Electrical Imaging: Investigating Cellular Function at High Resolution

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Electrical imaging of extracellular potentials reveals the activity of electrogenic cells and of networks thereof over several orders of magnitude, both in space and time. On a spatial scale, electrical activity propagates in nanometer-sized nerve fibers (axons, dendrites), which connect cells in a biological network over several millimeters. On a temporal scale, changes of the extracellular potential caused by action potentials occur on a sub-millisecond scale, while network activity may be modulated over seconds. Here, different electrode arrays are described, which are designed to image modulations of the electrical potentials over a wide spatiotemporal range. In the second part, typical applications and scientific questions in neuroscience research addressed so far are reviewed. The review ends with an outlook on expected developments.

1. Biotechnological Constrains of “Electrical Imaging”

Electrical imaging refers to the recording of electrical signals at a spatial resolution matching the size of individual electrogenic cells and at a temporal resolution matching the frequency response of these cells.[1–3] From a physical perspective electrical imaging comprises the recording and visualization of extracellular potential changes caused by the activity of electrogenic cells (or compartments thereof) using appropriate electrode arrays. The visualization of the recorded voltage changes is achieved using false color coding of the recorded signal.[4]

“Electrogenic cell” is a collective term for different cell types, which produce transmembrane ionic currents upon changing their cell membrane potential. Well studied electrogenic cells are the many neuronal cell types[5] or heart muscle cells.[6] More recently membrane currents from skeletal myotubes,[7] from glia or from glia-derived cancerogenic glioma cells[8] or from pancreatic beta cells[9] have been reported. In brain or muscle tissues different cell types interact. As a consequence the generated electrical signals comprise a rich frequency content ranging from few Hertz to several kilohertz.[10] Electrical signaling on sub-millisecond time scale occurs during so-called action potentials, when the transmembrane potential changes rapidly due to the opening and closing of voltage-gated sodium channels.

In this review we will discuss biotechnological aspects relevant for the “electrical imaging” technique and highlight applications in neuroscience. Related recent reviews discussed some of the technological backgrounds of microelectrode arrays[11] and some of their applications.[6]

To estimate the requirements needed to image the electrical activity in neurons and networks, we summarize important scales and numbers. A typical neuron comprises a cell body, which integrates the presynaptic signals using an elaborate dendritic network (dendritic tree) and sends an action potential (stereotyped transmembrane voltage signal) activity to synaptically connected neurons using a thin axonal cable-like fiber. Mammalian cell bodies are typically about 10–20 µm in diameter, while the cable-like dendritic and axonal structures have diameters ranging between a few tens of nanometers up to several micrometers.[12] The entire dendirctic tree of one neuron or of a synaptically connected neuronal network may cover an area ranging between few tens of micrometers up to tens of square millimeter.[12] Within the retinal ganglion cell layer or hippocampal cell layers the neuronal density may be as high as 5000–10 000 cells mm−2 (mouse retinal ganglion cells,[13] granule cells),[14] to name just two prominent neural tissues studied so far using electrical imaging. These numbers highlight the spatial range and resolution to be achieved for imaging the electrically activity generated and propagating therein at (sub) cellular resolution.

Optical imaging—the most common imaging modality in life sciences—achieves high-resolution digital imaging by magnifying and recording the light signal using a complementary metal-oxide semiconductor (CMOS) camera chip. Relevant parameters for optical imaging comprise (i) a large field of view, (ii) a high signal-to-noise ratio (SNR), and (iii) high spatial and (iv) high temporal resolution. The ratio between the sensitivity of the CMOS sensors (i.e., minimal number of detected photons) and the corresponding pixel noise sets the sensitivity limit.

Electrical imaging—potentially a complementary or alternative technique of optical imaging—deals with the same constrains. Here, instead of a light-detecting CMOS camera chip, the changing
The extracellular potential above recording electrodes is amplified using dedicated CMOS-based microelectrode arrays (MEAs).

State-of-the-art microelectrode arrays integrate several thousand sensors within the recording area, which typically ranges from one to few square millimeters.[15–19] Cell size (10–20 µm) and cell density (5000–10 000 cells mm$^{-2}$) dictate the high spatial resolution of about 10 µm. This high spatial resolution is achieved by a small electrode separation/pitch and on-chip multiplexing electronics which reduces the number of interconnects between electrodes and amplification stages. Two different types of CMOS-based microelectrode arrays (MEAs) are schematically shown in Figure 1.

In the first approach (Figure 1A) all recording electrodes are covered by a thin dielectric. The extracellular voltage change caused by the active electrogenic cell is amplified using an underlying sensing field effect transistor.[15,16] In the second approach (Figure 1B) openings for the metal electrodes are processed in an oxide passivation layer. To ensure long-term stability the electrodes are separated from the CMOS contacts using dedicated metal-interconnects.[17,20,21] These two CMOS MEA types also represent the two major recording modes currently used: full-imaging CMOS MEAs, where the number of available electrodes largely corresponds to the number of simultaneous readout channels,[15,16,18,22] and CMOS MEAs where all the electrodes are recorded in a sequential way using the so-called switch-matrix approach.[17,20] A comprehensive list of state-of-the-art CMOS-based MEAs is given in Table 1.

Two technological constrains of electrical imaging were discussed in greater detail over the last decade and will be reviewed in the following: (i) the SNR and (ii) the frequency range of the recording. The improvement of SNR is typically tackled by reducing the electrode noise. A common argument claims that low-impedance electrodes are required for high-quality recording.[11,23] For a planar, substrate-integrated metal-based electrode the impedance is inverse proportional to the electrode capacitance.[24] For MEAs the interconnect from the sensing electrode to the first amplification stage is insulated by a thin oxide layer, which represents a stray capacitance. The stray capacitance and the electrode capacitance sum up to the final capacitance “seen” by the first amplification stage. To avoid recording of parasitic signals the electrode capacitance needs to be much larger than the stray capacitance. Typical electrode materials such as fractal-like titanium nitride (TiN) or carbon-nanotube electrodes have specific capacitances of 2.5–10 mF cm$^{-2}$,[25] which translates to 2–10 nF for an electrode diameter of 10 µm. This value is about two to

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**Figure 1.** Schematic cross-sections of two different types of CMOS MEA used for electrical imaging. The electrodes record voltage changes caused by the current flow (indicated by arrows) in the resistive junction between cell membrane and electrode surface. A) Sensing electrodes are capacitively coupled to sensing transistors (field effect transistors) embedded in a CMOS chip. The entire chip surface is covered by a thin dielectric. CMOS MEA principle corresponds to refs. [15] and [16]. B) Metal electrodes are in direct contact to the electrolyte and shifted away from the locations of the original CMOS contacts to ensure long-term stability. CMOS MEA principle corresponds to refs. [17] and [20], see also Table 1. The vertical connections between electrodes and sensing transistors enable electrode pitches of ≈10 µm. In both schematics, the electronics for sensor selection and AD conversion are not shown. The junction resistance $R_{\text{junction}}$ between cell membrane and dielectric determines the signal quality and contributes to the noise of the recorded signal.
increase the total noise by up to 50% but can be actively used several millivolts (ref. [33] and recorded underneath one single cultured rat neuron can reach noise source arises from the “spreading” resistance [27] caused by the interfaced resistive tissue or by the junction resistance of the resistive cleft between adhesion cell membrane and electrode surface. This voltage drop is large by the seal resistance. For recording of action potentials generated by neurons embedded in brain tissue the point-contact model does not apply, given that now the cleft between cell membrane and electrode is in the same range or larger than the cell size. The signal amplitude recorded from pyramidal neurons in hippocampal slices ranges between 0.1 and 0.3 mV, both in vitro[40] and in vivo.[41]

The signal amplitude recorded from retinal ganglion cells, which are embedded in the high-resistive retinal tissue (=1–3 kΩ cm)[27,44] reaches up to few millivolts[42,45] in recordings using capacitive CMOS MEAs. In Figure 2C the recording from a mouse retina ganglion cell is presented with signal amplitudes exceeding 1 mV.[46] Surprisingly, much smaller amplitudes have been reported when using metal-based electrodes.[47,48] To clarify this discrepancy we recorded from the same retina using a metal-based MEAs (comprising 252 TiN-based electrodes, electrode diameter 10 μm, spatial separation: 60 μm),[43] under otherwise identical recording conditions (Figure 2D). As noted above, the (large) capacitance of the recording electrode and interconnect together with the cleft resistance lead to an “electrode-intrinsic” filter with a time constant given by the product of capacitance and resistance[28] thus low-pass filtering the recorded voltage.

Assuming that the specific resistance corresponds to the specific resistivity of the recording medium (66 Ω cm) and a specific capacitance of 2 mF cm−2 the time constant of the metal electrode is ≈0.06 ms only. The mammalian retina, however, has a high specific resistivity of 1.5 kΩ cm[27,44] and consequently a time constant of about 1.3 ms. We apply a low-pass filter (cut-off frequency: 1 kHz) to the recording shown in Figure 2C.E. The low-pass filtered extracellular voltage recorded from a retinal ganglion cell using a capacitive electrode matches the signal recorded by a metal-based electrode (Figure 2E).

### Table 1. Review of recent CMOS-based MEAs including the reported noise levels and signal amplitudes.

| Reference | Sensing type | Readout mode | Electrode pitch [μm] | Number electrodes | Simultaneous readout electrodes | Sampling rate [kHz] | Noise band width [kHz] | Input noise [μV] | Signal amplitudes [μV] |
|-----------|--------------|--------------|----------------------|-------------------|-------------------------------|-------------------|---------------------|----------------|----------------------|
| [16]      | eEOSFET      | Col. Multiplex | 7.8                  | 16 384            | 16 384                        | 2                 | n/a                 | <200           | 200–2000             |
| [17]      | Metal electrode | Switch matrix | 18                   | 11 011            | 126                           | 20                | 0.001–100          | n/a            | 50–100               |
| [18]      | Metal electrode | APS            | 42                   | 4096              | 4096                          | 8                 | 0.0004–5          | 26             | 100–600              |
| [19]      | Metal electrode | Metal electrode | 30                  | 16 384            | 1                            | 22                | 0.01–77            | 15             | 50–200               |
| [20]      | eEOSFET      | Col. Multiplex | 16.1                | 4225              | 1                            | 77                | 0.01–3.3           | 44             | 200–2000             |
| [22]      | Metal electrode | Metal electrode | 13.5               | 8640              | 425                           | 6.5               | 0.3–10             | 4               | 200–500              |
| [20]      | Metal electrode | Switch matrix | 16                   | 59 760            | 9216                          |                 |                    |                | 50–150               |
Finally, we calculated the SNR for populations of retinal ganglion cells using the two described types of MEA. The evaluation of the SNR may be biased when considering individual electrodes, which pick up signals from multiple cells. Therefore, we first performed a so-called spike sorting, i.e., the assignment of the detected signals to the generating cell.[49–51] The preprocessing steps for CMOS MEA and MEA recordings are the same, i.e., the raw data are band pass filtered (low pass 3 kHz, high pass 10 Hz). The spike sorting algorithms are different for CMOS MEA,[51] and MEA respectively.[52] The two different approaches lead to a small bias, because for the MEA data a fixed threshold enforcing an SNR larger than 5 has been selected. Next, for each cell a mean signal amplitude was calculated as well as the noise of that electrode recording the maximal amplitudes.[53] For each cell within a population of 50–100 cells mm$^{-2}$ we obtained one SNR value. The histogram of SNR values for four retinas is shown in Figure 2F. Given that the distribution is asymmetric we evaluate the median SNR for the four independent recordings, two using CMOS MEAs and two using metal-based MEAs. The median SNR for ganglion cell signals recorded by metal-based or by capacitive electrodes was $\approx6.5$, independent of the measurement. In summary, by carefully reviewing and analyzing recordings under identical conditions we have shown here that for one neuronal tissue (the retina) and two biophysically different approaches of electrical imaging the recording quality (SNR) are identical. A comprehensive SNR list comprising recordings from other MEA types cannot be given here. In the references cited in Table 1, only selected recordings are presented, often without stating the filter settings. Therefore, only the range of reported signal amplitudes is presented.

The last physical parameter to be considered for electrical imaging is the recording frequency. Relevant electrical signals in electrical imaging span several decades—from a few hertz found in slow-wave oscillatory brain activity up to kilohertz regime for mapping axonal signals.[27,29] A sampling frequency below 1 Hz may be used for the detection of slow signals generated by glioma cells[8] while very fast sampling of $\approx20$ kHz may be used to reveal the shape of the action potential waveforms. If the high sampling rate of $\approx20$ kHz is requested for all electrodes (i.e., full imaging) it comes at the cost of high noise level of the recording system and a high data rate (Table 1). Two approaches may alleviate this problematic. Full imaging may be reduced to imaging selected electrode fields using a switch matrix approach[17] and appropriate filters may be implemented on the recording hardware to select the desired frequency range and reduced the amount of data storage.[54]

To conclude, we have discussed different technological constrains for electrical imaging and how they may affect the interpretation of the data. (i) Filter properties of the recording electrode/sensor, (ii) signal-to-noise ratios, and (iii) spatial and temporal sampling of CMOS MEAs. In the following paragraph, we discuss recent neuroscientific applications of the electrical imaging.
2. Applications of Electrical Imaging in Neuroscientific Research

Extracellular recording using electrode arrays, first introduced in 1972 by Thomas et al., has by now a long tradition in neuroscientific research and application. The difference between extracellular recording and electrical imaging becomes evident when comparing classical “electrophysiological traces” (Figure 2A–D) to the 2D sequences of electrical images comprising the simultaneously recorded voltages within a defined area. Examples of such electrical images are shown in Figure 3. Instead of displaying hundreds of individual traces the evolution of the spatiotemporal extracellular voltage is displayed in movie-like manner.

In the following we review work from our lab making use of the high spatial density and the high temporal resolution characteristic for electrical imaging. A comprehensive list of application examples for electrical imaging in neuroscientific research is given in Table 2.

Three applications are reviewed in detail: (i) Electrical imaging of cellular activity propagating within axons (nerve fibers), (ii) electrical imaging of low-frequency field potentials, and (iii) electrical imaging of both—single unit activity and local field potentials.

Table 2. Review of published applications using CMOS-based MEAs and electrical imaging.

| Application            | Results (keywords)                                                                 | References                                      | Electrical imaging (CMOS MEA)                  |
|------------------------|-----------------------------------------------------------------------------------|-------------------------------------------------|------------------------------------------------|
| Retina coding          | Functional cell types, axonal conduction, neural coding, correlation analysis      | [45, 48, 58, 59]                                 | Yes (eEOSFET–MEA, APS–MEA) no (SM-MEA)         |
| Retinal waves          | Oscillatory field potentials, retinal waves, receptive field estimation            | [60, 61]                                        | Yes (eEOSFET–MEA, APS–MEA)                     |
| Brain slices           | Disease modeling, analysis local field potentials, single cell identification       | [21, 40, 62, 63]                                 | Yes (eEOSFET–MEA, APS–MEA, SM-MEA)             |
| Neuronal cultures      | Axonal conduction, cell connectivity, network dysfunction, disease modeling        | [64–67]                                         | Yes (eEOSFET–MEA, APS–MEA, SM-MEA)             |
| (iPSC-derived)         | Drug-induced cardiotoxicity, disease modeling                                    | [68, 69]                                        | Not shown                                     |
| Cardiomyocytes         | Network dysfunction, disease modeling                                             | [70]                                            | Not shown                                     |

Figure 3. Electrical imaging of neuronal activity at different temporal and spatial levels. A) Electrical imaging the propagation of a single action potential along an unmyelinated retinal axon. Adapted with permission. Copyright 2010, Frontiers Media. B) Electrical imaging the propagation of local field potentials in blind mouse retina. Frames are presented at selected intervals to demonstrate the oscillatory character but also to visualize yet to be explored differences. Adapted with permission. Copyright 2016, Frontiers Media. C) Electrical imaging the propagation of local field potentials along the hippocampal formation. Reproduced with permission. Copyright 2014, NMI, Natural and Medical Sciences Institute.
Probably the most impressive example of electrical imaging relies on the ability to visualize the activity in subcellular compartments, i.e., the activity within axons and neurites. The visualization of propagating activity has been demonstrated first in retinal axons (Figure 3A)\(^\text{[45,71–73]}\), followed by studies on dissociated neuronal cultures\(^\text{[39,64]}\) and most recently the electrical images within identified neurons in hippocampal slices.\(^\text{[46]}\) While in the retina signals propagate largely nonattenuated within the unmyelinated axons at a speed of 1–2 m s\(^{-1}\)\(^\text{[45,71–73]}\), the propagation in neurites of neuronal cultures appears to vary on a short local scale due to the kinked structure of the neurites.\(^\text{[64]}\) Most recently, the combination of electrical imaging the neurite structure of individual neurons and precise stimulation protocols enabled the identification of presynaptic contribution at multiple sites.\(^\text{[74]}\)

The changes of the extracellular voltage caused by correlated transmembrane currents are recorded as local field potentials (LFPs). LFPs represent spatially restricted changes of the extracellular voltage and last, depending on the brain structure between few milliseconds and seconds for slow-wave brain oscillations.

LFPs have been electrically imaged in various brain areas, such as the well-known propagation along the trisynaptic hippocampal formation\(^\text{[62,64]}\), or in cortical structures\(^\text{[75]}\), revealing epileptiform activities. An example of a propagating LFP along the hippocampal CA region is Figure 3C.\(^\text{[57]}\) LFPs in cultured, organotypic\(^\text{[65]}\) and in acute hippocampal slices\(^\text{[63]}\) have been used to analyze and quantify the effect of antiepileptics. Electrical imaging at a coarser spatial scale discussed the possibility of nonsynaptic propagation of epileptiform activity in the unfolded hippocampus.\(^\text{[74]}\)

Another goal of electrical imaging the different layers of the hippocampus is the inference about neuronal circuits. One strategy how this could be achieved has been suggested by electrically imaging the layer-specific distribution of LFP signal power in freely behaving animals.\(^\text{[77]}\) Crucial for the inference of neuronal circuitries is the simultaneous recording of both, single unit spiking and low-frequency activity. One example, where this has been achieved is discussed in the following.

Among the first results revealed by electrical imaging in the developing retina was the wave-like activity ("retinal wave") detected in the ganglion cell layer.\(^\text{[78]}\) This activity reflects near-synchronous ganglion cell activity over several millimeters, separated by second-long periods of inactivity. Recently, the electrical imaging at high spatiotemporal resolution revealed shrinkage of these waves during ontogeny down to the size of the spatial receptive fields of retinal ganglion cells,\(^\text{[60]}\) indicating a loss of synaptic inputs to the retinal ganglion cell. Whereas in the healthy retina the synchronous output largely disappears it is consistently detected in photoreceptor-degenerated retinas. However, the ganglion cell spiking alone does not provide a complete description of the functional changes occurring in these retinas. Strong subthreshold oscillations of transmembrane potential\(^\text{[79]}\) lead to local field potentials, which emerge spontaneously and propagate at different speeds across the retinal layers. A quantitative analysis of the detected LFP indicates a spatial spread over an area of \(\approx 200 \mu m\) (see Figure 3B and ref. [61]) suggesting that only a few cells contribute to the initiation of the rhythm. The LFPs recorded in different strains of photoreceptor-degenerated retinas either propagate due to aberrant electrical coupling or remain largely stationary.\(^\text{[80]}\) The electrically imaged LFPs in photoreceptor-degenerated retina occur in synchrony with the detected ganglion cell spiking. Pharmacological blockade of the spiking but not of the LFPs demonstrates that presynaptic cells are responsible for the aberrant oscillatory activity, which in turn leads to rhythmic spiking in the postsynaptic neurons.\(^\text{[61,80]}\)

3. Future Developments

From a technological perspective electrical imaging has been performed using substrate-integrated, planar electrodes. This restricts the investigation of neuronal networks to 2D cultures or slice preparations. Recently, arrays with 3D nanoelectrodes have been reported, which probe cardiacocytes cultures and image the propagation of intracellular voltages within a densely connected culture.\(^\text{[81]}\) However, the reported electrode spacing larger 100 \(\mu m\) questions the application of this approach for electrical imaging. Future nanoscale arrays may achieve a resolution in 10 \(\mu m\) range thus extending the capacity of electrical imaging into the third dimension.

Toward circuit reconstruction the described electrical imaging needs to be combined with other neurotechniques. Innovations in optogenetics provide valuable tools for cell-specific modulation. Optogenetic and optical stimulation has been applied in conjunction with CMOS-based MEA,\(^\text{[82]}\) demonstrating that the light induced artefact in the recording electrodes can be suppressed, thus revealing single cell spiking. Another, recent application employed recording using high-density microelectrode arrays to investigate the efficiency of firing rate modulation in blind retinas.\(^\text{[42,83]}\) Although no full electrical imaging of network activity during optical stimulation has been demonstrated yet, the presented evidence suggests that this will be achieved in the near future.

Here, we reviewed the technique of electrical imaging as a powerful tool for selected applications in neuroscience basic research and technological applications. We foresee applications extending beyond the ones reviewed here when combined with other techniques. Although the examples reviewed here were taken from neuroscience, many other electrogenic cells and networks thereof will be investigated, potentially including the emerging field of stem-cell derived microphysiological systems.\(^\text{[84]}\)

Conflict of Interest

The authors declare no conflict of interest.

Keywords

brain tissue, electrical imaging, microelectrode arrays, neurons, signal-to-noise ratios

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