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Synthetic Neurobiology for Brain Circuit Engineering

Ugwu Okechukwu Paul-Chima, Alum Esther Ugo and Okon Michael Ben

Department of Publication and Extension Kampala International University Uganda

ABSTRACT

Synthetic neurobiology is revolutionizing our ability to understand and manipulate brain circuits with precision. This field combines genetic engineering, molecular biology, and advanced imaging techniques to introduce novel tools like "neurobots" and "synthetic synapses" into living mammalian brains. These innovations enable high spatiotemporal resolution control over specific neural cell types, offering insights into the biophysics of neural circuits. This paper explores the fundamentals of brain circuit engineering, the development of tools such as optogenetics and chemogenetics, and their applications in neural prosthetics and brain-machine interfaces. Furthermore, it discusses the ethical and societal considerations that accompany these advancements. The potential for these technologies to transform neuroscience and medicine is vast, promising significant strides in brain circuit repair and regeneration.

Keywords: Synthetic Neurobiology, Brain Circuit Engineering, Neurobots, Synthetic Synapses, Optogenetics.

INTRODUCTION

The challenge of understanding the transfer function of (biological) neural circuits and the primary means to meet this challenge necessitates the development of a new toolset that can be used to reversibly and with high spatiotemporal resolution manipulate the biophysics of defined neural cell types in a fully behaving organism. Here, we describe the approach of using targeted genetic manipulations to introduce "neurobots" and "synthetic synapses" into the brains of living mammals, thereby providing a direct means to understand and modulate the operation of neural circuits as systems by deconvolving them into causal sub-circuits of specific cell types with biologically defined relationships to each other [1, 2]. Repetitive or sustained imaging of neural subpopulations is required for the biophysical study of a dynamic neural circuit. The establishment of a genetic imaging toolbox has a significant advantage over conventional molecular imaging in that the cell-type specificity in the activity of interest is introduced by genetic elements expressed in the target neural cells, allowing for stable and high count-rate biophysical measurements without externally administering contrast agents. For instance, genetically encoded optical activity indicators allow for precise spatiotemporal definitions of the cascade of cellular events associated with neural activities [3, 4].

OVERVIEW OF NEUROBIOLOGY AND BRAIN CIRCUITS

Multifaceted interactions among billions of neurons and glia result in the formation of brain circuits that process, store, and produce an output based on sensory inputs. The brain controls body functions and also supports cognitive processes that allow us to understand and communicate with the environment. Understanding the structure and function of the complex network, which includes trillions of synaptic connections, is an inherently fascinating question that has important medical implications. Neuroscience research is devoted to understanding how brain circuits form and function, at the levels of both anatomy and physiology. From the perspective of clinical neuroscience, it is clear that although many human neurodevelopmental, psychiatric, and neurodegenerative disorders are associated with the malfunction of specific brain regions, pinpointing the malfunctions in a specific circuit has been proven to be more challenging - but also particularly important, in both basic research and, ultimately, for the development of targeted therapeutic strategies [5]. The frontiers of molecular biology and systems biology have greatly enhanced our understanding of the principles that operate the circuit, providing precise molecular and cellular tools that can be applied to the investigation of specific circuits. At the development level, studies conducted in lower organisms also contributed to our understanding of how neuronal identity is determined and how synapses can form. These studies also introduced us to the general question of how brains compute. At the other end of the spectrum, human brain imaging and animal experiments have yielded important insight into high-level brain functions, complementing what we have learned from studies using in vitro preparations. Most of the specific functional properties that are associated with the circuits, like for example how movement coordinates across limb segments or how the hippocampus supports navigation, have been elucidated using animal experimentation. Overall, mice have proven to be particularly important for [basic] studies, not only as a model for the investigation of human brain organization and functions but also because the mouse brain is amenable to real experimental manipulation - permitting the insertion of "smart sensors" to directly record circuit activities [6].

FUNDAMENTALS OF BRAIN CIRCUIT ENGINEERING

A fundamental question of brain science is how the brain circuit, which is composed of a huge number of nerve cells with intricate connections, achieves the brain's function. This question is, of course, a scientific problem, but it is interesting that it should be very closely related to a problem of inverse estimation of the function or computational structure of interest from its input-output relationship. The brain circuit of particular interest to us is that of the retina, mediating visual perception. It is challenging to solve this kind of engineering problem using the original structure being developed through the long process of evolution, which may not be the optimal structure in the sense that the output function is the simplest or most directly engineered to implement. Neuroscience has been developed as experimental empiricism attempting to uncover actual brain function. But this era is coming to an end [7]. The fundamental principles underlying brain function are being unveiled one after another. Engineers can now implement the architectures possessed by the brain circuit in a computer and actually realize them in hardware in combination with state-of-the-art semiconductor technologies. For instance, on the computational neurobiology side, the VLSI (Very Large Scale Integrated Circuit) implementation of adaptive synapses and neurons, as well as real-time learning of air response, is being reported. This technology potentially allows the creation of sensory processing systems based on a neuromorphic large-scale neural circuit. These implementations are possibly used as building blocks in the design of hardware intelligent systems with bio-inspired perceptual capabilities. Furthermore, it has been hypothesized that the nervous system has a great capacity for adaptation in order to preserve its natural robustness. This can be exploited by means of plastic receptive fields and neurons. Exploiting also the brain plasticity, a hardware intelligent readout can be built. These achievements are extremely significant as a success in the implementation of VLSI neural circuits for brain-inspired perception, allowing to reduce power consumption and to improve the system real-time response [8].

NEURONAL COMMUNICATION AND SIGNALING

The nervous system consists of very many nerve cells which talk to each other in complex ways. It is an electronic system, based on the passage of messages from one cell to another as they talk to each other. The passing of messages within the nervous system is how the body communicates with itself. Neuronal communication is not the same as communication between people: when cells in the body communicate with each other they pass electro-chemical signals. These signals occur quickly, because they travel using the nerve cells at speeds of meters per second and not at the speed of sound like sound waves. In fact, the passing of electrical messages within the cells of the nervous system is the fastest form of communication in the entire body [9, 10]. Much of the nervous system is concerned with behavior; motor activity is brought about by the muscles and mediated by signals from the brain to peripheral muscle through motor nerves. Sensory and motor nerves are bundled together to create the spinal nerves which transmit messages to and from the spinal cord. Each nerve in the body is surrounded by a membrane that carries two main types of signals. Sensory neurons pass signals from the body to the brain, and motor neurons communicate from the brain to the muscle. These signals are simple in the sense that they contain information about only a specific part of the nervous system. However, they can contain a lot of information about that part of the nervous system [11].

TECHNIQUES AND TOOLS IN SYNTHETIC NEUROBIOLOGY

Technological development is a powerful driver in the neurobiological sciences. Most recently, the development of molecular, genetic, and imaging technologies led to a revolution in cellular neuroscience. The development of these enabling technologies continues at a rapid pace. In this section, we highlight projects in the Synthetic Neurobiology Group that are driving the development of new or improved molecular/cellular technologies for the manipulation of neural cells. These technologies are being employed to help build neural circuits that function in a predictive and reliable manner [12]. The Nanoscope project aims to create a toolkit that will enable in vitro and in vivo molecular reprogramming of the activity level of a small number of cells containing a desired molecular tag through the non-invasive delivery of user-specified quantities of bioactive molecules. The project is developing molecular techniques for delivering specific effector molecules to a living cell in order to manipulate the dynamics of the native and artificial signaling and regulatory networks that mediate endogenous cellular functions. Using molecular regulatory logic to understand the dynamics of canonical signal transduction pathways that control specified cellular states, it is designing and implementing computationally predicted molecular feed forward systems that enable temporal, spatial, and quantitative control of user-specified phase and amplitude modulation of a canonical signaling pathway. In the Nanoscope toolkit, molecular controllers that function in vitro and in vivo will be developed, tested for target cell selectivity, and combined with external devices for delivery in vivo [13].

OPTOGENETICS AND CHEMOGENETICS

In recent years, optogenetic and chemogenetic technologies have been transformative for the study of brain circuit function. These advances enable specific subtypes of neurons or specific projections or synapses to be activated or suppressed. This allows causative assessments of how the activity of specific circuits might contribute to behaviors or cognitive function. For optogenetics, Drosophila provide some of the earliest demonstrations, using the halorhodopsin or channelrhodopsin microbial transgenes to modulate neural activity. By expressing the light-activated ion channels in specific classes of neurons, it was possible to control the fly's locomotion, olfactory response, wing flapping, and courtship, among other behaviors. These studies opened up the possibility for using light to probe neural circuits in vivo, with high spatiotemporal accuracy [14]. The discovery and development of channelrhodopsins as a tool for using blue light to stimulate action potentials was made in Drosophila. In 2005, Ed Boyden and Karl Deisseroth engineered mammalian neurons to express channelrhodopsin-2 (ChR2), and demonstrated that by shining blue light on these cells, they could elicit action potential firing. Furthermore, using very fast pulse sequences, they could achieve temporal patterning of the neural output. Since then there has been an explosion of tools created from other species, the upregulated cycle time of the microbial opsins increase the relevant frequency to that 'blinking' threshold [15].

APPLICATIONS OF SYNTHETIC NEUROBIOLOGY

We are on the verge of having sufficiently comprehensive models and control systems of neural circuits to perform functional reprogramming of brain circuits in the mouse, in the service of brain regenerative medicine. These new tools are moving us much closer to being able to repair and regenerate complex neural systems than we have been in the past. We anticipate that this class of neuromodulatory and neurotransplantation tools for non-human animals will provide the foundation for developing a practical and clinically relevant new field of synthetic neurobiology [16]. In the short term, we expect that this field will have immediate preclinical application in understanding the mechanisms of neuromodulatory reprogramming of neural systems, and in the use of optogenetic neurotransplantation for understanding connections between cell types or as a potential therapy for neurodegenerative conditions. In the medium term, we anticipate that synthetic neurobiology will complement the development of organic therapies with artificial modifications to the neural signal transduction pathways that can be deployed on [17]. The last several years have seen the development of a set of tools that enable the genetic silencing of neural circuitry without causing lasting changes in that circuitry. This new class of tools relies on the introduction of light-activated molecular "tools" into neurons that are normally sensitive to light. With a short light pulse, these tools can be made to transiently change the electrical properties of the cells in which they are resident [18].

NEURAL PROSTHETICS AND BRAIN-MACHINE INTERFACES

Bioelectronic technologies for the brain – neural prostheses, brain-machine interfaces, deep brain stimulators for Parkinson's disease – have all had some success in both animals and humans, but all suffer from the drawback that they are designed to be used 'on top' of the brain. At the outset, synthetic circuit electrophysiology and other techniques for sensors, actuators, and integration will be very valuable in speeding our understanding of the brains of animals, humans, and AI. Essentially, the signal intelligence here is in algorithms, which decode the measurable electrophysiology of the nervous system into signals that can be used to control some external device. While these algorithms are quite sophisticated, they are a poor substitute for a neurobiological 'design', in other words, a circuit, which can make decisions, adapt, or modify itself on the fly. The reason the current technologies do not involve neurobiological circuits, but rather operate in a cognitive or motor feedback loop, is that we generally have little understanding of the circuits that generate those physical, chemical, or electrical signals [19]. Neural prostheses and brain-machine interfaces (BMIs) seem a likely location for an early PSC intersection, in part because they have the potential to dramatically affect the lives of people who have lost the ability to move. The goal is to implant a set of electrodes that are capable of both reading and writing information at a very high bandwidth into and out of the nervous system. Typically, these involve a set of electrodes on the brain's surface for sensing and another set for stimulation, often placed on the brain's motor or sensory parts. The traditional target of neural prostheses is to produce a solution to otherwise intractable conditions such as paralysis, blindness, or stroke. The fact that the sensory recording and motor output circuits are fundamentally distinct is occasionally obscured by the fact that the central circuitry between them – the motor cortex – receives an enormous input from the somatosensory cortex [20, 21].

ETHICAL AND SOCIETAL CONSIDERATIONS IN BRAIN CIRCUIT ENGINEERING

As the progress in the development of synthetic biology for brain circuit engineering continues to accelerate, we have both the luxury and the responsibility to consider the ethical aspects of the science, as well as its societal impacts. How can society safely control and appropriately regulate this emerging field? To address ethical and societal considerations, we invited leading bioethicists, biologists, clinicians, and legal scholars working in the fields of synthetic biology and cognitive neuroscience for a workshop on "Breaking a Wary Peace: Toward a Social Ethics of Synthetic Neurobiology," followed by a broader panel discussion. These experts identified a wealth of ethical considerations and identified several areas where training and support would have a considerable impact [22]. During the workshop, much of the discussion revolved around two-mode ethical issues. First, ethical issues arising at the bench during the development of the technology, and second, ethical issues that arise after the fact, during the application of the resulting technology. In addition, the experts identified knock-on ethical issues that stem from the changes in social structure or practice initiated by the use of synthetic neurobiology, as well as overspill considerations - concerns bridging multiple ethical modes. Finally, the scholars brought up certain areas ripe for increasing education and training. There should be concerns, of course, with every powerful new technology, particularly those that involve our selves and bodies, and especially our brains. What distinguishes the role of these technologies in brain circuit engineering is the extent to which this technological revolution requires us to question the very nature of what we consider wisdom, rationality, and even our humanness [23].

CONCLUSION

Synthetic neurobiology stands at the forefront of neuroscience, providing unprecedented tools for the precise manipulation and understanding of brain circuits. The integration of genetic, molecular, and imaging technologies has led to groundbreaking advancements in our ability to study and influence neural activities in vivo. These innovations pave the way for significant applications, from enhancing our understanding of brain functions to developing advanced neural prosthetics and brain-machine interfaces. As we move forward, the ethical and societal implications of these technologies must be carefully considered to ensure their responsible development and application. The future of synthetic neurobiology holds immense promise for both basic research and clinical applications, potentially transforming our approach to treating neurological disorders and injuries.

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