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REVIEW ARTICLE

Implantable neurotechnologies: bidirectional neural interfaces—applications and VLSI circuit implementations

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Abstract A bidirectional neural interface is a device that transfers information into and out of the nervous system. This class of devices has potential to improve treatment and therapy in several patient populations. Progress in very large-scale integration has advanced the design of complex integrated circuits. System-on-chip devices are capable of recording neural electrical activity and altering natural activity with electrical stimulation. Often, these devices include wireless powering and telemetry functions. This review presents the state of the art of bidirectional circuits as applied to neuroprosthetic, neurorepair, and neurotherapeutic systems.

Keywords Neuroprosthetics · Motor prosthetics · Sensory feedback · Electrical stimulation therapy

1 Introduction

Implantable devices that interface with the nervous system are becoming increasingly viable treatment options in prosthetic and therapeutic applications. Motor prosthetic devices record the electrical activity of the cerebral cortex [30, 60], or of peripheral nerves [38], to decode movement intention and actuate a robotic device. Modern neurotherapeutic devices stimulate the nervous system to treat epilepsy [48, 134], to treat chronic pain [72], and to aid rehabilitation following spinal cord injury [4, 56].

In the aforementioned applications, natural neural activity is *either* recorded *or* perturbed. The purpose of this article is to review evidence that bidirectional interfaces—systems that combine both recording and stimulation into a unified system—have potential to advance the state of the art in a broad set of fields. We define systems as "bidirectional" from a device engineer's point of view. For the purposes of this article, a system is "bidirectional" if it processes information extracted from a biological system and delivers information back to the biological system, regardless of the nature of that information. For example, a system that processes information from an efferent branch of the nervous system and delivers stimulation back to the efferent branch is bidirectional by our definition, even though the information flow is unidirectional.

Specifically, the devices we cover will fall into one of three categories illustrated schematically in Fig. 1: (1) neuroprosthetic, (2) neurorepair, and (3) neurotherapeutic. The first category, neuroprosthetic systems, consists of devices that restore motor function. Neuroprosthetic devices are being improved upon by providing the user with sensory information conveyed through electrical stimulation of the nervous system (Fig 1a). The second category, neurorepair, consists of systems that facilitate rehabilitation from brain injuries such as stroke and traumatic brain injury (TBI). These devices pair recorded brain activity with stimulation to modulate connections of neuronal populations or circumvent a damaged region (Fig 1b). The third category, neurotherapeutic systems, consists of devices that treat nervous system disorders (Fig. 1c). The debilitating effects of epilepsy can be mitigated in some patients using a device that detects seizure activity and truncates it with electrical stimulation [58].

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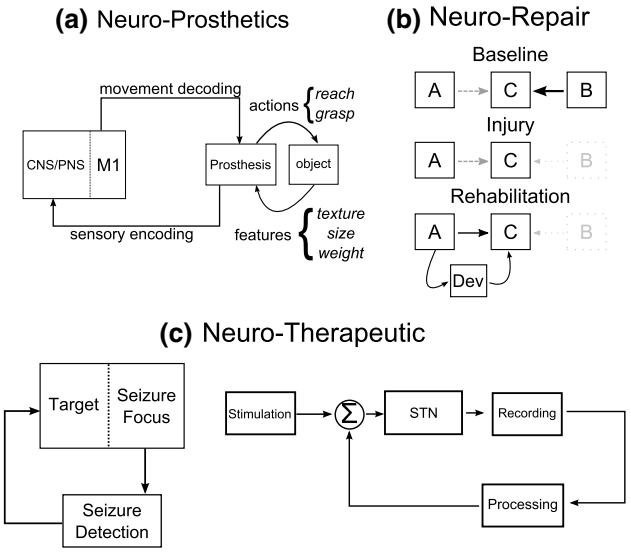

Fig. 1 Block diagram illustrations of three classes of bidirectional neural interfaces covered in this review. **a** Bidirectional neuroprosthetic devices decode movement intention and deliver sensory information to the user, or drive muscle or nerve stimulation. **b** Neurorepair devices pair neural stimulation with recorded neural activity to affect the connectivity of healthy neuronal populations. A, B, and C represent different neuronal populations. *Dark arrows* represent strong connections, and *gray arrows* represent weak connections. **c** Neurotherapeutic devices treat neurological disorders by detecting biomarkers of dysfunction and trigger or modulate stimulation. This could entail delivering stimulation to truncate a detected seizure (*left*), or altering the pattern of stimulation delivered to the sub-thalamic nucleus (STN) for treatment of PD (*right*)

Additionally, bidirectional neurotherapeutic devices may improve the efficacy of open-loop deep brain stimulation by modulating stimulation parameters based on biomarkers detected in real time.

This review is organized as follows. In Sect. 2, we discuss in detail how bidirectional prostheses are currently being applied to the variety of clinical needs mentioned above. Then, in Sect. 3, we describe implementations of these systems and highlight unique design considerations and challenges for these systems. This review is complemented by three companion papers with emphases on electrodes [103], integrated circuit amplifiers [92], and stimulators [89]. Together, they highlight milestones and challenges in the field of implantable neuroprostheses.

2 Applications

2.1 Neuroprostheses

The following subsections present recent advancements in the field of neuroprostheses as pertaining to motor neuroprostheses and providing sensory feedback to users of such systems.

2.1.1 Motor neuroprostheses

Brain–machine interfaces (BMIs) traditionally decode movement intention from neural signals to control an artificial device such as a robotic arm or computer cursor. However, an alternative strategy is to use decoded signals to drive spinal, peripheral nerve, or muscle stimulation. These systems contain both neural sensing and electrical stimulation capabilities.

Moritz et al. [85] trained non-human primate (NHP) subjects to control the firing rate of single neurons, which was used to control graded functional electrical stimulation (FES) of wrist muscles paralyzed by a peripheral nerve block. This created an artificial pathway between the subjects' cortex and the muscles, allowing them to control flexion and extension of the wrist despite compromised neural pathways. Ethier et al. [43] expanded on this strategy and restored grasping ability in two NHP subjects by translating population activity in motor cortex into FES of multiple muscle groups. Finally, Nishimura et al. expanded the paradigm by first using local field potentials (LFP) to control spinal stimulation. Additionally, the authors showed that a recurrent artificial connection could be used to restore some functionality. An NHP with partial upper limb paralysis collected juice rewards by producing and maintaining wrist torques of sufficient magnitude to cross an experimenter-defined threshold. In several sessions, the threshold was set such that the NHP could not naturally produce the torque necessary to collect rewards, due to the injury. The authors applied spinal stimulation upon detection of weak EMG signals in the paretic muscle. The EMG-triggered spinal stimulation amplified native muscle activity, restoring the subject's ability to complete the task [94].

The aforementioned systems are bidirectional in the sense that they record and stimulate neural tissue. However, for patients in which sensory pathways are not intact, these systems still suffer from the same drawback as traditional BMIs, in that they rely solely on a feed-forward control strategy–they do not provide sensory feedback. In the next sections, we discuss how bidirectional strategies can overcome this limitation by involving the somatosensory system.

2.1.2 Sensory feedback

Coordinated movements are facilitated by a rich set of sensory data communicated to the brain [61]. Such movements, therefore, are impaired in patients lacking sensory feedback [119]. In such cases, visual feedback alone is often relied upon in neuroprosthetic control for goal-directed movements [30, 60]. Although it has been shown that vision provides feedback adequate for some

enhancement of movement accuracy in these patients [51], other evidence suggests that somatosensory feedback would further enhance control of a prosthetic device [128].

In 1983, it was shown that natural sensory perception can be reproduced by electrically stimulating peripheral nerves [98]. Experimental work in the late 1990s and early 2000s offered strong evidence that providing somatosensory feedback, via electrical stimulation, was possible [114]. These findings have been replicated and supported by other contemporary work and work that has followed more recently [50, 99, 115]. These pioneering studies provided a firm scientific basis for future bidirectional motor prosthetic systems.

The studies mentioned and referenced above demonstrated the viability of providing somatosensory information via cortical and peripheral nerve stimulation. The following sections present the most current work performed in (1) cortical and (2) peripheral nerve stimulation.

2.1.3 Sensory feedback via cortical stimulation

In 2011, O'Doherty et al. [100] demonstrated the principle of providing sensory information via cortical stimulation in a bidirectional motor prosthesis. Using temporally patterned intracortical microstimulation (ICMS), they provided tactile feedback as part of a brain–machine–brain interface. The authors presented NHP subjects with multiple visually identical objects on a screen as subjects initially used a manual joystick to explore a virtual environment. As the cursor or virtual arm touched objects, different patterns of ICMS were applied to somatosensory cortex (S1) in an effort to convey different textures. After training the NHPs in this paradigm, O'Doherty and colleagues engineered a complete closed-loop brain controlled system. They simultaneously decoded movement signals from the motor cortex and delivered one of three ICMS patterns (null, low frequency or high frequency) to S1 to represent the texture of the objects in the virtual space.

One hurdle in simultaneously decoding motor signals and providing sensory feedback via ICMS lays in the recording artifacts caused by stimulation, which are several orders of magnitude larger than the signals being recorded. To circumvent this issue, O'Doherty et al. used alternating 50-ms intervals dedicated solely for either neural decoding or ICMS delivery. In this way, they guaranteed sufficient neural data would be available for decoding.

To extend this sensory feedback paradigm and provide more intuitive feedback with ICMS, investigations of stimulation parameters and strategies were conducted by Tabot et al. [129]. The authors hypothesized that stimulation applied in a way that attempts to reproduce the natural neural encoding of somatosensation would provide intuitive sensory feedback for a neuroprosthetic user. Contact location information was conveyed through precise stimulation of the regions with corresponding receptive fields in S1, pressure information was conveyed by stimulation amplitude, and the timing of object interaction was presented through phasic stimulation at the onset and offset of object interaction.

Furthermore, the group used a standard psychophysical paradigm to quantify the relationship between electrical stimulation amplitude and perception in two NHP subjects. With data from similar experiments using mechanical stimulation, they mapped perceived magnitudes of mechanical stimuli to perceived magnitudes of electrical stimuli to create a psychometric equivalence function [11, 129]. The authors then conducted two experiments to test whether stimulation amplitude, scaled in this manner, would be interpreted naturally. First, they applied mechanical stimulation to a prosthetic hand equipped with sensors, and converted the mechanical stimulation magnitude to electrical stimulation magnitude using the psychometric equivalence functions. The accuracy with which the subjects performed a discrimination task with the artificial sense of touch was similar to their natural ability. Second, the authors verified their psychometric equivalence function by having the subjects compare the amplitudes of mechanical stimulations with those of electrical stimulations, showing that subjects made errors in discriminating between stimuli as expected when the sensations being delivered were most similar. In conclusion, the group's work provides a "blueprint to convert the output of sensors on a prosthetic limb into patterns of ICMS that elicit somatosensory percepts that can then be used to guide the manipulation of objects." Interested readers are directed to a more specialized review for further details [10].

2.1.4 Sensory feedback via peripheral nerve stimulation

A multitude of peripheral nerve stimulation techniques exist. Perhaps the most general categories of these techniques are penetrating and non-penetrating. Within the category of nerve-penetrating stimulation are longitudinal intrafascicular electrodes (LIFEs) [37, 117], and transverse intrafascicular electrodes (TIMEs) [110]. Non-penetrating systems include standard nerve cuff electrodes [29, 106] and flat interface nerve electrodes (FINEs) [121, 131, 133]. A few significant studies will highlight the latest development of these systems.

In 2005, Dhillon and Horch successfully used four to eight LIFEs in six long-term upper limb human amputees to produce graded, discrete sensations of touch and movement of their phantom hands as feedback to a neurally controlled artificial arm [37]. Their work is reported as the first demonstration of "direct neural feedback from and direct neural control of an artificial arm in amputees." Similar

work was performed by Rossini et al. in 2010 [117]. This team implanted four LIFEs into the median and ulnar nerves of an amputee which "reliably recorded output signals for 4 weeks." A critical note is that, although each electrode recorded reliably for the duration of the experiment, stimulation efficacy decayed after 10 days. This study also demonstrated real-time control of motor output for three actions, localized and reproducible hand/finger sensations through selective stimulation, reversal of plastic changes in the primary motor cortex following sensory stimulation, and the alleviation of phantom limb syndrome. Although this study presents many impressive results which might recommend the use of intrafascicular electrodes, the decay of stimulation efficacy illustrates one of the major obstacles of using the electrodes for long-term recording and stimulation. The tissue response following device insertion significantly impacts these functions [122].

More recently, Raspopovic et al. [110] demonstrated a peripherally interfaced bidirectional prosthetic system using TIMEs, allowing an amputee to control a prosthetic hand and receive somatosensory feedback. The group used surface EMG recordings of the residual limb to decode movement intention and simultaneously electrically stimulated peripheral nerves to provide sensory feedback. The prosthetic hand was outfitted with pressure sensors on the index and little fingers. Raspopovic and colleagues linearly transformed readings from the sensors into stimulation currents, scaled in such a way as to prevent the stimulation currents from reaching predetermined pain limits, and ensuring the sensor output exceeded some minimum threshold before any stimulation was applied. The authors report that an amputee subject was able to use the bidirectional prosthesis to control three levels of force applied by a prosthetic hand (low, medium and high), and to discriminate between objects based on their composition (wood, plastic, or cotton) and shape (cylinder, large sphere, small sphere), without visual or auditory feedback.

In contrast to the nerve-penetrating LIFE and TIME electrodes, nerve cuff electrodes are placed around the nerve. Clippinger et al. [29] performed pioneering work with nerve cuff electrodes around the median nerve of amputees in 1974. More recently, Polasek et al. [106] showed that nerve cuff electrodes were both safe and stable in human subjects over periods spanning up to 3 years. The FINE electrode is a nerve cuff electrode designed to flatten the nerve to spread out the fascicles. Using FINEs, Tyler and Durand [133] demonstrated better access to nerve fibers for more selective stimulation and recording abilities than traditional nerve cuff electrodes. Schiefer and colleagues applied an eight-contact FINE to the human tibial nerve, which allowed selective activation of those muscles responsible for dorsiflexion, plantarflexion, ankle inversion,

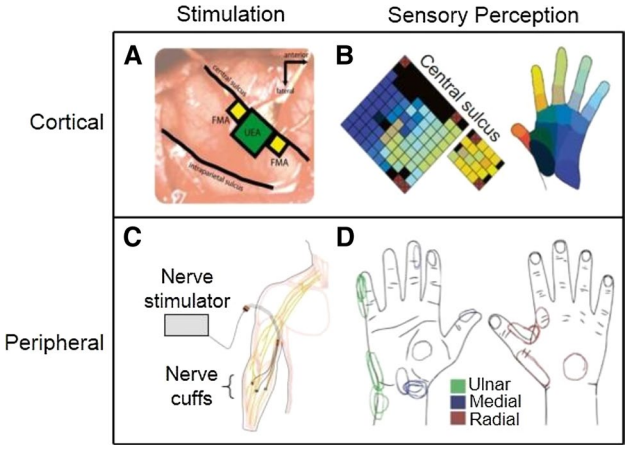

Fig. 2 Depiction of the two major sensory feedback paradigms: cortical and peripheral neural stimulation. **a** Cortical stimulation site [129]. **b** Somatosensory map in the stimulated region of the cortex along with perception locations on the NHP's hand [129]. **c** Peripheral never stimulation setup with nerve cuff electrodes implanted in the forearm of the human amputee subject [130]. **d** Sensory perception location on the subject's phantom hand elicited by peripheral nerve stimulation [130]. Adapted with permission from [129, 130]

and ankle eversion–a level of specificity likely not achievable with a circular nerve cuff electrode [121].

Most recently, Tan et al. [131] implanted two eight-contact FINEs and one four-contact spiral electrode around the median, ulnar, and radial nerves of two 46-year-old transradial amputee subjects. By varying the location and pattern of stimulation, the group produced repeatable, stable, and naturalistic touch perceptions at many locations on the phantom extremity of their subjects. The group reported consistent threshold and impedance measures 12 months post-implantation. These aspects, along with the ability to selectively stimulate the nerves at 19 of the 20 available contacts, provide strong support for the use of multi-contact FINEs for "a clinically ready, chronic system" of neural feedback in the PNS.

2.1.5 Comparison of CNS and PNS stimulation

Cortical and peripheral stimulation methods have distinct advantages and challenges. They also tend to serve different patient populations. For example, a patient suffering from a complete spinal cord injury would not benefit from peripheral nerve stimulation but would require cortical stimulation techniques to receive sensory feedback.

A benefit exploited by cortical stimulation is the highly organized structure of the tactile somatosensory cortex (Brodmann's area 3b). In low-level somatosensory cortex, it is straightforward to map stimulation location to percept location (Fig. 2). The somatotopy of the brain, however,

can reorganize itself following injury, leading to a drastic change in cortical representation of the affected and neighboring body parts [96, 107]. In cases with substantial cortical remapping, it may be difficult to artificially induce a percept in a part of the body that is no longer strongly represented on the cortex.

Compared with the somatosensory cortex, the fibers within a peripheral nerve are not arranged with a clear somatotopic map. Activating a large portion of a nerve produces a feeling of paresthesia, a tingling or slight burning sensation [29, 131]. However, the PNS is not completely chaotic. Stewart showed that afferent and efferent nerve fibers innervating similar regions of skin or muscle are generally grouped together "in accord with the somatotopic organization of the motor and sensory pathways in the central nervous system" [127]. Another complication is the fact that large nerve fibers are more easily activated by stimulation than small fibers. It has been proposed, though, that selective stimulation of even the smallest nerve fibers may be achievable by novel electrode design. Weber and colleagues advocate for high-density, nerve-penetrating microelectrode arrays with feature sizes on the order of microns [137]. Lacour et al. [75] developed a microchannel nerve interface which separated nerve fibers by promoting their growth into individual microchannels. Fitzgerald et al. [49] showed that a microchannel design could facilitate selective stimulation of individual nerve fibers.

One likely benefit of peripheral nerve stimulation is that signals can be accessed before they are subjected to the significant processing performed en route to the somatosensory cortex [122, 137]. Johnson and Hsiao address this issue stating, "The challenge in relation to form perception is to understand the transformations leading from the peripheral, isomorphic representation of form to the representations that flow into memory and perception" [64]. Isomorphism refers to a state in which the neural representation of a stimulus is in roughly the same form as the stimulus. Multiple processing stages in the somatosensory pathway transform the isomorphic neural representation into something with higher-dimensional form and meaning, i.e., isomorphic representations of sensory stimuli are transformed into non-isomorphic representations. It is therefore likely that a stimulus would be naturally perceived if the signal undergoes the natural processing of the nervous system, beginning with the activation of the lowest-order sensory neurons in the peripheral nervous system.

Finally, due to the invasiveness of both methods, the majority of research has been performed on NHP subjects until very recently. However, the barrier to human subject testing is diminishing, particularly for peripheral interface systems. For example, Tan et al. [131] developed a safe and reliable nerve interface technology, which allowed them to derive biomimetic stimulation patterns by implanting multichannel electrode arrays and having the subject directly describe the sensations produced.

2.2 Neurorepair

Restoring function or at least compensating for deficits following brain injury or disease is a potential application for bidirectional neural interfaces. Such interfaces are being developed to treat motor and cognitive deficits [12–14, 31, 41]. The strategies used to implement these two types of restorative prostheses (motor and cognitive) can be subtly different. In both cases, neural stimulation is provided in response to recorded activity. However, the goal of restorative motor prostheses is to induce plastic changes in the brain that allow injured subjects to regain lost function. In contrast, in the cognitive prostheses discussed here, a biomimetic model is constructed to bypass a damaged region of brain.

In the subsections to follow, we first discuss major results from bidirectional neural interfaces applied to the motor system (Sect. 2.2.1) and then describe the advances being made to enable memory prostheses (Sect. 2.2.2).

2.2.1 Restorative motor prostheses

The following process has been hypothesized to facilitate the recovery of functions lost to brain injury: activity recorded at one electrode acts as a "trigger" for stimulation at a different, "target" electrode. Mavoori et al. [83] first developed such a device, called the Neurochip, and soon after, Jackson et al. [62] showed that it could induce plastic changes in neural connectivity in vivo.

In a series of experiments, this group implanted autonomously operating Neurochips on freely behaving NHP subjects over periods of days, and characterized the changes in functional connectivity that resulted [62, 82, 93]. Interestingly, the nature of the device-induced reorganization, as well as the time course of the effects, differed depending on the locations of trigger and target. For example, Jackson et al. used a trigger and stimulation target both within motor cortex. The Neurochip shifted the efferent properties of the trigger network in the direction of the target network, and the effect was maintained for more than a week after the device was deactivated [62]. Alternatively, Lucas et al. [82] used muscle activity as a trigger and motor cortex as the stimulation target; the Neurochip reorganized the connectivity of neurons in M1 associated with the trigger muscle, but these effects extinguished within 24 h of device deactivation. Finally, Nishimura et al. [93] used a trigger within motor cortex and a target within spinal cord. The authors selectively strengthened or weakened the corticospinal connections under study by varying the timing of the stimulus relative to the trigger. The durations of plastic effects were

mixed; some changes lasted up to 2 days after stimulation ceased. A complete description of these works, which lay a neuroscientific foundation for the clinical application we describe next, is beyond the scope of this paper, and interested readers are directed to [41, 46], which provide more comprehensive treatments of these studies.

Since the initial work from 2006 [62], a number of laboratories have independently used this closed-loop stimulation paradigm to demonstrate similar results [111, 125]. These findings have fueled speculation that bidirectional neural interfaces could aid in the rehabilitation process from various brain injuries [31, 41, 68, 105]. Guggenmos et al. [53] used a rodent model of TBI to test the hypothesis that a bidirectional neural interface that delivers "spike-triggered" stimulation can facilitate rehabilitation. To enable this study, the authors created a custom device modeled after the Neurochip [83]. Azin et al. [7] designed an application-specific integrated circuit (ASIC) that contained recording and stimulating circuits as well as signal processing circuits implementing the algorithm described above [8].

Guggenmos and colleagues mounted the device on injured rats and could deliver closed-loop stimulation continuously for 24 h before requiring a change of battery. Then, during recovery from brain injury, the authors provided one group of rodents with closed-loop, spike-triggered stimulation and provided another group with constant frequency, open-loop stimulation. Over the course of recovery, rats regularly performed a reaching task to quantify forelimb dexterity. The performance of rats in the closed-loop group improved at a faster rate than those in the open-loop group. The authors analyzed the spiking activity recorded in both groups, and their results suggested different mechanisms mediating recovery in the two cases. This research represents an encouraging step forward, and successful replication of the results in higher-order animal models may clear the way for new therapies for human brain injury.

2.2.2 *Restorative cognitive prostheses*

One strategy for cognitive prostheses is to replace a damaged region of the brain with a biomimetic model. This model mimics how that region translates the spatial and temporal characteristics of neural firing at its input into a unique pattern at its output. Berger et al. developed a biologically inspired multiple-input, multiple-output (MIMO) model that could mimic the input–output relationship of a region of brain. The model parameters were obtained by recording spike trains from neurons projecting into the region concurrently with spike trains from neurons projecting out [14, 54]. While this model is general, in the sense it could be applied to any region of brain, the authors focus on the hippocampus and behavioral tests of memory.

Using a delayed non-match to sample (DNMS) paradigm with rats, Berger et al. [15] showed that the MIMO model could predict, in real time, when the subject was likely to make an error due to poor encoding of the stimulus location. The authors then stimulated the hippocampus during the task, which improved performance. Critically, the stimulation patterns were derived from the MIMO model. Furthermore, the authors created a pharmacological lesion in the hippocampus that impaired performance in the DNMS task. Berger et al. [15] restored performance to nearly baseline levels by stimulating with model-derived patterns online. More recently, Hampson et al. [55] demonstrated similar results in non-human primate models, and Opris et al. [101] applied the same principles to prefrontal cortex.

2.2.3 *Future for neurorepair devices*

The experimental evidence supporting a role for bidirectional interfaces in rehabilitation from brain injury is largely speculative and preliminary. Neural implants may 1 day improve rehabilitation outcomes for patients with brain injuries such as TBI and stroke. However, more evidence is needed supporting the beneficial effects of closed-loop stimulation. Previous failures in this field can partially be attributed to a rush to clinical trials in humans [105].

Here we've seen bidirectional systems applied to both the motor system and the memory system. In the case of motor rehabilitation, both closed-loop and open-loop stimulation have beneficial effects, albeit by seemingly different mechanisms. Modeling by Kerr et al. [15] indicates that open-loop stimulation restores a general drive signal [67]. In memory prostheses however, the application of stimulation was not enough to improve performance; the spatiotemporal properties of stimulation were critical, just as timing was critical to reshaping neural connectivity as shown by Jackson et al. [63], Lucas et al. [82], and Nishimura et al. [93]. These plastic changes induced by closed-loop electrical stimulation may underlie some of the results seen with memory prostheses. Interestingly, Hampson et al [54] demonstrated that over time, stimulation with MIMO model-derived patterns improved DNMS task performance on single trials when stimulation was not performed. This indicates stimulation induced some fundamental change within the underlying biology. Once stimulation was stopped permanently, these changes decayed over a timescale of days [54].

The works discussed above all represent exciting milestones in technological development and experimental applications. Several questions regarding the use of bidirectional neurorepair devices require further study. For restorative motor prostheses, would temporally non-regular open-loop stimulation also be an effective therapeutic

option in place of closed loop [53]? This option should be explored because it could reduce system complexity. Perhaps the biomimetic modeling approach would benefit restorative motor prostheses. Berger et al. [15] demonstrated a moderate benefit of "generic" stimulation patterns, derived from data from multiple animals. System complexity could further be reduced if the online implementation of the computationally expensive biomimetic modeling could be bypassed. One strategy would be to use a model to derive appropriate stimulation patterns offline, then a simpler algorithm be used to decide online, when to stimulate. Finally, further miniaturization and full implantation of the devices, as opposed to the head-mounted approach, may result in more robust systems, as the interface between the electrodes and the electronics in some cases can lead to device failure [53].

2.3 Neurotherapeutics

Electrical stimulation has been used for many years to treat a variety of neurological disorders. A large clinical trial, conducted 20 years ago, validated the ability of vagus nerve stimulation (VNS) to reduce the frequency of seizures. VNS therapy, for more than 15 years, has been an FDA approved therapy [16, 134]. Deep brain stimulation (DBS) has had major success treating movement disorders such as essential tremor (ET) and Parkinson's disease (PD) [9]. Likewise, DBS has been demonstrated to mitigate symptoms of obsessive-compulsive disorder and depression [84, 97].

These clinical successes were all based on open-loop stimulation. In the following subsections, we will show how bidirectional neural interfaces might improve upon these conventional therapies. In Sect. 2.3.1, we discuss an FDA approved device for the treatment of epilepsy, and in Sect. 2.3.2, we discuss progress made in improving deep brain stimulation therapy.

2.3.1 Epilepsy

Vagus nerve stimulation was the first FDA approved stimulation therapy for epilepsy. Morris and colleagues recently reviewed available clinical data and affirmed the therapeutic benefits of VNS and even suggests that VNS efficacy may improve over time, though this conclusion may be confounded by the uncontrolled effects of medication [87].

Of course, VNS is not universally effective and has undesirable side effects like hoarseness, voice change, throat pain, and cough [134]. Hence, much research has been directed at developing alternative stimulation strategies for reducing seizure frequency. These strategies include thalamic stimulation [48] and cortical stimulation [78].

Fisher et al. [123] demonstrated the benefits of open-loop thalamic stimulation in clinical trials. The authors implanted electrodes bilaterally in a thalamic nucleus mechanistically implicated in seizure propagation. Stimulation reduced median seizure frequency by 40 %, compared with 14.5 % in the control group [47]. Interestingly, both groups saw immediate seizure reductions of around 20 % in the month following surgery.

A bidirectional approach was recently approved by the FDA. This commercial device, the Responsive Neurostimulator System (RNS®)(NeuroPace, Mountain View, CA), continuously records intracranial EEG, extracts features from these signals, and triggers stimulation on detection of epileptiform activity. Both the detection and stimulus parameters are tailored by a physician to an individual patient's needs [58]. The electrode placement is patient dependent and may be located within the brain, or on its surface [86].

A multicenter clinical trial of this device showed a significant decrease in average seizure frequency of 37.9 % compared with 17.3 % in the control group during the blinded period [86]. Following the blinded period, the stimulator was activated for all subjects, and after 2 years, the median reduction in seizure frequency was 53 %. Note that the effect size for closed-loop stimulation was similar to that of open-loop stimulation discussed previously.

2.3.2 Movement disorders

Another promising application is online detection and treatment of movement disorders like PD. Implanted electrodes are used to record LFP, and computations on those recordings are performed to detect patterns indicative of a diseased state. This information would then be used to either (1) adjust the stimulation parameters to more efficiently ease symptoms [81, 109] or (2) apply therapeutic stimulation [116].

Quantitative biomarkers of Parkinson's disease are of great interest as they could provide a metric to automate evaluation of the therapeutic effects of stimulation. Patients implanted with deep brain stimulators currently offer scientists and clinicians brief windows of time to record from the brains of awake behaving human subjects using implanted electrodes [42]. This has implicated characteristic neural rhythms associated with movement disorders. Electrodes recording LFP in the sub-thalamic nucleus (STN) in PD patients have been shown to exhibit abnormally high power in the β band (10–35 Hz) that can be modulated by dopaminergic drugs [24, 71, 79, 108] or DBS [23, 70]. In addition to signals from deep brain structures, cortical signals also seem to be affected by PD. For example, Silberstein et al. [124] showed that coherence in the β

band is correlated with motor deficits, a trend reversed by application of DBS. Additionally, de Hemptinne et al. [33] demonstrated that surges of γ band power (50–300 Hz) in motor cortex appear phase-locked to β rhythms recorded from STN; here too, DBS decreased the magnitude of this feature.

These insights open the door for a responsive neurostimulator applied to movement disorders. In fact, Rosin et al. [116] used a closed-loop stimulation strategy in a non-human primate model of Parkinson's disease and showed that it was *more* effective at reducing Parkinson's symptoms than a standard open-loop DBS strategy.

Rosin et al. treated two NHP subjects with the neurotoxin MPTP to induce a Parkinson's like pathology. Following the application of MPTP, subjects lose the ability to make volitional movements. This group mounted accelerometers on the subjects' limbs to quantify motor symptoms and used the standard deviation of the accelerometer signals as a measure of motor activity. The authors then evaluated a number of different closed-loop stimulation strategies almost identical to the those discussed in Sect. 2.2.

Activity in motor cortex acted as the "trigger" which led to initiation of a train of DBS pulses. Open-loop and closed-loop stimulation strategies increased the subjects' ability to make volitional movements. However, the closed-loop strategy saw statistically significant improvements over standard DBS. In addition to behavioral improvements, closed-loop stimulation induced reductions in disease-state biomarkers.

2.3.3 Benefit of closed-loop neurotherapeutics

In the clinical trial for open-loop thalamic stimulation, the device delivered 90 μs, 5 V pulses at 145 Hz; the stimulation envelope had a 17 % duty cycle, on for 1 min and off for 5, which translated to 240 min/day [47]. For closed-loop strategies, the amount of stimulation delivered varies from patient to patient and from day to day. The median amount of stimulation delivered by the RNS® System was found to be 4.7 min/day [58]. The closed-loop strategy therefore stimulates almost 50 times less often than the open-loop strategy.

This increased power efficiency is a great benefit to implantable devices in two ways. For battery powered devices, the decreased power burden allows for the use of lower capacity and thus physically smaller batteries—this can significantly decrease the size of the implant. Additionally, lower power consumption confers a longer battery lifetime. When the battery in an implanted device dies, surgery is then required to replace the battery. Therefore, longer battery lifetime means a decreased probability for needing an additional surgery in older patients, and fewer additional surgeries over the course of their life for younger patients. To develop closed-loop stimulation paradigms that hold a therapeutic advantage over their open-loop counterparts will require combinations of modeling [17] and in vivo studies [116].

Bidirectional devices for treating neurological disorders, such as Parkinson's, would also benefit greatly from improved power efficiency for the same reasons. Additionally however, closed-loop systems might provide a means to automate selection of DBS parameters. The parameter space for DBS is extremely large; it includes amplitude, frequency, pulse width, and temporal pattern [19, 20, 22, 73]. Tuning of these parameters in practice must be performed manually by a highly trained neurologist to obtain acceptable trade-offs between alleviation of symptoms, severity of side effects, and battery life [3, 36, 136]. Automated algorithms for the optimization of stimulation parameters are therefore being explored [45].

3 Very large-scale integration (VLSI) implementations

There are numerous published examples combining recording and stimulation into a single system. In addition to the applications described above, it is a classical approach used in basic science research [5, 21] and allows for bidirectional bionic interactions [65, 112, 132]. Here, we restrict our focus to miniaturized or implantable systems designed to treat diseases of, or injuries to, the nervous system.

Implantable systems face extremely tight constraints on both power and size [138]. In bidirectional systems, these constraints become even more difficult to satisfy due to the need for signal processing algorithms to run in real time with the recording hardware, and the adulteration of microvolt neural signals caused by stimulation. Having established the utility of bidirectional interfaces, we turn in this section to hardware implementations of bidirectional neural interface systems.

3.1 VLSI systems for spike-triggered stimulation

VLSI systems intended for the applications described in Sect. 2.2 require a signal processing block capable of discriminating neural spikes in real time. For some applications, a single, tunable amplitude threshold may suffice. This requires a low-resolution DAC to set the threshold level and a comparator to detect threshold crossings [57, 88]. Alternatively, a number of groups have used the Teager energy operator (TEO), an algorithm that estimates the energy of a signal [66], for on-chip spike detection. This method detects transient rises in signal energy above the background noise level, and can be implemented with analog [52] or digital circuits [25, 39].

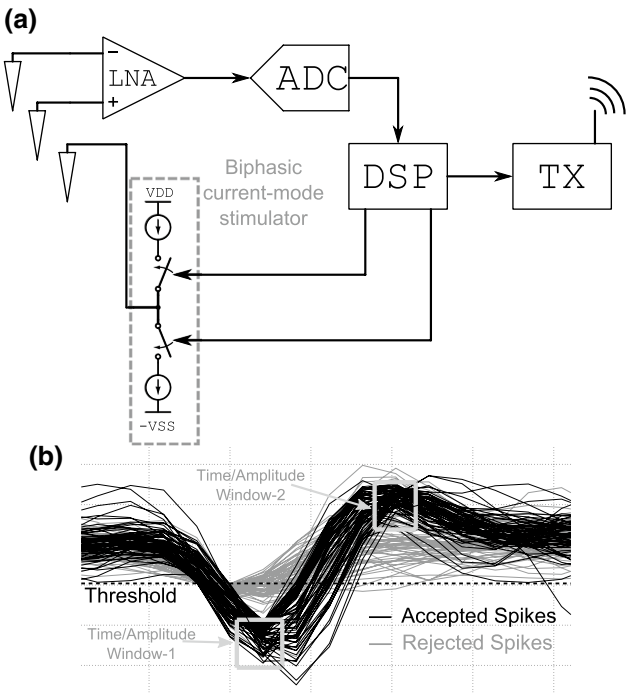

Fig. 3 **a** Conceptual block diagram of the bidirectional neural interface used to induce plastic changes in vivo in freely moving NHPs [62, 82, 83, 93]. A low-noise amplifier (LNA) extracts neural signals, which are then digitized and passed to an analog-to-digital converter (ADC). A digital signal processing unit (DSP) runs a spike discrimination algorithm and triggers stimulation and transmits data. **b** Graphical depiction of the spike detection algorithm: Upon passing through a threshold, the recorded signal is compared with two predefined time–amplitude windows. Waveforms that pass through both windows are classified as spikes. Two types of signals cross the threshold in this example: the *black traces* are counted as spikes, while the gray traces are ignored [83]

The spike detection algorithm used by Mavoori et al. (discussed in Sect. 2.2) is depicted graphically in Fig. 3b. A state machine waits for the input signal to cross a baseline threshold. A waveform is classified as a spike if it passes through two programmably defined time–amplitude windows ($W1$ and $W2$) [83]. These time–amplitude windows are set manually based on the signals available after electrode implantation. As discussed in Sect. 2.2, pairing the output of this algorithm with electrical stimulation induces plasticity in vivo.

Figure 3a depicts a block diagram of the Neurochip system discussed in Sect. 2.2. Mavoori et al. designed the original Neurochip system from discrete components. The authors amplified and filtered neural signals using commercial operational amplifiers and used a mixed-signal microcontroller to perform digitization, run the spike discrimination algorithm, and trigger a biphasic stimulator. On-board memory stored segments of recordings and spike detection statistics; the authors used an IR link to download the data. Azin et al. designed an eight-channel system similar to the Neurochip in a 0.35-μm CMOS process. Each channel contained (1) a recording front-end with an input-referred noise of $3.42\mu V_{rms}$ in a 5.1-kHz bandwidth, (2) a 10-bit successive-approximation (SAR) analog-to-digital converter (ADC), and (3) a constant-current biphasic stimulator. A digital processing block, shared among four channels, implemented a high-pass filter, and the spike discrimination algorithm described above and in Fig. 3b. Detected spikes, or patterns of spikes, autonomously triggered ICMS delivery. This processing unit consumed 12 μW of power and processed data from 4 channels, yielding an effective overhead of 3 μW per channel [7]. Azin and colleagues then integrated the custom chip with a minimal set of off-chip components to comprise a fully autonomous system. The final system weighed under 2 g and had 24 h of battery lifetime, amenable for use in unrestrained rodents [8, 53].

3.2 VLSI systems for treatment of epilepsy

Detection of biomarkers for both seizures and movement disorders requires more powerful digital processors than those described above. Usually, detection can be accomplished by calculating time and/or frequency domain features of a continuous EEG stream, and feeding those data to a classifier, trained on patient-specific data [26, 32, 126].

Stanslaski et al. [126] demonstrated three design innovations that make it possible to extract frequency domain features, even in the presence of a large stimulation artifact. First, the authors aimed to prevent sensor saturation. They performed differential sensing symmetrically around the monopolar stimulating electrode to maximize the common-mode nature of the stimulus artifact. They also used external passive filtering to attenuate common-mode signals, which prevented the stimulus artifact from exceeding the common-mode input range of the amplifier. Secondly, Stanslaski et al. mitigated spectral contamination of the sensed signal by judicious choice of stimulation parameters. The authors analyzed how the harmonics of the chopping waveform (chopper stabilization was used to remove $1/f$ noise in the front-end amplifier) interact with the harmonics of the stimulation waveform. This analysis provided guidelines for how to choose stimulation parameters to minimize contamination of the frequency band of interest. Finally, biomarker classification was performed with a support vector machine that used the state of stimulation (on or off) as a feature.

On-chip spectral analysis techniques have received considerable attention; analyzing the energy within specific signal bands of interest can be accomplished with either analog or digital circuits (Fig. 4). One analog-domain method merged the spectral extraction capabilities into the front-end amplifier [6]. Figure 4a illustrates a simplified

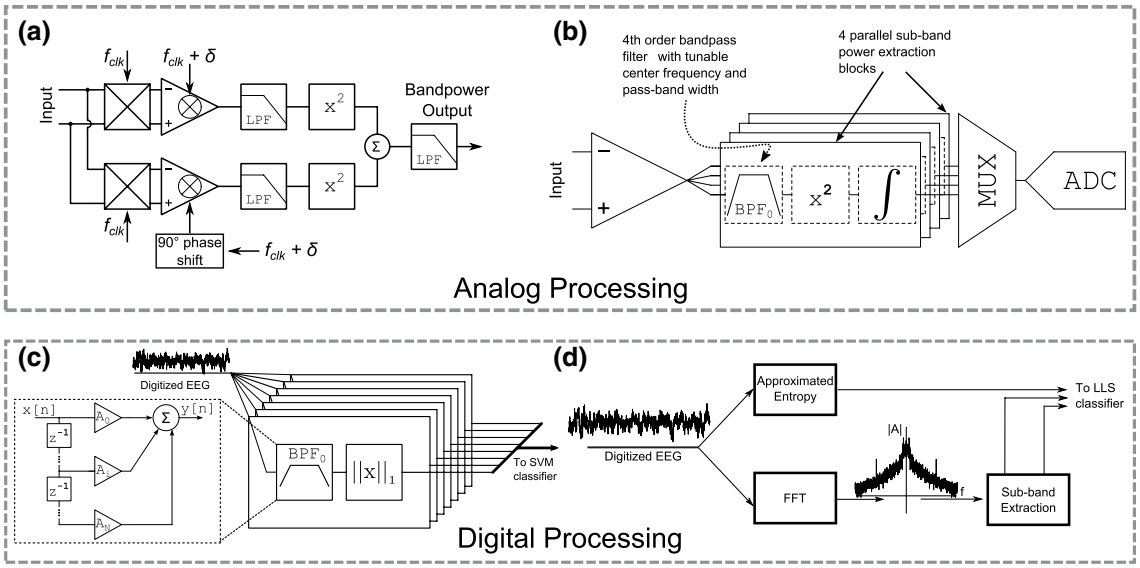

Fig. 4 Four architectures for on-chip signal processing of neural data. **a** In [6], by altering the frequency and phase of the chopping clock at various points within the front-end architecture, the authors produce an output signal that represents the power within a programmably set frequency band. **b** Sub-band power can be extracted after amplification and filtering using tunable analog bandpass filters [141]. **c** Alternatively, a bank of digital filters can be used to extract band power after digitization of neural signals, and the vector of sub-band power can then be used as the input to a classifier [139, 142]. **d** An alternative method for extracting sub-band power is to perform an FFT on digitized signals. This, along with other features, such as signal entropy, can be used as inputs into a classifier for seizure detection [28]

block diagram of how this was done. Avestruz et al. used chopping to remove low-frequency noise from the front-end amplifier. By manipulating the frequency and phase of the chopping clocks at various points within the circuit, the authors produced an analog output that represented the power in a band of interest. The center and width of this band could be tuned in a robust manner. Alternatively, Zhang et al. used four parallel switched-capacitor filters to extract the signal component in four different frequency bands of interest (Fig. 4b). The filter architecture allowed for band centers and widths to be digitally tuned. The authors then used a squaring circuit and switched-capacitor integrator to produce an output representing the energy in the respective signal band [141]. Finally, digital bandpass filters (BPFs) have been used by a number of groups to approximate the energy in different sub-bands [135, 139, 142]. Yoo et al. [139] designed an eight-channel seizure detection IC. Each channel contained seven digital BPFs to aid in the classification of seizure activity.

A complete bidirectional SoC for closed-loop epilepsy treatment was described and validated by Abdelhalim et al. [1]. The chip contained 64 low-noise amplifiers and stimulators. An innovative resource-sharing scheme allowed for the massive integration of 64 channels. Each channel could be configured as a recording channel or a stimulator. Depending on this setting, an in-channel DAC would be used either within a SAR ADC or to set the stimulation current. Likewise, the SAR logic was repurposed to set the pulse width of the stimulator. Further, the authors used two sets of FIR filters to separate the in-phase and quadrature components of the input signals. Resource sharing eliminated the need for hardware multipliers within the FIR filters, as the multiplications operations were merged directly into the ADC's SAR logic [2]. The in-phase and quadrature components of channel pairs were passed to on-chip CORDIC cores to extract a feature useful for seizure detection, the phase locking value (PLV). Abdelhalim and colleagues designed a feedback loop that triggered biphasic stimulation pulses when the PLV for a given channel pair exceeded a programmable threshold. This is illustrated in Fig 5; the authors induced seizure activity in a rat by injection of kainic acid. The large number of channels present in a single chip has important practical implications. For example, during the clinical trials for the RNS® System, issues with lead placement and damage occurred in a few patients [58]. Increased channel count would allow physicians to cast a wide net in capturing the seizure focus and potentially increase the proportion of patients responsive to the treatment.

3.3 Comparison of VLSI systems

Table 1 compares several academic and commercial bidirectional neural interfaces. Applications such as

Table 1 Comparison of state-of-the-art bidirectional neural interface systems

Reference	[83]	[140]	[7]	[14, 27, 44]	[35, 118, 126]	[1]	[90]	[113]	[28]	[18]
Year	2005	2011	2011	2012	2012	2013	2015$^{\alpha}$	2014	2014	2015
Technology	Discrete	Discrete	0.35μm	0.18μm	0.8μm, discrete	0.13μm	–	0.18μm	0.18μm	65 nm
Application	STS$^{\beta}$	STS	STS	Memory	General	Epilepsy	Epilepsy	CL-DBS$^{\gamma}$	Epilepsy	STS
# Stim Chan	1	3	8	8	8	64	8	2,8	1	8
Stim Res (bits)	5	–	6	–	8	8	–	6	1	6
Stim Range (mA)	0.1	0.2/5	0.945	–	25.5	1.09	11.5	4.1/0.116	0.03	0.9
Stim Supply Voltage (V)	14	$\pm 15/\pm 50$	5	± 3.3	± 10	3.3	12	5	10	8.7
# Rec Chan	1	3	8	16	4	64	4	4	8	64
Front-end BW (Hz)	500–5000	10–7500	1.1–12000	200–2000	0.05–120$^{\delta}$	1–5000	–	0.64–6000	0.5–7000	100–10000
Front-end Noise (μV_{rms})	6	2.7	3.12	4.24	1.1$^{\delta}$	5.1	–	6.3	5.23	7.5
ADC Type	Delta-sigma	–	SAR	SAR + Dual Slope	–	SAR	–	Pipeline (log)	Delta-modulated SAR	SAR
ADC Res. (bits)	8	8	10	12	–	8	–	8	10	10
Processing	Spike discrimination	Spike discrimination and sub-band power extraction	Digital HPF, Spike discrimination	Digital BPF, spike sorting, nonlinear MIMO neural network	Analog sub-band power extraction and SVM	Sub-band PLV	Line-length, area detector, or bandpass detector	Digital LPF/HPF, sub-band power extraction, and PI controller	FFT, Sub-band power extraction ApEn, LLS classifier	Spike discrimination
Telemetry	Infrared	Infrared	FSK	–	Inductive	UWB	Inductive	Backscatter transceiver	MedBand OOK transceiver	–
Power Supply	Battery	Battery	Battery	–	Battery	Battery	Battery	RF power harvesting or battery	Inductive coupling or battery	–
Power Consumption (mW)	40–120$^{\epsilon}$	284–420$^{\epsilon}$	0.375$^{\epsilon}$	–	0.04$^{\zeta}$	1.4$^{\zeta}$	0.062$^{\epsilon}$	0.448$^{\zeta}$	2.8$^{\zeta}$	0.193$^{\zeta}$

α Data here taken from user manual published online in 2015

β STS = Spike-triggered stimulation

γ CL-DBS = Closed-loop deep brain stimulation.

δ The noise and bandwidth figures are from [35]. When the IC is used in spectral extraction mode, a noise-penalty is incurred, but the bandwidth is also narrowed, allowing for a minimum detectable signal of $1\mu V_{rms}$ [6, 126]

ϵ Power figure includes power consumed by active stimulators

ζ Power figure does not include power consumed by active stimulators

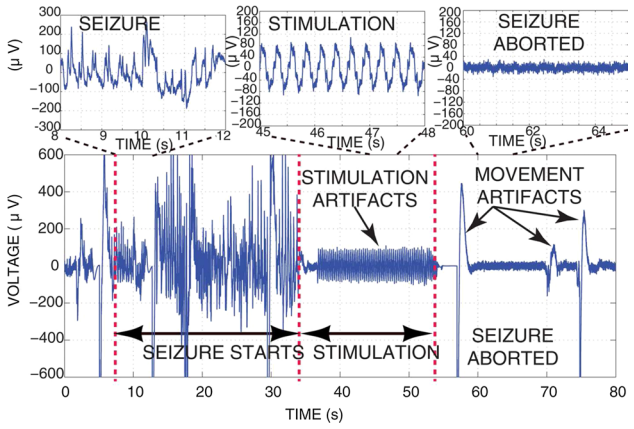

Fig. 5 Closed-loop seizure control. Seizure activity induced by injection of kainic acid begins around $t = 8$ s (*left inset*). This abnormal activity can be efficiently detected by analyzing the phase relationships between pairs of channels. After detection, a 5-Hz, 100-μA pulse train is triggered (*center inset*). Soon after, LFP activity returns to low-amplitude desynchronized activity (*right inset*). Adapted with permission from [1]

spike-triggered stimulation (STS), memory prostheses, treatment of epilepsy, or closed-loop DBS are represented. In cases where the signal processing is performed by an external programmable device, the application is listed as "general," as the application is not fixed.

Direct comparisons of total system power consumption across designs are difficult for bidirectional systems. System power dissipation will depend on the stimulation rate and amplitude, factors that may vary greatly from patient to patient. In fact, this variation across patients translates to a nearly 2-year difference in the system lifetime for patients in the 5th percentile versus the 95th percentile for the RNS® System [90]. Hence, where possible, the power consumption listed in Table 1 does not include power dissipated from the stimulator. In cases where the power figure does include the stimulation block, details on amplitude and frequency can be obtained from the references.

4 Conclusion

Bidirectional neural interfaces are enabling treatment and therapy with diverse and important applications. Significant advancements are needed in our understanding of neural processing and coding so that more effective therapeutic closed-loop strategies can be developed. Newman et al. [76] have created an open-source, closed-loop experimentation platform, [91], making the means to investigate such strategies widely available. For such systems to be widely adopted at the clinical level, performance of neural interfaces needs improvement in areas such as size, power consumption, implant lifetime, and cost. Therefore, for these systems to become a clinical reality, we need a more complete understanding of the underlying neural mechanisms, as well as smaller, more power efficient, and smarter sensors. Above all, the future of these systems depends on interdisciplinary collaborations. We believe that the challenges described above can only be solved via synergistic cooperation among scientists, clinicians, and engineers. In this way, it will be possible to progress rapidly from scientific discoveries to novel and appropriate technologies and finally to clinical validation and deployment.

This review is limited in certain ways. We have largely ignored noninvasive neural stimulation methods such as transcranial magnetic stimulation (TMS) [69], transcranial direct current stimulation (tDCS) [74], and transcranial focused ultrasound (tFUS) [77]. These methods are beginning to be seen as effective tools for studying neural function in humans, and there are ongoing efforts to translate them to clinical use [80, 95, 120]. A drawback shared among all noninvasive stimulation methods is their attainable spatial resolution. With TMS for example, the focality of stimulation is limited to regions on the order of 1 cm^2 [34]. Localization of the stimulation electrode is of paramount importance; hence, the spatial resolution of noninvasive methods could preclude their use in all cases. Further, noninvasive methods can only be applied sporadically for acute studies or treatments. Unlike implanted systems, these technologies are not available 24/7 over extended durations. Nevertheless, due to safety concerns associated with implanted systems, noninvasive neural modulation methods will likely always have a major clinical role.

Also, all optical methods, optical sensing and optogenetic stimulation, have not been included. Clinically relevant information can be gleaned from optical methods [102]; however, a complete treatment of these methods is beyond the scope of this article, for an in-depth review see [59]. Optogenetic stimulation has astounding potential given its ability to selectively target cell types, and has been used in animal models in bidirectional treatment of seizures [104]. The major impediments to human use are also beyond the scope of this article, however, significant progress is being made, especially with regards to optogenetic-based retinal prostheses [40].

In this review, we have discussed a diverse set of fields in which bidirectional neural interfaces are advancing the current state of the art. Neuroprosthetic devices may soon endow the user with chronic biomimetic sensory feedback, allowing artificial devices to feel like natural extensions of the body. Neurorepair devices are envisioned to accelerate and enhance recovery in patients following stroke or TBI, restoring pre-injury levels of function. Finally, neurotherapeutic devices are poised to treat the symptoms of neurological diseases in a patient-specific manner to more efficiently ease symptoms. Advances in the engineering

of VLSI systems, including the development of fully integrated systems, are helping to drive the field from the laboratory to the clinic.

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