Neuroscience at MIT

By Vincent C.K. Cheung and Emilio Bizzi

The Brain and Cognitive Sciences (BCS) Department of Massachusetts Institute of Technology (MIT) is a place where science and engineering intersect. Housed under the roof of the recently built BCS Complex (MIT Building 46) (Figures 1 and 2), the largest neuroscience facility in the world, BCS investigators work closely with engineers both to elucidate neural mechanisms behind our cognitive activities and to apply their neuroscientific knowledge to improve treatments for diseases of the brain. Here, we discuss Edward Boyden and Emery Brown, two BCS faculty members who employ genetic engineering techniques and signal-processing methods, respectively, to further enhance their understanding of the mysterious brain. We also brief about how the idea of dimensionality reduction, an important engineering concept, has helped us theorize how the brain and spinal cord control simple and complex movements of our daily lives.

Where Medical Science and Engineering Intersect

Optogenetics: Manipulating Neural Circuit Components Using Light

The human brain is an extraordinarily complex neural machine comprising approximately 10^{11} neurons; an average neuron is directly connected to at least 500 other neurons, thus resulting in roughly 50 trillion different connections. Somehow these billions of nerves cells wire up during development and then function as a cohesive, but continuously changing, circuit that is

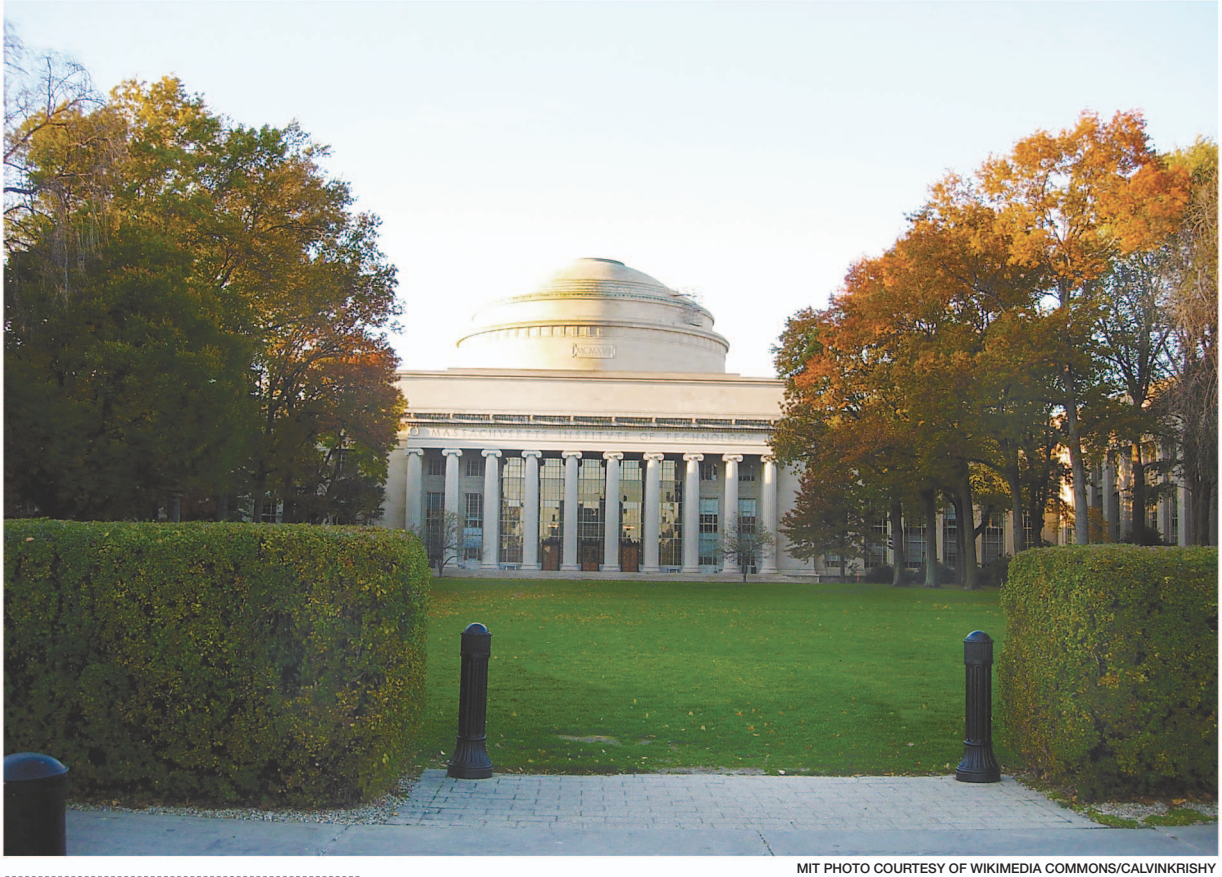

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FIGURE 1 A view from the reading room of the MIT BCS Complex, designed by the architect Charles Correa and opened in 2005. It is the largest neuroscience facility in the world. In the background is the Stata Center for Computer Sciences, designed by Frank Gehry.

responsible for our actions, feelings, memory, and thoughts. Adding to this complexity is the fact that there are thousands of neuronal cell types, each with different molecular, cellular, and computational properties. Neuroscientists trying to decipher the brain's circuitry are confronted with the challenge of selectively finding and then controlling individual circuit components embedded within a soup of entangled neurons.

The BCS Complex is the largest neuroscience facility in the world.

Neurons can fire action potentials both because a differential concentration gradient of sodium, potassium, and other ions is actively maintained across the cell membrane, and the cell membrane is lined with ionic channels, each of which opens for the selective passage of only an ion when the intracellular voltage lies within a particular range. Ultimately, a sine qua non for artificially activating or silencing a neuron is to have control over the conditions at which selective ion channels open to allow depolarization (or hyperpolarization, the opposite of depolarization) of the neuron's membrane potential. At BCS, Prof. Edward S. Boyden and his colleagues have been developing tools that would allow easy manipulation of complex brain circuits by turning on or off the electrical activity of specific, targeted neurons (for instance, neurons expressing a certain neurotransmitter or neurons in a particular layer of the cortex). Boyden observed that certain ion channels are light sensitive, in that they open and allow ionic passage only when they are exposed to light of certain frequencies. One such channel, called *channelrhodopsin-2* (*ChR2*), was originally isolated in photosynthetic algae, which use this channel to orient themselves toward light sources. Boyden and his colleagues realized that the *ChR2* gene can be artificially expressed in selective neurons using standard genetic engineering techniques, thereby making them fire only when exposed to light. This way the electrical behavior of a selective neuronal type can be easily and precisely manipulated, both spatially and temporally, just by controlling the characteristics of the light shining onto the neurons. This technique of manipulating genetically modified neurons using light has recently been referred to as *optogenetics* [1].

Optogenetic tools for activating or silencing neurons have become very attractive to neuroscientists for several reasons. Because the ChR2 and other light-sensitive opsins are very responsive and sensitive to light, researchers may drive the neurons in patterns that mimic the normal, physiological pattern of high-frequency neural activity. In addition, the gene for the channel can be expressed in selective cell types; this allows researchers to examine just one or several types of cells embedded within a heterogeneous neuronal population. Such a targeted activation would not be possible with the traditional technique of electrical stimulation, which delivers activation to all neurons surrounding the electrode regardless of cell type.

The use of optogenetics in nonhuman primates has also been explored recently by Boyden and two other BCS investigators, Ann Graybiel and Robert Desimone. Using

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FIGURE 2 The MIT BCS Complex is equipped with state-of-the-art research facilities, all built around this modern atrium.

a lentivirus vector, they delivered the *ChR2* gene to the frontal cortex of macaque monkeys [2]. They observed that *ChR2* was not only safely expressed in the cortex but could also mediate optically driven neuromodulation over many months. Their findings open up the possibility of using optogenetic methods in the future for cell-type specific intervention of neural circuits in the human brain for treating neurological and psychiatric diseases such as Parkinson's disease and major depression.

Probing the Mechanisms of General Anesthesia using Neural Network

Emery N. Brown is a medical doctor and a statistician by training. As a faculty member of the Harvard-MIT Division of Health Sciences and Technology and professor of computational neuroscience at the BCS, Brown directs the Neuroscience Statistics Research Laboratory whose research focuses on developing suitable statistical algorithms for analyzing neuroscientific data such as neural spike train recordings, electroencephalographic (EEG), and functional magnetic resonance imaging (fMRI) data. He and his laboratory members have been combining their engineering and quantitative skills with their clinical and physiological knowledge to tackle a wide variety of questions ranging from the dynamics of heart-beat regulation, the statistical properties of neuronal firing in the hippocampus, to the nature of the human circadian pacemaker through their analyses of different data using sophisticated signal-processing techniques. In addition to his role as a computational neuroscientist, Brown is a practicing anesthesiologist at the Massachusetts General Hospital (MGH). Naturally, he is also interested in studying how different drugs produce anesthesia, a very important topic in neuroscience whose elucidation may not only impact how doctors handle anesthetics but also shed insights on the neural underpinnings of human consciousness.

The technique of manipulating genetically modified neurons using light is referred to as *optogenetics*.

General anesthesia is a reversible condition characterized by the loss of response to painful stimuli, lack of subsequent memory of the events happened during anesthesia, immobility, and loss of consciousness. Ever since William T. G. Morton's first public demonstration of inducing general anesthesia using diethyl ether at MGH's surgical amphitheater (now known as the *ether dome*) in 1846, general anesthetics have been routinely administered in countless surgeries in the world. Yet, their mechanism of action is still a medical mystery. We now know that general anesthesia produces distinctive high-amplitude and low-frequency EEG patterns that, interestingly, resemble the EEGs from comatose patients, but not the EEGs recorded during sleep. In fact, in their recent review article published in the *New England Journal of Medicine*, Brown and his colleagues describe general anesthesia as "a reversible drug-induced coma," even though doctors usually "refer to it as 'sleep' to avoid disquieting patients" [3] (p. 2638). We also know that anesthetics produce the unconscious state by altering neurotransmission in multiple brain regions including the cerebral cortex, thalamus, and brainstem. Pharmacological studies have identified the Y-aminobutyric acid type A ($GABA_A$) receptor to be a major target of several anesthetics including the commonly used propofol. GABA, an inhibitory neurotransmitter, is released by interneurons that synapse onto a large number of excitatory output neurons in the cortex; thus, the enhanced $GABA_A$ inhibition effected by anesthetics like propofol can quickly inactivate multiple cortical regions for inducing unconsciousness.

Adding to the mystery of general anesthesia is the fact that anesthetics such as propofol, when administered at low doses, can induce behavioral and EEG manifestations of excitation, rather than sedation, despite the fact that they act on the inhibitory $GABA_A$ receptor. Brown and two of his collaborators, Michelle McCarthy and Nancy Kopell, at Boston University have recently attempted to understand this phenomenon of paradoxical excitation induced by propofol using a realistic neural network model. Published in the *Journal of Neuroscience* [4], their model includes hundreds of neurons, each of whose behavior is captured by a set of differential equations describing the dynamics of different membrane and synaptic currents. Propofol's actions are simulated by increasing the maximal conductance and the time constant of decay of the GABA current. They successfully reproduced paradoxical excitation in their model only at low doses of propofol. A careful analysis of the model reveals that the excitatory EEGs and behavioral changes may result from an interaction between the $GABA_A$ current and a slow potassium current that, at the network level, enables a switch from synchronous firing of interneurons to asynchronous firing. Such asynchrony, in turn, allows reproduction of the EEGs characteristic of propofol-induced paradoxical excitation. This study of Brown and his coworkers is an inspiring example showing how mathematical techniques can be profitably utilized for refining our understanding of biological phenomena.

Muscle Synergies: The Building Blocks of Movement

The ease with which we move every day belies the computational difficulty that our central nervous system (CNS) must overcome to generate even the simplest movement. For any given movement task, there usually exists multiple limb trajectories that can satisfy the task demands, and thus the CNS must somehow choose a suitable trajectory among many possibilities. Once the trajectory is set, the CNS must solve the inverse dynamics problem or the calculation of the joint torque required for executing a joint kinematic trajectory, which is computationally very intensive given that the vertebral limb is a system comprising multiple joints that are mechanically linked to each other. After joint torque calculation, the CNS

still has to translate the torque profile into a spatiotemporally precise pattern of activation for every muscle in the limb before movement can result. The human upper limb alone contains 52 muscles that represent 52 degrees of freedom to be specified and coordinated. The above description highlights the potential computational burden associated with movement planning and execution, and the immense volume of the space of possible motor commands that the CNS has to search through before arriving at a solution that translates a motor intention into a gracious movement. How the motor system circumvents such complexity and handles the large dimensionality of the search space have remained important questions in neuroscience.

The human brain is an extraordinarily complex neural machine comprising approximately 10^{11} neurons.

Since almost a decade ago, we have explored the idea that the CNS may simplify the computational complexity of movement production by activating groups of muscles together as individual units. Each of these groups, called a *muscle synergy*, represents a fixed coordinative pattern for the muscles within the group. Such groupings of muscles essentially limit the number of degrees of freedom needed to be specified and coordinated and, thus, significantly reduce the dimensionality of the search space. We and our colleagues have produced experimental evidence from both animals and humans, supporting that the CNS may produce motor commands for many muscles by linearly combining a small number of muscle synergies. Many of the synergies identified appear to be robust entities that stay invariant across a wide range of conditions, and thus the muscular compositions of these synergies are likely encoded by specific neural networks in the CNS. In much the same way as the 26 alphabets are the building blocks of the roughly 250,000 distinct words of the English language, or the four nucleotides, A, T, C, and G, are the building blocks of an infinite variety of genes in the genome, muscle synergies may be regarded as the fundamental building blocks available to the CNS for its flexible use for constructing diverse motor behaviors.

If muscle synergies are indeed robust, discrete modules used for motor control, one naturally wonders whether the networks organizing each synergy can be localized to a specific region of the CNS. Numerous experiments conducted in our laboratory using the frog spinal cord have demonstrated that the synergies for the frog hind limbs are very likely organized by the interneuronal networks of the spinal cord. This observation leads to the hypothesis that in humans, the intention for a voluntary action originating from the cortex is also translated into descending motor commands for combining synergies that are organized in the brainstem and spinal cord. Collaborating with the San Camillo Hospital in Venice, Italy, and, more recently, with Prof. Paolo Bonato of the Spaulding Rehabilitation Hospital in Boston, we have studied the muscle activation pattern of stroke patients with lesions in the motor cortical areas. We have shown that many synergies for the shoulder and upper-arm muscles used by stroke patients are very similar to those identified in healthy subjects, implying that the coordinative pattern of muscle synergies originates from networks downstream of the cerebrum [5]. We are now studying muscle synergies in stroke patients who show motor improvements after a rehabilitation intervention to see whether these synergies can be specific targets of reinforcement in a neurorehabilitation program.

Conclusions

Systems neuroscience seeks to establish causal relationships between the behavior of complex biological processes in the nervous system and the dynamics of the system's neuronal and molecular constituents. Owing to the tremendous complexity in the organization of the nervous system, many important neuroscientific questions can only be studied and addressed by using special technological tools developed originally for solving other engineering problems. We have highlighted three examples of utilizing engineering tools—transgenic techniques, artificial neural network modeling, and specialized factorization algorithms, respectively—for enhancing our understanding of the brain and spinal cord. There are certainly many more inspiring examples showing how neuroscientists and engineers can fruitfully collaborate at MIT and other institutions worldwide. It is apparent to many by now that the development of suitable technologies for studying the nervous system has become a rate-limiting step in the progress of the brain sciences. In the near future, engineers will certainly play an ever more important role in neuroscience, one of the most exciting frontiers of knowledge of this century.

Vincent C.K. Cheung (ckcheung@mit.edu) *and* ***Emilio Bizzi (ebizzi@mit.edu)*** *are with the Department of Brain and Cognitive Sciences and McGovern Institute for Brain Research, Massachusetts Institute of Technology, Cambridge.*

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