MBL

Catalyst

Biological Dis ery in Woods Hole

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THE BRAIN

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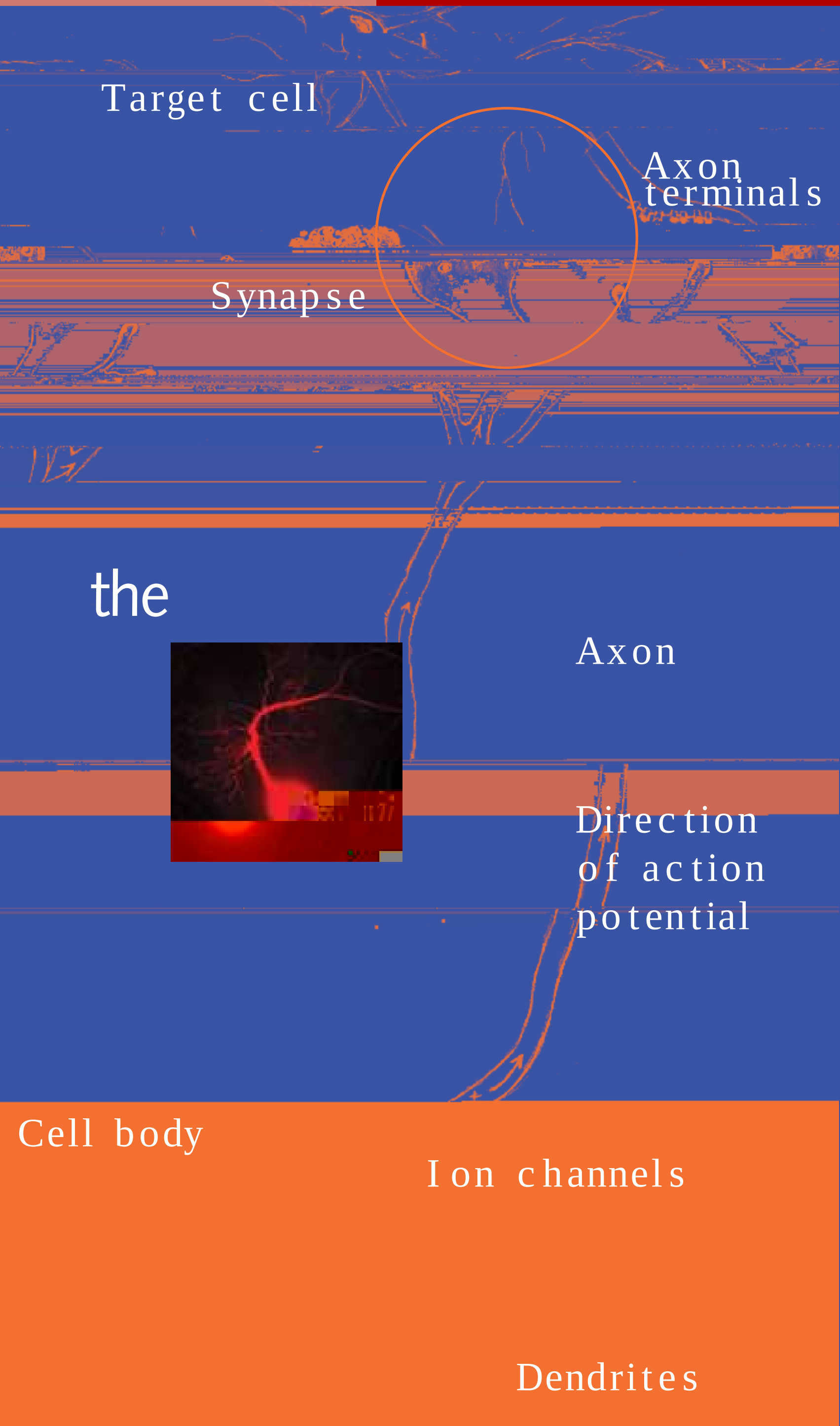
MBL ILLUMINATING the



How the brain works is one of the great mysteries of our time. Over the past century and in part at the MBL, scientists successfully detailed how neurons conduct electrical signals and "communicate." Through behavioral studies combined with brain imaging, they also discovered that each thought, perception, or feeling coincides with the frantic firing of neurons in a particular circuit or brain region. One set of neurons fires, and you taste an apple; another set fires and you feel joy, think of your child, or see the sky.

But despite heroic efforts, tracing the fine-scale, functional anatomy of the brain remains an enormous challenge, due to the sheer number (100 billion) of neurons it contains and the even more staggering number of interconnections. Discerning which neurons are electrically active, and in what sequence, is even more difficult, since they fire at millisecond-range speeds. Undeterred, neuroscientists are tackling

ANATOMY OF COMMUNICATION

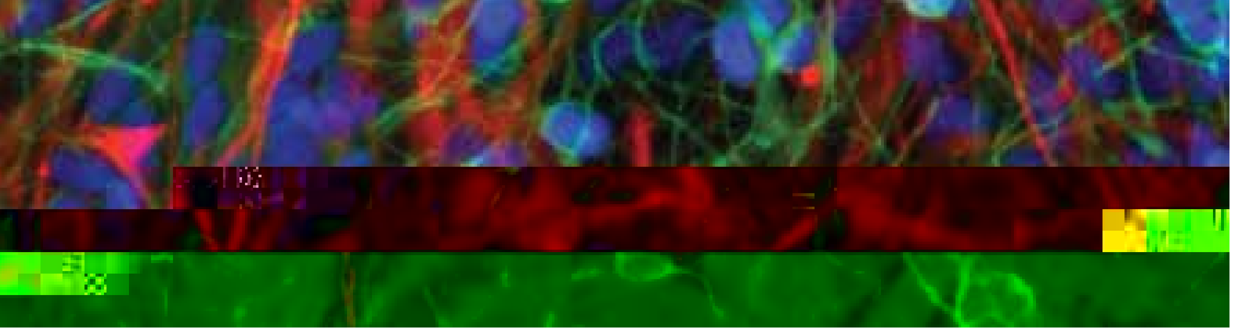
Neuron: from the Greek "bowstring, sinew." Basic unit of the nervous system, consisting of a **cell body** with two kinds of specialized extensions: one **axon** and (usually many) **dendrites**.

Axon or nerve fiber: tube-like extension of a neuron. Axons can be very long (e.g. from spinal cord to toe).

Dendrite: from the Greek "tree." Branched extension from a neuron body. Its membrane contains receptors that receive information from other neurons via **synapses**.

Action potential (or spike): propagation of electrical activity along the membrane of a cell. In most neurons this involves sudden influx of sodium ions followed by efflux of potassium ions, through **ion channels** in their membrane. Some cells fire 100 or more spikes per second.

Ion channel: protein embedded in the cell membrane that allows certain ions to cross the membrane. (Ions are atoms that have lost or gained one or more electrons.) The movement of (mainly) sodium, potassium, and calcium ions underlies electrical signaling in animal biology.



these major unknowns head on. The secrets of the brain, they believe, will be revealed through its connections.

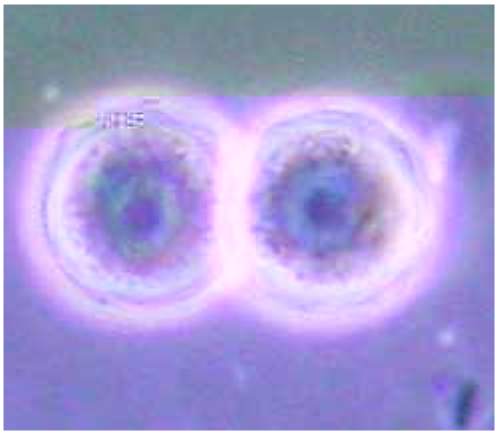
In the MBL's neuroscience community, as well, connections are all important. Hundreds of the field's top research faculty and students

The Neurobiology course studies the brain at the level of individual neurons and synapses. Both Ryan and Davis be-

scientists became keenly interested in the sensor. Across campus, and across the world, the Neurobiology course is "at the center of the neuroscience community," says faculty member Ryohei Yasuda, scientific director of the Max Planck Florida Institute.

Every five years, fresh co-directors take up the reins in each MBL summer course, updating its content to push the limits of knowledge and innovation. Add gifted research scientists serving as faculty; a select, interdisciplinary group of very sharp students; and $26 million in high-end research equipment loaned to the MBL by 140 vendors, and you get a transformative experience of scientific discovery, for students and faculty alike.

Evolution of Voltage-Gated Sodium Channels: The First 800 Million Years



Voltage-gated sodium channels are proteins in the membranes of neurons that rapidly open and close to allow a brief influx of sodium, initiating a nerve impulse. These channels underlie electrical excitability in all animals. Humans have 10 sodium channel genes and mutations in some of them cause epilepsy or other neurological diseases. Did sodium channels first evolve along with the nervous system? When did sodium channel genes increase in number, and what did this mean for humans? Answers to these questions are being found through the research of **Harold Zakon** of University of Texas, Austin, an adjunct scientist in the MBL's Bay Paul Center.

As reviewed in a recent article, Zakon's group discovered a gene for voltage-gated sodium channels in single-celled marine organisms called choanoflagellates, which are distant relatives of all animals. Since the common ancestor of animals and choanoflagellates lived 800 million years ago, sodium channels predated neurons, and were "recruited" by neurons as they evolved 600 million years ago in a jellyfish-like animal. Previously, the Zakon lab found that the number of sodium channel genes increased in tetrapods (amphibians, reptiles, birds, mammals) about 300-400 million years ago. This occurred during a period when many marine organisms became extinct. Our fish-like ancestors survived this extinction and prospered by leaving the water and colonizing the land. The brain increased its anatomical complexity at this time and Zakon believes that this, along with the increase in the number of sodium channel types, allowed the brains of our ancestors to perform more complex computations. (109: 10619-10625, 2012) •

Turtle Middle Ear is Specialized for Underwater Hearing

The turtle has been developed as a model organism for studying hair cells, specialized neurons of the vertebrate inner ear that sense sound, as well as balance and acceleration. Yet very little is known about turtle hearing sensitivity. In a recent study, Whitman Investigators **Jakob Christensen-Dalsgaard**, **Peggy Edds-Walton**, **Richard Fay**, and **Catherine Carr** and collaborators report that has a large, air-filled, tympanic middle ear that is specialized for underwater hearing. The auditory threshold for the turtle, they found, is approximately 20-30 dB lower in water than in air. This study, performed in collaboration with Darlene Ketten of Woods Hole Oceanographic Institution, adds to the understanding both of hair cell function and of the evolution of vertebrate auditory systems. (. . B: 279: 2816-24, 2012) •

First Map of the Bacterial Makeup of Healthy Humans is Published

Five years ago, the National Institutes of Health launched the ambitious Human Microbiome Project (HMP) to define the boundaries of bacterial variation found in 242 healthy human beings. More than 200 scientists nationwide recently reported the results, including **Susan Huse**, **Hilary Morrison**, and **Mitchell Sogin** of the MBL's Bay Paul Center. To analyze more than 5,000 samples of human and bacterial DNA, the HMP adopted state-of-the-art sequencing and analysis methods, some of which were developed at the MBL for the decade-long International Census of Marine Microbes. Perhaps not surprisingly, the HMP discovered that microbial distributions in the human body are not so different from those in ocean ecosystems. In both, microbial communities contain a few highly abundant bacterial types plus many, many more low-abundance types (the "rare biosphere"). The HMP also confirmed that in people, like in the ocean, which bacteria are abundant and which are rare varies from site to site. The common bacterium Bacteroides, for instance, can constitute nearly 100 percent of the microbes in one person's gut, yet be barely present in another's. "What this means is, there is not just one way to be healthy," says Huse. "There doesn't have to be one or two 'just right' gut communities, but rather a range of 'just fine' communities." Another key finding of the HMP is that nearly everyone, including healthy individuals, carries pathogens—microbes known to cause illness. Researchers now must figure out why some pathogens turn deadly and under what conditions, likely revising current concepts of how microorganisms cause disease. (486: 207-214; 486: 215-221; 7(6): e34242. doi:10.1371, 2012) •

Opening

A lively open house last July for the new Program in Sensory Physiology and Behavior drew scientists from all over the campus, which is just what it aimed to do. The PSPB provides a nexus for existing strengths in sensory biology at the MBL—especially for research on vision, balance, and hearing.

"We are forming a strong link between the MBL's resident laboratories in sensory biology and summer activities in this field, including at the Whitman Center, the Grass Laboratory, and in many of the neuroscience courses," says MBL Senior Scientist Roger Hanlon, who directs the PSPB. "The integration and interpretation of sensory information guides the lives of all animals and humans. There are many key questions in basic and applied sensory science to be addressed," he says, including treatments for human sensory disorders.

Judging from the mix of people at the open house, the program's goal of stimulating intellectual exchange and research collaborations through many channels (seminars, student and faculty residencies, outreach) had already begun. In the hallway, MBL Senior Research Scientist Richard Chappell, who studies the role of zinc in vision and disease, was chatting with Hanlon lab affiliate Robyn Crook, an evolutionary neuroethologist and squid expert. Encircling MBL Adjunct Scientists Enrico Nasi and Maria Gomez, experts on the electrical response of visual cells to light, were several students from the Universidad Nacional de Columbia whom they had brought to their MBL lab. Neurophysiologists from many corners of the MBL —Alan Kuzirian, Richard Rabbitt, Robert Baker—were rubbing elbows.

"The integration and interpretation of sensory information guides the lives of all animals and humans."

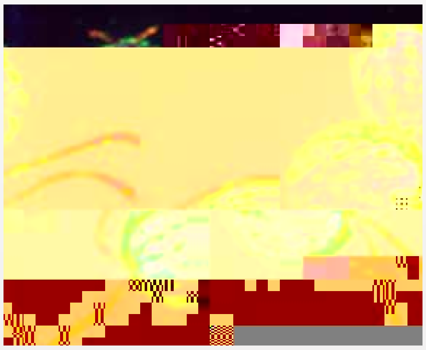
—Roger Hanlon, MBL Senior Scientist

"We especially encourage collaborations with people who take advantage of the unique resources at the MBL, and the marine organisms we can obtain," says Stephen Highstein, the program's associate director. Highstein is one of the world's foremost researchers on the inner-ear organs that govern balance and acceleration, and he has developed the toadfish and the turtle as model organisms for this purpose.

"There are many organisms at the MBL," says Felix Schweizer of UCLA's David Geffen School of Medicine. "And there is a lot to be learned from them. Many have functional and anatomical specializations that make it much easier to study certain research questions."

the Senses

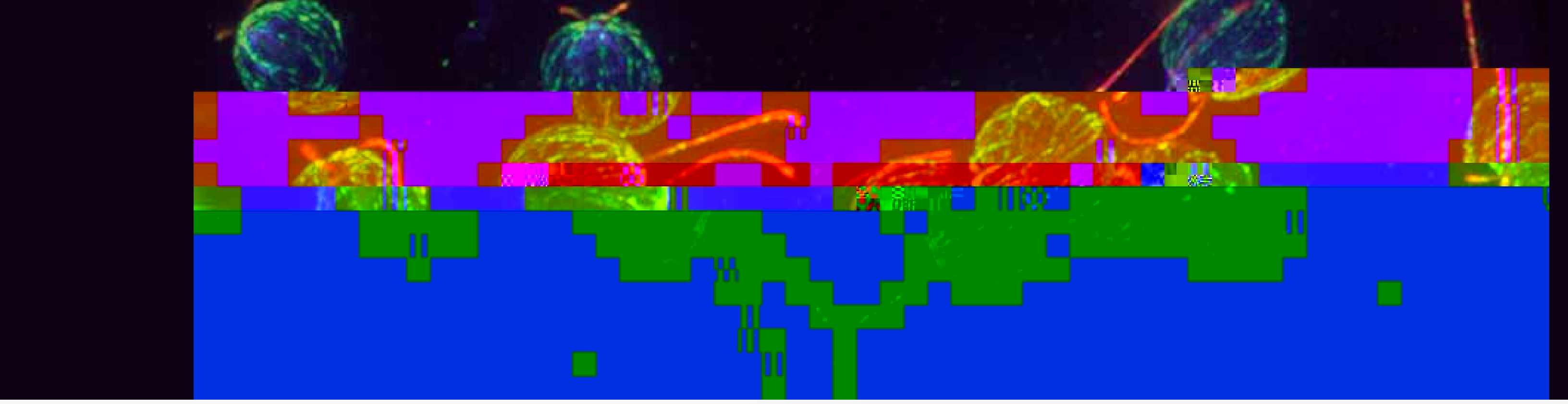
In terms of outreach, no one could have planned a more sensational kick-off for the PSPB than a video that went viral on the Internet. It came from one of those serendipitous encounters at the MBL that are often chalked up to the "MBL magic." In July, the program's first publication appeared, a Hanlon lab study that showed, for the first time, that squid have precise neural control of the iridescence cells in their skin. The authors [illegible]



familiar furnishing in the MBLWHOI Library is this elegantly penned motto of 19th-century zoologist Louis Agassiz: "Study Nature, Not Books." The wisdom of this phrase is often reproven, as in the serendipitous discovery of a green fluorescent protein (GFP) in jellyfish by Osamu Shimomura, now an MBL Distinguished Scientist, in 1961. Decades later, others turned GFP into a revolutionary tool for illuminating the workings of cells, one that brought Shimomura the Nobel Prize. Agassiz's motto still reverberates today, most recently in the form of a sensational technique that is taking neuroscience by storm: Optogenetics.

"Optogenetics is a revolution, and the MBL is in the midst of it," says George Augustine, a researcher and frequent course faculty member at the MBL since 1979. Barely ten years old, optogenetics is so promising that its discoverers are widely considered candidates for the Nobel Prize.

With amazing precision, optogenetics allows scientists to control the electrical activity of neurons simply by targeting them with beams of light. Besides being much less invasive than using electrodes—which has been the standard way to study neural activity since the 1930s—optogenetics allows scientists to turn on or off specific types of neurons in the brain (say, only those that produce dopamine), which is a huge advance. It throws open the door to pinpointing exactly which neurons and circuits cause specific human sensations, thoughts, and behaviors—and perhaps one day, to light-based therapies for mental and sensory disorders.



They were not prepared for how spectacularly well it would work. Using standard genetic engineering techniques, they inserted the Channelrhodopsin gene into mammalian neurons

MBL:

The **Gordon and Betty Moore Foundation** awarded a $2,258,548 grant to investigate microbial ecosystems at Axial Seamount, a deep-sea volcano in the North Pacific. Julie Huber is the principal investigator.t(BHbb0 AG7 Beybb bHe 0 -1.333 TD (‰ 34 Ž)-1

Accolades

The American Society for Cell Biology presented an award to the **Physiology course** "for its tremendous impact on developing the classical and modern eras of cell biology." The award was given in honor of the course's 120th anniversary.

The following members of the MBL community were elected to the National Academy of Sciences: **William Bialek**, faculty, Methods in Computational Neuroscience; **Karl Deisseroth**, alumnus, Methods in Computational Neuroscience, faculty, Neurobiology; **Gideon Dreyfuss**, faculty, Physiology; **Paul T. Englund**, emeritus Corporation member, alumnus, Invertebrate Zoology and Physiology, faculty and former director, Biology of Parasitism; **Roy Parker**, faculty, Physiology; **Mary Power**, alumna, Neural Systems & Behavior.

Senior Scientist **Jonathan Gitlin** was elected to the Institute of Medicine.

The following members of the MBL community were elected to the American Academy of Arts and Sciences: **Ben A. Barres**, faculty, Fundamental Issues in Vision Research; **Emery N. Brown**, alumnus, Computational Neuroscience, faculty, Neuroinformatics; **Sarah Elgin**, faculty, Physiology; **Margaret J. McFall-Ngai**, faculty, Microbial Diversity, Embryology; **Steven Siegelbaum**, faculty, Neurobiology; **Larry Simpson**, faculty, Biology of Parasitism.

Winfried Denk, faculty, Neurobiology, received the Kavli Prize in Neuroscience for elucidating the basic neuronal mechanisms underlying perception and decision. Denk shared the prize with Cornelia Isabella Bargmann and Ann M. Graybiel.

Whitman Investigator and Neural Systems & Behavior course alumnus **Richard Fay** received the Silver Medal in Animal Bioacoustics for pioneering studies of fish hearing by the Acoustical Society of America, the premier international scientific society in acoustics.

Gary Ruvkun, former director of the Biology of Aging course, and Victor Ambros were awarded the Dr. Paul Janssen Award for Biomedical Research. Ruvkun and Ambros identified and characterized the first microRNA, pivotal regulators of both normal and disease physiology. •

THE ULTIMATE OPTICAL

Voltage Sensor

A longstanding dream in neuroscience has been finding a way to monitor neural activity across the entire brain. In the 1960s, the only way to record a neuron's voltage was to stick an electrode in it, an approach limited to a few cells at a time. The person who changed all that is Larry Cohen of Yale University, who has been a near-constant summer presence at the MBL since 1962. "Larry is the original 'Mr. Light,'" says David Gadsby of Rockefeller University. "He pioneered the study of brain activity using electro-optical measures."

Cohen started his journey after co-discovering that when neurons fire, they undergo changes in light scattering and other optical properties. Perhaps a camera could record such changes, and use them as a proxy for electrical activity? The idea was "pretty far out," says Cohen's MBL colleague George Augustine. But it was evidently fertile, as functional neuroimaging is now a huge endeavor, at the MBL and around the world.

In 1973, Cohen, Vicencio Davila, and Brian Salzberg at the MBL successfully made the first optical recording of a leech neuron firing. They did this by bathing the neuron in a fluorescent dye. When the neuron fired, the fluorescence changed, and a detector captured the change. Since then, with many contributions from MBL researchers, various optical sensors have been introduced, the latest being genetically engineered ones that, in principle, can target specific neurons. Today, the race is on to design beest [illegible]

Treasures from the MBL's Archives

hen L.W. Williams first described the squid's nervous system at the MBL in 1910, he had no inkling he was launching a century of neuroscientific discovery. Little was known about how nerves work when J.Z. Young a quarter-century later suggested studying the squid, whose axons are "giant" compared to those in humans. By the late 1930s, MBL scientists like Kenneth Cole were putting electrodes inside the squid giant axon to measure electrical events associated with nerve impulses. Andrew Huxley (who died last May) and Alan Hodgkin pursued similar squid research in England. Using an improvement on Cole's electronics (the voltage clamp), they formulated their model of voltage-controlled nerve conductance to explain the nerve impulse. Hodgkin and Huxley won the Nobel Prize in 1963, along with John Eccles, who described nerve cell communication at the synapse. Each of these pioneers at some point worked at the MBL, and their intellectual descendants are still here today. As for the squid, it is now so familiar that it is valued for many

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In the Next *MBL Catalyst*

The MBL Turns 125

In celebration of the MBL's 125th anniversary in 2013, we will reflect on the laboratory's significant impact on the biological sciences and envision the next generation of inquiry and discovery.