

Brain–machine interfaces: computational demands and clinical needs meet basic neuroscience

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As long as 150 years ago, when Fritz and Hitzig demonstrated the electrical excitability of the motor cortex, scientists and fiction writers were considering the possibility of interfacing a machine with the human brain. Modern attempts have been driven by concrete technological and clinical goals. The most advanced of these has brought the perception of sound to thousands of deaf individuals by means of electrodes implanted in the cochlea. Similar attempts are underway to provide images to the visual cortex and to allow the brains of paralyzed patients to re-establish control of the external environment via recording electrodes. This review focuses on two challenges: (1) establishing a ‘closed loop’ between sensory input and motor output and (2) controlling neural plasticity to achieve the desired behavior of the brain–machine system. Meeting these challenges is the key to extending the impact of the brain–machine interface.

The idea of a brain in a jar, remotely controlling the actions of a ‘body’, belongs to often-questionable fiction. Occasionally, as in Mary Shelley’s *Frankenstein*, similar thoughts have inspired more solid works of art. But it was as recently as 1960 that Manfred Clynes and Nathan Cline created the word ‘cyborg’ [1], to describe the interaction of artificial and biological components within integrated ‘cybernetic organisms’ that were to be engaged in space exploration. In their words:

‘If man in space, in addition to flying his vehicle, must continuously be checking on things and making adjustments merely to keep himself alive, he becomes a slave to the machine. The purpose of the Cyborg, as well as his own homeostatic systems, is to provide an organizational system in which such robot-like problems are taken care of automatically and unconsciously, leaving man free to explore, to create, to think, and to feel.’ [1]

Today, the rapidly emerging field of brain–machine interfaces is bringing the same vision to the pursuit of other goals: creating more powerful computers and giving new hope to a broad segment of the disabled population.

Computers and the brain

During the last century, studies of computers and of the brain have evolved in a reciprocal metaphor: the brain is

seen as an organ that processes information, and computers are developed in imitation of the brain [2]. Despite the speed with which the computers of today execute billions of operations, their biological counterparts have as yet unsurpassed performance when it comes to recognizing a face or controlling the complex dynamics of the arm. The fascination with the computational power of biological systems has sparked intense activities aimed at mimicking neurobiological processes in artificial systems [3–7]. Recently, a more radical idea has begun to take shape: to construct hybrid computers in which neurons are grown over a semiconductor substrate [8–11]. Fromhertz and colleagues have developed a simple prototype, in which electrical signals are delivered by the substrate to a nerve cell [10]. The responses of the nerve cell are transmitted via an electrical synapse to a second cell and the activity of the second cell is read out by the semiconductor substrate.

New perspectives for the disabled

The first success story in brain–machine interfaces was the cochlear implant [12], a sensory neuroprosthesis. However, another driving force behind brain–machine interfaces arises from the need to provide communication, and a means of acting on the environment, to patients that have lost control of their body. Much of the clinically orientated brain–machine interface research has focused on ‘locked-in’ patients, who suffer from total paralysis following brainstem stroke or degenerative diseases such as amyotrophic lateral sclerosis (ALS) [13]. The goal is to extract control signals either from surface electroencephalographic (EEG) signals or from electrodes implanted in the cerebral cortex.

Brain signals for control

Surface recordings

For >20 years, the most systematic attempts at clinical application of brain–machine interfaces to the sensory–motor system have used specific components of EEG signals [14]. The μ -rhythm is an 8–12 Hz oscillation detected over sensorimotor cortex during both actual and imagined movements [15]. Wolpaw and co-workers trained both healthy and disabled subjects to control the position of a cursor in one or two dimensions on a monitor, based on the amplitude of the μ -rhythm [16–18] (Fig. 1a).

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Donchin and co-workers [19] have investigated the possibility of using other EEG signals associated with a novel visual pattern. They asked subjects to select and focus attention on one target, while other targets flashed at random. A specific event-related potential was observed whenever the selected target was illuminated. This response probably reflects the detection of contextual changes that trigger an update of a subject's working memory [20]. Other methods train subjects to control their EEG activity via operant conditioning [21]. Operant conditioning can be enhanced by detecting signal components that reflect the presence of an error in the operation of the brain-machine interface [22]. However, a technical limitation of EEG-based methods is the low information rate, which is currently limited to 20–30 bits min^{-1} .

Intra-cortical recordings

Because of the limited bandwidth of EEG processing, researchers have also undertaken more invasive approaches, based on extracellular recordings by microelectrodes. Understanding the connection between neuronal discharge rate and voluntary movement has been a mainstay of motor-systems studies since the pioneering work of Evarts [23]. Within four years of that research, Humphrey and colleagues [24] showed that linear combinations of three to five simultaneously recorded cells could significantly improve estimates of joint rotation. It is now possible to record simultaneously from at least an order of magnitude more cells. A wide range of procedures is being tested in an effort to extract information about movement intention from ensembles of neurons (reviewed in Ref. [25]). Although several of these offer real promise, few have been implemented as real-time control algorithms.

Brain signals for control

Despite anticipation of the theoretical possibility, the first use of CNS recordings as control signals did not occur until

advances in microelectrode, electronics and computer technologies made the approach technically feasible. Chapin and co-workers trained rats to retrieve drops of water by pressing a lever controlling the rotation of a robotic arm [26]. They used the activities of 21–46 neurons, recorded with microwires implanted in the M1 region of the motor cortex, as input to a computer program which, in turn, controlled the motion of the robot. Several rats learned to operate the arm using the neural signals, without actually moving their own limbs.

Subsequently, other groups demonstrated real-time control of robotic arms [27] or of a cursor on a computer display [28,29] (Fig. 1b). In these experiments, as many as 100 electrodes were implanted into the cerebral cortex of monkeys, and control was based on activities of 10–100 neurons. Andersen and co-workers [30] implanted electrodes in the posterior parietal cortex, a region that is believed to participate in movement planning. Monkeys were required to reach towards one of two targets displayed on a touch screen, and a probabilistic algorithm predicted the preferred target based on discharge recorded during the delay period preceding movement. Within 50 trials, the monkeys learned to modulate the discharge in the absence of movement to indicate the intended target.

Although several chronically implanted electrode systems have been tested in monkeys, the only one that has actually been used in human patients is the neurotrophic cone electrode [31] (Fig. 2). A microscopic glass cone contains a neurotrophic factor that induces neurites to grow into the cone, where they contact one of several gold recording wires. Four severely disabled patients were implanted with cone electrodes that provided input to a computer, and the most successful patient eventually learned to communicate at a rate of approximately three letters per minute.

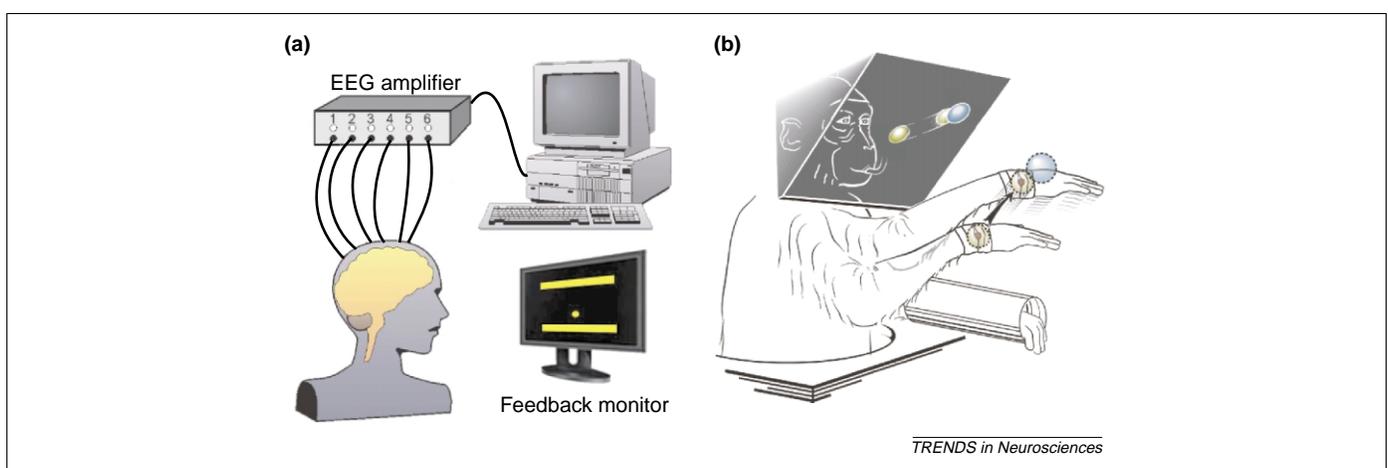


Fig. 1. Visual feedback of neuron-related signals. (a) Electroencephalographic (EEG) signals recorded from the scalp have been used to provide rudimentary communication or other environmental control to 'locked-in' patients, who are essentially completely paralyzed owing to brainstem stroke or neurodegenerative disease. The signals are amplified and processed by a computer, such that the patient can learn to control the position of a cursor on a screen in one or two dimensions. Among other options, this technique can be used to select letters from a menu in order to spell words. Reproduced, with permission, from Ref. [13], © (2001) American Psychological Association. (b) Visual feedback has also been provided to monkey subjects who have learned to control the 3D location of a cursor (sphere) in a virtual environment. The cursor and fixed targets are projected onto a mirror in front of the monkey. The cursor position can be controlled either by hand movements made by the monkey or by hand movements predicted in real-time on the basis of neuronal discharge recorded from electrodes implanted in the cerebral cortex. The ability of the monkey to move the cursor to both learned and novel targets using 'brain control' was enhanced when the monkey was able to track continuously the position of the hand with respect to the target. This is called 'feedback control'. Reproduced, with permission, from Ref. [28], © (2002) American Association for the Advancement of Science (<http://www.sciencemag.org>).

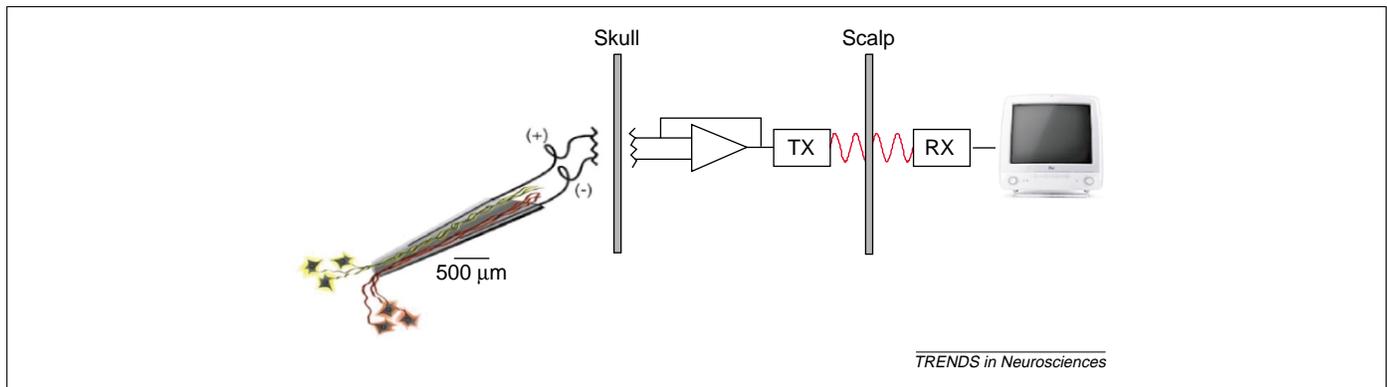


Fig. 2. Block diagram of the neurotrophic electrodes used by Kennedy and colleagues for implantation in human patients [31–33]. Neurites that are induced to grow into the glass cone make highly stable contacts with recording wires. Signal conditioning and telemetric electronics are fully implanted under the skin of the scalp. An implanted transmitter (TX) sends signals to an external receiver (RX), which is connected to a computer. Figure courtesy of Philip R. Kennedy.

Feedback is needed for learning and for control

Real-time feedback can dramatically improve the performance of a brain–machine interface. In the brain, feedback normally allows for two corrective mechanisms. One is the ‘online’ control and correction of errors during the execution of a movement. The other is learning: the gradual adaptation of motor commands, which takes place after the execution of one or more movements.

Online corrections and the problem with time delays

Patients attempting to control a cursor on a computer screen for purposes of communication receive visual feedback related to their EEG activity [16] or neuronal discharge [32,33]. However, the long delays intrinsic to the visual system (100–200 ms) make it unsuitable for the online correction of errors in a complex dynamic system such as the human arm. Patients suffering a loss of the normal, rapid proprioceptive feedback can move by relying on vision of their limbs, but the movements are typically slow, poorly coordinated and require great concentration [34,35]. Corrections tend to come too late, often causing a new error and resulting in jerky, unstable movements. The simplified dynamics of a virtual limb on a computer monitor (Fig. 1b), or a servomechanism enforcing a commanded trajectory, can lessen the effects of delays. However, even in these simplified conditions, errors can be corrected only after long visual latencies. This is likely to be a leading cause of the observed tracking inaccuracy. If the muscles of a paralyzed patient were to be activated through a brain–machine interface, the dynamics of the musculoskeletal system would need to be controlled by the neural signals and feedback delays would become more crucial.

Pathways for feedback signals

A possible means of reducing feedback delays would be to activate central sensory areas directly, by means of electrical stimulation. Cochlear implants [12] were among the earliest and most successful interfaces between brain and artificial systems. Currently, some 40 000 patients worldwide wear such an implant. Unfortunately, most attempts to stimulate more central areas have been less successful, probably because of the loss of important signal processing in the periphery [36]. Even if successful,

auditory feedback would be an unlikely modality for use in controlling a motor prosthesis.

Much effort has also been expended in the development of visual prostheses, including attempts to stimulate both the visual cortex [37,38] and the retina [39]. However, the latter methods are unlikely to provide useful feedback for a motor prosthesis, as they would suffer from the same long latencies as the intact visual system. Direct cortical stimulation might substantially decrease the delay but, as is the case for the auditory prosthesis, mimicking the sophisticated visual signal processing in the peripheral nervous system is a daunting prospect.

The somatosensory system, including proprioception, seems to be a more natural modality for movement-related feedback. Recordings from peripheral sensory nerves have been used as a source of feedback in functional electrical stimulation, for controlling grip [40]. Signals derived from a controlled robot might instead be used to stimulate these nerves as a means of approximating the natural feedback during reaching. However, in most of the situations in which such systems would be clinically useful, conduction through these nerves to the CNS is not present.

Limited experimental efforts have been made to investigate the perceptual effects of electrical stimulation in the somatosensory cortex. Monkeys have proven capable of distinguishing different frequencies of stimulation, whether applied mechanically to the fingertip or electrically to the cortex [41]. In a recent demonstration, the temporal association of electrical stimuli to the somatosensory cortex (cue) with stimuli to the medial forebrain bundle (reward) conditioned freely roaming rats to execute remotely controlled turns [42]. It is not yet known whether cortical stimulation could provide adequate feedback to guide movement in the absence of normal proprioception.

Adaptive control of brain–machine interactions

Some investigators have used the closed-loop interaction between nerve cells and external devices as a means to study neural information processing [11,43,44]. A crucial feature of such interactions is the possibility of combining the plastic properties of neural tissue with the adaptive control of the external devices [15]. Although vision plays a secondary role in the online control of movement, it is

crucial to the guidance of long-term adaptation of movement. Monkeys trained to control a cursor within the virtual environment (Fig. 1b) were able to use their intact visual system to adapt their 'brain control' of cursor movement. At the same time, the control algorithm was 'co-adapted' to accommodate the consequent changes in the directional properties of the recorded neurons [28]. In the course of each daily session, the directional tuning of a given set of neurons tended to settle into a stable configuration, suggesting that the changes were adaptive, occurring as the nervous system switched from 'direct control' to brain control.

Mussa-Ivaldi and co-workers [44,45] have investigated the possibility of using the feedback from a brain-machine interface for inducing controlled plastic changes at specific synapses. Figure 3 shows the bidirectional connections

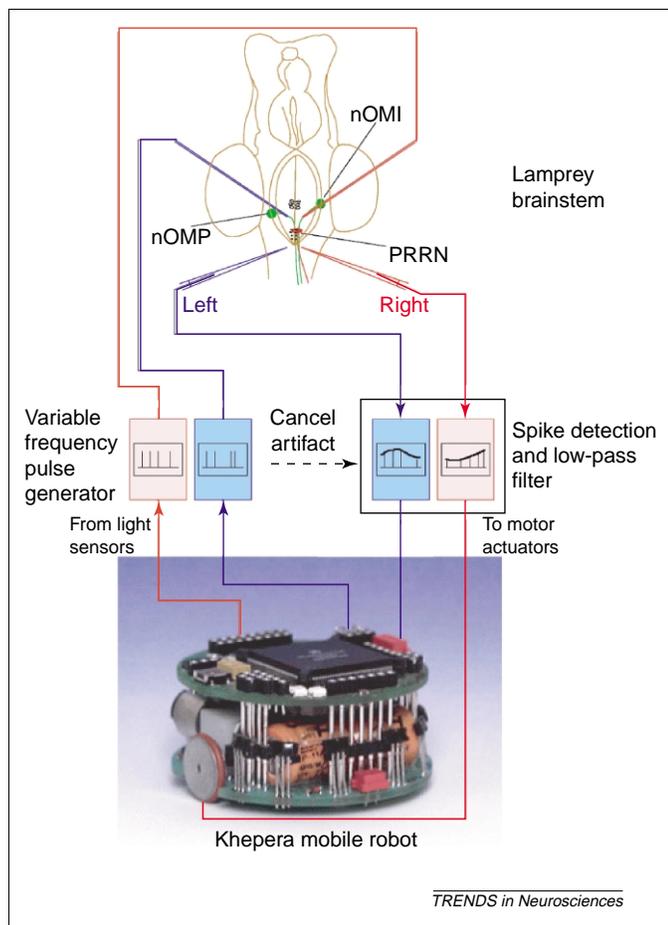


Fig. 3. A hybrid neuro-robotic system. Signals from the optical sensors of a Khepera (K-team) mobile robot (bottom) are encoded by the interface into electrical stimulations, the frequency of which depends linearly on the light intensity. These stimuli are delivered by tungsten microelectrodes to the right and left vestibular pathways of a lamprey brainstem (top) that is immersed in artificial cerebrospinal fluid within a recording chamber. The electrical stimuli are delivered to the axons of the intermediate and posterior octavomotor nuclei (nOMI and nOMP, respectively). Glass microelectrodes record extracellular responses to the stimuli from the posterior rhombencephalic neurons (PRRN). Recorded signals from right and left PRRN are decoded by the interface. First, the electric artifacts generated by the stimulation impulses are removed. Then, population spikes are detected. The resulting spike train is passed through a low-pass filter, which calculates an average firing rate over a 300 ms firing window. The average firing rate detected from each electrode is translated into a command to the corresponding wheel of the robot. The angular velocity of the wheel is set to be proportional to this average rate.

between a mobile robotic device and a lamprey brainstem that have been used to investigate the repertoire of operations carried out by neurons in the reticular formation. Signals generated by the two optical sensors of the robot were translated into electrical stimuli and applied to the vestibular pathways, to two populations of reticular neurons. The resulting discharge frequency of the reticular neurons commanded the right and left wheels of the robot. In this simple arrangement, the reticular neurons acted as a processing element that determined the closed-loop response of the neuro-robotic system to a source of light. These studies revealed that (1) different behaviors can be generated with different electrode locations, (2) the input-output relationship of the reticular synapses is well approximated by simple linear models with a recurrent dynamic component and (3) the prolonged suppression of one input channel leads to altered responsiveness long after it has been restored.

In a similar experiment, Deliagina, Grillner and co-workers [46] used the activity of reticulospinal neurons recorded from a swimming lamprey to rotate the platform supporting the fish. The lamprey was able to stabilize the hybrid system, and this compensatory effect was most efficient in combination with undulating swimming motions. These studies demonstrate the feasibility of closed-loop interactions between a specific region of the nervous system and an artificial device. Closed-loop brain-machine interfaces offer an unparalleled opportunity to investigate how plastic changes can be guided by modulating the input signals of the neurons based on the behaviors generated by the output of the same neurons. Furthermore, in such hybrid systems it is possible to replace the neural tissue with a computational model, thus providing a direct means for testing the predictions of specific hypotheses about neural information processing.

Challenges and trends

Research on brain-machine interfaces can be successful to the extent that we understand how sensory-motor transformations are learned and encoded by the nervous system. We have reviewed some of the ongoing studies related to the execution of simple movements. However, motor behavior is not only about movement but also about interaction with an ever-changing environment. Adaptation to the variable dynamics of the limbs and of the limb environment has generated an increasing volume of research [47-52] that is relevant to brain-machine interfaces. Understanding the neural mechanisms that allow the nervous system to form and to modify the representation of the controlled dynamics is a key element for developing brain-machine interactions that go beyond placing a cursor over a target on a computer screen. It is tempting to transfer the burden of adaptive control from the nervous system to a programmable brain-machine interface. Then, the nervous system would operate like an automobile driver, shielded from interactions with the environment by the power steering system. Despite the apparent advantages of this scenario, serious drawbacks would result from losing the ability to sense interaction forces – an essential element of successful manipulation.

Neural plasticity as a programming language

Much, if not all, of the research on brain-machine interfaces makes direct or indirect reference to the mechanisms of neural plasticity. For a neural prosthesis to be effective, the brain must learn to reorganize encoding and decoding mechanisms. Hearing-impaired patients must learn to decode the stimuli generated by a cochlear implant into meaningful sounds. The cortical neurons connected to a robotic arm must learn to generate new patterns of motor commands. In the latter case, experiments have demonstrated some success in operant conditioning based on visual feedback and reward information. A distinct challenge for current and future research on brain-machine interfaces is to understand the nature and location of plastic changes. In this respect, the challenge corresponds to endowing brain-machine interfaces with the 'programmability' typical of a computing system. A digital computer can be programmed to control a robotic arm by writing a sequence of instructions; brain cells cannot be programmed in the same way. However, the response of a neuron to an incoming signal is subject to a variety of plastic changes. These plastic changes are considered to be the way in which past experience shapes the operation of our brains. Therefore, a deeper understanding of the mechanisms of synaptic plasticity, such as long-term potentiation and long-term depression [53–57], and of the control of these mechanisms at specific sites, is likely to be the key to the transition from partially successful operant conditioning to fully programmable brain-machine interfaces.

An emergent family of tools for neuro-rehabilitation and basic science

The development of brain-machine interfaces capable of stimulating the cellular processes for learning and memory is likely to lead to extension of the computational and clinical applications of brain-machine interfaces. In addition to attempts to replace the function of a damaged nervous system, direct interaction between the nervous system and programmable artificial devices could accelerate the recovery from neurological injury [58–61]. Robotic manipulators are actively investigated as a means for rehabilitation following stroke [62–65], both as assistive and as resistive devices. The rationale behind an assistive device is to provide the patient's nervous system with kinesthetic feedback corresponding to execution of the movements that the patient is unable to produce without assistance. Resistive devices are based on the hypothesis that some compensatory adaptive mechanisms might have been spared from injury. The presence of a perturbing force could trigger these adaptive mechanisms and lead more quickly to the generation of effective patterns of compensatory muscle activity. Recent studies by Nudo and co-workers [66,67] have provided preliminary evidence that the combination of behavioral training and electrical stimulation of areas surrounding a cerebrovascular accident can lead to a significant acceleration of functional recovery. If results such as these find further support, one could envisage a future scenario in which the closed-loop interaction between a patient's brain and an external device will be used to facilitate the

reorganization of neural circuits that is necessary for re-establishing normal movement patterns.

The processes of development, adaptation in the normal nervous system, and repair in the damaged nervous system are fundamental to a successful clinical brain-machine interface. They are also the foundation of our understanding of the functioning brain. Thus, although the evolution of brain-machine interfaces is likely to remain driven by important clinical and practical goals, it will also offer a unique family of tools for challenging some of the most fundamental ideas of modern neuroscience.

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