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Novel transducers for high-channel-count neuroelectronic recording interfaces

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Neuroelectronic interfaces with the nervous system are an essential technology in state-of-the-art neuroscience research aiming to uncover the fundamental working mechanisms of the brain. Progress towards increased spatio-temporal resolution has been tightly linked to the advance of microelectronics technology and novel materials. Translation of these technologies to neuroscience has resulted in multichannel neural probes and acquisition systems enabling the recording of brain signals using thousands of channels. This review provides an overview of state-of-the-art neuroelectronic technologies, with emphasis on recording site architectures which enable the implementation of addressable arrays for high-channel-count neural interfaces. In this field, active transduction mechanisms are gaining importance fueled by novel materials, as they facilitate the implementation of high density addressable arrays.

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Introduction

Revealing the fundamental working mechanisms of the brain represents one of the biggest scientific challenges, with deep intellectual significance as well as huge clinical value for the treatment of neurological disorders. Since brain activity spans over multiple spatial and temporal scales, its study is particularly challenging. At microscale, high spatial resolution is needed to resolve single unit activity to capture local information processing. At macroscale, it is required to cover a large brain area to detect neural dynamics among different brain regions. At temporal level, synaptic transmission and spiking activity takes place on the timescale from milliseconds to seconds, while changes in the activity patterns related to learning, memory or disease ranges from seconds to months or years. Technologies intended to monitor brain activity must therefore span over these wide ranges of temporal and spatial scales, and also take into account the variability among species and individuals [1•,2].

Through the years, neuroscience has benefited from advances in a wide variety of research fields to develop neurotechnological tools able to tackle these outstanding challenges, combining information from different techniques to cover a wide range of scales [3]. Despite that large areas of the brain can be observed non-invasively with indirect measurements of the brain's activity via imaging techniques (fMRI or PET), the electrical basis of the brain activity makes electrophysiology of paramount importance for both fundamental and clinical applications [4,5]. Electrical interfaces with the nervous system have been used consistently to monitor neural activity at different spatial resolutions and invasiveness. Non-invasively, electroencephalography (EEG) is widely used in the clinical practice; however, the attenuation of the recorded signals by the skull limits its spatial resolution, requiring from more invasive neural interfaces to obtain relevant information such as electrocorticography (ECoG) or intracortical implants inserted in the cortex or deeper structures.

Currently, improvements in neural interface technology can be grouped in three main directions [6–8]. One major line of research is focused on minimizing the foreign body response which limits the long-term functionality of neural interfaces [9,10•]. A second line deals with increasing the number of recording sites, either for higher density or for larger brain area coverage. A major bottleneck for scaling up channel numbers is the connectivity of electrodes to acquisition circuits. Finally, another major challenge of neuroelectronic interfaces is the transduction efficiency to capture the neural signals with high fidelity and signal-to-noise ratio over the broad frequency

bandwidth of brain activity when downscaling the recording area.

Taking a neural interface system-engineering perspective, in this review, we focus on recent developments of novel transduction mechanisms for high-fidelity, large-area and high spatial resolution recording of brain activity. Active devices based on transistors are promising transducers to solve the challenge of connectivity that arises for high-channel count neural interfaces: they facilitate the implementation of addressable and multiplexed arrays, hence reducing the connectivity constrains and allowing interfaces with thousands of recording sites.

Transducer technologies

The activity of neuronal cells involves ionic trans-membrane currents that generate extracellular field potentials. Thus, any electrophysiology method requires an efficient transducer to convert ionic-generated field potentials into an electronic signal. To complete the recording system, a first signal conditioning is performed by an analog-front-end (AFE), and then an analog-to-digital converter (ADC) translates the neural signals into digital data streams (Figure 1a). The performance of the full acquisition chain can be characterized by the signal-to-noise ratio (SNR), the signal-to-distortion ratio (SDR), and the cross-talk between channels [11••,12,13]. As transducers work at the interface between the ionic charge carries of biological tissue and the solid-state charge carries of the acquisition system, their electrical properties are of paramount importance for a high-fidelity recording. Notably, the AFE also plays a significant role in the acquisition chain since it is the first element in contact with the transducer; the AFE provides a first amplification step but can also introduce noise and non-idealities that could severely affect the quality of the recorded signal. Since the operation of the transducer and the AFE are tightly coupled, it is convenient to discuss these two components together.

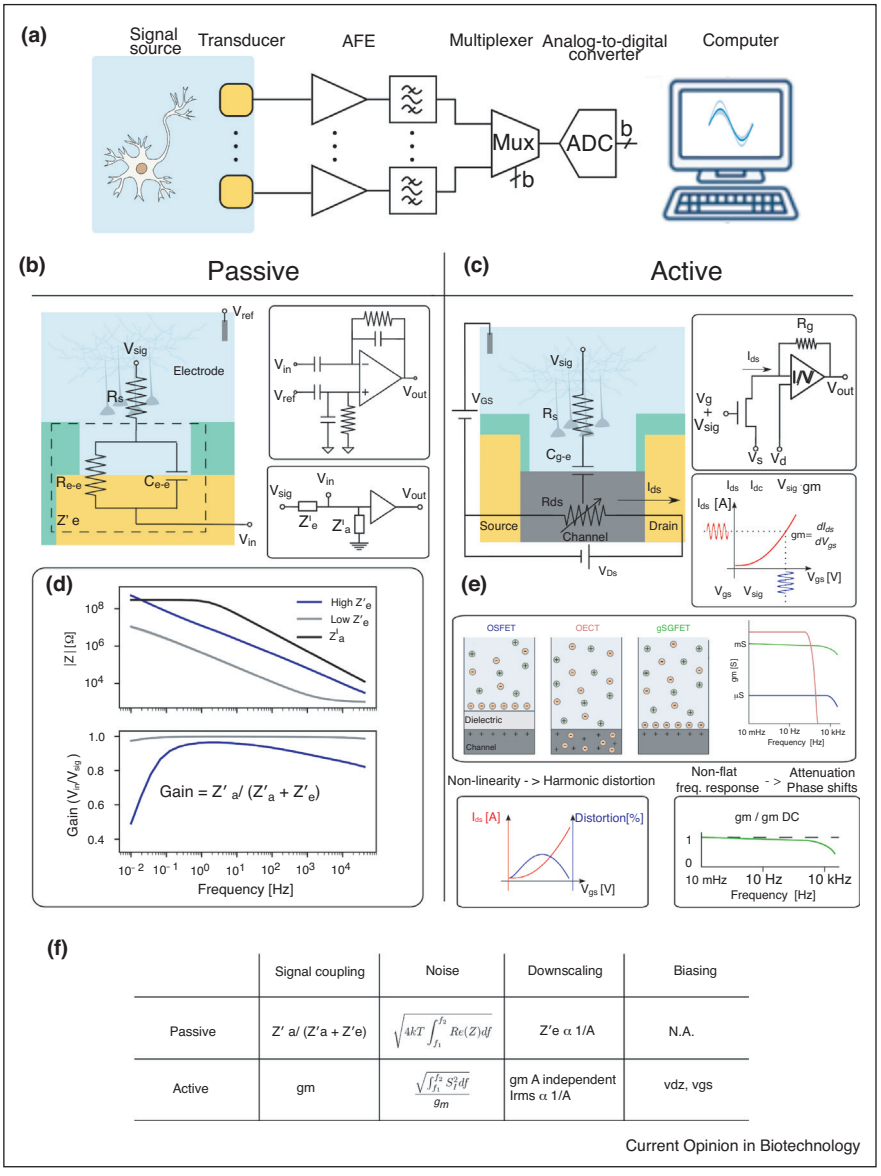
To rationalize the capabilities of micro-fabrication techniques for downscaling the recording sites and increasing their density [1•,2], the optimal electrode size and array configuration should be designed according to application-specific requirements. In particular, for detecting and distinguishing extracellular action potentials (EAPs) of nearby neurons, smaller electrodes (diameter $<$ 20 μm) should be used to minimize the spatial-averaging effect [14]. For local field potentials and infra-slow signals, on the other hand, large electrodes can offer a superior performance in terms of noise. However, the electrode size should be balanced with the required spatial resolution for determining the source of the signals, for example, to perform current source density analysis [11••].

Single addressed passive transducers

Historically, passive electrodes have been the most commonly used transducers for recording brain activity. Its progress has been closely related to improvements of microelectronic technology, which has enabled the evolution from simple microwire electrodes to modern mircroelectrode arrays (MEAs) [15]. The transducers' performance depends on the electrode-tissue interface, wherein the case of passive electrodes, its complex impedance is the main characteristic for recording applications [16]. In the literature, the impedance modulus at 1 kHz is often reported as a figure of merit to describe the electrode-tissue interface. However, as the electrode's intrinsic noise is associated to the real component of the electrode-tissue impedance, the integration of this component over the recording bandwidth could be proposed as a more informative parameter [17•]. Generally, the neural signal recorded with an electrode is amplified by a differential amplifier, forming a voltage divider between the electrode impedance (Ze) and the input impedance of the amplifier (Za) (Figure 1b). This configuration can lead to a non-negligible frequency-dependent attenuation when the Ze $<<$ Za condition is not fulfilled (Figure 1d) [18]. In addition, high impedance values also increase the cross-talk among channels [12]. Since the electrode impedance is inversely proportional to its area, the downscale capabilities provided by micro-fabrication techniques are limited by the increasing electrode impedance with decreasing electrode size. To overcome this limitation, most research efforts have been focused in the development of electrode materials with higher capacitance per unit area [19•]. One approach is to engineer materials to become porous, increasing their surface area and thus their capacitance for the same recording area [20,21]. Recently, the use of biocompatible platinum nanorods (PtNR) to implement thousands of recording sites has allowed mapping the complex temporal dynamics from the cortex [22••]. Alternatively, organic materials such as PEDOT:PSS are widely used as electrode coating to obtain low electrode impedance values [23,24]. In this case, the ions from brain tissue can diffuse within the electrode material, which result in a volume-dependent capacitance [25,26].

Passive transducers are susceptible to DC offsets and low-frequency drifts present at the electrode-tissue interface due to, for instance, slow electrochemical reactions and ion accumulation, impairing high fidelity recording of brain's infra-slow activity and introducing high common voltage offsets [27,28]. This limitation precluded the use of DC-coupled AFEs, and has promoted the use of high-pass filter (HPF) architectures [29] (Figure 1b). The low frequency corner of HPF ($\sim$0.1 Hz) leaves the infra-slow signals outside of the acquisition frequency band. Despite achieving low-frequency DC blocking and well defined signal bandwidth acquisition, at such frequencies the flicker noise from the CMOS amplifier can dominate over

Figure 1



Recording electrophysiological signals with active and passive transducers. **(a)**: Recording chain schematic including the signal source, the transducer, the analog front-end (AFE), the anti-aliasing filter, the multiplexer (Mux), an analog-to-digital covnerter (ADC) and a computer. **(b)–(f)**: Comparison of passive and active transduction. (b)–(c) left: Cross-section of the interface between the tissue and the transducer and superimposed electrical schematic. (b)–(c) right: electrical schematic of the transducer and first amplification stage. For passive transducers recordings is based on differential amplifiers (schematic shown in top) and signal is coupled through a voltage divider composed by the electrode (Z'e) and amplifier (Z'a) impedances. For active transducers recording requires device biasing (Vds,Vgs) and recording the modulated current signals. Signal coupling can be approximated by the derivative of the transfer function at the operation point (gm) (d): Impedance spectra for high and low electrode impedance and frequency response of the recording gain for each case. (e): Top. Cros-section of the mechanisms of different transistor types and comparison of the transconductance magnitude and frequency response. OSFET: Oxide-semiconductor field-effect transistor; OECT: Organic electrochemical transistor. gSGFET: graphene solution-gated field-effect transistor. Bottom: Non idealities such as harmonic distortion due to non-linear transfer curve and non-flat transconductance frequency response should be taken into account to achieve high-fidelity recordings. (f): Table comparing the scaling and dependence of the main figures of merit of passive and active transducers.

the brain signal. Therefore, noise mitigation techniques including chopping and correlated-double sampling strategies are required to ensure electronic noise values lower than intrinsic electrode noise [30].

Neurotechnologies aimed to record neural activity have also profited from the increased integration density of microelectronics. This evolution has allowed to improve the AFEs and the integration of several channels together

with digitizing circuitry into a single chip [31]. This integration, together with the availability of wireless technology, has simplified the experimental preparations, enabling data recordings in freely moving animal experiments under more realistic behavioral conditions [32–34].

Active transducers facilitate high density addressable arrays

The adoption of multiplexing or addressable strategies for increasing the channel count requires the incorporation of switching elements (Figure 2a, b) [2]. These elements introduce parasitic components in the signal path, decreasing the input impedance and therefore compromising the $Ze << Za$ condition for high density arrays. Alternative to passive transducers, active transducers based on transistors provide a local signal amplification thus minimizing the impact of parasitic elements. Moreover, they can be arranged in row-column addressable arrays, simplifying and reducing the connectivity [35•,36,37]. In active transducers, the extracellular field potential modulates the conductivity of the channel material, which is electrically contacted by two metal contacts (drain and source) resulting in a three terminal device with a transistor configuration. The third terminal (gate) is electrically contacted through the brain tissue with a reference electrode (Figure 1c). The efficiency of the modulation of the drain-source current by the gate voltage is given by the so-called transconductance (gm), which depends on the mobility of charge carriers in the channel and the interfacial (channel-tissue) capacitance. The chemical stability of the channel material in contact with the brain tissue plays an important role in the implementation of active transducers, resulting in different device configurations [38••,39] (Figure 1e).

Some semiconductor material, such as silicon, require the use of an insulation layer to prevent unwanted electrochemical reactions. However, benefiting from CMOS technology maturity, passive electrodes are connected to the gate of silicon transistors for implementing the so-called extended gate configuration. In this way, high integration density applications have been developed taking profit from the local amplification provided by the silicon transistor to build active sensing pixels [32,37,40,41••]. However, the materials used to implement the passive electrodes also suffer from the previously described DC offsets and drifts that can compromise the system performance. Decoupling of these unwanted drifts requires the use of a HPF, which increase the area of the active pixel. For that, different approaches have been used to minimize the area required for implementing this HPF. For instance, the use of an input capacitance (Figure 2a, b), together with resistances act as a HPF and help to set the transducer operating point [32,41••]. Another design approach that requires less area is based on the use of auto-zero structures based on a switching transistor [40,42•,43], which can reset any drift by switching with a given periodicity to define the HPF cut-off frequency (Figure 2b).

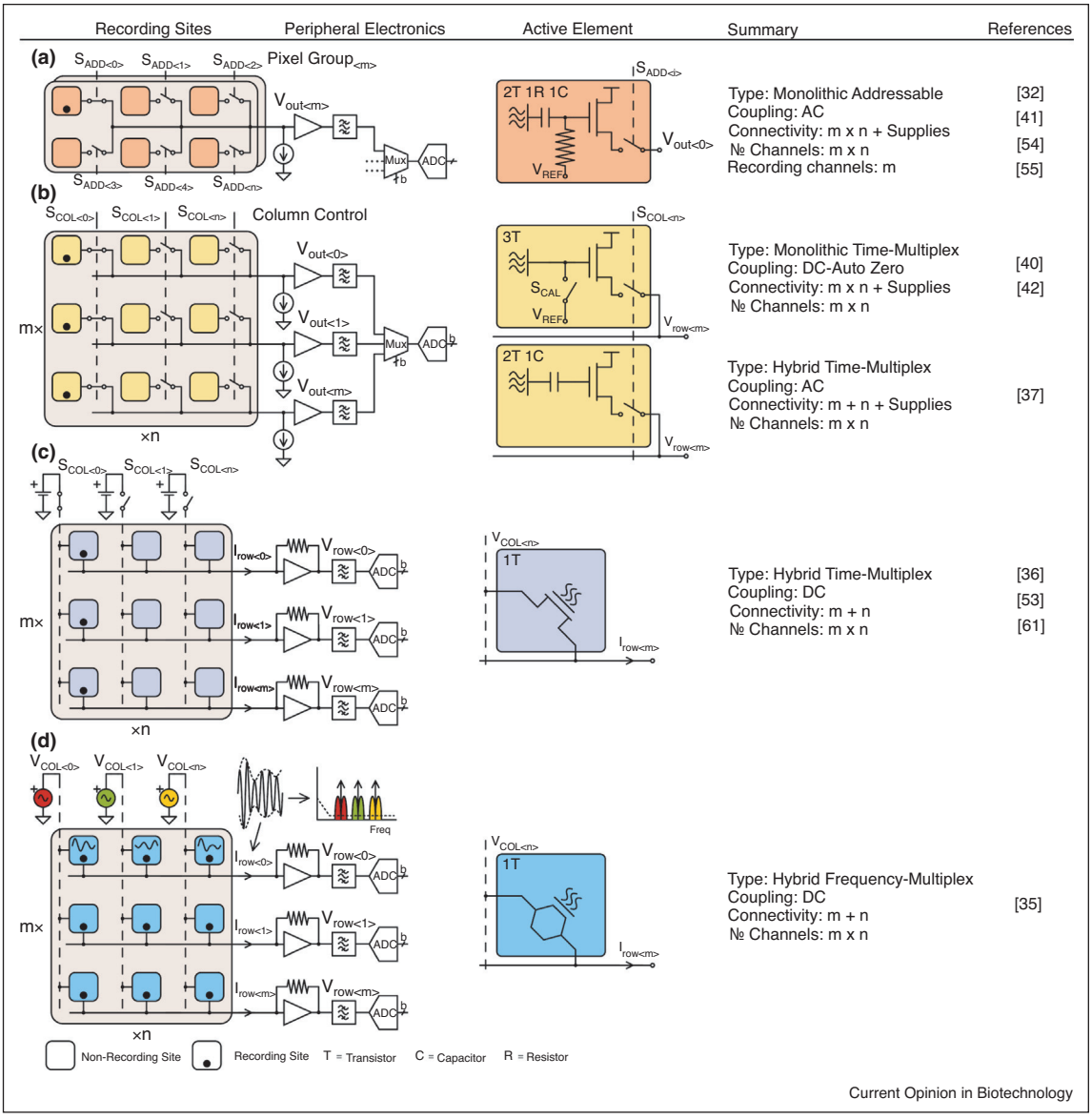
Other materials such as organic polymers or carbon-based materials can be used in direct contact with the brain tissue, resulting in larger transconductance values. Along this line, PEDOT:PSS has been used to implement the so-called Organic Electrochemical Transistors (OECTs). Despite the low carrier mobility of PEDOT:PSS, large transconductance values can be obtained thanks to its volumetric capacitance [44,45]. Other research has explored carbon-based materials for active neural transducers. Taking advantage of graphene's high carrier mobility, chemical stability and field-effect properties [39], graphene-based solution-gated field-effect transistors (gSGFETs) have been used in direct contact with the brain tissue [46,47]. gSGFETs are able to overcome the limitations of passive electrodes in DC-coupled operation. Graphene's chemical stability significantly reduces signal drift, and the signal coupling through the interfacial capacitance warrants a stable transconductance even at very low frequencies [48•]. This capability has led to the recent demonstration of high-resolution mapping of infraslow brain signals with gSGFETs [34,49].

Regarding signal quality, it is important to note that in active transducers the transconductance might be nonlinear and frequency-dependent (Figure 1e), limiting the fidelity of the transduction if not taken into account [13,50]. Importantly, the transistor's transconductance is not dependent on the channel area but on its aspect ratio (width/length), which allows reducing the transistor dimensions without impairing the transconductance performance. However, the major factor limiting transistor downscaling is its intrinsic noise, which is inversely proportional to the active area. The most representative figure of merit of noise is the gate voltage equivalent noise, defined as the integral over the operation bandwidth of the current noise divided by the transconductance (Figure 1f) [51,52].

Challenges of read-out electronics for high channel count recording interfaces

Two technology trends can be clearly defined in the effort towards the development of high-channel-count transducers, typically based on monolithic or hybrid technology solutions. In the case of monolithic solutions, the full acquisition chain, from the transducer to the digitizer, is built in the same device. Based on CMOS technology, this approach has resulted in important advances for intracortical recordings on the pursuit of high spatial resolution, enabling the identification of the activity of thousands of single neurons [40,41••]. On the other hand, in hybrid solutions, the transducers are built separately from the acquisition electronics [35•,37,53]. This approach has been favored in applications aiming to cover

Figure 2



Acquisition architectures for addressable arrays based on active transducers. **(a)**: Addressable array with ($m \times n$) available channels without multiplexing capabilities, where only (m) configurable channels can be recorded simultaneously. Where the anti-aliasing filter is located before the ADC minimizing the out of band noise folding. **(b)** and **(c)**: Time domain multiplexing array ($m \times n$) with reduced connectivity ($m + n$), where active sites are scanned sequentially (The sampling frequency for each row is $Fs \times n$, where Fs is the channel sampling frequency). (b) Top: Monolithic 3T active element with auto-zero integration to achieve AC coupling with better area efficiency than RC structures. (b) Bottom: Hybrid silicon integration on flexible substrates, with AC coupling (1C), on-site pre-amplification and column switch (2T). (c): Current mode DC-coupled active element, based on solution gated transistors (1T) with column switches placed outside the flexible array. **(d)**: Frequency domain multiplexing array ($m \times n$) without switches, where all sites are active at same time, and frequency band division scheme for each column.

large areas of the brain, enabling the mapping of brain functional circuits and rhythms across brain regions.

The growth of monolithic solutions has been powered by the increasing capabilities of CMOS fabrication techniques which allows integration of signal transducers in the same fabrication process. To optimize the area usage and reach high integration densities, having a dedicated amplifier for each recording site is not efficient. This has motivated the adoption of active pixel structures inherited from CMOS image sensors [43], allocating the resources not needed for the signal transduction far away from the recording area. To enable this reallocation, the connectivity with the recording area should be

simplified. For that, the arrangement of recording sites in addressable arrays has been widely used for reducing the number of connections: for a matrix of m x n recording sites (where m and n are the number of columns and rows, respectively), the number of connections is m + n and the number of required AFEs is m (Figure 2). As commented before, the use of active transducers has played an important role for implementing the addressable arrays, minimizing the pixel area while preserving the signal integrity [2].

While the adoption of addressable arrays improves the resources allocation, the signal read-out of these arrays presents some bottlenecks, for which the requirements of the target application should guide the adopted solution. Mainly, the signal of all sensors in the addressable array can be acquired simultaneously by using multiplexing approaches; alternatively, the addressing capabilities could be used to configure a selection of sensors to be read-out. The difference between both approaches relies in the location of the anti-aliasing filter into the acquisition chain, and its impact on both the sampling rate and noise performance [12]. Importantly, in the case of time division multiplexing (TDM), when all sensors are recorded simultaneously, the sampling rate of the multiplexing system should be higher than the sampling rate for each individual sensor (sampling rate scales linearly with the number of columns). To avoid the out-of-band noise folding inherent to TDM, the anti-aliasing filter should be placed before the switching elements. This means that it should be placed into the sensing pixel, where area is more scarce. Even though, some efforts have been done by implementing a current integration with a certain frequency to build a low pass filtering at pixel level [54]. Summarizing, while simultaneous multiplexing readings can be achieved at expenses of lower sampling rate and higher noise [40,54,55], addressable configurations are preferred to achieve a performance similar to that of point to point systems [41••,56]; in the case of the addressable configurations, the increased integration density provides certain degree of freedom to select the sensors to record.

In contrast to the monolithic designs described above, hybrid solutions are based on building separately the acquisition electronics from the array of transducers, taking advantage of recent advances in novel materials for flexible electronics technology [8,38••]. In contrast to the use of the rather invasive monolithic shanks, μECoG recordings on top of the cortex are able to provide information from large brain areas in a less invasive way [57]. The good performance of μECoG arrays relies on the substrate conformability to the brain's surface morphology, for which rigid monolithic solutions are not suitable. Hybrid interfaces can also employ addressable array configurations to reduce the connectivity footprint. For instance, the use of doped silicon nanoribbons integrated into flexible polyimide substrates has allowed to implement up to thousand recording sites with only 64 (36 + 28) connections by using a TDM read-out strategy [37,58••]; however, at the cost of a very complex integration. Alternatively, the use of active transducers compatible with flexible substrates can simplify the technology integration. In this line, OECT based on PEDOT:PSS have been explored to implement TDM by mixing an active transducer with an on-site switch in small arrays (Figure 2c) [59]. This approach was improved by the use of switchless arrays and enhanced conformability [36,60]. Taking advantage of the high carrier mobility in graphene, arrays of gSGFETs have recently been used to implement switchless arrays with TDM [61]. The impact of the tracks resistance on the signal quality and cross-talk should be considered. This is particularly relevant in the case of OECT and gSGFETs transducers, as the output impedance is lower than the extended gate implementations, thus being more sensitive to parasitic track resistances [53]. Moreover, the capability of gSGFETs to act as a signal mixer enables the study of amplitude modulation techniques for implementing frequency division multiplexing (FDM) strategies, avoiding the aliasing problems presented by TDM strategies (Figure 2d) [35•]. In both TDM and FDM gSGFETs implementations, the wide-bandwidth recording capability of these devices was demonstrated, preserving high-fidelity recording of infra-slow activity.

Conclusions and outlook

In the last decades, translation of microelectronics technology to neuroscience has resulted in integrated circuits that enable monitoring brain activity with thousands of recording sites. The increased spatial resolution provided by monolithic solutions, together with the simultaneous use of multiple shanks have revealed very detailed local information from different areas of the brain [40,41••]. On the other hand, hybrid solutions used in μECoG recordings aim to cover large areas of the brain, allowing to map brain functional circuits and rhythms [22••,34,58••], where active transducers compatible with flexible substrates are highly suited building blocks for high-channel-count flexible interfaces. However, despite the significant progress, there is no established a technology able to cover the wide range of spatial and temporal scales of the brain activity, requiring a choose according to the requirements of the target application. Translation of high-channel-count recording technology to human applications could provide many clinical benefits as also allow improved decoding efficiency in brain-machine interfaces. However, with the number of recording channels progressively increasing in the coming years, we foresee a shift from the technology-governed bottleneck of the number of recording sites to a bottleneck governed by data management, its transmission, storage, analysis and interpretation [62,63].

Conflict of interest statement

Nothing declared.

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