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14 Neuro-Engineering: from neural interfaces to biological computers

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Abstract. In this chapter, we report on the state of the art in the technology of neural interfaces, and describe in some detail a number of on-going projects, in which they are used to explore the neurobiology of learning and memory. In particular, it is proposed to use artificial multi-sensory information coming from a roving robot that interacts with the environment, under the perspective of feeding an in vitro network of real neurons with a set of time and space-dependent signal resembling those processed by the nervous system.

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14.1 Introduction

In standard man-machine interaction paradigms, the brain of the human operator is an (intelligent) component in a global functional system and the linkage between the biological and the artificial part is assured by the sensorimotor system, on one side, and an ergonomically correct set of sensors and actuators, on the other. There are obvious limitations to this kind of arrangement, such as the limited bandwidth of the sensorimotor channels, the integrity of the sensorimotor system, the requirement of specific training and of high levels of attention. In general we can say that traditional man-machine interfaces underexploit by order of magnitudes the computational power of the brain and thus it makes sense to look for alternative interface mechanisms that overcome the sensorimotor bottleneck and directly link the artificial part of the system to the nervous tissue.

A direct neural interface is a peculiar kind of man-machine interaction in which there is no direct participation of the sensory and the motor systems but, indeed, an artificial device communicates directly with the nervous system. Two main types of interfacing paradigms have been studied since the 60's:

- Brain-Computer Interfaces (BCIs) in which the activity of the nervous system is directly used to control external devices (computers, or prostheses);
- Neural Prostheses (NPs) in which external devices are designed to induce spatio-temporal patterns of neural activity.

Neural interfaces were first hypothesized in the early 60’s to augment body functionalities in astronauts or pilots, and since then they have been confined mostly in the realm of science fiction literature. However, several examples of actual neural interfaces are now under experimentation and even routinely used, mostly in the context of rehabilitation. Neural interfaces, in which a neural preparation interacts with the external world, will also be likely to represent an evolution of standard electro-physiological techniques for the investigation of the mechanisms underlying learning, memory, and of the way the nervous system codes and processes information.

In this chapter, we report on the state of the art in the technology of neural interfaces, and describe in some detail a number of ongoing projects, in which they are used to explore the neurobiology of learning and memory.

14.2 Brain-Computer Interfaces

The aim of BCI technologies is to use some measurement of the activity of the nervous system to control external devices, with no direct participation of peripheral nerves and muscles; see [1] for a review. In most cases, BCI systems use brain activity recorded at the scalp (i.e. electroencephalography, EEG), to control cursor movement and to select letters or icons on a screen.

For instance, subjects can be trained to control the amplitude of their μ- or β-rhythms (portions of the EEG signal whose power spectrum is, respectively, in the 8-12 Hz and 18-25 Hz range), recorded on the scalp in correspondence of sensorimotor cortical areas, to control a cursor on a computer screen in one or two dimensions [2].

BCIs have been investigated mainly as aids to patients with severe neuromuscular impairments (e.g., lateral amyotrophic sclerosis), but could in principle be used in different contexts. The key element in a BCI is a decoding algorithm, that converts the raw electrophysiological signal into an output that is suitable to control the external device. A prolonged learning phase is usually needed to train the subject to ‘encode’ the desired action into observable changes in his measured neural activity. Training can be driven by a kind of operant conditioning paradigm. State-of-art BCIs have been estimated to have a maximum information transfer rate of 5-25 bit/min [1]. Critical elements are the selection of the ‘relevant’ features in the neural signal, i.e. the ones which allow the best selection/discrimination of the different actions, and the psychophysical and cognitive factors that affect the rate of learning for a particular application.

More recently, it has been shown that in rats [3] and primates [4], the neural activity of populations of cells in the motor areas of the brain cortex, simultaneously recorded by means of cronically implanted microelectrodes, can be used for real-time control of a robot arm; even through the Internet [4]. In particular, in [3] the signals recorded from a population of neurons in the motor cortex of the rat were used to drive a mechanical lever which controlled the release of a food reward. The same cortical activity observed when the reward was obtained by a movement of the paw could also be maintained when the same reward was obtained by a movement of the mechanism and with the paw at rest.

This technique relies in the neurophysiological finding [5] that the activity of populations of neurons in the motor cortex accurately predicts direction and speed of the intended movement. In the near future, for subjects with severe neurological impairments, cortical BCIs will likely constitute a faster and more powerful alternative to those based on EEG signals [6].

14.3 Neural Prostheses

In neural prostheses, appropriately generated electrical stimuli are used to excite the nervous system by initiating action potentials in nerve fibers [7]. The stimuli can be applied to sensory nerves, thus mimicking the effect of sensory stimuli; to motorneurons, thus directly activating one or more muscles; or to portions of the nervous system that are neither sensory nor motor. The existing implementations range in scope from experimental trials with single individuals, to commercially available devices.

Sensory prostheses are used as substitutes for impaired sensory modalities, and always involve artificial replicas of the dysfunctional sensory receptors (or parts of them). The best known examples of sensory prostheses are *cochlear implants* [8,9,10], now widely used as aids for completely deaf patients, in which multi-channels electrodes, implanted in the internal ear (cochlea) are connected to an external processor which translates and codes sounds into electrical pulse patterns. A similar but much more ambitious family of devices is the *retinal implant* [11]. It shares with the cochlear implant the basic design principle and requirements but has quite different biomedical and technological constraints. The underlying pathologies are the degenerative processes (such as retinitis pigmentosa and macular degeneration) that selectively affect the photodetectors of the retina while leaving relatively intact the other retina neurons and the fibers of the optic nerve. The technology of retina implants is at a much earlier stage of development than cochlear implants (there is at least a 20-30 years gap) for several reasons: 1) the information density (thousands of hair cells on the basilar membrane vs. millions of photodetectors on the retina); 2) the structure of the sensor; 3) the metabolic/energetic requirements. Several projects are presently underway for the development of clinically testable prostheses in Germany, USA, and Japan. The German project is at a more advanced stage of development and is investigating two different design principles: EPI-ret [12,13] vs. SUB-ret [14,15]:

- In the EPI-ret design the prosthesis-neural interface is mounted on the top of the retina. Similar to the cochlear implant it is divided into two parts: an external part, called Retina Encoder (RE) and an implanted Retina Stimulator (RS). The linkage between the two is wireless and uses light for the transmission of both energy and signals. The RS is a 2D array of a few hundreds of electrodes on a flexible backing and is anchored on the top of the central part of the retina. In this way it is in direct contact with the layer of ganglion cells of the retina, i.e. the cell bodies of the optic nerve. Near the RS, another micro-chip is located in a more excentric position with the circuitry for receiving signals and power and piloting the electrode array. The RE is the most complex part of the system. In includes a small camera with a large number of photosensors and a programmable unit that mimics the pre-processing performed by the natural retina: reduction of information and filtering. The number of output elements is much smaller than the number of sensor elements (100-1,000 vs. 10.000-100.000) and each of them is characterized by a receptive field (or filtering mask) whose parameters are adaptable. A critical part of the design is the learning strategy, in order to allow patients to optimally adjust the filter parameters.

- In the SUB-ret design **t**he prosthesis is a totally implanted device without any external circuitry. It is mounted on the bottom of the retina (this is the reason of the name) and uses a great deal of the natural system (the eye): (i) the optical part, (ii) the transmission of light through the cell layers of the retina, (iii) some part of the retina pre-processing. The device is simply a monolithic silicon chip which is called MPDA (micro photodiode array). It contains 7,600 elements which include a photodiode and a metallic contact site. Given the type of mounting it is believed that the electrical stimuli delivered through the metallic electrodes are picked up mainly by the bipolar cells and thus the transmitted patterns on the optic nerve might exploit some the natural pre-processing of the retina. This type of design does not require any adaptation of system parameters and thus is computationally simpler; on the other hand it is less flexible.

Other examples of neuro-prostheses include artificial semi-circular canals (the receptors that mediate the sensation of body rotation) [16].

Sensory prostheses always include a computing or translation module that mimicks the transfer function of biological sensory receptors, so that they can be emulated by their artificial counterparts. However, as the neural activity evoked by the latter is not exactly the same as that expected from the actual ears or eyes, sensory prostheses must rely on the assumption that the nervous system is able, to a certain degree, to adapt to stimuli that differ from what expected. The problem of how physical quantities are ‘coded’ into spatiotemporal patterns neural activity is a major theoretical issue in neurobiology (see below). Usually, neural prostheses assume some form of rate coding, in which sensory information modulates the instantaneous stimulus frequency.

Like in BCIs, an important issue with sensory neural prostheses is how to optimally adapt the translation module to the user/operator, and vice-versa. In a sense this is a kind of 'computational ergonomy' which is analogous to the 'sensorimotor ergonomy' of standard man-machine interfaces and is equally critical from the functional point of view.

Motor neural prostheses [17] are based on Functional Electrical Stimulation (FES) techniques. They consist of stimulating motor nerves so that muscles are activated in a similar way as when they are in an intact nervous system. FES techniques have been used to help rehabilitation in spinal cord injuries, but also to completely replace the control of hand grasp and release in quadriplegia, and standing and stepping in paraplegia [18,19,20,21]. Additional examples of motor neural prostheses are the restoration of bladder function following spinal cord injury, and electrophrenic respiration in high-level quadriplegia.

Stimulation can be triggered by movement, voice, respiration, joystick or position transducers. One of the major problems with present generation FES systems is that suitable patterns of muscle stimulation (i.e., synergies), which are relatively stereotypical for grasping, or gait, are difficult to specify for goal-directed movements.

A miniature motor prosthesis has also been used to remotely control, via a radio link, the locomotion of a cockroach [22].

Deep brain stimulation, i.e. the stimulation of parts of the nervous system that are neither sensory- nor motor-related, has also proven to be an effective technique for disabilities like Parkinson's disease, Essential Tremor, and dystonia. The basic idea here is to use the artificial stimuli as substitutes of the ‘missing’ inputs from degenerated or lesioned portions of the nervous system.

Technical issues in neural prostheses include the features of the individual pulses (current vs voltage, mono-phasic vs bi-phasic) in order to minimize stimulus artifacts and tissue damage, and the type of electrodes (wires, nerve cuffs, but also surface in motor prostheses).

14.4 Bi-Directional Interfaces

A more general situation is when there is a bi-directional communication between the nervous system and an external device. This is the case when the latter is not just an actuator or a sensor, but integrates both in the same ‘hardware’. Muscles are indeed bidirectional devices, as they integrate actuators (muscle fibres) and sensors (muscle spindles).

In fact, in FES-generated movements, bi-directional communication would also be desirable to support some form of feedback control, or error correction. One possibility would be to record activity from muscle spindles, tactile sensors and other proprioceptive channels and use them to modulate the descending FES command; another would be to use artificial movement sensors [23].

A FES system could be conceivable that also integrates signals from the motor cortex (for instance, through a cortical BCI) in order to provide information on the intended movement. This could greatly increase its flexibility, thus allowing, for instance, to control goal-directed movements, like reaching.

14.5 Neural Interfaces for the Study of Neural Plasticity and the Neural Code

In recent years, our knowledge about the working of the Central Nervous System (CNS) of vertebrates has experienced several advances at all levels of description, i.e. from the protein tri-dimensional structure of single ion channels, to the functional real-time imaging of the living brain. Among these extremes, networks of neurons constitute an intermediate level of organization, where the emerging collective electrophysiological properties and functional, as well as structural plasticities, play a fundamental role [24].

The mechanisms of neural plasticity – the modification of neuronal excitability following past experience of input and output patterns - have been extensively studied in the last decade, and they are collectively referred to as long-term potentiation (LTP) and long-term depression (LTD) of individual synaptic responses [25]. LTP and LTD result in a persistent change of the effectiveness of the synaptic transmission between two neurons in a cultured network. As a consequence of LTP and LTD, a long-term artificial modulation can occur in the intrinsic, spontaneous, as well as the evoked patterns of electrophysiological activity. The standard approach to investigate neural plasticity consists of recording the neural activity in a portion of nervous system that has been dissected from the animal, and is kept alive *in vitro*. Test stimuli consist of isolated pulses, and LPT and LPD are induced by pulse trains of suitable frequency and duration, or by joint stimulation of different axons.

Another crucial issue is the problem of the neural code, i.e. how neurons in the brain represent, store and process information. In order to gain more information about the neural code, experimental paradigms based on the association of electro-physiology/behavior have been extensively employed in vivo [26]. In such a paradigm, researchers typically attempt at associating the spike trains taken from extra-cellular recordings (i.e. usually by means of a single- as well as multi-electrode chronic cortical implant) with the stimuli the animal was presented with, at the same time. The previous conceptual scheme has been widely used in in vivo neurophysiology, in order to approach and tackle fundamental mechanisms for information representation and processing in a sampled neuronal population, whose collective activity was recorded.

However, in either case standard approaches have limitations. In studies on synaptic plasticity, stimuli are far from the physical reality, in which time-varying sensory activity induces a continuous, time-varying flow of neural activity so that long-term changes of synaptic plasticity interact with shorter term effects. Moreover, synaptic changes are collective phenomena, which involve many neurons at the same time, and are likely to be influenced by the way neurons represent ('code') information. A kind of neural interface, in which a neural preparation is connected, possibly bi-directionally, to the external world, and in which it is possible to continuously monitor the activity of populations of neurons and that of sensory stimuli and/or motor commands, could overcome these limitations. At different levels of resolution, approaches based on the interaction of biological and artificial materials, have been proposed to study ion channels (i.e. the dynamic clamp technique, see [27]) and to study the collective properties of populations of neurons, by interfacing them with *silicon* neurons [28].

Ultimately, the combination of a neural preparation and a neural interface could itself be intended as a computing device, i.e. a sort of biological computer, which could possibly be trained to perform calculations and in general to process information, so that in fact biology would be the technology. An example of this approach is that of [29], who demonstrated that the chaotic behavior of portions of living neural tissue can be controlled and, ultimately, exploited for performing simple arithmetic calculations.

14.5.1 An Artificial Animal for the Study of Sensorimotor Adaptation

Studies of neural plasticity - based on the study of neural preparations *in vitro* - are difficult to relate with the actual behavior of the living animal[30]. Conversely, in behavioral studies on learning and memory it is the cellular level that is difficult to access. To establish a bridge between the cellular and the behavioral levels, Fleming et al. [31] have recently developed a hybrid system, consisting of a small mobile robot connected to a portion of living brain tissue, dissected from the reticular formation of the lamprey - a primitive eel-like vertebrate, and maintained alive *in vitro*.

The brain and the robot are interconnected in a closed loop; they communicate through an interface that transforms (a) light information from the robot's optical sensors into electrical stimulation applied to the lamprey's brainstem, and (b) recorded neural activity from two brainstem nuclei into motor commands sent to the robot's wheels (see Fig. 14.1).

Lampreys were chosen for this study, because of the easy access in this preparation to a system of very large neurons - the Muller cells in the reticular formation - that integrate command and sensory signals directed to the spinal motor centers.

In this brainstem preparation, they selected a portion of neural circuitry that in normal circumstances combines vestibular signals and motor commands to stabilize the orientation of the body during swimming. This system has been shown to be adaptive, as unilateral lesions of the vestibular capsules are followed by a slow reconfiguration of neural activities until the correct postural control is recovered. In our hybrid system, vestibular signals are replaced by light intensity signals. As the vestibular signals have a right and left source - the two vestibular capsules - so do the two light intensity signals originating from sensors on the right and left side of the robot. Therefore, the natural stabilizing behavior - in which the lamprey would track the vertical axis - corresponds, in the hybrid system, to a positive phototaxis; that is, a tendency of the robot to track a source of light. In these experiments, the lamprey's brain was maintained in vitro for periods ranging from 8 to 10 hours. In most cases, the preparation maintained its full responsiveness across the entire experiment.

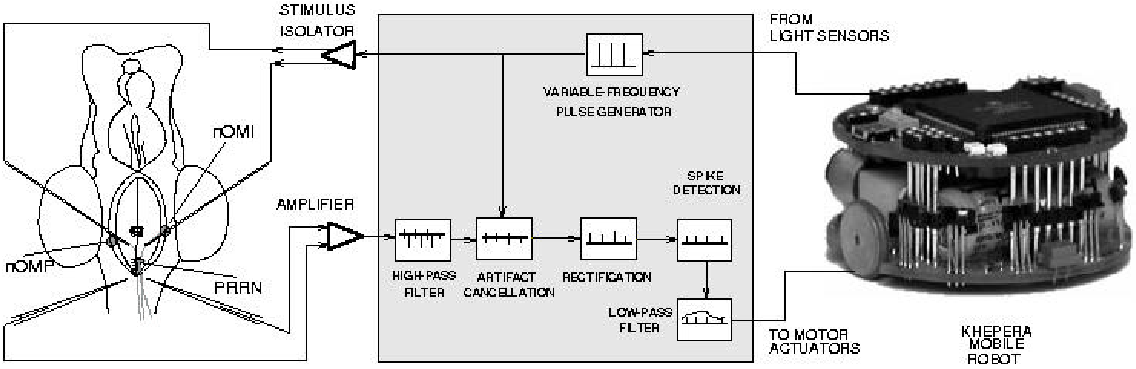

Figure 14.1 Schematic diagram of the neuro-robotic system. The neural interface (shaded area) translates the light sensor data from the robot (right) into a pattern of stimulation for the neural preparation (left); neural recordings are converted into motor signals for the robot.

An underlying assumption of this approach is that the properties of the information processing associated with natural behaviors may be explored by observing the information processing associated with artificial behaviors. In a way, this is a consequence of the abstract and generalized nature of information. An obvious advantage of this hybrid system, always from the point of view of experimental neurobiologists, is that, unlike natural motor behaviors, artificial behaviors do not interfere mechanically with the electrophysiological setup.

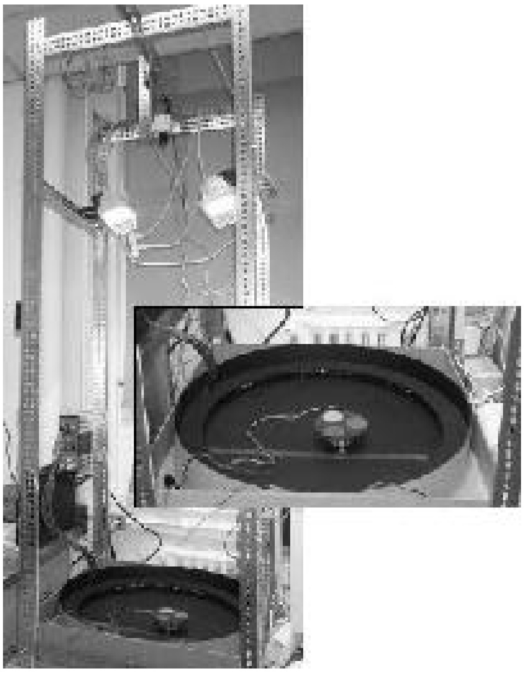

Figure 14.2 Robot setup. Using a pattern of colored circles (lower inset), the overhead camera tracks the robot.

From the perspective of neural computation, the hybrid system provides a means to test models of information processing by direct interaction with a biological neural network. The behavior of the robotic system is described by a relatively simple - and yet nonlinear - system of differential equations. To the extent that the brain properties may be considered stationary (over the time scale of robot movements), these equations describe an autonomous system whose properties are modulated by the structure of the neural pathways and connections intervening between stimulating and recording electrodes.

Conversely, the observation of the sensorimotor behaviors that emerge from this system offers an insight into the computational structure of the neural system.

Fleming et al. [31] did succeed in obtaining stable behaviors over extended periods of time, characterized by repeatable motor responses to a light source. Fig. 14.3 exemplifies a `stable' preparation. The four panels display four consecutive trajectory sets, separated by rest intervals of, respectively, 20 min, 10 min and 1 min: although the repeated trajectories display a certain amount of variability, the overall shapes are similar for trajectories elicited by the same lights.

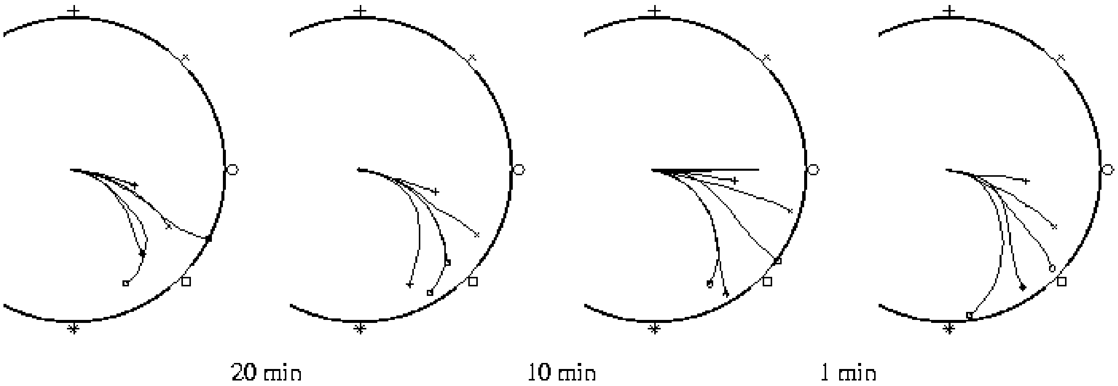

Figure 14.3 Stable robot trajectories. Times indicate the rest periods between consecutive trials.

In different preparations a variety of different behaviors was observed, including positive and negative phototaxis, circling and menotaxis - combinations between circling and phototaxis. These different behaviors can be related to different patterns of connectivity between the stimulated vestibular axons and reticular neurons. Although both ipsi- and contralateral (excitatory and inhibitory) connections have been documented between vestibular axons and reticular neurons, these results suggest a predominant effect of the contralateral excitatory connections. This effect is consistent with the observation of light-seeking behaviors in the majority of the experiments.

To measure the ability of the neural preparation to adapt, experiments were performed on the plasticity of the vestibular synaptic connections. Since the lamprey is able to recover following changes in vestibular stimulation, this natural adaptation was exploited to determine if a change in synaptic efficacy would occur following a period of non-symmetric illumination, by observing changes in robot trajectories. Figure 14.4 shows robot trajectories measured during an adaptation protocol. Initial trajectories were measured 60 minutes apart. Following the second trajectory measurement (0 min), the robot was positioned in a stationary configuration with illumination to the left side twice the illumination to the right side of the robot.

The robot remained in this configuration for five minutes. Trajectory sets then were measured after 35, 60, and 75 minutes. Stimulation to the left side of the robot, which had initially caused a large motor command to the right wheel, now caused diminished movements in the right wheel. Stimulation to the right side of the robot was less affected by the non-symmetric illumination. This suggests that during the five-minute non-symmetric illumination, the lamprey neural circuitry adapted to brighter illumination on the left side. Thus, the stable positive phototaxis recorded prior to the five-minute illumination was transformed into a long-lasting menotaxis, which is indicative of a long-term change in the efficacy of the synaptic network. Therefore, these preliminary observations indicate that indeed the prolonged increase of exposure to a light source on one side of the robot leads to a sustained modification of the light-following behavior. The closed-loop interaction between brain and robot is an important element in the study of unsupervised learning mechanisms. The movements determined by activities in the reticular neurons cause changes in the robot's exposure to the light generated by a fixed source. These changes, in turn, cause a variation in the electrical stimulus that is responsible for the activities in the same reticular neurons.

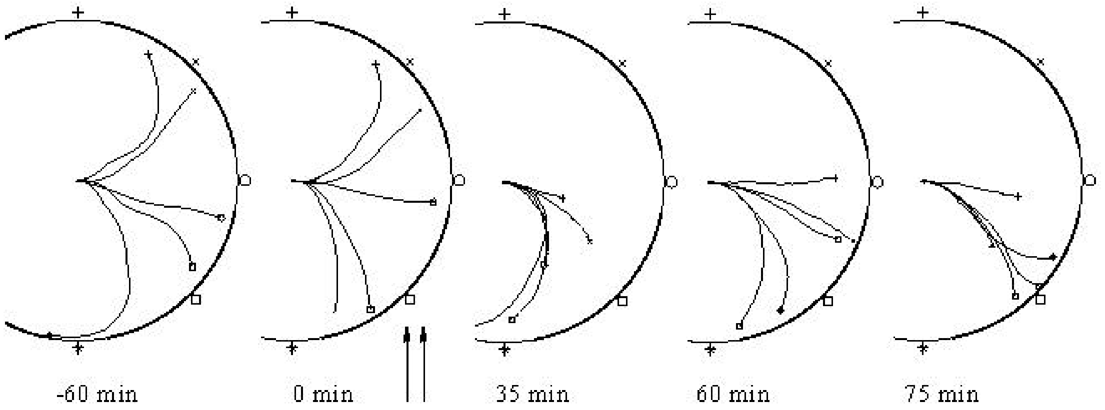

Figure 14.4 Trajectories measured 1 hr before (-60 min), immediately prior to (0 min), and following (35, 60, 75 min) five minutes of non-symmetric illumination (indicated by double arrows).

As a whole, these findings provide supporting evidence for the use of neuro-robotic systems in the study of the neurobiological mechanisms of sensorimotor learning.

A distinctive feature of this hybrid system is that it implements a closed-loop connection between neural tissue and robot: the light intensity detected by the optical sensors in the robot are converted into electrical stimuli delivered to the vestibular axons in the brainstem. These axons transport the stimuli to a monosynaptic connection with reticular neurons whose responses are recorded by micropipette electrodes. The computer interface extracts the spike information from the recorded signals and transforms it into a command for the robot's wheels.

In these experiments - which lasted only a few hours - stability was assessed by observing the repeatability of the trajectories triggered by light sources placed at different locations. Stability of the behaviors is clearly a necessary condition for proceeding with further analysis and, in particular, with investigations that assume that the neural connectivity remains invariant over the time scale of individual sensorimotor responses.

As pointed out by Braitenberg [32], the pattern of neural connections between sensors and actuators in a mobile vehicle together with the information processing carried out at these connections, determine a repertoire of sensori-motor behaviors. Conversely, this work is aimed at exploiting the observed artificial behaviors to extract informations about the neural information processing in the neural tissue connected to the robot. The observation of artificial behaviors also provides an important statistical tool for interpreting the neurophysiological data obtained by stimulating vestibular axons and recording the neural responses.

This new experimental paradigm is well suited for investigating the operation of Hebbian learning mechanisms, by which the strength of a given synapse is modified based on the correlation between pre- and post-synaptic activities. In summary, these initial findings offer strong support to the idea of using the combined observation of behavior and neural activities in neuro-robotic systems for acquiring a deeper understanding on the computational properties of neural tissue.

14.5.2. Networks of Cultured Neurons and Arrays of Micro-Electrodes

Networks of neurons can be cultured, and kept in healthy conditions for a long time in experimental preparations. In such reduced *in vitro* neurobiological systems, the strategies employed by the nervous system to represent and process information can be approached and investigated, since the neuronal physiology and the efficacy of synaptic connections between neurons can be quantitatively characterized and modulated by means of appropriate electrical and chemical stimulation protocols, exploiting the activity-dependent network modifications [24,25].

In particular, the in vitro generation of electrical activity, spontaneously arising in cultured neuronal population and classified as a functional collective network state, is present in networks of dissociated neurons, whose electric activity is characterized by periodic synchronized activations [35,36]. Such coordinated patterns can be at some extent persistently modified by a pharmacological as well as electrical manipulation of the neuronal as well as the synaptic physiology [35]. Moreover, it has been shown that appropriate temporal electrical stimulation protocol applied to neurons cultured in vitro can simultaneously produce both LTP and LTD on different network pathways [25].

Characterizing the collective emerging properties of a networks of neurons is more and more taking advantages of the tools offered by the microfabrication technologies, originally developed for the microelectronic industries. Therefore a new area of research is emerging at the interface between neurobiology and microelectronics, where neuroscience research issues are approached under brand new perspectives and by means of powerful new tools.

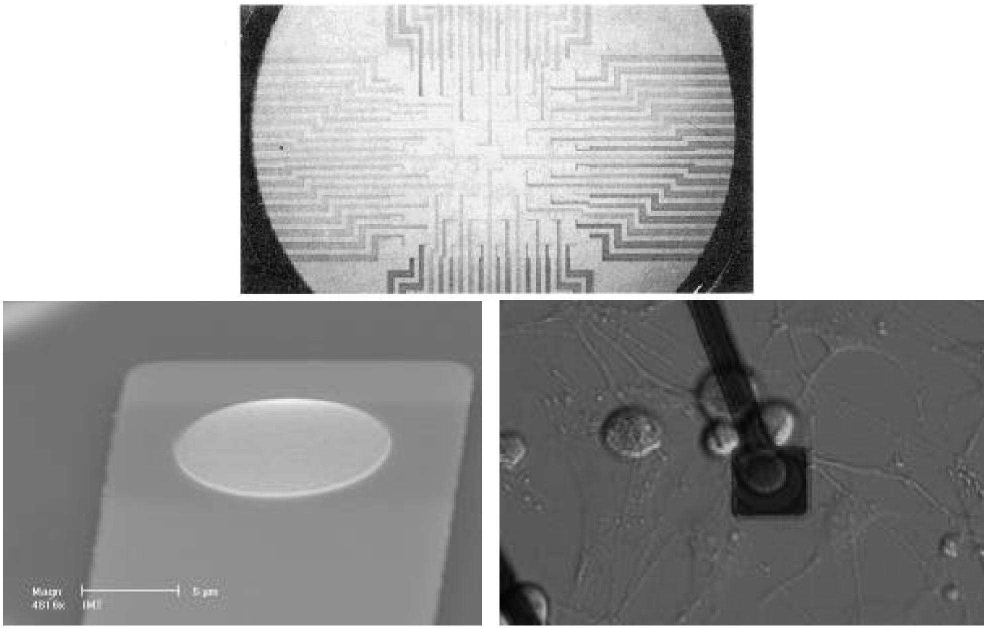

Figure 14.5 Top: Substrate array of planar microelectrodes, made by means of thin-film technologies and microphotolitographic processes on a glass substrate (scale bar: 0.5 mm). Bottom left: Detail of a platinum planar electrode and its electrical insulation layer (scale bar: 5 (m). Bottom right: Dissociated neurons in culture, coupled to a microelectrode of the array and randomly developing their neurites and synaptic connections.

A specific example of micro-hardware is represented by the development of thin-film based planar and 3D arrays of substrate microelectrodes (MEAs) to be in vitro coupled to populations of cultured neurons [35,36]. After a pioneering period at the beginning of the eighties, MEAs are now becoming a standard for a few neurobiological applications. Actually, MEAs technology offers the unique opportunity to simultaneously monitor/stimulate the multi-site spatial and temporal electrophysiological activity of cultured networks of neurons [35], on a time-scale that is long enough (i.e. up to weeks) to identify the emergence and development of synaptic connections and of spatial patterns of coordinated behavior.

For instance, Fig.14.6 shows the recordings from a single microelectrode of the electrophysological activity of a network of chick embryo spinal cord neurons. Specific reproducible patterns of activity are induced by distinct pharamacological conditions.

Figure 14.6 Recording of single array channel extracellular electrical potential, resulting from the network electrophysiological activity, under different pharmacological manipulations (upper panel: addition of NBQX; middle panel: control medium; lower panel: addition of cyclotiazide) that modulate the effectiveness of neuron-to-neuron synaptic transmission.

14.5.3 Cultured Neurons with a Body

As a further development of the above research, an in vitro neurobiological system (i.e. a network of cultured neurons) will be functionally interconnected to an artificial sensory-motor device (i.e. an artificial body) through an array of microelectrodes [35, 36] used both for stimulation and recording of the electrophysiological activity (see Figs.14.5,14.6), in order to make a network of real neurons learn environmentally constrained tasks by exploiting intrinsic plasticities. This involves a closed-loop repetitive spatio-temporal electrical and chemical stimulation (see Fig.14.7), structured according to the real-time interactions of a roving robot and its environment, determined by the electrophysiological activity of the network (see Fig.14.6), while feeding back sensory information to the network through the multielectrode stimulation itself (see Figs. 14.5,14.6) [27,31].

The aim of this presentation is just to discuss the development of a hybrid neurobiological/artificial system including the following issues [27,31]: the multi-site recording and stimulation of the electrophysiological activity of primary cultures of nervous tissue coupled to substrate MEAs; the characterisation of the dynamic repertoire of spontaneous network activity and the investigation on how in vitro cultured neuronal networks respond to precise spatio-temporal stimulation patterns; the identification, by means of appropriate algorithmic strategies [37,38], of the conditions of training stimulation, needed to induce permanent plastic changes in the network. As final steps the design and development of a closed-loop neurobiological / artifical system for real-time interaction between real biological neurons recorded from MEA and any physical device (computer, robot) is foreseen, followed by a description of the dynamical behavior of the robot in terms of the networks activity and plasticity, consequent to the closed-loop training stimulation.

A detailed analysis of the behavior of the proposed hybrid neuro-artificial system has a twofold relevance, both meaningful in the context of basic neuroscience research, under the perspectives of a better understanding of the way the CNS represents and stores the sensory-motor information (i.e. the neural code) and under the perspective of Information Technology as a source for inspiration for the design of new biologically-inspired artificial neural systems and electronic devices based on the hardware implementation of formal neural networks.

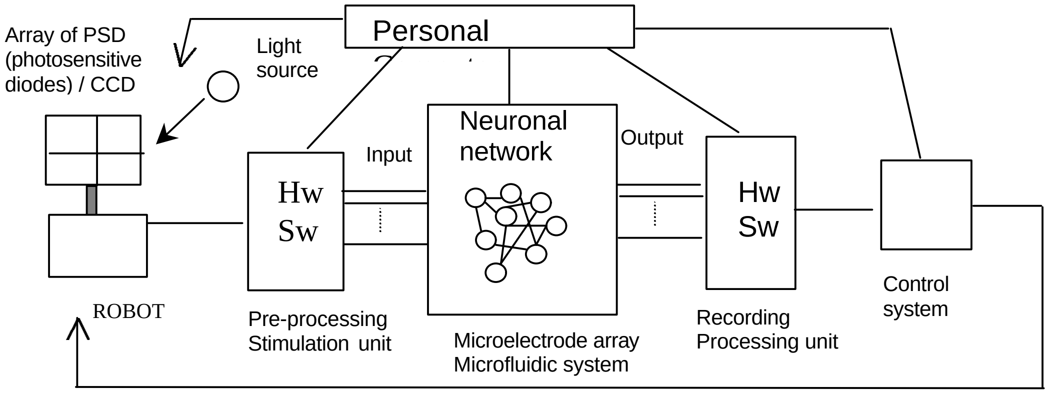

Figure 14.7 Sketch of the complete closed-loop hybrid system.

With respect to the first perspective, one of the most important research issues of neuroscience concerns the neural code, being the code used by neurons in the brain to represent, store and process information. In order to gain more information about the neural code, the electrophysiology/behavior association experimental paradigm was already extensively employed in vivo [26]. In such a paradigm, researchers typically attempt at associating the spike trains taken from extra-cellular recordings (i.e. usually by means of a single- as well as multi-electrode chronic cortical implant) with the stimuli the animal was presented with, at the same time. The previous conceptual scheme has been widely used in the in vivo neurophysiology, in order to approach and tackle fundamental mechanisms for information representation and processing in a sampled neuronal population, whose collective activity was recorded.

In the context of the present research, a similar long-term goal constitutes the major focus, although we mainly emphasize the in vitro aspects of neuronal information coding and representation. The several in vitro research advances, recently reported in the literature, dealing with small population of randomly connected cultured neurons, preliminary showed the intrinsic plasticity of an in vitro neurobiological system and resembling distributed properties and mechanisms that might be relevant for the distributed representation of sensory-motor information in the living nervous system. At different levels of resolution, approaches based on the interaction of biological and artificial materials, have been proposed to study ion channels (i.e. the dynamic clamp technique) and to study the collective properties of populations of neurons, by interfacing them with silicon neurons.

In our research, by focusing the interests towards the hardware implementation of a few non-standard algorithmic techniques and analysis strategies and more important, by employing a robot freely interacting with the environment, as opposed to a virtual environment, we close the behavioral sensory-motor loop at no computational cost; we envisage a very successful strategy to tackle the problem on how a network of neurons solve a problem.

We believe that the proposed approach will greatly expand the value of in vitro neurobiological experimentation, approximating much better than present in vitro experiments the complexity of the in vivo CNS behavior, thus providing greatly advanced tools to study neuronal plasticity and a substantial inspiration framework for artificial systems.

14.6 Concluding remarks

As briefly summarized in this chapter, neural intrefacing is an issue which has been around for several decades, feeding a number of studies and applications that frequently were unrelated and with little commong ground. However we can say that, in time, the level of understanding of the interfacing issues has improved at the system and molecular levels and substantial technological breakthroughs have been achieved in terms of micro-design of transduction and computing elements. In other words, the field of Neuro-engineering is maturing into a coherent set of methodologies and technologies that will allow to design whole new families of advanced cybernetic applications that bring together the power of the human brain and the artificial micro-devices.

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