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Challenges and Opportunities for Next-Generation Intracortically Based Neural Prostheses

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Abstract

Neural prosthetic systems aim to help disabled patients by translating neural signals from the brain into control signals for guiding computer cursors, prosthetic arms, and other assistive devices. Intracortical electrode arrays measure action potentials and local field potentials from individual neurons, or small populations of neurons, in the motor cortices and can provide considerable information for controlling prostheses. Despite several compelling proof-of-concept laboratory animal experiments and an initial human clinical trial, at least three key challenges remain which, if left unaddressed, may hamper the translation of these systems into widespread clinical use. We review these challenges: achieving able-bodied levels of performance across tasks and across environments, achieving robustness across multiple decades, and restoring able-bodied quality proprioception and somatosensation. We also describe some emerging opportunities for meeting these challenges. If these challenges can be largely or fully met, intracortically based neural prostheses may achieve true clinical viability and help increasing numbers of disabled patients.

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Index Terms

Artificial sensation; brain–computer interfaces; brain–machine interfaces; intracortical electrode arrays; intracortical microstimulation; optogenetics

I. INTRODUCTION

Neurological injury and disease often result in the permanent loss of motor function. In many cases, the disability is so severe that it is not possible to feed oneself or even communicate (e.g., [1]). Though surgical and pharmacological interventions have made it possible to repair nerves and promote recovery in the peripheral nervous system, most central nervous system impairments still do not have effective treatments. Electronic medical systems that interface with the nervous system, termed neural prostheses (also referred to as brain–machine interfaces or brain–computer interfaces), have started to fill some of these treatment gaps. Recent successes include cochlear implants for the profoundly deaf and deep brain stimulators to alleviate Parkinsonian tremor. In the relatively near term, epileptic-seizure disruption systems, artificial vision systems, and computer interface (communication) and prosthetic arm (motor) systems are believed to be possible (e.g., [2]–[6]).

In this perspective and review paper, we focus on communication and motor prostheses where a patient's expectation is to be able to type, move a computer mouse, or move a prosthetic arm as swiftly and as accurately as when able bodied [7]–[9]. Though complete restoration of lost neurological function is ideal, prostheses can become clinically viable when the anticipated quality-of-life improvement (benefit) outweighs the potential risks (burden). As such, considerable attention is being paid to maximizing benefit while minimizing burden [7], [10]. We briefly describe later the range of measurement techniques currently available, the need for quantitative assessment and comparison of benefits and burdens, and how the benefit-to-burden ratio is of central interest. We then turn our attention to the need for, and possibilities for, increasing performance, robustness, and sensory restoration in intracortically based neural prostheses.

II. MAXIMIZING BENEFIT, MINIMIZING BURDEN

Sensors which are external to the body, such as electroencephalography (EEG), magnetoencephalography, and functional near-infrared imaging, have been investigated extensively in recent decades (e.g., [11]). More recently, implantable electrode-array based techniques such as epi- and subdural electrocorticography (ECoG) and finely spaced ECoG electrodes (μECoG) have become a major research area. The closer proximity to the neural signal source should result in higher signal quality, which should in turn enable higher prosthetic performance (see [12], [13] for recent reviews). Over roughly the past decade, neural prostheses based on intracortical electrode arrays have also been investigated fairly extensively due to their ability to record action potentials from individual neurons, as well as local field potentials from small clusters of neurons (e.g., [5], [14]). This is possible since each intracortical electrode penetrates one to several millimeters into the brain (typically cerebral cortex), bringing the electrode tip into close proximity of the neurons of interest. Higher performance should result since these individual neurons are widely believed to be the fundamental information encoding units in the nervous system.

Thus, it is anticipated, but remains to be fully realized and demonstrated, that intracortical electrode arrays which have access to the highest temporal (individual action potentials, millisecond timescale) and spatial (individual neurons, micron spatial scale) information

possible should enable the highest performance and capability prosthetic systems (e.g., [7], [15]). If increased performance, capability, and robustness—as well as the new capability of high fidelity sensory "write in"—can be realized with intracortically based neural prostheses, this could offer an important option for patients and their treating physicians to consider.

Importantly, internal sensors such as ECoG and intracortical electrodes require a surgical implantation procedure, introducing risks to a patient's well-being that would not be present with nonsurgical options. However, the use of any medical intervention is associated with potential negative influences on wellbeing that may not be as obvious. For example, many patients would opt for a single, risky, potentially debilitating surgical procedure if it meant that they would be free from taking medication several times a day. These interventions (medication and surgery) may thus be thought of as nearly equivalent in this example, or indeed, the "riskier" option might be preferable, based on the impact on the patient's daily well-being. We propose the term "burden" to represent this aggregate negative impact on well-being. Surgical risk or invasiveness represents only one part of this burden.

Burden might be apportioned in various ways: "up front" burden in the form of surgical implantation risk; daily burden in the case of donning, doffing, recharging, or operating a complex system; cosmetic burden; financial burden; and others that could possibly include the burden on caregivers and society at large. Some degree of burden is unavoidably associated with the use of any assistive technology. Balancing the burden of technology use versus its benefits is a vital part of the decision-making process between physician and patient.

Fig. 1(a) provides one possible way of visualizing risk-benefit for current and future neural prostheses, with "performance" as a surrogate for benefit and "burden" as a measure of overall risk. At present, this can only be a notional sketch as the field is currently striving to conduct experiments that will better allow various neural prosthesis technologies to be placed quantitatively within this design space. The current lack of standardization of tasks (e.g., selecting keys on a keyboard, moving around obstacles), environments (e.g., quiet room with no distractions, or the opposite), or metrics (e.g., time to target, bits per second, how to quantitate burden) used or reported in the literature makes quantitative comparison among various laboratories results virtually impossible. However, if standardization could be agreed upon (e.g., ISO 9241-9 for performance [16], clinical consensus on defining burden), this type of performance versus burden plot could become powerful in helping to guide both clinical decision making and further research directions. Clearly, the optimal system would incorporate the lowest burden with the highest performance. However, absolute performance and absolute burden are likely not very meaningful on their own. It is their ratio that is important. In the end, it is this ratio that will help guide clinicians and patients when discussing appropriate treatment options.

Finally, it is widely recognized that there is no "one size fits all" when it comes to benefit-risk ratio in medical treatments and decisions, and this is also the case for neural prostheses. Interpreting the benefit-risk ratio associated with each treatment option is a personal decision. Some patients will not elect to have surgery under any circumstance, preferring the daily burden of system maintenance to the up-front burden of surgical risk. Thus, completely nonimplantable technologies (e.g., EEG) are clearly extremely important and must be pursued. Other patients seek the restoration of able-bodied levels of control of, for example, prosthetic arms and hands which have tens of degrees of freedom and extreme performance requirements, and thus may be willing to accept surgically implanted technologies, which carry more upfront risk (e.g., intracortical arrays). At the present time, nearly all neural prosthesis technologies carry significant burden that prevents their widespread adoption.

There are many opportunities to improve the performance (see Section III-A) and robustness (see Section III-B) of intracortically based systems to levels that could potentially allow their consideration as a clinically viable assistive technology.

III. THREE KEY CHALLENGES FOR NEXT-GENERATION INTRACORTICALLY BASED PROSTHESES

We now consider three key challenges for next-generation intracortically based prostheses. While other challenges certainly exist, for example the need for transmitting information wirelessly from the neural sensors to a nearby prosthetic device [17]–[19], such needs are not specific to intracortical array-based systems and, therefore, are not considered here.

A. Toward Able-Bodied Levels of Performance

1) Discrete Decoding for Communication Prostheses—Communication prostheses aim to provide the ability to select from among discrete targets, for example keys on a keyboard, in order to restore the ability to communicate. Performance for such systems is readily defined as the speed with which keys are selected times the accuracy with which keys are selected. More formally, this is known as bit rate (bits per second, b/s) and is often reported (e.g., [20]). The quest for higher performance led us to propose that “plan” or “preparatory” motor neural activity, which is present in posterior parietal, dorsal premotor (PMd), and primary motor (M1) cortex before movement (e.g., [21]), or even without any resulting movement, could be used in conjunction with a maximum likelihood (or other) discrete decoder to predict which one of the various possible targets should be selected [22]. This approach was born out in experiments with rhesus monkeys [23], and further optimization analyses and experiments demonstrated what is, to the best of our knowledge, the highest level of performance reported to date (6.5 b/s, or approximately 15 words/min) [24]. This is on par with able-bodied single-finger typing rates on an iPhone for example [Fig. 1(a), green] [25].

More recently, we have attempted to further increase performance by investigating multiple algorithmic avenues. First, we believe that it is possible to readily detect when a target (key) is being planned, so as to enable freely paced selections [26], [27]. Second, we found that it is possible to use the neural activity on each (specific) electrode array to determine where on the computer screen the targets should be placed, so as to optimally engage the information available in the neural population [28]. Third, we discovered that estimating eye position from the neural activity, in addition to the desired arm movement, effectively reduced noise and increased performance [29]. Fourth, we designed a factor-analysis-based decoder that is able to segregate out both fast and slow time-varying activity fluctuations, which are nominally present in all neural recordings, resulting again in increased performance [30]. Finally, we investigated a variety of more optimal decoding and firing rate estimation algorithms, some of which can increase performance [31] and some of which revealed that present methods appear adequate [32]. Taken together, it would appear likely that free-paced discrete decoding systems for communication prostheses could be demonstrated to push well beyond 6.5 b/s.

2) Continuous Decoding for Motor Prostheses—Motor prostheses enable moment-by-moment control of a computer cursor or an end effector such as a prosthetic limb. In the case of a computer cursor, motor prostheses have the potential to provide computer mouse like functionality. These systems also typically target motor cortices for electrode implantation, although additional areas have been investigated [33]. In experiments with rhesus monkeys, intracortical motor prostheses have demonstrated control of computer cursors in both 2-D [33]–[36] and 3-D [37] as well as control of prosthetic limbs (3-D and

hand open/close) [38]. Results from recent clinical trials of these systems with tetraplegic patients provide reasonable confidence that these proofs-of-concept and subsequent advances with rhesus monkeys will continue to translate readily to humans [39], [40].

These initial demonstrations of intracortical motor prostheses are compelling; however, their performance is far from that of the native limb. Thus, over the past decade research groups have focused on methods for improving performance. Roughly, this study falls into three categories: adding more sensory information, learning studies, and neural decoder design, which are complimentary because all three approaches could likely be used together to achieve even higher performance. Adding more sensory information, beyond vision alone, is a relatively new approach which reasons that by providing the full compliment of sensory signals present during natural arm movements the performance and capability of prosthetic arm movements should increase (e.g., [41]; see Section III-C). Learning studies aim to measure the neural system's ability to adapt to a neural prosthesis over short (hours) [42], [43] and long (days) [36], [44] timescales. Importantly, these studies suggest that relative performance, with respect to the first hour or day of the experiment, can indeed improve considerably over time as the user and neurons adapt to operating with the motor prosthesis.

In contrast, neural decoder design attempts to maximize performance of motor prostheses from their very first use onward. Work in this area falls into two subcategories: off-line reconstruction and online control. In off-line work, advances are designed and tested with prerecorded neural and behavioral data and the goal is to reconstruct the (natural arm) behavioral data from the neural observations [45]–[48]. Improved off-line reconstruction may not always translate into better online control, as system properties may change once the user is in closed loop with the neural decoder and the computer cursor (i.e., the new prosthetic plant has different dynamics than the natural arm) [49]. Thus, to fully vet potential algorithmic advances they must be tested online, as part of closed-loop prosthetic experiments [33]–[40], [44], [50].

However, online control experiments are more costly than offline reconstruction studies, both in terms of physical resources and time. Two intermediate approaches have been proposed recently that attempt to bridge the gap between off-line and online testing. One method is to design off-line simulations that attempt to better model the properties of online control [51]. Another method is to construct a human-in-the-loop "online prosthetic simulator" (OPS) wherein the subject's arm movements are used to create synthetic neural data that then course through a decoder to move a cursor on a screen [52]. By varying the number and noise characteristics of the synthetic neural signals, as well as the type of decoder and its parameter settings, it may be possible to discover decoders and parameter settings particularly well suited for online control across a range of neural signal properties. This approach appears promising as an initial OPS study employing a Kalman filter suggested that extremely brief neural integration times, in contrast to somewhat longer integration times indicated by traditional off-line reconstruction studies, should result in better online control and this has been born out in recent online control experiments with monkeys [52]–[55].

In our recent online closed-loop neural decoder study with rhesus monkeys [53], we focused on issues of closed-loop design. By viewing motor prostheses as a feedback control system, we made design decisions that alter existing decode algorithms and improve prosthetic performance on a task requiring the user to acquire and hold targets [e.g., achieving 70–80% of normal reaching speed, approaching the green region in Fig. 1(a)] [54]. These performance enhancements generalize to more complex tasks, including an obstacle avoidance task, and also increase robustness [55]. In order to measure performance gains,

we held task parameters constant as we made algorithmic changes, allowing us to compare performance metrics across algorithms.

Ideally, performance could be compared across the published literature; however, task designs and parameters vary considerably [see Section II and Fig. 1(a)]. By application of Fitts' law, which is used to evaluate the behavior of standard computing interfaces such as mice or track pads, it may be possible to compare performance when target sizes and distances are altered (e.g., [56]). However, these comparisons can be confounded by differences in required target hold times. Tasks with small or nonexistent hold times (and thus no "click/select signal") are fundamentally different than tasks with significant hold times (or another click/select signal). With no hold time, the neural cursor simply needs to run through the target; hold times require the cursor to slow down or stop when on target. Both tasks require an optimization between speed and accuracy, but hold time tasks add complexity by requiring stopping ability. Another potentially subtle difference is that for some tasks the neural decoder is reinitialized on every trial, while in others the decoder is free-running across trials. This choice can have a large impact on performance, as reinitialization provides more consistency across trials for the users, but consequently does not generalize to more complex tasks.

3) Testing and Extending Prostheses Performance—Incongruities in task design not only make it difficult to assess algorithmic advances, but also obscure comparisons between different signal sources [see Fig. 1(a)]. One possible solution is to standardize task design in an effort to provide consistent quantification [57]. Another possibility is to begin directly assessing these technologies as computer interface devices, as defined by ISO 9241-9 [16]. By mapping neural prostheses to these standards, the field will formally define new computer mouse and keyboard equivalents, providing quantifications of performance that can be directly compared to standard computer mouse and keyboard systems. It is important to note that existing computer interface standards are only a starting point, as neurally controlled systems are likely to be more sensitive to additional factors, such as environmental distractors, than traditional interfaces.

The monkey studies and methods described earlier are restricted to neural control while head position and body posture are relatively stationary, and the cognitive load of the environment is low. While these animal model studies appear to translate readily to immobile tetraplegic patients [39], [40], it is not clear that our understanding of motor/prosthetic cortical control will generalize when the user is capable of walking and moving freely around a real-world environment, as would be the case if such technology was applied to amputees. Fortunately, recent advances in electrophysiology techniques are enabling the study of motor control during free behavior in naturalistic environments [19]. These studies have the potential to expand our understanding of the benefits of neural prostheses for a larger patient population across tasks and environments.

B. Toward Multidecade Robustness

Another key challenge for intracortical based neural prostheses is robustness, which in turn depends on recording stability. By robustness we mean the ability to perform well, as discussed earlier and across multiple tasks and environments: 1) across several hours as we do daily when using a computer mouse, which is possible if the system works well enough that it is not "frustrating" to use; and 2) across several years, which is possible if the neural signals from the electrode array do not "disappear" (see Fig. 1(b), green line).

Previous intracortical work has focused primarily on decoding information from the activity of single neurons (e.g., [23], [24], [33]– [40]). This has two major difficulties. First, as schematically illustrated in Fig. 1(b) (solid red line), waveform amplitudes can change

dramatically from day to day, and even within a day and even while seated quietly [58], [59]. Fig. 2(a) shows an example of an electrode at various time points recorded over two weeks using a wireless system [60]. While the cause of these fast changes are not known for certain, they could be due to electrode movement termed micromotion [61], [62], or changes in the extracellular impedance (e.g., [63]). If these changes were limited to moderate amounts of signal change, due to either slow diurnal cycles or even occasional fast acceleration-induced shifts [62], it ought to be possible to use adaptive algorithms to track these changes [64]. This could then be combined with low-power spike sorting circuitry [65], [66] with the eventual goal of full implantation, and thereby retain the highest level of information extraction possible. However, an even more serious problem is that the amplitudes of single units can decay dramatically over the course of months or several years, also schematically illustrated in Fig. 1(b) (dashed red lines). Fig. 2(b) shows an array for which this happened particularly fast. The peak-to-peak voltage of the neuron with the largest action potential, on each electrode initially showing 200 μV or greater single unit activity, declined by 39% from 17 to 50 days after implantation (see Fig. 2 legend for details). This decline may be associated with the formation of scar tissue, engineering or material failures, or micromotion.

Despite these problems, it is important to recognize that neural prosthetic system performance may be less dependent than previously thought on single-neuron action potential amplitude and waveform isolation quality. This is likely an underappreciated point. Several studies have found only a small difference in system performance when decoding from sorted single units rather than unsorted multiunits garnered by setting a threshold level and counting threshold-crossing events [33], [59], [67]. Fig. 2(c) shows off-line decoder performance based on threshold-crossing event counts from the same array as in Fig. 2(b), during this period of rapid single unit decline. The ability to predict which one of four targets (directions) the monkey was reaching to showed no significant change over this time period [59]. Similarly, using a continuous linear decoder off-line, there was no significant change in two other performance metrics (correlation coefficient with hand position and mean distance to target; data not shown). This array continues to be used for online high-performance neural prosthetics experiments using threshold crossings over a year after implantation [53]–[55]. A second animal participating in these ongoing experiments was implanted approximately three years ago, and comparable online performance [54], [55] as well as off-line performance (average correlation coefficient with hand position of 0.85; linear decode) can be achieved.

These results suggest that threshold-crossing data (i.e., multiunit activity per electrode) are a rich source of data capable of supporting high prosthetic performance, and are less sensitive to action potential amplitude fluctuations and the multi-month/year decline in action potential amplitudes than appreciated historically. While this is encouraging news in the short term for animal and human translational studies alike [39], [40], next-generation systems will require stable recordings for multiple decades, which is a much larger challenge. This will likely require a comprehensive understanding of the (presumably) multiple mechanisms of electrode-tissue recording failure, including but not limited to electrode encapsulation, engineering and materials failures, and micromotion. Developing an accurate compartmental model of these effects could inform design choices for new arrays, as well as the instrumentation used to record from arrays. Studying these effects over clinically relevant timescales of multiple years may require the capability to record waveform and impedance data using multichannel low-power wireless devices [19]. In this way, array lifetime data can be gathered continuously between conventional experiments. Fully implantable wireless devices [18], [68] may also be crucial for removing infection risks and transcutaneous connector tethering forces that may be a major cause of array failure after multiple years. Finally, there may be opportunities to standardize good surgical

techniques that have been developed somewhat independently by various groups, but have not been systematically compared.

C. Toward Naturalistic Proprioception and Somatosensation

The performance and capability of prostheses will ultimately be limited if vision alone provides feedback [41]. Natural motor control relies on the integration and use of multiple senses, including proprioception and somatosensation, to coordinate multijoint movements, respond rapidly to unexpected perturbations, and operate in the absence of vision. An action as simple as picking up a styrofoam cup of water relies heavily on somatosensation since vision is often obscured, and even if the hand is clearly visible there is only a minute visual difference between gripping the cup too tightly and crushing it and not gripping it tightly enough and dropping it (e.g., [69]–[71]). It is possible to place joint angle sensors in prosthetic arms, and pressure sensors on prosthetic hands, affording the opportunity to then "write in" this artificial sensory information directly to the brain. The key challenge is how to format and deliver the artificial sensor signals into the appropriate region(s) of the brain in order to produce low-latency, naturalistic sensation that is readily usable as part of (increased) prosthetic performance and capability (e.g., [72]).

1) Electrical Intracortical Microstimulation Sensory "Write In"—Some progress has been made with electrical stimulation already [see Fig. 1(c)]. Electrical intracortical microstimulation (eICMS) in the proprioceptive area of the primary somatosensory cortex (area 3a) has been used as a potential means to deliver an artificial sense of proprioception to a monkey [73]. This study demonstrated that it is possible for monkeys to detect brief stimulus trains and to discriminate between trains of different frequencies. Similarly in the tactile domain, Romo and colleagues have demonstrated that vibrotactile stimuli delivered mechanically to the finger tip of monkeys can be substituted by eICMS (e.g., [74], [75]). The monkeys could readily equate sensations evoked by vibrotactile stimulation to those evoked by microstimulation in primary somatosensory cortex (S1). This is a strong argument in favor of perceptions evoked by eICMS being similar to those evoked by skin vibrotactile stimulation. However, in a similar study monkeys needed two weeks to transfer from vibrotactile to eICMS indicating a potentially different perceptual sensation from the two different stimulus types [76]. Irrespective of this potential caveat, this study also showed that such electrical write in to somatosensory cortex can be combined with a motor cortex read out; it was possible to record electrically during eICMS with only a small (1 ms) blackout period due to eICMS artifacts and, in this way, conduct conjoint neural prosthetic "read out" and eICMS "write in" experiments. In a related study, owl monkeys learned to discriminate spatiotemporal microstimulation patterns [77]. Information was conveyed to the brain through the interplay of microstimulation patterns delivered to multiple electrodes and the temporal order in which these electrodes were stimulated.

2) Limitations of Electrical Intracortical Microstimulation—While eICMS of the somatosensory cortex has delivered promising results, it remains an open question whether eICMS was perceived as the natural feeling of touch. Binary decisions, such as left versus right reported movements, do not afford this insight. A task with continuously varying stimulation parameters (e.g., frequency, intensity, position, and timing) is needed to mimic naturalistic tactile stimulations. However, neural recordings during such continuous and varied eICMS would likely present a problem. Even with advanced eICMS electrical artifact filtering, the blackout periods would be problematic since the continuous stimulation would cause continuous artifacts. This also hampers bidirectional neural prostheses since they require continuous reading out of motor commands and continuous writing in of proprioceptive and tactile information. A second caveat of using eICMS to imprint meaningful activity patterns into intrinsically highly interconnected areas like S1 is the

activation of fibers of passage leading to a spatiotemporal "blur" of activity [78]. There is substantial evidence from experimental work as well as from computer simulations that electrically evoked activity in gray matter is attributed mainly to the excitability of axonal elements and only to a small degree to somata and dendrites. More specifically, 2-photon calcium imaging was used to show recently that microstimulation-evoked activity is surprisingly sparse, and that the pattern of activation is greatly altered by small shifts in electrode position, suggesting that activation occurs primarily via neuronal processes in a small volume surrounding the electrode tip [79].

3) Optical Intracortical Microstimulation Sensory "Write In"—What is needed is a method for continuously stimulating and recording, as well as high spatial (individual neuron, specific neuron types, specific projection pattern) and temporal (millisecond timescale) write-in resolution. While electrical stimulation is challenged by these requirements, optogenetic stimulation methods have been designed to address exactly these issues. Optogenetics is based on light-sensitive proteins derived from bacteria and algae. Those proteins are integrated into the membranes of neurons using viral vectors and/or transgenic approaches thus rendering the cells light-responsive. Short light pulses of specific wavelengths in the millisecond range can be used to activate (blue light on Channelrhodopsin 2, ChR2) or inhibit (yellow light on Natronomonas Halorhodopsin, NpHR) neurons expressing the light-sensitive proteins [80], [81]. By using cell-type specific promoters, these opsins can also be targeted to subpopulations of neurons [82]–[84]. Further, the light stimulation does not cause any electrical artifact thus allowing continuous electrical recordings during stimulation. Finally, the activation or inhibition is extremely fast (millisecond range). This temporal precision is paired with a high spatial resolution. Since the opsins are only expressed by directly infected neurons, no fibers of passage are activated by optical stimulation, preventing spatial "blur." By combining opsin targeting, light beam focusing, and opsins with different activation spectra neurons can be activated in a spatially highly precise manner. Further, optical stimulation can be finely titrated by varying the light power. An additional means to restrict the activation to a small cortical field is a combination of excitatory and inhibitory opsins. In such a scenario, the patterned illumination with light of different wavelengths (e.g., a blue light beam surrounded by a yellow circle in an area injected with ChR2 and NpHR) would lead to submillimeter precision of activation.

Optogenetic tools were first used in cell cultures and mice, which are amenable to genetic manipulation. To apply them to neural prosthetics research, these tools must now be adapted to function in organisms which are better suited to study complex motor tasks such as rats and rhesus monkeys [85]. In the first study of optogenetics in primates, Lenti viruses were successfully used to target the excitatory channel ChR2 to excitatory neurons [86]. Adeno-associated viruses (AAV) can also be used to deliver ChR2 and other opsins, and these have traditionally been used for gene therapy in humans due to their lower biosafety risks (see [87] for additional discussion). We have recently used AAV vectors to introduce excitatory and inhibitory opsins into rhesus monkey cortex [87]. Subsequent illumination of the ChR2 and NpHR injected regions with blue or yellow light (the preferred activation wavelength of the inserted proteins) caused strong excitation [see Fig. 3(a)] or strong inhibition [see Fig. 3(b)] of single neuron activity. The expression of the opsins was targeted to neurons excluding astrocytes by using neuron specific promoters. New targeting tools capitalizing on specific viral tropisms and traveling properties now also allow expressing opsins specifically in projecting neurons. This approach does not require any specific promoter fragment or genetic definition of target cells which is a clear advantage for use in less genetically tractable species such as rats and monkeys [88].

New optoelectronic engineering challenges and opportunities also exist. New“coaxial” optrodes with a small single tip including fiber and electrode have been developed to reduce cortical damage [89]. These next-generation optrodes, and other variants, e.g., micro LED arrays [91], can be introduced in combination with multielectrode recording arrays in order to combine large-scale electrical recordings with artifact-free optical stimulation (e.g., [89], [90]). Such an optoelectronic array would allow spatiotemporal write in of sensory information directly to selected cortical sensory neurons while simultaneously reading out the neural population’s response (e.g., to “verify” write in, or study neural-circuit dynamics). An additional multielectrode array in an output area (e.g., PMd/M1) would allow the simultaneous recording and decoding of the desired prosthetic arm movement. Combining these high-throughput write-in and read-out arrays with dexterous behavioral tasks in nonhuman primates has the potential to accelerate neural prosthesis design and development, ultimately leading to neurally controlled prosthetic arms that enable the users to feel what they are grasping.

IV. CONCLUSION

The design of neural prostheses has progressed rapidly over the past decade, yielding communication and motor prosthetic systems based on EEG, ECoG, and intracortical electrode array measurements. This perspective and review paper focused on intracortical-based neural prostheses, where the need for further advances in neural “read out” as well as “write in” was highlighted and organized around three challenges. First, new mathematical decode algorithms are needed to more optimally convert the neural activity from intracortical arrays into higher performance systems that are on par with able-bodied performance. Second, new electrode array designs and algorithms are needed to increase system robustness from weeks/months, at present, out to several years/decades. Third, while eICMS can provide at least some semblance of artificial sensation, it is anticipated that the ability to continuously write information into specific neurons, of different types and projection patterns, will be needed to restore natural levels of sensation. Optogenetic methods and oICMS are a potential opportunity for meeting this challenge. Overall, a diverse set of approaches will certainly be needed to fully meet these three key challenge areas. Together, increased performance, increased robustness, and the increased ability to deliver artificial sensation should further increase the benefit (and benefit-risk ratio) intracortical-based neural prostheses can offer patients.

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REFERENCES

1. Anderson KD. Targeting recovery: Priorities of the spinal cord-injured population. J. Neurotrauma. 2004; vol. 21:1371–1383. [PubMed: 15672628]

2. Hatsopoulos NG, Donoghue JP. The science of neural interface systems. Annu. Rev. Neurosci. 2009; vol. 32:249–266. [PubMed: 19400719]
3. Scherberger H. Neural control of motor prostheses. Curr. Opin. Neurobiol. 2009; vol. 19:629–633. [PubMed: 19896364]
4. Nicolelis MAL, Lebedev MA. Principles of neural ensemble physiology underlying the operation of brain–machine interfaces. Nat. Rev. Neurosci. 2009; vol. 10:530–540. [PubMed: 19543222]
5. Andersen RA, Hwang EJ, Mulliken GH. Cognitive neural prosthetics. Annu. Rev. Psychol. 2010; vol. 61:169–190. [PubMed: 19575625]
6. Green AM, Kalaska JF. Learning to move machines with the mind. Trends Neurosci. 2011 Feb.; vol. 34(no. 2):61–75. [PubMed: 21176975]
7. Ryu SI, Shenoy KV. Human cortical prostheses: Lost in translation? Neurosurg. Focus. 2009; vol. 27:E5. [PubMed: 19569893]
8. Yu, BM.; Santhanam, G.; Sahani, M.; Shenoy, KV. Statistical Signal Processing for Neuroscience. New York: Academic; 2010. Neural decoding for motor and communication prostheses, ch. 7.
9. Linderman MD, Santhanam G, Kemere CT, Gilja V, O'Driscoll S, Yu BM, Afshar A, Ryu SI, Shenoy KV, Meng TH. Signal processing challenges for neural prostheses. IEEE Signal Process. Mag. 2008 Jan.; vol. 25(no. 1):18–28.
10. del R. Millan J, Carmena JM. Invasive or noninvasive: Understanding brain–machine interface technology. IEEE Eng. Med. Biol. Mag. 2010 Jan./Feb.; vol. 29(no. 1):16–22.
11. McFarland DJ, Sarnacki WA, Wolpaw JR. Electroencephalographic (EEG) control of three-dimensional movement. J. Neural Eng. 2010; vol. 7:036007. [PubMed: 20460690]
12. Leuthardt EC, Schalk G, Roland J, Rouse A, Moran DW. Evolution of brain-computer interfaces: Going beyond classic motor physiology. Neurosurg. Focus. 2009; vol. 27:E4. [PubMed: 19569892]
13. Moran DW. Evolution of brain–computer interface: Action potentials, local field potentials and electrocorticograms. Curr. Opin. Neurobiol. 2010; vol. 20:1–5.
14. Scherberger H, Jarvis MR, Andersen RA. Cortical local field potential encodes movement intentions in the posterior parietal cortex. Neuron. 2005; vol. 46:347–354. [PubMed: 15848811]
15. Vargas-Irwin C, Shakhnarovich G, Yadollahpour P, Mislow J, Black MJ, Donoghue JP. Decoding complete reach and grasp actions from local primary motor cortex populations. J. Neurosci. 2010; vol. 30:9659–9669. [PubMed: 20660249]
16. International Standard. 2000. Ergonomic requirements for office work with visual display terminals (VDTs)—Part 9: requirements for non-keyboard input *Ergonomic Requirements for Office Work With Visual Display Terminals (VDTs)—Part 9: Requirements for Non-Keyboard Input,"* 2000. ISO 9241-9:2000(E)
17. Harrison RR. The design of integrated circuits to observe brain activity. Proc. IEEE. 2008 Jul.; vol. 96(no. 7):1203–1216.
18. Nurmikko AV, Donoghue JP, Hochberg L, Patterson WR, Song Y-K, Bull C, Borton D, Laiwalla F, Park S, Ming Y, Aceros J. Listening to brain microcircuits for interfacing with external world—Progress in wireless implantable microelectronic neuroengineering devices. Proc. IEEE. 2010 Mar.; vol. 98(no. 3):375–388.
19. Gilja V, Chestek CA, Nuyujukian P, Foster J, Shenoy KV. Autonomous head-mounted electrophysiology systems for freely-behaving primates. Curr. Opin. Neurobiol. 2010; vol. 20:676–686. [PubMed: 20655733]
20. Taylor DM, Helms Tillery SI, Schwartz AB. Information conveyed through brain-control: Cursor versus robot. IEEE Trans. Neural Syst. Rehabil. Eng. 2003 Jun.; vol. 11(no. 2):195–199. [PubMed: 12899273]
21. Churchland MM, Cunningham JP, Kaufman MT, Ryu SI, Shenoy KV. Cortical preparatory activity: Representation of movement or first cog in a dynamical machine? Neuron. 2010; vol. 68:387–400. [PubMed: 21040842]
22. Shenoy KV, Meeker D, Cao S, Kureshi SA, Pesaran B, Mitra P, Buneo CA, Batista AP, Burdick JW, Andersen RA. Neural prosthetic control signals from plan activity. NeuroReport. 2003; vol. 14:591–596. [PubMed: 12657892]

23. Musallam S, Corneil BD, Greger B, Scherberger H, Andersen RA. Cognitive control signals for neural prosthetics. Science. 2004; vol. 305:258–262. [PubMed: 15247483]
24. Santhanam G, Ryu SI, Yu BM, Afshar A, Shenoy KV. A high-performance brain–computer interface. Nature. 2006; vol. 442:195–198. [PubMed: 16838020]
25. Allen, JM.; McFarlin, LA.; Green, T. An in-depth look into the text entry user experience on the iPhone; Proc. Human Factors Ergon. Soc., 52nd Annu. Meeting; 2008. p. 508-512.
26. Achtman N, Afshar A, Santhanam G, Yu BM, Ryu SI, Shenoy KV. Free-paced high-performance brain–computer interfaces. J. Neuroeng. 2007; vol. 4:336–347.
27. Kemere C, Santhanam G, Yu B, Afshar A, Ryu S, Meng T, Shenoy K. Detecting neural-state transitions using hidden Markov models for motor cortical prostheses. J. Neurophysiol. 2008; vol. 100:2441–2452. [PubMed: 18614757]
28. Cunningham J, Yu B, Gilja V, Ryu S, Shenoy K. Toward optimal target placement for neural prosthetic devices. J. Neurophysiol. 2008; vol. 100:3445–3457. [PubMed: 18829845]
29. Batista AP, Yu BM, Santhanam G, Ryu SI, Afshar A, Shenoy KV. Cortical neural prosthesis performance improves when eye position is monitored. IEEE Trans. Neural Syst. Rehabil. Eng. 2008 Feb.; vol. 16(no. 1):24–31. [PubMed: 18303802]
30. Santhanam G, Yu Yu, Gilja V, Ryu SI, Afshar A, Sahani M, Shenoy KV. Factor-analysis methods for higher-performance neural prostheses. J. Neurophysiol. 2009; vol. 102:1315–1330. [PubMed: 19297518]
31. Yu, BM.; Cunningham, JP.; Shenoy, KV.; Sahani, M. Neural decoding of movements: From linear to nonlinear trajectory models. In: Ishikawa, M.; Doya, K.; Miyamoto, H.; Yamakawa, T., editors. Neural Information Processing. Vol. vol. 4984. Berlin/Heidelberg, Germany: Springer-Verlag; 2008. p. 586-595.in chapter in
32. Cunningham J, Gilja V, Ryu S, Shenoy K. Methods for estimating neural firing rates, and their application to brain–machine interfaces. Neural Netw. 2009; vol. 22:1235–1246. [PubMed: 19349143]
33. Carmena JM, Lebedev MA, Crist RE, O'Doherty JE, Santucci DM, Dimitrov DF, Patil PG, Henriquez CS, Nicolelis MAL. Learning to control a brain–machine interface for reaching and grasping by primates. PLoS Biol. 2003; vol. 1:193–208.
34. Serruya MD, Hatsopoulos NG, Paninski L, Fellows MR, Donoghue J. Instant neural control of a movement signal. Nature. 2002; vol. 416:141–142. [PubMed: 11894084]
35. Mulliken GH, Musallam S, Andersen RA. Decoding trajectories from posterior parietal cortex ensembles. J. Neurosci. 2008; vol. 28:12 913–12 926.
36. Ganguly K, Carmena JM. Emergence of a stable cortical map for neuroprosthetic control. PLoS Biol. 2009; vol. 7:e1000153. [PubMed: 19621062]
37. Taylor DM, Tillery SIH, Schwartz AB. Direct cortical control of 3D neuroprosthetic devices. Science. 2002; vol. 296:1829–1832. [PubMed: 12052948]
38. Velliste M, Perel S, Spalding MC, Whitford AS, Schwartz AB. Cortical control of a prosthetic arm for self-feeding. Nature. 2008; vol. 453:1098–1101. [PubMed: 18509337]
39. Hochberg LR, Serruya MD, Friehs GM, Mukand JA, Saleh M, Caplan AH, Branner A, Chen D, Penn RD, Donoghue JP. Neuronal ensemble control of prosthetic devices by a human with tetraplegia. Nature. 2006; vol. 442:164–171. [PubMed: 16838014]
40. Kim S-P, Simeral JD, Hochberg LR, Donoghue JP, Black MJ. Neural control of computer cursor velocity by decoding motor cortical spiking activity in humans with tetraplegia. J. Neuroeng. 2008; vol. 5:455–476.
41. Suminski AJ, Tkach DC, Fagg AH, Hatsopoulos NG. Incorporating feedback from multiple sensory modalities enhances brain–machine interface control. J. Neurosci. 2010; vol. 30:16 777–16 787.
42. Jarosiewicz B, Chase SM, Fraser GW, Velliste M, Kass RE, Schwartz AB. Functional network reorganization during learning in a brain–computer interface paradigm. Proc. Natl. Acad. Sci. USA. 2008; vol. 105:19 486–19 491.
43. Moritz CT, Perlmutter SI, Fetz EE. Direct control of paralysed muscles by cortical neurons. Nature. 2008; vol. 456:639–642. [PubMed: 18923392]

44. Heliot R, Ganguly K, Jimenez J, Carmena JM. Learning in closed-loop brain–machine interfaces: Modeling and experimental validation. Proc. IEEE Trans. Syst. Man Cybern. B Cybern. 2009; vol. 6:3710–3715.
45. Kemere CT, Shenoy KV, Meng TH. Model-based neural decoding of reaching movements: a maximum likelihood approach. IEEE Trans. Biomed. Eng. 2004 Jun.; vol. 51(no. 6):925–932. [PubMed: 15188860]
46. Wu W, Black M, Mumford D, Gao Y, Bienenstock E, Donoghue J. Modeling and decoding motor cortical activity using a switching Kalman filter. IEEE Trans. Biomed. Eng. 2004 Jun.; vol. 51(no. 6):933–942. [PubMed: 15188861]
47. Yu BM, Kemere C, Santhanam G, Afshar A, Ryu SI, Meng TH, Sahani M, Shenoy KV. Mixture of trajectory models for neural decoding of goal-directed movements. J. Neurophysiol. 2007; vol. 97:3763–3780. [PubMed: 17329627]
48. Srinivasan L, Eden UT, Mitter SK, Brown EN. General-purpose filter design for neural prosthetic devices. J. Neurophysiol. 2007; vol. 98:2456–2475. [PubMed: 17522167]
49. Koyama S, Chase SM, Whitford AS, Velliste M, Schwartz AB, Kass RE. Comparison of brain–computer interface decoding algorithms in open-loop and closed-loop control. J. Comput. Neurosci. 2009; vol. 29:73–87. [PubMed: 19904595]
50. Wu, W.; Shaikhouni, A.; Donoghue, JP.; Black, MJ. Closed-loop neural control of cursor motion using a kalman filter; Proc. IEEE 26th Annu. Int. Conf. Eng. Med. Biol. Soc; 2004. p. 4126-4129.
51. Chase SM, Schwartz AB, Kass RE. Bias, optimal linear estimation, and the differences between open-loop simulation and closed-loop performance of spiking-based brain–computer interface algorithms. Neural Netw. 2009; vol. 22:1203–1213. [PubMed: 19502004]
52. Cunningham JP, Nuyujukian P, Gilja V, Chestek CA, Ryu SI, Shenoy KV. A closed-loop human simulator for investigating the role of feedback-control in brain–machine interfaces. J. Neurophysiol. 2010 doi: 10.1152/jn.00503.2010.
53. Gilja V, Nuyujukian P, Chestek CA, Cunningham JP, Yu BM, Ryu SI, Shenoy KV. High-performance continuous neural cursor control enabled by a feedback control perspective. Proc. Frontiers Syst. Neurosci.: Comput. Syst. Neurosci. (COSYNE) meeting. 2010
54. Gilja V, Nuyujukian P, Chestek CA, Cunningham JP, Fan JM, Yu BM, Ryu SI, Shenoy KV. A high-performance continuous cortically-controlled prosthesis enabled by feedback control design. Proc. Neurosci. Meeting Planner, Soc. Neurosci. 2010
55. Nuyujukian P, Gilja V, Chestek CA, Cunningham JP, Fan JM, Yu BM, Ryu SI, Shenoy KV. Generalization and robustness of a continuous cortically-controlled prosthesis enabled by feedback control design. Proc. Neurosci. Meeting Planner, Soc. Neurosci. 2010
56. Felton EA, Radwin RG, Wilson JA, Williams JC. Evaluation of a modified fitts law brain-controlled interface target acquision task in able and motor disabled individuals. J. Neural Eng. 2009; vol. 6:056002. [PubMed: 19700814]
57. Donoghue JP, Simeral JD, Kim SP, Friehs GM, Bouton CE, Masters MT, Hochberg LR, Black MJ. Toward standardized assessment of pointing devices for brain–computer interfaces. Proc. Neurosci. Meeting Planner, Soc. Neurosci. 2007
58. Chestek, CA.; Cunningham, JP.; Gilja, V.; Nuyujukian, P.; Ryu, SI.; Shenoy, KV. Neural prosthetic systems: Current problems and future directions; Proc. 31st Ann. Conf. IEEE EMBS; 2009. p. 3369-3375.
59. Chestek CA, Gilja V, Nuyujukian P, Foster JD, Fan JM, Kaufman MT, Churchland MM, Rivera-Alvidrez Z, Cunningham JP, Ryu SI, Shenoy KV. Long-term stability of neural prosthetic control signals from silicon cortical arrays in rhesus macaque motor cortex. J. Neural Eng. 2011 to be published. Expected online publication: May 2011 (preprint Jun. 2011).
60. Chestek CA, Gilja V, Nuyujukian P, Kier R, Solzbacher F, Ryu SI, Harrison RR, Shenoy KV. HermesC: Low-power wireless neural recording system for freely moving primates. IEEE Trans. Neural Syst. Rehab. Eng. 2009 Aug.; vol. 17(no. 4):330–338.
61. Bayly PV, Cohen TS, Leister EP, Ajo D, Leuthardt EC, Genin GM. Deformation of the human brain induced by mild acceleration. J. Neurotrauma. 2005; vol. 22:845–856. [PubMed: 16083352]

62. Santhanam G, Linderman MD, Gilja V, Afshar A, Ryu SI, Meng TH, Shenoy KV. HermesB: A continuous neural recording system for freely behaving primates. IEEE Trans. Biomed. Eng. 2007 Nov.; vol. 54(no. 1):2037–2050. [PubMed: 18018699]
63. Moffitt MA, McIntyre CC. Model-based analysis of cortical recording with silicon microelectrodes. Clin. Neurophysiol. 2005; vol. 116:2240–2250. [PubMed: 16055377]
64. Gilja V, Santhanam G, Linderman MD, Afshar A, Ryu SI, Meng TH, Sahani M, Shenoy KV. Optimizing spike sorting for brain computer interfaces with non-stationary waveforms. Proc. Soc. Neurosci. Annu. Meeting. 2007
65. Zumsteg ZS, Kemere C, O'Driscoll S, Santhanam G, Ahmed RE, Shenoy K, Meng TH. Power feasibility of implantable digital spike sorting circuits for neural prosthetic systems. IEEE Trans. Neural Syst. Rehabil. Eng. 2005 Sep.; vol. 13(no. 3):272–279. [PubMed: 16200751]
66. O'Driscoll S, Meng TH, Shenoy KV, Kemere C. Neurons to silicon: Implantable prosthesis processor. Proc. Int. Solid State Circuits Conf. (ISSCC). 2006:552–553. and 672.
67. Fraser GW, Chase SM, Whitford A, Schwartz AB. Control of a brain–computer interface without spike sorting. J. Neural Eng. 2009 Oct..vol. 6:055004. [PubMed: 19721186]
68. Kim S, Bhandari R, Klein M, Negi S, Rieth L, Tathireddy P, Toepper M, Oppermann H, Solzbacher F. Integrated wireless neural interface based on the utah electrode array. Biomed. Microdevices. 2009; vol. 11:453–466. [PubMed: 19067174]
69. Sainburg RL, Poizner H, Ghez C. Loss of proprioception produces deficits in interjoint coordination. J. Neurophysiol. 1993; vol. 70:2136–2147. [PubMed: 8294975]
70. Sober SJ, Sabes PN. Multisensory integration during motor planning. J. Neurosci. 2003; vol. 23:6982–6992. [PubMed: 12904459]
71. Abbott A. Neuroprosthetics: In search of the sixth sense. Nature. 2006; vol. 442:125–127. [PubMed: 16837993]
72. Fagg AH, Hatsopoulos NG, de Lafuente V, Moxon KA, Nemati S, Rebesco JM, Romo R, Solla SA, Reimer J, Tkach D, Pohlmeyer EA, Miller LE. Biomimetic brain machine interfaces for the control of movement. J Neurosci. 2007; vol. 27:11 842–11 846.
73. London BM, Jordan LR, Jackson CR, Miller LE. Electrical stimulation of the proprioceptive cortex (area 3a) used to instruct a behaving monkey. IEEE Trans. Neural Syst. Rehabil. Eng. 2008 Feb.; vol. 16(no. 1):32–36. [PubMed: 18303803]
74. Romo R, Salinas E. Flutter discrimination: Neural codes, perception, memory and decision making. Nat. Rev. Neurosci. 2003; vol. 4:203–218. [PubMed: 12612633]
75. Luna R, Hernandez A, Brody CD, Romo R. Neural codes for perceptual discrimination in primary somatosensory cortex. Nat. Neurosci. 2005; vol. 8:1210–1219. [PubMed: 16056223]
76. O'Doherty JE, Lebedev MA, Hanson TL, Fitzsimmons NA, Nicolelis MAL. A brain–machine interface instructed by direct intracortical microstimulation. Front Integr. Neurosci. 2009; vol. 3:20.
77. Fitzsimmons NA, Drake W, Hanson TL, Lebedev MA, Nicolelis MAL. Primate reaching cued by multichannel spatiotemporal cortical microstimulation. J. Neurosci. 2007; vol. 27:5593–5602. [PubMed: 17522304]
78. Butovas S, Schwarz C. Spatiotemporal effects of microstimulation in rat neocortex: A parametric study using multielectrode recordings. J. Neurophysiol. 2003; vol. 90:3024–3039. [PubMed: 12878710]
79. Histed MH, Bonin V, Reid RC. Direct activation of sparse, distributed populations of cortical neurons by electrical microstimulation. Neuron. 2009; vol. 63:508–522. [PubMed: 19709632]
80. Boyden ES, Zhang F, Bamberg E, Nagel G, Deisseroth K. Millisecond-timescale, genetically targeted optical control of neural activity. Nat. Neurosci. 2005; vol. 8:1263–1268. [PubMed: 16116447]
81. Zhang F, Wang L-P, Brauner M, Liewald JF, Kay K, Watzke N, Wood PG, Bamberg E, Nagel G, Gottschalk A, Deisseroth K. Multimodal fast optical interrogation of neural circuitry. Nature. 2007; vol. 446:633–639. [PubMed: 17410168]
82. Adamantidis AR, Zhang F, Aravanis AM, Deisseroth K, de Lecea L. Neural substrates of awakening probed with optogenetic control of hypocretin neurons. Nature. 2007; vol. 450:420–424. [PubMed: 17943086]

83. Gradinaru V, Mogri M, Thompson KR, Henderson JM, Deisseroth K. Optical deconstruction of parkinsonian neural circuitry. Science. 2009; vol. 324:354–359. [PubMed: 19299587]
84. Sohal VS, Zhang F, Yizhar O, Deisseroth K. Parvalbumin neurons and gamma rhythms enhance cortical circuit performance. Nature. 2009; vol. 459:698–702. [PubMed: 19396159]
85. Buchen L. Neuroscience: Illuminating the brain. Nature. 2010; vol. 465:26–28. [PubMed: 20445604]
86. Han X, Qian X, Bernstein JG, Zhou H-H, Franzesi GT, Stern P, Bronson RT, Graybiel AM, Desimone R, Boyden ES. Millisecond-timescale optical control of neural dynamics in the nonhuman primate brain. Neuron. 2009; vol. 62:191–198. [PubMed: 19409264]
87. Diester I, Kaufman MT, Mogri M, Pashaie R, Goo W, Yizhar O, Ramakrishnan C, Deisseroth K, Shenoy KV. An optogenetic toolbox designed for primates. Nature Neurosci. 2011; vol. 14(no. 3): 387–397. [PubMed: 21278729]
88. Gradinaru V, Zhang F, Ramakrishnan C, Mattis J, Prakash R, Diester I, Goshen I, Thompson KR, Deisseroth K. Molecular and cellular approaches for diversifying and extending optogenetics. Cell. 2010; vol. 141:154–165. [PubMed: 20303157]
89. Zhang J, Laiwalla F, Kim JA, Urabe H, Wagenen RV, Song Y-K, Connors BW, Zhang F, Deisseroth K, Nurmikko AV. Integrated device for optical stimulation and spatiotemporal electrical recording of neural activity in light-sensitized brain tissue. J. Neural Eng. 2009; vol. 6 art. 055007.
90. Zorzos AN, Boyden ES, Fonstad CG. Multiwaveguide implantable probe for light delivery to sets of distributed brain targets. Opt. Lett. 2010; vol. 35:4133–4135. [PubMed: 21165114]
91. Grossman N, Poher V, Grubb MS, Kennedy GT, Nikolic K, McGovern B, Berlinguer Palmini R, Gong Z, Drakakis EM, Neil MAA, Dawson MD, Burrone J, Degenaar P. Multi-site optical excitation using ChR2 and micro-LED array. J. Neural Eng. 2010; vol. 7:016004.

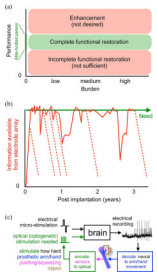

Fig. 1.

Three key challenges for intracortically based neural prostheses. (a) Notional sketch of the performance versus burden design space with the goal of complete functional restoration shown in green. (b) Notional sketch of how single-neuron-based information from intracortical electrode arrays varies (solid red line) and declines over time (dashed red lines, one for each hypothetical array implant) with the goal of high, stable, and long lasting information availability shown in green. (c) Block diagram illustrating the current capability to read out electrical neural signals, “write in” information using eICMS, and highlighting the need for high-fidelity information write in potentially enabled by oICMS (green) of optogenetically transfected neurons. A bidirectional prosthetic example is shown wherein neural activity is decoded to guide a prosthetic arm/hand (blue), and signals from electronic pressure sensors (magenta) are encoded into optical pulses (green) to provide the artificial sense of touch of an object (brown).

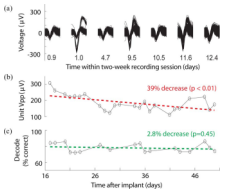

Fig. 2.

Action potential waveform instability and prosthetic decode performance stability. (a) Action potential waveforms from one example electrode at various times during a two-week wireless recording session. The electrode is one of 96 on the electrode array (Blackrock Microsystems) implanted in PMd of rhesus Monkey L. (b) Mean peak-to-peak voltages from neurons on the 96 electrodes that had $V_{pp} > 200$ μV on the first day of recording (i.e., selection criterion). These neurons came from 35 (of the 96) electrodes and reflect the "best neurons" on the array if relying on individual neurons and spike sorting for operating a prosthesis. The array was implanted in M1 in Monkey J. (c) Percent success classifying one of four reach directions with a maximum likelihood decoder using 500 ms of post-go cue threshold-crossing events ($-4.5 \times V_{RMS}$). This analysis was performed using threshold crossings from all 96 electrodes in M1 of Monkey J, but excluding approximately ten electrodes as the threshold-crossing rates on these electrodes was below our criterion of 0.2 threshold crossings per second. Threshold-crossing events were confirmed to be of neural origin (single neuron action potentials, or multiunit action potentials often referred to as "hash") by applying a shape heuristic and by visual inspection. This illustrates the relative stability of information derived from threshold crossings (panel c and Fig. 1(b), green line), and contrasts with the relatively unstable information available when reliant on individual neurons and spike sorting (panels a and b and Fig. 1(b), red lines). Adapted from [59].

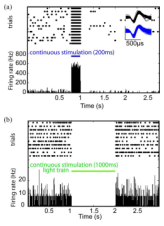

Fig. 3.

Response of an example ChR2 transfected neuron and an eNpHR2.0 transfected neuron in cerebral cortex of a rhesus monkey. (a) Raster plot and peri-stimulus time histogram (PSTH) showing an increase in action potential emission rate during blue light illumination. The neuron is from a site injected with AAV5-hThy-1-ChR2-EYFP. Spontaneous (black) and light-triggered action potential waveforms (blue) are indistinguishable in shape (insets). Monkey D. (b) Raster plot and PSTH showing a decrease in action potential emission rate during green light illumination. The neuron is from a site injected with AAV5-hThy-1-eNpHR2.0-EYFP. Monkey D. Adapted from [87].