Catalyst

Biological Discovery in Woods Hole

Founded in 1888 as the Marine Biological Laboratory

FALL 2014
VOLUME 10, NUMBER 1

IN THIS ISSUE

The Convening POWER of MBL IMAGING

MBL Catalyst

Fall 2014 Volume 10, Number 1

MBL Catalyst is published twice yearly by the Office of Communications at the Marine Biological Laboratory (MBL) in Woods Hole, Massachusetts. The MBL is dedicated to scientific discovery and improving the human condition through research and education in biology, biomedicine, and environmental science. Founded in Woods Hole, Massachusetts, in 1888, the MBL is a private, nonprofit institution and an affiliate of the University of Chicago.

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Images: *Inside cover:* Joan Ruderman (Bachrach Studios); *Sepia* skin with neurons in red (Trevor Wardill). *P. 1:* In a cell-free experimental system, interacting microtubule asters (green) recruit cytokinesis signals (Aurora B kinase, magenta) (Phuong A. Nguyen); *C. elegans* embryo, neuron in red (Ryan Christensen and Javier Marquina-Solis);Cell in anaphase, showing histones and 3D tracks of growing microtubule ends, color-coded by velocity (Eric Betzig); octopus (Roger Hanlon). *Pp 2-3: background*, *Sepia* skin with neurons in red (Trevor Wardill); *top to bottom*, Eric Betzig tests a microscope at the MBL (Tom Kleindinst); artificial tumor cluster generated using human *Schwannoma* cells expressing GPI-GFP (Shanta and Mark Messerli); Osamu Shimomura holding GFP that he purified from *Aequorea* jellyfish (Tom Kleindinst). *Pp 4-5: clockwise from top*, *C. elegans* embryo, neuron in red (Ryan Christensen and Javier Marquina-Solis); Hari Shroff and Amy Gladfelter (Tom Kleindinst); *C. elegans* embryo (Wicong Wu.) *Pp 6-7: clockwise from left*, Chemoreceptors in *E. coli* (Eric Betzig); luminescence (with intensity color-coded pink for high, blue for low) from living bacterial biosensors growing rapidly on a corn root tip in soil (Zoe Cardon); English Channel (Wikimedia); in a cell-free experimental system, interacting microtubule asters (green) recruit cytokinesis signals (Aurora B kinase, magenta) (Phuong A. Nguyen); eye of pyjama squid (*Sepioleidea lineolata*) (Roger Hanlon). *Pp 8-9: left to right*, A migrating fibroblast cell stained for actin (cyan) and focal adhesions (red). Focal adhesions are clusters of proteins that link the actin cytoskeleton to the extracellular matrix and are essential for the cell to sense its environment (Vinay Swaminathan and Clare Waterman, NHLBI/NIH); Clare Waterman (right) with (from left) Tomomi Tani, Shinya Inoué, and Rudolf Oldenbourg of the MBL's Cellular Dynamics Program (Tom Kleindinst). *P 10:* MBL Neurobiology course faculty member Darcy Peterka of Columbia University/HHMI (Tom Kleindinst). *Pp 12-13: clockwise from top left*, Erik Jorgensen with a "flash-and-freeze" instrument at the MBL (Daniel Cojanu); F.R. Lillie (MBL Archives); tomographic reconstruction of vesicles fusing in the active zone of a mouse hippocampal synapse (Shigeki Watanabe, Charité Universitätsmedizin Berlin). *P 14: left to right*, octopus (Roger Hanlon); Semester in Environmental Science Program student sampling sea grass (Tom Kleindinst). *P 15:* Students in 2014 MBL Physiology course (Tom Kleindinst). *P 16:* Amy Gladfelter (Eli Burkian, Dartmouth College) *P 17: top*, motor neurons in *Ciona* (MBL Logan Science Journalism Program); *bottom*, Louie Kerr, manager of the MBL Central Microscopy Facility (Tom Kleindinst). *Back cover:* MBL campus overlooking Eel Pond (Daniel Cojanu)

ABOUT THE COVER: In a cell-free experimental system, interacting microtubule asters (green) recruit cytokinesis signals (Aurora B kinase, magenta). See story on page 7. (Phuong A. Nguyen, Harvard Medical School and MBL)

Online extras: For full image descriptions, supplemental materials, and other information related to this issue, visit:

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From the Director

Dear MBL Friends and Colleagues,

When I first arrived at the MBL in the summer of 1974 to take the Embryology course, it was not even in my wildest thoughts that I might someday have the privilege and honor of joining the long line of distinguished MBL directors, which started with Charles Otis Whitman in 1888. In November, I completed my term as 14th MBL president and director, during which time the MBL formed a historic affiliation with the University of Chicago.

I have been extremely fortunate to have trained and taught at several remarkable institutions—Barnard College, MIT, Harvard Medical School, and Duke University—but, by far, the MBL is the institution that has had the most profound impact on me. As a student in one of the MBL courses said several years ago:

"Woods Hole is to scientists as Paris is to artists."

A lot of my most significant scientific work was done at the MBL, and many of my most important and long-standing professional relationships and personal friendships were forged in Woods Hole. The welcoming spirit of inclusiveness, the culture of sharing ideas, techniques, tools, and reagents, and the opportunities to interact easily with so many scientists from across the globe are unparalleled anywhere else.

Over the past two years, I have had the additional pleasure of working closely with MBL's year-round scientists and exceptionally dedicated support staff. Countless teams tackled scientific, financial, and structural challenges to the institution, while at the same time working to sustain and grow the MBL's flagship research and educational programs. Our colleagues at the University of Chicago have been thoughtful, energetic, and generous partners and we look forward to expanding and deepening our relationships at many different levels.

It seems fitting that my last Director's Letter for *MBL Catalyst* introduces an issue on microscopy and imaging. The history of the MBL is replete with cases in which major biological discoveries followed on the heels of revolutionary leaps in imaging technologies, which allowed scientists to see what once was hidden from view. One such case occurred at the MBL in the early 1980s, when video-enhanced microscopy was invented independently by Shinya Inoué and Bob and Nina Allen. I was a visiting scientist at the MBL then, working on cloning our newly discovered cyclin proteins and staying with my family in a cottage on Devil's Lane. I remember that my next-door neighbor, Mike Sheetz, would routinely work in his MBL lab until well after midnight, and then bang the screen door to his cottage as he returned home. That was the summer when—due in no small measure to the new video-enhanced microscopy—Mike and Ron Vale discovered the motor protein kinesin in Tom Reese's MBL lab. This was an extraordinary accomplishment that was recognized by the Lasker Award in Basic Medical Research to Mike and Ron in 2012. To this day, biological discovery at the MBL is propelled forward by its exceptional resources and culture of innovation in microscopy and imaging.

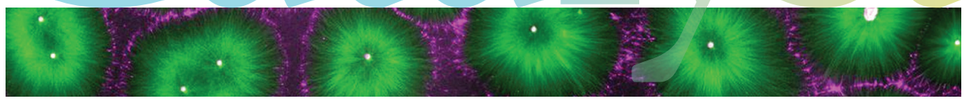
Thanks to Amy Gladfelter of Dartmouth College, our guest science editor for this issue, for helping to tell that story.

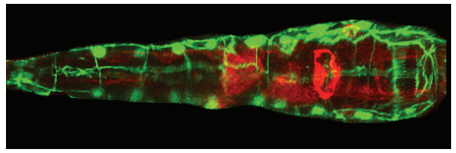
Joan Ruderman

Joan Ruderman, *President and Director*

In this Issue

Catalyst





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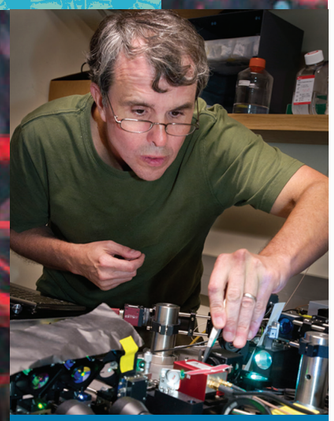
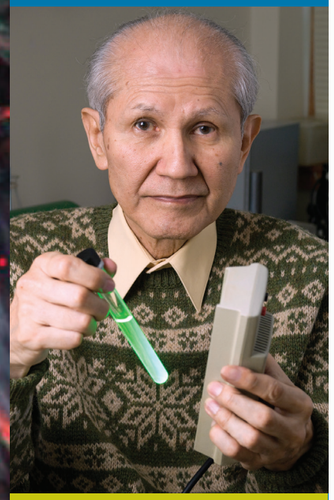
The Convening POWER of MBL Imaging



MBL Visiting Scientist Eric Betzig, 2014 Nobel Laureate in Chemistry for the development of super-resolution microscopy

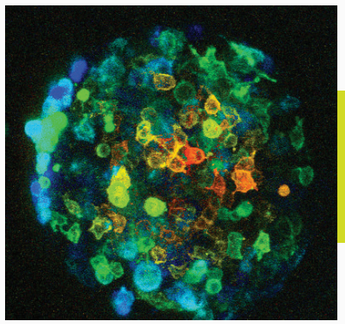


MBL Distinguished Scientist Osamu Shimomura, 2008 Nobel Laureate in Chemistry for the discovery of green fluorescent protein (GFP)

Eric Betzig is moving fast. Just weeks after winning a 2014 Nobel Prize in Chemistry for the "super-resolution" microscope he developed in 2006, Betzig is far more eager, in a phone conversation, to talk about his newest invention, the lattice light-sheet microscope. "The only thing that matters, in the end, is being able to answer a biological question that you couldn't answer by any other tool," Betzig says. As soon as he hangs up the phone, Betzig sends over breathtakingly sharp movies of cells in action—movies made with his brand-new "tool."

It's not just Betzig who is speeding ahead: the entire field of biological imaging is as well. "There's a revolution going on," says MBL Visiting Scientist William Green of the University of Chicago. "And the scientists taking part in it, some of the best in the world, tend to congregate at the MBL."

"We are in a golden age of microscopy, a really thrilling era of imaging," says MBL Adjunct Scientist Amy Gladfelter of Dartmouth College. "We are seeing things in much higher detail, much faster than we ever thought possible. We are rewriting our understanding of how cells, tissues, and organisms are built, because of very recent advances in microscopy and imaging."



Betzig, a group leader at Howard Hughes Medical Institute's Janelia Research Campus, knows the MBL is a fantastic place to bring a bleeding-edge, as yet untried microscope, because "all sorts of world-class cell biologists throw everything they can think of at it. We learn through trial by fire what works and what doesn't," he says. Over the past eight years, Betzig has brought two new microscopes to the MBL to test-drive them with diverse biologists, including the instrument that brought him the Nobel Prize (see page 6).

"The MBL is a unique place for imaging, a place where biologists and instrument developers can have an iterative conversation that really pushes the field," Gladfelter says. This productive feedback loop emerges from the confluence of several streams. One is the rigorous courses at the MBL in microscopy and imaging (see page 15). Decades ago, these courses pioneered a format now widely copied: The faculty includes experts not only from academia but from commercial companies, who bring their newest and best microscope systems for the students to use.

Today, that academic/private partnership has grown into an enormously rich "equipment loaner program" at the MBL. Last summer, more than 140 vendors brought $27 million worth of high-end microscopes, cameras, and other scientific instruments to the campus. This loaned equipment—some of it not even on the market yet—is primarily for the MBL courses, but visiting and resident scientists can use it, as well. It's an astonishing array of imaging tools that helps attract the most innovative biologists in the world to the MBL to teach or conduct research on still-mysterious life processes, such as the movement of molecules inside dividing cells as they develop into embryos; or how neurons build their communication machinery within the dense wiring of the brain.

Putting a beta-version microscope through its paces at the MBL has several advantages for a vendor or developer like Betzig. One is the atmosphere of risk-taking, of trying something new, that permeates the MBL courses and labs, which can lead to dramatic scientific successes as well as instructive misses. "The vendors will send us a demo model and say, 'Beat on it,' and then use our feedback to refine the design," says Martha Peterson of MBL Education.

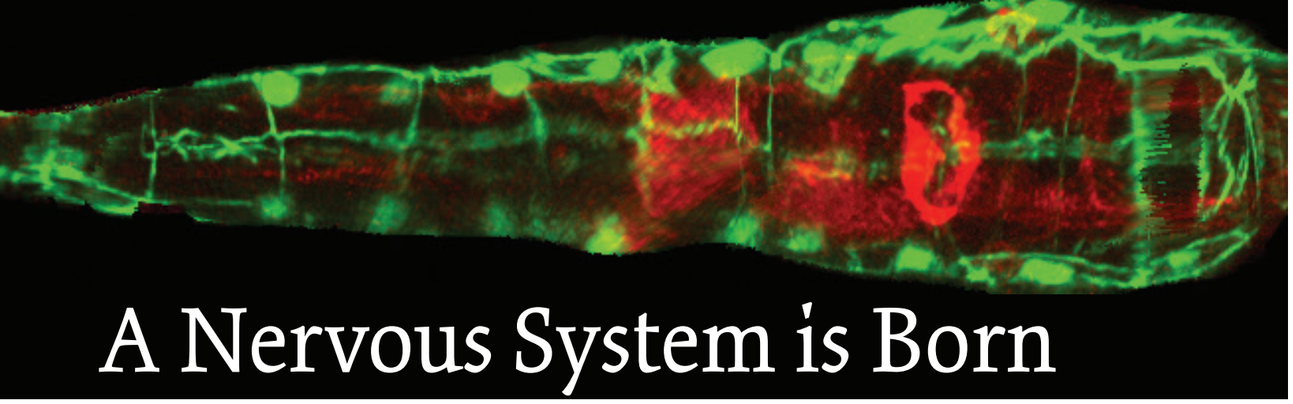
> "There is an elegant fusion at the MBL of microscopy and seeing what is important and essential in biology."
> *— Jonathan Gitlin, Deputy Director of Research and Programs*

Another plus is the varied biological expertise at MBL, especially in how to prepare a sample of cells or tissues so it will yield meaningful images from the microscope at hand. "Sample prep know-how is critical," says Jim McIlvain, a senior applications specialist at Zeiss who is based at the MBL. Betzig agrees. "Any good result I've ever had in my career is because of successful sample preparation," he says.

Essential to sample prep is using the right "probe": the agent that labels or tags the molecules of interest so the microscopist can see and track them. Probe design is also a field on fire with innovation, and many biologists and chemists who pursue it teach in the MBL courses or work in its labs. (Three scientists—all former MBL faculty or investigators—who developed one of the most widely used probes, green fluorescent protein, received the 2008 Nobel Prize in Chemistry for this major contribution to the imaging revolution.)

Innovative imaging is woven into nearly every MBL course and research lab. In the neuroimaging group, scientists are creating new ways to visualize neural processes, from the firing of single neurons to whole-brain activity. Physicists in the Cellular Dynamics Program are pioneers of noninvasive, live-cell imaging. In the Ecosystems Center, satellite and camera imaging are used to assess the impacts of environmental and climate change on landscapes. And in the Bay Paul Center, novel imaging approaches are revealing the structure of microbial communities in many niches, from the human mouth to the coastal ocean.

The MBL's affiliation with the University of Chicago promises to elevate its convening power in imaging to yet a new level. The latest digital microscopes and cameras don't just produce pictures—their output is huge 3D or 4D datasets that require new solutions for data transmission, storage, and analysis. The University and its affiliate, Argonne National Laboratory, have exceptional strengths in computation and image analysis. By bringing that expertise into the mix, imaging at the MBL is poised to visualize and discover life—from the atomic to the landscape levels—at speeds and in depth of detail that can now be only imagined. • —DK



A Nervous System is Born

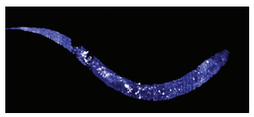
HARI SHROFF'S MICROSCOPE FOR IMAGING DEVELOPMENT WINS MANY FANS AT THE MBL

The buzz on campus started two summers ago, when Hari Shroff parked his custom-built, light-sheet microscope in the basement of Loeb Laboratory and invited anyone in the MBL community to try it. Scientists and students brought him all kinds of specimens, from bioluminescent bacteria to moss to sea urchins. The microscope knocked the socks off of some people, who "saw things in their cells that had never been seen before," says Amy Gladfelter of Dartmouth College.

Word of the microscope's power (see below) spread fast, but finding out what specimens it couldn't handle well—such as larger critters—was equally valuable for Shroff. "One of the best things about the MBL is you can always find biologists who will 'break' your microscope," he says. "A feedback happens here that is very good for the instrument developer. The biologist can see what is possible, and the developer sees what he still has to do!"

Shroff, an investigator at the National Institute of Biomedical Imaging and Bioengineering, came back to the MBL last summer with a more robust, accessible version of the microscope. "With the first one, you needed to be highly trained to acquire the images you wanted," says Shroff's collaborator, neuroscientist Daniel Colón-Ramos of Yale School of Medicine, who also spent the last two summers at MBL as a Whitman investigator. "Now, biologists can understand which parts of the microscope they can control and Hari has boxed in the parts they can't control, so it doesn't get inadvertently misaligned."

The microscope was a hit, and they decided to leave it at the MBL through mid-October for scientists, faculty, and students to use, including in the course on Optical Microscopy and Imaging in the Biomedical Sciences, which Shroff co-directs.



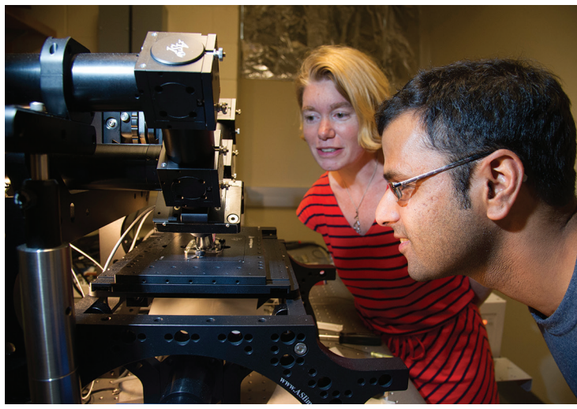
Lights, Camera, Action!

The gentlest way to image the small and delicate *C. elegans* embryos over the seven to eight hours in which neurodevelopment occurs, Shroff decided, would be to use a classic technology called light-sheet microscopy. Incoming light hits the embryo only at the plane in which the camera is recording, so the system eliminates extraneous, out-of-focus light that can damage or kill the specimen over time. Shroff's light-sheet microscope (called diSPIM, or dual view inverted selective plane illumination microscopy) adds several innovations over commercially available SPIM instruments. It introduces a glass cover slip for mounting specimens, which is how single cells and small embryos are typically imaged; it reduces distortion along the Z axis; and it's fast enough to take high-resolution, 3D snapshots of the developing—and writhing—worm. More information is at wormguides.org.

CATCHING THE WORM

Shroff originally designed the microscope for a wondrously ambitious effort: To make a movie of the birth and development of a worm's entire nervous system. The "film crew" for this collaboration with Colón-Ramos also includes Zhirong Bao of Memorial Sloan Kettering Cancer Center and William Mohler of University of Connecticut.

> "One of the best things about the MBL is you can always find biologists who will 'break' your microscope." – *Hari Shroff*



Hari Shroff and Amy Gladfelter with Shroff's hand-built microscope in Loeb Laboratory.

The worm (*C. elegans*) is the only animal for which a wiring diagram of its nervous system, or "connectome," has been mapped out. While the connectome shows the worm's 302 neurons and the 5,000 connections between them, it doesn't explain how the neurons behave in real time, or how they produce the animal's behaviors. Also mysterious is how that circuitry got there in the first place.

"Each neuron, as it develops, has many choices," Colón-Ramos says. "Am I going to be one kind of neuron or another? Branch this way or that way? We know that the endpoint, the nervous system, is fairly stereotyped across all *C. elegans*. What we don't know is how much flexibility there is in the process of establishing the connectivity. Our movie will show what decisions those neurons are making to reach their final form."

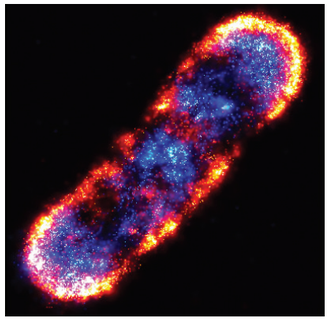
Sydney Brenner and colleagues established *C. elegans* as a model organism in the 1970s and published its draft connectome in 1986, groundbreaking work for which Brenner shared the 2002 Nobel Prize in Physiology or Medicine.

"Our project addresses profound questions that go back 50 years—questions Brenner was discussing with Francis Crick as he thought out using this simple animal as a model system," Colón-Ramos says. "How is genetic information transformed into a developmental program? How do different cells coordinate in a developing organism so they form an organ? How does the structure relate to the function? We are still trying to solve these questions, but with technology that didn't exist then."

The team needs to innovate in many ways, including Shroff's microscope, and draw on diverse expertise to accomplish this project. Colón-Ramos's laboratory engineers the worm embryos with fluorescently labeled neurons, so they can be imaged. Bao is developing new approaches to computationally track and analyze the decisions that many cells are making, in a choreographed way, as they organize as a nervous system. Mohler is spearheading ways to share, visualize, annotate, and analyze the massive 4D datasets they are producing, online and in real time in the cloud.

Their goal is to have a draft of the movie by 2016, the 30th anniversary of the *C. elegans* connectome. Because they are working with living organisms, they know complications will arise. But the solutions they'll find can apply to live-cell imaging in other organisms, perhaps someday to imaging the fantastically complex human brain. "The lessons we can draw from this collaboration can go all the way up the food chain," Shroff says. • —DK

Nobel Prize in Chemistry Awarded to MBL Visiting Scientist Eric Betzig



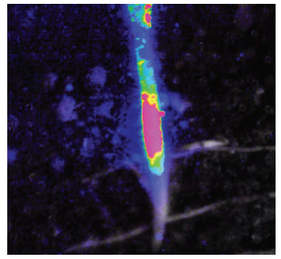
When Eric Betzig loaded his hand-built, "bleeding edge," super-resolution microscope into an SUV in 2007 and drove it up to the MBL for biologists to "test-drive" it, it was immediately embraced as a major breakthrough in biological imaging. In October, Betzig received the Nobel Prize in Chemistry for development of that microscope technology, which allows one to discriminate between molecules just a few nanometers (a billionth of a meter) apart, far better than the previous resolution limit of 200 nanometers. "Theoretically, there is no longer any structure too small to be studied," stated the Nobel Foundation in awarding the prize for developing "nanoscopy" to Betzig, a group leader at Janelia Research Campus, Howard Hughes Medical Institute; Stefan W. Hell of the Max Planck Institute for Biophysical Chemistry; and William E. Moerner of Stanford University. In 2007, Betzig brought his new instrument (called photoactivated localization microscopy, or PALM) into the MBL Physiology course at the invitation of Jennifer Lippincott-Schwartz, a course faculty member from the National Institutes of Health. Over two intense weeks, MBL faculty and students worked feverishly to push Betzig's microscope to its limits, to make it give back faster, sharper, and more richly informative images of the thousands of molecules at work inside a living cell. "It was a spectacular session," Lippincott-Schwartz says, one that led to publications on new uses for PALM, including multiple-molecule tracking. George Patterson in Lippincott-Schwartz's lab at the NIH, along with Michael Davidson of Florida State, designed the photoactivatable GFP probes for the original PALM microscope, which was built by Betzig and Harald Hess. Hari Shroff, then a member of Betzig's lab, built the second PALM microscope that the two brought to the MBL in 2007. Also active in developing PALM were James and Catherine Galbraith, then faculty from the NIH in the MBL Neurobiology course. Betzig came back to the MBL in 2010 to test-drive another new microscope, called Bessel beam plane illumination, and in 2011 and 2013 to lecture in several courses.•

Pyjama Squid Illuminates Photonic Material Design

Nearly all animals have some sort of adaptive coloration or camouflage patterning that can serve many functions, including defense against predators and communication with other members of their species. Humans have recently begun to engineer adaptive coloration materials for their own purposes, such as electronic paper (e-paper) for devices like the Amazon Kindle. The passive white light diffusers found in the skin of some camouflaging animals provide insight for photonic material design, especially for reflectance-based systems that require little energy input. Previously, MBL Senior Scientist Roger Hanlon's lab discovered that some cephalopods (squid, octopus, cuttlefish) produce low-energy, diffuse white coloration through proteinaceous spheres (Mie scatterers) in the skin. Recently, in a follow-up study led by Assistant Research Scientist Lydia Mäthger, they discovered an alternative, novel mechanism for producing white coloration in the pyjama squid (*Sepioleidea lineolata*). Ultrastructural examination of this animal's white stripes found that an unexpected arrangement of multilayer reflectors (Bragg stacks) produces diffuse whiteness over a wide range of viewing angles. To quantify the optical and physical properties of the system, the team used spectrometry, electron microscopy, morphometric analyses, and modeling techniques to determine how this diffuse whiteness is generated. This finding provides a new alternative, both in nature and in photonics, for creating passive, broadband, angle-independent diffusion. (*Advanced Materials,* doi: 10.002/adma.201400383, 2014) •

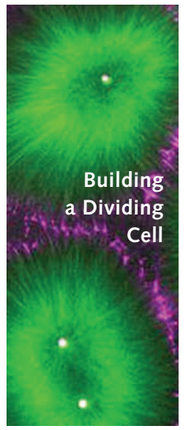
Novel Biosensor Reports on Microbial Growth Around Plant Roots

An active commodities exchange is underfoot, in soil. As plant roots grow, they release carbon as sloughed cells and secretions, fueling microbial growth and activities in nearby soil (the rhizosphere). Soil microbial activities, in turn, affect the availability of nutrients, such as nitrogen and phosphorus, which are scarce in soil yet essential for plant growth. But knowing when and where hotspots for soil microbial growth are occurring, fueled by plant roots, is impossible using the standard assays in agriculture and ecosystems science. Roots and microbes operate in microenvironments defined at millimeter and micrometer scales, not the coffee-mug-sized samples often dug from soil and homogenized for biogeochemical analyses. Because the root-microbe commodities exchange is critical for plant productivity and nutrient recycling but has been difficult to observe in action, MBL Senior Scientist Zoe Cardon and Daniel Gage of University of Connecticut developed a way to examine one component of the system (dynamic microbial growth around plant roots) using nondestructive imaging. They engineered the common soil bacterium *Pseudomonas putida* to express luminescence genes (from *Vibrio fisheri*) only when *P. putida* was growing rapidly. As plants grew in large, soil-filled, clear rectangular pots, a very sensitive CCD camera imaged roots and associated luminescing soil biosensors. Known species-specific patterns in timing of carbon movement from poplar, corn, and tomato shoots to roots, and differential loss of carbon along the length of roots, clearly affected dynamics and localization of microbial growth. This nondestructive method provides a new approach for disentangling ecologically important interactions between microbes and their plant root partners in soil, in real time. (*Frontiers in Plant Science*, doi: 10.3389/fpls.2013.00323, 2013)•



Marine Microbial Activity Potential is Modeled Using Remote Sensing Data of Ocean's Surface

Microbes mediate the global cycling of gases through the earth, ocean and atmosphere, including the greenhouse gas carbon dioxide (CO_2).By understanding the potential for a microbial community to produce or consume (metabolic turnover) CO_2, scientists can better predict what the future levels of this and other climate-active gases may be. Until recently, models describing microbial communities in the ocean could only predict the relative abundance of key taxonomic groups within the community. Going further to predict the functional potential of the microbial community members has been an elusive goal. Recently, a team of scientists from Argonne National Laboratory, the MBL, and other institutions generated the first microbial distribution model that predicts changes in, among other metabolites, the consumption or production of CO_2 over large time scales and distances (the English Channel in this study). Led by Peter E. Larsen and MBL Adjunct Scientist Jack A. Gilbert, both of Argonne National Laboratory, the team had previously developed a method for using satellite remote sensing data on surface ocean reflectance properties to predict microbial community structure. In the present study, in which MBL Senior Scientist Anton Post collaborated, the model was enhanced to also predict the relative abundances of annotated genes in the microbial community that encode enzyme activities, which can then be translated into the changing capacity of the community to consume or generate metabolites. An advantage of the model is its predictions generate discrete hypotheses about metabolic turnover in defined geographic areas, which may then be validated with directed experiments and observational studies. (*The ISME Journal*, doi: 10.1038/ismej.2014.107, 2014)•



Building a Dividing Cell

Building a cell from its components is a synthetic approach to understanding cell biology that has emerged as a hot research goal in the past few years. Recently, a team of MBL visiting scientists from Harvard Medical School built a fully controllable, cell-free experimental system that allows them to visualize and study the final phase of cell division (cytokinesis), when the cell splits in two. This system consists of supported lipid bilayers that mimic the cell membrane, artificial centrosomes, and extract from the cytoplasm of frog (*Xenopus*) eggs. It represents the first-ever reconstitution of cytokinesis signaling outside of living cells. The group was able to assemble arrays of antiparallel microtubules that recruit cleavage furrow proteins that signal to the cell cortex. The spatial scale was unusually large, since *Xenopus* eggs are huge relative to human tissue cells, and as a result the team could query the biophysics of cytokinesis signaling over many minutes and many microns using powerful imaging modalities, notably TIRF (total internal reflection fluorescence) microscopy. This led them to several significant mechanistic discoveries. The research team included Phuong Nguyen, Aaron Groen, Martin Loose, Keisuke Ishihara, Christine Field, and Timothy Mitchison. (*Science*, doi: 10.1126/science.1256773, 2014)•

An Idea Sticks

A Lillie Award team gains traction on how cells move

"It was a naïve idea that became very refined in the MBL Physiology course, because of the different 'brains' in there!" says Clare Waterman of the National Institutes of Health.

Waterman was co-directing the course in 2012 when the right constellation of students and faculty aligned to freshly approach a critical question: How do cells migrate in the body in a specific direction?

Answering this is important to many branches of medicine and drug discovery, from cancer and immunology to tissue repair.

Waterman and a few intrigued collaborators tested her idea of visualizing the mechanics of cell migration using fluorescence polarization microscopy, but it didn't quite work. "We didn't have a lot of experience in thinking about polarization, and we didn't set the experiment up correctly," she says.

They learned a lot about how to do it right, though, and she kept the idea in mind. When the University of Chicago and the MBL announced the Frank R. Lillie Research Innovation Awards to support novel, collaborative investigations at the MBL, Waterman knew she had a great opportunity.

"There is no better place to do this research than here. It's perfect," says Waterman. Selected for an inaugural Lillie Award, she and her collaborators tackled the problem anew at the MBL last summer. They already have exciting results, and will be back next summer to complete the work.

Getting a grip

Waterman, who has been studying how cells migrate for many years, is a distinguished investigator at the National Heart, Lung, and Blood Institute. It's an area known as "adhesion biology," because cells must adhere to a surface in order to gain traction, exert force, and then move.

One of the students in Waterman's 2012 Physiology course was Pontus Nordenfelt from Timothy Springer's lab at Harvard Medical School. Springer is an immunologist known for his co-discovery of the integrins—a family of very dynamic cell adhesion proteins—and for describing their crystal structure. ("If this guy doesn't win a Nobel Prize, there is something wrong with the world," Waterman says.)

The integrins are transmembrane proteins—part of them lies inside the cell, and part lies outside. Springer had partially figured out how the integrins are activated to attach the cell to its external environment.

"Springer showed that the integrins change shape when they are activated," Waterman says. "At first they're curled up, like an arm. When activated, they unfurl. It's like the arm stretches out so the hand, at the tip, can grab onto the extracellular matrix and adhere."

But what prompts the integrins to unfurl? Springer and Waterman thought it might be the pull of dynamic filaments inside the cell (the actin cytoskeleton), which bind to the integrins.

"A sea anchor is an analogy," says Springer, who spent his first summer at the MBL this year as part of Waterman's Lillie Award team. "When a boat is attached to an anchor at its bow, and the wind is blowing on it, the force of the wind will align the boat so the bow is facing toward the anchor and the stern is facing away. It is exactly the same way, we think, with the integrins. The integrins (the boats) get aligned by the forces (the actin cytoskeleton) acting on them."

"Clare had the idea that we could get at this question using fluorescence polarization microscopy. I was quite excited by that," says Springer.

Polarization microscopy, a specialty at the MBL (see sidebar), allows one to see how the molecules are aligned in a cellular structure, for instance in a cluster of integrins.

Waterman brought MBL microscopists Tomomi Tani and Rudolf Oldenbourg into her Lillie Award collaboration, as well as Satyajit Mayor, director of the National Center for Biological Sciences, Bangalore, who was part of her Physiology course faculty team.

Their results are very encouraging. "We've found that, no doubt, the integrins are aligned," says Springer. "We can tell that by the fluorescence. It's really quite remarkable. I think this is the first time that anybody has shown that a molecule on the cell surface (the integrin) gets oriented by something inside the cell, or anything else."

"I think this is going to be an important contribution to adhesion cell biology," Waterman says.

Integrin drugs in the clinic

There could be medical benefit, as well. Springer is active in drug discovery based on integrin biology; he has co-founded three drug companies and is in the process of starting a fourth. Two drugs currently in clinical use to treat patients—one for multiple sclerosis and one for ulcerative colitis—were developed from Springer's basic research.

It's too early to tell whether the Lillie Award research results will have an application in drug discovery, Springer says. "But the integrins are certainly very important drug targets, and the more we know about them, the more insight it gives us to develop new drugs and use existing drugs more effectively."

Springer looks forward to returning to Woods Hole next summer. "It was awesome being at MBL," he says. "I love going there for the ability to meet people I don't normally meet at Harvard. And there are a lot of very good physicists and microscopists at MBL that I enjoy hanging out with. It is really a gem of an institution." • —DK

The MBL is the perfect place to conduct this research, says Clare Waterman (right) with (from left) Tomomi Tani, Shinya Inoué, and Rudolf Oldenbourg of the MBL's Cellular Dynamics Program.

REVEALING THE CELL WITH POLARIZED LIGHT

"The only microscope in the world that can answer our question well is at the MBL," Clare Waterman says. She is referring to the TIRF PolScope built by Associate Scientist Tomomi Tani, which is part of a lineage of groundbreaking, polarized light microscopes invented at the MBL.

"TIRF is a fluorescence technology that allows you to see molecules right on the surface of cells, which is where the integrins are," Waterman says. "By adding polarization, Tomomi's microscope also tells you whether those surface molecules are aligned or not."

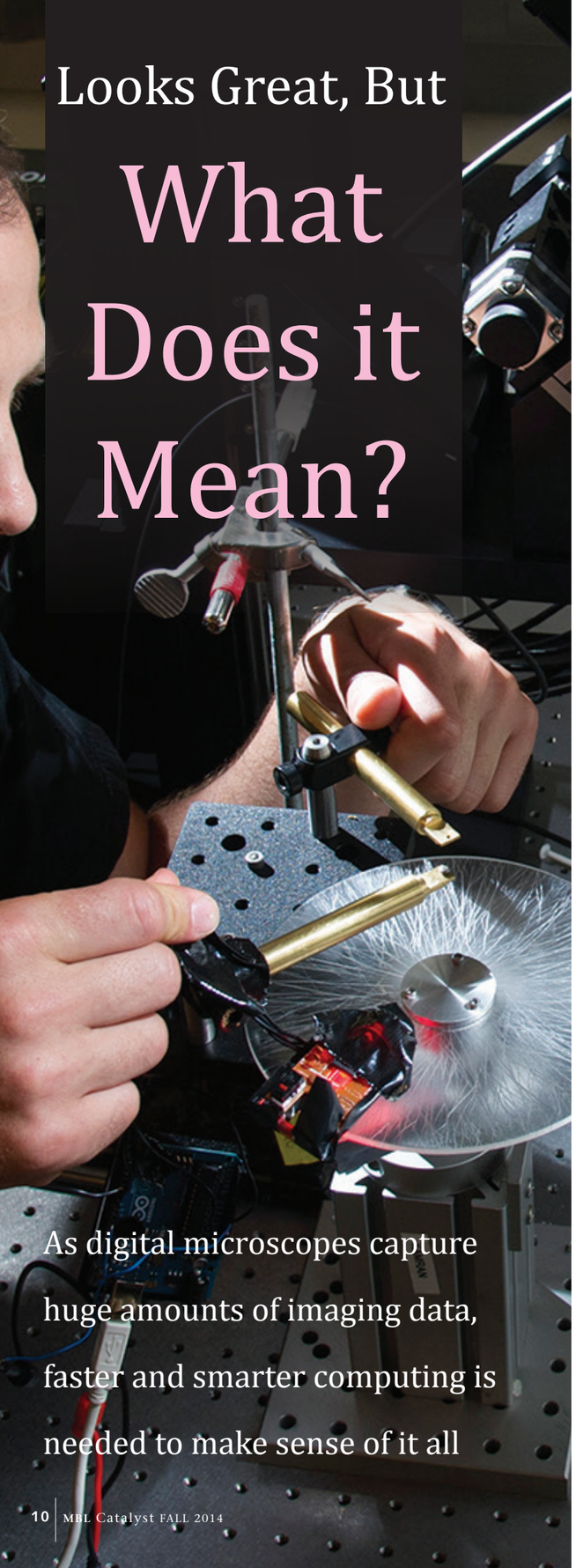
Other highlights of invention and discovery with polarized light at the MBL include:

1951 In Lillie Auditorium, Shinya Inoué shows spectacular, polarized-light movies of dividing cells that reveal parallel fibers ("the spindle") pulling on the chromosomes as the cells split. Previously, the reality of those fibers and their role in cell division had been seriously doubted. Using his hand-built microscopes, Inoué continued to push the power of polarized light to reveal the inner workings of cells over the next six decades as an MBL Distinguished Scientist.

Mid-1990s Senior Scientist Rudolf Oldenbourg and colleagues invent the LC-PolScope, now widely used in clinical and research settings around the world. In fertility clinics, it is used to assess the health of human eggs by observing their spindles.

Looks Great, But

What Does it Mean?



As digital microscopes capture huge amounts of imaging data, faster and smarter computing is needed to make sense of it all

It's often said that a picture is worth a thousand words. But what does a picture say if it contains nothing recognizable to the human eye? What story unfolds from a time-sequence of thousands of images of cells, all nearly indistinguishable from one another?

These are the sorts of challenges that cell and developmental biologists face now that they can observe cells in ever-finer detail and for far longer than ever before using the latest instruments, including polarized-light and light-sheet fluorescence microscopes—two highly promising technologies that MBL scientists are pioneering today.

Biologists have traditionally relied on the amazing ability of the human eye and brain to discern patterns in microscope images and extract quantitative information from them. Recent advances in digital microscope technology, however, have yielded a huge increase in the quality and quantity of images of cells and their complex behaviors. Further, many of these pictures are based on enormous datasets that require powerful computers and sophisticated software to decipher.

The methods by which researchers will best transform these vast amounts of dense image data into useful information remain somewhat unclear, but they will require novel computational methods. The changing nature of research methods poses growing concerns for investigators accustomed to both creating and analyzing—to "owning"—their microscope images, notes Gordon Kindlmann, Assistant Professor of Computer Science at the University of Chicago.

"There's a long history of biologists who say, 'I want to look at my data,'" he says. "But nowadays, they are working with abstractions that are representative of the cells in the frames rather than conventional visual images of them." This "once-removed" data hold considerably less immediacy for the biologists who produced it, which not only "raises practical concerns but cultural and even sociological issues," Kindlmann says.

New views

"Three technical developments have fueled the changing role that microscopy plays in the study of cells," says Gaudenz Danuser, co-director of the MBL's Computational Image Analysis in Cellular and Developmental Biology course and Professor of Biomedical Science at the University of Texas Southwestern Medical Center.

The first is a revolution in imaging that began when Osamu Shimomura, now an MBL Distinguished Scientist and Nobel Laureate, isolated green fluorescent protein (GFP) from the jellyfish *Aequorea*. By inserting GFP or other fluorescent tags into an organism's genome, biologists can closely follow the activity of molecules inside its cells. Second, improved optics and feedback-controlled (self-correcting) microscopes now enable the acquisition of large, high-quality image datasets. Finally, rapid advances in electronic detectors allow images to be recorded with ever-greater sensitivity, enabling researchers to garner deeper insights into cellular processes.

"These fast-paced advances have not, however, been matched by equivalent progress in image-analysis software," Danuser warns.

"The trouble is that today's advanced microscopes can easily yield a terabyte of image data a day," Kindlmann says, whereas "a digital photo is a few megabytes—about a million times less. So a gap has grown between the need for enough computational power to digest these huge amounts of data and the ease with which we can write and control software that can process it." It will take close collaboration between engineers, physicists, mathematician, statisticians, and biologists to close the breach, he says.

Image processing vs. analysis

Microscopy has progressed far beyond familiar image processing techniques, a set of tools that lets biologists manipulate pictures to "better see what needs to be seen," Danuser says. Image processing includes tasks such as contrast and color enhancement, deconvolution (a resolution-enhancement technique), image registration (aligning pictures to enable comparison), filtering (smoothing and enhancement by altering image values), and segmentation (identifying the boundaries of objects). None of these methods interpret the content of images, although they often greatly facilitate that job.

The ultimate task of assigning meaning to features and events—image analysis—has until recently been the sole purview of the human observer. But new digital microscopy techniques require the use of computer vision—such as artificial intelligence (AI) and machine-learning methods to enable researchers to computationally "see" and understand the samples that were imaged.

In cell and developmental biology, computer vision systems can now preclude the need for researchers "to stare at images for the purpose of describing a cellular process," Danuser says.

These high-level tasks require the machines to build abstract representations, or models, of image content, explains Patrick La Rivière, Associate Professor of Radiology at the University of Chicago, who collaborates with Kindlmann. Computer vision programs progressively adjust their information-processing strategies to the nature of the image content and to the knowledge they've acquired in previous steps. The goal of these software programs, he says, is to learn iteratively, as opposed to linearly, about what's contained in images.

Machine-learning systems can provide fast processing with little human interaction, more complete knowledge of the image content, and access to information in images that the human eye cannot discern. But getting AI programs to perform this sophisticated type of iterative analysis is no simple undertaking, Kindlmann states. To do so, "we need parallel computing methods," which perform multiple calculations simultaneously, "but writing parallel software code is slow and hard." Therein lies the rub.

Extracting meaning

The visual scene that the pixels display doesn't matter so much any more, Kindlmann continues. "Today, it's the underlying structure behind the image data that is becoming key [to interpreting the contents of images]." And understanding that structure requires new software that can automatically carry out the necessary mathematical transformations and mapping procedures that will rigorously convert unintelligible image data into comprehensible image knowledge. Exactly how to efficiently create smart parallel software programs that can deftly and validly handle this mass of "big data" remains to be seen.

"Cutting-edge microscopy is straining the comfort zone of how we do computation on image data," Kindlmann says. "But it's extremely exciting that there is a rare alignment between biologists' needs and pressing research questions in computer science."

To address these issues, La Rivière, Kindlmann, and their colleagues at the University of Chicago are teaming with MBL researchers to form stakeholder collaborations. They aim to find better ways to exploit existing computational imaging resources, explore opportunities for using novel imaging and feature-extraction techniques, and address network-level communications issues, such as how to tag and track imaging data to maintain provenance.

They also envision workshops and incubation programs to grow the community of builders and users at MBL and UChicago who are taking advantage of these powerful computational tools to see what, in some cases, has never been seen before. • —SA

MBL Moment with . . .

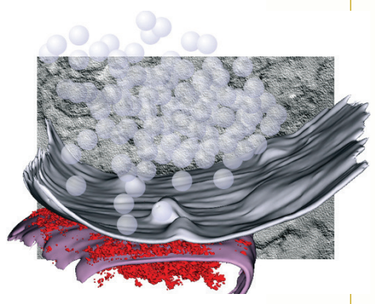
Erik Jorgensen

2014 Frank R. Lillie Research Innovation Award Recipient

Catching the Cell in the Act

Erik Jorgensen is a Distinguished Professor of Biology and a Howard Hughes Medical Institute Investigator at the University of Utah. His research focuses on the development and function of the nervous system in the nemotode worm, C. elegans.

Jorgensen first came to the MBL in 2003 to teach in the Neurobiology course and returned as a visiting scientist in 2008, when he received a Dart Scholarship in Learning and Memory. Most recently, Jorgensen was an inaugural recipient of a Frank R. Lillie Research Innovation Award from the MBL and the University of Chicago; these awards provide funding for novel, collaborative research at the MBL. Jorgensen received his Ph.D. with Richard Garber at the University of Washington in 1989 and was a postdoctoral fellow with H. Robert Horvitz at MIT. His professional honors include receipt of the Humboldt Prize in 2012.



Reconstruction of vesicles fusing in the active zone of a synapse.

When Erik Jorgensen had a bold experimental idea requiring a scientific instrument that didn't yet exist, he knew what to do. The MBL has a long tradition of "bringing in the latest and greatest equipment for scientists and course participants to use," Jorgensen says, and he knew that a freezer on loan to the Physiology course could possibly be customized for his experiment. Jorgensen came to the MBL that summer of 2008 and requested use of the freezer from Leica, the manufacturer. He and his graduate student, Shigeki Watanabe, modified the freezer by adding a light path and conducted their envisioned experiments. Their results are a major surprise, and shed light on a persistent controversy about how the nervous system works. At summer's end, Leica representatives brought photos of Jorgensen's customized "flash-and-freeze" microscope back to headquarters. The company subsequently introduced a commercial version, which Jorgensen now uses at the MBL. "It's based on our design," he says, "but it's much better than anything we built!"

You have said that, contrary to popular myth, scientific progress isn't driven by individuals but by technologies. What do you mean?

EJ The romantic view is that there are Einsteins out there who perform these brilliant experiments and we learn something completely new. In my mind, that is almost never the way experimental science progresses. The groundbreaking experiments aren't done by one smart person; they are done by many smart people and they are done because somebody built a new instrument that allows you to do things that could not be done before. An example is the "freeze slammer" built in the early 1970s by John Heuser and Tom Reese of the National Institutes of Health. Not only did that device prove what they had predicted, but it was used to discover processes that nobody had even imagined before. It brought about a revolution in neuroscience. Some of their work was at MBL, where Tom had a year-round lab. The freezer I am using now at MBL is a descendant of the Heuser-Reese device.

What did Heuser and Reese prove?

EJ In the 1950s, Bernard Katz had put forth a hypothesis of how nerve cells talk to one another. He proposed that when a nerve cell is stimulated, very small packets (called synaptic vesicles) containing chemical compounds (neurotransmitters) fuse to the cell membrane and release the neurotransmitter, which sends a signal to the next nerve cell. To prove that, somebody had to capture a synaptic vesicle fusing to the cell membrane after stimulation. The Heuser-Reese experiment did that. Moreover, they showed that the synaptic vesicles need to be "recycled" in the cell membrane; they have to be replenished or they will eventually be used up. This vesicle recycling is called endocytosis.

How did the freeze slammer work?

EJ It was a very ingenious contraption. First, they inserted wires into frog nervous tissue so they could stimulate the neurons by running a current. The device had a copper block cooled to 4 degrees Kelvin, and it allowed them to freeze the nervous tissue 5 milliseconds after it had been stimulated. Because 5 milliseconds is such a short amount of time, they had to stimulate the sample as it was falling through the air. So they calculated, using standard physical equations of acceleration, when the sample would hit the copper block and when they needed to stimulate. Then they would freeze the sample, fix and embed it in plastic, cut sections and image them on an electron microscope. They could see the release of the neurotransmitter and, if they waited 20 seconds, they could also see mechanisms to recycle the synaptic vesicles.

They discovered something important but they also provoked a controversy.

EJ Yes. At the same time that Heuser and Reese were performing their experiments, an Italian scientist, Bruno Ceccarelli, was performing almost the exact same experiment. He observed a much faster form of endocytosis than the one Heuser and Reese had observed. This faster one became known as kiss-and-run endocytosis.

Why did you decide to revisit this question at the MBL?

EJ Rather than use the frog as an experimental system, we wanted to use the nematode worm, *C. elegans*, which is easier to manipulate genetically. But we needed a deeper freezing depth with the worm than the Heuser-Reese device could provide. We solved that problem by using a high-pressure freezer.

Also, a new technology became available in the mid-2000s, called optogenetics, that allows us to stimulate the worm's neurons just by flashing light on them. We realized we could now do the Heuser-Reese experiment in an intact, living, perfectly normal animal. We could run a light pipe into a high-pressure chamber, flash the light on the worm—boom—the neurons are stimulated and crazy stuff starts happening, and then we can freeze the worm within milliseconds. We surprise the nerve cell, we catch it in the act. After we freeze it, we embed it in plastic and look at it under an electron microscope. We can see exactly what the cell was doing at that moment. We call this "flash-and-freeze" electron microscopy.

We saw a completely different form of endocytosis that has never been observed before. It's 500 times faster than the clathrin-mediated endocytosis that Heuser and Reese observed and 50 times faster than kiss-and-run. We call it ultrafast endocytosis (eLife 2: e00723, 2013).

Was your observation also controversial?

EJ Yes. We had a difficult time publishing that paper. I suspect people just didn't believe it. Nobody had ever seen ultrafast endocytosis before. Some people said, "This is very strange. Maybe this is only found in *C. elegans*." It became clear that we needed to show this was true in a more commonly used model system. So we demonstrated ultrafast endocytosis in the mouse (*Nature* 504: 242-247, 2013).

How has the Lillie Award helped you?

EJ The mouse work is a collaboration between my lab, based in Utah, and Christian Rosenmund's lab, based in Berlin. The Lillie Award gives us an opportunity to get our labs together in Woods Hole. Last summer at MBL, we prepared a follow-up paper that was just published in *Nature* in October 2014. We hope this paper makes it clear why people had never seen ultrafast endocytosis before. We will continue to work on this next summer. It's a fantastic thing for us to be able to do experiments together at MBL. — DK

For more information on the Lillie Awards, please visit: mbl.edu/research/lillie-awards

The Department of Defense/Air Force Office of Scientific Research awarded $1,283,846 for a four-year project titled "Biophotonic Coloration and 3-D Texture in the Flexible Skin of Cephalopods." Roger Hanlon is the principal investigator.

The National Institutes of Health awarded $1,065,915 over five years in support of the Neural Systems and Behavior course. William Reznikoff is the principal investigator.

The National Institutes of Health awarded $1,215,201 for a four-year project titled "Horizontal Gene Transfer as a Source of Evolutionary Innovation in Metazoans." Irina Arkhipova is the principal investigator.

The National Institutes of Health awarded $929,880 over five years in support of the Frontiers in Reproduction course. Mario Ascoli is the principal investigator.

The Burroughs Wellcome Fund awarded $300,000 in support of the Physiology course.

The Genentech Foundation awarded $150,000 to support Training the Next Generation of Neuroscientists.

An **anonymous donor** contributed $100,000 in support of the Semester in Environmental Science program. •

Ivan Valiela has been appointed MBL Distinguished Scientist, a rarely bestowed rank that recognizes a career of outstanding scientific achievements and service to the MBL. Valiela directed the MBL Marine Ecology summer course for seven years and taught in the Boston University Marine Program at the MBL from 1969 to 2008. He joined the Ecosystems Center staff in 2008. Valiela has made significant and sustained contributions to the study of coastal marine ecosystems and their management, and has educated generations of undergraduate and graduate students about coastal marine ecology and biogeochemistry. Through his groundbreaking, long-term experimental studies of Cape Cod salt marshes and bays, Valiela clearly demonstrated the coupling between watersheds and their receiving estuaries, and clarified the critical role of macroalgal blooms in coastal eutrophication and eelgrass decline. His research on Cape Cod, in many European coastal sites, and in tropical mangrove forests has led to models that are widely used for assessing coastal ecosystem health, developing policies to protect them from nutrient loading, and assessing the effects of global changes, such as sea-level rise and climate-driven shifts, on coastal environments.

MBL Trustee **Robert Haselkorn**, Fanny L. Pritzker Professor of Chemistry at the University of Chicago, was elected to the American Philosophical Society.

The Institute of Medicine of the National Academies elected several members of the MBL community in 2014: **Ben Barres**, Stanford University; **Walter F. Boron**, Case Western Reserve University; **Arturo Casadevall**, Albert Einstein College of Medicine; **James J. Cimino**, National Institutes of Health; **Daniel Drachman**, Johns Hopkins School of Medicine; **Gerald F. Joyce**, Scripps Research Institute; **Randy W. Schekman**, University of California, Berkeley; **Michael Shadlen**, Columbia University Medical Center; **Ronald D. Vale**, University of California, San Francisco.

The American Academy of Arts and Sciences elected the following members of the MBL community to its class of 2014: **Kenneth A. Dill**, Stony Brook University; **Leslie A. Leinwand**, University of Colorado, Boulder; **Claudio D. Stern**, University College London; **Dora E. Angelaki**, Baylor College of Medicine; **Bruce P. Bean**, Harvard Medical School; **John H.R. Maunsell**, University of Chicago; **David A. McCormick**, Yale University School of Medicine; **Larry J. Young**, Emory University; **Graham A.C. Bell**, McGill University.

Senior Scientist **Linda Deegan** was selected to serve on the Ecosystem Sciences and Management Working Group of the National Oceanic and Atmospheric Administration's Science Advisory Board.

MBL Purchasing Supervisor **Lionel Hall** was awarded the 2014 John K. Bullard Diversity Award. Hall was recognized for his efforts at the MBL, in the village of Woods Hole, and in Falmouth over the past 30 years to make Woods Hole a welcoming and inclusive community.

Adjunct Scientist **Richard Rabbitt** of the University of Utah received the 2014 Hallpike-Nylen Medal and Prize from the Bárány Society for his basic and clinical research on the neurophysiology of the inner ear.

The Microscope Built by You

For many researchers, the microscope they depend on every day is a black box: They put their sample in and get data out, without understanding what's going on inside.

Not so for the students in the MBL's Physiology course, who built their own microscopes from scratch this summer.

Microscopy has traditionally been included in the course's "boot camp" week, which pushes the students out of their comfort zones to learn new skills. Students with a biology background learn to program alongside engineering majors, and physicists suddenly find themselves handling squid.

"The boot camp section is about getting over your fears," says Heun Jin Lee, a staff scientist at Caltech. Lee led this year's Physiology boot camp week alongside Maria Ingaramo and Andrew York of the National Insitutes of Health.

In the past, representatives from top optics companies showed the Physiology students how to use their latest wares. This year, though, the boot camp instructors wanted them to gain a deeper understanding of how microscopes work.

"I find that you have a very different perspective as a user of technology than as a creator," says York, who designs new optical technology at the National Institute of Biomedical Imaging and Bioengineering. "You're a much more effective user if you have some sympathy for the creator, and vice versa."

Students worked in small groups to assemble one of three different types of microscopes from optical components such as lenses and lasers, which were donated by commercial companies and the MBL's Central Microscopy Facility. Lee and York compared them to Tinkertoys—building blocks that could be assembled in any number of ways.

Without an instruction manual, students solved the challenge set before them creatively. "We found the approaches of the biologists and the physicists and engineers to be hilariously distinct," says York. While the biologists dove right in, testing to see what would work and amending what didn't, the engineers spent more time planning before beginning to assemble their scopes.

"It was a very practical—and satisfying—experience," says Lian Zhu, a Physiology student from Princeton University. "When you're using a microscope in a lab, it's in a case—you don't get to see the parts. Here, they were all on the table for you to see." • — LH

Visualizing the Future

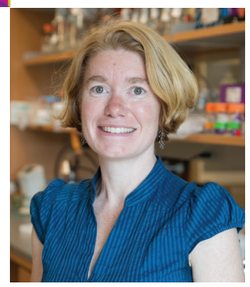
"The MBL is *the* place in the world to become trained as a microscopist," says Amy Gladfelter of Dartmouth College. Intensive training in imaging takes place in several of the MBL summer courses, such as Physiology, Embryology, and Neurobiology. Other courses are fully dedicated to standard and emerging imaging technologies, and some teach tool-buiding. They include:

- Analytical & Quantitative Light Microscopy
- Optical Microscopy & Imaging in the Biomedical Sciences
- Computational Image Analysis in Cellular & Developmental Biology
- Immunohistochemistry & Microscopy

For more information, visit mbl.edu/education

The Golden Age of Microscopy

By Amy Gladfelter



Amy Gladfelter is Associate Professor of Biological Sciences at Dartmouth College and an Adjunct Assistant Scientist in the MBL's Cellular Dynamics Program. A 1998 alumna of the MBL Physiology course, Gladfelter has received Colwin and Nikon fellowships to spend the past six summers at MBL collaborating with microscope developers and other biologists. Gladfelter is interested in how cells organize in time and space; currently she is exploring the timing of cell division cycles, the assembly of septin proteins, and cytoplasmic organization. Her research has led her to develop novel polarized fluorescence microscopy approaches in collaboration with MBL scientists Rudolf Oldenbourg and Tomomi Tani. Gladfelter earned her PhD in Genetics with Daniel Lew at Duke University in 2001 and her BA in Molecular Biology at Princeton University in 1996, where she studied with Bonnie Bassler.

Imagine being inside Antonie van Leeuwenhoek's mind the moment he first focused one of his handcrafted microscopes on a drop of pond water. No doubt he blinked, wiped the lens clean, and questioned his sanity as he witnessed the collective of single-celled creatures spinning through the water. Never before had a human gazed at life on this scale and seen this busy realm of the living that exists just beyond our detection.

This experience of raw wonder may seem impossible in our current digital age, but in fact there are many moments of awe yet to be had in the whirring, invisible world of a cell where the nanomachines of life hum. We are still, more than 300 years after the first microscopes, in the midst of a revolution in imaging. The latest advanced microscopes are revealing the crowded and dynamic landscape of cells and tissues at an unprecedented level of detail, both in time and space.

What fuels this quest to observe life at increasingly finer detail and faster speeds? On the technology side, just as early microscopists were also telescope builders, our current revolution in imaging rests on interdisciplinary work between physicists, biologists, and computational scientists. Light-sheet microscopes, some of which are featured in this issue, borrowed heavily from theoretical physics to enable the rapid and nondestructive filming of whole embryos in real time. Increasingly sensitive cameras, developed for telescopes to detect photons arriving after light years of travel from distant stars, are harnessed to collect photons from single fluorescent molecules jostling about in live cells. Optical resolution barriers, which previously were limited by the wavelength of light, have been broken in a number of ways by marrying sensitive detectors with fluorescent tag engineering and computational image analysis. These remarkable advances continue to lead to the observation of entirely new levels of organization within and between cells of whole organisms.

Where are the biologists in this frenzy of instrument development that is peeling back the veil of life? At the MBL, they are sitting in the darkened microscope room right beside the physicists and engineers, forming a powerful and efficient iterative loop of development and application. Resident biophysicists with expertise in polarized light and visiting microscopy developers from places such as HHMI's Janelia Research Campus and the National Institutes of Health are fed by a stream of intrepid biologists who bring creatures large and small, processes fast and slow, and molecules dim or bright to the hallowed labs of MBL. The challenges brought by each sample test the microscopes under development in diverse ways not possible anywhere else, because the diversity of applications and collaborators are simply not available at one time. The ability for microscopists and biologists to actively collaborate in the same space makes the MBL perhaps the most critical scientific ecosystem of our time for the advancement of imaging. The MBL's partnership with the University of Chicago has the potential to add computational prowess to the process. These are truly thrilling times to be watching the hidden, inner workings of the cell. •

Finding a Focal Point

One of the deep resources in MBL microscopy is Louie Kerr, who for the past 34 years has quietly and capably managed or staffed the Central Microscopy Facility. Visiting and resident scientists, faculty, and students can reserve time on the facility's electron and light microscopes, which are a mix of MBL-owned and loaned instruments. Just as importantly, they can gain from Kerr's steady hand and patient instruction on the instruments' use.

The Central Microscopy Facility informally began in 1952 when Albert Szent-Györgyi, an MBL resident scientist and 1937 Nobel Laureate, bought an electron microscope for $15,000 from RCA, the first company to commercially produce them. ("The microscope has essentially the same technology as the old tube-type TV," Kerr says.) Through the efforts of Szent-Györgyi's assistant, Delbert Philpott, the microscope was also made available to summer researchers. Today, Kerr manages more than a dozen microscope systems, some valued at close to a million dollars, and related equipment.

"The best word to describe me is facilitator," Kerr says."I work to interpret what the scientist wants to accomplish and connect that to the preparative technique and the equipment he or she needs to get it done."

Kerr is intrigued by "the interface between people, technology, and instrumentation. I'm working with both animate and inanimate objects and trying to make it all mesh." But he says the best part of his work "truly, is being able to help people." • — DK

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