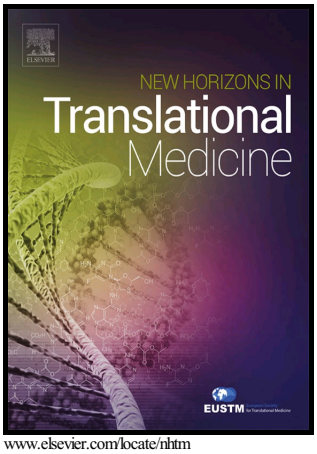

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Intelligent Biohybrid Systems for Functional Brain Repair

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ABSTRACT

In the quest for novel neurotechnologies to defeat brain diseases, intelligent biohybrid systems have earned a privileged role among unconventional brain repair strategies. These systems are based on the functional interaction between the nervous tissue and engineered devices, the establishment of which is mediated by artificial intelligence. As novel, previously unimaginable neurotechnologies are emerging, what are the translational impact and the practical consequences carried by these tools for the clinical practice?

In this review, we describe the progression of brain repair strategies, from the early pioneering demonstration of their feasibility to their recent implementation in the experimental and clinical settings. We will show how the convergence of different disciplines across the decades has led to the emergence of innovative concepts based on intelligent biohybrid designs. We discuss the advantages and limitations of the described approaches and we conclude by proposing possible solutions to the current shortcomings of available paradigms.

KEYWORDS

Artificial intelligence; brain damage; functional brain repair; neural engineering; neurotechnology.

FOCAL POINTS

- **Benchside**
  - Intelligent biohybrid systems represent the new era of cross-disciplinary brain repair strategies, where biological and artificial means complement each other.
  - Establishment of the cross-disciplinary research approach as a global vision will change the canonical concept of research team, leading to the exponential progress of biomedical applicative outcomes.
- **Bedside**
  - Intelligent biohybrid systems will become the landmark of future individualized therapeutic interventions for (self) repair of the damaged brain.
  - Aggressive pharmacological therapies will no longer be needed.
  - Risky repetitive neurosurgical interventions may no longer be needed: implantable biocompatible biohybrid systems act as autonomous stand-alone therapeutic agents that will require less frequent maintenance.
  - The foreign body reaction may be minimized or even prevented by the microfluidic-aided local delivery of immune-modulating pharmacological agents, without need of systemic immunosuppressive treatment.
- **Industry**
  - Industries belonging to the single specialty such as pharmaceuticals, electronic medical devices and nanotechnologies as well as stem cells & DNA banks will benefit from each other by joining a global industry for the development of implantable biohybrid devices.
- **Community**
  - The patients' quality of life will significantly improve while their life expectation will be prolonged.
  - The societal stigma associated with certain neurological conditions will be defeated.

- **Governments**
  - The inherent cross-disciplinary approach of Research & Development in the field of intelligent biohybrid neurotechnologies eliminates the requirement of planning time-consuming investigation-production chains, since these tasks will be performed simultaneously.
  - The more efficient use of funding along with the high impact of implantable biohybrid devices on health-care and society will attract funding from Governments to support the global engagement of research teams and industries.
  - The establishment of biohybrid therapeutics as the gold standard in the treatment of neurological disorders will significantly reduce the global burden of disease by cutting the costs of long-term care and of chronic treatment.
- **Regulatory agencies**
  - The advent of intelligent biohybrid neurotechnologies for brain self-repair will simplify the procedure of therapeutics approval thanks to **(i)** the possibility of leveraging self-grafting of patient-derived neuronal elements, **(ii)** *in vitro* testing of the functional features of intelligent biohybrid grafts *prior* to their transplantation to the patient's brain and **(iii)** simplified procedures for parameter optimization.

ABBREVIATIONS

ANN, Artificial Neural Network; **BMI,** Brain-Machine Interface; **CLDA**, Closed-Loop Decoder Adaptation; **CNS,** Central Nervous System; **CPG,** Central Pattern Generator; **DBS,** Deep-Brain Stimulation; **iPSC,** Induced Pluripotent Stem Cell; **SNN,** Spiking Neural Network; **TBI,** Traumatic Brain Injury; **tES**, Transcranial Electrical Stimulation; **TMS,** Transcranial Magnetic Stimulation

1. INTRODUCTION

One billion people worldwide suffer for disorders of the central nervous system (CNS). The greatest burden is carried by neurodegenerative diseases, epilepsy and stroke [1]. These patients (and their caregivers) face daily challenges in their lives due to cognitive and physical impairment. Moreover, the side effects inherent to the use of available medications or to routine neurosurgery interventions further impact on the patient's quality of life with significant consequences on public health-care and society.

Research on brain repair strategies has progressed exponentially over the last few decades. Several studies in the fields of regenerative medicine, from one side, and neural engineering, from the other side, are tackling the 'brain repair issue' by means of different, complementary approaches. The biological approaches rely on the activation of the endogenous regenerative capacity of the brain and on cell transplantation, while the engineering strategies include neuromodulation, replacing and bridging techniques and brain-machine interfaces (BMIs) (**Fig. 1**).

However, none of these strategies has actually proved sufficient to definitely heal functionally and/or anatomically a damaged brain due to the drawbacks inherent to their sole exploitation.

In light of these issues, the vision that biological and engineering means should complement each other through a functional partnership has started getting off the ground, which is why tools from artificial intelligence have come into play. Thus, intelligent biohybrid systems are starting to gain the general consensus of the brain repair scientific community, as they

challenge the limitations of conventional approaches. As recently reappraised [2], a system of biohybrid architecture is constituted whenever an artificial device is coupled to the brain and interferes with or is activated by its activity. *Intelligent* biohybrid systems additionally implement artificial intelligence, which is leveraged to aid in the seamless integration of biological and engineering components.

In this review we describe the concepts at the core of intelligent biohybrid systems at their current state of the art, relative to the neurotechnology field. To motivate the need of the intelligent biohybrid design, we first provide an overview of the current approaches explored by biology and engineering disciplines, portraying their historical development and describing the advantages and limitations of their sole use both in the experimental and in the clinical settings. Particular emphasis is given to the engineering approach in light of its predominance in biohybrid neurotechnologies. We then describe emerging unconventional strategies exploiting an intelligent biohybrid design and their applicative perspectives. We conclude by presenting some fundamental open questions and indicating possible new directions in approaching the functional and anatomical recovery of the damaged brain.

2. THE BIOLOGICAL APPROACH TO BRAIN REPAIR: RECONSTRUCTION OF THE DAMAGED BRAIN TISSUE BY ENDOGENOUS NEUROGENESIS OR BY NEURONAL TRANSPLANT.

The exciting discoveries on adult neurogenesis over a century ago [3-5] (reviewed by [6]), marked the inception of a new era in the neurosciences by rejecting the canonical tenet that the brain cannot repair itself. The prospective for brain self-repair is straightforward: by employing targeted bio-cues, it might be possible to guide the migration of adult newly-generated neurons so to aid in the anatomical and functional re-establishment of damaged brain areas. In 1962, the groundbreaking discovery of J. B. Gurdon challenged the dogma that specialization into a specific cell-type is an irreversible biological process: he demonstrated that differentiated cells still contain the machinery required to drive their development into any cell-type [7]. In the wake of this pioneering demonstration, a new

milestone has been achieved in the next few decades, when induced pluripotent stem cells (iPSCs) were first generated from mice [8] and soon after from somatic cells of adult humans by two independent laboratories [9, 10], making another landmark in the history of regenerative medicine and a fundamental advancement in brain repair research. Indeed, iPSCs may be differentiated into any cell-type, thus making it possible to 'patch' damaged brain tissue with a great degree of flexibility. Similarly, grafting of embryonic neurons has been proposed as a promising strategy to reestablish lost brain connections in the adulthood [11]. Techniques from tissue engineering have also put forward the transplantation of *neurospheroids* (i.e., *in vitro* pre-made 3D neuronal networks) with encouraging results [12]. More recently, the generation of self-organized three-dimensional 'mini-brains' (so-called *brain organoids*) from human iPSCs [13] has provided new means for inducing the natural development of structured nervous tissue that realistically reproduces the architecture of a real brain and validate its functional features outside the patient's body. Such a discovery has tremendous implications for functional brain repair, since it envisages the possibility of generating *ad hoc* neuronal grafts straight from the patient's iPSCs and modulate their structural and functional features *before* their transfer into the patient's brain.

Each of these biological means has a great prospective potential but is nonetheless inherently prone to fundamental drawbacks that limit their clinical application. Most importantly the integration of exogenous neuronal elements or the migration of endogenous neuronal stem cells along with their proliferation, differentiation and survival within the pathological environment needs to be carefully considered when translating these techniques to the clinical setting [14, 15]. Indeed, while intrinsically endowed with plasticity and adaptation, biological cells might evolve beyond control and in turn endanger the patient's safety unless adequately fine-tuned. The pathological environment might predominate over the newly generated nervous tissue and imprint pathological features to it, or the new cellular elements might lead to the unexpected development of brain tumors. Moreover, the inflammatory response triggered by brain damage generates a non-permissive environment for endogenous regrowth and recovery of the nervous tissue, as

well as for the functional integration of grafted cells. For example, it has been shown that the number of cellular elements and the timing of their transplantation (the so-called 'safe window') relative to the brain damage [16, 17] are critical factors. In this scenario, it should ideally be possible to halt the immune reaction of the host environment while fine-tuning the growth and the functional features of the regenerative neuronal elements. As recently reviewed [18-20], targeting both the extrinsic and intrinsic factors contributing to the non-permissive axon-scar environment is a strategy worth to explore. Indeed, it has been shown that the enzyme chondroitinase can break down the tangled scar tissue which surrounds the brain lesion, so to free neuronal processes from its restraining action and allow them to grow again [21, 22]. Moreover, antibody therapy has proved promising in neutralizing the action of negative neuronal growth regulators, such as Nogo [23-25]. Along with counteracting neuronal growth inhibition, enhancement of the intrinsic growth potential of neurons *via* genetic or pharmacological manipulation has produced encouraging axonal regeneration [26, 27]. These strategies have significantly improved the functional recovery in animal models of CNS injury. However, despite these remarkable results, the available means strategically used to improve the chance of successful brain regeneration or exogenous repair have not yet defeated the main challenge of long-distance axon regeneration, i.e., the recovery of functional and structural features to a level that resembles the intact CNS. It follows that while the effectiveness of cell-based therapies is in the first place undermined by the adverse reactions of the hosting environment, the long-term functional and anatomical outcomes of these approaches are unpredictable and may ultimately lead to treatment failure. **Table 1** summarizes the advantages and limitations of the described biological approaches both in the experimental and clinical settings.

Whereas control of the immune reaction and tissue growth is intensively addressed by the study of pharmacological agents, biological cues and gene therapy, imprinting of the desired functional (electrophysiological) features to the regenerative nervous tissue is still far from being a possible route. In fact, it would require the coordinated modulation of the developing tissue patch and of the damaged host brain so to avoid pathological electrical entraining of

the healthy graft while allowing it to exert its healing function. To achieve this outstanding goal, tools from control engineering must come into play and mediate the seamless integration of the graft into the host nervous tissue under a controlled predictable environment.

Table 1 – Biological Means for Brain Repair: Key-points Summary

	Advantage(s)		Limitation(s)	
Description	**Bench**	**Bedside**	**Bench**	**Bedside**
iPSCs	• Can be differentiated into any cell-type • Can be obtained directly from the patient to be treated • Can be easily obtained from a bio-bank	• Versatility of transplants generation • Allow for self-cells transplantation	• Lack of 'know-how' to induce a specific molecular sub-phenotype for any known cell-type • iPSCs-derived cells might not take into account the inter-individual variability deriving from human experience	• Possible loss of control over the behavior and the growth of the transplanted elements • Transplanted elements cannot be removed
Embryonic neurons	• Already possess the neuronal phenotype • More versatile than adult, specialized neurons	• Versatility of transplants generation	Cannot be obtained from the patient to be treated	• Requires an external donor • Possible graft-versus-host disease • Possible loss of control over the behavior and the growth of the transplanted elements • Transplanted elements cannot be removed
Engineered nervous tissue	• Allows for *ad hoc* production	• Versatility of transplants generation • Can be obtained from the patient's iPSCs for self-repair	• The tissue size that can be obtained is still too small • Blood supply might be an issue • The 3D architecture is dictated by the human operator	• Possible graft-versus-host disease if heterologous cells are used • Possible loss of control over the behavior and the growth of the transplanted elements • Transplanted elements cannot be removed • The small tissue size that can be obtained might not suffice to 'patch' the damaged brain area
Brain organoids	• Allows for *ad hoc* production of grafts • Self-organized architecture that resembles the natural brain architecture • Allows testing therapeutic intervention *in vitro* prior to the administration to the patient	• Versatility of transplants generation • Can be obtained from the patient's iPSCs for self-repair • The self-organized 3D architecture is closer to the human brain	• The tissue size that can be obtained is still too small • Blood supply might be an issue	• Possible loss of control over the behavior and the growth of the transplanted elements • Transplanted elements cannot be removed. • The small tissue size that can be obtained might not suffice to 'patch' the damaged brain area

3. THE ENGINEERING APPROACH TO RESTORE BRAIN FUNCTION: CONTROL, REPLACEMENT AND BRIDGING.

The engineering approach to brain repair makes use of artificial devices to restore the physiological brain function by **(1)** stimulating the CNS (neuromodulation), **(2)** connecting the brain with an end effector (BMIs) **(3)** replacing/bypassing the damaged brain tissue (neuroprosthetics).

In this section we describe the most basic engineering interventions that represented a breakthrough in functional brain repair and we discuss the technical limitations that have led to the development of more sophisticated engineered devices based on advanced intelligent algorithms. Being coupled to the brain tissue, these artificial devices inherently give origin to a system of biohybrid architecture (see [2]). Here, we use the terms *engineering approach* to describe the different designs of these engineered components and *neuroprostheses* to indicate prosthetic devices having a direct connection with the CNS.

3.1 Neuromodulation

Neuromodulation refers to techniques of different levels of invasiveness used to stimulate selected brain areas thereby modulating their activity with therapeutic purposes in otherwise intractable patients. Specifically, neuromodulation may be used to **(1)** interfere with and rectify pathological brain activity and **(2)** favor functional brain recovery (e.g. following injury) by aiding in plasticity phenomena. The therapeutic effects may be achieved *via* electrical or magnetic stimulation delivered through the skull (transcranial electrical stimulation (tES) and transcranial magnetic stimulation (TMS), respectively) or via electrical pulses delivered directly into target deep brain areas (deep brain stimulation, DBS). Here, we focus on DBS and tES systems in light of their technical suitability and their current relevance to the design of intelligent biohybrid systems for functional brain repair. Most of the primary knowledge on

the therapeutic effects of these neuromodulation techniques has been based on human research because of lacking faithful animal models. However, the relatively recent availability of more reliable tools for preclinical testing have largely contributed to the development of modern experimental paradigms to further the investigation of these techniques in CNS disease models.

The therapeutic effects of electricity on the human body have been known since ancient times, when the electric ray was named *Torpedo Nobiliana* by the Romans and *Narke* by the Greeks after its ability of inducing torpor and narcotizing those who had been shocked by the contact with it. *Scribonius Largus* [28] used to employ the bioelectricity generated by the *Torpedo* to treat chronic pain, headache and a variety of other medical conditions [29, 30]. The first public demonstration that the brain cortex can be modulated by the application of electrical pulses and in turn produce effects on the human body was provided in the early XIX century by Giovanni Aldini [31], whose research was inspired by the seminal work of his uncle Luigi A. Galvani [32, 33]. In the next years, Aldini was able to successfully treat a patient affected by severe *melancholia* using transcranial galvanism (see [34]). The first ever direct electrical stimulation of the brain cortex of an awake human was performed in 1874 by Robert Bartholow [35, 36]. Electrical therapy has since then been intensively studied to treat a wide spectrum of neurologic and psychiatric disorders (see [34, 37-40] for historical reviews).

The first neuromodulation technique to be actually introduced in the experimental clinical practice was tES at the beginning of the XX century[41], thanks to the practical feasibility of the external approach. tES was used for induction of sleep and anesthesia [42], but in the late 1960's it became clear these were rather side effects of the electrical stimulation, which opened the possibility of several therapeutic applications. Meanwhile, the advent of the first stereotactic apparatus for humans in the late 1940's [43] had made routine employment of DBS feasible. Stereotactic DBS was first applied in the early 50's [44] to treat psychotic patients [45, 46]. Its chronic application was then proposed in the early 90's as a stand-alone therapeutic strategy to control movement disorders [47, 48].

While tES has been widely used in the past century as electroconvulsive treatment of depression and psychosis, the Food & Drug Administration (FDA) has recently reevaluated the efficacy and safety of this approach [49]. Nonetheless, the advantage of non-invasive neuromodulation is in favor of further investigation on potential use. Increasing evidence supports the adjuvant role of tES in post-stroke rehabilitation to improve motor learning [50] and functional recovery [51], possibly due to promotion of structural plasticity phenomena that are crucial for recovery from a brain lesion [52]. However, a significant drawback of the transcranial approach is the low focality of the delivered current, i.e., stimulation of highly selective targets is still impractical [53]. Conversely, DBS is to date an established approach that finds clinical application in a variety of movement disorders [54], being officially approved by the FDA since 1997. Several clinical trials have also shown promising therapeutic effects against epileptic syndromes [55, 56], chronic pain [57], primary headache disorders [58] and psychiatric syndromes [59, 60], with constantly expanding investigations [61-65]. Although invasive, the greater popularity of DBS is possibly due to the advantage of targeting *in situ* specific (even small and deep) brain areas with the aid of stereotactic and imaging guidance, while being relatively safe.

Besides the target brain area, relevant to brain repair are also **(i)** the stimulation parameters and **(ii)** the algorithms that control the stimulating device, whether DBS or tES is used.

As for the parameter choice, the CNS disease (and the neuronal pathways involved) plays a major role, but intra-individual and inter-individual variability along with the progression of the clinical condition and electrode/signal degradation in the case of DBS should also be taken into account. Indeed, parameter fine-tuning is first done at the time of electrode application whereas follow-up adjustments are inherently required. Moreover, the functional improvement ceases upon stimulation withdrawal. Needless to mention, the stress caused to the brain tissue by a constantly-on DBS paradigm is not negligible. Autonomic effects [66] and modulation of neuronal pathways functionally connected to the stimulated brain area [67] have also been frequently described: although reversible, these effects might represent undesired outcomes of neuromodulation and should not be underestimated. Last but not

least, similar to heart pace-makers, DBS devices run on a battery, which needs to be replaced at some point in time, essentially subjecting treated patients to 'maintenance' neurosurgery (on average every 5 years).

With regard to the algorithms employed to control the stimulating device, the systems currently used in the clinical setting mainly provide a fixed-frequency stimulation (also called *periodic pacing*). As their function is not influenced by the ongoing brain activity, these devices do not exhibit intelligent performance; rather they act as brain pace-makers and are said to be unidirectional. The operation of these devices is also regarded as *open-loop*, indicating that no feedback mechanism is involved to forward the modulated brain activity back to the modulator so to allow real-time adjustments of the control algorithm (**Fig. 2**).

In practice, open-loop neuromodulation does not offer the possibility of an individualized treatment, with the consequent shortcoming of increased brain tissue stress (in the case of DBS) and shorter battery life. Thus, despite the significant relief of clinical symptoms, many aspects should be considered in the reckoning of pros and contra of open-loop paradigms.

Advanced neuromodulation techniques leverage the electrical brain activity to trigger the stimulating apparatus. As the performance of these devices depends on the feedback received from the brain, their operation is regarded as *closed-loop* (**Fig. 2**). Some of these elements are set to provide a single output, i.e., they enforce a *reactive* behavior as in the case of electrical pulses delivered to a cortical area upon detection of an electrical signal. Others are more flexible in that they are programmed to generate different predefined built-in options according to different brain inputs, enforcing a *responsive* behavior (see [2]).

Using a reactive stimulation algorithm in brain-injured adult rats, the group of Randolph J. Nudo demonstrated that the loss of motor control could be successfully recovered by delivering electrical pulses to select cortical areas with a predefined delay following the detection of an electrographic event in the somatosensory cortex [51]. This simple but effective *phase-locked stimulation* paradigm, defined by the authors as 'activity-dependent

stimulation', was employed in the context of a bridging approach (see below). Exploitation of a similar design has also been reported to ameliorate Parkinsonism [68].

A responsive design was proposed by Beverlin & Netoff [69]. By using computer simulations, the authors were able to decrease the seizing state of a simulated neural network by enforcing a frequency-dependent stimulation policy. The algorithm was instructed to change its stimulation frequency according to the neural firing frequency, based on built-in knowledge incorporated in the algorithm by the experimenters. It is worth noting that the authors improperly define this operating mode as 'adaptive', which implies intelligent behavior (see [2]). However, this is not strictly the case here. Indeed, the proposed design requires a knowledgeable external supervisor instructing the algorithm on how to proceed, i.e., it is based on *supervised learning*, while the ultimate goal of the actions chosen by the algorithm is not a required parameter.

Responsive neuromodulation has recently obtained the FDA approval for clinical application as adjunctive treatment for drug-refractory epileptic syndromes [70]. The implantable device is pre-programmed by a skilled neurosurgeon or physician who sets the sequences of therapeutic interventions to be implemented upon electrographic detection of a seizure [71, 72]. The electrical stimulation patterns are triggered one after the other in the exact sequence established by the human operator so to maximize the efficacy of the intervention (seizure arrest). Despite being a valuable therapeutic tool to ameliorate the clinical manifestations (and thus the quality of life) of epileptic patients who do not respond well to the canonical pharmacological treatments, the responsive operation of this DBS system inherently requires a time lag to recognize a seizing state. Thus, responsive neuromodulation for epileptic disorders is not capable of predicting and thus preventing an imminent seizure: it can only halt its progression to the full-blown manifestation.

From what has been described so far, the benefit of neuromodulation is unquestionable. However, the control logic at the core of the operation of these devices does not allow for a flexible performance. As already stressed, the output of available neuromodulators is still passively bound to the ongoing brain activity in the most advanced closed-loop designs.

However, the patient would receive a greater benefit if a device were able to deliver an electrical pulse only when it is most needed. To this aim, intelligent stimulation algorithms based on real-time *prediction* of forthcoming electrical events and *adaptation* to the ongoing brain electrical activity would be required. In the wider context of biohybrid brain repair strategies, intelligent neuromodulation would also serve the fundamental function of fine-tuning the functional features of the interacting graft and host nervous tissues.

3.2 Brain-Machine Interfaces

Brain-Machine interfaces (BMIs) are systems mediating the communication between the brain and an external effector. This branch of the neurosciences was developed with the aim of restoring missing motor functions in patients who had lost such abilities due to disabling neurological diseases, CNS injury or limb amputation.

Almost 50 years ago Eberhard E. Fetz [73] demonstrated that trained monkeys were able to voluntarily modulate the activity of their cortical motor neurons in the absence of motion production. These discoveries inspired the pioneering visions of Edward M. Schmidt [74], who was able to demonstrate, ten years later, that monkeys could modulate their cortical activity (recorded with chronically implanted microwire arrays) so to move an effector external to their bodies. In the same period Apostolos P. Georgopoulos and colleagues [75] studied the electrical activity of cortical motor neurons in the forelimb areas of behaving monkeys and observed that each neuron was selectively increasing its firing rate when the primate was moving its forelimb in a given direction. These observations lead to the conclusion that specific movement trajectories activate specific ensembles of cortical motor neurons and thus these ensembles are functionally linked to a *preferred direction*. This unprecedented discovery helped Georgepoulos and his colleagues predict the desired direction of the primate's forelimb movement by computing the *population vector*, i.e. the vector obtained by linearly combining the vectors specified by each neuron's preferred direction, weighted by the neuron's instantaneous firing rate. All these studies laid the foundation for brain signal decoding and the development of neuroprosthetics. However, twenty years more of research had to elapse before BMIs were born.

The first pioneering demonstration of the feasibility of this neuroengineering approach dates back to 1999, when Chapin and colleagues [76] showed that rats could move a robotic arm by modulating the activity of their motor cortical neurons (**Fig. 3**).

These pioneering experiments suggested the possibility of creating a new generation of neuroprosthetic devices based on the decoding of brain signals in order to operate an end effector. A decoding algorithm (*decoder*) is a programmatic routine used to decode neuronal signals into their functional meaning. The seminal work by Chapin and colleagues represented its first applicative demonstration, which was followed by various decoder designs to interface brain and machines making use of different kinds of recording techniques. In 2006 the group lead by John P. Donoghue [77] described the first successful prototype of BMI used in a human with tetraplegia. The BMI was able to decode motor intentions from the hand motor area of the brain cortex of the patient and translate it into the movement of a cursor on a screen so to perform simple actions such as opening emails and controlling television. The same group was later able to successfully establish the functional connection of a robotic arm to the brain of a patient with tetraplegia, allowing her to reach, grasp and drink a cup of coffee [78]. A more advanced *reactive* BMI design has been recently realized by Chad E. Bouton and colleagues [79]. With the aid of microwire arrays chronically implanted in the motor cortex of a quadriplegic young man, electrical signals corresponding to motor intentions were decoded and translated into patterns of stimulation which were forwarded to a custom neuromuscular electrical stimulation system that consequently activated forearm muscles. The authors demonstrated that this BMI design is able to translate intentions to motions thereby restoring fine hand-wrist movement in a paralyzed human by providing for single finger control resulting in six different hand motions.

As seen, BMIs generally record brain signals from the hand or arm areas of the motor cortex in order to decode motor intentions and use this information to drive the end effector. In a recent study, Alessandro Vato and coworkers [80] built a BMI in rodents that was able to drive the motion of a mass in a virtual field by recording from the whiskers motor area and

consequently stimulating the naturally connected whisker somatosensory area. They demonstrated that it was possible to use two connected brain areas to implement a control policy over the external end effector, even if the controlled task (i.e. the motion of the virtual mass) was not directly linked to the intrinsic physiological role of the brain regions used.

3.3 Brain prostheses for replacing or bypassing the damaged brain tissue

Brain-prostheses can be defined as a special kind of neuroprostheses in which an artificial system, either software or hardware, is used to bypass or replace a damaged brain area in order to regain the lost functionality. Two are the main scientific and technological outcomes which brought to the realization of these systems. In 1993 Sylvie Renaud and colleagues [81] established the first communication channel between an artificial neuron and a biological neuronal network. An evolution of that system was later published in Nature by Le Masson et al. [82], who reconstructed a hybrid thalamocortical pathway by combining a biological network and an artificial system constituted by a dedicated analog integrated circuit. In this way the authors were able to work with a real biological system while maintaining complete control over the parameters of the model neuron. In 2000 Ferdinando A. Mussa-Ivaldi and coworkers [83] created the first hybrid neuro-robotic system: a two-way communication between the brain of a lamprey and a small mobile robot. These studies allowed the establishment of a new concept of neuroprostheses ‘for the brain’ aimed at *replacing* the damaged neural tissue with a structure incorporating an artificial component or on *bridging* two brain areas to promote functional recovery following a brain damage.

The realization of such prostheses implies the knowledge of how to interact with neuronal cell assemblies, taking into account the intrinsic spontaneous activation of neuronal networks and understanding how to drive them into a desired state in order to produce a specific behavior. This outstanding long-term goal requires the development of computational models to be fed with the recorded electrophysiological patterns so to yield the appropriate brain stimulation pattern that would recover the lost or compromised function(s). The models used in this framework can be essentially of two types: **(i)** bio-inspired and **(ii)** biomimetic. A *bioinspired* model is a system inspired by nature, capturing an

essential idea underpinning a biological system so to implement its abstraction in technology, like the design of an aircraft equipped with wings is inspired by a flying bird. A *biomimetic* model mimics the nature's *modus operandi*, trying to replicate features, like early aircraft designs implementing flapping of the wings. More pertinent to biohybrid systems for brain repair is the typical example of central pattern generators (CPGs), i.e., neuronal assemblies that intrinsically generate rhythmic patterned outputs: a bio-inspired model catches the essential feature of *cyclic rhythm* and would be a simple oscillator, where frequency and duty cycle are kept constant, whereas a biomimetic model further implements the *features* that a CPG exhibits in the real world by introducing variable frequency and duty cycle in the oscillator's design [84].

Replacing neuroprostheses –The first example of brain prosthesis for replacing a damaged brain circuit was proposed by the group of Theodore Berger. They worked on the development of hippocampal prostheses by using both in *in vitro* and *in vivo* experimental models for memory enhancement. In one experiment [85] they employed a non-linear software computational model to approximate the transformation between the input and output spike trains of an observed neuronal network. An iterative procedure was able to determine all the parameters so that the model could predict the observed input-output firing patterns.

Neuromorphic devices (i.e., engineered systems that mimic the complex parallel processing of the human brain) represent the latest advancement in replacement neurotechnologies for brain repair. In 2015, Roni Hogri and coworkers [86] built a hardware biomimetic circuit implementing cerebellar functions. The chip was interfaced in real-time with cerebellar input and output nuclei of anaesthetized rats. They demonstrated that functional rehabilitation can be achieved by reproducing cerebellar-dependent learning. The team of the EU-funded project *Brain Bow* presented the first results related to the realization of a neuromorphic brain prosthesis to replace a damaged neuronal cluster in a multi-compartment neuronal network of dissociated cortical neurons [87]. The neuromorphic computational model was a implementation of a Spiking Neural Network (SNN), based on Izhikevich model neurons [88].

Neuromorphic devices have been so far exploited for replacing purposes. Nonetheless, the versatility at the core of their concept promises theoretically unlimited implementations, including advanced architecture and performance of bridging neuroprostheses.

Bridging neuroprostheses – In 2006 the group of Eberhard E. Fetz [89] showed that cortical reorganization can be induced by activity-dependent plasticity achieved by implementing a causal relationship between presynaptic and postsynaptic activities. Some years later, the group led by Randolph J. Nudo [51] applied these finding to the treatment of stroke and demonstrated the very first example of a *neural bridge* aimed at promoting functional re-connection between two cortical areas (i.e. the premotor cortex and the somatosensory cortex) in a rat model of Traumatic Brain Injury (TBI). The artificial bridge was based on an activity dependent stimulation protocol (*phase-locked reactive* stimulation, *cf* §4.1 - Neuromodulation) implemented through a custom, wireless chip interconnecting the two far away cortical areas via *closed-loop* interaction (*cf* **Fig. 2**).

Overview

From what has been described so far, it clearly shows that the engineering strategies offer a higher degree of functional control as compared to biological approaches, because the human designer programs the *core* operation of these devices, thereby instructing them on how to behave. Yet, the limited flexibility and the technological constraints of most of these devices is a non-negligible cost. Indeed, modern BMIs commonly enforce predefined policies or they simply provide for a unidirectional stereotyped replacement of the compromised or lost brain function resulting somewhat stiff in their operation. **Table 2** provides a key-points overview of advantages and limitations of the described engineering approaches both in the experimental and clinical settings.

At last, it needs to be stresses that the structural plasticity phenomena that intrinsically characterize biological neurons can only be simulated computationally in an artificial device whereas the physical structure of its electronic components will remain unchanged. This picture envisages the synergetic exploitation of the intrinsic plasticity of biological neurons

and of the high degree of control offered by engineering tools in order to achieve the necessary balance between flexibility and stability.

Table 2 – Engineering approaches to restore brain function: Key-points Summary

	Advantage(s)		Limitation(s)	
Description	**Bench**	**Bedside**	**Bench**	**Bedside**
Neuromodulation	• Simple to implement in *in vitro* and *in vivo* models of CNS disease so to test a variety of stimulation paradigms and help in parameter fine-tuning • May aid in structural plasticity of involved brain areas (tES) • May help gain more insight into brain function and plasticity	• Effective and generally well tolerated • Can be switched on and off at the patient's need with a remote controller • Easy to monitor the effectiveness through clinical manifestations	• Limited availability of reliable animal models • Requires knowledge of neuroanatomy and neurophysiology • Cannot take human inter-individual variability into account	• May be invasive (DBS) • Requires a trained physician and a multidisciplinary team • May lose efficacy over time • May cause systemic autonomic and central side-effects • Implanted electrodes (DBS) may trigger foreign body reaction • Not indicated for all patients • Time-consuming parameter fine-tuning may be required
BMI	• Suitable for use in *in vivo* animal models of CNS disease • In *in vivo* animal models, allows investigation of various brain-interfacing techniques before translation to humans • In *in vivo* animal models, allows gaining more insight into brain function, plasticity and learning	• Possibility of achieving fine control of end effector through learning • Allows bypassing the damaged brain area by deputing other areas to fulfill a given task	• Limited stability of the recorded signals • Movement artifacts might contaminate the recorded signals adding complexity to their interpretation by decoding algorithms • Implanted electrodes may trigger foreign body reaction	• Limited stability of the recorded signals over time • Movement artifacts might contaminate the recorded signals adding complexity to their interpretation by decoding algorithms • Implanted electrodes may trigger foreign body reaction
Replacing and bridging	• Suitable for use in *in vivo* animal models of CNS disease • In *in vivo* animal models, allows investigation of various replacing and bridging techniques before translation to humans	• Possibility of restoring brain physiological operation	• Implanted device may trigger foreign body reaction	• Implanted device may trigger foreign body reaction

	• In *in vivo* animal models, allows gaining more insight into brain function, plasticity and learning

4. AT THE CORE OF INTELLIGENT BIOHYBRID SYSTEMS: THE HISTORY OF ARTIFICIAL INTELLIGENCE AND ITS IMPLEMENTATION IN NEUROBIOLOGY & NEUROENGINEERING.

The foundation of Artificial intelligence (AI) as an academic discipline was laid by The Dartmouth Conference in 1956 ('the birth of AI' [90]), where visionary scientists converged their world-changing ideas with the commitment to build humane machines. In the wake of this legacy, the treatment of neurological disorders has been revolutionized by novel concepts based on the active implementation of AI to neurobiology means. This cross-disciplinary approach based on converging sciences has led to the unprecedented design of intelligent biohybrid neurotechnologies, i.e. systems of biohybrid architecture whose performance is enhanced by the additional implementation of the theoretical principles of AI. These devices are based on a reciprocal interaction between the biological and the artificial element(s) ultimately aiming at establishing a functional partnership between them.

The artificial element is designed to provide an output (e.g., electrical stimulation, movement of a robotic arm) in response to an input signal generated by the brain. As opposed to open-loop devices providing a fixed output independent of the ongoing brain activity (**Fig. 2a**) and to closed-loop devices operating according to built-in instructions (**Fig. 2b**), intelligent biohybrid systems operate in closed-loop but they adapt their output to the input signal(s) received from the brain area they are connected to (**Fig.3**). The intelligent algorithms implemented in these systems are capable of real-time adjustment, since they are built upon an input/output (I/O) function that is set to self-evolve and take autonomous decisions as to which intervention policy is best at each point in time. Thus, intelligent biohybrid neurotechnologies may reach high levels of sophistication up to exhibiting autonomous goal-directed behavior.

In the next sections, we explain the concepts at the core of intelligent operation and we present practical examples of these new generation approaches, with particular emphasis on **(1)** intelligent neuromodulation and **(2)** intelligent neuroprostheses, i.e., **(i)** replacement and bridging based on neuromorphic performance, such as memristor-based devices and organic electronic biomimetic neurons and **(ii)** innovative BMIs.

4.1 Intelligent neuromodulation

Whether applied through the skull (tES) of directly into deep brain structure (DBS), electrical modulation of brain activity may benefit of intelligent control algorithms to operate real-time adjustments of the stimulation policy based on the detected ongoing brain signals.

In order to achieve the outstanding goal of prediction and prevention of pathological brain discharges, more advanced designs have leveraged statistical machine learning techniques. These strategies are based on providing the algorithm with a goal as the sole parameter, while letting it *learn* the best intervention policy through the presentation of learning problems. This paradigm is referred to as *reinforcement learning* [91] and is distinguished from the supervised learning technique used in responsive DBS algorithms in that it is not based on examples provided by a knowledgeable external supervisor; rather it is based on mapping (and linking) situations and actions in order to maximize a numerical reward or a reinforcement signal. Algorithms based on this paradigm do not receive any instruction on *how to* behave (e.g., which stimulation to choose according to the detected brain signal); they are programmed to discover which intervention policy yields the highest reward by trial-and-error. Thus, reinforcement learning is not defined by characterizing learning methods, but by characterizing a learning problem, where trial-and-error and delayed reward are the two most salient features. The goal-directed behavior of these intelligent agents relies on their capability of sensing the state of the surrounding environment and of capturing its most relevant aspects so to take consequent actions in relation to how the environment must be changed in order to maximize the reward. Sensation (signal detection), action (stimulation) and goal (halting pathological brain activity) are the three fundamental prerequisites for

these advanced neuromodulation algorithms, which are referred to as *adaptive* (**Fig. 3**), since they are capable of *self-evolving* and *autonomous decisional power* ([2]). Reinforcement learning techniques have been successfully implemented to build adaptive stimulation algorithms for seizure control using computer simulations and *in vitro* models of epileptiform activity [92-94]. Based on a set of choices derived from previously established periodic pacing policies [95, 96], the proposed adaptive design exhibited self-evolving behavior and autonomous decisional power as to whether stimulation was required at each point in time and to which stimulation policy to enforce. The novel adaptive stimulation algorithm exhibited similar suppression rate of seizure-like events when compared to the most effective periodic pacing policy (i.e., 1 Hz, *cf* [96]), while requiring the delivery of a smaller number of electrical pulses, thereby benefitting the brain tissue of less electrical stress. Moreover, this work definitely clarified the importance of the stimulation pattern in addition to the target site (*cf* [12]) by demonstrating that the efficacy of seizure control was smaller when applying periodic pacing at the average pulse frequency delivered by the adaptive algorithm. In the broader perspective of imprinting functional features to *in vitro* generated graft nervous tissue, this aspect is highly relevant, since it further corroborates the vision that a close dialogue between brain and machine is a crucial prerequisite to obtain cutting-edge biohybrid transplants for functional brain repair.

As previously emphasized, improved therapeutic DBS treatments may rely on the prediction of the ensuing undesirable brain activity pattern, such as a seizure, in order to prevent, rather than halt, its occurrence. Predictive algorithms may also be useful when it is required that the response of the stimulated brain area be known in advance so to operate a case-by-case choice of the best stimulation policy in order to rectify pathological brain activity in real-time. Needless to say, this is not a trivial achievement, as most predictive algorithms are theoretically based on exact neurophysiology knowledge, including the underlying dynamics and transition states (i.e., from normal to pathological activity) of the probed neuronal network (so-called ‘first principles’ approach). More recently, Bush and colleagues [97] have proposed an evidence-based mathematical modeling approach, which is capable of

capturing robust, informative features of the state of neuronal networks. The described model is built upon abstract rules, i.e. on the evidence acquired from observation independent of detailed neurophysiology knowledge. This approach is very intriguing, since it offers the possibility of predicting the outcome of neuromodulation and screening a variety of interventions while bypassing the need of detailed knowledge of the probed neuronal network dynamics as required by first principles approaches. The proposed evidence-based model may prove useful both as a simulator and as a predictor, so to aid in the initial choice of stimulation parameters based on simulation results as well as in the real-time fine tuning of adaptive stimulation algorithms based on real-time prediction of the neuronal network response to electrical stimulation.

4.2 Intelligent neuroprostheses – replacement and bridging

Electronic memory transistors (*memristors*) are fundamental electronic circuit elements characterized by a dynamic relationship between current and voltage, whose most relevant feature is the capability of retaining memory of past voltages or currents that have passed through them. Memristors were formally introduced in 1971 by Leon Chua [98]. In his seminal paper, Chua provided the first mathematical description of what he proposed to be the (theoretical) fourth fundamental circuit element (along with capacitor, inductor and resistor), which he named ‘memristor’ as a short from the term ‘memory resistor’. The existence of memristors has remained a theoretical assumption until recently, when the groundbreaking work by Strukov and colleagues [99] demonstrated the natural arising of memristive elements and their role in hysteretic phenomena that are commonly observed in electronic devices as well as in biological neurons (i.e., whenever a current-voltage relationship is in play). Most relevant was the demonstration that a memristor can retain the value of its most recent resistance even when the electric power supply is turned off and remember it until it is next turned on. Since this pioneering demonstration, memristors have been catching much attention within the Computer and Electronic Engineering field and, more recently, within the neurotechnology field and the brain repair scientific community. Indeed, the performance of these electronic elements resembles (rather than simulate) that

of biological neurons, since it combines the functions of memory and logic that are intrinsic to synaptic plasticity and neurotransmission [98]. A further step towards the generation of intelligent 'self-evolving' neuromorphic devices has been recently made by Kim and colleagues [100]. The group has been able to create an artificial hybrid circuit capable of mimicking the fundamental features of brain function by stacking the first functioning memristor array on a conventional complementary metal-oxide semiconductor (CMOS) circuit. This outstanding achievement is a critical progression in the development of intelligent machines and opens the possibility of exploiting their functional similarity to the brain as a repair strategy. Recent work within the EU-funded project *RAMP – Real neurons-nanoelectronics Architecture with Memristive Plasticity* – has indeed leveraged the plasticity phenomena that can be easily induced in biological neurons to imprint memories in memristors so to artificially mimic brain function [101, 102]. This design appears to be paradoxical, since the electronic elements should interact with biological neurons to guide their plasticity rather than acquiring it from them, whereas in this paradigm 'real' neurons are exploited to improve the flexibility and thus the long-term (evolutionary) performance of the artificial device. Nonetheless, memristors provide an intriguing perspective for the design of biohybrid brain repair strategies by virtue of the high degree of flexibility that is inherent to their operating mode, which outclasses the stereotyped behavior of most modern engineered controllers while in turn offering a more controllable behavior than real neurons. However, it needs to be stressed that the electrical activity of the surrounding (possibly) dysfunctional brain as well as the growth of the anatomical component that would reconstitute the lost brain matter cannot be modulated by memristors, which instead would integrate themselves into a (most likely) pathological environment. Thus, memristors might not suffice by themselves to heal a brain dysfunction or might even end-up contributing to the worsening of it, unless adequately designed.

Recent advances in biomimetic materials and organic electronics have led to the unprecedented realization of *organic electronic biomimetic neurons* [103]. These artificial neuronal elements are distinguished from Artificial Neuronal Networks (ANN) by virtue of

their organic components along with highly sensitive chemical sensors and ionic pumps that allow delivering neurotransmitters and generating ionic currents in response to the chemical and electrical inputs received from the brain tissue they are connected to. Thus, although artificial in their manufacture, these 'neuronal replicas' actually behave like their biological counterpart. A biohybrid solution based on organic artificial neurons is highly intriguing and opens the visionary possibility of reconstructing an artificial brain that is capable of fully resembling the behavior of its biological counterpart. Nonetheless, as already stressed for memristive devices, it remains to be established how these artificial organic neurons can be guided to appropriately integrate themselves within the damaged host nervous tissue and induce a functional healing process that would not evolve towards pathological behavior. The possibility of programming electronic neurons so to modulate their output activity according to the desired functional features might represent a fundamental leap in brain repair research, possibly eliminating the complex bench work required to generate biological neuronal grafts with specific structural and functional features.

4.3 Intelligent neuroprostheses – innovative BMIs

In the BMI field some examples of intelligent behavior can be found in the routine regulating the operation of the decoding algorithm. In general, given the variability and also the degradation of the quality and quantity of the recorded brain signals, BMI performance tends to decrease over time and also within a single BMI-training session. This phenomenon could be tackled by continuous re-calibrations of the decoder but this approach would detriment the structural plasticity of the brain associated to the BMI task. To overcome these issues, the group of Jose M. Carmena recently implemented *adaptive* behavior in a BMI decoder design, which they define closed-loop decoder adaptation (CLDA) [104]. The group demonstrated that this approach could improve the initial BMI performance and compensate for changes in neuronal recordings [104]. CLDA could be implemented using various algorithms [105-107] and its purpose was to update the parameters of the decoder according to past recorded data. CLDA was therefore performed at the beginning of each session and

within each session, every time a significant drop in BMI performance was observed. This paradigm was used until the subject was able to successfully fulfill the BMI task again.

Overview

Although promising, the neuroengineering approaches are still far from being used in clinical applications. For example, in the case of BMI, Bouton showed that the tetraplegic young man successfully learned to use the neuroprosthesis and was able to play a toy electronic guitar in a videogame, which requires coordination of fast, fine finger movements. However, the BMI was a bulky device and its set-up and operation required the presence of the (skilled) research team. These major constraints make the use of current BMIs in the daily life (and thus their routine clinical application) impractical. However, the rapid technological progress let us we foresee the diffusion of such systems in the next decades. For instance, wireless communication would free BMI users from cables and plug outlets, while allowing physicians to remotely monitor the functional state of the machine. Nanotechnologies applied to miniaturized computers might help put aside bulky BMIs and open a new era of 'portable' neuroprosthetic devices.

5. WHAT ARE WE STILL MISSING?

Many of the described approaches are groundbreaking achievements that have made possible what used to be a dream until a few decades ago. Cell transplantation and 'mini-brains', intelligent neuromodulation algorithms that learn from experience and outclass the human knowledgeable operator, BMIs allowing to read emails, play videogames or even perform complex coordinated fine movements will surely lead the era of novel intelligent biohybrid systems for functional brain repair. Nonetheless, we cannot stress enough that each of these strategies alone, at their current state of the art, will likely fail the challenge of routine clinical application due to their inherent drawbacks. The depicted points evidence the need of reaching beyond the current state of the art and design unconventional brain repair strategies that would make the most out of the good of biology and engineering means. Specifically:

(1) Implantable artificial devices are prone to trigger foreign body reaction [108] which is detrimental both for the patient and for the implanted device. For example, the stability of electrical signals recorded with intracortical electrodes is subject to degradation over time due to the formation of reactive tissue against the electrodes [109]. Bouton and colleagues [79] indeed reported that the number of recorded signals from individual neurons diminished from 50 to 33 in as little as 15 months. As closed-loop neurotechnologies are by nature based on the detection of brain electrical signals in order to operate, the degradation of their quality and quantity is an unacceptable shortcoming and research is already exploring new strategies to overcome this major limitation [104]. Along with the constant search of new biocompatible materials, significant advancements have been recently achieved in the field of implantable organic electronics by including a microfluidic component [110]. These novel 'all-in-one' implantable technologies allow delivering drugs both as therapeutic agents and as suppressors of the immune reaction directly from the implanted device, promising to cross out the substantial drawback carried by the foreign body reaction in the near future.

(2) The plasticity phenomena that are intrinsic to biological neurons are a fundamental prerequisite to achieve the functional reestablishment of the injured brain. However, as neuronal plasticity intrinsically implies the risk of losing control over a biological neuronal graft, tools from control theory are crucial to guarantee the functional stability of the grafted nervous tissue and of the brain hosting it. On the other hand, a too stiff control algorithm will inevitably compromise flexibility and thus decrease the chance of integration of the graft into the host nervous tissue. Undoubtedly, to overcome these limitations it is required that a highly flexible synergetic interaction between artificial and biological components be established. In this scenario, artificial intelligence may represent the solution to orchestrate the seamless integration of the biohybrid graft within the damaged brain while providing a controlled environment. As described above, some solutions to these primary issues have been recently proposed. For example, the intrinsic plasticity of biological neurons is being exploited with promising outcome to generate advanced highly-performing memristors [101,

102], while organic electronic biomimetic neurons have been recently proposed as a highly realistic artificial replacement of their biological counterpart [103].

(3) It would be highly desirable to be able to rely on brain repair strategies that are not disease-specific in their design, whereas current biohybrid neurotechnologies are mainly conceived to target a specific CNS dysfunction. It may be argued that detailed knowledge of brain pathways is a prerequisite to restore their function and that the repair strategy cannot overlook essential anatomical and (patho)physiological information. Moreover, such a revolutionary achievement would require identification of the functional 'building-blocks' of neuronal communication and knowledge of the relation between structure and function of neuronal networks. This missing knowledge is crucial to understand how different combinations of functionally distinct building-blocks may be exploited to achieve the desired functional features of neuronal grafts and to predict their influence on the activity of the extended neuronal network they would be embedded in (the brain). In this context, a 'reverse engineering' approach might be a valuable asset to bypass the need of detailed biophysical models based on first principles and possibly the need of extensive anatomical and functional characterization of neuronal pathways. Indeed, as recently demonstrated [97], computational approaches exploiting an evidence-based strategy make it possible to faithfully reproduce the responses of brain tissue to electrical inputs and thus to also predict how a brain area would react to a variety of electrical input patterns, even without prior observation of the neuronal network dynamics. It is reasonable to anticipate that in the near future it will be possible to reverse the operating mode of prediction and simulation algorithms so to establish which missing input signal should be replaced in a dysfunctional brain in order to recover the desired electrical activity. In turn, this would allow imprinting the desired functional features to engineered nervous tissue to be used as graft and ultimately anticipating the outcome of its interaction with the host brain.

6. CONCLUDING REMARKS

We have stepped through the historical developments of brain repair strategies from the origin of groundbreaking discoveries and the seeds of revolutionary visions to the actual realization of previously fantasized intelligent biohybrid neurotechnologies. We provide a visual overview in **Fig. 4** to help explore possible new roadmaps to beat the challenge of defeating CNS dysfunctions. There are still many open questions to be answered and as many obstacles to be overcome. However, in the era of exponential progression in medicine and technology, we envisage the future possibility of inducing a self-repair process in a damaged brain thanks to the availability of versatile, highly efficient, cost-effective intelligent biohybrid neurotechnologies that will offer personalized interventions to "help the brain help itself "[111].

EXECUTIVE SUMMARY

- Neurotechnologies are artificial means to understand and/or modulate brain function.
- Intelligent biohybrid neurotechnologies are neurotechnologies based on the joint exploitation of biological and artificial components, whose interaction is mediated by intelligent control algorithms.
- The development of intelligent biohybrid neurotechnologies for functional brain repair will lead to the global engagement of research and industry establishing an unprecedented explosion of cross-disciplinary translational biomedical research.
- Achievement of a smooth self-repair process in the damaged brain will drop the global burden and the societal impact of neurological diseases, while abating the cost of (often inefficient and too aggressive) canonical treatments.
- Brain self-repair strategies based on a non disease-specific design will offer treatments that are intrinsically tailored to the patient's need.
- The 'self-repair' therapeutic approach will simplify the approval procedures of regulatory agencies.

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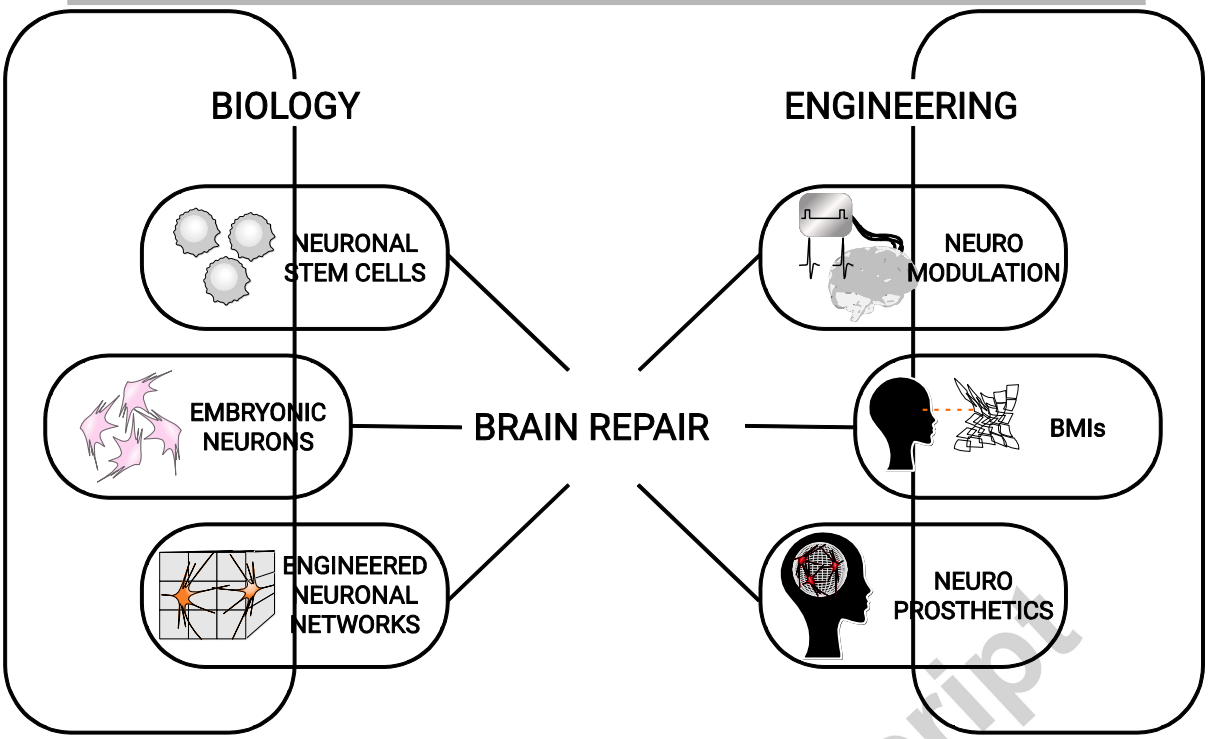
Figure 1 – Biological and engineering approaches to functional brain repair. Schematic renditions of the currently available biological (left) and engineering (right) means exploited to repair the dysfunctional brain tissue.

Figure 2 – Neuromodulation. Open loop devices deliver electrical pulses at a fixed frequency regardless of the ongoing brain electrical activity. Closed-loop devices may be based on a *reactive* policy (stimulation is phase-locked to brain patterns) or on a *responsive* policy, where the device's output changes according to built-in options. In this rendition brain pattern *a* triggers output *a'* while brain pattern *b* triggers output *b'*. Grey traces: ongoing brain electrical activity. Black traces: evoked brain electrical responses. Black vertical bars: time-stamps of delivered electrical pulses.

Figure 3 – The first BMI – Experimental paradigm. In *lever-movement/robot-arm mode* (a) **rats were trained to obtain a water reward by pressing the lever** (b)**, which was electronically connected to a robot arm** (c) **used to collect water drops from the sipper tube** (e) **hidden by a barrier** (d)**. The rest position of the robot arm was by the rat, through a slot in the barrier. An electronic controller was used to translate the lever displacement and proportionally slide forward the robot arm through the slot in order to reach the sipper tube and collect water drops. The robot arm carrying the water reward then passively moved back to its rest position by the rat. In *neuronal-population-function/robot-arm mode*** (f)**, rats were chronically implanted with multi-electrode arrays** (f) **in the M1 cortex and VL thalamus for simultaneous recordings of single-neuron electrical activity** (g) **to extract spike trains** (h) **and neuronal-population (NP) function by principal component analysis** (i)**. A switch** (j) **was used to select the input source (lever movement *versus* NP function) and consequently control the robot-arm position. In experiments, rats typically began moving the lever. The input was then switched to the NP function, yielding robot arm movements (and thus water reward) when the rat was to press the lever (i.e., before it was actually displaced). The animal eventually learned to obtain water through direct brain control of the robot arm (from Chapin et al. *Real-time control of a robot arm using simultaneously recorded neurons in the motor cortex*. Nature neuroscience 2 (7)(1999) 664-670 [76]).**

Figure 4 – Intelligent biohybrid systems implement adaptive control algorithms. An intelligent neuromodulator is depicted. The device receives feedback (thick arrow-lines) from the brain (grey trace) and from the performance evaluator, a programmed routine that compares the actual output (modulated brain pattern, black traces) with the desired output at each trial. Good and bad performances are scored according to a reward function built in the evaluator program. Performance evaluation implies a learning process so that the algorithm modifies its intervention policy according to its past experience, aiming at maximizing a reward. Ultimately the intelligent neuromodulator adapts its behavior and becomes autonomous: it chooses the most appropriate action at each point in time, independent of human intervention.

Figure 5 – Biohybrid neurotechnologies: from their origin to modern application. A visual portrait of the evolution of biohybrid neurotechnologies. Neuromodulation – 1803: **Giovanni Aldini uses of galvanism to treat *melancholia*.** 1947: **The first apparatus for human stereotactic neurosurgery (images [43] from with permission).** 1997: **Following the advent of human stereotactic neurosurgery, DBS firstly achieves FDA approval for movement disorders.** Biomimetic technologies – 1993: **The first functional dialogue between a biological neuronal network and a computational model neuron is described by Sylvie Renaud-LeMasson and colleagues [81].** 2012: **Kuk-Hwan Kim and colleagues [100] introduce the first neurmorphic chip based on memristive circuit elements.** 2015: **Daniel T. Simon and colleagues present the first organic electronic biomimetic neuron [103].** Neuroprostheses, top row: BMIs – 1999: **Chapin and colleagues [76] provide the first proof of concept of the application of decoding algorithms to interface brain and machine.** 2006: **The team of Donoghue [77] achieved the first BMI allowing a tetraplegic patient to use a computer.** 2012: **The same research team is able to successfully connect a robotic arm to a tetraplegic patient's brain allowing basic brain-controlled movements of the robotic end effector [78].** 2016: **Chad Bouton and colleagues describe the design of a brain prosthesis allowing for fine finger movements in a tetraplegic patient [79].** Neuroprostheses, bottom row: brain prostheses – 2006: **The group of Fetz is able to induce changes in motor cortical maps (cortical reorganization) using neurochip-mediated cortical conditioning (activity-dependent plasticity) in non-human primates (from Jackson et al. *Long-term motor cortex plasticity induced by an electronic neural implant.* Nature 444 (7115)(2006) 56-60. [89]).** 2013: **The group of Randolph J. Nudo recovers reaching and grasping function of a rat undergone brain ischemic lesion (from *Guggenmos et al. Restoration of function after brain damage using a neural prosthesis*. Proceedings of the National Academy of Sciences of the United States of America 110 (52)(2013) 21177-21182 [51**



NHTM Intelligent Biohybrid Systems ***Figure 1***

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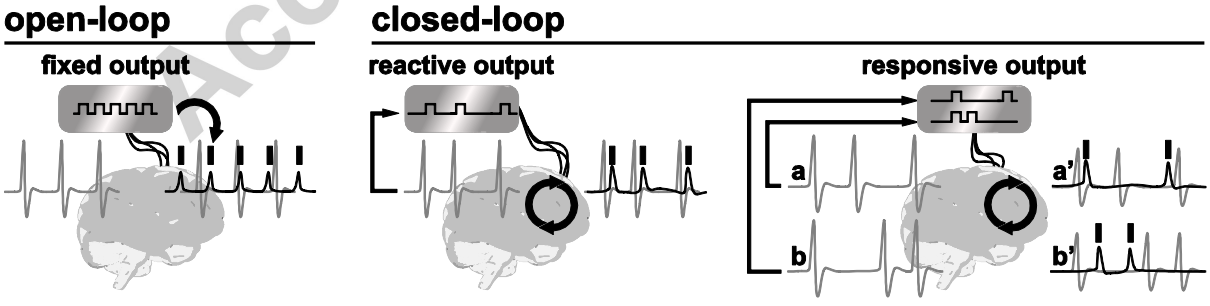
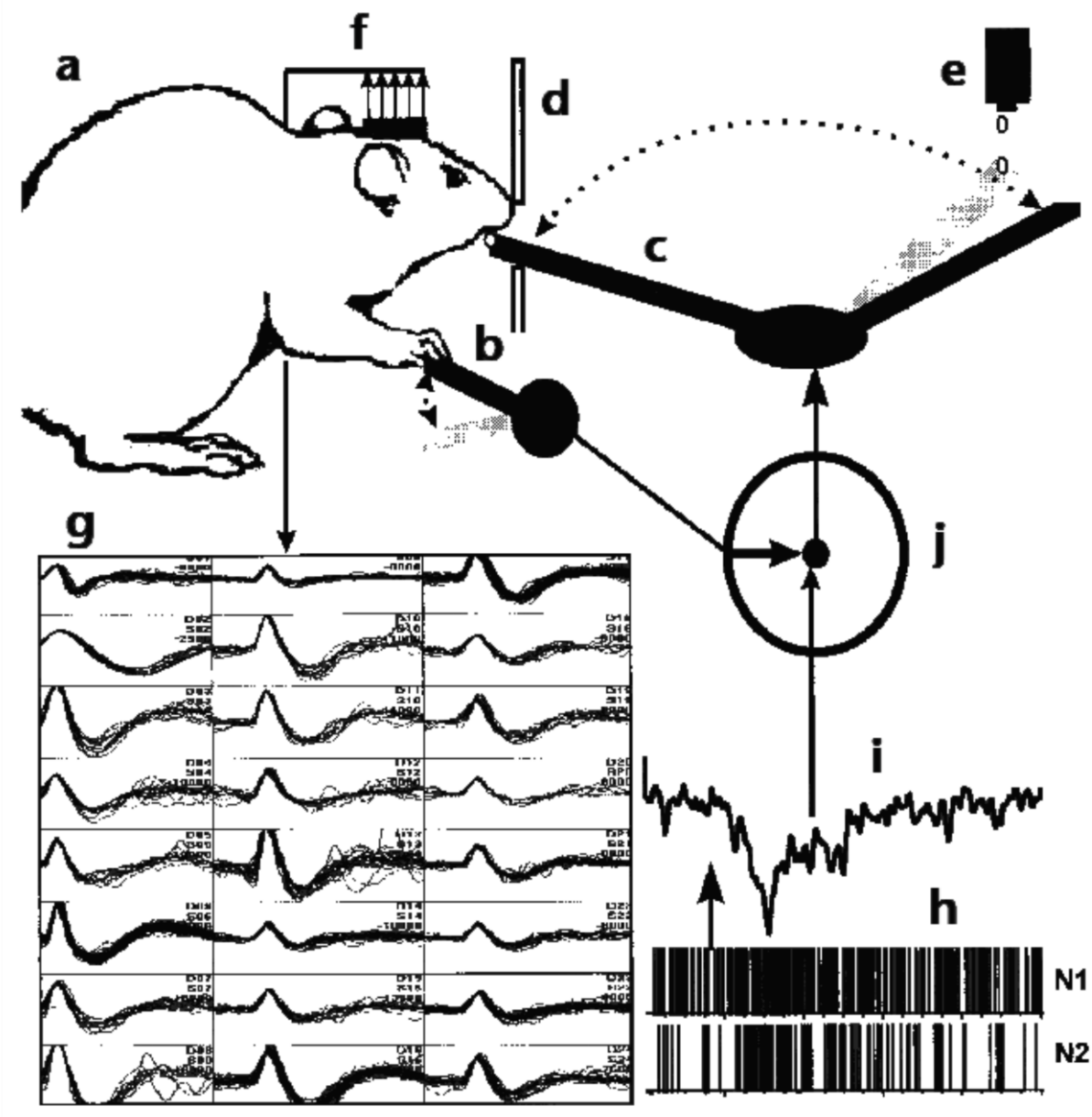
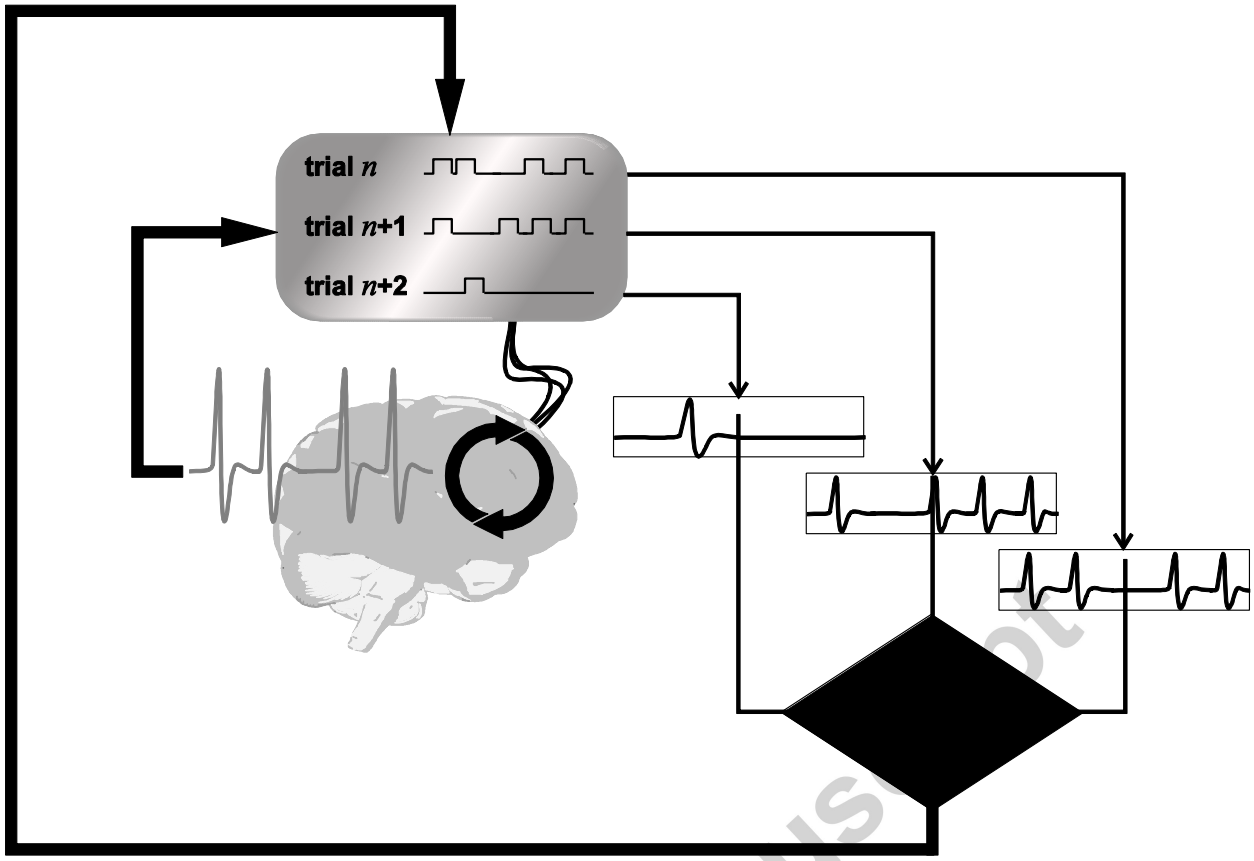


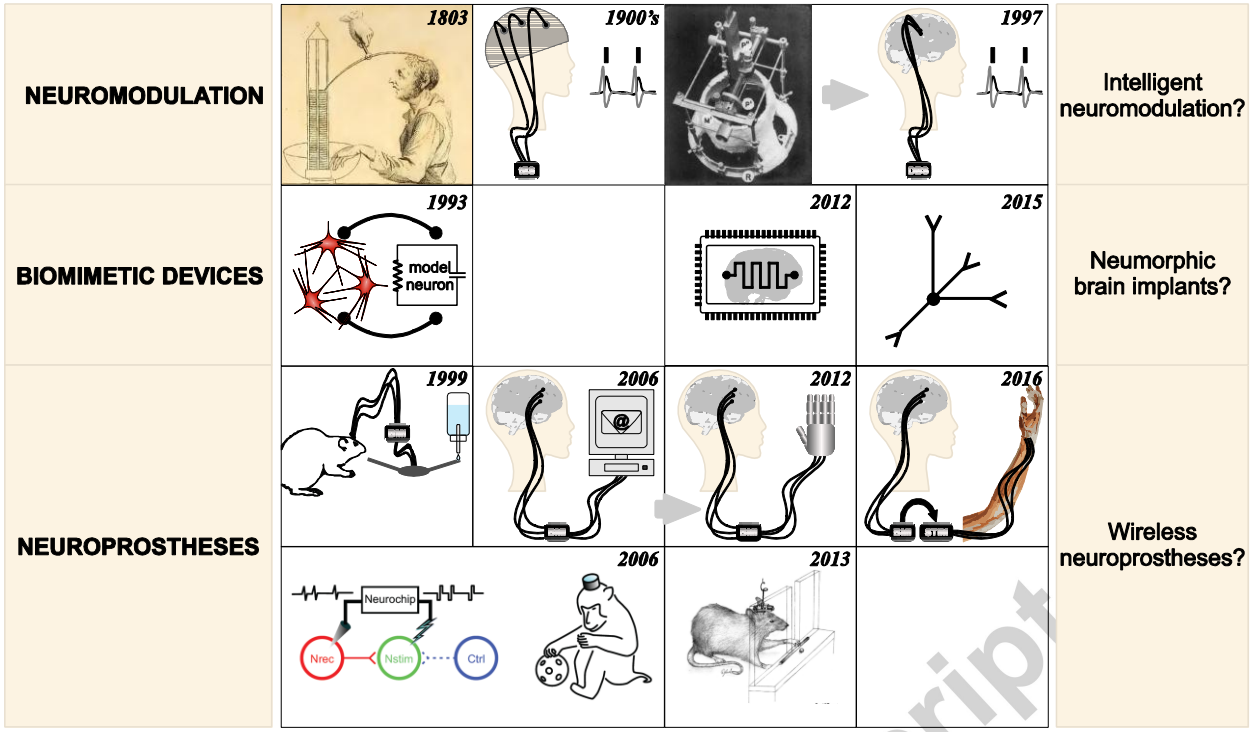
NHTM Intelligent Biohybrid Systems ***Figure 2***



NHTM Intelligent Biohybrid Systems ***Figure 3***



NHTM Intelligent Biohybrid Systems Figure 4



NHTM Intelligent Biohybrid Systems ***Figure 5***