Dr. Frankenstein's Dream Made Possible: Implanted Electronic Devices

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***Abstract*— The developments in micro-nano-electronics, biology and neuro-sciences make it possible to imagine a new world where vital signs can be monitored continuously, artificial organs can be implanted in human bodies and interfaces between the human brain and the environment can extend the capabilities of men thus making the dream of Dr. Frankenstein become true. This paper surveys some of the most innovative implantable devices and offers some perspectives on the ethical issues that come with the introduction of this technology.**

I. Introduction

Advances in wireless sensors technology have had significant impact in improving, both from life-style and economics point of views, health care by allowing monitoring of and even administering drugs remotely to elder patients suffering of chronic diseases. Advanced signal processing algorithms and circuits allow monitoring of patients even when they are on-the-move. Ultra-low-power electronics enables a continued miniaturization of sensor systems, facilitating their integration in patch devices [1-6] that minimize the inconvenience of carrying sensors 24 hours a day. Wearable ECG patches monitor cardiac activity for over a week, allowing early detection of cardiovascular disorders. Wireless EEG headsets allow remote monitoring brain activity. A network of wearable sensors distributed over the body (body sensor network) measures physiological responses correlated to a particular mental or emotional state [6]. Recent research results on Brain-to-Machine Interfaces (BMI) go way beyond the state-of-the-art: the possibility of introducing electrodes inside the brain for monitoring single or for clusters of neurons on the cortex area are making possible to control a prosthetic device or to help patients who are affected by a stroke, Parkinson, Alzheimer and other degenerative syndromes. The possibility of investigating neuronal plasticity opens new vistas for curing drug and alcohol addictions and depressive syndromes.

In this paper, we review *some* of the many relevant achievements in wireless implantable devices. The paper is organized as follows. In Section 2 multi-sensing patch (e.g., for cardiac beat monitoring and wireless EMG system) is described. In Section 3 an innovative solution for type-1 diabetes, called artificial pancreas is presented. In Section 4, the brain machine interface system for prosthetic device control is discussed. In Section 5 a new trend in brain activity monitoring (optogenetics) is presented showing its possibilities and limitations. In Section 6 ethical issues surrounding the use of implantable devices are discussed and conclusions presented.

II. Smart Skin

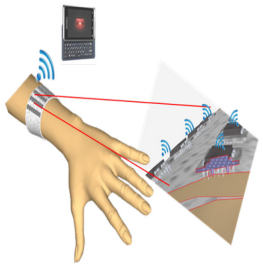

Fig. 1 EMG microelectrodes (Courtesy: Danilo De Marchi, IIT, Torino, Italy)

An ultrathin 'electronic tattoo' that adheres to human skin to track muscle activity, heart rate and other vital signs has been recently proposed [4, 5]. The electrical patch, which bends, wrinkles and stretches with the mechanical properties of skin, has been demonstrated in [5]. The patch consists of an array of electronic components mounted on a thin, rubbery substrate that includes sensors, LED, transistors, radio frequency capacitors, wireless antennas and solar cells. The potential of this device in biomedical applications is large: the technology could one day help patients with muscular or neurological disorders communicate. It can even be used (as already shown in [5]) to control a video game. The next step will be to combine additional sensors on this substrate to use skin as an access to the body and to transmit data wirelessly to a transponder. Interesting examples of this trend are given by the wireless EMG (figure 1) proposed in [6] for exoskeleton control with space and medical applications and the heart beat monitoring patch proposed in [1-3].

III. Artificial Pancreas for Type-1 Diabetes

In a patient with Type-1 diabetes, the body's immune system attacks and kills insulin, secreting beta cells and causing an increase in blood glucose. Over time, glucagon-secreting alpha cells tend to fail causing people with Type 1 diabetes to exhibit episodes of extremely low blood sugar [7-9]. An artificial pancreas has been recently developed [10-12] that has the potential of 'closing the loop' on Type 1 diabetes. The artificial pancreas consists of an electrochemical sensor that monitors blood sugar levels continuously, an integrated circuit that mimics the unique electrical characteristics of alpha and beta cells in the human pancreas, and two small pumps worn on the body. The integrated circuit implements a control

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algorithm that has to mimic the very different behaviors of the two cell populations. An alpha cell tends to react to rapid electrical events (spikes), while the beta cell tends to react in bursts of voltage spikes, punctuated by low voltage silent periods that last for seconds or even minutes. When glucose concentrations rise, the beta cells remain in the high voltage burst state longer, secreting more insulin as a result [9, 10]. The "bionic pancreas" mimics this biological process by detecting the user's glucose level via a sensor every five minutes. If it reports a high level of glucose, the silicon beta cell generates a signal that drives a motor that pushes a syringe dispensing insulin into the tissue beneath the skin until the glucose reading at the sensor drops. If the sensor reports a low glucose value, the silicon alpha cell activates the second pump to administer glucagon instead.

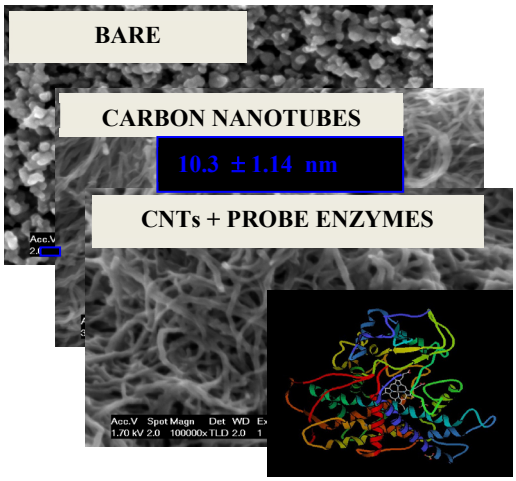

Fig. 2 Nanobiosensor macro assembly (courtesy Sandro Carrara, EPFL, Lausanne, CH)

This approach differs from today's dominant method of delivering only insulin using a relatively simple control system. The artificial pancreas system eliminates the need for multiple insulin injections and administers the insulin in a more biologically faithful way. This approach reduces complications and alleviates the need for patients to worry about what they eat and drink. This system has been used in a wide range of implantable biosensor devices for monitoring and controlling drugs absorption [13-15] and delivering the drug right dose when needed.

IV. Monitoring and Controlling the Brain

A challenging goal in neuroscience is reading out, or decoding, mental content from brain activity [16-19]. Functional magnetic resonance imaging (fMRI) studies have already decoded orientation [20] position [21] and object category [22] from activity in the visual cortex [23-26]. However, these studies typically used relatively simple stimuli (for example, gratings) or images drawn from fixed categories (for example, faces and houses), and decoding was based on previous measurements of brain activity evoked by the same stimuli.

Today, brain mapping and interfaces with the external world are possible by reading the signals emitted by the cells in the brain. The target is to let the brain interact directly with prosthetic devices or with humanoid robots. The target of Brain-to-Machine Interfaces (BMI) is shown in Figure 3. The BMI for clinical applications should be implanted 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 should also be equipped with the touch and position sensors from which signals can be transmitted back to the subject's brain. BMIs are characterized according to whether they utilize invasive (i.e. intra-cranial) or non-invasive methods of electrophysiological recordings.

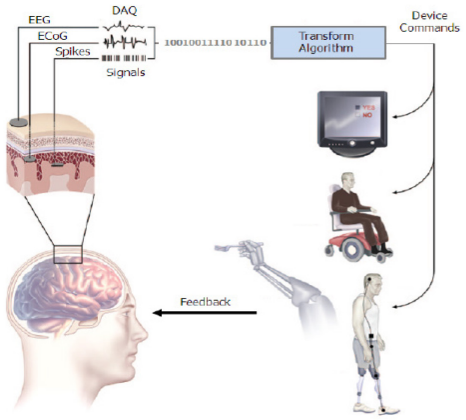

Fig. 3. Brain machine Interface possible applications

A. *Non-invasive monitoring system*

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 [27]. 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 and spatial resolution. In fact brain electrical signal can be recorded from the scalp with a large number of electrodes - 16 to 256 - with good temporal resolution, which can be composed with electromyographic (EMG) signals, even if this often requires extensive user training. Their typical transfer rate is currently 5–25 bits [21, 22]. Although such a transfer rate might not be sufficient to control the movements of prosthetic arms or legs that have multiple degrees of freedom, from field data, it seems feasible to 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 BMIs. For instance, virtual-reality systems can provide a realistic feedback that can be efficient for BMI 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 BMIs, 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 BMIs are expected to have better accuracy and shorter training times than BMIs based on EEGs [30].

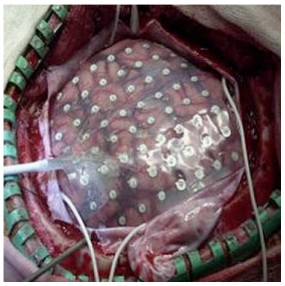

Fig. 4. ECoG array recordings of neuronal signals at frequencies up to ~300 Hz from the cortical surface of the brain

EEG-based BMIs have been implemented as solutions for patients suffering from various degrees of paralysis. These BMIs (in the case of patients with advanced amyotrophic lateral sclerosis) 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 this approach was based on the utilization of slow cortical potentials to control a computer-aided spelling system [30, 31]. BMIs 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 BMI that detected beta waves in his sensorimotor cortex and activated a functional electrical stimulation device, learned to grasp objects using his paralyzed hand [33].

In addition to using EEGs, imaging techniques such as fMRI, have been explored as a new source of brain-derived signals to drive BMIs [34]. Although fMRI-based BMIs 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 [35]. Myoelectric systems that make use of voluntary activations of unaffected muscles, in partially paralyzed and amputees subjects [36–39], and use these signals to control limb prostheses and exoskeletons, offer an alternative to the existing non-invasive BMIs. Currently, these systems are more practical for everyday situations than EEG based BMIs [36].

In summary, paralyzed patients can re-acquire basic forms of communication and motor control using EEG-based systems. Yet motor recovery, obtained using these systems, has been limited. No clear breakthrough that could significantly enhance the power of EEG-based BMIs has been reported in the literature [36]. This by no means reduces the clinical utility of these systems. Some of them have improved the quality of life of patients, such as the BCI for spelling [37]. 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 [38-40].

B. Invasive monitoring system

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) [41-46]. These approaches have their roots in the pioneering studies conducted by Fetz and colleagues in the 1960s and 1970s [47, 48]. 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, 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 [49]. 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. These bottlenecks were overcome because of a series of experimental and technological breakthroughs that led to a new electrophysiological methodology for chronic, multi-site, multi-electrode recordings [50–52]. A BMI approach that relies on long-term recordings from large populations of neurons (100–400 units) evolved from experiments carried out in 1995 [52]. After the introduction of this approach, a series of studies demonstrated that neuronal readout of tactile stimuli could be accomplished using pattern-recognition algorithms [51,52].

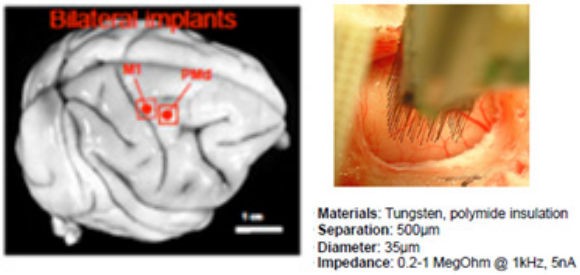

Fig. 5. Rhesus monkey brain and neuronal cortical electrodes

These developments paved the way to the first experiment in which neuronal population activity recorded in rats enacted movements of a robotic device that had a single degree of freedom. A similar BMI approach was shown to work on rhesus monkeys [53–54] (Figure 5). As a result of these experimental efforts, in less than six years several laboratories reported BMIs that reproduced primate arm reaching [54] and the combination of reaching and grasping movements, using either computer cursors or robotic manipulators as actuators. There are several important differences that distinguish these BMIs. 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 ones described in [55], all BMIs tested in monkeys have relied on single cortical site recordings either of local field potentials or of small samples (<30) of neurons or

multi-units. Most of these small-sample, single-area BMIs utilized neural signals recorded in the primary motor cortex, although one group has focused on BMIs that processed neural signals recorded in the posterior parietal cortex [64]. In [56] a BMI strategy was recently implemented based on single-unit recordings made during intra-operative placement of deep-brain stimulators in Parkinson patients [56].

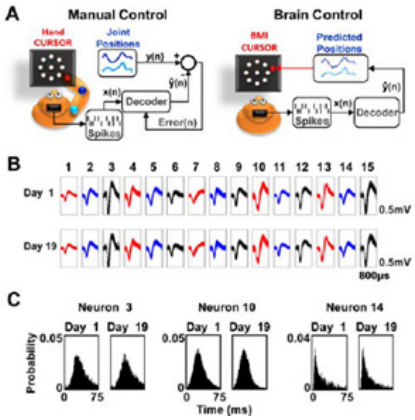

Fig. 6 Experimental setup and stability of ensemble recordings. (A) Schematics for manual control (MC) and brain control (BC). (B) Stability of putative single units across multiple days.C) Stability of firing properties across time. (courtesy: Josè Carmena UC Berkeley US)

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 [53, 54]. 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 (Figure 6 [53]). 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. Such plasticity will result in sensory and motor areas of the brain representing the prosthetic device.

V. Optogenetics

To improve understanding of psychiatric and neurological disorders, it is important to identify which neural circuits may be responsible, to pinpoint the precise nature of the causally important aberrations in these circuits and to modulate circuit and behavioral dysfunction with precise and specific interventions. However, such a deep, circuit-level understanding of neuropsychiatric disorders, or indeed even of normal neural circuit function, has been challenging for traditional methods. The complexity of neural circuitry has historically precluded the use of genetically and temporally precise manipulations to probe detailed mechanisms of function and dysfunction.

Optogenetics [57-59] involves the use of microbial opsins, or related tools, that can be activated by illumination to manipulate cells with high specificity and temporal precision even within intact tissue or live animals. Optogenetic approaches have been used to dissect neural circuits in animals to identify symptoms that are relevant to fear, anxiety, depression, schizophrenia, addiction, social dysfunction, Parkinson disease and epilepsy. Successful probing of complex diseases in this way depends on the validity of using animals used to identify the crucial circuit elements and activity patterns that are involved in each cluster of symptoms, and the precision and efficiency of interventions designed to selectively target these elements or patterns. However, several limitations, caveats and considerations are in order. A very important limitation of optogenetics is the production of heat with illumination. Heated neurons may not only alter their activity in a nonspecific manner but may also be detrimental to cell health. Appropriate controls, as well as assessment of light source stability and performance, must be carefully and frequently examined to ensure precise and reliable light output and interpretation of light effects [59].

Another limitation of optogenetics is the potential for toxicity at very high expression levels or long-term expression. With so many variables, it is important to carefully validate with imaging, physiology, or c-FOS (protein encoded for by the *FOS* gene) staining that neurons are being manipulated with the strength and specificity intended before interpreting any experimental results.

VI. Conclusions and Ethical Considerations

The field of micro-devices and algorithms for monitoring and controlling body functions is exciting and wonderfully rich of challenging scientific and engineering problems. Results can only be achieved by leveraging multiple disciplines ranging from medicine, to biology, from chemistry to material science, from computer science to electronics and mechanical engineering. We do believe that this field will grow to become a major scientific and economic sector in the years to come.

However, there are deep ethical issues that need to be addressed. The question will certainly loom that if functions can be restored for those in need, is it right to use these technologies to enhance the abilities of healthy individuals as well? It is essential that devices are safe to use and pose few, if any, risks to the individual counter-balanced with benefit. But the ethical problems that these technologies pose are not vastly different from those presented by existing therapies such as antidepressants. In brain-controlled prosthetic devices, signals from the brain are decoded by a computer that sits in the device. These signals are then used to predict what a user intends to do. Invariably, predictions will sometimes fail. Who is responsible for involuntary acts? This question was already considered years ago, when the automatic pilot was introduced in airplanes but today becomes more pressing as the host is the human brain. In [60] other possible questions are underlined: is it the fault of the computer or the user? Will a user need some kind of "license" and "obligatory insurance" to operate

prosthesis? What if machines change the brain? To the philosophical question: "What is a man?" Aristotle answered: "Man is a rational animal." If our brain is driven by a decoder that takes for us decisions on the base of an optimal searching algorithm, are we still men or are we robots then? The classic approach of biomedical ethics is to weigh the benefits for the patient against the risk of the intervention and to respect the patient's autonomous decisions [61]. This should also hold for the proposed expansion of deep brain stimulation [DBS] to treat patients with psychiatric disorders [62].

What is enhancement and what is treatment depends on defining “normality” and “disease”, and this is notoriously difficult. In [60] several opinions on this issue are considered. Christopher Boorse, a philosopher at the University of Delaware, defines disease as a statistical deviation from "species-typical functioning" [63]. As deafness is measurably different from the norm, it is thus considered a disease. This definition has been influential and has been used as a criterion for allocation of medical resources [64]. From this perspective, for instance, the intended medical application of cochlear implants seems ethically unproblematic. Nevertheless, Anita Silvers, a philosopher at San Francisco State University and a disability scholar and activist, has described such treatments as a "tyranny of the normal" [65], designed to adjust people who are deaf to a world designed by the hearing, ultimately implying the inferiority of deafness [65]. Although many have expressed excitement at the expanded development and testing of brain–machine interface devices to enhance otherwise deficient abilities, Silvers suspects that prostheses could be used for a "policy of normalizing". These serious concerns should not prevent further research on brain–machine interfaces. Still, whether brain-technology applications are a proper option remains dependent on technological developments and on addressing important safety issues. One issue that is perhaps more pressing is how to ensure that risks are minimized during research. Animal experimentation, where allowed (i.e. in Europe is not allowed if not under conditions established by EU regulation), will probably not address the full extent of psychological and neurological effects that implantable brain–machine interfaces could have [66-70]. Research on human subjects will be needed, but testing neuronal motor prostheses in healthy people is ethically unjustifiable because of the risk of bleeding, swelling, inflammation and other, unknown, long-term effects. People with paralysis, who might benefit most from this research, are also not the most appropriate research subjects. Because of the very limited medical possibilities and often severe disabilities, such individuals may be vulnerable to taking on undue risk [60]. Brain–machine interfaces promise therapeutic benefit and should be pursued. The technologies pose ethical challenges, but these are conceptually similar to those that bioethicists have addressed for other therapies. The limit is the respect of the human dignity as already underlined, by Immanuel Kant in [71]: “Act in such a way that you use the humanity in your own person and in the person of any third party at all times as an end in itself and never simply as a means to an end”. In this common objective, ethics and neuroscience research can cooperate for the treatment of chronic disease.

VII. Acknowledgments

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References

[1] IMEC Annual report 2010

[2] R. F. Yazicioglu, T. Torfs, J. Penders, I. Romero, H. Kim, et. al.,“Ultra-Low-Power Wearable Biopotential Sensor Nodes,” IEEE EMBS conf., pp. 3205-3208, Sept. 2009.

[3] Sunyoung Kim, Torfs T.; Merken, P., Van Hoof C. A 30μW Analog Signal Processor ASIC for Biomedical Signal Monitoring 2010 IEEE International Solid-State Circuits Conference Feb. 2010

[4] Kim et al., Epidermal Electronics, Science 12 August 2011: Vol. 333 no. 6044 pp. 838-843

[5] R. Highfield Epidermal electronics' tattoos: a giant step forward for cyborgs The Telegraph April 2012

[6] D. Demarchi, G. Piccinini, M. Graziano, J. Barokas, S. Schintke, P. Morey-Chaisemartin, S. Tzanova (2012) Hands-On Laboratories in the NanoEl Project. In: 9th European Workshop on Microelectronics Education (EWME), Grenoble, 9-11 May 2012. pp. 124-126.

[7] Weber C, Schnell O. The assessment of glycemic variability and its impact on diabetes-related complications: an overview. Diabetes Technol Ther 11(10):623-633, 2009.

[8] K. Kumareswaran, M. L. Evans, R. Hovorka: Closed-loop Insulin Delivery: Towards Improved Diabetes Care Discovery Medicine; ISSN: 1539-6509; Discov Med 13(69):159-170, February 2012.

[9] Choudhary P, Shin J, Wang Y, Evans ML, Hammond PJ, Kerr D, Shaw JA, Pickup JC, Amiel SA. Insulin pump therapy with automated insulin suspension in response to hypoglycemia. Diabetes Care 2011; 34: 2023–5.

[10] Danne T, Kordonouri O, Holder M, Haberland H, Golembowski S, Remus K, Bläsig S, Wadien T, Zierow S, Hartmann R, Thomas A. Prevention of hypoglycemia by using low glucose suspend function in sensor-augmented pump therapy. Diabetes Technol Ther 2011 Aug 9

[11] E. Dassau, C. Lowe, C. Barr, E. Atlas, M. Phillip: Closing the loop, 2012 Blackwell Publishing Ltd Int J Clin Pract, February 2012

[12] Weinzimer SA, Steil GM, Swan KL, Dziura J, Kurtz N, Tamborlane WV. Fully automated closed-loop insulin delivery versus semiautomated hybrid control in pediatric patients with type 1 diabetes using an artificial pancreas. Diabetes Care 2008; 31: 934–9.

[13] Carrara, D. Torre, A. Cavallini, D. De Venuto, G. De Micheli,“Multiplexing pH and Temperature in a Molecular Biosensor” Proc of Biomedical Circuits and System Conference (BioCAS2010) Paphos,Cyprus, 3-5 November 2010

[14] D. De Venuto, S. Carrara, G. De Micheli: “pH sensing with temperature compensation in a Molecular Biosensor for Drugs Detection” Proc. Of The 12th International Symposium on Quality Electronic Design, Santa Clara, CA 14-16 March 2011

[15] Carrara et al. Multi-panel drugs detection in human serum for personalized therapy Biosensors and Bioelectronics 2011

[16] Kay KN, Naselaris T, Prenger RJ, Gallant JL. Identifying natural images from human brain activity. Nature. 2008 Mar 20;452(7185):352-5

[17] Haynes, J. D. & Rees, G. Predicting the orientation of invisible stimuli from activity in human primary visual cortex. Nature Neurosci. 8, 686–691 (2005).

[18] Kamitani, Y. & Tong, F. Decoding the visual and subjective contents of the human brain. Nature Neurosci. 8, 679–685 (2005).

[19] Thirion, B. et al. Inverse retinotopy: inferring the visual content of images from brain activation patterns. Neuroimage 33, 1104–1116 (2006).

[20] Cox, D. D. & Savoy, R. L. Functional magnetic resonance imaging (fMRI) ‘‘brain reading’’: detecting and classifying distributed patterns of fMRI activity in human visual cortex. Neuroimage 19, 261–270 (2003).

[21] Haxby, J. V. et al. Distributed and overlapping representations of faces and objects in ventral temporal cortex. Science 293, 2425–2430 (2001).

[22] Haynes, J. D. & Rees, G. Decoding mental states from brain activity in humans. Nature Rev. Neurosci. 7, 523–534 (2006)

[23] Kralik JD, Dimitrov DF, Krupa DJ, Katz DB, Cohen D, Nicolelis MA. Techniques for long-term multisite neuronal ensemble recordings in behaving animals. Methods. Oct.2001 25(2):121–150.

[24] Suner S, Fellows MR, Vargas-Irwin C, Nakata GK, Donoghue JP. Reliability of signals from a chronically implanted, silicon-based electrode array in non-human primate primary motor cortex. IEEE Trans. Neural Syst. Rehabil. Eng. Dec.2005 13(4):524–541. [PubMed: 16425835]

[25] Jackson A, Fetz EE. Compact movable microwire array for long-term chronic unit recording in cerebral cortex of primates. J. Neurophysiol. Nov.2007 98(5):3109–3118

[26] Stanley, G. B., Li, F. F. & Dan, Y. Reconstruction of natural scenes from ensemble responses in the lateral geniculate nucleus. J. eurosci. 19, 8036–8042 (1999)

[27] H. Sheikh et al. Electroencephalographic (EEG)-based communication: EEG control versus system performance in humans Neurosci. Lett., 345 (2003), pp. 89–92

[28] J.R. Wolpaw Brain-computer interfaces (BCIs) for communication and control: a mini-review Suppl. Clin. Neurophysiol., 57 (2004), pp. 607–613

[29] N. Birbaumer Brain–computer-interface research: coming of age Clin. Neurophysiol., 117 (2006), pp. 479–483

[30] S.P. Kelly et al.Visual spatial attention control in an independent brain–computer interface IEEE Trans. Biomed. Eng., 52 (2005), pp. 1588–1596

[31] E.W. Sellers, E. Donchin A P300-based brain–computer interface: initial tests by ALS patients Clin. Neurophysiol., 117 (2006), pp. 538–548

[32] N. Birbaumer et al. The thought translation device (TTD) for completely paralyzed patients IEEE Trans. Rehabil. Eng., 8 (2000), pp. 190–193

[33] G. Pfurtscheller et al. Mu rhythm (de)synchronization and EEG single-trial classification of different motor imagery tasks NeuroImage, 33 (2006), pp. 153–159

[34] G. Pfurtscheller et al. Graz-BCI: state of the art and clinical applications IEEE Trans. Neural Syst. Rehabil. Eng., 11 (2003), pp. 177–180.

[35] J.R. Wolpaw, D.J. McFarland Control of a two-dimensional movement signal by a noninvasive brain–computer interface in humans Proc. Natl. Acad. Sci. U. S. A., 101 (2004), pp. 17849–17854

[36] G. Pfurtscheller, F.H. Lopes da Silva Event-related EEG/MEG synchronization and desynchronization: basic principles Clin. Neurophysiol., 110 (1999), pp. 1842–1857

[37] J.D. Bayliss, D.H. Ballard A virtual reality testbed for brain–computer interface research IEEE Trans. Rehabil. Eng., 8 (2000), pp. 188–190

[38] G. Pfurtscheller et al. Walking from thought Brain Res., 1071 (2006), pp. 145–152

[39] E.C.Leuthardt et al. A brain–computer interface using electrocorticographic signals in humans J Neural Eng, 1 (2004), pp. 63–71

[40] T. Hinterberger et al. A brain–computer interface (BCI) for the locked-in: comparison of different EEG classifications for the thought translation device Clin. Neurophysiol., 114 (2003), pp. 416–425

[41] A. Kubler et al. Patients with ALS can use sensorimotor rhythms to operate a brain–computer interface Neurology, 64 (2005), pp. 1775–1777

[42] G. Pfurtscheller et al. 'Thought' control of functional electrical stimulation to restore hand grasp in a patient with tetraplegia Neurosci. Lett., 351 (2003), pp. 33–36•

[43] N. Weiskopf et al. Self-regulation of local brain activity using real-time functional magnetic resonance imaging (fMRI) J. Physiol. (Paris), 98 (2004), pp. 357–373

[44] C.M. Light et al. Intelligent multifunction myoelectric control of hand prostheses J. Med. Eng. Technol., 26 (2002), pp. 139–146

[45] X. Navarro et al. A critical review of interfaces with the peripheral nervous system for the control of neuroprostheses and hybrid bionic systemsJ. Peripher. Nerv. Syst., 10 (2005), pp. 229–258

[46] R. Okuno et al. Compliant grasp in a myoelectric hand prosthesis. Controlling flexion angle and compliance with electromyogram signals IEEE Eng. Med. Biol. Mag., 24 (2005), pp. 48–56

[47] E.E. Fetz Are movement parameters recognizably coded in activity of single neurons? Behav Brain Sci., 15 (1992), pp. 679–690

[48] E.E. Fetz, M.A. Baker Operantly conditioned patterns on precentral unit activity and correlated responses in adjacent cells and contralateral muscles J. Neurophysiol., 36 (1973), pp. 179–204 [49] E.E. Fetz, D.V. Finocchio Correlations between activity of motor cortex cells and arm muscles during operantly conditioned response patterns Exp. Brain Res., 23 (1975), pp. 217–240

[49] M.A. Nicolelis et al. Sensorimotor encoding by synchronous neural ensemble activity at multiple levels of the somatosensory system Science, 268 (1995), pp. 1353–1358

[50] M.A. Nicolelis et al. Chronic, multisite, multielectrode recordings in macaque monkeys Proc. Natl. Acad. Sci. U. S. A., 100 (2003), pp. 11041–11046

[51] M.A. Nicolelis et al. Reconstructing the engram: simultaneous, multisite, many single neuron recordings Neuron, 18 (1997), pp. 529–537

[52] M. A Nicolelis et al Real-time prediction of hand trajectory by ensembles of cortical neurons in primates Nature, 408 (2000), pp. 361–365

[53] J.M. Carmena et al. Learning to control a brain-machine interface for reaching and grasping by primates PLoS Biol., 1 (2003).

[54] A. C. Koralek, X. Jin, J. D. Long, R. M. Cost, Jose M. Carmena Corticostriatal plasticity is necessary for learning intentional neuroprosthetic skills Nature vol.483 15 March 2012

[55] http://www.duke.edu/

[56] Patil, P.G. et al. Ensemble recordings of human subcortical interface. Neurosurgery 55, 27–35 (2004)

[57] Deisseroth, K. Optogenetics. Nature Methods 8, 26–29 (2011).

[58] Lin, S. C., Deisseroth, K. & Henderson, J. M. Optogenetics: background and concepts for neurosurgery. Neurosurgery 69, 1–3 (2011).

[59] L. Fenno, O. Yizhar, K. Deisseroth The Development and Application of Optogenetics Annu. Rev. Neurosci. 2011.34:389-412

[60] J. Clausen Man, machine and in between *Nature* 457, 1080-1081 (26 February 2009) | doi:10.1038/4571080a; Published online 25 February 2009

[61] Beauchamp, T. L. & Childress, J. F. Principles of Biomedical Ethics Oxford Univ. Press, 2009

[62] Synofzik, M. & Schlaepfer, T. E. Biotechnol. J. 3, 1511–1520 (2008).

[63] Boorse, C. Phil. Sci. 44, 542–573 (1977)

[64] Daniels, N. Just Health Care (Cambridge Univ. Press, 1985)

[65] Silvers, A. in Enhancing Human Traits: Ethical and Social Implications (ed. Parens, E.) 95–123 (Georgetown

[66] Greely, H. T. Minn. J. Law, Sci. Technol. 7, 599–637 (2006).

[67] Hochberg, L. R. et al. Nature 442, 164–171 (2006).

[68] Mandat, T. S., Hurwitz, T. & Honey, C. R. Acta Neurochir. (Wien) 148, 895–897 (2006).

[69] Velliste, M., Perel, S., Spalding, M. C., Whitford, A. S. & Schwartz, A. B. Nature 453, 1098–1101 (2008)

[70] Weaver, F. M. et al. J. Am. Med. Assoc. 301, 63–73 (2009).

[71] I. Kant. *Grundlegung der Metaphysik der Sitten*, Königsberg, Friedrich Nicolovius, 17971797.