Review article

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Recent developments and future perspectives on neuroelectronic devices

https://doi.org/10.1515/nf-2021-0019

Abstract: Neuroscientific discoveries and the development of recording and stimulation tools are deeply connected. Over the past decades, the progress in seamlessly integrating such tools in the form of neuroelectronic devices has been tremendous. Here, we review recent advances and key aspects of this goal. Firstly, we illustrate improvements with respect to the coupling between cells/tissue and recording/stimulation electrodes. Thereafter, we cover attempts to mitigate the foreign body response by reducing the devices' invasiveness. We follow up with a description of specialized electronic hardware aimed at the needs of bioelectronic applications. Lastly, we outline how additional modalities such as optical techniques or ultrasound could in the future be integrated into neuroelectronic implants.

Keywords: electrical recording; electrical stimulation; implants; microfabrication; neuroelectronics.

Zusammenfassung: Neurowissenschaftliche Entdeckungen und die Entwicklung von Ableitungs- und Stimulationsmethoden sind stark verknüpft. Im Laufe der letzten Jahrzehnte hat sich ein immenser Fortschritt im Hinblick auf die nahtlose Integration solcher Methoden in Form von neuroelektronischen Schnittstellen ergeben. In diesem Artikel geben wir einen Überblick über aktuelle Entwicklungen in diesem Feld. Wir beleuchten zuerst Verbesserungen der Kopplung zwischen Zellen/Gewebe und Ableitungs- bzw. Stimulationselektroden. Danach betrachten wir Ansätze zur Vermeidung von Fremdkörperreaktionen durch eine reduzierte Invasivität der Schnittstellen. Anschließend beschreiben wir spezialisierte elektronische Hardware für bioelektronische Anwendungen. Zuletzt zeigen wir auf, wie neue Modalitäten z.B. durch optische Techniken oder Ultraschall zukünftig in neuroelektronische Implantate integriert werden könnten.

Schlüsselwörter: Elektrische Ableitung; elektrische Stimulation; Implantate; Mikrofabrikation; Neuroelektronik.

Introduction

Since its very beginning, neuroscience has been deeply intertwined with methods and technologies of measuring or controlling the electrical activity in biological tissue. Ultimately, this intricate connection can be traced back to the founding experiments of Luigi Galvani on frog legs (Galvani, 1791). In the 1950s, the development of tungsten microelectrodes enabled recordings from single neurons in living animals (Hubel, 1957). Continuing the push toward higher resolution, Neher and Sakmann introduced the patch-clamp technique in the 1970s, which allowed characterizing individual ion channels (Neher and Sakmann, 1976). These developments have reshaped neuroscience since the middle of the 20th century triggering an ever-accelerating technological development. In particular over the past decades, new microfabrication approaches, as well as dedicated efforts on merging biology and artificial probes, have led to a cornucopia of new tools. Probes to interrogate the nervous systems are constantly improving in terms of signal quality, number of channels, and seamlessness of their integration (Won et al., 2018). At the same time, the accompanying electronics are becoming smaller and require less energy (van Dongen and Serdijn, 2016) while additional modalities such as optical or chemical stimulation are added.

This review aims to provide an overview of recent developments as well as the core challenges met when integrating artificial devices with the nervous system or biological systems in general. While the main focus is on technologies to be used in *in vivo* applications, a few examples for *in vitro* applications are discussed as well to demonstrate specific approaches in this domain. In doing so, we do not aim for a complete historical overview.

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Instead, we hope to provide the reader with an insight into the central aspects and most recent advances in the field of bio- and neuroelectronics. Overall, the review is structured in four sections that mirror the key aspects toward which efforts have been directed over the past years (compare Figure 1). First, we will illustrate improvements in the coupling between the electrode and the tissue. Thereafter, approaches to reduce the devices' invasiveness for better long-term applicability will be described. Next, we will outline technological progress with regards to detection principles and the underlying electronics of the devices. The last section will shortly highlight novel approaches to include other-than-electrical principles (e.g. optical or fluidic technologies) into neuroelectronic devices before we conclude the review.

Electrode–tissue coupling

The vast majority of techniques are concerned with recording or eliciting electrical signals, which is rooted in the critical role that electrical activity plays in the nervous system. In this context, the interface between an electrode and the cells or tissue of interest takes a central place. The properties of this interface are dominated by several factors. In particular, the interface impedance contributes to the attenuation of signals that are supposed to be recorded

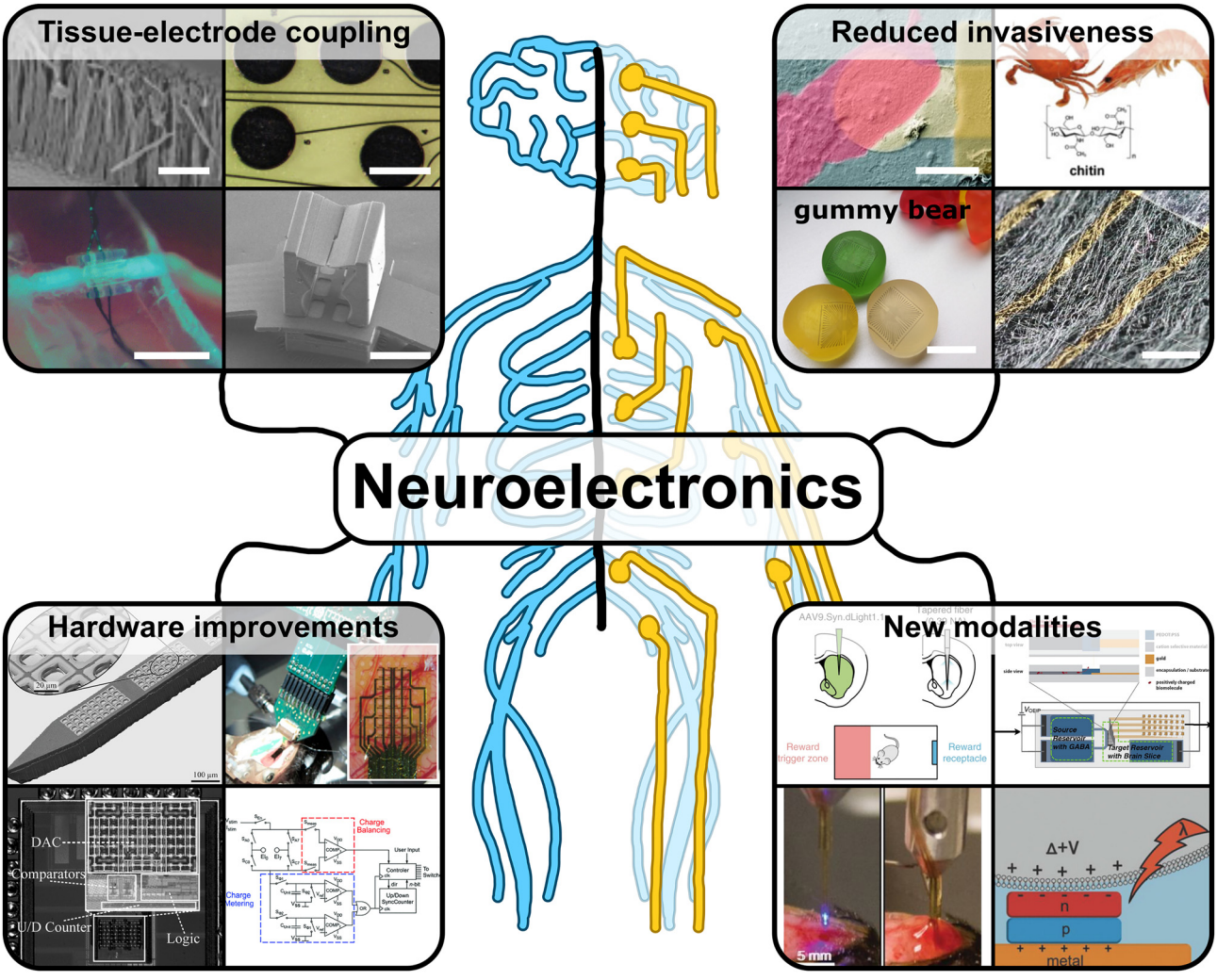

Figure 1: Schematic illustrating the four sectors in which neuroelectronic devices have advanced over the past years. Improvements in tissue–electrode coupling (top left; scale bars correspond to 2, 250, 500, and 200 µm, top-left to bottom-right, respectively) yield better signal transduction. A reduction in the devices' invasiveness (top right; scale bars correspond to 25 µm, approx. 10 mm, and 200 µm, top-left to bottom-right, respectively) mitigates the foreign body response. Specialized hardware (bottom left) delivers higher sensitivity and reduced power and spatial requirements for the accompanying electronics. The introduction of new modalities for recording and stimulation (bottom right) expands the neuroelectronic toolset. Details and copyright information for all four subpanels can be found in Figures 2, 3, 4, and 5.

by the electrode or likewise to be elicited in the tissue. At the same time, the impedance is a crucial factor in the voltage noise observed when recording with the electrode. On a general level, a lower impedance will mean better signal transduction and lower noise. Another factor is the so-called seal or junction resistance. This resistance represents undesired electrical pathways between the electrode and the ground. Increasing the seal resistance by tightening the tissue–electrode connection will generally result in improved signal fidelity.

Modifying the interface impedance

In the simplest case, the interface impedance can be approximated as an *RC* element. As such, the majority of interface modifications target either an increase in capacitance (e.g. by increasing the effective interface area) or a decrease in the interface resistance (e.g. by facilitating Faradaic charge transfer). A typical example is the functionalization of electrodes with platinum black. Since improvements in the adhesion of platinum black were made in the late 1980s (Marrese, 1987), it has been a predominant method to decrease the interface impedance by roughening the surface. Even despite known cytotoxic side effects (Schuettler et al., 2005), improvements in platinum black coating continue to pose a viable alternative for impedance reduction (Boehler et al., 2015; compare Figure 2a and b). Similar to the deposition of platinum black, electroplated gold was shown to be able to decrease the interface impedance by increased surface roughness (Brüggemann et al., 2011; Cui and Martin, 2003a). Aside from modifications to the surface geometry, chemical modifications have also been shown to bear great benefit in optimizing the interface for signal transduction and noise reduction (Bettinger, 2018; Ferro and Melosh, 2018). Among these, the application of conductive polymers takes a special place. The charge transport in such materials is often a mixture of electron/hole and ionic mechanisms. Applied to the electrodes of a neuroelectronic device, they can greatly improve the interface properties (Inal et al., 2018; Liang et al., 2021). Consequently, conductive polymers have found numerous applications in bioelectronic settings (Bettucci et al., 2021) with a continuously increasing toolset for structuring them on the microscale (Zhang and Travas-Sejdic, 2021).

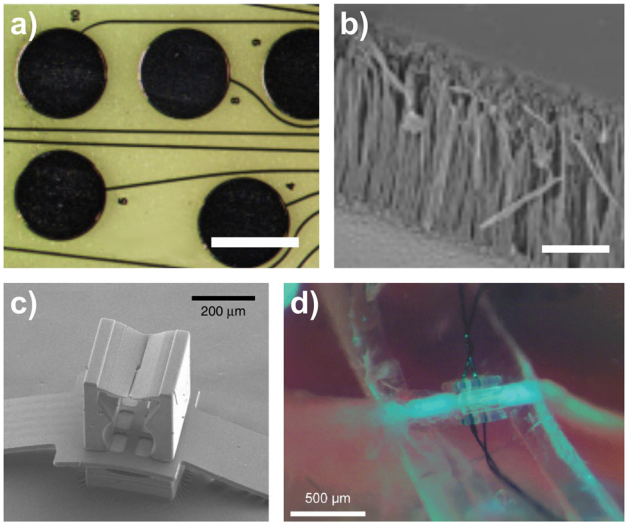

Figure 2: Improvements in tissue–electrode coupling. **a)** and **b)** Platinum nanograss functionalized electrodes and cross-sectional electron micrograph, respectively (Scale bars correspond to 200 and 2 µm, respectively; adapted from Boehler et al., Copyright (2015), with permission from Elsevier). **c)** and **d)** Microfabricated clips can be used to ensure a tight seal between peripheral nerves and recording/stimulation electrodes (**c** adapted from Otchy et al., 2020, **d** adapted from Lissandrello et al., 2017, © IOP Publishing. Reproduced with permission. All rights reserved).

While a number of conductive polymers have been applied in modifying bioelectronic interfaces, poly(3,4--ethylenedioxythiophene) (PEDOT), in particular when doped with polystyrene sulfonate (PSS), is considered by many to be the gold standard in this context (Liang et al., 2021). Already early on, the fuzzy nature of electrodeposited PEDOT:PSS films was not only shown to be beneficial for the electrode impedance but also for cell growth *in vitro* (Cui and Martin, 2003b). In addition to its benefits in a recording context, PEDOT was also shown to be an excellent choice for modifying stimulation electrodes. Similar to recording scenarios, the low interfacial impedance is beneficial for signal transduction across the interface. In this context, it was found that PEDOT-modified electrodes exhibit excellent charge storage capacities (Wilks et al., 2009). This property describes the amount of charge that can be applied through an electrode before undesired electrochemical reactions take place. As such, an increased charge storage capacity helps mitigate the increased current density requirements resulting from electrode miniaturization. Despite its long-standing history in this field, PEDOT:PSS has not lost its relevance as demonstrated by its recent application in conjunction with conductive hydrogels (Ferlauto et al., 2018) or in the realization of stretchable peripheral nerve interfaces (Decataldo et al., 2019).

Naturally, both approaches of impedance reduction can be combined, i.e. the application of conductive polymers can be tuned in order to increase their surface area to ultimately lower the overall impedance. Specifically, conductive polymers can be deposited in ways that render them porous (Yang and Martin, 2004a, b) or in the form of nanotubes that

offer an increased surface area due to their low dimensionality (Abidian and Martin, 2008; Abidian et al., 2009). Such nanotube-decorated electrodes have been shown to also promote improved adhesion of cells to the electrode (Abidian et al., 2010), an effect that was also observed when coating electrodes with blends of conductive polymers and biomolecules (Cui et al., 2001; Kim et al., 2007).

Tightening the tissue–electrode connection

As illustrated by these last examples, the degree of contact between the tissue and the electrode plays a similarly crucial role when probing biological tissue. Conceptually, a tighter coupling to the target tissue results in a higher seal or junction resistance and thereby more efficient transduction of signals both when recording or stimulating. Consequently, an interface as described above with cells closely interacting with the electrode's pores or nanostructures is expected to improve the electrode performance. However, the modification of the interface does not have to be performed before the addition of the cells. Instead, a tight interface can also be created by electropolymerizing PEDOT directly in the intercellular space both in cell culture studies and in living tissue explants (Richardsony-Burns et al., 2007a, b). Effectively, such approaches try to integrate the electrode directly into the target tissue's natural structure. Vice versa, a variety of methods use structural motives that the cells spontaneously engulf, i.e. they result in the tissue integrating more tightly with the electrode. Since the nanotechnology boom of the 2000s a large toolset to generate structures similar in size to those naturally encountered by cells is available. Numerous examples of how such structures can be used to create a tight tissue–electrode connection have been presented ranging from nanoparticles over nanopillars to nanocones and nanomushrooms (Angle et al., 2015; Spira and Hai, 2013). The majority of these techniques aim at tightening the contact between the electrode and the cell body. As such, they are to a certain degree focussed on applications in the central nervous system (CNS). While a number of these approaches will also bear advantage in applications involving the peripheral nervous system (PNS), there are also dedicated techniques that capitalize on properties specific to the PNS. One such property is given by the cylindrical nature of most structures found in the PNS. Exploiting this symmetry to create a more intricate tissue–electrode seal, microfabricated clip systems that embed electrodes for recording and stimulation have recently been presented (Lissandrello et al., 2017; Otchy et al., 2020; see Figure 2c and d). Other approaches make use of, for instance, adhesive hydrogel patches that wrap around the electrode and the nerve (Forssell et al., 2019; Horn et al., 2021; Ong et al., 2018).

Reduced invasiveness

The previous section highlighted the crucial importance of a tight coupling between the neuroelectronic device and the tissue of interest. In most cases, however, this coupling is required to last over days, if not months, in order to conduct biologically or clinically meaningful studies. Such timescales open up a new challenge as they allow activation of the body's defense mechanisms – the 'foreign body response' (FBR). Two of the main drivers of the FBR are suspected to be adsorption-related conformation changes in proteins (Hu et al., 2001) and a mechanical mismatch between the implanted materials and the target tissue (Moshayedi et al., 2014). The result is a cascade of events that attacks and encapsulates the implant leading to device failure (Barrese et al., 2013; Xie et al., 2014) or loss of neurons in the implant's vicinity (Biran et al., 2005). To counteract the FBR, neuroprobes are required to smoothly integrate into the soft, wet, and constantly moving environment of the body (Renz et al., 2018). The following section will thus illustrate strategies to mitigate FBR-related decreases in probe performance. In doing so, we will describe approaches that use modifications of the probe surface, soft materials to reduce mechanical mismatch, and overall reduced size to cause as little trauma in the target tissue as possible.

Surface modification

As described above, the probe surface can have a strong influence on the degree of FBR observed upon device implantation. Thus, modification of the device surface is an attractive candidate for effective mitigation strategies. In this context, not only a variety of both chemical but also structural approaches allow tuning of the cell–surface interaction (Stevens and George, 2005). Due to their soft and biologically inspired nature, hydrogels lend themselves to this application (Kim et al., 2010). Recent developments even yielded photostructurable gelatin systems that could be integrated into standard fabrication processes (Kang et al., 2020). While beneficial for cell adhesion, such coatings increase the electrode–cell distance and thereby lower the seal resistance. To mitigate this aspect, conducting polymers can be electropolymerized inside of the hydrogel. The thereby obtained structure of the conducting polymers

even decreases the electrode impedance potentially making up for the loss in seal resistance (Kim et al., 2004). Besides hydrogels, a number of bio-derived materials such as silk, collagen, chitin, or cellulose have already been demonstrated as viable substrates for bioelectronic interfaces (Pradhan et al., 2020; see Figure 3b). Increasingly, progress in the processability of these materials is blurring the line between classical microfabrication and bio-derived materials (Ju et al., 2020; compare Figure 3a). An approach that renders this line even less clear is based on so-called biohybrid interfaces. Early examples of this approach demonstrated that stem cell-seeded implants show lower neuron loss and glial encapsulation immediately after implantation (Purcell et al., 2009). Since then, the use of cells to relay or amplify artificial electronic signals has been realized in numerous studies *in vitro* and *in vivo* targeting both the PNS and the CNS (Rochford et al., 2019).

Addressing the mechanical mismatch

As highlighted by Moshayedi et al. (2014), the mechanical properties of neuroelectronic devices are another important factor in how well they fare in long-term applications. In this context, two strategies are commonly applied. The first employs materials that exhibit low Young's moduli, i.e. show mechanical properties closer to those of biological tissue than classic silicon or metal materials. Here, bio-friendly or bio-derived substrate materials have been demonstrated (compare Figure 3c; Adly et al., 2018; Maiolo et al., 2019). A common problem, however, is posed by the fact that metals usually suffer from a strong dependence of their conductivity on the applied strain, i.e. bending or stretching of the device results in a strong increase in the resistance. To mitigate this aspect, mesh-like conductor networks made from e.g. metal nanowires or carbon nanotubes can be applied (Lienemann et al., 2021; Terkan et al., 2020; Tybrandt et al., 2018). Alternatively, the microstructure of gold films can be engineered so that they remain conductive even when exposed to notable strain rates (Lacour et al., 2003, 2006). Both approaches have been successfully implemented in the recording and stimulation of nerve activity (Lienemann et al., 2021; Minev et al., 2015). Another approach is represented by using elastic conductive materials (Giagka and Serdijn, 2018; Jeong et al., 2015; Rogers et al., 2010; Sunwoo et al., 2020), such as composites of PEDOT:PSS and polyurethane (Cuttaz et al., 2019) or liquid metal conductors (Dong et al., 2021). Recent advances in this context cover rapid prototyping of soft bioelectronic implants (Afanasenkau et al., 2020) and ultrasoft mesh structures that seem to pose no hindrance to the mechanical activity of cardiac cells (Lee et al., 2018; see Figure 3d).

The second strategy is based on the fact that absolute mechanical stiffness is not only dependent on a material's bulk properties but also on its size and geometry. Similar to how both fingernails and hair consist of keratin, thinning down a macroscopically "stiff" material can result in highly pliable structures. As device thicknesses in the range of only a few micrometers are not uncommon in this area, materials that are sufficiently robust to allow handling and insertion are needed. Two of the most common examples in this category are polyimide (Borda et al., 2020; Kireev et al., 2019; Sperry et al., 2018) and parylene (Khodagholy et al., 2011, 2013, 2015), both of which offer additional benefits in terms of chemical inertness and biocompatibility. To increase the number of channels while maintaining a small form factor, multilayered and multiplexed devices have been proposed (Leccardi et al., 2019; Viventi et al., 2011). Overall, technological progress in this context has achieved a stage where even signals of individual cells can be detected (Almasri et al., 2020; Khodagholy et al., 2015), and transparent devices allowing parallel optogenetic modulation (Lee et al., 2017) have become possible. In terms of overall technology readiness, NeuraLink has recently presented a

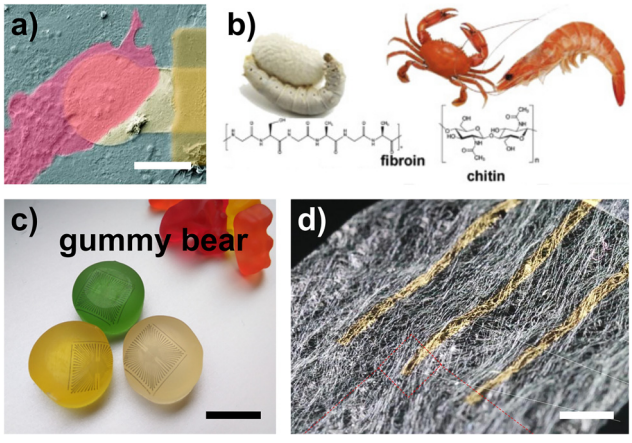

Figure 3: Reducing the invasiveness of neuroelectronic devices using novel materials. **a)** Scanning electron micrograph of a cardiomyocyte-like cell (pink) on an electrode (light yellow) insulated with photostructurable silk fibroin (dark yellow; scale bar corresponds to 25 µm; adapted from Ju et al., 2020). **b)** Sources and structures of silk fibroin and chitin (left and right, respectively; adapted from Pradhan et al., 2020). **c)** Electrode arrays printed on soft gelatin from gummy bears (scale bar correspond to approx. 10 mm; adapted from Adly et al., 2018). **d)** Ultrasoft polyurethane meshes with gold electrodes to record cardiac activity without disturbing mechanical activity (scale bar corresponds to 200 µm; adapted by permission from Lee et al., © Springer Nature 2018).

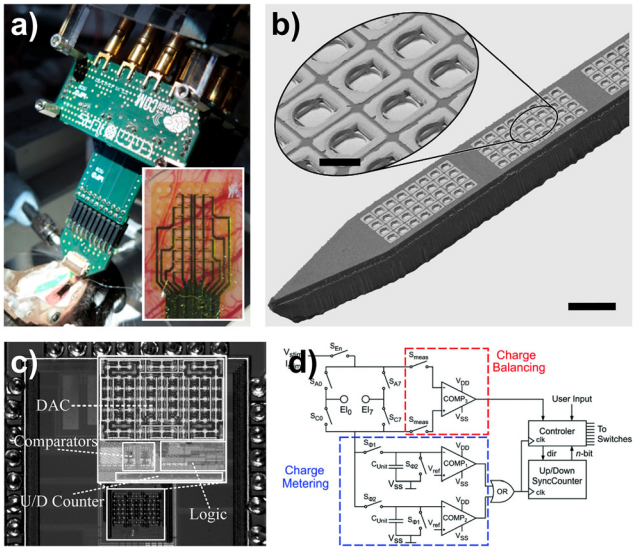

Figure 4: Specialized hardware for neuroelectronic devices. **a)** A graphene-based transistor array is used to record neuronal activity from the surface of the brain (adapted with permission from Garcia-Cortadella et al., © 2020 American Chemical Society). **b)** Complementary metal-oxide-semiconductor fabrication can be used to fabricate implantable electrode arrays with dense electrode spacing (scale bars in the main image and the inlay correspond to 100 and 20 µm, respectively; © 2018 IEEE. Adapted, with permission, from Sayed Herbawi et al., 2018). **c)** A specialized analog to digital converter consuming as little as 0.5 µW (© 2013 IEEE. Adapted, with permission, from Li et al., 2013). **d)** Circuit diagram for safe (i.e. charge-balanced) and power-efficient stimulation hardware (© 2020 IEEE. Adapted, with permission, from Guan et al., 2020).

platform that performs robotic implantation of and wireless recordings from thousands of channels in living animals (Musk and Neuralink, 2019). In particular, recordings from pigs and proof-of-concept brain-computer interface scenarios using monkeys have been demonstrated. Lastly, apart from thin probes, the importance of probe geometry in reducing glial scaring was shown early on (Seymour and Kipke, 2007). Since then, this approach has been heavily explored to yield shuttle techniques that only leave thin implants within the tissue (Williamson et al., 2015), injectable micron-scale meshes (Zhou et al., 2017), carbon fiber arrays (Jiman et al., 2020), and highly parallelized microwire bundles coupled to complementary metal-oxide semiconductor (CMOS) chips (Kollo et al., 2020; Obaid et al., 2020).

Hardware developments

So far, we have covered the progress neuroelectronic devices have made in increasing the efficiency of signal transduction as well as preventing the body from rejecting them. However, before such signals can be interpreted by a researcher they have to be both amplified and digitized. Here, several aspects of importance will be illustrated in the following section. Firstly, principles of local amplification to prevent long leads from introducing noise will be described. Subsequently, we will briefly dive into specialized electronics that aim to keep both spatial and energy requirements at a minimum. Lastly, wireless approaches to minimize constraints during e.g. behavioral studies will be introduced.

Local amplification

Despite the aforementioned advances in improving transduction, biological signals remain low in amplitude in the majority of scenarios. At the same time, they commonly have to be routed over significant lengths before they can be captured by recording electronics. For the most part, this combination results in challenging signal-to-noise ratios at the point of digitization. To address this challenge, different approaches aim to amplify the signal *before* routing – and thereby before the introduction of noise. A prominent approach to achieve such a local amplification is to use field-effect transistors (FETs) as recording elements. Bioelectronic applications of FETs have been presented not only on the basis of both PEDOT:PSS (Leleux et al., 2015) but also two-dimensional materials such as graphene (compare Figure 4a; Garcia-Cortadella et al., 2020; Schaefer et al., 2020). Alternatively, it was shown that it is even possible to directly integrate the necessary amplification circuitry within the recording device (Frey et al., 2009). The fabrication complexity needed to accomplish this is currently only manageable with CMOS fabrication. At the same time, however, CMOS allows ultra-dense electrode arrays that enable tracking action potentials down to a subcellular resolution (Bakkum et al., 2013; Lewandowska et al., 2015). More recently, CMOS fabricated shank electrodes that bring a similar electrode density to *in vivo* applications have been presented (Boi et al., 2020; Sayed Herbawi et al., 2018; see Figure 4b).

Specialized electronics

Despite the sizeable challenges of detecting biological signals, the electronic backend needed to digitize and record the data often represents a major bottleneck. This can have a number of reasons starting from the sheer amount of data to be handled to size or energy constraints when considering wireless, implantable systems. Driven by these constraints

and the increasing demand in terms of the functionality of neuroelectronic devices, the development of specialized hardware for bioelectronic recordings is a vivid field of research. In particular, the combined demands of recording, stimulation, and ideally pre-processing of the signals are of central interest (Liu et al., 2020; Rincón Montes et al., 2019). Especially when considering non-tethered, mobile applications, power consumption is a crucial factor. Here, digitization elements requiring only µW of power (Li et al., 2013; see Figure 4d), low-energy signal processing elements (Haddad and Serdijn, 2009; Hiseni et al., 2009), or efficient stimulation circuitry (compare Figure 4c; van Dongen and Serdijn, 2016; Guan et al., 2020; Kolovou Kouri et al., 2021) have been proposed. In particular for the latter, development has reached a point where even syringe-injectable stimulation hardware is within reach (Li et al., 2015).

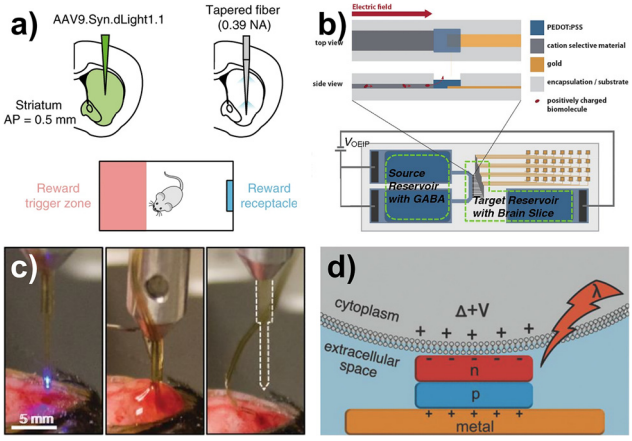

Figure 5: New modalities to broaden the neuroelectronic toolset. **a)** Tapered fibers can be used in depth-resolved photometric recordings (adpated by permission from Pisano et al., 2019). **b)** Schematic of a bioelectronic neural pixel, a device that can record electrically and deliver chemical stimuli in the same position (Jonsson et al., 2016). **c)** Image sequence of the insertion of an injectable, cellular scale optoelectronic device (From Kim et al., 2013. Reprinted with permission from AAAS). **d)** Schematic of direct photocapacitive stimulation. Shining light onto the stimulation site results in polarization of the photocapacitor, which in turn depolarizes adjacent cells (Rand et al., 2018).

New recording/stimulation modalities

Up to this point, the main focus of most applications we discussed revolved around purely electrical recording and stimulation. While electrical signals are – particularly with respect to the nervous system – of unquestionable importance, a range of other physical phenomena can be recorded from biological systems or used to elicit biological signals (Rivnay et al., 2017). Examples of such multimodal recordings include, for instance, the detection of strain and/or temperature in biological tissue (Xu et al., 2014; Yokota et al., 2015). Apart from the measurement of such physical quantities within the tissue, chemical signals belong to the body's own communication system. Here, protocols that counteract the common problem of electrode fouling have recently been presented to allow long-term monitoring of biologically relevant electroactive species *in vivo* (Weltin et al., 2019). In order to deliver chemical stimuli, passive release from the aforementioned conductive polymer nanotubes was investigated (Abidian and Martin, 2009). In applications that require a more discrete delivery of chemicals, electrophoretic (Proctor et al., 2019; Simon et al., 2009), electrochemical (Boehler et al., 2017), or microfluidic (Guo et al., 2021) delivery were shown to be viable options. In order to directly measure the tissue response to the stimulus, even chemical stimulation and electrical sensing with the very same electrode were demonstrated (Jonsson et al., 2016; compare Figure 5b).

The spread of optogenetics over the past two decades has demonstrated how versatile of a tool optical light can be. Naturally, implantable optoelectronic devices that allow coupling between the techniques described above and the potential of optogenetics are thus of great interest (Pisanello, 2019; Pisanello et al., 2016). But apart from delivering stimuli, optical tools can also be used to record photometric data in freely behaving animals (Pisano et al., 2019; refer to Figure 5a). Similar to electrical devices, optical technology was also advanced to reach wireless (Park et al., 2015; Samineni et al., 2017) or injectable (Kim et al., 2013; see Figure 5c) levels. Even without genetic modification, the use of photocapacitive or photofaradaic (i.e. materials that convert light into electricity) allows harnessing the tether-free nature of optical stimulation (Ghezzi et al., 2011; Paltrinieri et al., 2021; Rand et al., 2018; compare Figure 5d). Similarly, even ultrasonic or magnetoelectric signal transduction has been discussed (Seo et al., 2016; Singer et al., 2020).

Conclusions

Over the past 20 years, the key barriers for efficient multimodal recording and seamless integration of neuroelectronics devices have been identified and put under scrutinous investigation. Although some of these barriers have proven tougher than expected, immense progress was made to the point where clinical applications of more

sophisticated bioelectric approaches are within reach. Minev et al., for instance, were able to use soft neuroelectronic implants to restore locomotion after paralyzing injury in rats (Minev et al., 2015). They were able to demonstrate that their thin, soft implant not only limits inflammation but also results in a more natural gait after recovery. Similarly, the improved device-tissue coupling offered by hydrogel-supported electrode arrays allows fiber-selective stimulation of the vagus nerve in rats while presumably limiting compression (Forssell et al., 2019; Horn et al., 2021). In the CNS, organic electrochemical transistor arrays can record dopamine levels in different positions over time. Such recordings recently revealed a complex cross-talk between mesolimbic and nigrostriatal pathways in the rat brain (Xie et al., 2020).

We believe that in particular the concerted efforts from different fields such as electronic engineering, biochemistry, material science, and microfabrication ensure steady progress toward further blurring the line between technology and biology. Once this line is passed, neuroelectronic devices will deliver on their promise for many applications in prosthetic, diagnostic, and therapeutic applications.

Author contributions: All the authors have accepted responsibility for the entire content of this submitted manuscript and approved submission.
Research funding: None declared.
Conflict of interest statement: The authors declare no conflicts of interest regarding this article.

References

Abidian, M.R. and Martin, D.C. (2008). Experimental and theoretical characterization of implantable neural microelectrodes modified with conducting polymer nanotubes. Biomaterials *29*, 1273–1283.

Abidian, M.R. and Martin, D.C. (2009). Multifunctional nanobiomaterials for neural interfaces. Adv. Funct. Mater. *19*, 573–585.

Abidian, M.R., Ludwig, K.A., Marzullo, T.C., Martin, D.C., and Kipke, D.R. (2009). Interfacing conducting polymer nanotubes with the central nervous system: chronic neural recording using poly(3,4-ethylenedioxythiophene) nanotubes. Adv. Mater. *21*, 3764–3770.

Abidian, M.R., Corey, J.M., Kipke, D.R., and Martin, D.C. (2010). Conducting-polymer nanotubes improve electrical properties, mechanical adhesion, neural attachment, and neurite outgrowth of neural electrodes. Small *6*, 421–429.

Adly, N., Weidlich, S., Seyock, S., Brings, F., Yakushenko, A., Offenhäusser, A., and Wolfrum, B. (2018). Printed microelectrode arrays on soft materials: from PDMS to hydrogels. NPJ Flex. Electron. *2*, 15.

Afanasenkau, D., Kalinina, D., Lyakhovetskii, V., Tondera, C., Gorsky, O., Moosavi, S., Pavlova, N., Merkulyeva, N., Kalueff, A.V., Minev, I.R., et al. (2020). Rapid prototyping of soft bioelectronic implants for use as neuromuscular interfaces. Nat. Biomed. Eng. *4*, 1010–1022.

Almasri, R.M., AlChamaa, W., Tehrani-Bagha, A.R., and Khraiche, M.L. (2020). Highly flexible single-unit resolution all printed neural interface on a bioresorbable backbone. ACS Appl. Bio Mater. *3*, 7040–7051.

Angle, M.R., Cui, B., and Melosh, N.A. (2015). Nanotechnology and neurophysiology. Curr. Opin. Neurobiol. *32*, 132–140.

Bakkum, D.J., Frey, U., Radivojevic, M., Russell, T.L., Müller, J., Fiscella, M., Takahashi, H., and Hierlemann, A. (2013). Tracking axonal action potential propagation on a high-density microelectrode array across hundreds of sites. Nat. Commun. *4*, 2181.

Barrese, J.C., Rao, N., Paroo, K., Triebwasser, C., Vargas-Irwin, C., Franquemont, L., and Donoghue, J.P. (2013). Failure mode analysis of silicon-based intracortical microelectrode arrays in non-human primates. J. Neural Eng. *10*, 066014.

Bettinger, C.J. (2018). Recent advances in materials and flexible electronics for peripheral nerve interfaces. Bioelectron. Med. *4*, 6.

Bettucci, O., Matrone, G.M., and Santoro, F. (2021). Conductive polymer-based bioelectronic platforms toward sustainable and biointegrated devices: a journey from skin to brain across human body interfaces. Adv. Mater. Technol. 2100293, https://doi.org/10.1002/admt.202100293.

Biran, R., Martin, D.C., and Tresco, P.A. (2005). Neuronal cell loss accompanies the brain tissue response to chronically implanted silicon microelectrode arrays. Exp. Neurol. *195*, 115–126.

Boehler, C., Stieglitz, T., and Asplund, M. (2015). Nanostructured platinum grass enables superior impedance reduction for neural microelectrodes. Biomaterials *67*, 346–353.

Boehler, C., Kleber, C., Martini, N., Xie, Y., Dryg, I., Stieglitz, T., Hofmann, U.G., and Asplund, M. (2017). Actively controlled release of dexamethasone from neural microelectrodes in a chronic *in vivo* study. Biomaterials *129*, 176–187.

Boi, F., Perentos, N., Lecomte, A., Schwesig, G., Zordan, S., Sirota, A., Berdondini, L., and Angotzi, G.N. (2020). Multi-shanks SiNAPS Active Pixel Sensor CMOS probe: 1024 simultaneously recording channels for high-density intracortical brain mapping. BioRxiv 749911.

Borda, E., Ferlauto, L., Schleuniger, J., Mustaccio, A., Lütolf, F., Lücke, A., Fricke, S., Marjanović, N., and Ghezzi, D. (2020). All-printed electrocorticography array for *in vivo* neural recordings. Adv. Eng. Mater. *22*, 1901403.

Brüggemann, D., Wolfrum, B., Maybeck, V., Mourzina, Y., Jansen, M., and Offenhäusser, A. (2011). Nanostructured gold microelectrodes for extracellular recording from electrogenic cells. Nanotechnology *22*, 265104.

Cui, X. and Martin, D.C. (2003a). Fuzzy gold electrodes for lowering impedance and improving adhesion with electrodeposited conducting polymer films. Sens. Actuators Phys. *103*, 384–394.

Cui, X. and Martin, D.C. (2003b). Electrochemical deposition and characterization of poly(3,4-ethylenedioxythiophene) on neural microelectrode arrays. Sens. Actuators B Chem. *89*, 92–102.

Cui, X., Lee, V.A., Raphael, Y., Wiler, J.A., Hetke, J.F., Anderson, D.J., and Martin, D.C. (2001). Surface modification of neural recording electrodes with conducting polymer/biomolecule blends. J. Biomed. Mater. Res. *56*, 261–272.

Cuttaz, E., Goding, J., Vallejo-Giraldo, C., Aregueta-Robles, U., Lovell, N., Ghezzi, D., and A. Green, R. (2019). Conductive elastomer composites for fully polymeric, flexible bioelectronics. Biomater. Sci. *7*, 1372–1385.

Decataldo, F., Cramer, T., Martelli, D., Gualandi, I., Korim, W.S., Yao, S.T., Tessarolo, M., Murgia, M., Scavetta, E., Amici, R., et al. (2019). Stretchable low impedance electrodes for bioelectronic recording from small peripheral nerves. Sci. Rep. *9*, 10598.

Dong, R., Liu, X., Cheng, S., Tang, L., Chen, M., Zhong, L., Chen, Z., Liu, S., and Jiang, X. (2021). Highly stretchable metal-polymer conductor electrode array for electrophysiology. Adv. Healthc. Mater. *10*, 2000641.

van Dongen, M. and Serdijn, W. (2016). Introduction. Design of Efficient and Safe Neural Stimulators: A Multidisciplinary Approach. M. van Dongen and W. Serdijn, eds. (Cham: Springer International Publishing), pp. 1–8.

Ferlauto, L., D'Angelo, A.N., Vagni, P., Airaghi Leccardi, M.J.I., Mor, F.M., Cuttaz, E.A., Heuschkel, M.O., Stoppini, L., and Ghezzi, D. (2018). Development and characterization of PEDOT:PSS/alginate soft microelectrodes for application in neuroprosthetics. Front. Neurosci. *12*, 648.

Ferro, M.D. and Melosh, N.A. (2018). Electronic and ionic materials for neurointerfaces. Adv. Funct. Mater. *28*, 1704335.

Forssell, M., Sciullo, M., Mou, C., Sun, F., Simpson, T.W., Xiao, G., Fisher, L.E., Bettinger, C., Horn, C.C., and Fedder, G.K. (2019). Compliant adhesive cuff electrode for selective stimulation in rat vagus nerve. 2019 IEEE SENSORS, pp. 1–4.

Frey, U., Egert, U., Heer, F., Hafizovic, S., and Hierlemann, A. (2009). Microelectronic system for high-resolution mapping of extracellular electric fields applied to brain slices. Biosens. Bioelectron. *24*, 2191–2198.

Galvani, L. (1791). De viribus electricitatis in motu musculari commentarius. Bologna Accad. Delle Sci.

Garcia-Cortadella, R., Schäfer, N., Cisneros-Fernandez, J., Ré, L., Illa, X., Schwesig, G., Moya, A., Santiago, S., Guirado, G., Villa, R., et al. (2020). Switchless multiplexing of graphene active sensor arrays for brain mapping. Nano Lett. *20*, 3528–3537.

Ghezzi, D., Antognazza, M.R., Dal Maschio, M., Lanzarini, E., Benfenati, F., and Lanzani, G. (2011). A hybrid bioorganic interface for neuronal photoactivation. Nat. Commun. *2*, 166.

Giagka, V. and Serdijn, W.A. (2018). Realizing flexible bioelectronic medicines for accessing the peripheral nerves – technology considerations. Bioelectron. Med. *4*, 8.

Guan, R., Zufiria, P.G., Giagka, V., and Serdijn, W.A. (2020). Circuit design considerations for power-efficient and safe implantable electrical neurostimulators. IEEE 11th Latin American Symposium on Circuits Systems (LASCAS), 2020, pp. 1–4.

Guo, J., Yu, Y., Cai, L., Wang, Y., Shi, K., Shang, L., Pan, J., and Zhao, Y. (2021). Microfluidics for flexible electronics. Mater. Today *44*, 105–135.

Haddad, S.A.P. and Serdijn, W.A. (2009). Ultra Low-Power Biomedical Signal Processing: An Analog Wavelet Filter Approach for Pacemakers (Springer Netherlands: Heidelberg).

Hiseni, S., Sawigun, C., Ngamkham, W., and Serdijn, W.A. (2009). A compact, nano-power CMOS action potential detector. IEEE Biomedical Circuits and Systems Conference, 2009, pp. 97–100.

Horn, C.C., Forssell, M., Sciullo, M., Harms, J.E., Fulton, S., Mou, C., Sun, F., Simpson, T.W., Xiao, G., Fisher, L.E., et al. (2021). Hydrogel-based electrodes for selective cervical vagus nerve stimulation. J. Neural Eng. *18*, 055008.

Hu, W.-J., Eaton, J.W., Ugarova, T.P., and Tang, L. (2001). Molecular basis of biomaterial-mediated foreign body reactions. Blood *98*, 1231–1238.

Hubel, D.H. (1957). Tungsten microelectrode for recording from single units. Science *125*, 549–550.

Inal, S., Rivnay, J., Suiu, A.-O., Malliaras, G.G., and McCulloch, I. (2018). Conjugated polymers in bioelectronics. Acc. Chem. Res. *51*, 1368–1376.

Jeong, J.-W., Shin, G., Park, S.I., Yu, K.J., Xu, L., and Rogers, J.A. (2015). Soft materials in neuroengineering for hard problems in neuroscience. Neuron *86*, 175–186.

Jiman, A.A., Ratze, D.C., Welle, E.J., Patel, P.R., Richie, J.M., Bottorff, E.C., Seymour, J.P., Chestek, C.A., and Bruns, T.M. (2020). Multi-channel intraneural vagus nerve recordings with a novel high-density carbon fiber microelectrode array. Sci. Rep. *10*, 15501.

Jonsson, A., Inal, S., Uguz, I., Williamson, A.J., Kergoat, L., Rivnay, J., Khodagholy, D., Berggren, M., Bernard, C., Malliaras, G.G., et al. (2016). Bioelectronic neural pixel: chemical stimulation and electrical sensing at the same site. Proc. Natl. Acad. Sci. *113*, 9440–9445.

Ju, J., Hu, N., Cairns, D.M., Liu, H., and Timko, B.P. (2020). Photo-cross-linkable, insulating silk fibroin for bioelectronics with enhanced cell affinity. Proc. Natl. Acad. Sci. *117*, 15482–15489.

Kang, P.-L., Lin, Y.-H., Settu, K., Yen, C.-S., Yeh, C.-Y., Liu, J.-T., Chen, C.-J., and Chang, S.-J. (2020). A facile fabrication of biodegradable and biocompatible cross-linked gelatin as screen printing substrates. Polymers *12*, 1186.

Khodagholy, D., Doublet, T., Gurfinkel, M., Quilichini, P., Ismailova, E., Leleux, P., Herve, T., Sanaur, S., Bernard, C., and Malliaras, G.G. (2011). Highly conformable conducting polymer electrodes for *in vivo* recordings. Adv. Mater. *23*, H268–H272.

Khodagholy, D., Doublet, T., Quilichini, P., Gurfinkel, M., Leleux, P., Ghestem, A., Ismailova, E., Hervé, T., Sanaur, S., Bernard, C., et al. (2013). *In vivo* recordings of brain activity using organic transistors. Nat. Commun. *4*, 1575.

Khodagholy, D., Gelinas, J.N., Thesen, T., Doyle, W., Devinsky, O., Malliaras, G.G., and Buzsáki, G. (2015). NeuroGrid: recording action potentials from the surface of the brain. Nat. Neurosci. *18*, 310–315.

Kim, D.-H., Abidian, M., and Martin, D.C. (2004). Conducting polymers grown in hydrogel scaffolds coated on neural prosthetic devices. J. Biomed. Mater. Res. A *71A*, 577–585.

Kim, D.-H., Richardson-Burns, S.M., Hendricks, J.L., Sequera, C., and Martin, D.C. (2007). Effect of immobilized nerve growth factor on conductive polymers: electrical properties and cellular response. Adv. Funct. Mater. *17*, 79–86.

Kim, D.-H., Wiler, J.A., Anderson, D.J., Kipke, D.R., and Martin, D.C. (2010). Conducting polymers on hydrogel-coated neural electrode provide sensitive neural recordings in auditory cortex. Acta Biomater *6*, 57–62.

Kim, T., McCall, J.G., Jung, Y.H., Huang, X., Siuda, E.R., Li, Y., Song, J., Song, Y.M., Pao, H.A., Kim, R.-H., et al. (2013). Injectable, cellular-scale optoelectronics with applications for wireless optogenetics. Science *340*, 211–216.

Kireev, D., Rincón Montes, V., Stevanovic, J., Srikantharajah, K., and Offenhäusser, A. (2019). N3-MEA probes: scooping neuronal networks. Front. Neurosci. *13*, 320.

Kollo, M., Racz, R., Hanna, M.-E., Obaid, A., Angle, M.R., Wray, W., Kong, Y., Müller, J., Hierlemann, A., and Melosh, N.A., et al. (2020). CHIME: CMOS-hosted *in vivo* microelectrodes for massively scalable neuronal recordings. Front. Neurosci. *14*, 834.

Lacour, S.P., Wagner, S., Huang, Z., and Suo, Z. (2003). Stretchable gold conductors on elastomeric substrates. Appl. Phys. Lett. *82*, 2404–2406.

Kolovou Kouri, K., Soloukey, S., Harhangi, B., Serdijn, W.A., and Giagka, V. (2021). Development of Dorsal Root Ganglion (DRG) Multichannel Stimulator Prototype for use in Early Clinical Trials. Abstract from 8th Dutch Biomedical Engineering Conference (BME) 2021, Netherlands.

Lacour, S.P., Chan, D., Wagner, S., Li, T., and Suo, Z. (2006). Mechanisms of reversible stretchability of thin metal films on elastomeric substrates. Appl. Phys. Lett. *88*, 204103.

Leccardi, M.J.I.A., Vagni, P., and Ghezzi, D. (2019). Multilayer 3D electrodes for neural implants. J. Neural Eng. *16*, 026013.

Lee, W., Kim, D., Matsuhisa, N., Nagase, M., Sekino, M., Malliaras, G.G., Yokota, T., and Someya, T. (2017). Transparent, conformable, active multielectrode array using organic electrochemical transistors. Proc. Natl. Acad. Sci. *114*, 10554–10559.

Lee, S., Sasaki, D., Kim, D., Mori, M., Yokota, T., Lee, H., Park, S., Fukuda, K., Sekino, M., and Matsuura, K., et al. (2018). Ultrasoft electronics to monitor dynamically pulsing cardiomyocytes. Nat. Nanotechnol. *1*, 156–160.

Leleux, P., Rivnay, J., Lonjaret, T., Badier, J.-M., Bénar, C., Hervé, T., Chauvel, P., and Malliaras, G.G. (2015). Organic electrochemical transistors for clinical applications. Adv. Healthc. Mater. *4*, 142–147.

Lewandowska, M.K., Bakkum, D.J., Rompani, S.B., and Hierlemann, A. (2015). Recording large extracellular spikes in microchannels along many axonal sites from individual neurons. PLoS ONE *10*, 1–24.

Li, X., Serdijn, W.A., Zheng, W., Tian, Y., and Zhang, B. (2015). The injectable neurostimulator: an emerging therapeutic device. Trends Biotechnol. *33*, 388–394.

Li, Y., Zhao, D., and Serdijn, W.A. (2013). A sub-microwatt asynchronous level-crossing ADC for biomedical applications. IEEE Trans. Biomed. Circuits Syst. *7*, 149–157.

Liang, Y., Offenhäusser, A., Ingebrandt, S., and Mayer, D. (2021). PEDOT:PSS-based bioelectronic devices for recording and modulation of electrophysiological and biochemical cell signals. Adv. Healthc. Mater. *10*, 2100061.

Lienemann, S., Zötterman, J., Farnebo, S., and Tybrandt, K. (2021). Stretchable gold nanowire-based cuff electrodes for low-voltage peripheral nerve stimulation. J. Neural Eng. *18*, 045007.

Lissandrello, C.A., Gillis, W.F., Shen, J., Pearre, B.W., Vitale, F., Pasquali, M., Holinski, B.J., Chew, D.J., White, A.E., and Gardner, T.J. (2017). A micro-scale printable nanoclip for electrical stimulation and recording in small nerves. J. Neural Eng. *14*, 036006.

Liu, Y., Urso, A., Martins da Ponte, R., Costa, T., Valente, V., Giagka, V., Serdijn, W.A., Constandinou, T.G., and Denison, T. (2020). Bidirectional bioelectronic interfaces: system design and circuit implications. IEEE Solid-State Circuits Mag. *12*, 30–46.

Maiolo, L., Polese, D., and Convertino, A. (2019). The rise of flexible electronics in neuroscience, from materials selection to *in vitro* and *in vivo* applications. Adv. Phys. X *4*, 1664319.

Marrese, C.A. (1987). Preparation of strongly adherent platinum black coatings. Anal. Chem. *59*, 217–218.

Minev, I.R., Musienko, P., Hirsch, A., Barraud, Q., Wenger, N., Moraud, E.M., Gandar, J., Capogrosso, M., Milekovic, T., Asboth, L., et al. (2015). Electronic dura mater for long-term multimodal neural interfaces. Science *347*, 159–163.

Moshayedi, P., Ng, G., Kwok, J.C.F., Yeo, G.S.H., Bryant, C.E., Fawcett, J.W., Franze, K., and Guck, J. (2014). The relationship between glial cell mechanosensitivity and foreign body reactions in the central nervous system. Biomaterials *35*, 3919–3925.

Musk, E. and Neuralink (2019). An integrated brain-machine interface platform with thousands of channels. BioRxiv 703801.

Neher, E. and Sakmann, B. (1976). Single-channel currents recorded from membrane of denervated frog muscle fibres. Nature *260*, 799–802.

Obaid, A., Hanna, M.-E., Wu, Y.-W., Kollo, M., Racz, R., Angle, M.R., Müller, J., Brackbill, N., Wray, W., Franke, F., et al. (2020). Massively parallel microwire arrays integrated with CMOS chips for neural recording. Sci. Adv. *6*, eaay2789.

Ong, X.C., Huang, W.-C., Kwon, I.S., Gopinath, C., Wu, H., Fisher, L.E., Gaunt, R.A., Bettinger, C.J., and Fedder, G.K. (2018). Ultra-compliant peripheral nerve cuff electrode with hydrogel adhesion. 2018 IEEE Micro Electro Mechanical Systems (MEMS), pp. 376–379.

Otchy, T.M., Michas, C., Lee, B., Gopalan, K., Nerurkar, V., Gleick, J., Semu, D., Darkwa, L., Holinski, B.J., Chew, D.J., et al. (2020). Printable microscale interfaces for long-term peripheral nerve mapping and precision control. Nat. Commun. *11*, 4191.

Paltrinieri, T., Bondi, L., Đerek, V., Fraboni, B., Głowacki, E.D., and Cramer, T. (2021). Understanding photocapacitive and photofaradaic processes in organic semiconductor photoelectrodes for optobioelectronics. Adv. Funct. Mater. *31*, 2010116.

Park, S.I., Brenner, D.S., Shin, G., Morgan, C.D., Copits, B.A., Chung, H.U., Pullen, M.Y., Noh, K.N., Davidson, S., Oh, S.J., et al. (2015). Soft, stretchable, fully implantable miniaturized optoelectronic systems for wireless optogenetics. Nat. Biotechnol. *33*, 1280–1286.

Pisanello, F. (2019). Implantable micro and nanophotonic devices: toward a new generation of neural interfaces. Microelectron. Eng. *215*, 110979.

Pisanello, F., Sileo, L., and De Vittorio, M. (2016). Micro- and nanotechnologies for optical neural interfaces. Front. Neurosci. *10*, https://doi.org/10.3389/fnins.2016.00070.

Pisano, F., Pisanello, M., Lee, S.J., Lee, J., Maglie, E., Balena, A., Sileo, L., Spagnolo, B., Bianco, M., Hyun, M., et al. (2019). Depth-resolved fiber photometry with a single tapered optical fiber implant. Nat. Methods *16*, 1185–1192.

Pradhan, S., Brooks, A.K., and Yadavalli, V.K. (2020). Nature-derived materials for the fabrication of functional biodevices. Mater. Today Bio *7*, 100065.

Proctor, C.M., Uguz, I., Slezia, A., Curto, V., Inal, S., Williamson, A., and Malliaras, G.G. (2019). An electrocorticography device with an integrated microfluidic ion pump for simultaneous neural recording and electrophoretic drug delivery *in vivo*. Adv. Biosyst. *3*, 1800270.

Purcell, E.K., Seymour, J.P., Yandamuri, S., and Kipke, D.R. (2009). *In vivo* evaluation of a neural stem cell-seeded prosthesis. J. Neural Eng. *6*, 026005.

Rand, D., Jakešová, M., Lubin, G., Vėbraitė, I., David-Pur, M., Đerek, V., Cramer, T., Sariciftci, N.S., Hanein, Y., and Głowacki, E.D. (2018). Direct electrical neurostimulation with organic pigment photocapacitors. Adv. Mater. *30*, 1707292.

Renz, A.F., Reichmuth, A.M., Stauffer, F., Thompson-Steckel, G., and Vörös, J. (2018). A guide towards long-term functional electrodes interfacing neuronal tissue. J. Neural Eng. *15*, 061001.

Richardson-Burns, S.M., Hendricks, J.L., Foster, B., Povlich, L.K., Kim, D.-H., and Martin, D.C. (2007a). Polymerization of the conducting polymer poly(3,4-ethylenedioxythiophene) (PEDOT) around living neural cells. Biomaterials *28*, 1539–1552.

Richardson-Burns, S.M., Hendricks, J.L., and Martin, D.C. (2007b). Electrochemical polymerization of conducting polymers in living neural tissue. J. Neural Eng. *4*, L6–L13.

Rincón Montes, V., Gehlen, J., Lück, S., Mokwa, W., Müller, F., Walter, P., and Offenhäusser, A. (2019). Toward a bidirectional communication between retinal cells and a prosthetic device – a proof of concept. Front. Neurosci. *13*, 367.

Rivnay, J., Wang, H., Fenno, L., Deisseroth, K., and Malliaras, G.G. (2017). Next-generation probes, particles, and proteins for neural interfacing. Sci. Adv. *3*, e1601649.

Rochford, A.E., Carnicer-Lombarte, A., Curto, V.F., Malliaras, G.G., and Barone, D.G. (2019). When bio meets technology: biohybrid neural interfaces. Adv. Mater. *32*, 1903182.

Rogers, J.A., Someya, T., and Huang, Y. (2010). Materials and mechanics for stretchable electronics. Science *327*, 1603–1607.

Samineni, V.K., Yoon, J., Crawford, K.E., Jeong, Y.R., McKenzie, K.C., Shin, G., Xie, Z., Sundaram, S.S., Li, Y., Yang, M.Y., et al. (2017). Fully implantable, battery-free wireless optoelectronic devices for spinal optogenetics. PAIN *158*, 2108–2116.

Sayed Herbawi, A., Christ, O., Kiessner, L., Mottaghi, S., Hofmann, U.G., Paul, O., and Ruther, P. (2018). CMOS neural probe with 1600 close-packed recording sites and 32 analog output channels. J. Microelectromechanical Syst. *27*, 1023–1034.

Schaefer, N., Garcia-Cortadella, R., Martínez-Aguilar, J., Schwesig, G., Illa, X., Lara, A.M., Santiago, S., Hébert, C., Guirado, G., Villa, R., et al. (2020). Multiplexed neural sensor array of graphene solution-gated field-effect transistors. 2D Mater. *7*, 025046.

Schuettler, M., Doerge, T., Wien, S.L., Becker, S., Staiger, A., Hanauer, M., Kammer, S., Stieglitz, T. (2005). Cytotoxicity of platinum black. 10th Annual Conference of the International Functional Electrical Stimulation Society: IFESS 2005. Proceedings, pp. 343–348.

Seo, D., Neely, R.M., Shen, K., Singhal, U., Alon, E., Rabaey, J.M., Carmena, J.M., and Maharbiz, M.M. (2016). Wireless recording in the peripheral nervous system with ultrasonic neural dust. Neuron *91*, 529–539.

Seymour, J.P. and Kipke, D.R. (2007). Neural probe design for reduced tissue encapsulation in CNS. Biomaterials *28*, 3594–3607.

Simon, D.T., Kurup, S., Larsson, K.C., Hori, R., Tybrandt, K., Goiny, M., Jager, E.W.H., Berggren, M., Canlon, B., and Richter-Dahlfors, A. (2009). Organic electronics for precise delivery of neurotransmitters to modulate mammalian sensory function. Nat. Mater. *8*, 742–746.

Singer, A., Dutta, S., Lewis, E., Chen, Z., Chen, J.C., Verma, N., Avants, B., Feldman, A.K., O'Malley, J., Beierlein, M., et al. (2020). Magnetoelectric materials for miniature, wireless neural stimulation at therapeutic frequencies. Neuron *107*, 631–643.e5.

Sperry, Z.J., Na, K., Parizi, S.S., Chiel, H.J., Seymour, J., Yoon, E., and Bruns, T.M. (2018). Flexible microelectrode array for interfacing with the surface of neural ganglia. J. Neural Eng. *15*, 036027.

Spira, M.E. and Hai, A. (2013). Multi-electrode array technologies for neuroscience and cardiology. Nat. Nanotechnol. *8*, 83–94.

Stevens, M.M. and George, J.H. (2005). Exploring and engineering the cell surface interface. Science *310*, 1135–1138.

Sunwoo, S.-H., Han, S.I., Joo, H., Cha, G.D., Kim, D., Choi, S.H., Hyeon, T., and Kim, D.-H. (2020). Advances in soft bioelectronics for brain research and clinical neuroengineering. Matter *3*, 1923–1947.

Terkan, K., Zurita, F., Jamal Khalaf, T., Rinklin, P., Teshima, T., Kohl, T., and Wolfrum, B. (2020). Soft peripheral nerve interface made from carbon nanotubes embedded in silicone. APL Mater. *8*, 101111.

Tybrandt, K., Khodagholy, D., Dielacher, B., Stauffer, F., Renz, A.F., Buzsáki, G., and Vörös, J. (2018). High-density stretchable electrode grids for chronic neural recording. Adv. Mater. *30*, 1706520.

Viventi, J., Kim, D.-H., Vigeland, L., Frechette, E.S., Blanco, J.A., Kim, Y.-S., Avrin, A.E., Tiruvadi, V.R., Hwang, S.-W., Vanleer, A.C., et al. (2011). Flexible, foldable, actively multiplexed, high-density electrode array for mapping brain activity *in vivo*. Nat. Neurosci. *14*, 1599–1605.

Weltin, A., Ganatra, D., König, K., Joseph, K., Hofmann, U.G., Urban, G.A., and Kieninger, J. (2019). New life for old wires: electrochemical sensor method for neural implants. J. Neural Eng. *17*, 016007.

Wilks, S.J., Richardson-Burn, S.M., Hendricks, J.L., Martin, D., and Otto, K.J. (2009). Poly(3,4-ethylene dioxythiophene) (PEDOT) as a micro-neural interface material for electrostimulation. Front. Neuroeng. *2*, 7.

Williamson, A., Ferro, M., Leleux, P., Ismailova, E., Kaszas, A., Doublet, T., Quilichini, P., Rivnay, J., Rózsa, B., Katona, G., et al. (2015). Localized neuron stimulation with organic electrochemical transistors on delaminating depth probes. Adv. Mater. *27*, 4405–4410.

Won, S.M., Song, E., Zhao, J., Li, J., Rivnay, J., and Rogers, J.A. (2018). Recent advances in materials, devices, and systems for neural interfaces. Adv. Mater. *30*, 1800534.

Xie, K., Wang, N., Lin, X., Wang, Z., Zhao, X., Fang, P., Yue, H., Kim, J., Luo, J., Cui, S., et al. (2020). Organic electrochemical transistor arrays for real-time mapping of evoked neurotransmitter release *in vivo*. ELife *9*, e50345.

Xie, Y., Martini, N., Hassler, C., Kirch, R.D., Stieglitz, T., Seifert, A., and Hofmann, U.G. (2014). *In vivo* monitoring of glial scar proliferation on chronically implanted neural electrodes by fiber optical coherence tomography. Front. Neuroeng. *7*, 34.

Xu, L., Gutbrod, S.R., Bonifas, A.P., Su, Y., Sulkin, M.S., Lu, N., Chung, H.-J., Jang, K.-I., Liu, Z., Ying, M., et al. (2014). 3D multifunctional integumentary membranes for spatiotemporal cardiac measurements and stimulation across the entire epicardium. Nat. Commun. *5*, 3329.

Yang, J. and Martin, D.C. (2004a). Microporous conducting polymers on neural microelectrode arrays: I. Electrochemical deposition. Sens. Actuators B Chem. *101*, 133–142.

Yang, J. and Martin, D.C. (2004b). Microporous conducting polymers on neural microelectrode arrays: II. Physical characterization. Sens. Actuators Phys. *113*, 204–211.

Yokota, T., Inoue, Y., Terakawa, Y., Reeder, J., Kaltenbrunner, M., Ware, T., Yang, K., Mabuchi, K., Murakawa, T., Sekino, M., et al. (2015). Ultraflexible, large-area, physiological temperature sensors for multipoint measurements. Proc. Natl. Acad. Sci. *112*, 14533–14538.

Zhang, P. and Travas-Sejdic, J. (2021). Fabrication of conducting polymer microelectrodes and microstructures for bioelectronics. J. Mater. Chem. C *9*, 9730–9760.

Zhou, T., Hong, G., Fu, T.-M., Yang, X., Schuhmann, T.G., Viveros, R.D., and Lieber, C.M. (2017). Syringe-injectable mesh electronics integrate seamlessly with minimal chronic immune response in the brain. Proc. Natl. Acad. Sci. *114*, 5894–5899.

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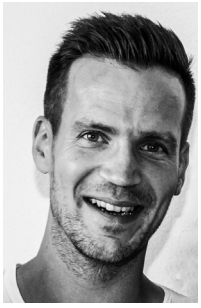

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Philipp Rinklin conducted his PhD research at the Research Center Jülich. His thesis on the mechanical, chemical, and thermal stimulation of cellular networks earned him a PhD title with RWTH Aachen in 2014. Following additional postdoctoral research in Jülich, Dr. Rinklin joined in starting the Neuroelectronics lab at the Technical University of Munich in 2015. Since then he focuses on printing-based fabrication for bio- and neuroelectronics. His interests cover inkjet, aerosol jet, stereolithography, or capillary plotting in this context. In particular, he aims to exploit these technologies in the development of large-area, low-cost sensor and stimulator arrays.

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Bernhard Wolfrum is Professor for Neuroelectronics at the Technical University of Munich (TUM). His research focuses on the development of neurotechnology devices and electrochemical sensor concepts. He studied physics in Göttingen and Santa Barbara (UCSB) before obtaining his PhD at the University of Göttingen. Afterward he conducted postdoctoral research at the Institute of Bio and Nanosystems, Forschungszentrum Jülich, and the Kavli Institute of Nanoscience, University of Delft. He led a Helmholtz Young Investigator Group at the Peter Grünberg Institute, Forschungszentrum Jülich, from 2009 until 2015 and lectured as a junior professor at RWTH Aachen (since 2011) before joining TUM in 2015. In 2017, he conducted research as a visiting associate professor at Tohoku University in Sendai.