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Toward the Next Generation of Neural Iontronic Interfaces

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Neural interfaces are evolving at a rapid pace owing to advances in material science and fabrication, reduced cost of scalable complementary metal oxide semiconductor (CMOS) technologies, and highly interdisciplinary teams of researchers and engineers that span a large range from basic to applied and clinical sciences. This study outlines currently established technologies, defined as instruments and biological study systems that are routinely used in neuroscientific research. After identifying the shortcomings of current technologies, such as a lack of biocompatibility, topological optimization, low bandwidth, and lack of transparency, it maps out promising directions along which progress should be made to achieve the next generation of symbiotic and intelligent neural interfaces. Lastly, it proposes novel applications that can be achieved by these developments, ranging from the understanding and reproduction of synaptic learning to live-long multimodal measurements to monitor and treat various neuronal disorders.

1. Introduction

A central challenge of the 21st century will unquestionably be the study of the brain, be it to tackle neural disorders or to unravel the learning and computational principles of neural networks to transform our energy-hungry software and hardware infrastructures. The understanding and the technological adaptation of the information processing principles of our brain are currently revolutionizing the fields of computer science as well as modern ways of utilizing complex sensor systems, capable of handling, evaluating, and classifying many complementary inputs similar to the human body (**Figure 1**).

The last decade in neural engineering has seen incredible progress from the biology side, enabling neuroscientists to create intricate model systems ranging from single cells, carefully engineered living neural networks,[1–5] human stem-cell-derived organoids,[6–9] and even assembloids.[10] While our understanding of neural function can be largely expanded by these biological systems that we can create and investigate with a variety of methods, a major limitation is still the degree of detail at which we can observe physiological processes in order to understand neuronal interactions and computation, be it the access to intracellular potentials at the network scale, subthreshold potentials, neurotransmitter concentrations, precise connectivity of networks, etc.

To obtain a full picture of neuronal network function requires three key parts: the neural networks' detailed connectivity, the electrical activity of individual cells comprising the network, and

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Figure 1. To harness the full potential of neural interfaces to interoperate with neural systems, they will have to integrate seamlessly into the biological tissue.

the chemical makeup of the cell-to-cell interactions in which neurochemical interactions via neurotransmitters are of particular interest.

A rapidly expanding suite of optical techniques provides a powerful way of non-invasively studying neural systems in great detail, as it enables high-resolution mapping of network morphology, measuring the neural activity of large neural networks at the single-cell level, and the ability to selectively stimulate neural populations via light-sensitive opsins.[11–13] However, most optical techniques to study neural activity are inherently limited by their low penetration depth, with even advanced tools like multiphoton microscopy being limited to penetration depths below one millimeter in live brain tissue, which severely hinders the study of non-transparent organoids or larger brains.[14] Furthermore, most applications rely on viral transfection to induce the production of light-sensitive opsins or reporter molecules in the tissue,[15] which can degenerate the function of neural tissue or alter the genetic integrity of tissues afflicted by single-gene mutations in the frame of neurodegenerative diseases.[16] Furthermore, the use of such optogenetic techniques is currently not permitted in human trials due to unknown long-term effects that can result from the genetic alteration of neural tissue.[17] A complementary approach to studying neural networks is to directly measure the fast electric potentials, called action potentials, that are produced by neurons to transmit binary events to downstream cells. These potentials can be measured by placing electrodes in the immediate vicinity of target neurons without requiring genetic modification of the neural tissue. The temporal resolution of signal acquisition for electrical measurements also allows capturing the waveform of single action potentials that optical techniques still struggle to resolve. Where optical techniques excel in spatial resolution, capturing the anatomy and connectivity of neural systems, electrical techniques provide the best temporal resolution and access to deeper brain regions[18,19] While recent advances in optics and molecular biology have largely expanded the toolbox of optical techniques, electrical techniques are catching up due to the development of high-density and flexible recording arrays,[20,21] and the application of new biocompatible organic and metal-organic hybrid materials. Here, we showcase these ongoing technological advances in electronics, microfabrication, and material engineering that are pushing electrical recording techniques to a new level. Furthermore, with recent developments in biosensing, such as highly sensitive and specific aptamer sensors or biochemical sensor principles,[22] new iontronic interfaces will be able to capture specific molecules and transduce biochemical signals to electrical ones, thereby capturing an integral part of neural communication and paving the way for truly integrated neural devices (**Figure 2**).

1.1. Fundamentals of Neuroelectronic Interfaces

An electrical neural interface consists of two main parts: the bulk of the device and the sensing electrodes. For in vitro cultures of dissociated neurons or brain slices, planar micro-electrode arrays can be used to record the electrical activity of neurons. Electrodes block light access and therefore devices can be transparent only for sparse electrode configurations. To resolve this issue and allow combined electro- and opto-physiological applications, different materials such as graphene, indium tin oxide (ITO), and conductive polymers are being explored to engineer optically transparent electrodes that are also resistant to light-induced artifacts.[48–50] However, a major remaining challenge is that the implants' interconnects are usually still made of metal, thus reducing device transparency with increasing electrode density. Transparency is important to allow optical access for

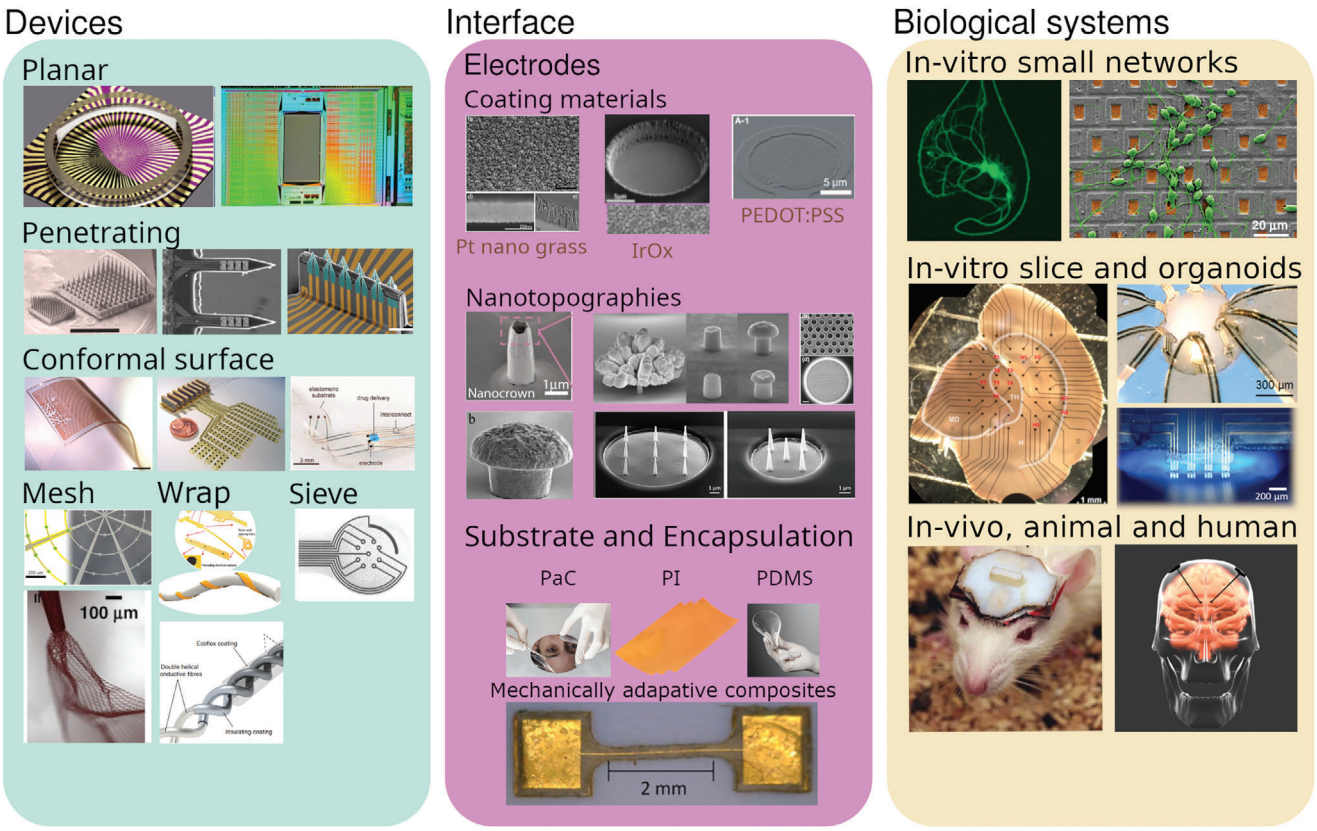

Figure 2. Overview of established neural interface technologies: A wide range of devices are available to fulfill various requirements of size, electrode density, conformability, depth, and transparency. These devices have to achieve locally tight coupling to their electrodes (or transistors) while the encapsulation interacts globally with the tissue and is tailored to specific needs such as transparency, deformability, stretchability, and biocompatibility. Devices can be planar (reproduced with permission.[20] Copyright 2014, IEEE), penetrating (reproduced with permission.[23–25] Copyright 1997, 2021, 2022, Elsevier, American Association for the Advancement of Science [AAAS], Springer Nature), or conformally adapt to irregular shapes. Reproduced with permission.[26–28] Copyright 2018, 2009, 2015, Wiley-VCH GmbH, IOP Publishing, AAAS. The devices can also have low footprint like meshes (reproduced with permission.[29,30] Copyright 2020, 2019, Elsevier, Springer Nature), wrap around thinner structures (reproduced with permission.[31,32] Copyright 2016, 2021, Wiley-VCH GmbH, Springer Nature), or resemble sieves to adapt to nerves. Reproduced with permission.[33] Copyright 2002, Wiley Periodicals LLC. The electrodes can be made of various materials (reproduced with permission.[34–36] Copyright 2015, 2021, 2012, Elsevier, Forschungszentrum Jülich, Frontiers), or nanotopograhpic shapes (reproduced with permission.[37–41] Copyright 2022, 2015, 2022, 2017, 2019, Springer Nature, Springer Nature, Wiley-VCH GmbH, IOP Publishing, American Chemical Society) to improve cell-adhesion. The insulation around the electrodes, which makes the bulk of the device, can be of various ceramics, elastomers, or even biomimetic materials. Reproduced with permission.[35,42] Copyright 2021, 2012, Forschungszentrum Jülich, Springer Nature. The combination of the global geometry, the choice of electrodes, and the bulk material enable the study of a host of systems ranging from a few neurons in vitro (reproduced with permission.[43,44] Copyright 2018, 2020, Elsevier, Springer Nature) to slices and organoids (reproduced with permission.[35,45,46] Copyright 2021, 2021, 2021, Forschungszentrum Jülich, Elsevier, AAAS) to even full brains. Reproduced with permission.[47] Copyright 2015, Springer Nature.

functional imaging or optical stimulation. In high-density microelectrode arrays, which commonly rely on CMOS technologies and switch matrices for selecting a specific subset of electrodes,[20] the substrate inevitably becomes opaque, making the combination of electrical and optical methods more challenging. For more invasive recordings, for instance from retinal neurons,[51,52] organoids,[53] thicker brain slices, or intact brain tissue,[54] penetrating electrode configurations are used in which a shank, a needle, or other sharp structure can be inserted into the tissue to access neurons in deeper regions. Such technologies are commonly used in sparse configurations, such as the UTAH array,[23] but high-density electrode configurations, such as Neuropixels arrays[18,24,55] have recently become more widespread and are likely to become the standard in future applications. Recent developments even offer transistor-based penetrating probes with improved recording sensitivity.[25,56] Some applications also require conformable or soft electronics, such as clinical electrode arrays and ECoG arrays for source localization,[57] but especially for chronic recordings in intact brains where the mechanical mismatch between stiff electrodes and the flexible, moving neural tissue can create neural damage and trigger an inflammatory response.[26–28,30–32,58] Conformability is also a strategy that is pursued for inserting devices long-term into brain tissue, allowing the measuring electrodes to move and adapt within the neural tissue without causing damage or an immune response.[30,58] To achieve such mechanical properties, the components of the device should have a low footprint of less than ten microns, which also preserves the larger cellular structures

(e.g ventricular zones in organoids). The small dimensions required do not lend themselves to the use of elastomers. Indeed, when made too thin, they are permeable to ions present in the cell medium, which would lead to an electrical short of all the recording sites within the device over time.[59,60] Therefore, careful engineering of the device encapsulation is needed to allow hard ($\geqslant$ 1GPa), electrically insulating materials to become conformable and flexible to seamlessly interface with the cells.

The electrodes are typically made of biocompatible, non-oxidizable metals like gold, platinum, or Iridium-oxide. However, the critical parameter controlling the quality of the recorded signals is how tightly the neuron couples to the electrode. This has prompted nanotopographic engineering of the electrode's surface whereby, depending on the local curvature radii of the nanostructures, the cell membrane of neurons undergo spontaneous endocytosis, engulfing the structures and thereby coupling themselves to within a few nanometers of the electrode.[61] Similarly, surface roughness seems to play an important role in adequate adhesion to the electrode. To exploit this concept, a metal electrode can be coated with conducting polymers such as poly(3,4-ethylenedioxythiophene) polystyrene sulfonate (PEDOT:PSS).[62] Metal electrodes with or without polymer coating have the advantage of being easily microfabricated and mature processes have already been established.

Alternatively to microelectrodes, field-effect transistors (FET), particularly graphene-FETs,[56,63] have also been investigated to record potentials by using the cells as transistor's gate. In contrast to microelectrodes, FETs do not have high impedance at low frequencies and could, for example, measure slow oscillations such as alpha, theta and delta waves[64,65] which remains a challenge today. A hinderance to their wider uptake in the electrophysiology community is the difficulty to fabricate reliable FET arrays in common university clean rooms as well as their inability to deliver electrical stimuli.

An emerging trend in order to extract intracellular signals from neurons is to interface them with devices capable of porating the cell membrane, thus giving a direct electrical path to the inside of the neuron. The pore in the membrane can be opened by a localized electrical pulse from a microelectrode, by optical excitation of localized plasmons generating a large enough electric field or by acoustic excitation of nanowaves in porous substrates.[37,66–68] However, it is still an open question whether long-term poration of the cell membrane, despite its ability to heal, is a viable approach for chronic neural interfaces.

Currently, the choice of a specific neural interface comes from evaluating a list of trade-offs about electrode density, transparency, mechanical compliance, bi-directional capabilities, biocompatibility, among many other features. There is a need to close the technological gaps in 1. fabrication-processing to allow single-cell to whole-organ resolution, 2. material-engineering to create biocompatible, electromechanically compliant, and ion-sensitive materials and 3. material-science to provide electrically-adaptive materials to create active electronics capable of complex autonomous behavior. By doing so, it is our position that we will be able to usher-in a new age of intelligent, symbiotic, multifunctional, bidirectional and high-resolution neural interfaces. We highlight the most important features that need improvement in our opinion to induce a paradigm shift in neural interfaces.

2. Next Generation Devices

2.1. Bandwidth

A fundamental problem when measuring the electrical activity of neural networks, is that only a very small subset of the neurons within a network can be measured and the required amount of observed neural activity to gain a sufficient understanding of neural network dynamics and function is often unclear.[69,70] Typical electrode layouts consist of 32 to 128 electrodes in most microfabricated devices, allowing the recording of dozens to hundreds of neurons. There are three main reasons for the relatively low number of simultaneously measured electrodes. First, each recording electrode needs to be routed via a metallic wire. Lithography techniques allow to reduce the width of the wires to about a micron, but even so one starts to run out of space to route many electrodes. Even if techniques such as e-beam lithography were employed to further reduce the dimension of the wire, its impedance would start causing issues with the quality of the recording.[71] Second, there are only a few solutions for digitizing signals (e.g., Intan Technologies, Multichannel Systems, White Matter) from more than 128 electrodes, making their simultaneous recording highly challenging. The scarcity of solutions is even worse if one wants to operate with transistor arrays, for which one needs to manually build the readout electronics as no commercial solution exists to our knowledge. A potential solution for this issue is active multiplexing, where multiple electrodes can be read out through the same channel, which allows using fewer wires but requires powered electronics. This is the third reason why the number of electrodes is sparse, as there aren't solutions to incorporate powered electronics into the electrode arrays with lithographic techniques. High-density micro-electrode arrays (4000+ simultaneous channels) solve this issue with CMOS fabrication technology. Aside from the prohibitive cost considerations, such approaches make the devices flat, stiff, and non-transparent.

A possible avenue to increase the number of electrodes in such designs could be performed via so-called passive multiplexing. By using various materials and nanotopographies of several electrodes attached to the same route wire, it could be possible to alter the shape of recorded signals enough to be able to attribute the signal to a specific electrode. The attribution would be done by routine time-series classifier in artificial neural networks.[72]

Improving the electrode count will be critical to capture a detailed view of the interactions within the neural network and understand its dynamics.

2.2. Biological Compliance

Long-term experiments require the neural tissue not to reject the measurement device due to poor adhesion or an inflammation response. To improve the integration of the device, one can optimize its geometry and material properties.

The natural environment of cell interaction is at odds with our typical engineering approaches, where devices are pristine, flat, and designed with sharp right angles and perfect circular shapes. As such artificial arrangements are not encountered in nature and there is mounting evidence that biomimetic designs have far larger success to co-integrate with biological systems,[30,73–76] future designs of electrical interfaces need to match the

architecture of their biological counterparts.[74] However, the current design tools are still limited and typically do not cover generative design rules mimicking natural evolution. A successful example are fractal features that replicate similar structures at various scales such as the vascular system.[77] Furthermore, depending on the physical property one would like to optimize for, such as heat dissipation, optimal analyte diffusion through a perfusion device for drug delivery, mechanical compliance, or kirigami-shaping, multiphysics topological optimization algorithms should be popularized and further developed, as currently, it is technically very challenging to implement these algorithms.

From the material side, it is becoming evident that striving toward softer materials (in the 10-100 kPa range), such as hydrogels or viscoelastic materials, achieve tighter interaction with biological tissue.[42,78–81] These materials bear the potential for lifelong implantation and continuous monitoring and interaction with the surrounding tissue by further displaying biomimetic (and conductive) tissue-like architectures, which can be achieved through innovative techniques such as additive manufacturing and bioprinting. However, it is still challenging to create devices with such materials with a high electrode count, as they are not compatible with standard microfabrication techniques and chemicals, thereby introducing many extra steps that make the processing highly manual and labor-intensive. Likewise, there are size limits to how small and thin they can be made to use them as encapsulation as they can become permeable to ions at critically small dimensions.[60]

We believe that achieving biomimetic neural interfaces comprise not only neuron-like designs like the form factor, morphology, and topology of the target system but also neuron-like materials that will allow neuron-like behavior (e.g., electronic and ionic), such as capturing electrical signals and releasing neurotransmitters. Such materials range from lipid-bilayer-based interfaces, extra-cellular-matrix-emulating surfaces, ion-pump-mimicking organic electronics and neurotransmitter-releasing materials.[73,82–84] These devices will be beneficial for the long-term integration of devices into neural tissue and more research is needed on the particular form of biomimetic designs that would work best.

2.3. Cell-Electrode Coupling

When neurons fire an action potential, they produce a voltage change on the order of 100 mV. Even when placing an electrode in close contact with the neuron, the cell membrane and the remaining gap between the electrode and the cell change the shape of the electromagnetic signal and strongly reduce its amplitude by about a thousand-fold.[85] One cannot change the cell-membrane characteristics without affecting neural function, but there are several approaches to reduce the gap between the cell and the electrode to improve the signal-to-noise ratio.[37,86] This is highly advantageous because a better cell-electrode coupling allows the separation of signals from different neurons and the detection of even detailed changes in the shape of generated action potentials.[87,88] This can be used to identify specific types of neurons, quantify the effect of certain therapeutics, and even enables the detection of sub-threshold excitatory postsynaptic potentials (EPSPs)[39] which is an important feature of intracellular neural computation and signal integration. Furthermore, high-impedance electrodes, and poor cell-electrode coupling reduce the electrode's charge injection efficacy, requiring larger voltages to inject current and generating enough charge to stimulate neurons. Larger voltages can produce tissue damage due to acidification and the production of hydrogen peroxide,[89] leading to electrode deterioration over time which prevents long-term applications.

Another way to improve an electrode's recording and stimulation capability is to increase the porosity of electrodes to obtain a higher capacitance and thus reduce electrode impedance.[34,90] Furthermore, increasing the roughness and porosity of the interface enhances cell adhesion and contact area, thus also intensifying the cell-electrode coupling.[91,92] Detailed structuring of the roughness and porosity offers yet another possibility for creating functional electron and ion conductive scaffolds via alternative fabrication strategies, known from phase separation processes.[80] Such scaffolds could either be built by self-assembly of porous unit-cells organizing into a superstructure or by directly 3D printing an intricate porous conductive object.

Coating the metal electrode with conductive polymers acts in a similar fashion, by lowering the impedance of the electrode and also promoting cell adhesion. Aside from mere surface contact, there have been some recent advances in nanopatterning cavities, pillars, needles, volcano- and mushroom-shaped electrodes of various dimensions to promote endocytosis, whereby the cell membrane wraps itself around the feature, showing sometimes signal qualities similar to that of patch-clamp in contact mode (very high signal-to-noise ratio).[39,86,93,94] These features can be either fabricated by standard lithography strategies or 3D-printing via two-photon lithography if higher complexity is required. However, we still do not know the best arrangement, size, spacing, and optimal shape of these features to create a close and long-term stable coupling between cell and electrode. Furthermore, because of their aspect ratio, it is complicated to make more complex topographic structures conductive, which requires the presence of a bulk metal electrode below them to capture the signal. Lastly, some promising work has shown how the self-assembling of lipid bilayers on top of electrodes can support biorecognition processes such that cells perceive their native environment and spontaneously adhere to the electrode surface.[61,95,96] This can decrease the cell-electrode distance of individual neurons down to within 5 nm without requiring complicated 3D features to be patterned on the electrode as compared to 50–100 nm, when standard coatings such as laminin or other components of the extracellular matrix are used on planar surfaces.[97] By utilizing biomimetic 3D shapes for cell interaction, a whole new class of devices that offer much better and more durable mechanical and electrical cell-sensor contacts come into reach.

Overall, improving the mechanical, physicochemical, and electrochemical cell-electrode coupling will strongly improve the performance of future devices by providing more and better-resolved measurements of the electrical activity of neural networks, lowering the voltage threshold for targeted stimulation of neural activity, and extending the lifetime of the cell-electrode interface.

2.4. Stimulation Paradigms

One can not only record neural network activity but also excite or perturb individual neurons by current injections with a voltage pulse. This is an important part of studying neural dynamics as one can probe the system by measuring its response to various stimulation patterns, how they change over time, and how they are affected by other factors such as the local release of neuromodulators or changes in pH. This is done by a signal generator that controls a stimulation buffer, a device capable of delivering controlled currents or voltage through a specific electrode. A common approach is to deliver charge-balanced biphasic square pulses in order to have net zero charge injected into the electrolyte surrounding the cells. This is done to prevent acidifying or alkalifying the surrounding of the cell while affecting the target cell enough to fire an action potential. The square pulse is certainly not optimal, as it delivers huge capacitive currents on the rise and fall of the square, and it is energetically not optimal.[98] The precise way in which neurons do get stimulated by voltage pulses is poorly understood, as shown by puzzling effects such as bipolar cancellation.[99] Furthermore, most recording/stimulating devices offer only rudimentary control of the waveform and very few independent stimulator units (typically three or four independent signal shapes can be used simultaneously). If we wish to achieve interoperation with the local neural network, the measurement system has to be able to "respond", i.e., stimulate the neural network on the same temporal and spatial scale as the network itself, instead of having only a few different patterns of activity it can stimulate at a given time. Another way of achieving closed-loop interactions at the device interface is the use of active materials, such as organic polymers to release neurotransmitters or drugs at specific locations,[100] or by using integrated optical stimulation techniques.[101] The ability to stimulate neurons across multiple dimensions with high efficiency and least damage is paramount to achieve powerful, symbiotic neural interfaces.

2.5. Intelligent Closed-Loop

Achieving rich, on-demand stimulation devices opens the door for the next generation of closed-loop interoperation. Most neural interfaces run in a passive mode, collecting neural data, and then performing an analysis offline, or applying rudimentary stimulation protocols that are also analyzed after the fact. With the advent of reinforcement-learning (RL) architectures like MuZero,[102,103] highly versatile artificial intelligence algorithms could be used to generate complex stimulus patterns to, among other things, regulate the epileptic activity of neural tissue. Deploying such RL algorithms, which have demonstrated the ability to surpass human performance in many tasks,[104] relies on the ability of these devices to deploy an arbitrarily complex spatiotemporal stimulus pattern to the neural networks they interface with.

With the advent of inorganic and organic neuromorphic devices, which consist of circuit elements capable of changing for example their conductance, and thereby the efficacy to which they inject charge into the neurons, we envision the possibility of encoding the learned stimulation paradigms by directly integrating RL algorithms into a neuromorphic architectures that could regulate the activity of neural networks in a closed-loop fashion while requiring very low power to do so as well as implementing network level operations[105] and ultimately being integrated into soft substrates.[106] Moreover, organic neuromorphic platforms have also recently achieved functional hybrid coupling with biological counterparts both in vitro and in vivo featuring short and long term plasticity through neurotransmitter modulation.[107] Such integrated, intelligent neural interfaces could be powerful tools for regulating pathological neural activity patterns for example, in Parkinson's disease or epilepsy.

2.6. Multifunctionality

Electrical signaling is only one aspect of neural network function. A complex interplay of different neurotransmitters plays a crucial role in learning, and memory consolidation, with dysregulations causing a large array of neural disorders. Furthermore, other factors of the local extracellular environment, such as changes in pH level,[108] pressure, or temperature,[109] have an important effect on neural activity. The new generation of neural interfaces should therefore not only record and stimulate neural activity, but also be able to monitor and influence neurochemical properties such as local pH or neurotransmitter levels, and measure the release of neurotransmitters, via the use of substrate-integrated optical and spectroscopic techniques.[110] This would yield a multidimensional picture of the state of the neural network that goes far beyond the current state in electrophysiology, which is largely focused on information coding in action potential discharge.

To measure neurotransmitters, the field of aptamer functionalization shows a promising avenue. Aptamers are able to selectively capture certain molecules such as glutamate, dopamine, and serotonin and the capture event can be transduced electrically.[111–113] To also release neurotransmitters into the tissue, slow-release hydrogels could be combined into the neural interface, alternatively, a microfluidic dispensing system running in parallel with the interface,[114] or could even use ultrasound-triggered aptamers to release the chemical compound on-demand.[115]

The more dimensions along which the neural network is measured and stimulated will yield ever more sophisticated interoperation possibilities that could help both in therapies and in the fundamental understanding of neuronal function (**Figure 3**).

3. Application in Biological Systems

The envisioned novel devices could enhance the study of current model systems and potentially enable the study of novel biological systems. Here, we provide some examples of such model systems and the role the proposed novel devices play in their study.

3.1. Reconstructed In Vitro Assemblies

Many model systems tackle the complexity of living tissue by deconstructing and analyzing the various components in order to understand what influence each of them has in the particular function of interest.[116,117] For instance, in the study of peripheral

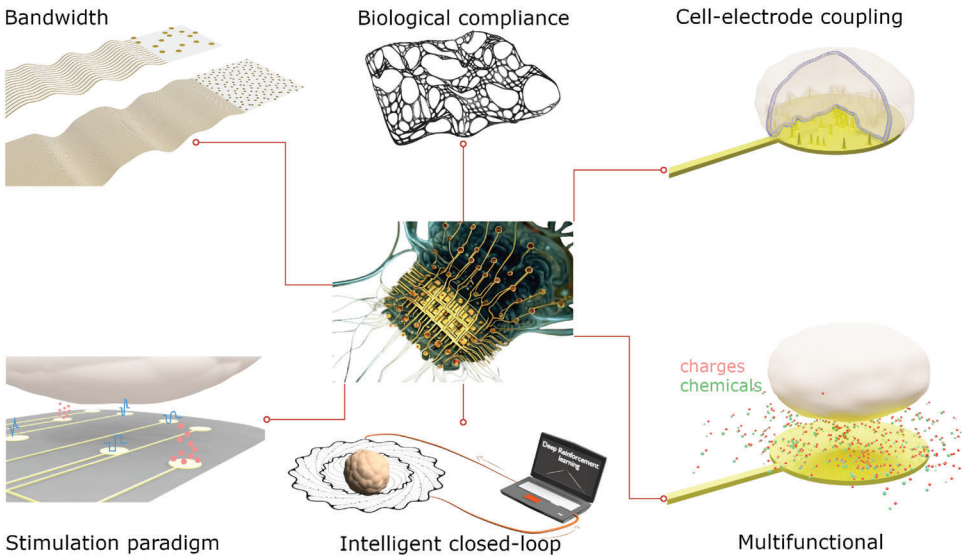

Figure 3. Roadmap to achieve the next generation of neural iontronic devices: Increased bandwidth is necessary to record and stimulate as many neurons as possible. Biological compliance is important for cells to attach and interface the device seamlessly. In order to increase signal quality and stimulation capabilities, the surface of electrodes needs to be tailored to increase cell-electrode couplings. Similarly to electrical stimulus and readout, devices need the capability to also operate in the chemical domain, for example by measuring and delivering neurotransmitters. In light of this, more understanding of what stimulus waveforms and concentrations should be used along their spatio-temporal coherence to best impact the neural system under study. Finally, these technologies should enable to have artificial-intelligence powered closed-loop control over neural systems by enabling rich, varied input (stimuli) into the network with a high-bandwidth, and a high-quality readout of the network's response.

pain, an innervated 3D skin model is needed in order to understand what drives hypersensitization of sensory neurons and how they causes chronic neuropathic pain. To this end, a combination of sensory neurons from the dorsal-root-ganglia (DRG) neurons with skin cells is constructed using e.g., hydrogels to support their 3D assembly.[118–120] In the study of cardiac tissue, stem-cell-derived cardiomyocytes are cultivated on a flexible substrate to test how their ability to contract is altered in response to various drugs and how healing could be promoted following a heart attack.[121,122] In the study of the retina, various layers of neurons play a role in potentially restoring vision in blind patients.[123,124] For fundamental studies, explanted retinae are interfaced with planar or penetrating microelectrode arrays to study their activity and the most optimal electrical and optoelectronic stimulation protocols.[51,125,126] Thereby, transparent substrates for the microelectrode arrays are of high interest. It is also known that during typical neurodegeneration processes in the eye such as Retinitis Pigmentosa or age-related macula degeneration, the neural networks undergo morphological as well as functional reorganization and the state of degeneration is strongly specific to the individual patient.[127,128] Flexible, adaptable, multifunctional implant systems, which offer electronic and biochemical, bi-directional communication with more than 1000 communication sites are therefore of high interest for developing the next generation of retinal implants toward vision restoration.

For all these constructs, device geometry is crucial. Forcing these tissue constructs onto planar, stiff, 2D substrates may alter tissue function, as it is known from the gene expression of 2D versus 3D neural cultures. The electrode array may need to have a 3D shape allowing it to recapitulate the native spatial organization of the tissues and follow the cell growth within the in vitro assembly. For cardiac tissues, it seems that the best biologically relevant tissue is grown when the culture substrate beats at typical heart rates.[129] It may therefore be necessary for the microelectrode array to act like a scaffold that also has the ability to perform a mechanical beating while recording. We posit that creating electronic devices that through their geometry can symbiotically integrate with the tissue their study will yield a biologically more relevant scenario and improve the lifetime of such devices.

3.2. Small Neural Networks

The rise of human induced pluripotent stem cells (iPSCs) has sparked a huge interest in studying the electric activity of patient-derived excitable cells, especially neurons. Neuropathic pain, but also epilepsy, are often associated with variants in ion channels, severely affecting cellular excitability. Stem cells derived from patients can be differentiated into cardiomyocytes, central and peripheral neurons, and even specific subtypes, such as sensory or motor neurons.[130] The major advantage of this approach is that one finally has the possibility to investigate human cells. Even more: they contain the complete genetic code of the patient they were derived from and thus provide the patient-specific cellular environment, which defines the cellular function and excitability. This approach ideally fits to understand the patient-specific pathophysiology and to support the development of personalized medicine.[131,132]

Induced-pluripotent-stem-cell-derived neurons need weeks of maturation during which they need to adhere to their culturing surface and cannot be replated without affecting their function.[130] Thus, culturing dishes and devices, which integrate electrical and chemical readouts are highly desirable. Currently, 2D multielectrode devices are used and high-density MEAs allow

for the detection of AP initiation and propagation[133] - two features of cellular excitability, which often are affected by genetic variants linked to neuropathic pain or epilepsy.[134,135] Neurons cultured in 2D form synapses with each other, leading to self-initiation of network activity. Growth of neurons can also be directed, e.g. by combining MEAs with microfluidics, allowing for detailed and controlled studying of network activity, synaptic plasticity, and their controllability, and finally drug testing.

Cultured cell populations can also be leveraged to create implantable biohybrid devices that can form a natural-like bond with neural tissue. The electrodes of biohybrid devices are coated with a support structure, such as a hydrogel, that contains living cells which act as a natural interface with the neural tissue.[136] Especially when cultured from the target tissue itself, these cultured cells can form dense synaptic connections and act as biological amplifiers to transmit synaptic signals from the neural tissue to the device and vice versa.[137] Biohybrid devices, therefore, offer an alternative approach to achieve closed-loop systems, where the stimulation of cultured cells at the interface can be directly converted into complex synaptic signaling to the host tissue. Moreover, the integration of living cells with active electronics such as organic electrochemical transistors can be used to replicate neural behavior in the device, such as synaptic plasticity.[107] Such devices could be engineered to perform an autonomous regulation of the neural network they connect to. For instance, epileptic neural activity could be disrupted by carefully engineered biohybrid devices that detect and prevent hyper-synchronized activity patterns before an epileptic event.

3.3. Organoids and Assembloids

Neurons and cells derived from iPSCs - when cultured under favorable conditions - have the tendency to form organoids:[138] small organs resembling those of the human body, such as mini-brains, ganglia of sensory neurons, or cardiac tissue.

These organoids recapitulate the cellular organization of the brain and could therefore be an excellent model system to study distinct brain regions and genetic diseases.[7,8] Organoids of different brain regions or tissues can be co-cultured and they spontaneously fuse and innervate each other with neural processes as they would in normal developmental conditions. When two or more organoids are co-cultured and start to interact/innervate each other, forming an assembloid, new, unforeseen possibilities for studying small human systems in the dish arise[10,46] A major challenge in measuring the electrical activity of these organoids and assembloids is not to disturb their 3D organization and function by pressing them on a flat micro-electrode array or inserting shank-electrodes as this is likely to cause damage when done repeatedly. The spatial organization of the neurons in these organoids and assembloids should ideally not be altered by the presence of a measurement device.

Low-footprint electrode arrays akin to fishnets (mesh-electrode-arrays) are a promising platform whereby the organoids at an early developmental stage grow around and engulf these devices.[30] Thus, these devices cannot only provide a technical readout of the electric activity but may also provide a structure to support the 3D growth of the organoids/assembloids. The features comprising some mesh-electrode-arrays are smaller than a cell body and therefore can weave into the organoids without disturbing the spatial arrangement of the cells.

Being able to perform chronic measurements, even from the early stages of the organoids and assembloids, is critical in studying developmental aspects and various diseases of the central and peripheral nervous system.[9] If coupled with smart closed-loop capabilities, such devices could, if given enough time, learn stimulation protocols to disrupt e.g. epileptic seizures or pain attacks. Furthermore, organoids currently suffer from a lack of vascularization and are therefore thought to be hypoxic at their core due to the slow diffusion of oxygen through their tissue[139]. To resolve this issue, the mesh-electrode array could contain a complementary microfluidic network to deliver various molecules of importance, either supporting differentiation, 3D structure, and development or interfering with mutation-induced pathophysiology to allow the development of novel personalized therapy approaches.

The study of the neurobiology of human brain organoid growth is highly promising. In order to harness everything in this emerging field, the neural interfaces need to become multifunctional, while being chronically integrated in a symbiotic fashion with the neuronal tissue.

3.4. Investigation of Human Brain Circuits

The limited success in translating findings from rodent and cellular models into effective new treatments for human disease calls for a thorough examination of the functional properties of the human brain at the resolution of cell types and circuits. Towards this goal, human brain circuits can be investigated at the subcellular, cellular, and local network level, using ex vivo brain slices that are derived from human brain surgeries[140,141]. For example, the electrophysiological and neurochemical properties of dysfunctional neural circuits can be characterized, and coupled with state-of-the-art sequencing techniques, such as spatial transcriptomics and Patch-Clamp RNA-Sequencing to elucidate human brain circuit dysfunction[142,143]. Moreover, studying healthy human neural tissue that is also resected during neurosurgical procedures allows the probing of their electrophysiological properties at the single cell and small network level [144–148]. In addition, keeping adult human cortical neurons intact for functional and morphological analysis for extended periods also provides a technical option for a much broader spectrum of experimental approaches. In a recent study, we could show that viral transduction using adeno-associated virus (AAV) of human organotypic slice cultures is feasible,[140], which was also confirmed by several other groups.[149] Taking advantage of the ability to use these human organotypic slice cultures, we apply and investigate novel gene therapy approaches (such as promotor-driven modulation of gene expression) to modify the properties of adult human brain cells. Furthermore, it allows the testing of essential basic mechanisms and investigation of disease mechanisms on longer time scales and might be used for the integration of next-generation technical devices described above.

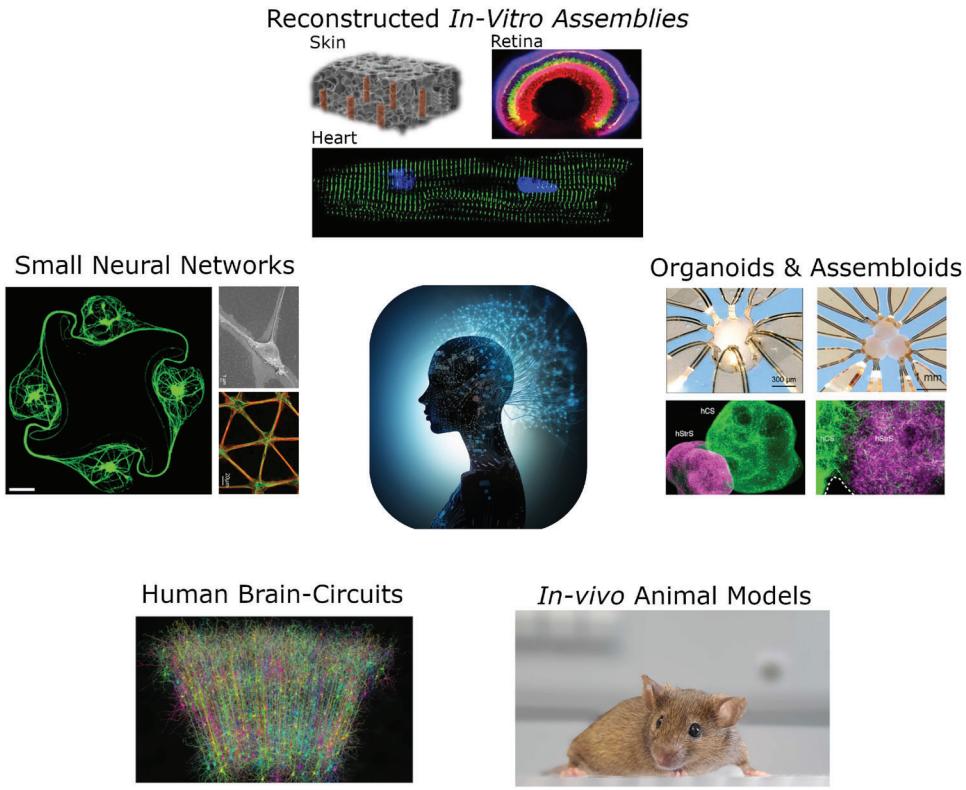

Figure 4. Applications to biological systems: The technological innovations that would lead to neural interfaces of higher-bandwidth, intelligent closed-loop capabilities, with biologically compliant shapes, increased cell-electrode coupling, with multifunctional (electrical, chemical) stimulation and read-out possibilities could greatly benefit several systems of interest. Among these, reconstructed in vitro assemblies could benefit from soft, 3D shapes and higher bandwidth. Reproduced with permission.[151,152] Copyright 2014, 2020, The Company of Biologists, Frontiers. Small neural networks would benefit from high-density, high-bandwidth closed-loop, and neuromorphic devices. Reproduced with permission.[153–155] Copyright 2022, 2005, 2009, The Royal Society of Chemistry, Elsevier, Springer Nature. Organoids and assembloids need higher-banwidth and closed-loop devices with perfusion capabilities of medium, oxygen and neurotransmitters. Reproduced with permission.[10,46] Copyright 2022, 2021, Springer Nature, AAAS. Human brain circuits and in vivo animal models require in addition biologically highly compliant devices for long-term interfacing of the neural tissue (images of brain-circuit M.Hausser at University College London).

3.5. In Vivo Animal Models

Animal models offer the study of neural network function in the context of a living organism and relate activity patterns directly to observable behavior or different disease phenotypes. Correspondingly, a plethora of animal models is used in neuroscience research and acts as an important bridge between findings from in vitro studies and clinical applications in human subjects [150]. Since measurement devices in animal models are often implanted in the brain or other relevant tissues connected to the nervous system (e.g., retina, spinal cord) there is an even stronger need for compliant integration of measurement devices to avoid foreign body rejections or inflammatory tissue responses. A potential way to achieve this is through injectable mesh electronics or flexible neural implants that can be integrated into neural tissue without long-term degradation to allow for lifelong chronic applications [58]. Moreover, chrfonic devices with closed-loop capabilities should have very low power consumption and could be powered by body temperature or muscle activity.

Applications in living brain tissue are also more representative of the complex biological environment that devices need to operate under for applications in humans. This involves movements of the tissue, which could be compensated for by flexible devices, but also immune responses, which could be reduced by using biohybrid devices or coated electrodes. Lastly, to measure and interact with the multitude of different cell types and electrochemical signaling in the living brain, devices with multimodal biosensing and electrochemical release would be highly valuable to emulate the language of living brain circuits and create a new generation of versatile neural devices (**Figure 4**).

4. Outlook

In order to symbiotically interface brain tissue, biomimetic, compliant neural interfaces are required. Furthermore, to extract the most information from neural networks and to interoperate with them in a closed-loop fashion, these devices need to be able to record and stimulate cells and tissue electrically as well as biochemically. In fact, new technological solutions should account for fundamental ionic-electronic transduction both for sensing and stimulation while fulfilling structural integration to the target tissue. Moving from the conventional electrical engineering conceiving to tissue-inspired electronic biomaterial design is necessary for the required paradigm shift for the next generation

neuronal probes. As such, we propose that 'biontronic' interaction between the probes and the diverse neuronal systems is strongly entangled and would also support further development into self-adaptive neurointerfaces. Such endeavors require interdisciplinary interactions between domain experts and experts at the interface between fields that can coordinate and streamline efforts in the various subdomains. We envision that universities will have to dedicate centralizing departments focusing all the necessary skills and expertise, cell laboratories, and cleanrooms, in collaboration with close-by clinics to efficiently usher in this new era of intelligent, biontronic platforms.

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Conflict of Interest

The authors declare no conflict of interest.

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