REVIEW

The potential of microelectrode arrays and microelectronics for biomedical research and diagnostics

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Abstract Planar microelectrode arrays (MEAs) are devices that can be used in biomedical and basic in vitro research to provide extracellular electrophysiological information about biological systems at high spatial and temporal resolution. Complementary metal oxide semiconductor (CMOS) is a technology with which MEAs can be produced on a microscale featuring high spatial resolution and excellent signal-to-noise characteristics. CMOS MEAs are specialized for the analysis of complete electrogenic cellular networks at the cellular or subcellular level in dissociated cultures, organotypic cultures, and acute tissue slices; they can also function as biosensors to detect biochemical events. Models of disease or the response of cellular networks to pharmacological compounds can be studied in vitro, allowing one to investigate pathologies, such as cardiac arrhythmias, memory impairment due to Alzheimer's disease, or vision impairment caused by ganglion cell degeneration in the retina.

Keywords Biochips · Biosensors · Electroanalytical methods · Microelectrode array · CMOS

Introduction

The growing importance and increasing sophistication of biomedical technology is leading a trend toward the

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diagnosis and study of disease on the microscale. While well-established methods in electrophysiology, such as the electrocardiogram (ECG) and electroencephalogram (EEG), are regularly used to monitor the health of patients and in models of disease, there is an increasing need for methods that measure the electrical activity and biochemistry of tissue in ever greater detail. In recent years, rapid advances in complementary metal oxide semiconductor (CMOS) technology have made construction of circuits on a microscale possible. This technology provides information about electrophysiological and biochemical events that occur at the cellular or even molecular level can be obtained.

Planar CMOS microelectrode arrays (MEAs) are the focus of this review, as they are ideally suited for the study of complex cellular networks and sensitive molecule detection in vitro. Such technology is crucial in applications such as pharmacological drug screening and high-throughput systems for electrophysiological testing. Furthermore, such a system is invaluable in basic research, where a complex in vitro system can be used to examine network behavior in cell populations. CMOS technology has the advantage of being robust, straightforward to use, and it can yield immense amounts of data from biological systems in vitro.

Electrophysiology and multielectrode arrays

The vital processes in the human body are regulated by the activity of electrogenic cells that are connected in networks. Some examples of such activity are: information processing and neurotransmission between cells in the brain; light-driven responses transmitted through retinal ganglion cells; the synchronized beating of cardiomyocytes in the heart.

Electrogenic cells essentially behave as signal receivers and generators, conveying information from one part of the body or organ to another via intercellular transmission. Cellular signals originate in the following manner: each cell has a concentration gradient of ions across its membrane, which means that there is an electrochemical potential difference across the membrane, called the membrane potential. A transitory alteration of the membrane potential is caused by the acceptance and release of ions across the cell membrane, causing the number of ions in the extracellular environment—and therefore the local charge density—to change. When the membrane potential becomes more positive and reaches a threshold value greater than its normal resting membrane potential, the cell depolarizes rapidly, causing an action potential, followed by a repolarization back to baseline.

In the field of electrophysiology, there are two principal methods by which the electrical activity of electrogenic cells can be measured: intracellular and extracellular. Intracellular electrophysiologic activity of the cell is detected by the patch clamp device; this is a device, which features an electrode that is inserted into the cell, and a second electrode that, e.g., can be sealed to a small region of the cell and measures the flux of ions across the membrane [1, 2]. There are multiple patch clamp configurations (single ion channel, whole cell, etc.) and there are also robotically controlled multi-patch clamp setups that can patch several cells simultaneously [3]. External microtransducers are used to measure the extracellular electrophysiological activity, which occurs outside of the cell membrane [4–14]. Microtransducers measure the concentration of ions in their vicinity, which changes according to the activity of the cell. Upon the occurrence of electrical activity of the cell, a so-called action potential, ions, mostly sodium and potassium ions, travel across the cell membrane in and out of the cell. These moving ions generate an electric field, which can directly influence the open-gate region of a field-effect transistor [15, 16], or which can be recorded by means of metal microelectrodes [17–21], as shown in the schematic in Fig. 1. This enables the measurement of the extracellular voltage or current that is produced by the cell when it undergoes an action potential. Additional methods that indirectly indicate the voltage change of a cell include optical measurements using voltage-sensitive or fluorescent dyes [22–24].

Measurement of the simultaneous and interdependent activity of electrogenic cells is crucial, since the cells respond to a complex set of environmental and contextual stimuli. It is therefore desirable to have the capability to measure the behavior of many cells simultaneously to reveal network characteristics and, at the same time, to have the possibility to conduct measurements at high spatial resolution, ideally subcellular resolution, to reveal details of
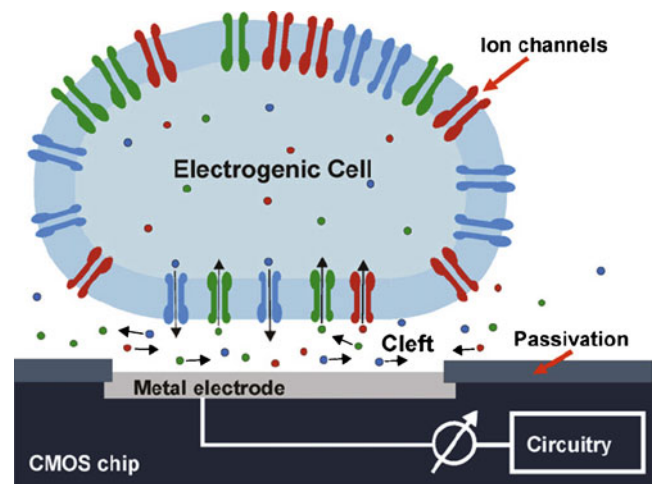
Fig. 1 Schematic of a cell in close proximity to an example planar microtransducer (open-gate transistor/electrode). The displayed cell features ion channels; ions that move through these channels generate an electric field or voltage change that is recorded by the microtransducer [25]

cellular signaling. The previously mentioned techniques of directly measuring the electrophysiological signal are limited in this respect; to overcome these limitations, a multielectrode array (MEA) or multitransducer array may be a more suitable device. An MEA is a two-dimensional grid of biocompatible microtransducers embedded in an insulating surface, such that each microtransducer is electrically independent of its neighbors. Each transducer is connected to a differential amplifier, which measures voltage or current with respect to a common reference. Thus, an MEA provides a regular spatial sampling of the voltage or current signals across a two-dimensional plane. A high-density (HD) MEA is a two-dimensional array of densely packed transducers that can measure the responses from many cells simultaneously; depending on the density and capabilities of the array and the cell density, signals can be acquired simultaneously from all cells within a culture or slice. Finally, it should be noted that in contrast to methods such as patch clamping, cells can be maintained for up to several months so that long-term studies can be conducted.

While it is useful to have the ability to record the activity of cells, there are some instances in which intrinsic activity alone does not provide sufficient information; stimulation of the slice or culture is necessary to study certain aspects of cellular network behavior or activity; for example, phenomena such as memory formation in brain tissue or pacemaking in the heart often require an external stimulus. To provide this capability, some MEA devices have bidirectional functionality, meaning that they can not only record activity, but can deliver either a current or voltage stimulus, thereby eliciting a response in a population of electrogenic cells. These devices can be used to stimulate a single cell or small number of cells with one or more

electrodes. The subsequent cell population response can then be recorded with the non-stimulating electrodes [26–29]. Likewise, chemical concentrations and gradients provide a wealth of information about cell processes and communication. Two- or three-electrode measurements can be made by using MEAs, which detect the presence of electroactive or non-electroactive neurotransmitters or other relevant ions or molecules [30].

The MEA as a device for electrophysiological recording has been in existence for several decades and has undergone several improvements throughout this time. One of the early planar MEAs was described in a 1972 publication by Thomas et al. (Fig. 2), who aimed to record electrical activity from cells using a noninvasive device, allowing them to address questions involving plasticity and electrical interaction among cells. The array comprised 15 gold electrodes with 100 μm spacing; experiments with dorsal root ganglion cells were carried out [31]. A similar MEA device was published 5 years later by Gross et al. [32], while the first successful recordings from dissociated neurons were reported by Pine in 1980 [33]; in the latter case, an MEA with two parallel rows of 16 planar gold electrodes measuring 10×10 μm^2 with a 250-μm spacing was developed.

An alternative approach to the use of metal electrodes was presented in 1970 by Bergveld [35]. He developed an open-gate field-effect transistor (FET) in order to measure ionic concentrations in a solution. This device, called ISFET (ion-sensitive FET), relies on the same working principle as a normal metal oxide semiconductor FET

(MOSFET); however, the current flow is regulated (gated) by a reference electrode and the concentration of ions in the solution (Fig. 2) instead of a metal gate electrode (MOSFET). Bergveld successfully used ISFETs to measure ions fluxes around a nerve [36]. Similarly, in 1981 Jobling et al. reported a nine-electrode MEA in which the gates of a FET on a silicon chip were used as electrodes [37]. The firing neurons were located close to the exposed gate of the transistor, which behaved as a sensor; changes in the extracellular potential directly modulated the current flowing through the transistor. Successful recordings from hippocampal slices with high signal-to-noise ratio were demonstrated.

CMOS technology

There are a variety of MEAs available for electrophysiological measurements. In most commercially available systems (e.g., Multi Channel Systems GmbH, Germany; Panasonic Inc., Japan; Plexon Inc., USA), passive metal electrode arrays are employed. These devices usually consist of 64 electrodes and are aligned on a glass or silicon substrate with externally situated signal recording and filtering components. However, transducers can also be realized by using standard integrated circuit or complementary metal oxide semiconductor (CMOS) technology. There are three primary advantages to using this technology: (1) connectivity: on-chip multiplexing means that many electrodes can be addressed, allowing for measurements at high spatiotempo-

Fig. 2 *Top*: diagrammatic cross section of microelectrode array forming the floor of a culture chamber, reprinted from [31]. *Bottom*: schematic representation of a standard metal oxide semiconductor field-effect transistor, MOSFET (**a**) and an ion-sensitive field-effect transistor, ISFET (**b**). Reprinted from [34]
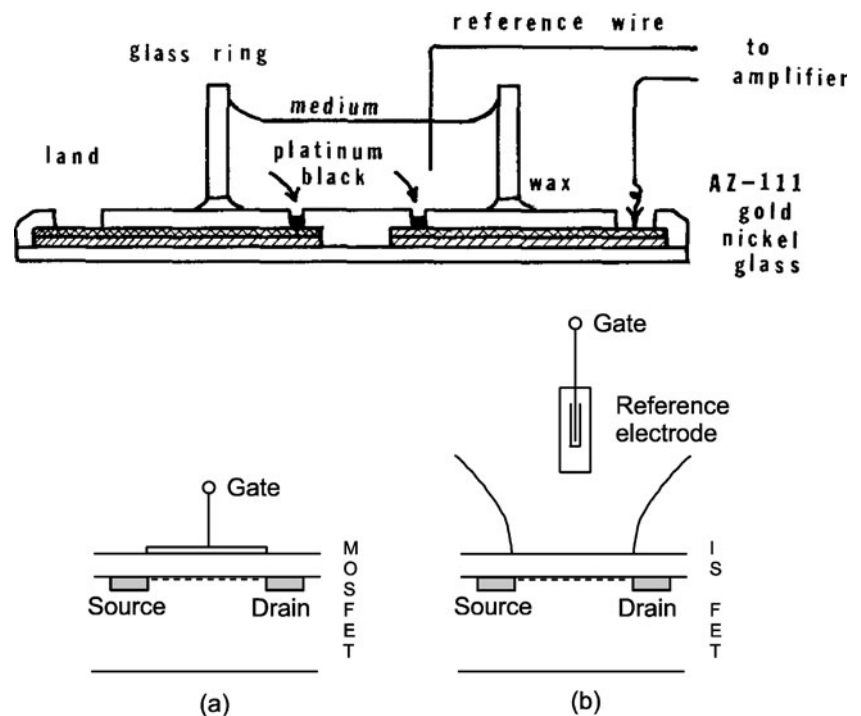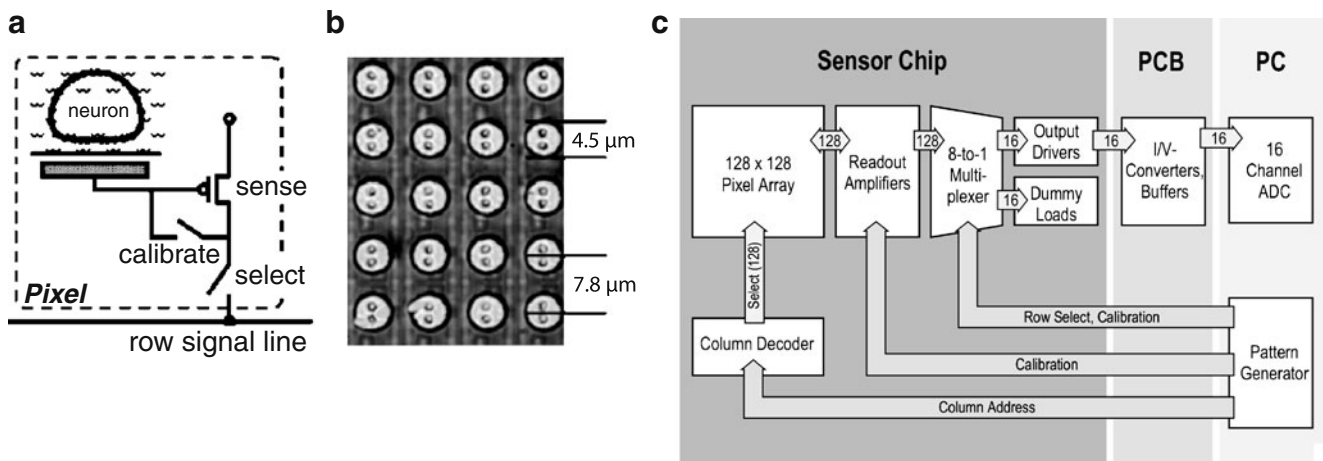
Fig. 3 High-density sensor array with 16,384 pixels based on open-gate field effect transistors on a 1×1 mm^2 area. **a** Pixel schematic. **b** Zoom-in on sensor array. **c** System architecture [40]

ral resolution; (2) signal quality: signal processing circuitry can be located directly below the electrode, facilitating the detection of weak signals through immediate signal conditioning and digitization; (3) ease of use: many functions can be implemented via user-friendly software that communicates with on-chip logic units through a digital interface. Moreover, the use of CMOS technology allows for the realization of small system chips with large numbers of electrodes; arrays of up to 16,384 electrodes on 6 mm by 6 mm chips have been reported [38–42].

High-density microelectrode arrays realized in standard CMOS technology offer the potential to perform recordings at single-cell or even subcellular resolution [42]. When designing such systems, a compromise between noise performance and spatial resolution must be made. To achieve high spatial resolution, small electrodes are preferred; unfortunately, thermal noise is inversely correlated to electrode size. A further impediment is that, because of spatial constraints, filters and amplifiers with large noise-reducing capacitors cannot be used.

Another issue that must be taken into account with CMOS MEAs is the packaging of the chip. The standard metal used in CMOS technology is aluminum, which is a neurotoxin, so it must not come into contact with cell cultures. Moreover, electronic circuits are corroded and destroyed by aqueous salt solutions, so the chips themselves need to be protected from the very things they measure.

A device relying on FET transducers in CMOS technology was developed at the Max Planck Institute for Biochemistry, Germany, by the group of P. Fromherz [40, 43]; this CMOS MEA featured 16,384 open-gate FETs at a pitch of 7.8 μm (16,000 sensors/mm^2), as shown in Fig. 3.

The array was composed of 128×128 pixels, each comprising three transistors for voltage sensing, pixel selection, and calibration to compensate for transistor mismatch and leakage. The sensor chip also incorporates a column decoder to control each pixel, a readout amplifier for each of the 128 rows, and an 8-to-1 multiplexer to drive the outputs of the amplifiers. The generated output currents are transferred to a set of off-chip current-to-voltage converters whose output is digitized by 16 analog-to-digital converters (ADCs). In order to maintain high spatial resolution, a small pixel size must be balanced against the need for circuits that are sufficiently large to reduce signal noise, which can range from 70 to 250 μV$_{RMS}$ [38, 40].

CMOS-based devices relying on planar metal electrodes also have been devised: an MEA with integrated multiplexers and in-pixel amplifiers that can simultaneously record from 4,096 aluminum or gold electrodes was presented by Berdondini et al.; the electrodes were constructed with a 40-μm pitch, which is equivalent to approximately 500 electrodes/mm^2 [39, 44–46]. The system is based on the active pixel sensor (APS) concept, originally designed for image sensors; it is composed of a 64×64 pixel or electrode array with a pixel area of 40×40 μm^2. Data streams can be collected from the whole array at 7.7 kHz, but it is also possible to select specific regions of interest and to record at higher temporal resolutions of up to 120 kHz [44, 45]. In this design, noise-optimized and spatially optimized operational transconductance amplifiers consisting of only five transistors have been employed. The noise of the system is approximately 10–20 μV$_{PP}$. The chip also includes filtering circuits, high-speed addressing logic, and a field-programmable gate-array interface, which provides dynamic analog-to-digital (AD) conversion as well. The system is linked to a computer running custom software for data acquisition and analysis. A chip micrograph, the overall system overview, and the amplifier schematics are shown in Fig. 4.

A CMOS chip with stimulation capabilities was presented by the group of Kovacs at Stanford [47], using an
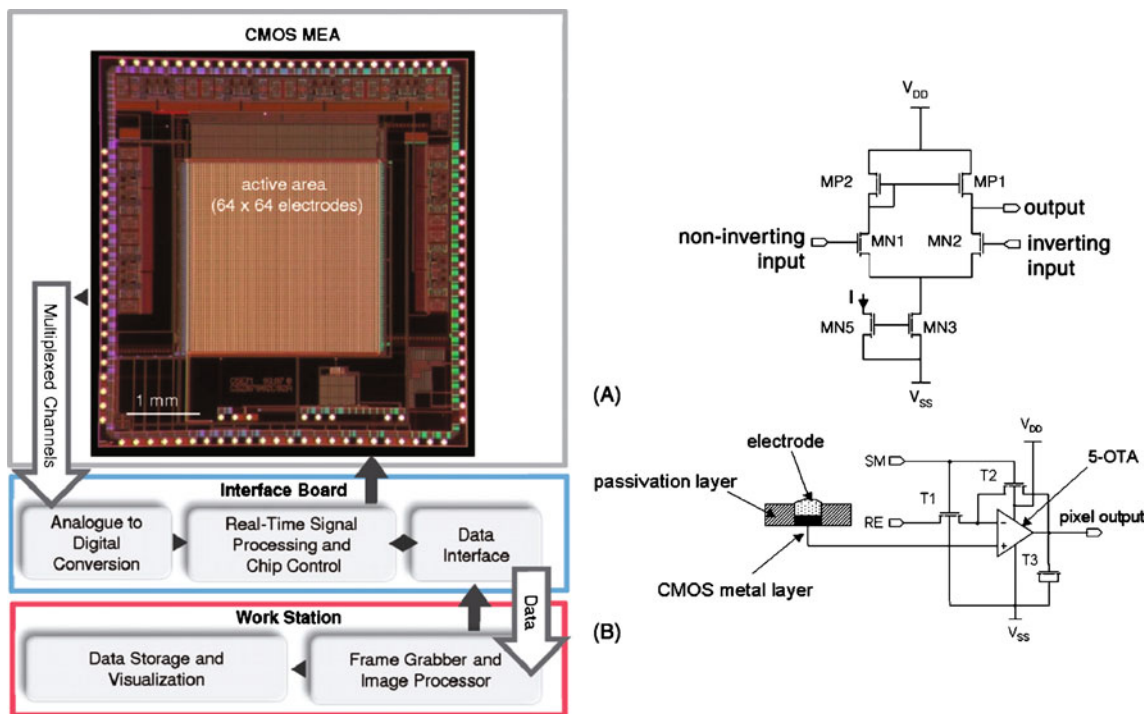
Fig. 4 *Left*: chip micrograph and system overview of the high resolution CMOS-MEA presented in [46]. *Right*: **a** schematic of the in-pixel five-transistor preamplifier. **b** Complete schematic of the in-pixel amplifier (OTA, operational transconductance amplifier). Reprinted from [39]

integrated stimulation electrode outside the recording electrode array. CMOS-based needle arrays featuring stimulation and recording electrodes for insertion into living tissue were reported by Wise and Najafi [5, 48, 49]; these devices for in vivo applications feature multiple electrodes per needle shank and integrated circuitry units, including radio frequency transmission, on the chip base. Several of them can be assembled in 3D electrode arrays.

Monolithic bidirectional CMOS MEAs, which have stimulation and recording capabilities, have been published by Heer et al. [25, 50, 51] and Frey et al. [41, 42]. Both system chips employ planar metal electrodes and are used directly as a substrate for cell and slice culturing or for accommodating acute tissue slices; they include circuitry for stimulation, immediate cell signal modulation, analog-to-digital conversion, and a digital interface, thus allowing a rapid interaction approaching real-time functionality.

The system of Heer et al. includes 128 electrodes and a reference electrode. Each pixel is adjacent to an electrode and contains a band-pass filter, a mode storage unit, a buffer for stimulation; the pixel pitch is 250 μm. The chip also includes a digital control unit in order to provide multiplexing, the electrode selection for stimulation, the resetting of single electrodes and the AD converters, and the interface to the external world. A temperature sensor is included to ensure that electrogenic cells are at the correct temperature. The close proximity of filters and buffers to each electrode offers several advantages: (1) reduced

interference-induced noise at connection lines; (2) a high-pass filter, which reduces offset and drift; (3) a low-pass filter that limits noise bandwidth and prevents aliasing in the multiplexing and analog-to-digital conversion stages. The measured noise of the in-pixel circuitry is 11.7 μV$_{RMS}$, and the total power dissipated is 120 mW. Any arbitrary stimulation configuration can be applied to any subset of electrodes. Moreover, every recording channel can be reset to its initial state in order to suppress stimulation artifacts.

Figure 5 shows the implementation of Frey et al.'s design that achieves high signal-to-noise ratios and high spatial resolution. The system features 11,011 electrodes and an analog switching matrix, located directly underneath the electrode array. This switching scheme is compact, has low-noise characteristics, and allows the routing of an arbitrarily selectable subset of electrodes to 126 readout channels.

In this system, electrodes are small, with a diameter of 7 μm and a pitch of 17 μm. Signal modification circuitry has therefore to be placed outside of the array, where space constraints are no longer a concern. The array area is 2× 1.75 mm^2, which yields a density of 3,150 electrodes/mm^2. The electrode selection can be adapted to the biological sample of interest, while the integrated circuitry can be optimized for noise, which is as low as 4 μV$_{RMS}$. Moreover, the large redundancy of the data obtained from such a multi-data point recording (each neuronal activity is simultaneously recorded by many electrodes because of the
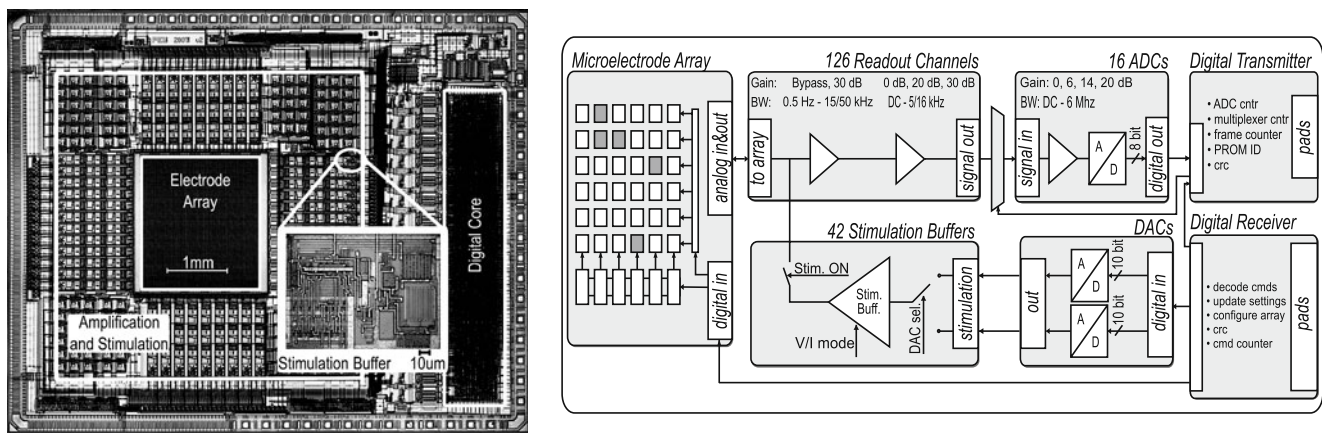
Fig. 5 *Left*: 11,011-electrode CMOS chip micrograph. The electrode array is in the *center*, surrounded by the analog circuitry for filtering, amplification, and stimulation; on the *right side* sits the digital interface. *Right*: block diagram of the on-chip circuitry. Reprinted from [52]

tight spacing) can be used for spike sorting software algorithms that separate action potentials based on shape and occurrence pattern. This system makes it possible to obtain a high spatially and temporally resolved reconstruction of the extracellular activity of a cell or cell population.

A block diagram of the system is depicted in the right side of Fig. 5. The recorded signals are amplified and filtered in three stages, each of which has programmable gain. After the second stage, signals are multiplexed, sampled, and digitized; finally, the data are transferred by a digital interface to off-chip computational machines. The same interface also controls the array configuration and stimulation mode settings. Stimulation is performed by integrated buffers, which have both voltage and current modes for stimulation delivery at an arbitrary electrode subset [52].

Both the Heer and Frey systems were fabricated with standard 0.6-µm CMOS technology; special post-CMOS processing and packaging for operation under physiological conditions were subsequently applied. Electrodes were covered by biocompatible platinum and a four-layer passivation stack of alternating silicon dioxide and silicon nitride was deposited on the chip and opened at the site of the electrodes [50]. Finally, the chips were mounted on a custom-designed printed circuit board (PCB) for long-term culturing.

Biological preparation methodology

The most common biological preparations studied using MEAs are divided into two main categories: acute tissue slices, which are recorded immediately after they are removed from the animal; and cell cultures, which can be further divided into dissociated cell cultures and organotypic tissue cultures. Dissociated cultures are cells whose

relative in vivo positions are no longer preserved, whereas organotypic tissue cultures are slices that are maintained in vitro over a period of time. These variations encompass the spectrum from short-term, functionally preserved tissue slices to long-term organotypic or cell culture preparations.

Several parameters must be taken into consideration when using MEAs as a tool for recording from cells. Most importantly, the neuron–electrode interface must be optimized so that tight coupling between the cells and electrodes is established, maximizing the signal-to-noise ratio. Acute slices, for example, have a layer of dead cells that are damaged during the cutting of the tissue, which introduces a degree of isolation between the active cells and the electrodes. To promote the adhesion of cells or the tissue mass, MEAs are coated with cell-adhesion substrates such as poly-D-lysine, laminin, collagen, and fibronectin [53, 54]. Successful tactics for making recordings from tissue sections utilize, for example, cellulose nitrate or coagulated plasma/thrombin clots to stabilize the slices on the MEA surface [55].

Acute tissue slices, including brain tissue and retina, preserve the structural and functional relationships between groups of cells because there is no opportunity for the cells to alter their relative formation from the initial in vivo state. Acute slices are cut at a thickness ranging from approximately 100 to 400 µm, although the maximum distance away from an electrode that a signal can obtained is approximately 100 µm [56]. Some high-density MEAs are capable of recording from as far away as 100 µm, but the signal-to-noise ratio drops off rapidly with distance [57]. Brain slices prepared from mice and rats at postnatal day 6–12 were reported to exhibit optimal cell health and maintained neurogenesis [58].

The major limitation of acute slice preparations is the duration of viability, which is typically up to several hours

following slice preparation. Furthermore, a perfusion system is necessary for the delivery of carbogen gas (95% O_2/5% CO_2) and nutrients, which are required to sustain the physiologic processes of the cells. It must also be considered that inputs originating from diffuse neuro-modulatory systems, which exert effects on neurons via neurotransmitters, are absent in acute slice preparations. To restore the inputs, co-cultures of slices from various brain regions have been used to study effects of neuro-modulators [59].

Dissociated and randomly seeded cell cultures of electrogenic cells, such as neurons or cardiac myocytes, have been well established as biological preparations with MEAs [11, 27, 39, 60, 61] as shown in Fig. 6. Primary neurons are usually isolated from brains of embryonic or postnatal rodents, since these cells exhibit a high degree of plasticity, a characteristic that is required for developing neuronal networks in vitro [62]. The ability to record and stimulate cultured cells has provided unique experimental setups for studying the cellular activity over extended periods of time, ranging from hours to weeks [63, 64]. Moreover, patterned neuronal networks have been used to further increase the number of occupied electrodes [65, 66].

The organotypic tissue slice preparation is the third type of tissue preparation and provides a compromise between the longevity of the cell culture and the in vitro characteristics of the acute slice (Fig. 7). The preparation of organotypic slices is similar to that used for acute slices, except that the cultures must be rotated through liquid medium and the ambient gas during the culturing and maturation phase, which lasts for up to 4 weeks [68]. After several days, the cultures stabilize with high cell viability. Prior to recording, the culture chamber must be removed
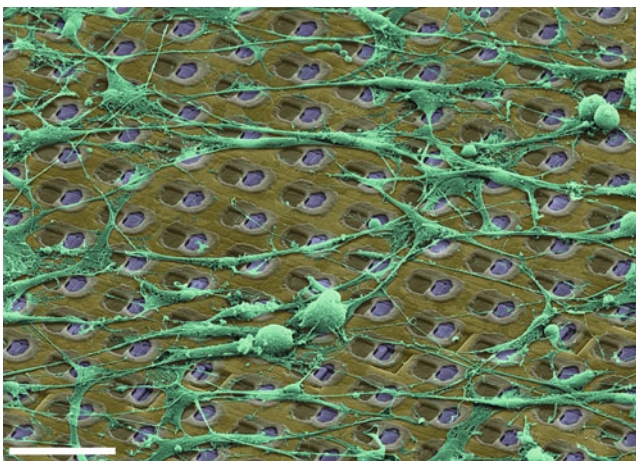
Fig. 6 A scanning electron micrograph with false coloring of chicken dorsal root ganglion neurons on the HD-MEA after 2 days of in vitro culture. Microelectrodes are colored *blue* and neurons are colored *green*; (*scale bar* is 30 μm) [67]

from the cell culture incubator; a slow perfusion system is then used to supply carbogen gas and nutrients.

Numerous studies have involved the administration of pharmacological compounds to organotypic brain slices on MEAs for simulating pathological conditions leading to neuronal death and neurotoxicity. Examples include studies on the use of hippocampal slices cultured on MEAs and the time-course of synaptic responses and neuronal damage by using glutamate receptor agonists, *N*-methyl-D-aspartate (NMDA) and α-amino-3-hydroxy-5-methyl-4-isoxazole-propionic acid (AMPA) [70, 71], as well as the long-term recording of long-term potentiation (LTP) after tetanic stimulation [72, 73].

Diagnostic applications

CMOS technology can provide electrophysiological data at unprecedented spatiotemporal resolution for several applications in basic research, as well as in applied science and industry. As an electrophysiology modality, the CMOS MEA can be considered relatively high throughput, as many data points can be collected from one sample. As already mentioned, longitudinal studies are possible, which offers the possibility to conduct chronic drug exposure studies. As will be described below, the MEA can be used for several applications: here, its potential for research in the cardiac, ocular, and nervous systems as well as its implementation for molecule detection is discussed.

Cardiac system

Arrhythmias are rhythmic disruptions of the heart, which can cause death [74]. A leading culprit for arrhythmia manifestations are arrhythmogenic prescription medications such as antibiotics, antipsychotics, antihistamines, and antiarrhythmics [75], many of which have been taken off the market because of these effects [76]. An increase in the time required for the ventricle of the heart to repolarize—known as the "QT interval"—has been associated with ventricular tachyarrhythmia in patients [77]. The QT interval is a measure of the time between the start of the Q wave and the end of the T wave in the heart's electrical cycle. A prolonged QT interval is a risk factor for ventricular tachyarrhythmia and sudden death.

Ventricular depolarization and repolarization are the result of the complex activities of many cellular membrane ion channels, particularly the calcium and sodium channels. At the cellular level, the action potential duration (APD) of individual cardiomyocytes in vitro is the amount of time required for the cell's membrane to depolarize and repolarize back to resting membrane potential. In a simplified sense, the QT interval of the heart is a

Fig. 7 Organotypic cultures on an MEA. a A 9-day-old organotypic co-culture of entorhinal cortex and dentate gyrus from rats and mice. b Signals recorded using the MEA following stimulation (location of stimulation is marked by asterisk). Each waveform represents the electrophysiologic activity recorded by the corresponding electrode. Dotted lines indicate locations of entorhinal cortex and dentate gyrus [69]
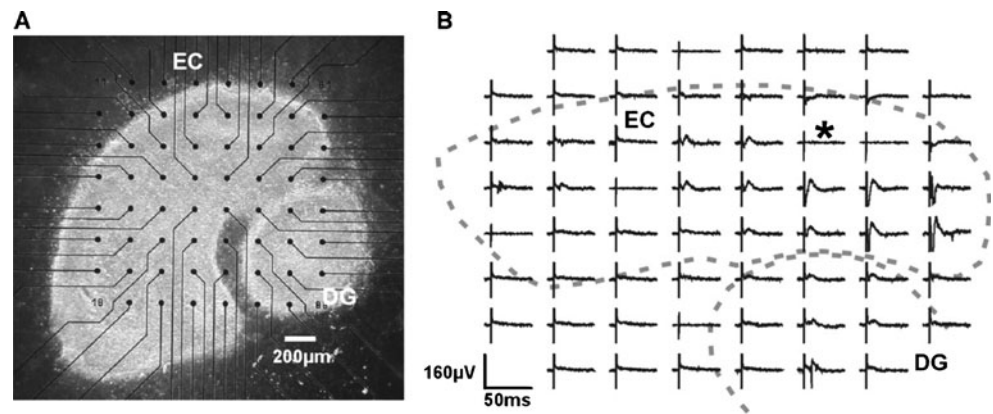
summation of the APDs of individual heart cells (the cardiomyocytes) of the heart's ventricular compartment. It is for this reason that in vitro measures of ADP in heart cells are of relevance as a screen for drug-induced disorders of the heart [19, 78, 79].

While the above-mentioned screening methods are in use regarding the risk of QT prolongation associated with certain drugs, they are laborious and costly. An MEA, on the other hand, can provide electrophysiological information about the activity of cardiomyocytes on a finer scale, describing microcircuitry of the cardiac tissue, which may lead to a better understanding and characterization of QT prolongation [79], as shown in Fig. 8.

There have not only been several studies in which an MEA was used to record from cultured cardiomyocytes, but

the effects of pharmacological agents have also been investigated [61, 80–82]. Using a 60-electrode array, Stett et al. used antiarrhythmatic drugs quinidine and sotalol and hERG blocker E4031 to show a change in field potential of myocytes of embryonic chicken ventricles [19]. Another group used the same MEA measurement of repolarization in human embryonic stem cell-derived cells using the antiarrhythmic agent sotalol to show prolongation of the APD [83]. Meyer et al. used an MEA1060 system from Multi Channel Systems GmbH, Reutlingen, Germany recording from 60 channels, to characterize the effects of antiarrhythmic agents E4031, amiodarone, quinidine, sotalol, and verapamil on cultured embryonic chicken cardiomyocytes [78, 84]. The results for the first four drugs confirmed their QT-prolonging effects, while verapamil was

Fig. 8 Recordings of human stem cell-derived cardiomyocytes [79]. a Cardiomyocytes on an 8×8 MEA. b Corresponding signals from electrodes of the MEA. c A recording from one electrode channel, shown at a larger timescale
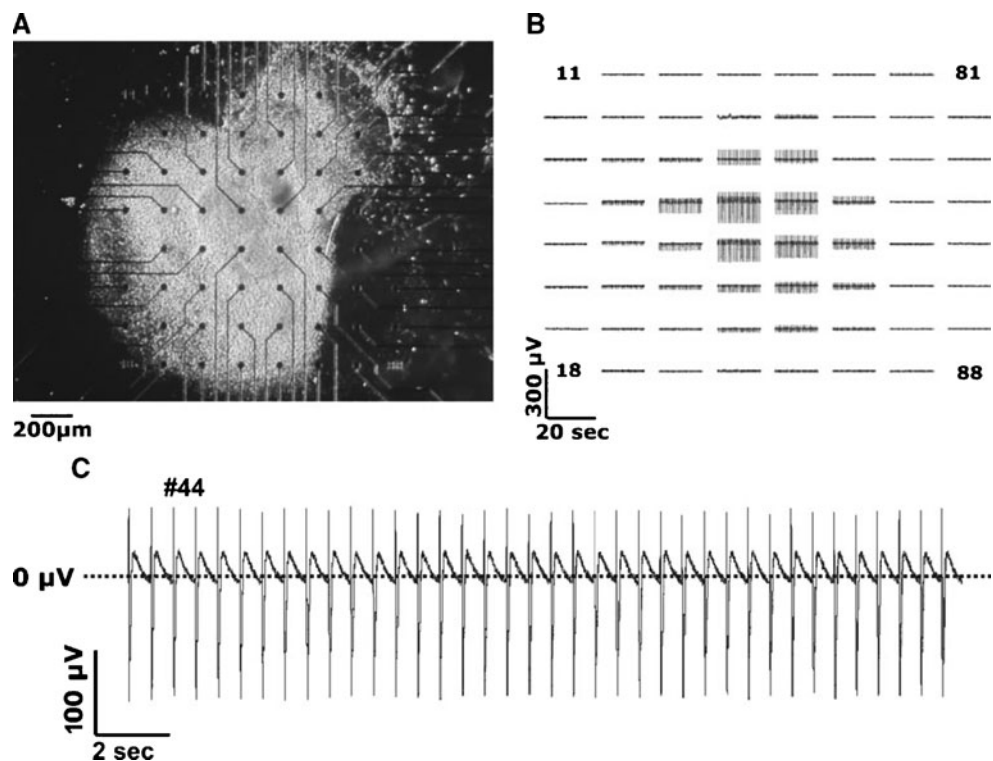
a false positive. The overall successes of these studies show the suitability of MEA systems for the characterization of antiarrhythmic agents.

Cardiac infarctions in patients have been shown to cause a phenomenon called reentry, which is a condition whereby abnormal action potential wavefronts occur in cardiac tissue; this can lead to ventricular tachycardia [85–87]. Hong et al. used optical mapping and MEAs to measure cardiac excitation waves in dissociated cardiac cell cultures. They found that high-density cultures of cardiac cells are able to sustain reentries [88].

Certain types of heart disease and rhythm disturbances cause arrhythmogenic remodeling within the heart, affecting the distribution of gap junction channels within the cardiac tissue [89]; among many effects, the cell coupling is altered [90]. Subtle changes, including action potential propagation speed, can be characterized with an MEA, which is not possible with other recording systems. Using a high-density MEA with a resolution of 17 μm, it was shown that the antiarrhythmic agent lidocaine modified the action potential shape as well as the signal propagation speed [61, 82].

Retina

The retina contains complex circuits of neurons that extract specific features from the visual input, such as changes in light intensity, color variations, and the direction of moving objects [91]. The final output of the retina is computed in the ganglion cell layer and consists of complex spatiotemporal patterns of action potentials that can be recorded with MEA technology [92]. Therefore, MEAs are ideal for accessing the electrodynamics of retinal ganglion cell populations because their cell bodies and axons are aligned in a 2D layer (Fig. 9).

Multisite extracellular recordings showed synchronized activity between retinal ganglion cells [96–98] and demonstrated that specific features of the visual scene are coded by this correlated activity across the retina [93, 99] (Fig. 9); furthermore, pharmacological studies in combination with

Fig. 9 **a** A patch of salamander retina placed over a multielectrode array. Ganglion cell and axon bundles are fluorescently stained with rhodamine dextrane (*green*) [92]. **b** Simultaneously recorded signals from six retinal ganglion cells as the direction of a dark bar near their receptive field centers is reversed [93]. **c** Responses of retinal ganglion cells to electrical stimulation on MEAs [94]. **d** Representation of epiretinal and subretinal implants for visual restoration [95]
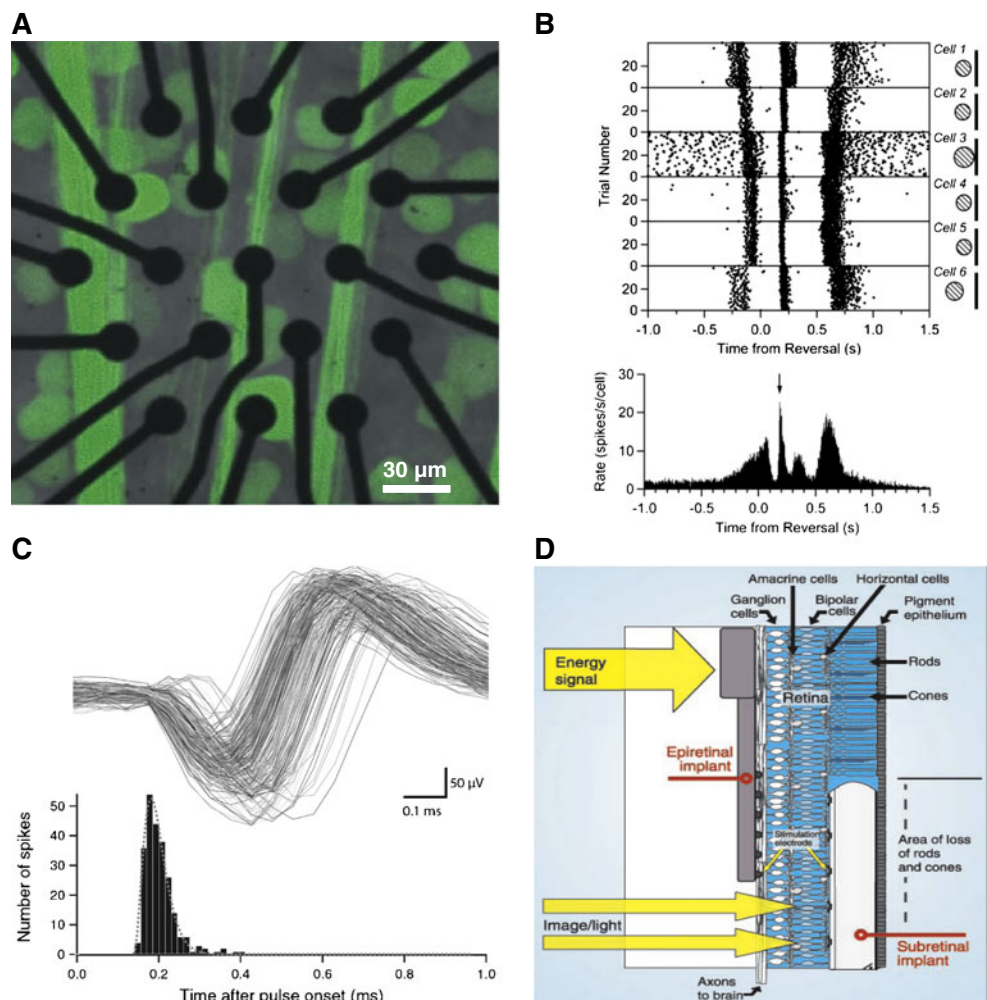
microelectrode array recordings have revealed distinct types of temporal correlations [100]. The majority of these correlations arise from electrical and chemical synapses and cause redundancy in the retinal output [101].

All these studies indicate the potential of MEAs as a fundamental tool for analyzing how retinal populations code visual input in order to communicate with higher brain centers. In addition, MEA technology provides a platform in biomedical research for developing new strategies to cure retinal diseases. Vision loss affects thousands of people around the world [102] and, in most cases, poor vision or blindness is caused by photoreceptor degeneration [103].

Multielectrode arrays have been used to analyze how electrical stimulation evokes spiking activity in retinal ganglion cells [94] (Fig. 9). Such electrical stimulations are essential for developing retinal implants for vision restoration. There are two types of retinal implants currently showing promise in clinical trials: epiretinal implants (on the retina) and subretinal implants (behind the retina), see Fig. 9d. Epiretinal implants sit on top of the retina, directly stimulating ganglia using signals sent from an external camera and power sent from an external transmitter, whereas subretinal implants sit under the retina, stimulating bipolar or ganglion cells from underneath and have provided promising results recently [104]. In the epiretinal approach, the prosthesis adjacent to the ganglion cell layer bypasses the entire retinal circuitry [95].

An alternative approach to restore photosensitivity in the retina is to express genes encoding light sensitive functions in specific retinal neuron subtypes [105]. Microelectrode arrays are a required support for this strategy because they provide a rapid and detailed analysis of the response induced by the expressed gene.

Furthermore, MEA technology is applied in developmental studies of retinal circuits [106] and to analyze the spatiotemporal properties of retinal ganglion cell receptive fields [107]; accurate description of spatiotemporal receptive fields is used to create models predicting the output of specific subtypes of retinal ganglion cells [108].

Commercial MEAs have been routinely used for retina research, nevertheless the electrode density is still too poor to access the rich amount of information coded by the different retinal ganglion cell subtypes. CMOS-based MEAs with high spatiotemporal resolution will be crucial to increase our knowledge of the retinal code and to develop efficient medical application to treat diseases of vision.

Central and peripheral nervous system

Because of its high level of complexity, our understanding of the human brain is still largely a work in progress. Elucidating the various functional circuitry of the brain has been the subject of many studies, yet the disorders that occur in the brain have not been fully characterized. It has been shown that conditions such as Alzheimer's disease (AD) and epilepsy depend on the concerted activity of neural networks. Use of cultures as surrogates for in vivo experiments is contingent on the premise that the "functional units" of the brain are distinct cellular populations [109]. As such, cultured networks of neurons can be considered the "functional unit of functional organization" in the brain [110]. The elucidation of such functional units may be expanded by using the MEA, facilitating the study of brain disorders and pathologies [69].

One of the characteristic symptoms of AD is the impairment of memory function [111]. Although memory mechanisms are still not well understood, two processes, long-term potentiation (LTP) and long-term depression (LTD), are thought to be opposing forces that are responsible for memory storage [112, 113]. Some light has been shed on mechanisms that cause AD: in the cerebral cortices of human subjects with Alzheimer's disease, amyloid beta protein (Ab) oligomers inhibit LTP, enhance LTD, and reduce dendritic spine density in normal rodent hippocampus [114]; at the Alzheimer's Association International Conference on Alzheimer's Disease in 2009, the toxic effects of Ab oligomers were demonstrated by using cultured hippocampal neurons on an MEA, confirming previous data from patch clamp studies [115].

Epilepsy is the most common neurological disorder, affecting 50 million people worldwide [116]. MEA recordings were acquired from pharmacologically induced models of epileptiform activity in rat acute hippocampal slices. Hill et al. [117] used the introduction of 4-aminopyridine (4-AP) and the removal of external Mg^{2+} ions as in vitro models of epilepsy, as shown in Fig. 10. The effects of two anticonvulsant drugs, felbamate and phenobarbital, were assessed on these model platforms; phenobarbital was shown to completely repress all induced epileptic bursting in the slices. The characteristics typically seen in vivo, such as changes in burst duration, frequency, and amplitude, were measured in these slices [117].

For the investigation of pharmacological compounds, cultured neural networks provide a highly sensitive platform. Such a system is stable over the long-term for evoked or spontaneous electrophysiological activity [27, 61, 63]. Furthermore, sensitivities to certain compounds can be regulated by the increase or decrease of receptor expression [118]. It has also been established that cultured neural networks respond to neurotransmitters, blockers, and many pharmacological substances such that in vivo behavior of neurons can be mimicked in vitro [11, 119–122]. For example, bicuculline blocks the main inhibitory neurotransmitter γ-aminobutyric acid (GABA), causing an increased spiking frequency, as does the chloride channel antagonist

Fig. 10 Models of epilepsy in hippocampal slices. a A hippocampal acute slice from an adult rat ($p=30$) mounted on an MEA. *Scale bar* is 200 μm. b, c Recordings of epileptiform bursts in the slice induced by the potassium channel blocker 4-aminopyridine (4-AP) and the absence of Mg^{2+} in extracellular solution [117]. d, e Representative bursts from b and c [117]
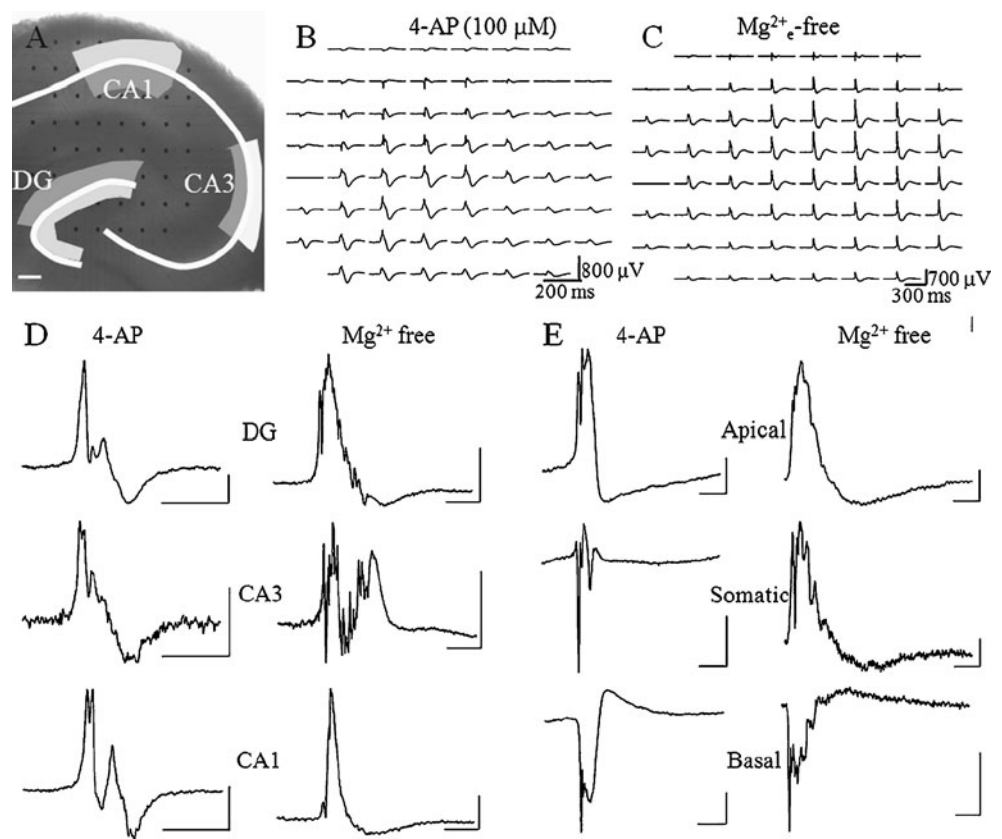
strychnine (Fig. 11). Such cultures are cultured for long-term monitoring of neuronal electrophysiological activity including development, neuronal plasticity, and axonal regeneration [123, 124], all of which may be affected by the introduction of pharmaceutical compounds.

Neurotoxicity assessment studies for new compounds, as per the guidelines of the Organization for Economic Co-operation and Development and European Community, require only in vivo neurobehavioral and neurotoxicity testing. Such testing procedures do not always accurately predict responses in humans, are costly, and require the use of numerous laboratory animals, the number of which could be reduced by the use of in vitro methods, such as described in the preceding paragraph [122]. At the 11th International Neurotoxicology Association Meeting, several in vitro models were discussed [125]. Two groups used primary dissociated cultures from mouse or rat cortex and spinal cord neuronal networks to study spontaneous and evoked neuronal activity. The effect of several pharmacological agents on spontaneous activity of cultured neural networks was assessed. A standard neurotoxicant, trimethyltin chloride, had a dose-dependent effect in mouse central nervous system (CNS), specifically the spinal cord and auditory cortex [121]. The group established five
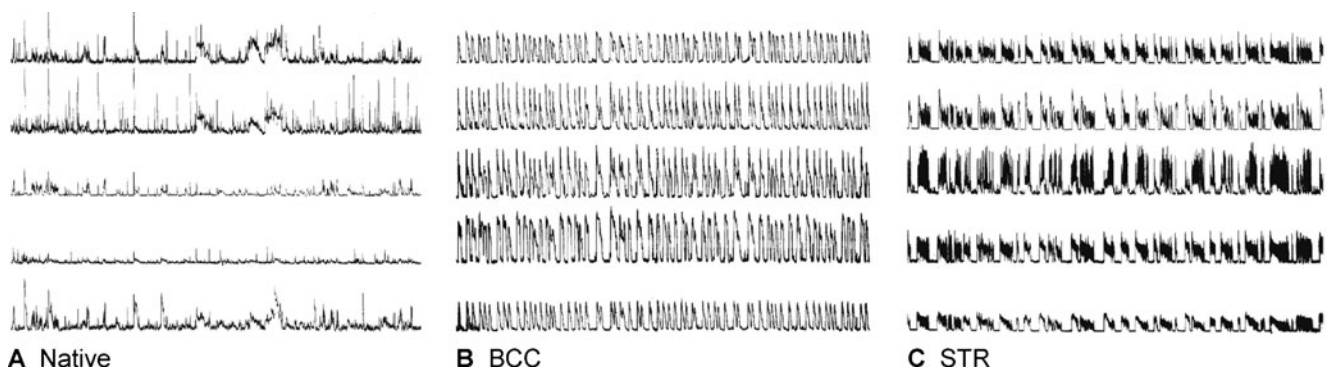
Fig. 11 Recordings from five neurons in spinal cord cultures. a Control recordings. b GABA receptor blockage by bicuculline (BCC) and c chloride channel antagonist strychnine (STR) [122]

distinct drug-induced oscillatory activity states by blocking common neurotransmitter receptors. This study created "fingerprints" of characteristic responses to known and unknown substances, which can be used to evaluate responses to drugs [122, 125, 126].

The peripheral nervous system has also been the focus of several studies. Czarnecki et al. used MEAs to study the repetitive patterns of neural activity in spinal cord that are responsible for behavior such as locomotion; they investigated neuronal networks of cells from the vertebrate spinal cord, and coupling properties were elucidated by using pharmacological methods. Bursting network activity and intrinsic activity in these cultures were modulated by 5-hydroxytryptamine (5-HT, serotonin) and the cholinergic agonist muscarine [127]. Rhythmic activity in spinal cord slices has been monitored over long durations using MEAs [128], as has been circadian rhythm activity in organotypic slices of the hypothalamic suprachiasmatic nucleus [129, 130].

Biochemical sensors

Biochemical sensors are devices that reveal information about the chemical composition of a biological system either in vitro or in vivo in real time. They make it possible to discriminate the relevant species from biologically significant background molecules and to signal the presence of a chemical or measure its concentration with an electrical signal such as current, voltage, or frequency. While some medical equipment has become more complex and more expensive, the nature of and specific applications for biochemical sensors associated with diagnosis drive them to become more compact and more economically viable.

Electrode-based electrochemical sensors constitute the oldest and most diverse group of chemical sensors, as they can be used for a large variety of applications. Potentiometric, conductometric, and voltammetric measurement techniques can be employed depending on the mechanism of the reaction to be analyzed. Potentiometric sensors operate at the equilibrium state: a potential is measured while no current is allowed to flow. The potential is thus proportional to the logarithm of the concentration of the electroactive species, as described in the Nernst equation [131]. Chemically sensitive field-effect transistors (ChemFETs) and ISFETs, in which the gate voltage is supplied by the studied chemical process, are examples of potentiometric sensors that can be used to measure pH [34]. Two-dimensional 10×10 arrays of pH sensors have been constructed, which can continuously monitor sub-second pH changes in a solution and output visual images [132]. Conductometric sensors measure impedance (resistance or capacitance) changes between sets of electrodes with a

sensing layer between them before and after exposure to analytes. Conductometric sensors are usually employed as gas sensors [131]. Capacitive sensors can also be used as gas sensors, although are more typically employed as humidity sensors [133]. Either of these types of gas sensors can be used for diagnostic purposes, such as for evaluating lung performance or measuring acetone concentration in the breath, which can indicate an exacerbation of diabetes [134], as long as they are specific and discriminating enough in real-world conditions. Notably, DNA hybridization has been detected by using arrays of capacitive sensors as well [135]. This approach will be examined in greater detail below. Finally, voltammetric sensors feature potentiostats, which enable them to perform dynamic experiments such as voltammetry (coulometry) where the voltage is modulated and the resulting current is measured, or vice versa. These electrochemical sensors are two- to three-electrode configurations and rely on charge transfer reactions between analytes and electrodes that oxidize and reduce species of interest. The resulting signals are usually linearly proportional to the concentration of the electroactive species of interest. The use of standardized reference electrodes in combination with the potentiostat allows a single half-cell reaction to be studied. Combinations of linear sweeps, pulses, and cycling of these methods within different ranges and at varying scan rates provide a wealth of information about the system being studied. Cyclic voltammetry and fast scan voltammetry are two well-known techniques, which are used to discern information about charge exchange, chemical concentrations, and adsorption of reactants [136].

CMOS chips can be designed with innumerable electrical functions, and can have electrodes or other microstructures built onto them in batch processes. These interfaces can additionally be chemically or enzymatically activated, making the possibilities of CMOS chips as biological or chemical signal sensors extensive [131].

One CMOS chip that is based on voltammetric techniques combines a multiplexed MEA of 576 platinum sensors, on-chip reference and counter electrodes, and an on-chip potentiostat, which can be used for electrochemical detection of processes such as DNA hybridization for disease detection, e.g., HIV, HSV, and malaria, and neurotransmitter detection for fundamental research or drug screening [137]. For DNA hybridization sensing, a conducting polymer and then a linking/spacing polymer are sequentially electrodeposited, and thus unlabeled, unmodified single-stranded DNA is immobilized via its naturally occurring phosphate groups onto the chip [138]. Cyclic voltammetry, in which the potential between the working and reference electrodes is ramped up and down, is applied before and after the introduction of sample ("target") DNA, and hybridization is measured as a diminution in the

current. The MEA structure creates excellent opportunities in terms of diagnosis in that different DNA can be deposited on different electrodes, making it possible to test for many diseases or strains of a disease with a single sample and in a single measurement cycle [137, 138].

Another chip, which utilizes a capacitance variation upon DNA hybridization, further demonstrates the versatility of CMOS to accomplish the same goal (Fig. 12). Thiolated, single-stranded DNA covalently bonds to gold electrodes in one chamber of a dual-chambered 8×16 array of interdigitated electrodes [139]. Sample DNA is then introduced into both chambers (bare electrodes and immobilized target DNA) and the changes in capacitance are measured by converting changes in voltage to changes in frequency. This is accomplished by exciting the electrodes with current pulses and measuring their responses, which are voltage changes whose waveform time constant is dominated by the capacitive component of the interface impedance.

Yet another approach functions both as a hybridization and polymerization sensor, and could therefore be used to sequence DNA [140]. Probe DNA is immobilized over a polymer layer by spotting, and target DNA of a different length is then introduced. The shorter strand is then extended via computer-controlled deoxynucleotide triphosphate (dNTP) release, and at each incorporation of a nucleotide, a proton is released which diffuses quickly away. This transient current is the measured signal [141].

For all of these CMOS approaches, redundant measurements for improved statistics can be performed, since many different electrodes can easily be prepared with the same DNA. Additionally, chips can be activated with many kinds of DNA specific to a subset of patients based on their

Fig. 12 Microsensor MEA chip with 8×16 array of capacitive sensors shown with printed circuit board (PCB) and fluidic cell [139]

susceptibility or exposure so that a single measurement could test for many diseases and parasites.

Several of these chips can also be used to detect electroactive neurotransmitters, such as dopamine, norepinephrine, epinephrine, and serotonin [142], or can be functionalized with enzymes for the detection of neurotransmitters that are oxidized by those enzymes and produce the electroactive by-product hydrogen peroxide (i.e., glutamate, acetylcholine, choline, glucose—each oxidized by its respective oxidase) for in vitro and in vivo applications [143]. Although noble metal electrodes have rarely been used for detection via oxidation of electroactive neurotransmitters (carbon fiber electrodes were most often used), they are now becoming more popular as they can be coated with polymers which extend their potential [144]. With metal electrodes, techniques such as fast scan cyclic voltammetry, in which entire measurement cycles can be made in milliseconds, and differential pulse voltammetry can be used to identify chemicals of interest and monitor their concentrations. It is important to have very sensitive and selective techniques because many different chemicals are present in the brain, which interact and interfere with each other [30]. The electrochemical techniques are very useful for the application, but other methods are needed for non-electroactive neurotransmitters. For these, enzymes can be affixed to only one of two adjacent electrodes and differential measurements can be performed. Selective membranes (permeable only to certain molecules) can also be used as long as they do not slow down reaction times to unacceptable levels [30].

There also exist a number of different other non-electrochemical mechanisms, which can be employed for the recognition of the pertinent molecule(s) as well as for signal transduction, which have evolved and become significantly more sophisticated over the years. With regard to sensing methods that can effectively be realized in CMOS, mass-sensitive, thermal, or optical detection means have been developed, which can employ either equilibrium or kinetic selectivity measures [145]. Mass-sensitive sensors, e.g., employ techniques such as the deflection or resonance of very small stiff cantilevers upon mass accretion. These can be produced on CMOS as microelectromechanical or nanoelectromechanical structures (MEMS or NEMS), and detect changes of mass due to adsorption, deposition, evaporation, or erosion or as a result of an affinity binding reaction [145]. Commercially available CMOS image sensors have become popular in digital cameras, although more sensitive devices than these are required for the very small signals associated with biochemical sensing. CMOS-photodiode microluminometers for the detection of chemi- or bioluminescent signals from as few as 5,000 fluorescently labeled cells (pA currents) have been realized [146], as have arrays with
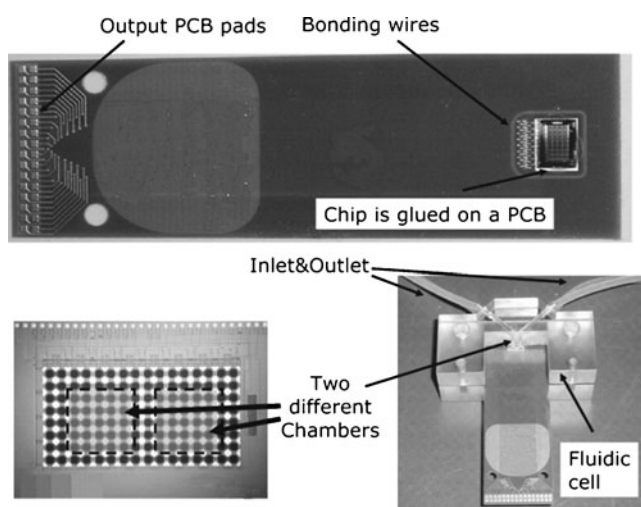
high frame rate imagers with timing resolutions exceeding 150 ps which are able to resolve fluorescent lifetimes [147].

Conclusion

CMOS has been shown to be a powerful technology for the construction of microdevices for biomedical research and pharmaceutical screening. The planar MEAs described are capable of measuring electrophysiological activity of multiple cells simultaneously, providing information about the activity of individual cells at high spatiotemporal resolution. Moreover, integrated electrode arrays are suitable tools to perform highly localized and distributed electrochemical sensing in biological preparations.

In the future, systems with an increased number of recording and stimulation electrodes will be developed. The use of CMOS technologies with small minimum feature size (i.e., 0.35-μm or 0.18-μm technology) will accelerate system innovation, allowing also the integration of more advanced analog front ends and digital interfaces with even smaller size and lower power consumption, which are needed to reduce heating that could damage the on-chip cultured cells. At the same time, such complex systems generate huge amounts of data, requiring advanced data sorting and compression. The development of novel algorithms and filters will allow data acquisition in real time. Finally, MEAs will be integrated with different sensor types, such as chemical sensors, so that even more comprehensive studies can be performed, such as the observation of cell metabolism, monitoring of neurotransmitters, the study of cell location and of tissue morphology.

The devices described have important implications in biomedical research, opening up new avenues for understanding human disease. Vastly complex organs, such as neuronal ensembles or cardiac tissue, can be investigated at a greater level of detail and pathologic mechanisms can be mimicked, studied, and perturbed by using pharmacologic or electrophysiological stimuli. The authors of this review anticipate that MEAs will have a substantial impact on diagnostics and pharmacology in the near future. While MEAs have not yet been formally accepted as a standard method for such diagnostics, it seems highly probable that these devices will play an increasingly vital role in the field as physiologic testing platforms for pharmacology require ever higher throughput dynamics and capabilities.

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