Institute for Medical Engineering and Science

Founded in 2012, the Institute for Medical Engineering and Science (IMES) pioneers novel research and graduate education paradigms by bringing together engineering, science, and clinical medicine to advance human health. IMES is an integrative force, catalyzing academic and strategic partnerships within MIT and with hospitals and industry to confront major challenges, particularly in the areas of infectious and autoimmune disease, neurological disorders, cardiovascular disease, and diagnostics.

IMES is home to the Harvard-MIT Division of Health Sciences and Technology (HST). HST also maintains an office at the Harvard Medical School (HMS) quadrangle campus in Boston as one of the five medical societies at HMS. HST director Emery Brown reports to the IMES director, and the director at Harvard Medical School reports to the HMS dean of medicine and dean for graduate education.

IMES is also the home of the Medical Electronic Device Realization Center (MEDRC), directed by Professor Charles Sodini; the MIT Clinical Research Center, led by Professor Elazer Edelman; and the Center for Microbiome Informatics and Therapeutics. In addition, IMES led the creation of the strategic partnership between MIT and Massachusetts General Hospital (MGH).

New Faculty Arrivals

As part of the establishment of IMES, at least eight new faculty members with research interests focused on bringing together engineering, science, and medicine will be recruited. Half of the teaching and service duties of these faculty members will be committed to IMES and HST, while the other half will be devoted to a partner department at MIT. In this way, the IMES faculty members will create a hub for efforts focused on advancing health and serve as spokes that connect IMES to all of MIT, thus also linking various other units to each other. Five faculty members whose recruitment to MIT was led by IMES illustrate how this model works.

Kwanghun Chung developed the first method (CLARITY) to optically image the whole brain, a technique that is expected to be central to the national brain mapping initiative. His appointment as an assistant professor was made in partnership with the Department of Chemical Engineering and the Picower Institute for Learning and Memory.

Thomas Heldt developed the first non-invasive method for monitoring intracranial pressure, a key clinical metric of traumatic brain injury. He also has interests in medical devices for diverse applications and is a member of MEDRC. His appointment as an assistant professor was made in partnership with the Department of Electrical Engineering and Computer Science (EECS).

James Collins is widely regarded to be one of the founders of the field of synthetic biology. He is developing and applying approaches from synthetic biology to work on problems related to medical sensors, antibiotics, drug-resistant bacteria, and the microbiome. Collins's appointment as a full professor was made in partnership with the Department of Biological Engineering and the Broad Institute.

Alex Shalek develops and applies methods in systems biology to study problems related to infectious diseases and brain function. He is also a member of the Broad Institute. Shalek's appointment as an assistant professor was made in partnership with the Department of Chemistry and the Ragon Institute of MGH, MIT and Harvard.

Ellen Roche has experience in industry and academia and expertise in advanced device manufacturing, soft robotics, device tissue interaction, regenerative cell therapy, biomaterial synthesis, soft material mechanics, and numerical modeling. She will lead a laboratory focused on translational research in cardiovascular devices and therapies. Her appointment as an assistant professor was made in partnership with the Department of Mechanical Engineering.

Academic Program

Graduate Degree Programs

HST is among the largest biomedical engineering and physician scientist training programs in the United States, with 303 students enrolled in its graduate degree programs during AY2015:

- 181 MD and MD/PhD students
- 108 Medical Engineering and Medical Physics Program (MEMP) PhD students, including seven MEMP/MD students
- 14 Speech and Hearing Bioscience and Technology program PhD students

HST graduate students work with faculty and affiliated faculty members from MIT, Harvard, and affiliated teaching hospitals. Whether pursuing careers in medicine, research, industry, or government, HST graduates have made outstanding contributions to advances in human health care.

The MEMP PhD program trains students as engineers or physical scientists who also possess extensive knowledge of medical sciences. The program provides preclinical and clinical training to students. On average, students complete the PhD program in six years, and in some cases they also pursue an MD. MEMP students are extremely successful in obtaining outside funding support for their graduate studies, with 37% of them holding external fellowships in AY2015.

Two specialized programs within MEMP are the Neuroimaging Training Program and the Mentored Research Program in Bioastronautics. The Neuroimaging Training Program is supported by a grant from the National Institute of Biomedical Imaging and Bioengineering (NIBIB). Professors Bruce Rosen and Randy Gollub, both members of the HST faculty based at the Martinos Center at Massachusetts General Hospital, co-direct the program. Trainees are identified from among those already enrolled in MEMP with specific interests in neuroimaging. They take additional classes in a curriculum tailored for the program and participate in community-building activities with faculty and students who have related research interests.

The Mentored Research Program in Bioastronautics, founded in 2006, is funded by an education grant from the National Space Biomedical Research Institute. Professor Laurence Young of the Department of Aeronautics and Astronautics, who is also a member of the HST faculty and an associate member of the IMES faculty, directs the program. One or two new students enroll in MEMP/Bioastro each year, joining a small, focused cohort of approximately seven students. Now in its 10th year, this specialized educational offering continues to attract substantial student interest, and enrolled students have received numerous fellowships and awards.

The HST MD program is aimed at students interested in a research-based medical career. While eligible to complete the program in four years, many students take an optional fifth year to engage in more extensive research. Approximately 80% of HST MD alumni follow a career path in academia.

Graduate Education in Medical Science Certificate Program

Graduate Education in Medical Sciences (GEMS) is a certificate program open to doctoral students in MIT's Schools of Engineering and Science who are interested in working at the intersection where engineering and science meet medicine and real-world health care. GEMS runs concurrently with the normal course of an MIT PhD program and can be completed in two years without prolonging a typical PhD career. In addition to coursework in pathology and pathophysiology, participants attend seminars with HST students and engage in individually tailored clinical experiences. GEMS students learn how advances in basic science and engineering become medically relevant therapies and tools for the improvement of human health while developing a professional network that includes medical researchers, clinicians, and physician-scientists.

GEMS was initially established with support from a Howard Hughes Medical Institute (HHMI) program that encouraged graduate schools to integrate medical knowledge and an understanding of clinical practice into PhD curricula. Thirty-two MIT PhD students enrolled in GEMS between 2007 and 2011. The program, which became dormant after the HHMI funding ended, was revitalized after the founding of IMES, enrolling nine new students in AY2014 and three in AY2015.

IDEA^2

Problem identification and definition are integral to graduate education and to innovation, yet the process of learning to select and develop a research question is largely unstructured for most graduate students. This is especially challenging for students in interdisciplinary fields and for those who wish to engage in research that will translate rapidly from lab to clinic. The overarching objective of IDEA^2 is to provide a structured process that guides, mentors, and supports HST students as they learn to define and develop research questions that can impact human health.

IDEA^2 accepts applications from HST students who have identified a specific biomedical research problem but are still early in their training. Following a review process, successful applicants are matched with mentors from outside their research labs, who guide the students as they refine their research proposals. Participating students benefit from an early experience in independently defining, articulating, and defending a research idea while simultaneously developing and engaging a network of advisors from different disciplines, professions, and sectors.

IDEA^2 is supported by the generosity of the Peter C. Farrell (1967) Fund and provides partial financial support to participating students. In AY2015, IDEA^2 distributed $107,000 in student support and individually matched 13 students with 26 mentors selected from a pool of established biomedical entrepreneurs, practicing clinicians, and accomplished scientists/engineers in academia and industry.

Summer Institute

Patterned after MIT's Summer Research Program, HST offers two specialized Summer Institute programs, one in biomedical optics (offered in collaboration with the Wellman Center for Photomedicine at Massachusetts General Hospital) and the other in biomedical informatics (offered in collaboration with the Center for Biomedical Informatics at Harvard Medical School). Thirty-nine students participated in these two programs in summer 2014, and 37 are enrolled for summer 2015.

These programs offer a unique opportunity for outstanding undergraduate college students considering a career in biomedical engineering and/or medical science. Through hands-on research and in-depth lectures, participants learn about either biomedical optics or bioinformatics and engage in the application of these fields to solving problems in human health. Through individual tutorials and workshops, students learn to communicate their research findings effectively in written and oral formats. Shared living arrangements and a variety of technical and social activities enable Summer Institute participants to develop a network of peers and build strong, enduring connections with faculty working in the field.

Faculty Honors and Promotions

Dr. Elfar Adalsteinsson was promoted to professor of electrical engineering and computer science and health sciences and technology.

Dr. Sangeeta Bhatia was inducted into the American Academy of Arts and Sciences and the National Academy of Engineering, was named one of *Foreign Policy* magazine's 100 Leading Global Thinkers, and received a Bose research grant and the Heinz Award.

Dr. Emery Brown was elected to the National Academy of Engineering in February 2015, making him now a member of all three branches of the National Academies. He received the first James Gavin Award from the Robert Wood Johnson Foundation, a 2015 Guggenheim Fellowship in Applied Mathematics, and the 2015 Excellence in Research Award from the American Society of Anesthesiologists.

Dr. Kwanghun Chung was selected as a 2014 Searle Scholar and was named to Cell's 40 Under 40 list.

Dr. Elazer R. Edelman received the Clemson Award for Basic Research from the Society for Biomaterials and the Lifetime Achievement Award at the International Conference on Innovation. He was inducted as a fellow in the American Academy of Arts and Sciences and the National Academy of Inventors.

Dr. Robert Langer received honorary degrees from the University of Maryland, Hanyang University, the University of New South Wales, Drexel University, and the University of Western Ontario. He was elected a foreign corresponding member of the Austrian Academy of Sciences and received the Queen Elizabeth Prize for Engineering, the Kyoto Prize in Advanced Technology, the Scheele Award, the Breakthrough Prize in Life Sciences, the Biotechnology Heritage Award, the Chemical Pioneer Award, the ETH Zurich Chemical Engineering Medal, and the Mack Memorial Award.

Dr. Alex Shalek was named the Hermann L.F. Von Helmholtz Career Development Professor of Health Sciences and Technology at MIT, a Searle Scholar, and a Beckman Young Investigator, and he was part of a team with Paul Blainey (MIT Biological Engineering/Broad Institute) that won the National Institutes of Health (NIH) Follow That Cell Challenge.

Faculty Mentoring and Teaching Awards

Dr. Farouc Jaffer was honored with HST's Seidman Prize for MD Research Mentorship.

Dr. Isaac Kohane won HST's Thomas A. McMahon Mentoring Award.

Dr. Albert Lam was honored with HST's Irving M. London Teaching Award.

Student Honors and Awards

The thesis research of Leah Acker (MEMP PhD, 2014) was featured in a McGovern Institute for Brain Research video (*Leah Acker: Engineering the Brain*).

HST MD/PhD student Alexander Bick and MEMP PhD student Christopher Lee (Xiang Li) were named to the *Forbes* 30 Under 30 list in the field of health care, while HST MD/PhD student Eran Hodis was named to the list in the field of science.

Katelyn Burkhardt, a PhD student in the MEMP program, received the Zonta International Foundation's Amelia Earhart Fellowship.

MEMP PhD students Colin Buss, Erica Mason, and Ben Mead received National Science Foundation Graduate Research Program Fellowships.

MEMP PhD student Conor Cullinane was awarded a NASA Space Technology Research Fellowship.

James Dahlman (MEMP PhD, 2015) was presented a Harold Weintraub Graduate Student Award by the Fred Hutchinson Cancer Research Center.

Mai Dao, Jessica Ruiz, and Alireza Samiel, all HST MD students, received Howard Hughes Medical Institute Medical Research Fellowships.

MEMP PhD student Or Gadish received the Hugh Hampton Young Memorial Fellowship from the Office of the Dean for Graduate Education.

HST MD students Daniel Haldar and Emily Rosen received Physician-Scientist Career Development Awards from the American Society of Hematology.

William Hwang (HST MD, 2015) received HST's Seidman Prize for Outstanding Graduating MD Student Thesis.

MEMP PhD student Mie Kunio received the Collamore-Rogers Fellowship from the Office of the Dean for Graduate Education.

MEMP PhD student Christopher Lee (Xiang Li), was the inaugural recipient of the newly established IMES Broshy Fellowship.

MD student Justin Lo (MEMP PhD, 2015) and MEMP PhD student Andrew Warren received two of the five Student Design and Research Awards for graduate students from the Biomedical Engineering Society.

HST MD student Jesus Luevano received a Clinical Research Mentorship award from the Doris Duke Charitable Foundation.

Katerina Mantzavinou and Kelli Xu, both MEMP PhD students, were named 2015 Graduate Women of Excellence by the Office of the Dean for Graduate Education.

MEMP PhD student Sam Osseiran received the Henry C. (1926) and Frances Keany Rickard Fund Fellowship from the Office of the Dean for Graduate Education.

Shalin Patel (HST MD, 2015) received the Leonard Tow Humanism in Medicine Award, presented by the Arnold P. Gold Foundation.

HST MD/PhD student Sana Raoof received Harvard Medical School's Award for Excellence in Public Health.

HST MD/PhD student Yakir Reshef and HST MD student Andre Shomorony received Paul & Daisy Soros Fellowships for New Americans.

MEMP PhD student Roman Stoyarov received a National Defense Science and Engineering Graduate Fellowship.

MEMP PhD student Nikhil Vadhavkar was part of the team that won the 2015 MIT $100K Entrepreneurship Competition for Raptor Maps, which uses unmanned aircraft to provide crop analytics to agribusiness clients.

Staff Awards

Carol Bailey, IMES administrative assistant II, was presented an MIT Unsung Hero Award. The award recognizes teams and/or individuals who consistently go above and beyond without fanfare; fill in when and wherever needed and always perform at a high level; take the initiative to solve problems and improve work situations without being prompted; demonstrate reliability, perseverance, and a focus on results; and help others by sharing knowledge of Institute practices and resources or job-related skills.

Irene Huang, IMES senior financial officer, received a School of Engineering Infinite Mile Award for Excellence. These awards, which are intended to support the objectives and strategic goals of each organizational area within the Institute, are given to teams and individuals for significant accomplishments in departments, labs, or centers.

Research Program

Core Faculty

Elfar Adalsteinsson is associate director of the Madrid-MIT M+ Vision Consortium, which recruited a fourth class of fellows in the past year. The M+ Vision Catalyst program continues to conduct innovative work in biomedical technology, with fellows and their teams garnering awards and recognition for their efforts.

Professor Adalsteinsson's magnetic resonance imaging (MRI) group focuses on medical imaging, with ongoing developments in estimation of brain oxygenation parameters by MRI, parallel transmission technology, image reconstruction methods for accelerated acquisitions through undersampling, and imaging of the unborn child and the placenta. As part of an NIH-funded collaboration, Professor Ellen Grant (Boston Children's Hospital), Professor Larry Wald (MGH), and Adalsteinsson are addressing the relatively underserved space of fetal imaging, where traditional methods perform poorly due to involuntary subject motion and low tolerance for long scan times.

Sangeeta Bhatia's laboratory engineered genetic circuits in probiotic bacteria to yield liver cancer–detecting biomarkers. By harnessing the power of synthetic biology, Bhatia's group engineered bacteria to home to tumors and emit signals that can be detected in the urine. Many types of cancer, including colon and pancreatic, tend to metastasize to the liver, and the outcome of treatment depends largely on early detection. Bacteria are known to grow in tumors, where there are many nutrients and the body's immune system is compromised. Bhatia and colleagues integrated their diagnostic circuits into a harmless strain of *Escherichia coli* and explored delivering the bacteria orally, just like the probiotics found in yogurt. In tests in mice with colon cancer that has spread to the liver, the orally delivered probiotic bacteria colonized nearly 90% of the metastatic tumors but did not exhibit any harmful side effects. With the new system, Bhatia's group can detect liver tumors larger than about one cubic millimeter, offering more sensitivity than existing imaging methods. Bhatia's team is now pursuing the idea of using probiotic bacteria to treat cancer as well as for diagnosing it.

This year, Emery Brown and his colleagues deepened their understanding of the neurophysiological mechanisms through which anesthetics induce altered states of arousal, establishing that a fundamental part of this process is induction of oscillations that impair the ability of brain circuits to represent and transmit information. Professor Brown's group has shown that different anesthetic drugs have different electroencephalogram signatures and that these patterns change in a systematic way with brain development and typical brain aging. Brown is using these findings to develop a new electroencephalogram-based paradigm that will reliably monitor the anesthetic state of patients receiving general anesthesia and sedation.

Professor Brown's group developed a new Bayesian spectral decomposition framework—spectrotemporal pursuit—to compute spectral estimates that are smooth in time and sparse in frequency. They used a statistical interpretation of sparse recovery to derive efficient algorithms for computing spectrotemporal pursuit spectral estimates. Also, they applied spectrotemporal pursuit to achieve a more precise delineation of the oscillatory structure of human electroencephalogram and neural spiking data under propofol general anesthesia. Spectrotemporal pursuit offers a principled alternative to existing methods for decomposing a signal into a small number of oscillatory components.

In addition, Brown's group selectively activated brainstem cholinergic neurons to determine their role in rapid eye movement (REM) sleep regulation. They found that activation of cholinergic neurons during non-REM sleep increased the number of REM sleep episodes but not REM sleep duration. Their data demonstrate that brainstem cholinergic neurons are important modulators of REM sleep and clarify their role in REM sleep initiation.

Hemholtz Career Development Assistant Professor Kwanghun Chung started his position in IMES and the Department of Chemical Engineering in October 2013. He is also a principal investigator at the Picower Institute for Learning and Memory. His interdisciplinary research team is devoted to developing and applying novel technologies (e.g., CLARITY) for integrative and comprehensive understanding of large-scale complex biological systems. Professor Chung has continued to improve and develop CLARITY, a tissue-clearing technology he invented during his postdoctoral training at Stanford. CLARITY is widely recognized for providing new capacity in comprehensive studies of large-scale biological systems. Recent research advances by Chung include active transport of charged molecules within and/or from a charged matrix, and the resulting technology has been filed with the US Patent Office. Professor Chung has traveled extensively to speak about CLARITY imaging at various invited lectures, including Baylor College of Medicine, Case Western Reserve School of Medicine, and Stanford University.

Professor Chung taught HST.562 Imaging and Sample Processing, and has been responsible for the IMES Distinguished Lecture Series. He also served on the IMES Committee on Academic Programs and the Department of Chemical Engineering's Graduate Admissions Committee.

Professor Richard Cohen was on sabbatical leave during the fall of 2014. During his leave, he worked on a book on the use of evidence in decision making in medicine and other fields. The book presents examples of widely accepted medical practices that—although based on both clinical experience and knowledge of the underlying biomedical science—in fact were proven to be harmful once prospectively tested in randomized clinical trials. The thesis of the book centers on the importance of prospectively testing even the most “commonsense” beliefs and practices.

During his sabbatical leave, Professor Cohen also served as an expert witness in a biomedical patent litigation case. This experience will inform his teaching activities in the area of biomedical entrepreneurship.

In the spring of 2015, Professor Cohen directed a course he developed in collaboration with the Sloan School of Management, 15.S67 Medicine for Managers and Entrepreneurs Proseminar. This course teaches clinical medicine in a business context to students with a career interest in launching or running a biomedical business.

This year a multi-center study initiated by Professor Cohen was released demonstrating that a non-invasive diagnostic technology developed in his laboratory, Microvolt T-Wave Alternans Testing, successfully guided implantable defibrillator therapy in a large cohort of patients at risk of sudden cardiac death from cardiac arrhythmias.

This past year, James J. Collins joined the IMES faculty as the Termeer Professor of Medical Engineering and Science. He is also a professor of biological engineering at MIT, a member of the HST faculty, a core founding faculty member of the Wyss Institute for Biologically Inspired Engineering at Harvard University, and a member of the Broad Institute of MIT and Harvard. His research group works in synthetic biology and systems biology, with a particular focus on using network biology approaches to study antibiotic action, bacterial defense mechanisms, and the emergence of resistance. This past year, Collins’s team made a number of important advances in synthetic biology and antibiotics research, the most notable being the development of an in vitro paper-based platform for synthetic biology that provides an innovative medium for the distribution of engineered gene circuits outside of the lab. This platform enables inexpensive, sterile, and abiotic distribution of synthetic biology–based technologies for in vitro applications and establishes a foundation for a new class of rapid, programmable in vitro diagnostics. Of note, Collins and his team, in under 12 hours, used the platform to build and test inexpensive (less than $1) paper-based Ebola sensors that provide a diagnostic readout in under 25 minutes.

Professor Elazer R. Edelman’s research interests combine his scientific and medical training, integrating multiple disciplines including controlled drug delivery, growth factor biology, tissue engineering, and biomaterials-tissue interactions. His laboratory set the way for optimization of endovascular stents and percutaneous heart valves. His work on angiogenesis includes basic studies of endothelial cell and vascular biology, computational modeling of vessel formation, and clinical trial examinations of controlled angiogenic factor release.

This year he and his group have published some 31 critical papers and been acknowledged on the international stage. Edelman received the Clemson Award for Basic Research from the Society for Biomaterials, and a Lifetime Achievement Award at the International Conference on Innovation. He was inducted as a fellow in the American Academy of Arts and Sciences and the National Academy of Inventors. In addition, he presented this year's Dean's Distinguished Lecture at Weill-Cornell Medical School and was the Massimo Calabresi Lecturer at Yale University.

A new finding from the laboratory of John Gabrieli concerned the brain basis of attention deficit hyperactivity disorder (ADHD). About half of patients with childhood ADHD (which occurs in 11% of US children) persist in their diagnosis as adults, but the other half remit from the diagnosis. Nothing had been known about the functional brain difference between those who persist and those who remit. To characterize the neurobiological differences and similarities of persistence and remittance, Gabrieli and his group performed resting-state functional magnetic resonance imaging among individuals who had been longitudinally and uniformly characterized as having or not having ADHD in childhood and again in adulthood. Intrinsic functional brain organization was measured in patients who had a persistent diagnosis in childhood and adulthood, in patients who had the diagnosis in childhood but not in adulthood, and in control participants who had never had ADHD. A positive functional correlation between the posterior cingulate and medial prefrontal cortices, major components of the default-mode network, was reduced only in patients whose diagnosis persisted into adulthood. This is the first evidence of a neurobiological distinction between persistent and remitted ADHD.

Professor Martha Gray leads the Biomedical Technology Innovation Group. Her research program focuses on formalizing approaches that drive innovation to create impact, particularly in the context of predoctoral and postdoctoral research training. This work occurs primarily through the M+ Vision Catalyst program she developed, which has demonstrated success in enhancing the ability of all involved (fellows, faculty, and collaborators) to be more strategic in their research approaches so as to increase the likelihood of impact. To date, the 34 fellows recruited internationally have initiated 20 projects involving teams that include other M+ Vision Fellows, collaborators from institutions and hospitals, and catalysts and mentors from industry or relevant business communities in Madrid and Boston. Despite starting from scratch, many of these projects have already shown sufficient proof-of-concept to begin human studies or work on a project specification plan. The fellows and their projects have generated over 50 conference and journal publications, 25 invention disclosures, 15 patent applications, and seven grant awards totaling nearly $1 million, and the work has spawned several other initiatives. Highlights include the following.

- M+ Vision team NeuroQWERTY: NeuroQWERTY won the $100K Singapore Challenge and received a grant from the Michael J. Fox Foundation for their creation of a new transparent technology to detect early signs of neurodegenerative disorders via finger interaction with electronic devices.
- M+ Vision team Leuko: This team's project was designed to enable people to better manage their health through a technology allowing noninvasive measurement of white-blood cell counts, a first-line indicator of infection and risk of infection. The work has attracted funding through an NIH cancer technology program.
- M+ Vision team Cell: This team has developed a laser-free approach to measurements now made with flow cytometry. Cytognos S.L. has recently

licensed the technology, and the project has garnered two grants for further development.

- MIT IMPACT program: The approaches developed through the M+ Vision Catalyst program were adapted to support career and research development for postdocs at MIT. This program was offered as part of MIT's new Innovation Initiative.

Professor Thomas Heldt's Integrative Neuromonitoring and Critical Care Informatics Group is leveraging multivariate bedside monitoring data and mathematical models to understand the physiology of the injured brain, to improve diagnoses, and to accelerate treatment decisions for the critically ill. During 2014–2015, the group expanded its data acquisition and data archiving infrastructures from the Beth Israel Deaconess Medical Center (BIDMC) to Boston Children's Hospital and the Boston Medical Center. These prospective data collection efforts now cover a wide range of clinical conditions (hydrocephalus, severe traumatic brain injury, subarachnoid hemorrhage, brain tumors, and elective neurosurgeries). The resultant database is unprecedented in size. The primary focus of the Heldt group's work with its clinical collaborators in neurocritical care and neurosurgery rests with validating the group's approach to noninvasive intracranial pressure monitoring.

In collaboration with colleagues from the MGH Department of Emergency Medicine, Professor Heldt has begun a new research avenue on the early identification of patients at high risk of developing sepsis. Sepsis and severe sepsis have exceedingly high mortality rates but have been difficult to diagnose. With his clinical colleagues, Heldt is creating a database of about 500,000 emergency department admissions to develop automated algorithms for flagging at triage of patients who are at high risk of having a systemic infection and among whom early therapy should be initiated expeditiously.

In the past year, Professor Roger G. Mark served as chair of the MEMP Board of Advisors, as a MEMP faculty advisor, and as an EECS graduate student counselor. Professor Mark's group comprises two major programs: Integrating Data, Models, and Reasoning in Critical Care and PhysioNet.

The objective of the Critical Care program's research, supported by NIBIB, is to develop and evaluate advanced intensive care unit (ICU) patient monitoring and decision support systems that will improve the efficiency, accuracy, and timeliness of clinical decision making in critical care. This research led to the creation of MIMIC II, a large, highly detailed database of deidentified clinical data from BIDMC ICU patients that is distributed openly to the research community.

Clinical databases such as MIMIC provide a unique opportunity to evaluate both practice variations and the impact of diagnostic and treatment decisions on patient outcomes. This year, data from approximately 20,000 additional ICU admissions was incorporated, bringing the total to more than 60,000. The program is exploring ways of enlarging MIMIC to encompass additional institutions, including hospitals in London, Berlin, and Paris. There are now approximately 1,400 MIMIC users worldwide.

The group led by Dr. Leo Celi has formed teams consisting of clinicians (nurses, doctors, pharmacists) and scientists (database engineers, modelers, epidemiologists) who translate clinical questions into study designs, conduct analyses, and publish their findings. The studies fall into the following broad categories: identification and interrogation of practice variations, predictive modeling of clinical outcomes within patient subsets, and comparative effectiveness research on diagnostic tests and therapeutic interventions.

In September 2014, we hosted a highly successful "Critical Data" conference and hackathon that attracted approximately 200 attendees who shared our enthusiasm for generating new knowledge from clinical data. This event was funded in part by SAP.

In December 2014, we signed an agreement with Philips Healthcare that will give us access to an enormous database (approximately three million cases) of structured ICU patient data from hundreds of hospitals in the United States. Although the bulk of this data will be restricted to use by our lab, we will be able to release approximately 100,000 records to the research community via PhysioNet. We expect this agreement to be a long-term collaboration.

We are beginning a new two-year project in collaboration with the emergency department at BIDMC that will extend the MIMIC II database to incorporate data from the emergency department, including chest x-ray image data. This project is part of the new MIT-Philips collaboration.

PhysioNet, supported by NIBIB and the National Institute of General Medical Sciences, offers free web access to large collections of recorded physiological signals and related open-source software. Each month, approximately 45,000 visitors worldwide use PhysioNet, retrieving about four terabytes of data. PhysioNet is also the mechanism by MIMIC is distributed.

PhysioNet Challenges, our annual signal processing and machine-learning open competitions, continue to attract worldwide participation in proposing innovative solutions to important biomedical issues. The 2015 challenge deals with reducing false arrhythmia alarms in ICU monitors. Papers will be presented at the annual Computing in Cardiology meeting in September 2015. The best papers will be published in a special issue of *Physiological Measurement*.

Next year, Professor Mark plans to focus on two major research projects.

- Critical care informatics: An ambitious goal is to expand our critical care database using ICU data from BIDMC as well as from other hospitals in the United States, Europe, and possibly Singapore. We hope to develop the necessary computational infrastructure to support mining this information in the form of a unified database and to build research collaborations between clinicians and engineers to derive new knowledge from massive and diverse data archives. Plans are under way for a new project in natural language processing to create human-readable summaries of medical records. We have recruited a new postdoc funded by SAP for this three-year project. Another new project will focus on integrating emergency department data into MIMIC.

- PhysioNet: We plan to continue to add new databases to our open archives, to develop improved search and display technologies, and to support the federal Interagency Multiscale Modeling and Analysis Group in sharing data and models from individual investigators.

Professor Leonid Mirny's interdisciplinary research team integrates genomic approaches with biophysical modeling to understand complex and multiscale biological phenomena. The main efforts of the Mirny lab have been focused on two problems: (1) characterizing 3D organization of the human genome and (2) understanding cancer progression as an evolutionary process. In the last year, the Mirny lab has made significant progress in both directions. Toward characterizing 3D genome organization, it collaborated with the group of Professor Shiv Grewal from NIH to study the genome of fission yeast and discovered that the genome of this simple eukaryote resembles certain architectural elements observed in the human genome. The Mirny lab further developed polymer models of genome organization and discovered new biophysical mechanisms by which genes can be regulated. Toward analysis of cancer progression, the Mirny lab has developed a mathematical model of mutation accumulation during cancerogenesis and integrated these theoretical results with analyses of cancer genomics and cancer incidence data. The study, published in *Proceedings of the National Academy of Sciences* (2014), suggests that cancer progression is an ongoing tug of war between driver mutations that are beneficial to cancer and passenger mutations that can be damaging to it. This idea suggested a new approach to cancer treatment that the lab has started exploring with its collaborators. The Mirny lab has been also actively involved in PRIMES, a high-school outreach program. Last year, Mirny was elected a fellow of the American Physical Society "for elucidating principles of protein-DNA search, and for applying concepts and methods of polymer physics to characterize the three dimensional organization of genome within a cell."

Professor Alex Shalek's lab co-developed an ultra-high-throughput, low-cost, droplet-based single-cell RNA sequencing technology called "Drop-Seq." In this methodology, cells are first separated into nanoliter-sized aqueous droplets, where a unique barcode is associated with each cell's mRNA, before they are then sequenced together. This technique allows for simultaneous analysis of mRNA transcripts from thousands of individual cells while still retaining each transcript's cell of origin. Through this approach, 44,808 primary mouse retinal cells were profiled to reveal 39 transcriptionally distinct cell populations, creating a molecular atlas of gene expression for known retinal cell classes and novel candidate cell subtypes. Shalek envisions that Drop-Seq will accelerate biological discovery by enabling routine and cost-effective transcriptional profiling at single-cell resolution, affording researchers the opportunity to identify, from first principles, the cell types and states found in their complex samples, such as healthy or diseased tissue, and their associated molecular signatures. His lab is currently working to realize a clinically deployable variant of the approach to help usher in and inform an era of precision medicine.

This year, Shalek was named the Hermann L.F. Von Helmholtz Career Development Professor of Health Sciences and Technology at MIT, a Searle Scholar, and a Beckman

Young Investigator, and was part of a team with Paul Blainey (MIT Biological Engineering/Broad Institute) that won the NIH "Follow That Cell" Challenge.

Professor Collin Stultz and the Computational Biophysics Group are focused on advancing our understanding of, and our ability to treat, human disease. Over the past year, the group's efforts focused on two disorders associated with considerable morbidity and mortality in the United States and abroad. The first, Alzheimer's disease (AD), is the most common cause of dementia in the aging population. Although much effort has been devoted to understanding the molecular mechanism of AD-related dementia, a plethora of unanswered questions exist, and no cure is in sight. One factor that seems clear is that the formation of neurotoxic protein aggregates in the brains of affected patients plays a role in neurodegeneration. Consequently, studies that clarify the mechanism of protein aggregation in AD are of particular interest. The group's recent computational work has provided a window into the mechanism of protein aggregation at an unprecedented level of detail, and these data have helped to explain a number of experimental observations that were previously unclear. The ramifications of this work are broad, as a deeper understanding of the aggregation process is the first step on the path toward the development of novel therapies for AD.

Professor Stultz and his group have also been involved in the development of novel methods for assessing the risk of adverse outcomes in patients who have atherosclerotic heart disease. Atherosclerotic coronary artery disease accounts for roughly 2.4 million hospital discharges per year. Current practice guidelines for these disorders emphasize risk stratification in order to appropriately gauge the intensity of therapy needed to reduce the risk of cardiovascular complications. The development of accurate, low-cost, non-invasive methods for identifying patients at high risk of adverse cardiovascular outcomes would improve health care delivery through treatment of patients who are truly at the greatest risk and would thereby decrease the number of patients unnecessarily receiving expensive and invasive therapies. In contrast to traditional medical expert systems, the group's techniques incorporate no a priori knowledge about disease states and therefore facilitate the discovery of unexpected events that are difficult to predict. Their work in this area started with the hypothesis that subtle variations in the shape of the electrocardiogram (ECG) signal contain information that can contribute to post–acute coronary syndrome (ACS) risk stratification. They conjectured that variations that appear to be noise in small segments of the ECG in fact constitute an interesting signal that can be extracted from longer ECG segments. Recently, they have built upon this approach and developed new methods for analyzing long-term ECG data. Their results demonstrate that powerful prognostic metrics can be developed from such data. Indeed, these metrics can be more powerful with respect to identifying high-risk patient subgroups than many existing metrics that are commonly used in clinical settings. The ultimate goal is to use these methods to uncover novel patterns with prognostic significance from databases containing large amounts of clinical information.

Associate Faculty

Professor Charles Sodini leads the MIT Medical Electronic Device Realization Center, which seeks to revolutionize medical diagnostics and treatments by bringing health care directly to individuals and to create enabling technology for the future information-driven health care system. MEDRC has established a partnership between microelectronics companies, medical device companies, medical professionals, and MIT to collaboratively achieve needed radical changes in medical device architectures, enabling continuous monitoring of physiological parameters such as cardiac vital signs, intracranial pressure, and cerebral blood flow velocity. Since its founding in 2011, MEDRC has grown from two to five sponsoring companies with several other companies in serious discussions. There are currently 15 MEDRC-funded research projects, and MEDRC companies support approximately 20 students. A visiting scientist from a project's sponsoring company is present at MIT. Ultimately, this individual is the champion who helps translate the technology back to the company for commercialization and provides the industrial viewpoint in the realization of the technology. MEDRC projects have the advantage of insight from the technology, medical, and business arenas, thus significantly increasing the chances that the devices developed will fulfill a real and broad health care need as well as be profitable for the companies supplying the solutions. With the new trend toward increased health care quality, disease prevention, and cost-effectiveness, such a comprehensive perspective is crucial.

Events

Health Sciences and Technology Faculty Poster Session

Approximately 125 people attended the 10th annual HST Faculty Poster Session, held on October 23, 2014, at the Tosteson Medical Education Center at Harvard Medical School. Fifty-one faculty posters, representing 48 labs, were on exhibit. Some posters represented broad research programs, while others presented specific research projects; some included student co-authors. This annual event familiarizes faculty members with their colleagues' research and allows them to recruit students to their laboratories. It also assists students beginning the process of selecting laboratories and mentors for their research.

Forum

The 28th HST Forum was held on April 16, 2015, at the Tosteson Medical Education Center at Harvard Medical School. This event highlights the depth and breadth of HST student research for applicants admitted to HST's MD and PhD programs as well as current students, faculty, staff, and other members of the Harvard and MIT communities.

This year approximately 150 people attended the forum, including 29 students who presented posters on their current research. The poster session was followed by a keynote address given jointly by Harvard University professor Pardis Sabeti and her advisee, HST MD student Jacob Lemieux, who treated the audience to a unique view of a dynamic mentor/mentee relationship. The joint address was well received by current and prospective members of the HST community.

In the context of an impressive array of articulately presented student research, the following students received the Martha Gray Prize for Excellence in Research in the categories named:

- Timothy O'Shea (MEMP), Regenerative and Rehabilitative Biomedical Engineering
- George Huang (MD program), Physiology and Systems Biology
- Daniel Goodman (MEMP), Bioinformatics and Integrative Genomics
- Anthony Nguyen (MD/PhD program), Cell and Molecular Biology
- Jingzhi An (MEMP), Biomedical Devices

Institute for Medical Engineering and Science Distinguished Lecture Series

This year IMES held four well-received invited lectures that included the following speakers and subjects:

- David Ku, "The Fastest Bond in Biology—Can Save You or Kill You!" (November 3, 2014)
- Stuart Schreiber, "Integrating Chemistry and Biology to Discover Small-Molecule Therapeutics" (December 3, 2014)
- Uri Alon, "Design Principles of Biological Circuits" (February 26, 2015)
- Cato Laurencin, "Regenerative Engineering: The Theory and Practice of a Next Generation Field" (April 9, 2015)

Arup Chakraborty
Director
Robert T. Haslam Professor of Chemical Engineering
Professor of Biological Engineering, Chemistry, and Physics