

Brain–machine interfaces: past, present and future

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Since the original demonstration that electrical activity generated by ensembles of cortical neurons can be employed directly to control a robotic manipulator, research on brain–machine interfaces (BMIs) has experienced an impressive growth. Today BMIs designed for both experimental and clinical studies can translate raw neuronal signals into motor commands that reproduce arm reaching and hand grasping movements in artificial actuators. Clearly, these developments hold promise for the restoration of limb mobility in paralyzed subjects. However, as we review here, before this goal can be reached several bottlenecks have to be passed. These include designing a fully implantable biocompatible recording device, further developing real-time computational algorithms, introducing a method for providing the brain with sensory feedback from the actuators, and designing and building artificial prostheses that can be controlled directly by brain-derived signals. By reaching these milestones, future BMIs will be able to drive and control revolutionary prostheses that feel and act like the human arm.

Introduction

Less than a decade ago, hardly anyone could have predicted that attempts to build direct functional interfaces between brains and artificial devices, such as computers and robotic limbs, would have succeeded so readily, and in the process would have led to the establishment of a new area at the frontier of systems neuroscience. Born as a highly multidisciplinary field, basic research on brain–machine interfaces (BMIs) has moved at a stunning pace since the first experimental demonstration in 1999 that ensembles of cortical neurons could directly control a robotic manipulator [1]. Since then, a continuous stream of research papers has kindled an enormous interest in BMIs among the scientific community and the lay public. This interest stems from the considerable potential of this technology for restoration of motor behaviors in severely handicapped patients.

Indeed, BMIs have been primarily conceived as a potential new therapy to restore motor control in severely disabled patients, particularly those suffering from devastating conditions such as amyotrophic lateral

sclerosis (ALS), spinal cord injury, stroke and cerebral palsy. As this technology advances and the risks of invasive brain recordings decrease, BMIs might also hold promise for amputees. In addition to the systems controlling upper-limb prostheses, BMIs dedicated to the restoration of locomotion and speech are likely to emerge.

However, such stellar progress also breeds unrealistic expectations that such a future is just around the corner. Thus, the understandable eagerness in attaining the lofty goal of helping severely disabled patients has to be carefully calibrated by an objective analysis of the current state and future directions of the field. Such analysis indicates that, despite the optimism raised by a barrage of new accomplishments, there are still many issues that preclude straightforward translation of experimental BMIs into clinical applications. Indeed, most of the invasive BMIs have been tested only in experimental animals. Thus, despite recent enthusiasm to move emergent, and in some cases not thoroughly tested, BMI-related technology into clinical trials, much experimentation remains to be done before BMIs can become a safe and efficient rehabilitation tool.

Here, we highlight some of the fundamental obstacles faced by BMI research and propose a series of milestones that can transform recent experimental advances into viable clinical applications in the next 10–20 years. The roadmap detailed here takes into account the recent history of the field, the factors that influenced its growth, and a critical analysis of the published work.

Non-invasive BMIs

Figure 1 depicts a classification of the BMIs (or brain–computer interfaces, BCIs) developed during the past decade. The first feature that distinguishes BMIs is whether they utilize invasive (i.e. intra-cranial) or non-invasive methods of electrophysiological recordings. Non-invasive systems primarily exploit electroencephalograms (EEGs) to control computer cursors or other devices. This approach has proved useful for helping paralyzed or ‘locked in’ patients develop ways of communication with the external world [2–11]. However, despite having the great advantage of not exposing the patient to the risks of brain surgery, EEG-based techniques provide communication channels of limited capacity. Their typical transfer rate is currently 5–25 bits s⁻¹ [2,11]. Although such a transfer rate might not be sufficient to control the movements of an arm or leg prosthesis that has multiple degrees of freedom, past and recent research in this field seems to

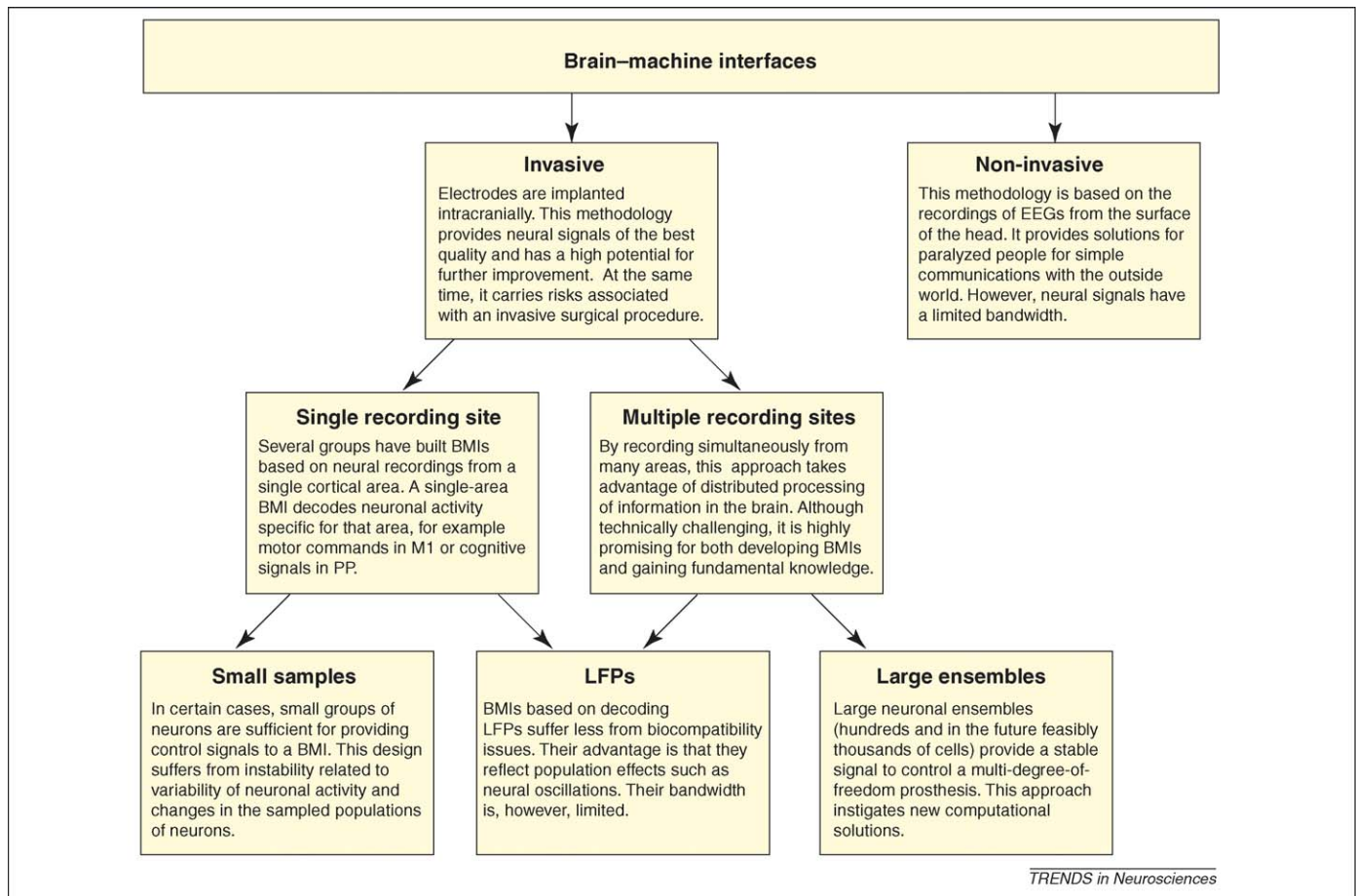


Figure 1. Classification of brain-machine interfaces. Abbreviations: BMI, brain machine interface; EEG, electroencephalogram; LFP, local field potential; M1, primary motor cortex; PP, posterior parietal cortex.

indicate that EEG-based BMIs are likely to continue to offer some practical solutions (e.g. cursor control, communication, computer operation and wheelchair control) for patients in the future.

Original attempts to provide subjects with feedback signals derived from their own brain activity were made in the 1960s and 1970s. Primarily, these attempts were aimed at enabling human subjects to gain voluntary control over brain rhythms. Nowlis and Kamiya claimed that, after training with an EEG biofeedback, human subjects acquired an ability to detect their own alpha rhythms [12], and this claim was later scrutinized by Plotkin [13]. Serman and colleagues came to similar conclusions by utilizing the sensorimotor mu rhythm in cats [14] and humans [15]. In addition, Black operantly conditioned dogs to control their hippocampal theta rhythm [16]. Clearly, the results of these pioneering experiments helped pave the way for the introduction, a few years later, of EEG-based BCIs.

Generally, EEG-based BCIs try to decipher the subject's voluntary intentions and decisions through measurements of the combined electrical activity of massive neuronal populations. As such, both the spatial and temporal resolution of EEGs become limited owing to the overlapping electrical activity generated by different cortical areas. Furthermore, during the passive conductance of these signals through brain tissue, bone and skin, resolution is also lost owing to the low-pass filtering of the EEG signals.

EEGs are also susceptible to electromyographic (EMG), electrooculographic (EOG) and mechanical artifacts.

Despite these well-known shortcomings, EEG techniques can detect modulations of brain activity that correlate with visual stimuli, gaze angle, voluntary intentions and cognitive states. These properties have led to development of several classes of EEG-based systems, which differ according to the cortical areas recorded, the features of EEG signals extracted, and the sensory modality providing feedback to subjects. One class of BCIs makes use of visual evoked potentials (VEPs). These BCIs detect the VEPs that occur when subjects look at particular items on a computer screen [17,18] or attend to them [19]. BCIs based on the P300 evoked potential uncover the subjects' choices by distinguishing parietal cortex responses to the preferred versus non-preferred stimuli [20–22]. Several BCI designs continuously drive computer cursors. Both slow cortical potentials, recorded over several cortical areas [23], and faster mu (8–12 Hz) and beta (18–26 Hz) rhythms, recorded over sensorimotor cortex [24–26], have been exploited in such BCIs. For example, one such system relies on event-related synchronization and desynchronization of the EEGs associated with motor imagery [25,27].

Training to operate EEG-based BCIs can take many days [2]. Visual feedback is the essential part of such training. Some BCI designs rely on the subjects' ability to develop control of their own brain activity using biofeedback, whereas others utilize classifier algorithms that

recognize EEG patterns related to particular voluntary intentions. Recently, adaptive algorithms that constantly update the classifier parameters during training have been implemented [26].

Several strategies have also been proposed to provide feedback to users of EEG-based BCIs. For instance, virtual-reality systems can provide a realistic feedback that can be efficient for BCI training [28]. In a recent demonstration of this approach, subjects navigated through a virtual environment by imagining themselves walking [29].

In an effort to improve the resolution of brain potentials monitored by the BCIs, more invasive recording methods, such as electrocorticograms (ECoGs) recorded by subdural electrodes, have been introduced. ECoGs sample neuronal activity from smaller cortical areas than conventional EEGs. In addition, they contain higher-frequency gamma rhythms (>30 Hz). Consequently, ECoG-based BCIs are expected to have better accuracy and shorter training times than BCIs based on EEGs [30].

EEG-based BCIs have been implemented as solutions for patients suffering from various degrees of body paralysis. These BCIs (in the case of patients with advanced ALS) enable control of computer cursors, which the patients use to communicate with the external world or to indicate their intentions. The first successful and most well received application of such an approach was based on the utilization of slow cortical potentials to control a computer-aided spelling system [3,31].

BCIs based on mu and beta rhythms have also been tested in severely paralyzed people [32]. One study reported that a tetraplegic patient, aided by a BCI that detected beta waves in his sensorimotor cortex and activated a functional electrical stimulation device, learned to grasp objects using his paralyzed hand [33]. A motor imagery-based system [32], coupled to an implanted neuroprosthesis system [34] (Freehand[®]) has been used to help a partially paralyzed patient. In addition, tetraplegic patients were able to gain some degree of control of the P300-based BCI [21]. Off-line analyses showed that P300 potentials can be used to obtain information about stimulus selections made by patients with ALS [22].

In addition to using EEGs, imaging techniques such as functional magnetic resonance imaging (fMRI), have been explored as a new source of brain-derived signals to drive BCIs [35]. Although fMRI-based BCIs are not suitable for everyday use and suffer from temporal delays of several seconds, they have good spatial resolution and, most importantly, can sample the activity of deep brain structures. Recently, fMRI was used to measure brain activation during the operation of a BCI based on slow cortical potentials [4].

Myoelectric systems that make use of voluntary activations of unaffected muscles in partially paralyzed subjects and amputees [36–39], and use these signals to control limb prostheses and exoskeletons, present an alternative to the existing non-invasive BCIs. Currently, these systems are more practical for everyday situations than EEG-based BCIs [11]. The details of their operation are beyond the scope of this review.

In summary, severely and partially paralyzed patients can reacquire basic forms of communication and motor control using EEG-based systems. Yet motor recovery obtained using these systems has been limited, and no clear breakthrough that could significantly enhance the power of EEG-based BCIs in the near future has been reported in the literature [11]. This by no means reduces the clinical utility of such systems. Some of them have improved the quality of life of patients, such as the BCI for spelling [3]. But if the goal of a BMI is to restore movements with multiple degrees of freedom through the control of an artificial prosthesis, the message from published evidence is clear: this task will require recording of high-resolution signals from the brain, and this can be done using invasive approaches.

Invasive BMIs

Invasive BMI approaches are based on recordings from ensembles of single brain cells (also known as single units) or on the activity of multiple neurons (also known as multi-units). These approaches have their roots in the pioneering studies conducted by Fetz and colleagues in the 1960s and 1970s [40–45]. In these experiments, monkeys learned to control the activity of their cortical neurons voluntarily, aided by biofeedback indicating the firing rate of single neurons. A few years after these experiments, Edward Schmidt raised the possibility that voluntary motor commands could be extracted from raw cortical neural activity and used to control a prosthetic device designed to restore motor functions in severely paralyzed patients [46].

Largely owing to technical difficulties associated with obtaining the needed cortical signals and implementing real-time interfaces quickly enough, thorough experimental testing of Schmidt's proposition took almost two decades to be accomplished. These bottlenecks were passed because of a series of experimental and technological breakthroughs that led to a new electrophysiological methodology for chronic, multi-site, multi-electrode recordings [47–51]. The BMI approach that relies on long-term recordings from large populations of neurons (100–400 units) evolved from experiments carried out in 1995 [47]. After the introduction of such an approach, a series of studies demonstrated that neuronal readout of tactile stimuli could be uncovered using pattern-recognition algorithms, such as artificial neural networks [52,53]. These developments paved the way for the first experiment in which neuronal population activity recorded in behaving rats enacted movements of a robotic device that had a single degree of freedom [1]. Soon after this first demonstration, a similar BMI approach was shown to work in New World [54] and rhesus monkeys [55–58]. As a result of these experimental efforts, in less than six years several laboratories reported BMIs that reproduced primate arm reaching [1,54–58] and the combination of reaching and grasping movements [57], using either computer cursors or robotic manipulators as actuators.

During the past three years, most of the published studies on BMIs have been conducted in behaving rhesus monkeys. There are several important differences that distinguish these BMIs (Figure 1). These include:

the number of cortical implants (e.g. uni-site or multi-site recordings); the cortical location of implants (e.g. frontal or parietal cortex, or both); the type of neural signal recorded (local field potentials versus single-unit or multi-unit signals); and the size of the neural sample. With the exception of the BMIs used at Duke University (<http://www.duke.edu/>), all BMIs tested in monkeys have relied on single cortical site recordings either of local field potentials [59–62] or of small samples (<30) of neurons or multi-units [55,56,63]. Most of these small-sample, single-area BMIs utilized neural signals recorded in the primary motor cortex [55,56], although one group has focused on BMIs that processed neural signals recorded in the posterior parietal cortex [64]. At Duke University, a BMI strategy has recently been implemented based on single-unit recordings made during intra-operative placement of deep-brain stimulators in Parkinsonian patients [65].

Principles of BMI operation

Invasive BMIs rely on the physiological properties of individual cortical and subcortical neurons (or pools of neurons) that modulate their activity in association with movements. First documented four decades ago by Evarts [66–68], such modulations are highly variable, from neuron to neuron and from trial to trial [69–72]. Thus, as much as neighboring neurons might display highly distinct firing modulation patterns during the execution of a particular movement, single-neuron firing can vary substantially from one trial to the next, despite the fact that the overt movements remain virtually identical. Yet averaging across many trials reveals fairly consistent firing patterns. By the same token, averaging across large populations of neurons significantly reduces the variability of signals derived from single neurons [54,69].

Extracting motor control signals from the firing patterns of populations of neurons and using these control signals to reproduce motor behaviors in artificial actuators are the two key operations that a clinically viable BMI should perform flawlessly [51,73]. To be accepted by patients, BMI devices will also have to act in the same way and feel the same as the subjects' own limbs. Recent findings suggest that this task might be accomplished by creating conditions under which the brain undergoes experience-dependent plasticity and assimilates the prosthetic limb as if it were part of the subject's own body. Until recently, such plasticity was achieved using visual feedback. However, a more efficient way to assimilate the prosthetic limb in the brain representation could be to use multiple artificial feedback signals, derived from pressure and position sensors placed on the prosthetic limb. These feedback signals would effectively train the brain to incorporate the properties of the artificial limb into the tuning characteristic of neurons located in cortical and subcortical areas that maintain representations of the subject's body. We predict that such plasticity will result in sensory and motor areas of the brain representing the prosthetic device.

A proposed roadmap for the future of BMI research

To achieve the ambitious goal of creating a clinically useful invasive BMI for restoring upper-limb mobility, one has to pass the following key bottlenecks:

- Obtaining stable, very long-term recordings (i.e. over years) of large populations of neurons (i.e. hundreds to thousands) from multiple brain areas. This task encourages development of a new generation of biocompatible 3D electrode matrices that yield thousands of channels of recordings while producing little tissue damage at implantation and minimal inflammatory reaction thereafter.
- Developing computationally efficient algorithms, that can be incorporated into the BMI software, for translating neuronal activity into high-precision command signals capable of controlling an artificial actuator that has multiple degrees of freedom.
- Learning how to use brain plasticity to incorporate prosthetic devices into the body representation. This will make the prosthetic feel like the subject's own limb.
- Implementing a new generation of upper-limb prosthetics, capable of accepting brain-derived control signals to perform movements with multiple degrees of freedom.

We now discuss some potential avenues for addressing the first three of these major challenges. A thorough discussion of the fourth challenge (i.e. engineering a new generation of prosthetic arms) is beyond the scope of this review.

Long-term recordings of neuronal activity from multiple brain areas

Although recording from single neurons is the first choice of neurophysiologists, multi-unit signals that comprise activity of a few neurons can also be efficiently used in BMI control [57]. In addition, several reports have suggested using local field potentials [59–62]. It is conceivable that, in future, advanced neuroprosthetic devices will use hybrid solutions in which a combination of several types of neural signals are recorded and processed. Here, however, we focus on using single-unit and multi-unit signals as the primary input to a BMI. This choice raises a fundamental question: how many neurons does a BMI need to sample to produce effective motor outputs?

This question, first raised several years ago [51,73], remains a matter of debate. Some groups [55,56,63] have strongly claimed that recordings from a small number of neurons can be sufficient for good performance of a BMI. Selected populations of highly tuned neurons can indeed accurately predict movement parameters [74]. However, highly tuned neurons are rare in a typical random sample of cortical cells. Given that the neuronal yield of all chronic recording techniques is produced by random sampling of neurons, it is unrealistic to expect that a large fraction of these cells will be highly tuned to a particular motor variable. Moreover, it would be even more unrealistic to expect that a small neuronal sample would represent several variables of interest. Therefore, large samples of recorded neurons are preferable, at the very least to enable selection of a sufficient number of highly tuned neurons. Besides, the reason for relying on large neuronal populations goes far beyond the issue of selecting the best performing cells. Both the accuracy [54,57,70] and the

reliability [69] of predictions improve considerably with the number of simultaneously recorded neurons, because motor information seems to be represented in the cortex in a highly distributed way. Thus, as the neuronal sample increases in size, errors related to individual neuron firing variability decrease significantly [69]. So looking into the future, it seems unlikely that invasive BMIs based on a small group of neurons will be capable of continuously reproducing in artificial limbs the range of fine movements normally performed by the human arm and hand.

Currently, chronically implanted microwire arrays offer the best compromise between safety, recording longevity and neuronal yield required to operate BMIs [48,51,54,57,58,73]. It is clear that this methodology will continue to be applied in experimental settings, but several significant improvements are required before it becomes fully applicable for long-term (months to years) chronic clinical applications in humans. First and foremost, the broad and challenging issue of biological compatibility [75–80] has to be properly addressed and solved. Second, fully implantable technologies using wireless headstages for amplification of neuronal signals have to be implemented to reduce the risks of infection introduced by the use of cables that connect brain implants to external hardware.

Current microelectrode designs typically enable good quality recordings to be made for several months. In certain cases and species, these recordings can last for several years [81]. However, recording quality often deteriorates, probably owing to a process of electrode encapsulation by fibrous tissue and cell death in the vicinity of the electrode [77]. Some authors have proposed that electrodes that contain neurotrophic medium [82–85], or are coated with factors that promote neuronal growth (e.g. nerve growth factor, brain-derived neurotrophic factor or laminin) and various anti-inflammatory compounds (e.g. dexamethazone) [77,86–91], might be a way to cope with encapsulation. Currently, it is unclear whether these approaches will be useful.

Efforts to resolve the biocompatibility issues will probably have to be pursued in parallel with the development of new 3D electrode matrices, which should aim to increase the average yield to thousands of neuronal signals per implanted probe. Current alternatives to such microwires (e.g. the Utah probe [92], which implements arrays of rigid, single-ended electrodes) have yet to prove their adequacy to support the haste in which this technology was moved into clinical applications. Judging from the published evidence, such arrays are best suited to sample neuronal activity from flat surfaces of cortical gyri in animal experiments. However, this design might not be suitable for long-term use in human patients. In addition to issues of how electrodes are inserted into the cortex, the inability to sample from deep cortical layers, and many unanswered biocompatibility questions, the reliability of the recording system utilized by currently available probes is also compromised by the continuous stress of a daily routine that involves external cables and plugging and unplugging of external head-stages. These operations carry a risk of causing tissue damage, bleeding and brain infection. Such a risk of failure, which might be tolerable in animal experiments, is unwanted in practical applications

for humans. Cyberkinetics Neurotechnology Systems (<http://www.cyberkineticsinc.com/content/index.jsp>) has recently started clinical trials in severely paralyzed patients of a BCI based on a probe developed at the University of Utah (<http://www.utah.edu/>). Because no peer-reviewed publication has appeared related to this work, the exact outcome of this study remains unknown.

From these considerations, it is clear that the issues related to the long-term functionality of implantable micro-electrodes, and to the development of fully implantable electronic devices for amplification of a large number of neuronal signals and their wireless transmission to the actuator, are the major technological challenges that will determine the success or failure of future clinical applications of BMI technology. These technological developments are necessary not only to increase the practical usefulness of the BMI (more neurons mean better stability and accuracy) but also to ensure that risks to patient health are minimized. Auspiciously, telemetry transmission methods [93–97] for effective wireless transmission of multi-channel neuronal signals have already started to appear in the literature [98,99]. These solutions are currently being tested in animal experiments.

Many new ideas of how to improve neuronal recordings have been proposed recently. These range from ceramic-based multi-electrode arrays [100] to nanotechnology probes that access the brain through the vascular system [101]. In this latter design, probes record neuronal activity without compromising brain parenchyma. Undoubtedly, much more testing will be needed to conclude which of these ideas are viable.

Developing algorithms for translating neuronal activity into command signals for artificial actuators

Currently, neuroscientists are far from obtaining a clear understanding of how motor and cognitive information is processed by the populations of neurons that form large brain circuits. Rate encoding, temporal encoding and population encoding principles have been suggested, and various experimental paradigms, including BMIs, have been developed to test the validity of these concepts. However, precise knowledge of computations performed by brain circuits is not crucial for the construction of clinically relevant BMIs. Mostly, BMI platforms take advantage of the well known correlation between discharges of cortical neurons and motor parameters of interest, and perform a reverse operation: they predict motor parameters from patterns of neuronal firing. Generally, predictions of motor parameters do not signify a causal relationship between the neuronal activity and the generation of movements. One type of correlation between neuronal activity and movement is known as directional tuning [102,103], and correlations of neuronal activity with kinematic [104–106] and kinetic [107–109] parameters of movements have also been described.

Although a wealth of linear and nonlinear algorithms for translating neuronal activity into commands to artificial actuators have been suggested [1,54,56,57,70,110–116], relatively simple multiple linear regression models have proved to be efficient in many practical BMI designs [54,55,57,58,65,117]. In these models, predicted motor

parameters are derived from the weighted sums of neuronal rates of firing, measured at different time points in the past. The number of regressors in the model and the time window used for predictions can be optimized for each concrete BMI application [70,74,117]. Linear methods, such as population vector predictions, can incorporate adaptive algorithms that continuously update the model parameters while the subject trains [56].

Basic research using the BMI paradigm has lent support to some fundamental principles of neural information coding. For example, studies in which several independent linear models were run in parallel revealed that several motor parameters, such as arm position, velocity, acceleration and hand gripping force, could be predicted simultaneously by separate combinations of the activity of the same original pool of neurons [57]. This finding supports the notion that multiple motor parameters are processed by overlapping neuronal ensembles. As a corollary, a single cortical neuron can contribute to several predictions simultaneously.

The choice of motor parameters extracted in future clinical BMIs will depend on the main rehabilitation or therapeutic goals of these applications. For example, an experimental BMI for reaching and grasping [57] predicted hand velocity and gripping force that matched the characteristics of a robotic arm equipped with a gripper. In the near future, this design could lead to the implementation of neuroprosthetic devices that help quadriplegic or 'locked in' patients to reach and grasp objects in the surrounding space. We can also envisage that BMIs that synthesize speech, based on neuronal signals recorded in intact speech-related regions, could one day help patients suffering from aphasia due to cortical strokes recover their ability to communicate.

Future clinical applications might also take advantage of BMIs that predict EMG signals [117]. The main benefit of this design compared with a BMI that predicts kinematic parameters is that the signals of individual muscles can control biologically-inspired devices, which would produce a whole range of actuator stiffness. This is an important property needed for a future generation of prosthetic limbs that should be able to manipulate objects with different physical characteristics. Another powerful future application for BMIs that decode EMGs is the construction of brain-muscle interfaces that directly stimulate the muscles of paralyzed patients and thereby restore mobility by using the patient's own musculoskeletal apparatus [37,118,119]. Such BMIs are likely to be much more acceptable to patients, particularly because the hardware needed for amplification, transmission and processing of brain-derived control signals, and the muscle stimulators driven by these neural signals, such as the BION [120], can be entirely encased in the patient's body. In the future, it is conceivable that such BMIs could merge the current cortically driven paradigm with methods and new technologies developed in the field of functional electrical stimulation.

Early BMI designs focused on decoding motor parameters from neuronal activity [1,54–56,117]. More recently, it was suggested that BMIs that decode cognitive signals, for example those that decode intended reach direction during the delay periods preceding movement

execution [64,121–123], could also be efficient. Although this idea is very attractive, a BMI based exclusively on cognitive signals cannot execute continuous control of movement parameters. Instead, it decodes higher-order characteristics of movements, such as reach direction or characteristics of objects being grasped, and delegates lower-order details of motor execution to the actuator controller. Recently, we have proposed that a hybrid BMI, based on a shared control mode of operation [124], can improve the accuracy with which the prosthetic implements the voluntary intentions of the subject. A shared-control mode of operation would be achieved by a combination of high-order brain-derived signals, conveying the subject's voluntary intentions, and low-level artificial 'reflex-like' circuits, designed to improve the precision with which prosthetic limb movements are generated.

In the future, BMIs that take advantage of the higher-order neuronal representations of movement-related variables will also emerge. These BMIs will probably derive information from representations of movement sequences [125,126], reference frames [127–130], potential movement targets [131] and simultaneous encoding of multiple spatial variables, such as movement direction, orientation of selective spatial attention, and gaze angle [132,133]. Utilization of this wide array of information will endow BMIs with a much more flexible control of prosthetic limbs.

In the same context, we also believe that future BMIs will take advantage of new insights on how neural circuits encode temporal characteristics of movements. Recent studies [134–137] have indicated that a rather distributed representation of temporal information might exist in the brain. Recordings obtained from primary motor and premotor cortical ensembles while monkeys performed self-timed button presses [138] enabled prediction of both the time that had elapsed since the monkey pressed the button and the time until the button would be released. Because any motor behavior has a temporal structure, and because episodes of movement execution are typically intermingled with periods of immobility during which movements are being prepared, a BMI that decodes behavioral time will be able to inhibit movements of the actuator during waiting periods and release the actuator at appropriate times. These operations will be based on the voluntary intentions of the user.

Making use of brain plasticity to incorporate prosthetic devices into the body representation

Controlling an artificial actuator through a BMI can be thought of as a process somewhat similar to the operation required by subjects to operate tools – a capacity that is inherent only in higher primates such as chimpanzees and humans [139]. Almost 100 years ago [140], Head and Holmes suggested that the 'body schema' – that is, the internal brain representations of one's body – could extend itself to include a wielded tool. This idea was validated by the experimental demonstration that cortical neurons extend their visual receptive fields along the length of a rake used by monkeys to retrieve distant objects [141]. Psychophysics experiments also support the notion that tool usage leads to remapping of the 'body schema' in

humans [142,143]. Accordingly, a recent neuroimaging study [144] described specific activations of the right ventral premotor cortex during manipulation of a myoelectric prosthetic hand. Altogether, these results suggest that long-term usage of an artificial actuator directly controlled by brain activity might lead to substantial cortical and subcortical remapping. As such, this process might elicit the vivid perceptual experience that the artificial actuator becomes an extension of the subject's body rather than a mere tool. This suggestion is supported by the report of primary sensorimotor cortex activation during perceived voluntary movements of phantom limbs in amputees [145].

Perhaps the most stunning demonstration of tool assimilation by animals was observed when both rats and primates learned to operate an actuator through a BMI, without the need to move their own limbs [1,56–58]. In these experiments, decoding algorithms were initially trained to predict limb movements of animals from the activity of neuronal populations. Remarkably, after these animals started to control the actuator directly using their neuronal activity, their limbs eventually stopped moving, while the animals continued to control the actuator by generating proper modulations of their cortical neurons. Interestingly, during these episodes neuronal tuning to movements of the subject's own limbs decreased while the animals continued to control the artificial actuator by their brain activity [58]. The most parsimonious interpretation of this finding is that the brain was capable of undergoing a gradual assimilation of the actuator within the same maps that represented the body [57,58]. Neuronal mechanisms mediating such plasticity are far from being understood.

However, it is fair to state that there is a growing consensus in the literature that continuous BMI operations in primates lead to physiological changes in neuronal tuning, which include changes in preferred direction and direction tuning strength of neurons [56–58]. In addition, broad changes in pair-wise neuronal correlation can be detected after BMIs are switched to operate fully under brain-control mode [57,58].

Along with these physiological adaptations of neuronal firing patterns, behavioral performance improves as animals learn to operate BMIs effectively [56–58]. Initial training to operate a BMI is characterized by an increase in neuronal firing rate variance, which cannot be simply explained by changes in limb or actuator movements [146]. As the quality of BMI control improves, initial elevation of neuronal firing variability subsides. Plastic changes in neuronal firing patterns during BMI control, leading to the physiological incorporation of the artificial actuator properties into neuronal space, could account for these changes in firing rate variance. This interpretation is in accord with the theory of optimal feedback control [147–149]. According to this theory, a motor system acts as a stochastic feedback controller that optimizes only those motor parameters that are necessary to achieve the goals of a particular task. During the brain-control mode of operation of a BMI, the goals of a motor task are achieved only by direct brain control of an artificial actuator. Thus, in terms of optimal feedback control theory, neuronal ensembles should adapt their physiological tuning properties to represent better the goal-related variables of the task performed by the BMI.

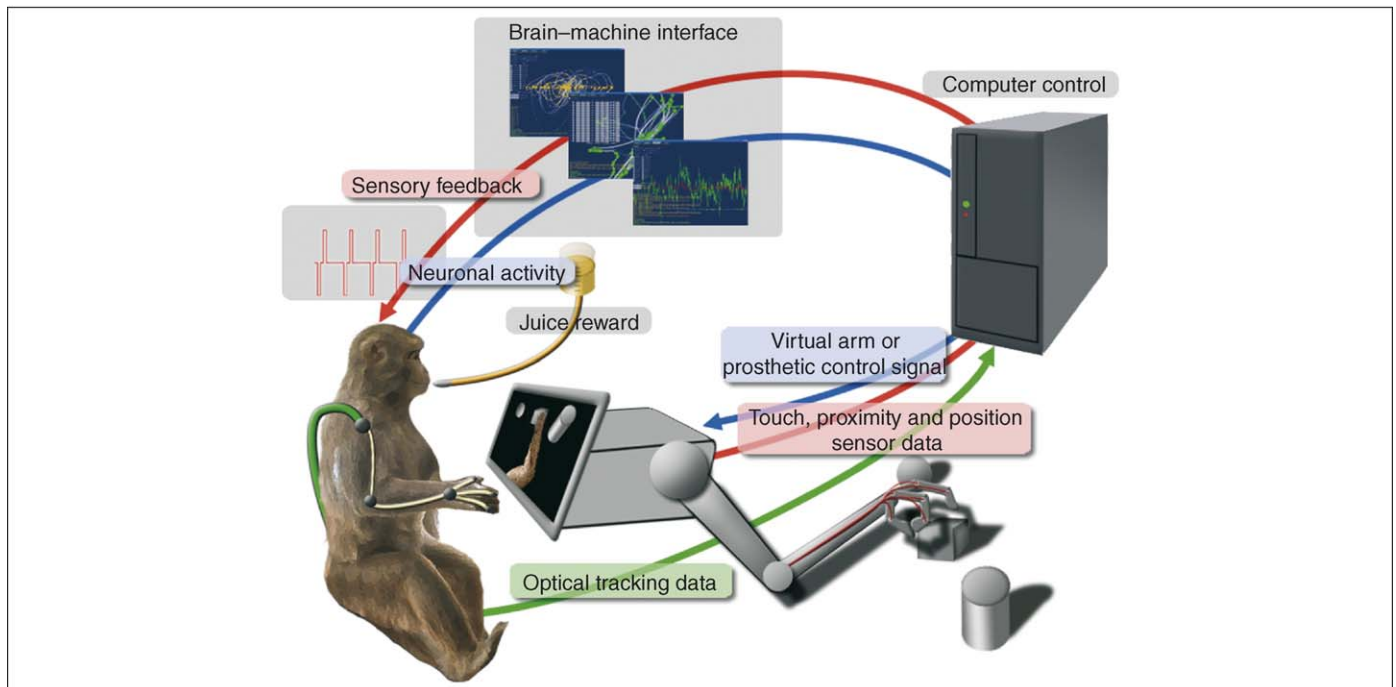


Figure 2. A BMI with multiple feedback loops being developed at the Duke University Center for Neuroengineering. A rhesus macaque is operating an artificial robotic manipulator that reaches and grasps different objects. The manipulator is equipped with touch, proximity and position sensors. Signals from the sensors are delivered to the control computer (right), which processes them and converts to microstimulation pulses delivered to the sensory areas in the brain of the monkey, to provide it with feedback information (red loop). A series of microstimulation pulses is illustrated in the inset on the left. Neuronal activity is recorded in multiple brain areas and translated to commands to the actuator, via the control computer and multiple decoding algorithms (blue loop). Arm position is monitored using an optical tracking system that tracks the position of several markers mounted on the arm (green loop). We hypothesize that continuous operation of this interface would lead to incorporation of the external actuator into the representation of the body in the brain. Figure designed by Nathan Fitzsimmons.

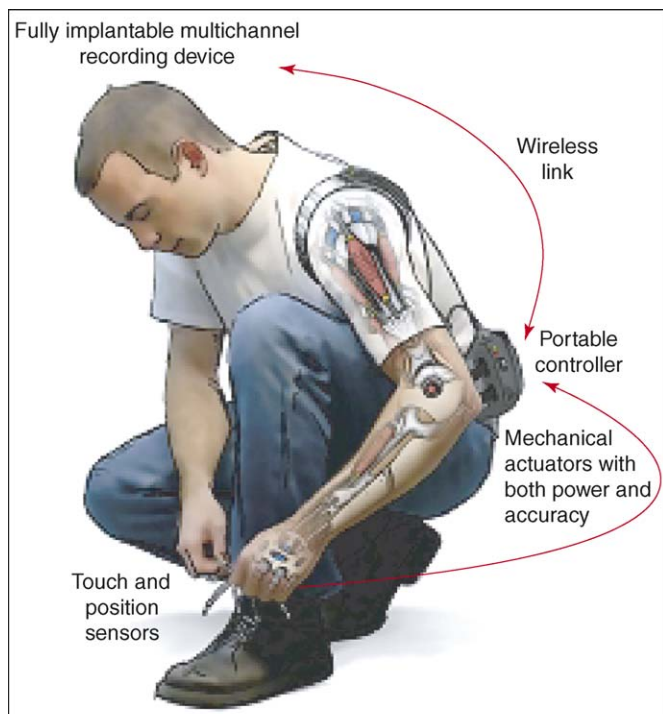


Figure 3. How a fully-implantable BMI could restore limb mobility in paralyzed subjects or amputees. Although the details of this system have to be worked out through future research, it is clear that the BMI for human clinical applications should be encased in the patient's body as much as possible. Wireless telemetry offers a viable solution for this purpose. The prosthesis not only should have the functionality of the human arm in terms of power and accuracy of the actuators, but also should be equipped with the sensors of touch and position from which signals can be transmitted back to the subject's brain.

Making the prosthetic feel like the subject's own limb using microstimulation of cortical sensory areas

Peripheral tactile and proprioceptive signals contribute to the normal operation of one's limbs and the perception that they are part of the body [142,143]. For a neuroprosthesis to behave and feel as a natural appendage of the subject's body, it will have to be instrumented with various sensors that can provide multiple channels of 'sensory' information back to the subject's brain. In most current BMI designs, animal subjects receive sensory information from the actuator through visual feedback [55–58]. Predictions of motor parameters are less stable in the absence of visual feedback [70] than when it is present [55–58].

Curiously, the use of tactile and proprioceptive-like feedback in BMI research remains largely unexplored. Recently, in collaboration with John Chapin, we have started to explore the intriguing possibility of delivering such sensory feedback information, generated in the actuator, to the brain through the use of multi-channel microstimulation of somatosensory cortical areas (Figure 2). Previous studies have shown that monkeys sense microstimulation patterns and can use them to guide their behavioral responses [150,151]. In a recent long-term study, owl monkeys could learn to guide their reaching movements by decoding vibratory stimuli applied to their arms [152]. Next, instead of vibratory stimulation, matching patterns of microstimulation were applied through the electrodes implanted in the primary somatosensory cortex [153]. Monkeys were still able to interpret correctly the

instructions provided by cortical microstimulation, and their behavioral performance eventually surpassed the level of performance observed when the vibratory stimulus was applied to their skin. These results suggest that cortical microstimulation might become a useful way to deliver long-term feedback from prosthetic limbs controlled by a BMI, and might contribute to the development of a completely new generation of neuroprosthetic devices for restoring various motor behaviors in severely impaired patients.

Concluding remarks

Our vision of neuroprosthetic developments that might emerge in the next 10–20 years includes a fully implantable recording system that wirelessly transmits multiple streams of electrical signals, derived from thousands of neurons, to a BMI capable of decoding spatial and temporal characteristics of movements and intermittent periods of immobility, in addition to cognitive characteristics of the intended actions (Figure 3). This BMI would utilize a combination of high-order motor commands, derived from cortical and subcortical neuronal activity, and peripheral low-level control signals, derived from artificial 'reflex-like' control loops. Such a shared-control mode of BMI operation would either command an actuator with multiple degrees of freedom or directly stimulate multiple peripheral nerves and muscles through implantable stimulators. Highly instrumented artificial actuators, containing arrays of touch and position sensors, would generate multiple streams of sensory feedback signals that could be directly delivered to cortical and/or subcortical somatosensory areas of the subject's brain, through spatiotemporal patterns of multi-channel microstimulation. Such closed-loop, hybrid BMIs would get one step closer to the dream of restoring a large repertoire of motor functions to a multitude of patients who currently have very few options for regaining their mobility.

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