may exhibit slow field potentials as well as fast spikes arising from action potentials. The passive spread of cellular signals in tissue slices has

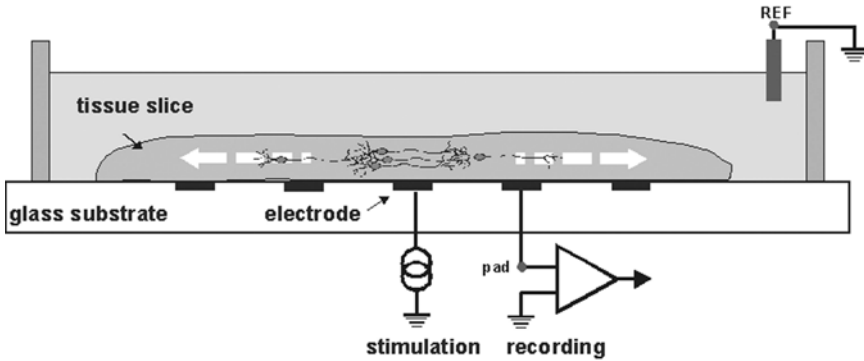


FIGURE 2.3. Stimulation and recording of electrical activity in tissue slices with a MEA. The substrate-integrated planar electrodes can be used both for stimulation and recording.

been investigated by Egert et al. (2002). They could detect spike activity with MEA electrodes at distances of up to $100\ \mu\text{m}$ from a neuron in an acute brain slice. Typically, signal sources are within a radius of $30\ \mu\text{m}$ around the MEA electrode center.

2.1.3 Extracellular Electrical Stimulation with MEA

The MEA electrodes are also used for extracellular electrical stimulation by applying either current or voltage impulses to the electrodes. In principle, the equivalent circuit is the same as for recording when the amplifier is replaced by the stimulation source.

Application of voltage to the electrodes charges the capacity of the electrical double layer of the metal–electrolyte interface. This leads to fast, strong, but transient, capacitive currents with opposite sign at the rising and falling edges of voltage pulses resulting in transient hyperpolarization and depolarization of cellular membranes (Fromherz and Stett, 1995; Stett et al., 2000). This is similar to the effect of brief biphasic current pulses commonly used for safe tissue stimulation (Tehovnik, 1996). In both cases, however, membrane polarization of the target neurons is primarily affected by the voltage gradient generated by the local current density and tissue resistance in the vicinity of the cells. Thus the stimulation efficacy depends on the effective spread of the injected current within the electrode–tissue interface and within the tissue. It is customary to express the stimulation strength in charge injected per pulse, often standardized to the geometric area of the stimulation electrode. The charge injected with current pulses depends only on the amplitude and duration of the pulse, whereas in the case of controlled voltage pulses the charge additionally depends on the tissue resistance and the capacity of the electrode–tissue interface.

For electrochemical reasons, the voltage at the electrodes should always be controlled and as low as possible. Hence microelectrodes should offer a high

charge-injection capacity, a parameter that describes the limit of a MEA electrode to be charged without leading to an irreversible electrochemical reaction at the electrode/electrolyte interface.

2.2 MEA Design: Current State and Future Layouts

Micro-electrode arrays were developed in the early 1970s by several research groups (for a historical perspective, see Potter, 2001). Initially, MEAs were mainly made out of Au as the electrode material. Inasmuch as planar Au electrodes have a high impedance, a common practice is to platinize Au electrodes in order to reduce the impedance and thus achieve a better S/N ratio. However, Pt-treated Au electrodes are not stable over a long time period due to the degradation of the Pt-layer and thus they have to be replatinized in order to be used again. To overcome this disadvantage the NMI set out to develop a new MEA with a low and long-term stable electrode impedance.

The standard MEA electrode now is made of TiN by plasma-enhanced chemical vapor deposition (PECVD), and the insulator is made of silicon nitride (Si_3N_4). The PECVD process of a Ti target under a nitrogen atmosphere leads to a fractal deposition of a TiN electrode on the MEA (Figure 2.4). Due to the nanocolumnar 3-D structure the overall surface area of the TiN electrode is much increased compared to a standard 2-D Au or Pt-electrode with the same electrode diameter (Haemmerle et al., 1994; Nisch et al., 1994). The high surface area yields an increase in the overall capacitance and thus leads to a reduced noise level of the electrode, and allows a continuous and reliable electrical stimulation, even over a time period of several weeks (van Bergen et al., 2003). We routinely observe a noise level of less than $\pm 10 \mu\text{V}$, measured with a $30\text{-}\mu\text{m}$ MEA electrode at a frequency cut-off of 1 Hz to 3 kHz and a sampling rate of 25 kHz. Increasing demand for specific MEA layouts based on specific biological questions has prompted the NMI for an ongoing development

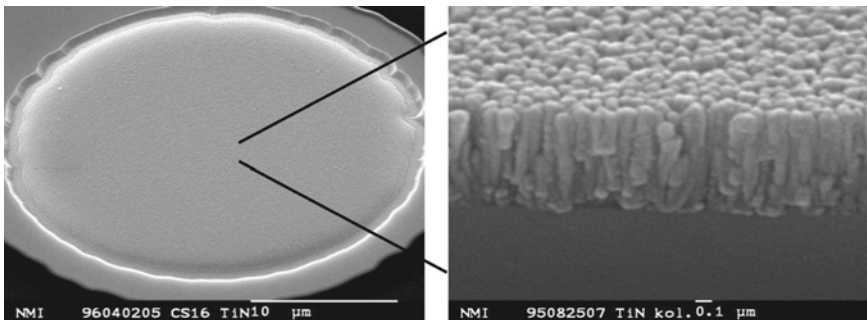


FIGURE 2.4. A single TiN MEA electrode is shown at μm and nm resolution. Note the nanocolumnar structure of the electrode, revealed by the REM image on the right.

of MEAs with custom-designed layouts geared towards specific applications. So far, specific MEA layouts have been designed for the following applications.

2.2.1 *The Standard Line of MEA*

MEAs come in a pattern of 8×8 or 6×10 electrodes. They are used for acute brain slices, single-cell cultures, and organotypic preparations, and are made out of Ti (titanium) or ITO (indium tin oxide) leads and titanium nitride (TiN) electrodes with a diameter of either 10 or 30 μm . Noteworthy to mention is the fact that MEAs can be optionally delivered with an internal reference electrode and different culture rings/chambers are available to accommodate everyone's need for either acute recordings or long-term cultures, or even combining patch/intracellular approaches with MEA recordings. The insulation is made out of Si_3N_4 in all cases.

2.2.2 *Thin MEA*

A special approach towards combining MEA recording and imaging has been achieved with the introduction of the "Thin"-MEA. In particular, high-power objectives with a high numerical aperture usually have a very low working distance on the order of only several hundred micrometers. Thus inverted microscopes using such high-power lenses are not able to image through standard MEA due to the thickness of 1 mm. To circumvent this problem MEA have been constructed using cover slip glass. This so-called "Thin"-MEA has a thickness of only 180 μm , and the conductive leads and contact outer pads are made of ITO. The Thin-MEA is mounted on a ceramic support to prevent breakage and can be readily used in combination with high-power objectives (Eytan et al., 2004).

2.2.3 *2×30 MEA*

This design is intended for studying local responses at a high spatial resolution while at the same time looking at functional connectivity between two organotypic slices placed next to each other. The 60 electrodes are split into two groups. Each group is composed of a 6×5 electrode pattern, and the groups are separated by 500 μm . Within a group the electrode spacing is just 30 μm and the electrode diameter is 10 μm . This allows an unparalleled insight into local connectivity and interconnectivity over a wide range of 500 μm . Moreover, these MEAs are being used to record multi-unit activity, for instance, in slices of the retina. Here, the small interelectrode distance plays a special role as a two-dimensional multi-trode sensor, giving rise to improved spike separation. In principle, the activity of a single neuron is picked up by more than one MEA electrode due to the small inter-electrode distance. Because the distance of the MEA electrodes to a particular cell varies slightly, neighboring MEA electrodes record a slightly different waveform from the very same cell at the same time point. Thus this multi-dimensional fingerprint-like pattern identifies a single cell more precisely than conventional spike

sorting methods based simply on a one-dimensional waveform analysis (Segev and Berry, 2003).

2.2.4 *Flex MEA*

Multi-channel recordings in vivo and in semi-intact preparations require a different approach to utilize MEA. Here a flexible 6×6 MEA layout based on polyimide has been constructed. It is currently being used to record surface electrocorticograms of the somatosensory cortex in rats and to electrically stimulate the same region via the flex-MEA (Molina-Luna et al., 2004). Conductive leads and outer pad contacts are made out of Au, and the 32-channel flex-MEA electrodes are made out of TiN and have a diameter of $30\text{ }\mu\text{m}$ and spacing of $300\text{ }\mu\text{m}$, respectively. In addition to the 32 recording electrodes, 2 indifferent and 2 large ground electrodes are incorporated in this design. The polyimide is perforated to allow better attachment of the tissue to the array as well as axonal growth.

2.2.5 *High-Density MEA*

For various reasons, spatial resolution is important when conduction velocity or synaptic delays are to be measured precisely over a long distance. Given 60 electrodes there is either a very good spatial resolution (small interelectrode distance) and a small recording area, or vice versa. Hence a MEA with a high density of electrodes covering a large area should alleviate these problems. A first step towards such a MEA is currently under development. The layout is comprised of 256 electrodes in a square grid pattern utilizing a $100\text{-}\mu\text{m}$ interelectrode distance in the center and $200\text{ }\mu\text{m}$ in the periphery, yielding a total recording area of about $2.8 \times 2.8\text{ mm}$ (Figure 2.5). The chip is wire-bonded to a standard PC chip socket. Thus the chip can be easily mounted in an industry standard socket holder.

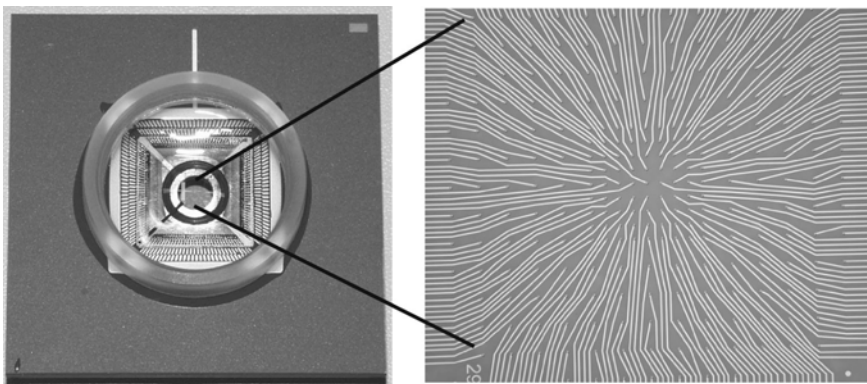


FIGURE 2.5. A high-density MEA is wire-bonded to a standard IC socket commonly used in personal computers. The layout of the high-density HD-MEA is shown on the right.

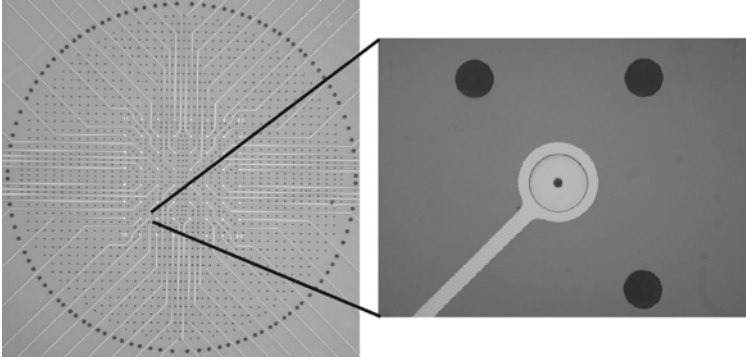


FIGURE 2.6. A MEA with holes in the substrate. The ring enclosing the actual MEA field consists of perfusion holes with 50- μm diameter. The openings in between the MEA electrodes are 20 μm in diameter and negative pressure enhances the contact of the tissue onto the substrate. The hole in the center of the MEA electrode is 5 μm .

2.2.6 Perforated MEA for Tissue Recording

A prerequisite for extracellular recordings with good signal-to-noise ratio is a tight contact between tissue and the electrodes. Working with acute brain slices, positioning and fixation of the slices on the electrode array are often hardly achieved and the distance between the electrode surface and intact cell layers is too large. To avoid these difficulties, we developed MEAs with numerous openings in the substrate (Figure 2.6). By applying negative pressure to these openings from the bottom side it is possible to position and fixate the slices on the electrode side of the MEA substrate. Negative pressure also enhances the contact between tissue and electrodes and therefore the magnitude of extracellular recorded signals is enhanced. The evoked potentials from acute brain slices recorded with this new MEA reach up to 3 mV_{P-P} (preliminary data). Additionally, the openings can be used to perfuse the slice from the bottom side.

2.3 The MEA60 System

The MEA60 System was originally introduced in 1996 by MULTI CHANNEL SYSTEMS (MCS) and many researchers throughout the world are using the system with a variety of biological preparations and for diverse applications. For a more detailed description and applications with the MEA60 system we refer to various chapters in this book. The main components are described briefly, inasmuch as in-depth information about the system has been published and can be found elsewhere (www.multichannelsystems.com).

The 60-channel amplifier has a compact design (165 \times 165 \times 19 mm), and due to the surface-mounted technology (SMD) of pre- and filter amplifiers the complete

electronic circuit and amplifier hardware was built into a single housing. This ensures optimal signal-to-noise ratio of the recording, because no further cables are necessary other than a single SCSI-type cable connecting the amplifier to the data acquisition card. This results in an overall low noise level of the complete amplifier chain ($\times 1200$, 12-bit resolution, 10 to 3 kHz) of $\pm 3 \mu\text{V}$, which is well within the ± 5 to $10 \mu\text{V}$ noise level of a MEA TiN electrode. Given the low noise of the recording system single units in the lower range of 20 to $30 \mu\text{V}$ can be readily detected (Granados-Fuentes et al., 2004).

Standard PC technology is used as the backbone of high-speed multi-channel data acquisition. The data acquisition card is based on PCI-bus technology and allows the simultaneous sampling of up to 128 channels at a sampling rate of 50 kHz per channel. Three analog channels and a digital I/O port are accessible, allowing the simultaneous acquisition of analog data such as current traces from a patch clamp amplifier or temperature together with the MEA electrode data. The digital I/O port features trigger IN/trigger OUT functionality. This is an important feature when, for instance, a stimulator is set up to elicit a stimulation pulse to one or more MEA electrodes once a physiological parameter such as the amplitude of a field potential or the spike rate has reached a certain and user-defined threshold. This circuit allows for recurrent feedback stimulation in the system, most notably used in studies revealing developmental properties in neuronal networks (DeMarse et al., 2001; Eytan et al., 2003; Bakkum et al., 2004).

Historically, electrophysiologists are used to standard 19-in. hardware racks where they can plug in amplifiers, oscilloscopes, filters, and so on. Usually this results in lots of cables and wiring prone to catch up noise. Hence the goal was to create a virtual and purely software-based rack with the most common instruments implemented in a digital way. In essence, if one starts to think about software for multi-channel data handling and analysis, what comes immediately to one's mind is the amount of data. Given a 50 kHz sampling rate and 128 channels, several gigabytes of raw data could be acquired in only one hour of recording. Thus the software was actually designed to not get what you see. On the contrary, the data to be recorded is strictly defined by the user, and so is the content of the various oscilloscope-like displays.

The concept of data streams is the core concept of the MC_Rack software. Here, tools can be chosen for displaying data, for digital filtering, for extracting spikes out of raw data, for analyzing the slope/amplitude of an evoked response, and/or calculating the spike rate. They can be used independently of each other, and multiples of the same instrument can be implemented and always stay independent, creating their own data streams. Each time you plug in an instrument in the virtual rack a new data stream is created. These data streams and the MEA electrode channels can now be independently selected and shown on the monitor and/or stored on the disk. Thus the user has full flexibility in terms of what he or she wants to see on the screen and what should be stored on the hard disk. In this way data reduction is achieved and only the important information is stored.

2.4 Multi-Site Stimulation and Artifact Suppression

A common problem in MEA stimulation is to address several MEA electrodes in parallel to deliver a current or voltage pulse to the tissue while retaining the recording properties of the MEA electrodes. Although a few custom-made solutions have been presented (Jimbo et al., 2003; Wagenaar and Potter, 2004), a commercial system readily available to the public has only recently been introduced by MCS. The MEA1060-BC amplifier in combination with the MEA_Select software enables the user to address any of the available MEA electrodes as stimulation sites simply by mouse-click. Thus, one, ten, or even all sixty MEA electrodes can be selected for stimulation. Two distinct stimulation patterns can be fed into the amplifier and readily distributed among the MEA electrodes.

Moreover, in order to retain the recording properties of the MEA electrodes selected for stimulation an electronic Blanking Circuit (BC) has been incorporated into the amplifier. This blanking circuit utilizes electronic switches to actively decouple all MEA electrodes from the main amplifier input stage during the time course of stimulation. The ON and OFF states of the switches are driven by the rising and falling phase of a TTL pulse which is supplied by the stimulator and simultaneously fed into the amplifier. The total time the switches need to be active depends on the actual stimulus strength and waveform. The user can define the time for activating the switches in the MEA_Select software. Although artifact suppression at nonstimulated MEA electrodes retains the recording property less than 1 msec past stimulation, the stimulated MEA electrodes need more time to discharge, and even in the case of using biphasic pulses in current mode to actively discharge a MEA electrode, it was shown that it takes more than 1 msec before the stimulated MEA can be used again for recording. Wagenaar and Potter (2004) reported the recording of spike activity 40 msec to 160 msec past stimulation on stimulated MEA electrodes. In our hands we did observe similar values but we strongly emphasize that more complicated stimulation patterns other than simple square wave pulses may lead to a reduction in discharge time, rendering the MEA electrodes for recording on a much faster time scale. Wagenaar et al. (2004) have also studied current and voltage square wave stimulation patterns in detail. They argue that although the negative phase of a current pulse is more effective than the positive flank in eliciting a biological response, a positive then negative going controlled voltage pulse is even more effective (Wagenaar et al., 2004). However, stimulation patterns other than biphasic square wave patterns have not been investigated.

In general, the blanking circuit is built into a DC-coupled headstage with a gain of $\times 50$, and a filter amplifier with a gain $\times 20$ is added after the headstage. Thus a total amplification similar to the standard MEA1060 amplifier is achieved. A schematic drawing of the blanking circuit in the headstage is depicted in Figure 2.7.

In order to provide a real-time feedback approach to MEA recording a new four- and eight-channel stimulator has been developed. Here a 12-Mbps fast download via USB provides an instantaneous stimulus sequence to selected MEA electrodes.

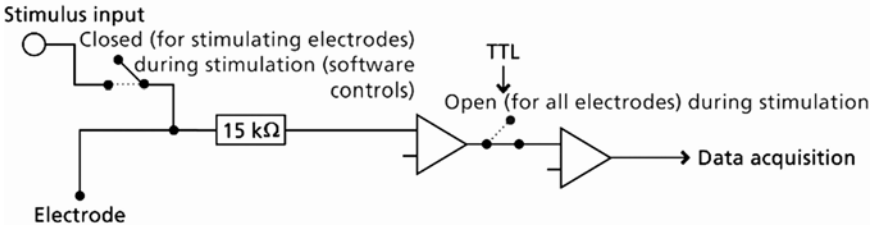
Switch positions during recording and stimulation

FIGURE 2.7. The diagram shows the principal operation of the blanking circuit. A TTL pulse operates the opening and closing of electronic switches to actively decouple the preamplifiers in the headstage off the main filter amplifier circuit.

Even more, once a particular stimulus sequence has been preloaded to the stimulator and waits for a trigger to be sent to the MEA, a real-time feedback can be achieved, because the time necessary to send a preloaded stimulus sequence to the MEA electrodes is 40 μ s at most. The online capability of the new stimulator series allows a continuous alteration of the stimulus patterns on all channels independently, making it ideal for arbitrary waveforms to be used for stimulating a neuronal network on a MEA through selected stimulation sites.

2.5 Up-Scaling MEA Systems

The demanding necessity in basic research and pharmaceutical applications to record from more than one MEA simultaneously has posted us to develop a scaleable MEA60 system. In essence, up to four amplifiers can now be hooked up to a single computer and 120 out of a potential 240 MEA electrodes can be recorded. This is particularly useful if statistical questions are being addressed in terms of network activity studying circadian rhythms (Van Gelder et al., 2003; Granados-Fuentes et al., 2004), or applying compounds to see if the substance causes a similar effect in all four MEA preparations. Because automation is a clear and defined goal of MCS, developments are under way to enhance automation of recording from multiple MEAs. In particular, compound application and data analysis as well as the addition of flag conditions, for instance, the question if a response is stable over time, will be automated to enhance throughput in the pharmaceutical industry.

2.6 Outlook and Conclusions

Remarkable progress in MEA recording has been made over the last five years or so, both in hardware design and software features. However, customer feedback always results in new ideas and approaches to a more sophisticated and integrated

system. There are at least two important routes to be taken in the future. First, 60 electrodes seem a lot, but on the other hand this results in a reduced spatial resolution. As an example, Current Source Density (CSD) analysis is a popular analytical tool to define active current flow into a cell caused by synaptic activation (current sinks) and passive recurrent flow due to the basic law of closed current loops (current sources). A one-dimensional CSD analysis requires a constant conductivity throughout the medium in order to yield meaningful results. The greater the distance between two recording sites the greater is the potential error in estimating the conductivity values. Thus the closer the recording sites the better the result of a CSD analysis will be. Hence the high-density MEA will lead to a better estimation of current sinks and sources while at the same time recording over a wider range will be achieved compared to a MEA with 60 electrodes with the same interelectrode distance.

Secondly, with the number of recording channels increasing a new concept of data acquisition and transfer is needed and by the same token portability is a debated issue. The general concept is to amplify and digitize the data streams directly in the amplifier housing. Then the USB port will be used for a fast data transfer directly to the personal computer. In general, a lab-in-a-box MEA system will comprise a new hardware and software concept which, in our hands, has at least these advantages: (1) transferring digital data, even over a longer distance, is much less error prone than transferring amplified analog data; (2) utilizing the USB port allows the use of high-end laptop computers, making this system truly portable; and (3) incorporating the stimulator and blanking circuit into the MEA system will provide additional sophistication and user-friendliness. A single box then will incorporate all of the functionalities which up to now are separated and only available by distinct standalone products. Thus this new system will provide a ready-to-go portable MEA recording and stimulation workstation, in particular when MEA applications are increasingly developed as multi-recording and stimulation assays used for drug screening in the pharmaceutical industry (Stett et al., 2003).

To conclude, the basic foundations of extracellular stimulation and recording have led to new concepts in multi-channel MEA recording in basic research and the pharmaceutical industry. Several new MEA layouts are now readily available and the first important steps have been made to provide standardized commercial systems, so that users can communicate and form a platform to discuss their results based on an established technology, similar to patch clamp approaches. Nevertheless, more sophistication is needed and this will result in portable systems using MEA with more electrodes, giving rise to a higher spatial resolution and improved data collection and analysis.

References

- Bakkum, D.J., Shkolnik, A.C., Ben-Ary, G., Gamblen, P., DeMarse, T.B. and Potter, S.M. (2004). Removing some 'A' from AI: Embodied Cultured Networks. In: Lida, F., Steels, L., and Pfeifer, R. eds., *Embodied Artificial Intelligence*, Springer-Verlag, Berlin.

- Buitenweg, J.R., Rutten, W.L., and Marani, E. (2002). Modeled channel distributions explain extracellular recordings from cultured neurons sealed to microelectrodes. *IEEE Trans Biomed Eng.* 49: 1580–1590.
- Buitenweg, J.R., Rutten, W.L., and Marani, E. (2003). Geometry-based finite element modeling of the electrical contact between a cultured neuron and a microelectrode. *IEEE Trans Biomed Eng.* 50: 501–509.
- DeMarse, T.B., Wagenaar, D.A., Blau, A.W., and Potter, S.M. (2001). The neurally controlled animat: Biological brains acting with simulated bodies. *Autonomous Robots* 11: 305–310.
- Egert, U., Heck, D., and Aertsen, A. (2002). 2-Dimensional monitoring of spiking networks in acute brain slices. *Exp Brain Res.* 142: 268–274.
- Eytan, D., Brenner, N., and Marom, S. (2003) Selective adaptation in networks of cortical neurons. *J Neurosci.* 23(28): 9349–9356.
- Eytan, D., Minerbi, A., Ziv, N.E., and Marom, S. (2004). Dopamine-induced dispersion of correlations between action potentials in networks of cortical neurons. *J Neurophysiol.* 92(3): 1817–1824.
- Fromherz, P. and Stett, A. (1995). Silicon-neuron junction: Capacitive stimulation of an individual neuron on a silicon chip. *Phys Rev Lett.* 75: 1670–1673.
- Granados-Fuentes, D., Saxena, M.T., Prolo, L.M., Aton, S.J., and Herzog, E.D. (2004). Olfactory bulb neurons express functional, entrainable circadian rhythms. *Eur J Neurosci.* 19(4): 898–906.
- Gross, G.W. (1979). Simultaneous single unit recording in vitro with a photoetched laser deinsulated gold multimicroelectrode surface. *IEEE Trans Biomed Eng* 26(5): 273–279.
- Haemmerle, H., Egert, U., Mohr, A., and Nisch, W. (1994) Extracellular recording in neuronal networks with substrate integrated microelectrode arrays. *Biosens Bioelectron.* 9(9–10): 691–696.
- Jimbo, Y., Kasai, N., Torimitsu, K., Tateno, T., and Robinson, H.P. (2003). A system for MEA-based multisite stimulation. *IEEE Trans Biomed Eng.* 50(2): 241–248.
- Molina-Luna, K., Buitrago, M.M., Schulz, J.B., and Luft, A.R. (2004). Thin-film microelectrode array for motor cortex mapping. Progr. Nr. 190.24.2004 Abstract/Itinerary Planner, Washington, DC, *Soc Neurosci* 2004.
- Nisch, W., Bock, J., Egert, U., Haemmerle, H., and Mohr, A. (1994) A thin film microelectrode array for monitoring extracellular neuronal activity in vitro. *Biosens Bioelectron.* 9(9–10): 737–741.
- Potter, S.M. (2001). Distributed processing in cultured neuronal networks. In: Nicolelis, M.A.L. (ed.), *Progress in Brain Research, Vol. 130: Advances in Neural Population Coding*, Elsevier Science B.V., pp. 49–62.
- Segev, R. and Berry II, M.J. (2003). Recording from all of the ganglion cells in the retina. *Soc Neurosci Abstr.* 264: 11.
- Stett, A., Barth, W., Weiss, S., Haemmerle, H., and Zrenner, E. (2000). Electrical multisite stimulation of the isolated chicken retina, *Vision Res.* 40: 1785–1795.
- Stett, A., Egert, U., Guenther, E., Hofmann, F., Meyer, T., Nisch, W., and Haemmerle, H. (2003). Biological application of microelectrode arrays in drug discovery and basic research. *Anal Bioanal Chem.* 377(3): 486–495.
- Tehovnik, E.J. (1996). Electrical stimulation of neural tissue to evoke behavioral responses. *J Neurosci Methods.* 65: 1–17.
- Thomas, C.A. Jr, Springer, P.A., Loeb, G.E., Berwald-Netter, Y., and Okun, L.M. (1972). A miniature microelectrode array to monitor the bioelectric activity of cultured cells. *Exp Cell Res.*, Volume 74(1), pp. 61–66.

- Van Bergen, A., Papanikolaou, T., Schuker, A., Moeller, A., and Schlosshauer, B. (2003). Long-term stimulation of mouse hippocampal slice culture on microelectrode array. *Brain Res Protoc.*, 11(2): 123–33.
- Van Gelder, R.N., Herzog, E.D., Schwartz, W.J., and P.H. Taghert (2003). Circadian rhythms: In the loop at last. *Science* 300: 1534–1535.
- Wagenaar, D.A., and Potter, S.M. (2004). A versatile all-channel stimulator for electrode arrays, with real-time control. *J Neural Eng.* 1: 39–45.
- Wagenaar, D.A., Pine, J., and Potter, S.M. (2004). Effective parameters for stimulation of dissociated cultures using multi-electrode arrays. *J Neurosci Methods* 38(1–2): 27–37.
- Wise, K.D. and Angell, J.B. (1975) A low-capacitance multielectrode probe for use in extracellular neurophysiology. *IEEE Trans Biomed Eng.* 22(3): 212–219.

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