Institute for Medical Engineering and Science

Founded in 2012, the Institute for Medical Engineering and Science (IMES) pioneers novel research and education paradigms by bringing together engineering, science, and 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 Program in Health Sciences and Technology (HST). HST also maintains an office at the Harvard Medical School (HMS) Longwood campus in Boston as one of the five medical societies at HMS. The MIT HST director, Professor Emery Brown, reports to the IMES director, and the HMS HST director reports to the HMS dean for medical education and the HMS dean for graduate education.

New Faculty

In the past year, IMES recruited two new core faculty members.

Tami Lieberman: Lieberman's research group focuses on uncovering the principles governing colonization, niche range, and personalization in the human microbiome. Her group conducts studies that help predict which therapeutic strains and co-administered treatments (prebiotics) provide the most potential for colonization and help identify which microbial-based therapies have the potential to treat a wide range of diseases. This appointment as a Hermann L. F. von Helmholtz Career Development Professor was made in partnership with Civil and Environmental Engineering.

Ellen Roche: Roche's research group aims to design and develop implantable medical devices that augment or assist native function. Her group borrows principles from nature to design implantable, biomimetic, therapeutic devices. Her research is broadly categorized into three areas (1) mechanical assist and repair devices, (2) biomaterial and therapy delivery devices, and (3) enhanced preclinical and computational test model development. Ultimately, the combined aim of her group's work is to translate enhanced therapeutic devices into the clinical arena. This appointment as a Hermann L. F. von Helmholtz Career Development Professor was made in partnership with Mechanical Engineering.

Centers and Strategic Initiatives

IMES is home to three centers that extend resources to investigators and students.

- The Center for Microbiome Informatics and Therapeutics (CMIT) builds a community of researchers who investigate and inform how the microbiome regulates and impacts health, focusing initially on ulcerative colitis and inflammatory bowel disease with hospitals and the Broad Institute.
- The Clinical Research Center (CRC), led by Professor Elazer Edelman, is a preclinical testing/consulting facility on the MIT campus working closely with Beth Israel Deaconess Medical Center, Boston Children's Hospital, Brigham and Women's Hospital, and Massachusetts General Hospital (MGH).

- The Medical Electronic Device Realization Center (MEDRC), directed by Professor Charles Sodini, works with medical device companies, clinicians, and MIT researchers to transform the device industry—including wearables and minimally invasive monitoring, imaging, and portable lab instrumentation.

IMES is also home to several strategic partnerships.

- MGH is a key strategic partner of IMES in many spheres. With MGH, IMES pursues projects too innovative to likely receive funding from standard federal granting mechanisms. Research topics include noninvasive diagnosis and neurological, infectious, and autoimmune diseases.
- Philips HealthCare, which recently moved an important research facility to Boston, is providing significant funding while working with members of the IMES faculty on problems of mutual interest, primarily medical analytics and new devices.
- Tufts University Clinical and Translational Science Institute (CTSI), a member of the National Institutes of Health's Clinical and Translational Science Awards Consortium, collaborates with IMES faculty on using clinical insights to fine-tune early device testing and designing sequences of promising ideas to make them more likely to become successful medical applications.
- One Brave Idea, a $75 million collaboration among Brigham and Women's Hospital, IMES faculty, and other researchers, will pursue new biomarkers for atherosclerosis, the hardening of the arteries that kills about 500,000 people in the United States every year.
- The MIT-GSK (GlaxoSmithKline) Gertrude B. Elion Research Fellowship Program for Drug Discovery and Disease is a five-year partnership between MIT and GSK. The fellowship will fund selected fellows to conduct post-doctoral research with a goal of promoting basic research while introducing scientists to key aspects of pharmaceutical research and development.

Academic Program

The Harvard-MIT Program in Health Sciences and Technology is among the largest biomedical engineering and physician-scientist training programs in the United States, with 307 students enrolled in its graduate degree programs during AY2018:

- 109 Medical Engineering and Medical Physics (MEMP) PhD students, including three MEMP/MD students
- 198 MD and MD-PhD students, including three MEMP/MD students

HST graduate students work with 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.

HST's MEMP PhD program, housed in IMES at MIT, 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 also pursue an MD. MEMP students are extremely successful in obtaining outside funding support for their graduate studies, with 37% of MEMP students holding external fellowships in AY2018.

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 training grant from the National Institute of Biomedical Imaging and Bioengineering. 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 networking and enrichment activities with faculty and students with related research interests.
- The PhD Program in Bioastronautics was founded by Professor Laurence Young (MIT Aeronautics and Astronautics, member of the HST faculty, associate member of the IMES faculty) and is now directed by Professor Dava Newman (MIT Aeronautics and Astronautics, member of the HST faculty). This program combines the biomedical training of HST's MEMP PhD curriculum with hands-on research exposure at NASA's Johnson Space Center. One or two new students enroll in MEMP/Bioastro each year, joining a small, focused cohort of approximately seven students. This program was founded in 2006 with the support of an education grant from the National Space Biomedical Research Institute (NSBRI). This financial support ended in 2017, and alternative funding sources have not yet been secured. IMES/HST will continue to offer the academic program as part of MEMP without dedicated funding.
- The HST MD program, housed in the London Society at HMS, 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 career paths in academia.

Graduate Education in Medical Sciences 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 an individually tailored clinical experience. 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 founded 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. Since 2012, 21 new students have enrolled in GEMS, six of those in AY2018.

Summer Institute

Patterned after MIT's Summer Research Program, HST offers a specialized Summer Institute program in Biomedical Optics, offered in collaboration with the Wellman Center for Photomedicine at MGH. Twenty-six students are enrolled in summer 2018.

This program offers 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.

Honors and Awards

Faculty Honors and Promotions

Sangeeta Bhatia received the 2017 Catalyst Award, Science Club for Girls; 2017 "Innovation at the Intersection" Xconomy award; 2017 American Institute for Medical and Biological Engineering STEM Award; and 2017 Honorary Doctorate, Utrecht University, the Netherlands. Bhatia was elected a member of the National Academy of Sciences in 2017. At the 2018 National Academy of Sciences annual meeting, Bhatia spoke at a session highlighting the research of new members, representing Class III.

Lydia Bourouiba was the 2018 recipient of the Smith Family Foundation Odyssey Award for creative and innovative junior investigators working on high-impact ideas to generate breakthroughs and drive new directions in biomedical research; she was elected as a full member of the Centre for Applied Mathematics in Bioscience and Medicine, McGill University, Canada; selected as a board member of the MIT International Policy Laboratory; became an affiliate faculty member, Harvard Medical School; and continued to be on the advisory board of the National Institute for Mathematical and Biological Synthesis.

Emery Brown was elected as a member of the Florida Inventors Hall of Fame and served as interim director of IMES.

Arup K. Chakraborty was elected a member of the National Academy of Medicine in 2017, making him one of only 21 individuals who are members of all three National Academies (Science, Engineering, and Medicine). He also received a Guggenheim Fellowship in 2018.

James J. Collins was elected a fellow of the World Academy of Sciences and became a full member of Sigma Xi, the Scientific Research Honor Society. Collins received the "Lab Coat of the Future" Challenge Award from Johnson & Johnson Innovation, the Gabbay Award

in Biotechnology and Medicine from Brandeis University, the Engineering Biology Award from SynBioBeta, the Emerging Leader Award from the Bay Area Lyme Foundation, and won first prize (student-advisor team) at the National Collegiate Inventors Competition.

Elazer R. Edelman was appointed as director of IMES. He was also appointed the Edward J. Poitras Professor in Medical Engineering and Science (IMES) ; adjunct professor in Biomedical Engineering, National University of Ireland, Galway, College of Engineering and Informatics; and adjunct professor, Tufts Clinical and Translational Science Institute. Edelman received the Transcatheter Cardiovascular Therapeutics Career Achievement Award, Cardiovascular Research Foundation 2017; the Distinguished Scientist Award 2018, American College of Cardiology; and the Giulio Natta Medal in Chemical Engineering 2018, Department of Chemistry, Materials and Chemical Engineering, Politecnico di Milano.

Martha Gray received the ISSSTE (Instituto de Seguridad y Servicios Sociales de los Trabajadores del Estado) Memorial Award and the Program Award for a Culture of Excellence in Mentoring from Harvard Medical School.

Thomas Heldt was promoted to associate professor without tenure as of July 1, 2017, and was appointed as visiting professor at Eidgenössische Technische Hochschule (ETH) Zürich.

Robert Langer received honorary degrees from the Gerstner Graduate School at Memorial Sloan Kettering Cancer Center; the National Institute of Astrophysics, Optics, and Electronics (Mexico); the University of Illinois; the University of Limerick (Ireland); and the University of Laval (Canada). He received the Kabiller Prize in Nanoscience and Nanomedicine, the Memorial Sloan Kettering Medal for Outstanding Contributions to Biomedical Research, the American Chemical Society Leadership Award for Historic Scientific Advancement, and the Alpha Omega Dental Fraternity Achievement Medal Award. In 2018, he was inducted into the Advanced Materials Hall of Fame, and in 2017 *Nature Biotechnology* named him as the top translational researcher for 2016.

Tami Lieberman and Ellen Roche were both appointed as a Hermann L. F. von Helmholtz Career Development Professor.

Alex K. Shalek was elected to the Pew-Stewart Scholars for Cancer Research, received the Alfred P. Sloan Research Fellowship in chemistry, was an associate editor for *Science Advances*, and received the Pfizer-Laubach Career Development Professorship at MIT.

Peter Szolovits was elected an International Academy of Health Sciences Informatics fellow.

Laurence R. Young received the lifetime achievement award from the American Institute of Aeronautics and Astronautics in Orlando, FL, in January 2018, for flight simulation research and teaching. He also received the lifetime achievement award for space flight experiments from the Aerospace Medical Association, Space Medicine Branch in Dallas, TX, in April 2018. Young was appointed by the Translational Research Institute for Space Health as the head of science education.

Many members of the faculty delivered named lectures.

Faculty Mentoring and Teaching Awards

Sydney S. Cash was honored with HST's Seidman Prize for MD Research Mentorship.

John A. Assad was honored with HST's Irving M. London Teaching Award.

Leia Stirling was honored with HST's Thomas A. McMahon Mentoring Award.

In addition, HST Director's Awards recognized H. Franklin Bunn, Jeffrey Behrens, Julie DeSander, Heather Vital, and A. Elizabeth Wagner for their outstanding teaching contributions in HST.

Student Honors and Awards

The following HST students received fellowships, awards, and honors this year.

- **Canadian Institutes of Health Research (CIHR) Doctoral Foreign Study Award (DFSA)**
  Lucy Hu, MEMP
- **Doris Duke Foundation Fellowship**
  Simone Sasse, MD
- **Howard Hughes Medical Institute Medical Research Fellows Award**
  Uday Agrawal, MD
  Erik Bao, MD
  Min Young Megan Jang, MD
  Patrick Lee, MD
- **HMS – Henry Asbury Christian Award**
  Wilfredo Garcia Beltran, MD
  Kristen Knouse, MD
- **HMS – Multiculturalism and Diversity Award**
  Jessica Ruiz, MD
- **HMS – Seidman Prize for Outstanding HST Senior Medical Student Thesis**
  Ryan Park, MD
- **HMS – Soma Weiss Student Research Day Speakers**
  Eric Bao, MD
  Donna Leet, MD
  Anthony Tuan Nguyen, MD
- **HMS – Soma Weiss Student Research Day Poster Award**
  Ling-Ya Monica Chao, MD
  Joseph Scott Goodwin, MD (honorable mention)
  Malia McAvoy, MD (honorable mention)
  Andrew Thai Nguyen, MD
- **HMS – James Tolbert Shipley Prize**
  David Yang, MD

- **HST – Martha Gray Prizes for Excellence in Research (HST Forum)**
  Annabelle Anandappa, MD
  Nil Gural, MEMP
  David Miranda-Nieves, MEMP
  Rida Mourtada, MEMP
  Ryan Park, MD
  Agata Wisniowska, MEMP
- **MIT – Elie Shaio Memorial Award**
  Efrat Goffer, MEMP
- **MIT – Goodwin Medal for Outstanding Teaching by a Graduate Student**
  Or Gadish, MEMP
- **MIT – Hugh Hampton Young Memorial Fellowship**
  Avilash Cramer, MEMP
- **MIT – IMES - Broshy Scholarship**
  Avilash Cramer, MEMP
  Lucas Cahill, MEMP (Runner-up)
- **MIT – Koch Institute - Ludwig Center for Molecular Oncology Fellowship**
  Jesse Kirkpatrick, MEMP
- **MIT – Lemelson-MIT Graduate Student Prize, Cure It! Category**
  Tyler Clites, MEMP
- **MIT – Priscilla King Gray Center, IDEAS Global Challenge Winner**
  Olivia Waring, MEMP
- **MIT – Tata Frontier Fellowship**
  Kriti Subramanyam, MEMP
- **MIT – Unitec Bio Fund Fellowship**
  Claudia Varela, MEMP
- **MIT – Whitaker Health Sciences Fund Fellowship**
  Shriya Srinivasan, MEMP
- **National Science Foundation Graduate Research Fellowship**
  Melinda Chen, MEMP
  Brennan Jackson, MEMP
  Nalini Singh, MEMP
  Claudia Varela, MEMP
- **Radiological Society of America Trainee Research Prize**
  Anji Tang, MD
- **Swedish-American Foundation Fellowship**
  John Samuelsson, MEMP
- **The Paul and Daisy Soros Fellowship for New Americans**
  Suchita Nety, MD

Staff Awards

Caitlin Vinci, IMES administrative assistant to the Chung, Cohen, and Heldt laboratories, was awarded a School of Engineering Infinite Mile Award for Excellence. This award is given to individuals whose work is of the highest quality. Vinci stands out because of the high level of commitment and enormous energy and enthusiasm she brings to her work. She has made extraordinary contributions to help the Institute carry out its mission.

Research Program

Core Faculty

Elfar Adalsteinsson: Magnetic Resonance Imaging (MRI) has been a transformative medical imaging modality for diagnostic and scientific applications in adults, but its applications in pregnancy remain limited and progress is hindered by unpredictable motion of a non-compliant subject, namely the fetus. Further compounding the problem is MRI geometry and equipment that is poorly fit to the pregnant mother. Current fetal MRI relies on severely compromised image acquisition stage to mitigate the degradations in diagnostic quality due to subject motion. Adalsteinsson's research group has increasingly focused their attention on these motion-driven problems for fetal imaging with MRI. This work is supported by the National Institutes of Health to image the fetus and placenta, with teams of colleagues at MIT, MGH Martinos Center, and Boston Children's Hospital. Another active research topic in the group is magnetic resonance spectroscopy—in particular, the design of algorithms for optimization of main magnetic field inhomogeneity for a novel hardware called a "shim array." The shim array was developed by colleagues at the Martinos Center; new algorithms and optimization for the spectroscopic imaging application were developed by graduate student Nick Arango in collaboration with his advisor, Professor Jacob White.

Daniel G. Anderson: Anderson's laboratory focuses on developing new materials for medicine. His work has led to advances and products in a range of areas, including medical devices, cell therapy, drug delivery, gene therapy, and material science. In the past year, particular progress has been made in the development of nanoparticles capable of in vivo genome editing (e.g., Yin et al., *Nature Biotechnology, Nature Chemistry*), new approaches to RNA therapeutics (e.g., Wesselhoeftas et al., *Nature Communications*), and the generation of superbiocompatible materials and formulations for medical devices (Doloff et al., *Nature Materials*). These technologies are now being advanced clinically at companies based on MIT patents. For example, over $100 million has been invested towards the translation of "living therapeutics," devices composed of cells and biomaterials created in Anderson's laboratory to treat human diseases such as diabetes.

Sangeeta Bhatia: The World Health Organization has set malaria eradication as one of its current goals, yet a major roadblock facing this effort is the lingering, dormant-yet-deadly "hypnozoite" form of *Plasmodium vivax*, which has been shown to spontaneously reactivate in formerly "cured" patients—re-initiating the disease and a new round of contagious infection. This rare and poorly-understood parasite lives in the human liver, but has not been interrogated in a systematic way due to a lack of models with which to study it, which has also left the field without a biomarker with which to identify hypnozoites. In work published in *Cell Host & Microbe*, Bhatia and colleagues succeeded

in growing patient-derived *P. vivax* hypnozoites in their natural human hepatocyte host cells, using their engineered in vitro platform to test the efficacy of candidate drug interventions—and yielding the first transcriptomic data from human-infecting malaria parasites. Their efforts pave the way for improved, high-throughput screening of new, small-molecule drugs, assaying for tools to "wake" dormant hypnozoites and render them sensitive to existing therapeutics, and—most importantly—position the field to uncover specific biomarkers for the parasites themselves, and to diagnose infected individuals, perhaps even those with dormant, otherwise invisible, parasite loads.

Publication

N. Gural, L. Mancio-Silva, AB Miller, A. Galstian, VL Butty, SS Levine, R. Patrapuvich, SP Desai, SA Mikolajczak, SHI Kappe, HE Fleming, S. March, J. Sattabongkot, and SN Bhatia. "*In vitro* culture, drug sensitivity, and transcriptome of Plasmodium vivax hypnozoites," *Cell Host Microbe*, 23 (2018), pp. 395-406.

Emery Brown: Below are two significant publications from this academic year.

1.) EN Brown, K. Pavone, and M. Naranjo, "Multimodal General Anesthesia, Theory and Practice, Anesthesia and Analgesia," in press.

Balanced general anesthesia, the most common management strategy used in anesthesia care, entails the administration of different drugs together to create the anesthetic state. Anesthesiologists developed this approach to avoid sole reliance on ether for general anesthesia maintenance. Balanced general anesthesia uses less of each drug than if the drug were administered alone, thereby increasing the likelihood of its desired effects and reducing the likelihood of its side effects. To manage nociception intraoperatively and pain post-operatively, the current practice of balanced general anesthesia relies almost exclusively on opioids. While opioids are the most effective anti-nociceptive agents, they have undesirable side effects. Moreover, over-reliance on opioids has contributed to the opioid epidemic in the United States.

Spurred by concern of opioid overuse, balanced general anesthesia strategies are now using more agents to create the anesthetic state. Under these approaches, called multimodal general anesthesia, the additional drugs may include agents with specific central nervous system targets, such as dexmedetomidine, and ones with less specific targets, such as magnesium. It is postulated that use of more agents at smaller doses further maximizes desired effects while minimizing side effects. Although this approach appears to maximize the benefit–side effect ratio, no rational strategy has been provided for choosing the drug combinations. Nociception induced by surgery is the primary reason for placing a patient in a state of general anesthesia. Hence, any rational strategy should focus on nociception control intraoperatively and pain control postoperatively.

Brown and his collaborators have reviewed the anatomy and physiology of the nociceptive and arousal circuits and the mechanisms through which commonly used anesthetics and anesthetic adjuncts act in these systems. They propose a rational strategy for multimodal general anesthesia predicated on choosing a combination of agents that act at different targets in the nociceptive system to control nociception intraoperatively

and pain postoperatively. Because these agents also decrease arousal, the doses of hypnotics and/or inhaled ethers needed to control unconsciousness are reduced. Effective use of this strategy requires simultaneous monitoring of anti-nociception and level of unconsciousness. This article illustrates the application of this strategy by summarizing anesthetic management for four representative surgeries. It also provides a new, principled strategy for administering anesthetics that reduces dramatically use of opioids and hypnotic agents, leads to more rapid recovery, and reduces the likelihood of post-operative cognitive dysfunction.

2.) SE Kim, M. Behr, D. Ba, EN Brown, "State-space multitaper time-frequency analysis," *Proceedings of the National Academy of Sciences*, 2018 Jan 2;115(1): E5-E14.

Rapid growth in sensor and recording technologies is spurring rapid growth in time series data. Non-stationary and oscillatory structure in time series is commonly analyzed using time-varying spectral methods. These widely used techniques lack a statistical inference framework applicable to the entire time series. We develop a state-space multi-taper (SS-MT) framework for time-varying spectral analysis of non-stationary time series. We efficiently implement the SS-MT spectrogram estimation algorithm in the frequency domain as parallel, one-dimensional, complex Kalman filters. In analyses of human electroencephalograms recorded under general anesthesia, the SS-MT paradigm provides enhanced denoising (> 10 dB) and spectral resolution relative to standard multi-taper methods, a flexible time-domain decomposition of the time series and a broadly applicable, empirical Bayesian framework for statistical inference.

Arup K. Chakraborty: Chakraborty continued efforts to understand the mechanistic bases of how a specific and systemic immune response to pathogens occurs and how its aberrant regulation leads to disease. Research aimed at understanding how this knowledge can be harnessed for the rational design of vaccines and therapies is also an important facet. Chakraborty, in collaboration with Professors Sharp and Young, launched a new project on understanding how genes critical for maintaining healthy cell states are regulated. Chakraborty is also working on two books on immunology, one for an audience of physical scientists who want to, or have entered, the field, and one for a general audience. Chakraborty served as director of the IMES until December 31, 2017, and co-chaired MIT's committee on digital health. He continues to serve as a member of the US Defense Science Board and as a senior editor of *eLife* (one of the premier journals in biology).

Kwanghun Chung: Chung leads an interdisciplinary research team devoted to developing and applying novel technologies to the holistic understanding of large-scale, complex biological systems. In the past year, his group has continued to develop new technologies to accelerate the pace of scientific discovery and development of therapeutic strategies in a broad range of biomedical research. Recent research advances by the Chung Lab include the development of SHIELD technology that simultaneously and globally protects tissue physicochemical properties while allowing multiscale molecular imaging. The Chung Lab has openly shared the SHIELD reagents and protocols with more than 40 labs worldwide. The group has active collaborations with many researchers at MIT, the Broad Institute, MGH, and Harvard, and has co-authored eight articles in the past year. Chung has traveled extensively, including to the University of Munich, Columbia University, Seoul National University, and the University of British

Columbia, as well as to Merck and the Gordon Research Conferences to speak about his group's research. He taught 10.302 Transport Processes, and HST.562 Pioneering Technologies for Interrogating Complex Biological Systems. He also served on the IMES Committee for Academic Programs, as well as the IMES graduate admission and Brain and Cognitive Sciences graduate admission committees. Chung has recently founded a startup, LifeCanvas Technologies, that aims to advance the adoption and usage of Chung Laboratory technologies developed at MIT.

Richard Cohen: Cohen continued to support MIT's entrepreneurship effort and the Sloan Healthcare Certificate program by directing one of the core required courses (15.132/ HST.972 Medicine for Managers and Entrepreneurs) and one of the elective courses (HST.973/15.124 Evaluating a Biomedical Business Concept). In addition, he served as one of two faculty members on the certificate program's board. He was also the faculty sponsor of the MIT Professional Education Short Program "Organizations, Innovation, and Technology: Putting Ideas to Work." Also, as co-founder and consultant, he worked with Sirona Medical Technologies, Inc. to develop a novel catheter technology for the treatment of life-threatening cardiac arrhythmias. This technology combines electrical mapping with focused radio frequency ablation and promises to improve both the efficacy and safety of this important and rapidly growing means of therapy.

James (Jim) J. Collins: Collins, the Termeer Professor of Medical Engineering and Science, continued to develop innovative, synthetic biology platforms that can be used to address critical issues in medicine, biotechnology, and the life sciences. This past year, Collins and his team developed probiotic strains that can detect and suppress cholera infections. Microbiota-modulating interventions are an emerging strategy to promote gastrointestinal homeostasis. Yet, their use in the detection, prevention, and treatment of acute infections remains underexplored. Collins developed a probiotic-based strategy to promote colonization resistance and point-of-need diagnosis of cholera. The team discovered that oral administration of *Lactococcus lactis*, a common dietary fermentative bacterium, reduced intestinal burden of cholera and improved survival in infected infant mice through the production of lactic acid. Furthermore, the team engineered an *L. lactis* strain that specifically detects quorum-sensing signals from cholera in the gut and triggers expression of an enzymatic reporter that is readily detected in fecal samples. This innovative work, published in *Science Translational Medicine*, sets the stage for dietary interventions with natural and engineered probiotics as an alternative, inexpensive strategy to combat the spread of cholera in vulnerable populations.

Elazer Edelman: Edelman's research combines his scientific and medical training, integrating multiple disciplines. His research continues to focus on the applied and basic sciences of cardiovascular diseases. The work of his students and fellows have redefined the nature of critical diseases like aortic stenosis, atrial fibrillation, and coronary artery disease. On a basic level, his students have redefined the nature of endothelial cell heterogeneity and the paracrine regulation by the endothelial cells of complex diseases like atherosclerosis and cancer. The laboratory has also focused on using advanced material science to explain the unexpected failure of the most promising emerging medical devices. This year, he and his group have published 29 critical papers and have been acknowledged on the international stage.

Academic Committees

MIT Digital Medicine Steering Committee

National Academy of Engineering (NAE) Grand Challenge Scholars Program Steering Committee (NAE and MIT)

Invited Presentations

Featured Lecture: Redefining Aortic Stenosis – Can Quantitative Metrics Replace Symptom-Directed Intervention for Aortic Stenosis, Heart Valve Society 4th Annual Meeting, New York City, April 12, 2018

Moderator, Commemorative Plenary Session - Celebrating the 50th Anniversary of the Circulation Aortic Stenosis Natural History Manuscript Heart Valve Society 4th Annual Meeting, New York City, April 12, 2018

Plenary Speaker Session – Biomechanics: Unifying Force Advancing Science and Health, 8th World Congress on Biomechanics, Dublin, Ireland, July 8–12, 2018

John Gabrieli: The Gabrieli Lab made advances in understanding two difficulties that affect many children: dyslexia (difficulty in learning to read) and depression (feelings of severe despondency and dejection). For dyslexia, both adults and children with dyslexia exhibited reduced brain plasticity for many kinds of materials. Reduced brain plasticity offers a novel understanding of why about 15% of children struggle to read. For depression, children at familial risk for developing depression had brain difference relative to children not at risk. Such brain measures of risk for depression in children could be used to promote early intervention to reduce the likelihood of developing depression.

Lee Gehrke: Gehrke is a molecular virologist who directs the HST Human Functional Anatomy course at Harvard Medical School and the HST Medical Maker subject at MIT. He studies RNA viruses, including Zika, West Nile, Dengue, and others. The Gehrke laboratory has been active in designing and building rapid diagnostic tests to detect viruses in serum and urine. In collaboration with the laboratories of Rudolf Jaenisch and David Sabatini (Whitehead Institute), the Gehrke Lab is developing two- and three-dimensional tissue models for investigating neurotropic virus infections.

Martha Gray: 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 pre- and post-doctoral research training. One particular highlight is work demonstrating a non-invasive approach to identifying people who have dangerously low neutrophil (white blood cell) levels. One intended use for this technology is in the context of chemotherapy. Chemo reduces white blood cell levels, and when these levels are very low, patients are at heightened risk of acquiring an infection. Presently, a blood test is required to identify dangerously low levels; this technology offers the potential for regular (at-home) monitoring. Results from the first clinical test (published in *Nature Scientific Reports*) are encouraging and the work has garnered many awards in business competitions and, thanks to new funding, will form the basis for a new startup, Leuko Labs.

Thomas Heldt: Heldt directs the Integrative Neuromonitoring and Critical Care Informatics Group at IMES. Using physiologically-based, dynamic models, his group leverages multivariate bedside monitoring data—on the second to hour timescale—to understand the physiology of the injured brain, to improve diagnoses, and to accelerate treatment decisions in the critically ill. Heldt's group continues very strong and active collaborations with clinicians at Boston Children's Hospital, Boston Medical Center, MGH, and Beth Israel Deaconess Medical Center (BIDMC) in the areas of neurocritical and neonatal critical care, as well as other areas of patient monitoring.

Over the past year, the collaboration between Heldt's group and Drs. Andrew Reisner and Michael Filbin further analyzed patterns of sepsis care at the MGH Department of Emergency Medicine. The group discovered that septic patients presenting to the emergency department with vague symptoms that may not immediately point to an infectious etiology are at much greater risk of death than those patients in whom infection is leading the differential diagnosis. This work is forthcoming in the journal *Critical Care Medicine* and has been corroborated in an independent multicenter cohort study. Additionally, the team's Shock Precaution on Triage (SPoT) sepsis risk score has now been rolled out in Epic across all hospitals in the Partners Healthcare system.

In the domain of neonatal intensive care, Heldt's team continues to collaborate with Drs. Wendy Timpson and Munish Gupta at the BIDMC Department of Neonatology. Over the past year, the team provided a detailed characterization of the bedside monitoring alarm burden in the BIDMC neonatal intensive care unit and has executed an interventional study that reduced the incidence of tachycardia alarms by a factor of two without increasing the risk to the infants.

Finally, the group has now validated a model-based, calibration-free, and noninvasive approach to continuous intracranial pressure (ICP) estimation in a diverse set of patients ranging in age from two years to over 70 years and spanning a diverse set of etiologies, including traumatic brain injury, hydrocephalus, stroke, cerebrovascular malformations, and metabolic disorders. The estimates continue to compare well compared to the clinical gold standard and they outperform some of the invasive ICP measurement technologies still in occasional use.

Tami Lieberman: Lieberman started her group in January 2018. Her group seeks to gain mechanistic insights into the drivers of long-term bacterial colonization in the microbiome using a combination of experimental, computational, and theoretical approaches. A key tool in the lab is whole-genome evolutionary reconstruction, which enables inference of bacterial survival strategies and migration routes in the human environment. Her group is tackling fundamental questions that are poorly understood for all human microbiomes using a variety of systems, including the bacteria that colonize facial pores. Lieberman has established a variety of promising collaborations—including a new multi-year collaboration with a private K-8 school (Acera School) that will enable her to follow children and their families as they age. She has won a pilot grant from the Center for Microbiome Informatics and Therapeutics, was part of a finalist team for a large Simons-National Science Foundation (NSF) collaborative grant, and is the MIT nominee for the Pew Biomedical Scholars competition. Since joining MIT, she has been invited to give prestigious seminars at University of California San

Francisco, Harvard, Brown, Rockefeller, University of Michigan, and Cold Spring Harbor Laboratory, among other places. She will be teaching HST 508 Evolutionary and Quantitative Genetics this fall and is designing a new undergraduate course for the spring focused on applications of evolution in real time.

Roger G. Mark: In the past year, Mark taught two courses: 6.022J/HST.542J Quantitative Systems Physiology, tailored to undergraduates and early graduate students from multiple engineering departments; and HST.201, 202 Introduction to Clinical Medicine and Medical Engineering I, II, for advanced MEMP students. His laboratory's objective is to improve health care through the generation of new clinical knowledge and new monitoring technology and decision support through the application of data science and machine learning technology to large collections of critical care data. His lab has developed the widely used MIMIC (Medical Information Mart for Intensive Care) database that is freely available to more than 7,000 credentialed investigators worldwide. The lab also developed and supports *PhysioNet*, an extensive open archive of physiological signals. Mark's administrative and service responsibilities include: MEMP Board of Advisors (chair), HST-IMES Committee on Academic Programs, MEMP Qualifying Exam in HST Committee, MEMP Faculty Advisor, and Electrical Engineering and Computer Science (EECS) graduate student counselor.

Leonid Mirny: Mirny is leading a research program aimed at understanding the organization of the human genome in 3-D; he is a co-director of the Center for 3-D Structure and Physics of the Genome funded by the National Institutes of Health (NIH) 4D Nucleome Program. In the last year, the Mirny Lab has published several high-profile papers in *Nature, Cell, Science, Proceedings of the National Academy of Sciences (PNAS),* and other journals—proposing and supporting a novel mechanism of genome organization by active loop extrusion. The most significant achievement of the last year was a study that established how human DNA is folded inside a mitotic chromosome, a question that has puzzled biologists for more than 100 years. The Mirny Lab and its collaborators have integrated genetic, genomic, and computational approaches to characterize the key steps in mitotic chromosome formation. They found that a chromosome is formed by growing loops that wind around a helical spiral staircase scaffold. This study was published in *Science* and has been featured by *Quanta Magazine* and many news agencies. Mirny teaches the graduate course HST.508 Quantitative Genomics, and 8.592 Statistical Physics in Biology, and a freshman seminar HST.A01 Quantitative Biology—in which students learn concepts of genomics through interactive games and tabletop experiments.

Ellen Roche: Roche started her laboratory at IMES in August 2017. She has a joint appointment in Mechanical Engineering and IMES, and works on the design of innovative therapeutic devices, including their enabling technologies. Research in Roche's lab is focused on the design and development of implantable medical devices that augment or assist native function, borrowing principles from nature to design implantable, biomimetic therapeutic devices. Her work is broadly categorized into mechanical assist and repair devices, biomaterial and therapy delivery devices, and enhanced pre-clinical and computational test model development, with the ultimate goal of translating enhanced therapeutic devices into the clinical arena. Since starting her lab, she has published in *Nature Biomedical Engineering* and other journals. She was granted a patent on a cardiac assist device she invented and she licensed a catheter-based technology to a spin-out company based in Europe. She was recently appointed

the Helmholtz Career Development Professor. This year, she gave invited plenary or symposium talks at the European Society of Organ Transplant Meeting, the Engineering in Medicine and Biology Conference, and IMPACT 2018.

Alex Shalek: In collaboration with clinicians at Brigham and Women's Hospital, the Shalek Lab leveraged Seq-Well, an ultra-high-throughput, low-cost, nanowell-based, single-cell RNA-Seq platform co-developed by the lab (Gierahn et al., *Nature Method*s, 2017), to systematically examine the cellular basis of the barrier tissue dysfunction that informs chronic allergic inflammation. Profiling minute primary human nasal surgical samples and scrapings that span the disease spectrum—from mild inflammation (rhinitis) to severe polyposis—they reported the first transcriptomes for human respiratory epithelial, immune, and stromal cell types/subsets from an allergic inflammatory disease, and mapped key mediators. They found striking differences between the epithelial compartments of the non-polyp and polyp cellular ecosystems, identifying and validating a global reduction of cellular subset diversity in polyps. Further, they detected an aberrant basal epithelial stem cell differentiation trajectory in polyps, and proposed cell-intrinsic, epigenetic, and cell-extrinsic factors that lock polyp basal progenitor cells into this uncommitted state. Finally, they functionally validated that basal cells ex vivo can retain intrinsic memory of allergic immune responses (IL-4/IL-13 secretion), and tested the potential for clinical administration of antibody blockade of these signals to restore basal and secretory epithelial cell states in vivo. Overall, their work demonstrated that epithelial stem cells may contribute to the persistence of human disease by serving as repositories for allergic memories.

In parallel, through local, national, and international collaborations, the Shalek Lab pursued deep mechanistic inquiry across a diverse array of species and tissue isolates, defining healthy tissue compositions as well as deviations induced by different infections (e.g., M. tuberculosis; HIV-1/SHIV; malaria; Ebola; HCV; HBV; leprosy), inflammatory diseases (e.g., ulcerative colitis in gut mucosa, psoriasis, alopecia, granuloma annulare), and cancers (e.g., pancreatic and lung cancer, leukemia, and leptomeningeal disease)—with a view to novel therapeutic and prophylactic ends.

Publication

Ordovas-Montanes, J., Dwyer, DF, Nyquist, SK, Buchheit, KM, Deb, C., Wadsworth, MH, Hughes, TK, Kazer, SW, Yoshimoto, E., Bhattacharyya, N., Katz, HR, Berger, B., Laidlaw, TM, Boyce, JA, Barrett, NA, & Shalek, AK, "Reduced cellular diversity and an altered basal progenitor cell state inform epithelial barrier dysfunction in human type 2 immunity," Nature, In Press.

Charles Sodini: The vision of the MIT Medical Electronic Device Realization Center (MEDRC) is to revolutionize medical diagnostics and treatments by bringing health care directly to the individual and to create enabling technology for the future information-driven healthcare system.

The MEDRC, launched in May 2011, currently has four member companies (ADI, Nihon Kohden, Novartis, Philips Research) supporting approximately 15 projects, with 25 students/postdocs, and seven principle investigators—with funding of approximately two million dollars annually.

The MEDRC serves as a focal point for engagement with researchers across MIT, the medical device and microelectronics industry, venture-funded startups, and the Boston medical community. Recently, there has been tremendous interest in digital biomarkers from local pharma companies to monitor and track neuro degenerative diseases. The center hopes to add a few local pharma companies to MEDRC in FY2019.

David Sontag: Sontag initiated several new collaborations to advance research on machine learning in health care. In collaboration with Dr. Sanjat Kanjilal, from MGH infectious diseases, and funded by a grant from the MGH-MIT Grand Challenge, Sontag began studying antibiotic resistance with the aim of using data in the electronic health record to predict a patient's antibiogram. Sontag launched a new project with Professor Eric Alm to develop a novel diagnostic method using untargeted metabolomics. Sontag also began two new projects funded by the MIT-IBM Watson AI Lab, the first on disease progression modeling, and the second on the opioid crisis. Sontag began serving as the theme lead for healthcare in the MIT-IBM Watson AI Lab, was the chair of the data subcommittee of MIT's committee on digital health, and served on a subcommittee of Governor Charlie Baker's Mass Digital Health Council.

Collin Stultz: Research in the Research Laboratory of Electronics (RLE) Computational Biophysics Group is focused on three areas: (1) understanding conformational changes in biomolecules that play an important role in common human diseases, (2) using machine learning to develop models that identify patients at high risk of adverse clinical events, and (3) developing new methods to discover optimal treatment strategies for high-risk patients. The group uses an interdisciplinary approach combining computational modeling and machine learning to accomplish these tasks.

In recent years, this group has become more involved in using machine learning for patient risk stratification. The team developed a neural network for predicting patients at high risk of adverse outcomes after an acute coronary syndrome. The method uses a novel feature engineering method to extract useful information for ECG time series. This was published in *Nature Scientific Reports*.

More generally, the group is working with MGH collaborators to develop an MIT-MGH Center for Cardiovascular Engineering and Data Science for Personalized Medicine. The proposed center represents a combined effort between MIT's Department of Electrical Engineering and Computer Science and the division of cardiology at MGH. Following several conversations with NIH, the group has been approved to apply for a grant to fund this center.

Publication

Myers, PD; Scirica, BM.; Stultz, CM. "Machine Learning Improves Risk Stratification After Acute Coronary Syndrome," *Nature Scientific Reports* 7 (2017), Article number: 12692.

Committee Chair

NIH, National Heart, Lung, and Blood Institute Board of Scientific Counselors Chairperson

Invited Talks

July 11, 2017, "Dynamics of alpha-synuclein aggregation," Drug Discover and Therapy World Conference, Boston MA.

August 25-29, 2017, "What does it mean for a protein to be disordered? Insights from experiment and molecular simulations," Biophysical Society Thematic Conference, Berlin Germany

May 9, 2018, "Enhancing ECG-based Risk Stratification for Patients at Risk for Sudden Cardiac Arrest," Ricbac Foundation, Boston MA.

Associate Faculty

Brett Bouma: Bouma's research focuses on the development of new instrumentation and methods for imaging and characterizing the microstructural properties of biological tissues. The work spans from innovation through development and into clinical applications in cardiovascular and gastrointestinal imaging. In the past year, Bouma's team has developed coherence polarimetry for measuring depth-resolved depolarization of light by tissue (*Nature Photonics* DOI:10.1038/nphoton.2017.128) and have applied this method for measuring the depolarization induced by the retinal pigment epithelium in the human eye (*Journal of Biophotonics*, accepted for publication). In parallel, the methodology for polarimetry has been applied for characterizing human coronary artery atherosclerosis. In the past year, the team conducted the first human clinical pilot study to image the coronaries of patients undergoing cardiac catheterization and have demonstrated robust reproducibility of polarimetric measurements (*Transactions in Medical Imaging*, DOI: 0.1109/TMI.2018.2815979). With this approach, they have demonstrated that polarimetry provides a unique, endogenous image contrast for determining coronary plaque composition (*Journal of the American College of Cardiology: Cardiovascular Imaging*,

Lydia Bourouiba: This past year, the Bourouiba Lab published key papers revisiting canonical fluid dynamics problems of droplet formation that are paving the way to new detection, tracking, and capture tools of droplets formed from the breakup of contaminated fluids with human health and food safety. She continued to establish fundamental collaborations with the Centers for Disease Control and Prevention and local infection control teams. She launched and executed the first phase of a flu transmission study this past spring, her team working closely with the MIT Clinical Research Center and MIT Medical Urgent care teams. Bourouiba's work continues to draw significant attention as she was selected to be one of the TEDMED speakers of 2018.

Selected Press

MIT News – "New theory describes intricacies of a splashing droplet," May 16, 2018.

Invited Talks

Bourouiba gave more than 12 invited talks, including as keynote speaker at the 2018 Engineering Mechanics Institute Conference and International Aerosol Conference, the 2017 Congress of the American Society of Mechanical Engineers, and the 2017 Congress of the International Society for Aerosols in Medicine. She presented talks at Stanford University, Fields Institute in Canada, Université Pierre et Marie Curie in France, at the US Food and Drug Administration, and at Novartis and Pfizer.

Selected Teaching and Service

Bourouiba continued to improve, expand, and teach two classes in which hands-on modules are being incorporated and tested for improved learning objectives.

1.631/HST.537/2.250 Fluids and Diseases. 2018 Instructor evaluation rating: 6.3/7

1.062/18.354/12.207 Nonlinear Dynamics and Turbulence. 2018 Instructor evaluation rating: 6.7/**7**

Polina Golland: In collaboration with colleagues at Mass General Hospital, Golland and her group aim to develop methods that will enable application of computational analysis pipelines to severely undersampled MRI scans typically acquired as part of the clinical practice. Their approach is to generate an anatomically plausible, high-resolution volume that is consistent with the clinical scan that can be analyzed by standard software. Golland and her collaborators use machine learning to build a model of anatomical variability from a large collection of clinical images and to fill in the missing values in these images. This work promises to enable computational analysis of the vast image collections accumulated by the hospitals as part of their routine imaging. The resulting insights would illuminate disease effects on anatomy and physiology from very large patient cohorts. This work is supported by the Neuroimage Analysis Center.

Publication

AV Dalca, KL Bouman, WT Freeman, NS Rost, MR Sabuncu, and P. Golland. "Population Based Image Imputation," In Proc., International Conference on Information Processing in Medical Imaging, LNCS 10265, 659-671, 2017.

Robert Langer: Throughout 2017 and early 2018, Langer received honorary degrees from the Gerstner Graduate School at Memorial Sloan Kettering Cancer Center, the National Institute of Astrophysics, Optics and Electronics (Mexico), the University of Illinois, the University of Limerick (Ireland), and the University of Laval (Canada). He received the Kabiller Prize in Nanoscience and Nanomedicine, the Memorial Sloan Kettering Medal for Outstanding Contributions to Biomedical Research, the American Chemical Society Leadership Award for Historic Scientific Advancement, and the Alpha Omega Dental Fraternity Achievement Medal Award.

Langer presented the Suslick-Sessler Lecture in Materials Chemistry (University of Illinois), the Henry Louis Smith Lecture (Davidson College), the Tetelman Lecture (Yale University), the Stetson Lecture (University of Vermont Larner College of Medicine), the Deloitte Endowed Lecture (Dana-Farber Cancer Institute), the Alfred Stracher Memorial Lecture (State University of New York Downstate Medical Center), the Bernal Distinguished Lecture (University of Limerick, Ireland) and the Anderson Distinguished Lecture (University of Virginia School of Medicine). He was also the commencement speaker for the Memorial Sloan Kettering Cancer Center's Gerstner Graduate School.

Phillip A. Sharp: Recent recognition that liquid-liquid phase transitions in cells can concentrate factors into membraneless bodies in cells and that RNA is frequently a component of these assemblies stimulated the speculation that super-enhancers, SEs, might be a manifestation of these phenomena. Richard Young introduced the concept of SEs as large regions of DNA bound by transcription factors that dramatically stimulate

transcription from proximal promoters. Further, he showed that SE-associated genes are frequently critical for normal development and that new SEs appear near many disease genes. Given that phase transitions can concentrate factors in a highly cooperative fashion to enhance the rate of reactions, we conjectured that SEs function as a large membraneless assembly of factors that enhanced the rate of transcription from adjacent promoters. In collaboration with the Chakraborty and Young Labs, we developed a model of phase transitions that illustrated their high dependence on valences and low dependence on affinity (Hinsz et al., 2017) and outlined how its properties are consistent with many of the known phenotypes of SEs. Over the past year, this team has shown that SEs associated with specific genes have dynamic properties of condensates formed by liquid-liquid phase transitions (reference below). Since these condensates are highly sensitive to drug inhibitors that reduce the valency of interactions between their constituent, this insight potentially offers new opportunities to treat many diseases. This research is ongoing.

Publication

Sabari, BR; Dall'Agnese, A.; Boija, A.; Klein, IA; Coffey, EL; Shrinivas K.; Abraham BJ Hannett, NM; Zamudio, AV; Manteiga, JC; Li, CH; Guo, YE; Day, DS; Schuijers, J.; Vasile, E.; Malik, S.; Hnisz, D.; Lee, T.; Cisse, II; Roeder, RG; Sharp, PA; Chakraborty, AK; Young, RA. "Coactivator condensation at super-enhancers links phase separation and gene control." *Science*. June 21, 2018, pii: eaar3958. doi: 10.1126/science.aar3958. [Epub ahead of print]

Leia Stirling: The aim of Stirling's research is to quantify human performance and human-machine fluency in operational settings by advancing the use of wearable sensors for space, medical, and military applications. Team fluency is the well-synchronized meshing of actions between a human and system and is required for coordinated human-in-the-loop tasks. Quantifying these measures is key for augmenting human performance, mitigating injury risk, and providing relevant feedback to subject matter experts across many domains. Development of human-in-the-loop applications requires understanding the human capability to complete required tasks while utilizing additional technology, such as exosystems (rigid exoskeletons and soft exosuits). In many domains, human motor performance is assessed visually by subject matter experts, but what is needed is the capability to assess performance when direct visual assessment is not possible. Stirling enhances the ability to make decisions when the person is not observable (e.g., an astronaut in a spacesuit), the subject matter expert is not present (e.g., telehealth), or the action is fast (e.g., military readiness) by enabling wearable sensors to quantify these qualitative assessments. While wearable sensors passively sense information about humans or their environment, exosystems are technologies that actively affect human motor actions, and may restore, enhance, or provide new human perceptual, cognitive, or physical abilities. The active assist is informed by wearable sensors and needs to anticipate and co-adapt with the operator. Through her research, Stirling enables wearable sensors and exosystems to be translated to operational environments.

Publications

Stirling, Leia, and Julie MacLean. "Roadmap for the Development of at-Home Telemonitoring Systems to Augment Occupational Therapy." *IEEE Transactions on Human-Machine Systems* 46, no. 4 (2016): 569-580.

Stirling, Leia, Chika Eke, and Stephen Cain. "Examination of the Perceived Agility and Balance During a Reactive Agility Task." PLoS ONE 13, no. 6 (2018).

Bequette, Blake, Adam Norton, Eric Jones, and Leia Stirling. "The Effect of a Powered Lower-Body Exoskeleton on Physical and Cognitive Warfighter Performance," Human Factors and Ergonomics Society Annual Meeting, Philadelphia, PA, 2018.

McGrath, Timothy, Richard Fineman, and Leia Stirling. "An Auto-Calibrating Knee Flexion-Extension Axis Estimator using Principal Component Analysis with Inertial Sensors." *Sensors* 18, no. 6 (2018).

Stirling, Leia, Ho Chit Siu, Eric Jones, and Kevin Duda. "Human Factors Considerations for Enabling Functional Use of Exosystems in Operational Environments." *IEEE Systems Journal* (in Press).

Peter Szolovits: Szolovits continued to do research on natural language processing of clinical notes and building predictive models that estimate the risks of various morbid events and the likelihood of success of different therapeutic interventions. He served as overall Principal Investigator of the medical collaboration between Philips and MIT and continues to collaborate with colleagues at MGH, Harvard Medical School, University of Massachusetts at Lowell, and George Mason University on a variety of projects. One of his doctoral students, Tristan Naumann, has finished his PhD and is joining Microsoft Research, probably with an adjunct faculty appointment at University of Washington. Szolovits' postdoc, Marzyeh Ghassemi, is joining the computer science faculty at University of Toronto. The group has participated in several conference and had a number of journal publications.

Laurence Young: The following publications were authored by Lawrence Young.

Publications

Clark T.K., Young L.R., "A Case Study of Human Roll Tilt Perception in Hypogravity." *Aerospace Medicine and Human Performance*, 2017 Jul 1; 88(7) 682–687. PMID: 28641686.

Diaz-Artiles, Ana, Priesol, Adrian J., Clark, Torin K., Sherwood, David P., Oman, Charles M., Young, Laurence R., Karmali, Faisal, "The Impact of Oral Promethazine on Human Whole-Body Motion Perceptual Thresholds," Journal of the Association for Research in Otolaryngology, August 2017, Volume 18, Issue 4, pp. 581–590

Charles, J., Young, L.R., et.al. "Review of NASA's Evidence Reports on Human Health Risks: 2017 Letter Report," The National Academies of Sciences, Engineering, and Medicine, 2018, Washington, DC: The National Academies Press.

Professors of the Practice

Joseph Frassica: Frassica leads the Philips Research Americas Laboratories. His research interests cover a broad range of topics from the use of high-resolution physiologic data and clinical information to create predictors of patient trajectories in critical care, developing new measurements for ultra-mobile ultrasound to the application of whole genome sequencing, to tracking the spread of multi-resistant bacteria within geographies and health care environments.

Over the past several years, the Philips Genomics team has collaborated with several clinical and academic partners including the University of Massachusetts and New York Medical College to develop and test a system that combines genomic and clinical data to provide real-time insights into the spread of hospital acquired infections.

The lab recently won a joint Department of Defense Grant in collaboration with Professor Heldt to develop a prototype of a device to non-invasively measure intracranial pressure. This $3 million grant spans three years and will bring to life a concept initially developed by Heldt. The combined expertise of the Heldt and Philips Labs has moved this novel idea closer to the bedside. Philips North America Laboratory continues its collaborations with multiple labs across the Institute.

This past year, Frassica taught the Respiratory Physiology spring 2018 section of 6.022 Quantitative Systems Physiology.

Bruce Walker: Walker—director of the Ragon Institute of MGH, MIT, and Harvard, and Howard Hughes Medical Institute Investigator—was appointed professor of the practice in IMES at MIT in 2016.

The over arching goal of the Walker Laboratory is to define the interplay of immunologic, virologic, and host genetic factors that determine control of human viral infections, and to guide vaccine development and immunotherapeutic interventions. To address this goal, the lab focuses on HIV infection, an ongoing global epidemic with enormous medical, societal, and economic implications. A global solution requires an effective vaccine or cure, which remains elusive. A fully preventive HIV vaccine will likely require induction of broadly neutralizing antibodies (bNAbs) and effective T cell immunity, which have thus far defied induction by vaccination. However, optimism for vaccine-mediated control derives from infected individuals who maintain T cell-mediated HIV control without treatment ("controllers"), some for 35 years or more. Vaccines currently entering efficacy trials are unlikely to fully prevent infection, but would represent a successful "functional cure" if vaccines maintain viremia below this level. The Walker Lab focuses on understanding this remarkable T cell-mediated control of HIV, building on successive discoveries by studying human immunology in HIV-infected persons. Notable past advances include the initial description of HIV-specific CD8+ T lymphocytes (CTLs) and CD4+ T lymphocytes; immune enhancement through antiretroviral therapy; immune dysregulation by PD-1 and CTLA-4; CTL escape in HIV transmission, progression, super-infection, and viral fitness; and the interplay of HLA and epitope recognition in viral control and evolution.

During the past year, the Walker Lab has leveraged extensive investments in unique patient cohorts, collaborative networks in Africa, and investments in new research facilities to define mechanisms of immune control, immune failure, and immune enhancement in infected persons. Notable accomplishments include studies demonstrating that infected macrophages contribute to HIV pathogenesis due to impaired killing of macrophages by CTLs relative to the killing of CD4+ T cells associated with prolonged effector cell-target cell contact and enhanced production of pro-inflammatory chemokines that recruit monocytes and T cells (*Nature Immunology*, PMC5526341). Similar results were obtained when macrophages presented other viral antigens, suggesting a general mechanism for macrophage persistence as antigen-presenting cells that enhance inflammation and

adaptive immunity. The lab also continued to collaborate with investigators in KwaZulu-Natal Province, South Africa, expanding research capacity through investments in infrastructure, equipment, and cohorts. Given the 8%–10% yearly HIV incidence in young women in KwaZulu-Natal, the FRESH (Females Rising through Education, Support and Health) cohort was established with two goals: to study "hyperacute" infection from the onset of plasma viremia and to provide a pathway out of poverty by incorporating a twice-weekly curriculum aimed at empowerment, life skills, and HIV prevention education—with the goal of eventual placement in school or employment. The lab has shown that HIV-specific antibody responses are impaired with early treatment of infection, yet T cell responses are robust and exhibit features associated with long-term memory formation that are absent in persons with untreated infection.

Other collaborative studies address the mechanisms of host genetic modulation of HIV disease outcome. In a study of 9,763 HIV-infected individuals performed with one of the founding members of the Ragon Institute, Mary Carrington, higher HLA-A levels were shown to confer poorer control of HIV due to enhanced levels of an HLA-A-derived signal peptide that specifically binds and determines expression levels of HLA-E, the ligand for the inhibitory NKG2A natural killer (NK) cell receptor (*Science*, PMC5933048). HLA-B haplotypes that favor NKG2A-mediated NK cell licensing exacerbate the deleterious effect of high HLA-A on HIV control, consistent with NKG2A-mediated inhibition impairing NK cell clearance of HIV-infected targets. Therapeutic blockade of HLA-E:NKG2A interaction may yield benefit in HIV disease. Additional studies using samples from persons who are able to control HIV without the need for antiviral medications revealed modulation of immune control of HIV by NK cells (*The Journal of Clinical Investigation*, PMC5919796) and dendritic cells (*Genome Biology*, PMC5789701).

In separate, collaborative studies with Ronald Weiss at MIT, the Walker Lab contributed to the development of new technologies through demonstration of the utility of a modular platform for intrabody-based protein sensing-actuation developed by the Weiss Lab. This method provides a means to link varying cellular conditions with robust control of cellular behavior for scientific and therapeutic applications (*Nature Communications*, PMC5951936).

In the past year, Walker's scientific contributions have been recognized through receipt of the German Heinrich-Pette lectureship and presentation of the Plenary Lecture for the Keystone Symposium on tuberculosis and HIV. Walker teamed up with Howard Heller to teach the highly popular undergraduate course Evolution of an Epidemic in South Africa in January. The class consisted of both lectures and field trips to interact with affected communities and visit traditional healers, hospitals, and clinical research sites. In addition, in 2017 Walker's HHMI funding was renewed for another seven years.

Events

HST Faculty Poster Session

Approximately 125 people attended the 2017 HST Faculty Poster Session, held on October 5 at the Courtyard Café at Harvard Medical School. Thirty-nine faculty posters representing 35 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 into their laboratories. It also assists students beginning the process of selecting laboratories and mentors for their research.

HST Forum

The 32nd HST Forum was held on April 12, 2018, 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 125 people attended the Forum, including 42 students who presented posters on their current research. The poster session was followed by a keynote address given jointly by Harvard Medical School professor Benjamin Ebert and his advisee, HST MD-PhD student Emma Fink, in which they provided the audience with a view of a dynamic mentor/mentee relationship.

The following students received the Martha Gray Prize for Excellence in Research in the categories named:

- Nil Gural (MEMP) Bioinformatics and Integrative Genomics
- Ryan Park (MD) Physiology and Systems Biology
- David Miranda-Nieves (MEMP) Biomedical Devices
- Annabelle Anandappa (MD) Cell and Molecular Biology
- Agata Wisniowska (MEMP) Imaging, Acoustics, and Optics
- Rida Mourtada (MEMP) Regenerative and Rehabilitative Biomedical Engineering

Distinguished Speaker Series

This year, IMES organized three invited lectures that included the following speakers and subjects:

- Michaek Longaker. "Skin and Bones: Scar Wars and Skeletal Steam Cells." October 19, 2017
- Mauro Ferrari. "Post-Nanomedical Vistas." February 15, 2018
- Joseph Loscalzo. "Disease Networks and Drug Discovery." April 19, 2018

Research Progress Talks

IMES hosted a series of events to increase awareness of different research within the Institute. Each month, postdocs and students from two lab groups presented their research to the IMES community, including faculty, researchers, students, and staff. These events encourage collaboration between labs at IMES and are great opportunities for postdocs to practice their talks before applying for jobs or presenting at conferences.

Elazer Edelman
Director