State of the Art and Future Prospects of Nanotechnologies in the Field of Brain-Computer Interfaces

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Abstract— **Neuroprosthetic control by individuals suffering from tetraplegia has already been demonstrated using implanted microelectrode arrays over the patients' motor cortex. Based on the state of the art of such micro & nano-scale technologies, we review current trends and future prospects for the implementation of nanotechnologies in the field of Brain-Computer Interfaces (BCIs), with brief mention of current clinical applications.**

Micro- and Nano-Electromechanical Systems (MEMS, NEMS) and micro-Electrocorticography now belong to the mainstay of neurophysiology, producing promising results in BCI applications, neurophysiological recordings and research. The miniaturization of recording and stimulation systems and the improvement of reliability and durability, decrease of neural tissue reactivity to implants, as well as increased fidelity of said systems are the current foci of this technology. Novel concepts have also begun to emerge such as nanoscale integrated circuits that communicate with the macroscopic environment, neuronal pattern nano-promotion, multiple biosensors that have been "wired" with piezoelectric nanomechanical resonators, or even "neural dust" consisting of 10-100µm scale independent floating low-powered sensors. Problems that such technologies have to bypass include a minimum size threshold and the increase in power to maintain a high signal-to-noise-ratio. Physiological matters such as immunological reactions, neurogloia or neuronal population loss should also be taken into consideration. Progress in scaling down of injectable interfaces to the muscles and peripheral nerves is expected to result in less invasive BCI-controlled actuators (neuroprosthetics in the micro and nano scale).

The state-of-the-art of current microtechnologies demonstrate a maturing level of clinical relevance and promising results in terms of neural recording and stimulation. New MEMS and NEMS fabrication techniques and novel design and application concepts hold promise to address current problems with these technologies and lead to less invasive, longer lasting and more reliable BCI systems in the near future.

Keywords— **Brain computer interface, microelectrode, nanoscale, nanotechnology, neuroprosthetics.**

I. INTRODUCTION

Brain-Computer Interfaces (BCIs) and Brain-Machine Interfaces (BMIs) are collective terms used to describe a neural interface technology that allows recording of brain activity, translation of volition encoded in that activity and indirect control of external devices (computers or machines for communication and movement) through that activity [1]. They constitute a multidisciplinary field of research that encompasses clinical and theoretical Neurosciences, Computer Science and Biomedical Engineering among other disciplines. Brain activity can be extracted either by non-invasive neurophysiological methods (such as Electroencephalography [2] or functional Magnetic Resonance Imaging [3]) or by invasive recordings such as Electrocorticography (ECoG) [4] and implanted cortical microelectrodes [5].

Invasive BCIs in general offer higher quality of neural signals and precision of recordings [6]. Neuroprosthetic control by human patients suffering from tetraplegia has already been demonstrated using implanted microelectrode arrays over their motor cortex [7],[8],[9]. On the other hand, invasive interfaces also hold many disadvantages associated with acute and delayed neural injury, immunological reactions, as well as ethical issues [6].

The introduction of Nanotechnology in BCI research is considered a recent development that holds promise to offer improvements in several aspects of this field, such as increased precision and reliability of recorded neural activity, durability of signal quality and reduced invasiveness of implanted neural interfaces [10]. Different directions of Nanotechology research are investigating the miniaturization of recording and transmission systems [11] as well as the manipulation of biological properties of implanted materials through nanofabrication in order to reduce reaction [12]. Even more radical concepts have begun to emerge, such as the development of injected floating nano-electrodes for wireless recording and transmission of neural activity [13].

Based on the state-of-the-art of micro- and nano-scale technologies we review current trends and future prospects for the implementation of nanotechnologies in the field of BCIs. We attempt to identify those issues of BCIs where Nanotechnology may offer reliable solutions, discuss the

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limitations of such approaches, as well envision the possible role that Nanotechnology will play in the future of BCIs.

II. STATE OF THE ART OF MICRO- AND NANO-TECHNOLOGIES IN THE FIELD OF BRAIN-COMPUTER INTERFACES

A. Current Microtechnologies and Neurophysiology

Micro- and Nano-Electromechanical systems (MEMS, NEMS) are miniaturized devices primarily developed either using photolithography (chip design) techniques borrowed from integrated circuit fabrication, chemical self-assembly techniques or a combination of the two.

With respect to precision, photolithography can generally provide more control over the shaping of the final structures, as the device is gradually built using successive masking and material deposition layers. Moreover with regard to complexity, photolithography is currently the technology of choice for MEMS and NEMS fabrication, as it can produce elaborate mechanical structures in the micro- and nano-scale which possess integrated sensors, mixed signal nanoelectronics, on board analogue to digital conversion, digital memory, RF electronics and even energy harvesting nano-generators [14],[15]. An EEG BMI with MEMS-fabricated electrodes/circuits boards has been demonstrated for wireless use (low-power consumption) in real world setting, with comparable characteristics to medical-grade systems [15]. Flip-chip and flexible substrate electronics technologies are also proving to be valuable complementary assets, particularly with respect to BCI electrode array in-vivo installation and maintenance and have allowed the fabrications of high-density MEMS electrode arrays (100 elements on 400*400μm) [16]. This type of technology has been clinically tested with patients suffering from paralysis with remarkable results regarding precision and durability [7],[8],[9].

BCIs and BMIs have used various types of microelectrodes in order to record either single neuron activity (action potentials) or neuronal ensemble activity (local field potentials) [1],[8]. However, ECoG seems to be a promising technique to capture potential changes in the cortical surface, thus it can be exploited for sophisticated BCI approaches. Indeed, there is a large body of research linking the intended motor movements with specific brainwaves [4],[17],[18]. More importantly, another approach to this neurophysiological method proposed a flexible thin film of micro-scale ECoG (μECog) for both BCI application, as well as monitoring epileptic activity and other applications [19],[20]. Their design utilizes flexible film electrodes so as to keep the electrode array in place, without applying much pressure to the brain, avoiding any potential injury. These systems have been tested on monkeys with promising results regarding BCI control and chronic durability and tolerance.

In recent years, significant scientific attention has also been focused on the application of nanomaterials as part of biosensors in order to detect and monitor not only brain signals but also various other processes in the central nervous system [21],[22]. These biosensors are designed to capture specific properties of the cerebral activity, such as the levels of various neurotransmitters. Important examples of this approach include, among others, nanoelectrodes that are used to measure the acetylcholinesterase [23] employing a gold-nanoparticle CaCOf hybrid material, while a combination of gold and platinum nanoparticle sensor was used to quantify the levels of glutamate [24]. Moreover, other crucial neurotransmitters were also quantified, like the dopamine, using a combination of glass capillary nanoelectrodes with gold nanoparticles [25], the serotonin with platinum electrode modified with carbon nanotubes [26] and norepinephrin with film modified glassy carbon electrodes [27]. Considering that dopamine is an important neurotransmitter involved in various neurological and psychiatric diseases, the application of nanoelectrodes for the accurate quantification of dopamine in real time can lead to the development of novel BMI systems for the treatment of dopamine-related conditions. On the other hand serotonin and norepinephrin appear to be altered in several forms of depression and anxiety disorders, and selective serotonin/norepinephrin reputake inhibitors (SSRIs/SNRIs) are often used to treat such disorders. It can be envisioned that a novel method which is able to quantify the serotonin and norepinephrin levels in the human brain can potentially lead to the development of BMI systems for their regularization, having a very insightful impact on the diagnosis and treatment of various mood disorders. This concept has been examined in rat models, using implantable microfluidic devices on the rats' cortex to alter brain acute and chronic reaction around the implantation site [28].

An obstacle often cited by skeptics is the difficulty in maintaining the electronics interface (and especially interface reliability) to any tissue, particularly neural tissue. This is especially inside the brain where there is need to maintain good quality signal over long time periods within a very challenging environment. One technique to overcoming this obstacle is currently, taking advantage of the versatility of MEMS/NEMS structures lie with movable microelectrode chips [29],[30]. This technique has produced promising results in experiments on rodents. Another emerging technique with promising results on maintaining reliability of neural interface within the unique brain environment can be identified at stain-induced, self-folding microtubes [31] that hold the capability of application on nano-scale BMIs. Self-folding microtubes [31] and nanopowder molding [32] can be used to create complex maze-like networks and electrodes for recording and stimulation of neural tissue. High-fidelity and high-reliability recordings have also been demonstrated by in-cell recording by extracellular electrodes [33], comparable to conventional microelectrodes. These mushroom-shaped electrodes also hold the key ability of stimulation that a BCI system could take advantage.

B. A Short Note on Current Clinical Neurological and Neurosurgical Applications

Neural restoration through the use of implantable devices has long been recognized as a focus area of functional neurosurgery and commonly used "neural interfaces" in neurosurgical practice include, among others, deep brain stimulation (DBS) devices for tremor, dystonia and Parkinson's disease and neurostimulator devices for epilepsy [6]. The application of implantable BCIs on human patients, such as those based on electrocorticography (ECoG) and intracortical electrodes, also lies within the field of functional neurosurgery. Furthermore, Spinal Cord Injury (SCI), stroke, amyotrophic lateral sclerosis (ALS) and locked-in syndrome, disorders that share a disconnection of volition and action, have rather recently become a focal point for BCI research [1]. The concepts of computer-assisted practice (virtual reality, robotics) and the pharmacological and neurophysiological capabilities of nanotechnology, given the example of successful sensory neuroprosthetics such as retinal implants, while still at an infant level seem to be much awaited by the clinical community [34],[35]. An emphasis is also placed on awaited new "metamaterials" based on graphene [36].

Invasive (implantable) BCIs and neuroprosthetics, while still at a laboratory level of maturity, have started to produce exciting results for human patients. Microelectrode arrays in particular have produced the most promising results in terms of functional restoration of human patients. SCI and brainstem stroke patients were shown to be able to control external devices (such as computers and televisions) and even anthropomorphic robotic arms with a BCI that records activity by means of an implanted array even three years after the initial injury [8] or five years after the stroke [9]. These arrays boast 96 microelectrodes on a 4*4mm surface and are implanted over the motor cortex of patients, have appeared to remain functional for relatively long periods of time [9] and have achieved high performance (>90%) control of neuroprosthetics (anthropomorphic robotic arm) after a period of BCI training [7]. These examples of microelectrode BCIs also demonstrate the most natural and fluid restoration of movement that has been achieved up to today.

III. FUTURE PROSPECTS OF NANOTECHNOLOGIES IN BRAIN RESEARCH

A. Novel Concepts & Limitations

There are several directions towards which novel nanotechnology concepts could potentially offer novel solutions or improved performance to existing issues. An important aspect in neural recording and stimulation is the capability of specific targeting of neuronal populations and areas. Abnormal brain plasticity and cell death can alter the specificity and reliability characteristics of implanted systems. The ability to promote neuronal adhesion and alongside the creation of patterned neuronal networks has been demonstrated using detonation nanodiamond monolayer coatings [37]. The ability to create such neuronal patterns on tracks designed by this nanodiamond technology could have influential implications in BCI MEMS and NEMS system design. Towards the same direction, nanofabricated neural probes are believed to resolve several problems of extracellular array recording, including invasiveness and low density of implanted electrodes [38]. Such probes integrate circuits for signal amplification, filtering and recording, demonstrate low noise characteristics and are capable of large-scale data recording on the cerebral surface [38] and a lot of progress has been made towards the design and fabrication of appropriate materials for such systems [39]. Functional electrodes and neural prosthetic systems below a certain size are disproportionate difficult to be produced due to power limitations and noise-to-signal ratio trade-off as the size decreases but novel materials such as gold nanoparticles are expected to provide solutions to these limitations [40]. Similar improvements could be applied to the peripheral end of brain-machine and body-machine interfaces. Injectable devices for interfacing with the peripheral neural system, known as BION devices, used for long-term electrical stimulation of nerves and muscles are currently at the milli-scale [41]. The implementation of nanotechnology in these devices could result in less invasive and more accurate functional electrical stimulation (FES) applications and neuroprosthetics at the micro or nano scale. Even more exotic concepts, such as is the "neural dust" [13], composed of thousand of micro-scale free floating independent sensors-transmitters could represent the future of extracellular neural recording and stimulation devices – even BCIs, assuming they are able to surpass physiological and mechanical restrictions.

B. Answering Real Needs in Research and Practice

BCIs, a concept that already dates at least three decades as a standalone field within Neurosciences has only recently been able to reliably answer specific needs of human patients. It stands for reason that one could argue that the applicability of Nanotechnologies in BCIs may lack actual value for neurological conditions but it seems that there are areas of BCI development that Nanotechnologies could answer real needs [42]. BCIs and BMIs that aim to serve as reliable clinical solutions have yet to solve specific challenges such combined high density of electrophysiological recording with chronic stability of those recordings and long-lasting power autonomy [13],[43]. Large-scale, high-density neuronal recordings are a need that was recently underlined by the goals of he Brain Research through Advancing Innovative Neurotechnologies initiative (BRAIN) [44]. Novel concepts, such those we previously described, seem to hold potential to answering these needs efficiently in the future and the future of BCIs may indeed lie with fully nano-scale actuated recordings, processing and transmission of information or even pinpoint drug delivery [13]. On the present day, wireless implantable BCIs make use of size, power-consumption and invasiveness reduction through the application of nano-fabricated materials, such as neuroprocessors implemented on nano-FPGA [42]. Reduction of brain tissue response to foreign materials and following immunological reactions and tissue damage is another critical need of implantable neural interfacing systems [40],[43]. This need can be met by the reduction of size of neural recording electrodes that has been made possible to the point of single cell recordings, using single-crystal gold nanoparticles of subcellular dimensions (100nm) [43].

IV. CONCLUSIONS

The state-of-the-art of current microtechnologies in BCIs demonstrate a maturing level of clinical relevance and promising results in terms of functional restoration in patients suffering from paralysis. Micro and nanotechnologies are used for miniaturization of neurophysiological recording and stimulation systems, improvement of reliability and durability, decrease of neural tissue reactivity to implants, as well as increased fidelity of the aforementioned systems. New MEMS and NEMS techniques and novel concepts hold promise to answer current problems of these technologies and to produce better, less invasive, longer lasting and more reliable BCI systems in the near future.

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CONFLICT OF INTEREST

The authors declare that they have no conflict of interest.

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