Defining Ecological Strategies in Neuroprosthetics

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Neurological disorders disrupt the equilibrium within the brain and spinal cord ecosystems. Ecology reuses, recycles, and reduces to help maintain the balance across ecosystems. Likewise, neuroprosthetics can help the brain help itself with ecoprosthetic designs that integrate the principles of the "three 'R's."

Nervous System Habitats

The word ecology derives from the Greek *oikos*, meaning habitat, and *logos*, science. Thus, ecology is the science of habitat. The CNS is a complex habitat wherein multifaceted nervous structures have been piled up during evolution. Each of these neural elements occupies dedicated niches that constantly interact to maintain the finely tuned balance within their ecosystem: the brain and spinal cord.

Natural ecosystems combine multiple habitats arranged in horizontal and vertical stratifications that are both autonomous and interdependent. Similarly, the CNS is an assembly of modular subsystems that combine high-density local circuits and long-range connectivity. Local circuit organization enables a high degree of automaticity (Grillner, 2006). For example, the functional modules of the spinal cord are able to produce complex locomotor behavior without the need for brain input (Grillner, 2006; van den Brand et al., 2012). In fact, most of our daily movements escape our conscious attention. In turn, long-range connections and distributed connector hubs enable seamless communication between the subsystems, which is critical to maintain harmony across the habitats. Thus, our nervous systems seek both automaticity and interdependence to minimize the overall energy expenditure while allowing production of refined motor and cognitive behaviors. This apparent simplicity dissimulates highly complex interactions to maintain equilibrium within and between the ecosystems (Figure 1A).

Emergence of natural disasters or deprivation of resources leads to a sudden or progressive imbalance in the ecosystems that endangers living organisms throughout the stratifications. Similarly, acute or chronic dysfunction in one seemingly insignificant circuit or processing loop of our nervous systems can, and often does, lead to dramatic consequences that induce transient or permanent deficits in cognitive ability and motor control (Borton et al., 2013).

Our ecological footprint and its threatening impact on biodiversity, natural resources, and human health triggered environmental strategies to preserve our ecosystems. This awareness is changing the lifestyles in occidental countries, which have anchored the "three 'R's" principles in the regulation of individual and collective behaviors (Figure 1B).

The field of neuroprosthetics has too reached an age of maturity, when similar questions need to be addressed and ecological strategies defined and implemented to ensure the sustainability of ongoing and contemplated therapeutic developments.

Ecoprostheses

Neuroprosthetics emerged nearly 40 years ago. The discovery of key physiological principles underlying brain functions and advances in electronic and computer industries supported the invention of engineered systems that are chronically implanted in the body to treat neurological disorders. These neuroprosthetic treatments tap into spared elements of the nervous system to replace or restore lost or impaired neurological functions. Neuroprosthetic treatments conceived in the past century have translated into common medical practices that have improved the lives of countless individuals. Cochlear implants restore hearing in deaf people, deep-brain stimulation alleviates Parkinsonian symptoms, and spinal cord neuromodulation attenuates chronic neuropathic pain (Borton et al., 2013). These successes triggered a massive infatuation of scientists, engineers, clinicians, politicians, and the general public for neuroprosthetics, which unleashed substantial funding opportunities. This virtuous conjecture encouraged the frantic development of myriad neurotechnologies, leading to a exponential increase in the number of scientific publications that contrasts with the anecdotal number of new clinical applications (Wolpaw and Winter Wolpaw, 2012). Admittedly, recent neuroprosthetic demonstrators enticed our imagination with realizations that a few years ago were in the realm of science fiction. For example, paralyzed people have been able to operate multi-articulated prosthetic arms to execute activities of daily living using brain activity only (Collinger et al., 2013; Hochberg et al., 2012). However, these breakthroughs remain confined to the sophisticated environment of research laboratories, where highly skilled engineers continuously tune onerous, delicate, unaesthetic, and unpractical technologies.

How to explain the discrepancy between the acceleration of technological progress and the lack of concrete clinical dissemination? We argue that the insufficient ecology of current neuroprosthetic designs contributes to hindering the translation of new methods and devices toward patient benefit. In turn, an effective strategy to catalyze developments toward useful medical practices is to respect the principles of ecology. We first propose an analogy between the ecological concept of the three "R"s—reuse, recycle, and reduce—and neuroprosthetics. We then discuss the necessity to merge these concepts in patient-centered ecoprosthetic designs that reach clinical fruition at the fastest possible pace.

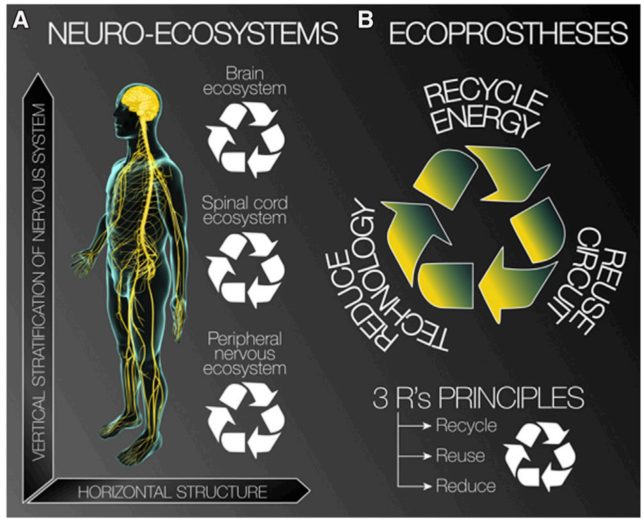

Figure 1. Ecoprosthetic Design
(A) The nervous system is organized in finely interacting ecosystems combining high-density local circuits and long-distance connections, similar to the horizontal and vertical stratifications of natural habitats, such as forests.
(B) Application of the three "R"s ecological principles to neuroprosthetic designs.

Reuse

CNS disorders typically spare the vast majority of nerve fibers and neurons in the brain and spinal cord. However, the loss of neurons, circuits, and/or connections disrupts the functionality of spared neural elements and leads to multifaceted adaptations of their properties. For example, a spinal cord injury physically disconnects the brain from some or all of the neuronal circuits in the spinal cord. Functional and anatomical cartographies of cortical territories projecting to denervated regions documented pronounced reorganization of these neuronal networks. These adaptive changes, termed homeostatic plasticity, contribute to reestablishing the balance within brain ecosystems (Davis, 2013). Likewise, a dramatic remodeling of neurons, fibers, and synapses takes place within denervated spinal segments, below injury. However, these responses are maladaptive and often lead to neuronal dysfunction, spasticity, and chronic pain—an ensemble of neuropathologies that significantly impact the quality of life for spinal cord-injured individuals.

Neuroprosthetics has deployed two strategies to reuse spared neuronal elements, broadly divided into replacement and restoration strategies (Borton et al., 2013). Replacement primarily refers to the field of brain-machine interface. These interventions exploit sensing neural interfaces that are plugged into spared brain regions to read neuronal activity. Translation algorithms map features decoded from brain signals to intended prosthetic actions. Brain-machine interfaces have enabled healthy and paralyzed people to control sophisticated devices including computers, robots, and prosthetic arms (Collinger et al., 2013; Hochberg et al., 2012).

Restoration refers to neuromodulation therapies. These interventions exploit pharmacological, electrical, and optical neuromodulation paradigms to write into the brain and spinal cord in order to regulate dysfunctional circuits or reawaken dormant neuronal networks. For example, dopamine precursors and deep-brain stimulation of the basal ganglia circuitry have become common therapies to alleviate cognitive and motor symptoms associated with Parkinson's disease. Electrochemical neuromodulation has also shown the ability to transform spinal locomotor circuits from dormant to highly functional states after injury. The combination of a monoamine replacement therapy and electrical stimulation applied over the dorsal aspect of lumbar segments restored full weight-bearing locomotion in rats with complete spinal cord injury (van den Brand et al., 2012). Electrical neuromodulation of lumbar segments also improved standing and restored supraspinal control of movements in paraplegic individuals (Angeli et al., 2014). The mechanisms through which neuromodulation therapies mediate functional benefits remain elusive. The underlying physiological principles are likely distinct for each neurological disorder, neuromodulation modality, and anatomical location (Lozano and Lipsman, 2013). However, neuromodulation therapies all have in common that they mediate immediate effects through their direct or indirect influences on anatomically intact but dysfunctional neuronal elements—these therapies reuse spared circuits.

Augmented Reuse

Various replacement and restoration strategies reuse spared neural elements that have lost their output communication channels or have become isolated from the rest of the habitat. Nevertheless, the amount of reused circuits and connections represents a fraction of the vast reservoir of preserved brain and spinal cord regions. For example, even the most sophisticated brain-machine interfaces leveraged fewer than 300 neurons located in a small patch of cortex to interpret the individual's intended motor action. Neurotechnology capable of stimulating and recording large-scale brain activity wirelessly is becoming available for basic research and clinical applications (Yin et al., 2014). Therefore, a network of bidirectional neural implants covering functionally distinct brain regions is likely to equip brain-machine interfaces with more natural, sensorized, stable, and expanded control capacities. This ecological approach requires a more profound knowledge of neural processes underlying cognition, motor planning, and execution. To this end, the Human Brain Project (https://www.humanbrainproject.eu/) and the BRAIN Initiative from the National Institutes of Health (http://www.braininitiative.nih.gov/index.htm) may well expand the range of available options to reuse circuits in ecoprosthetic designs.

The same reasoning applies to neuromodulation therapies. For example, electrical neuromodulation of the spinal cord has mediated significant improvement of locomotor functions in animal models (van den Brand et al., 2012) and humans (Angeli et al., 2014) with spinal cord injury. However, existing neuromodulation therapies deliver stimulation to restricted spinal cord locations and remain constant throughout gait execution, regardless of the subject's intention or the current locomotor state. Walking requires the activation of spatially distributed spinal motor circuits following precise temporal sequences (Grillner, 2006). Accordingly, spinal neuromodulation therapies delivering stimulation at the correct location and with the correct timing to reproduce the natural dynamics of spinal motor circuit activation are likely to mediate superior facilitation of locomotion after neurological disorders. This approach is ecological, as the goal is to reuse the largest possible amount of spared circuits while minimizing the overall amount of injected energy at any given time. The same principles apply to a wide spectrum of neuromodulation therapies. This awareness has motivated the ElectRx program of the Defense Advanced Research Projects Agency (http://www.darpa.mil/newsevents/releases/2014/08/26.aspx). This program, which is part of the BRAIN Initiative portfolio, aims to develop intelligent pacemakers that personalize neuromodulation therapies through closed-loop control of stimulation parameters.

Recycling

Neuroprosthetics integrate the concept of recycling along two timescales. The first strategy, which produces immediate therapeutic effects, consists of recycling energy within neuronal circuits. The second, long-term strategy seeks to recycle spared circuits and connections into de novo elements to prevent waste of potentially useful neuronal material.

Excessive use of natural resources by a restricted group of individuals can exhaust habitats. In Galapagos, the gluttony of marine iguanas has depleted commercial fish, destroyed marine environments, and crippled the local community. Similarly, schizophrenia or obsessive-compulsive disorders are in part due to excessive activity in restricted brain regions or specific processing loops. While disparate in their etiologies, these neurological conditions share comparable disorders of circuit function, also termed circuitopathies (Lozano and Lipsman, 2013). In consequence, neuroprosthetics responded with a common methodology: the delivery of energy into pathogenic circuits to dissimulate abnormal activity or scramble error messages. This surgical approach, primarily based on deep-brain stimulation, aims to recycle energy throughout unbalanced ecosystems in order to recalibrate circuit dynamics. According to https://www.clinicaltrials.gov/, there are nearly 100 ongoing clinical trials that are exploring the impact of deep-brain stimulation for alleviating detrimental effects of many neurological disorders, including major depression disorder, obsessive-compulsive disorder, chronic pain, and dystonia.

Natural catastrophes can devastate lands and dwindle resources. For example, a forest fire can extinguish the majority of habitats across a broad landscape. However, these catastrophic events also offer the opportunity to recycle spared elements in order to rebuild ecosystems. Likewise, traumatic injuries, cerebral infarction, and other sudden neural damage open a window of opportunity for enhanced neuroplasticity, which can mediate extensive restoration of functions after moderate insults. Currently, neurorehabilitation is the only common medical practice to harness the potential for neuroplasticity after neurological disorders. However, neuroprosthetic interventions can boost activity-dependent neuroplasticity when delivered during training. For example, robot-assisted gait rehabilitation enabled by electrochemical neuromodulation of spinal circuits promoted extensive and ubiquitous remodeling of spared neuronal connections after severe spinal cord injury. This neuroprosthetic rehabilitation reestablished supraspinal control over refined locomotor movements in otherwise paralyzed rats (van den Brand et al., 2012). Neuroprosthetic systems have also been integrated in the rehabilitation of upper limb functions after spinal cord injury or stroke (Dimyan and Cohen, 2011). In all these applications, the neuroprostheses introduce energy into the brain, spinal cord, or muscles to increase activity and thus augment neuroplasticity. The resulting circuits and connections differ from those of the original ecosystem—they are recycled—but they effectively improve functionality throughout the habitats.

Augmented Recycling

Delivery of energy into CNS structures alleviates pain and ameliorates cognitive and motor deficits after various neurological disorders. However, current approaches remain empirical. Neurologists tune the locations and parameters of stimulation based on visual observations. After titration, the patient has no or very limited control over stimulation features. The amount of injected energy is not adapted to the current state of pathogenic circuits or to the intended behavior. This brute-force approach not only results in a waste of energy, but also fails to exploit the full therapeutic potential of these interventions. Instead, automated closed-loop control systems based on detection of pathological neural activity yield great potential to optimally titrate therapies to meet dynamic, patient-specific needs (Rosin et al., 2011). Brain-machine interface technology offers the opportunity to incorporate brain signals into closed-loop stimulation algorithms. The user regains a direct access to the onset and adjustment of neuromodulation therapies. Preliminary experiments suggest that electrical stimulation protocols guided by online extraction of motor intention enhance neuroplasticity and recovery after stroke (Biasiucci et al., 2013). The industry has developed chronically implantable, closed-loop neuromodulation platforms with concurrent sensing and stimulation capacities to support the design of such ecoprostheses (Stanslaski et al., 2012). This ecological strategy is equivalent to smart grid technology platforms that automatically gather information about behaviors of suppliers and consumers to improve the efficacy and reliability of the production and distribution of electricity.

Reduce, Reduce, Reduce

The proliferation of bulky exoskeletons, phantasmagoric cyborgs, and "brain-to-X" interfaces are vivid examples of the waste of resources in neuroprosthetics.

While technological innovations are essential avenues to continue, a more immediate clinical impact may arise from reduction and refinement of current treatments.

Neural engineers have developed a flurry of non-invasive rehabilitation technologies including robots, stimulation paradigms, and brain-machine interfaces based on electroencephalographic signals. These neuroprostheses have enabled disabled people to control devices and to mobilize their muscles. Despite the potential of these neuroprostheses to enhance rehabilitation outcomes, they have yet to incorporate the toolbox of professional therapists. Likewise, electrical vehicles have become mature technologies that could compete with non-ecological transportations, but the lack of recharging infrastructures is preventing their adoption by consumers. Novel translational incentives are thus necessary to standardize neurotechnologies, educate care providers, and build consortiums capable of personalizing neuroprosthetic treatments at the bedside (Borton et al., 2013). While safety and monetary considerations remain the chief concerns in our modern societies, it is imperative that discoveries and technological developments populating the field of neuroprosthetics are delivered to patients at the fastest pace possible.

Deep-brain stimulation relies on dated technologies developed in the 1980s. The past two decades have brought major advances in electronic, computer, energy, and communication industries, which offer an arsenal of technologies to improve the efficacy and comfort of this treatment. These ameliorations include reduction of implant size, enhanced lead features, increased battery life, infrastructure to recharge batteries at hospitals and homes, closed-loop control of titration, improved stimulation algorithms, expanded external communication range, user-friendly communication interfaces, etc. These incremental improvements may contribute to increasing patient acceptance of implantable devices, intensifying the dissemination of these treatments. However, these developments require massive investments to establish the technologies and pass the regulatory hoops, which have refrained industries from refining their devices at a fast pace. Policy-makers responded to the reticence of industry to follow ecological principles with incentive measures. Funding agencies and academic circles promote the contrary. The culture and philosophy of decision-making basic scientists encourage the selection of disruptive ideas and innovations against pragmatism. Despite the grand goal of helping patients, research-funding committees reluctantly support incremental science or validation of technologies in a clinical scenario.

This oxymoron applies to the flourishing field of brain-machine interface. Basic discoveries and technology-driven breakthroughs have escalated. Highly publicized publications in high-impact-factor journals have rewarded the involved scientists, fostering academic careers in rapidly expanding neural engineering departments. However, the translation of these technologies into tangible patient benefits will require more than pairing an academic laboratory with a medical team. Academic systems will not reward translational neuroprosthetic scientists who are constrained to operate in large multidisciplinary teams that dissimulate individual contributions. Whose responsibility is it, then, to shepherd translation-oriented bench discoveries toward the bedside? We believe that this responsibility is incumbent upon neuroscientists in academy and hospitals who have discovered basic principles with translational potentials. These scientists have the more profound knowledge on the pros and cons of their findings. They have at heart to continue basic research to decipher the therapeutic mechanisms, which is essential for efficient translation from bench to bedside (Duda et al., 2014).

Involvement of basic scientists in translation requires the implementation of ecological principles throughout the bench to bedside, starting with the organization of universities. The academic system is educating countless engineers, doctors, and postdoctoral fellows who have only a few years to demonstrate their scientific and intellectual capacities. The brightest minds achieve basic discoveries or fabricate cutting-edge technologies, but then leave them behind in a no man's land. Reduction of seasoned investigator cohorts for the perennial stabilization of mature translational scientists is essential to bridge the ten-year gap separating basic discoveries and early-stage neurotechnologies to neuroprosthetic treatments (Alberts et al., 2014). This reduction implies a change in the academic culture. Reward systems must focus not only on the number and quality of publications, but also value the translational impact of neuroscientists, their patent portfolio, and even their ability to commercialize medical devices (Sanberg et al., 2014). This unconventional distribution of human resources necessitates dedicated translational hubs and novel funding mechanisms. These research infrastructures must gather neuroscientists, neurologists, neurosurgeons, and neuroengineers who partner with leading industries, medical device experts, patent specialists, and regulatory bodies (Duda et al., 2014). A few initiatives are emerging to support such translational efforts. For example, the Swiss entrepreneur and philanthropist Hansjörg Wyss donated unprecedented single endowments to establish translational biomedical centers in Boston, Geneva, and Zurich. These centers provide high-end research infrastructures, skilled human resources, and industrial connections to accommodate selected translation-oriented basic research projects. The mission of these centers is to bridge the difficult in-between step separating basic discoveries from viable neurobusiness.

Merging the Three "R"s to Reach Clinical Fruition

We sought to establish parallels between ecological principles and neuroprosthetic designs. We proposed illustrative examples to reuse circuits, recycle energy, and reduce technology for the development of useful patient-centered ecoprostheses. These provocative analogies are the biased views of a basic neuroscientist lost in translation and a functional neurosurgeon frustrated by translational roadblocks who have joined forces to fertilize neuroprosthetic platforms in the Swiss health valley. Our reflections and struggles led us to believe that the systematic integration of the three "R"s principles in neuroprosthetic treatment designs and decision-making policies may help to accelerate clinical fruition. But challenges lie ahead. Without a drastic change in scientist mindsets, academic reward system, research infrastructures, stakeholders' mentalities, and funding mechanisms, the sum of accumulated neurotechnologies and knowledge will not result in concrete patient benefits.

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