MIT Research Applicable to Point-of-Care Medical Diagnostics

This report by MIT's Industrial Liaison Program identifies selected MIT faculty and research staff whose expertise and research activities are potentially applicable to development of point-of-care and at-home medical diagnostic equipment and methods. MIT's research falls into the following categories, as illustrated in this report:

1. Wearable medical sensors and systems
2. Spectrophotometric diagnostic methods
3. Nanomaterials useful in diagnostics
4. “Lab-on-a-chip” technology that could be the basis for point-of-care wet-chemical diagnostic instrumentation
5. Computation, modeling, analysis

For more information, please contact MIT's Industrial Liaison Program at +1-617-253-2691.

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WEARABLE MEDICAL SENSORS AND SYSTEMS

Bioinstrumentation systems; wearable sensors; sensing environments

PROF. H. HARRY ASADA
Ford Professor of Engineering; Director, d’Arbeloff Robotics Lab; Head, Control, Instrumentation, and Robotics, http://meche.mit.edu/people/faculty/index.html?id=5

Research Interests: Robotics, Biomedical Engineering, Dynamic Systems and Control, Information Technology, Design, and Manufacturing

“Wearable blood pressure sensor offers 24/7 continuous monitoring: Device could help diagnose hypertension, heart disease”
Anne Trafton, News Office, April 8, 2009

...Visits to the doctor’s office can provoke anxiety that distorts blood pressure readings, and even when accurate, such visits provide only one-time snapshots of the patient's condition. To overcome these obstacles, MIT engineers have built a wearable blood pressure sensor that can provide continuous, 24-hour monitoring.

Blood pressure can change from minute to minute, so continuous monitoring offers a much broader picture of cardiovascular health. The new monitor, which loops around the wrist and the index finger, is just as accurate as traditional cuff devices but much less cumbersome, allowing it to be worn for hours or days at a time.

"The human body is so complex, but the cuff gives only snapshot data," says Harry Asada, an MIT mechanical engineer who led the development of the new monitor. "If you get signals all of the time you can see the trends and capture the physical condition quite well."

Such devices could be used to keep tabs on hypertension as well as sleep apnea, which causes sufferers to stop breathing many times throughout the night. Eventually, doctors may be able to use data gathered from continuous monitoring to predict when a heart attack may occur, says Asada, the Ford Professor of Engineering and director of MIT’s d’Arbeloff Laboratory for Information Systems and Technology.

CardioSign, a company launched by Asada's former student, is working on commercializing the device and hopes to start clinical trials soon. Asada said he believes a commercial version of the device could be available within five years... See: http://web.mit.edu/newsoffice/2009/blood-pressure-tto408.html

Wearable Sensors and Wearable Health Monitoring
Date: 01/03/08, d’Arbeloff Laboratory Bio-Robotics Program

The ultimate objective of our wearable sensors / wearable health monitoring research is to enable adaptive, real-time, continuous and non-invasive healthcare for home and out-of-hospital
environments. To this end, we are investigating (1) novel sensor technologies to develop biosensors that can measure high-quality biological signals, and (2) advanced system identification and signal processing algorithms to extract valuable clinical information therein.

http://darbelofflab.mit.edu/node/28

**Wearable Blood Pressure Estimation Using Adaptive Hydrostatic Calibration of Peripheral PTT Measurements**

... We are working towards the development of an optical based blood pressure sensor that utilizes adaptive hydrostatic calibration to estimate blood pressure from peripheral pulse transit time (PTT) measurements. The device combines not only a unique dual in-line photoplethysmograph device architecture with the adaptive hydrostatic calibration but also novel system identification techniques to accurately estimate the calibration parameters.

http://darbelofflab.mit.edu/node/28

**Multi-Channel Cardiovascular System Identification for Cardiovascular Health Monitoring**

... In an attempt to resolve the above mentioned problem and extend the CV monitoring techniques to diverse physiologic conditions, we came up with an innovative idea that by having additional peripheral measurements the CV system can be viewed as a multi-channel system, and this multi-channel CV system can be identified by exploiting the blind system Identification methodology, which is able to identify multi-channel systems without using the unknown input signal. We have been investigating several aspects related to this multi-channel CV system Identification problem including the model structures, identification / de-convolution algorithms and persistent excitation / model identifiability / asymptotic variance analysis...

http://darbelofflab.mit.edu/node/28

**PROF. ANANTHA P CHANDRAKASAN**


Prof. Chandrakasan’s research interests include micro-power digital and mixed-signal integrated circuit design, wireless microsensor system design, ultra-wideband radios, and emerging technologies.

**Platforms for Ultra-Low-Power Biomedical Electronics**

The Platforms for Ultra-Low-Power Biomedical Electronics team leverages highly digital techniques to increase energy efficiency of circuits and systems used in physiological sensing and activation. The broad scope of the group covers the IC design and platform integration of stimulation circuits, instrumentation front ends, analog-to-digital converters, digital signal processors, electronic textiles, and wireless transceivers.

http://www-mtl.mit.edu/ulp_medical/projects.shtml
**EEG Acquisition & Processing**

Principal Investigators: Profs. Anantha P Chandrakasan, John Guttag

... This project aims to develop very low-power and integrated EEG acquisition circuits, digitization circuits, and processing circuits to derive and classify feature-vectors for a continuous, wearable seizure detection system suitable for everyday use by epilepsy patients. The implemented algorithms are based on 536 hours of patient tests to ensure efficacy, and the system is intended to be highly portable and low-power for very long-term use.

http://www-mtl.mit.edu/ulp_medical/epilepsy.shtml


**Healthy Radios**

Principal Investigators: Profs. Anantha P Chandrakasan, Dina Katabi, Muriel Medard, Dana Weinstein

An important emerging application direction is personal and environmental health monitoring, where physiological and mechanical signals of people, machines, and buildings are monitored in a preventative fashion to ensure optimal operation and improved quality of life. Monitoring is accomplished by acquiring data and transmitting it over a self-forming wireless network for further processing and observation at a remote site. Unfortunately, traditional wireless techniques require circuits that consume significant energy, forcing devices to use large, obtrusive batteries. Body-worn applications in particular require small devices that can last for days, weeks, years or potentially forever, depending on the application. In many cases, the devices must operate from an energy scavenging source (e.g., body heat, ambient lighting or human motion), which can be highly unreliable. While considerable work has been done in the area of wireless sensor networks over the past decade, a number of new challenges is presented by Body Area Networks (BANs).

http://www-mtl.mit.edu/ulp_medical/healthy_radios.shtml

**Wearable EKG Platform**

Principal Investigators: Profs. Anantha P Chandrakasan, Joel Dawson, Charles Sodini

Advances in mobile electronics are fueling new possibilities in personal ambulatory medical monitoring, in which sophisticated, wearable devices can monitor a patient’s vital signs. As illustrated in the figure below, these signals can be securely transmitted via a local relay (often a cell phone or PDA) to the internet, whereby a physician or an emergency medical monitoring center can observe the data for preventative medicine, diagnostics, or emergency monitoring purposes.
This project aims to develop a platform of scalable, energy-efficient integrated circuits such as reconfigurable analog front-end circuits, ultra-low voltage medical processors and short range communication circuits involving body-area networks to consolidate and transmit sensor node data. From a system level perspective, reconfigurability (in voltage, bandwidth and precision) in the front-end circuits is needed to accommodate a wide range of physiologic signals which can vary by several orders of magnitude in amplitude and frequency... More at: http://www-mtl.mit.edu/ulp_medical/wearable_ekg.shtml

A Micro-Power EEG Acquisition SoC with Integrated Seizure Detection Processor for Continuous Patient Monitoring

Principal Investigator: Prof. Anantha P Chandrakasan
Other Investigator: Prof. John V Guttag
Date: 10/19/09, MTL

Epilepsy, a neurological disorder affecting 50 million people worldwide, causes sudden seizures that result in convulsions, loss of coherence, or even death. Seizure detection, before the onset of these symptoms, can improve the lives of patients tremendously by providing an early warning to them and their caregivers, or by triggering therapy to stop the seizure. Early detection, however, requires sophisticated processing to separate normal and abnormal neural activity, which varies greatly from patient-to-patient.

We present a system-on-chip, integrating an ultra-low-power instrumentation amplifier, ADC, and digital processor. The chip continuously senses a patient’s neural firings through non-invasive electrodes on the scalp (i.e. EEG). The neural signals are processed to extract the subtle information necessary to detect seizure onset. Seizures are then detected through further processing using a machine-learning classifier. By compressing the neural information, it can be transmitted wirelessly with 14x lower system power, eliminating hazardous cables from the patient’s scalp. The detection algorithm has been tested through 536 hours of patient tests, and the chip consumes less than 10 micro-Watts/channel (depending on the patient, up to 18 channels may be used).

Wearable Medical Monitoring Platform

Date: 10/16/09, Microsystems Technology Laboratories

Advances in mobile electronics are fueling new possibilities in medical monitoring in which sophisticated, wearable devices can monitor a subject’s vital signs. These signals can be securely transmitted over the internet via a local relay (often a cell phone or PDA) for preventative medicine, diagnostics, or emergency monitoring purposes. In these applications, comfort and convenience are important considerations, motivating a high level of integration to achieve small form factors and long operating lifetimes from a small battery or scavenged energy. Fortunately, the low rates of biological signals, which are typically on the order of tens to hundreds of Hz, make basic monitoring applications amenable to low-power processing. To support the wide range of signals, sensors, and algorithms, we propose a reconfigurable and energy-efficient platform for medical monitoring.

The system requires a flexible sensor front-end and ADC that can interface with different types of sensors. The sensor front-end must have adjustable gain, bandwidth, and noise settings, as signals from different sensors can vary by several orders of magnitude in amplitude and...
The ADC should have configurable resolution from 8 to 12 bits to enable a variety of applications. A processor retrieves the digitized data from the ADC and performs local processing tasks specified in software. To save energy, the processor can operate at a low voltage and frequency when executing simple algorithms, but it maintains flexibility by elevating its voltage when high performance is needed. The architecture includes hardware accelerators to speed up computations. When not in use, each accelerator can be powered off to reduce idle leakage. To further save energy, local sensor nodes transmit processed data only to the local relay, instead of directly to the cellular network. The short transmission distance (1-2m) and inherently low data rates (1-10kbps) promote the design of highly-digital, energy-efficient communication circuits involving wired clothing networks and/or wireless ultra-wideband. A high-powered radio, as typically found in a PDA, can then consolidate sensor node data and transmit them over the cellular network to the internet for monitoring purposes.

“Self-powered sensors”
MIT News, February 11, 2010

...It can be inconvenient to replace batteries in devices that need to work over long periods of time. Doctors might have to get beneath a patient’s skin to replace batteries for implanted biomedical monitoring or treatment systems. Batteries used in devices that monitor machinery, infrastructure or industrial installations may be crammed into hard-to-reach nooks or distributed over wide areas that are often difficult to access.

But new technology being developed by MIT researchers could make such replacements unnecessary.

Soon, such devices could be powered just by differences in temperature between the body (or another warm object) and the surrounding air, eliminating or reducing the need for a battery. They would use new energy-scavenging systems being developed by Anantha Chandrakasan, MIT’s Joseph F. and Nancy P. Keithley Professor of Electrical Engineering and director of the MIT Microsystems Technology Laboratories, and Yogesh Ramadass SM ’06, PhD ’09...

PROF. JOEL L DAWSON
Mark Hyman, Jr Career Development Associate Professor of Electrical Engineering; Chair, Microsystems Technology Laboratories (MTL) Seminar Series Committee,
http://www-mtl.mit.edu/~jldawson/

The Dawson research group designs RF and mixed-signal CMOS ICs for communications systems and medical applications. Our research approach centers on the idea that we work in an extremely interesting era for such circuits. Economic forces favor a heavily digital chip, and it is often not profitable to make device and process concessions for the analog circuits. Given that we have millions of digital gates at our disposal, together with analog devices that are fast but otherwise far from ideal, what is the new optimal division of functionality between the analog and digital domains? We seek answers to this question in part by exercising architectural creativity. In addition, we explore the application of mathematical optimization techniques to allocate resources between analog and digital subsystems.
Digitally-Assisted Analog Front-End for Biomedical Sensors

Principal Investigator: Prof. Joel I Dawson
Other Investigator: Prof. Anantha P Chandrakasan, Joseph F and Nancy P Keithley Professor of Electrical Engineering; Director, Microsystems Technology Laboratories (MTL), http://www-mtl.mit.edu/~anantha/index.html
Date: 10/19/09, Microsystems Technology Laboratories

Biomedical sensors are used to measure a myriad of biopotential signals including electroencephalogram (EEG), electrocardiogram (EKG), electromyogram (EMG), and neural field potential (NFP) signals. Most of the useful information in these signals resides in the frequency range of 0.5 Hz to 1 kHz, allowing ultra-low power circuits to be used when processing them. This is critical for systems that are implanted, since energy is extremely scarce, and the lifetime of the device must be on the order of 10 years. Unfortunately, these signals are often as small as 10 µVs, and their low frequency location make them vulnerable to aggressors such as DC offset, powerline noise, and flicker noise. DC offset can result from charge accumulation at the interface between the metal electrodes and the skin, and also from amplifier offsets caused by random mismatches. While chopper stabilization has proved effective at mitigating the effects of amplifier DC offset and flicker noise, electrode DC offset cannot be removed through chopping and must be high-pass filtered at the front end of the system to prevent saturation. Powerline noise, typically at 50 or 60 Hz, is mostly a common-mode signal that requires adequate common-mode rejection. However, if there are mismatches or inductive loops in the electrodes, these aggressors can become differential-mode signals, corrupting the desired signal, and potentially saturating the system. In closed-loop deep brain stimulation systems, another aggressor arises from stimulation artifacts. In that case, the NFPs can be much smaller than stimulation artifacts placing stringent requirements on the dynamic range of the system and potentially leading to signal corruption.

We propose a mixed-signal sensor interface that mitigates the effects of all of the aforementioned aggressors in an area efficient manner. Area efficiency is particularly compelling in implantable devices that use tens or hundreds of electrodes, such as neural recording systems. The proposed system uses a chopper stabilized operational amplifier with capacitive feedback to achieve accurate gain (The system is shown as single-ended for simplicity, but is implemented in a fully differential manner). We show a simplified schematic of the amplifier, including a novel input chopper that creates a switched capacitor resistance between its inputs and a reference voltage. This resistance is shown as Rp and is used to create a high-pass filter with a corner frequency well below 1 Hz, while setting the common-mode voltage of the input to a desired level. The pole frequency is actually set by the Miller-multiplied feedback capacitor Cf and is inversely proportional to the amplifier’s gain AV, allowing a reduction of many orders of magnitude in component sizes. An additional feedback path is introduced that includes the filter, ADC, DSP, and a feedback DAC. This path can be used to notch out unwanted signals such as powerline noise or stimulation artifacts before they can saturate the system.

SAR ADC with Local Supply Capacitors and Adiabatic Charging for Use in Medical Implants

Date: 10/19/09, Microsystems Technology Laboratories

The proposed research program has two primary goals. The first goal is to improve the evaluation and treatment of patients with diabetes and a variety of movement disorders, including Parkinson’s disease, restless legs syndrome, and essential tremor, by allowing doctors to...
continuously monitor relevant biomarkers over much longer time scales and with better precision than currently possible. The second goal is that the proposed implant be a platform for electronic sensory monitoring that is inexpensive and flexible and that can be used with a wide variety of sensors and for a wide variety of purposes, such as chemical sensors for monitoring blood chemistry. In this work, we develop an energy-efficient analog-to-digital converter designed to operate with a power management scheme using ultracapacitors as opposed to a battery.

Two techniques are employed to save on energy for the entire system. The first is the use of an integrated capacitor that acts as a local supply for the data conversion circuit. This technique allows for us to duty-cycle the bandgap reference circuit used for power management. The second technique is to use adiabatic charging of the capacitors contained in the SAR ADC. This application is ideal for adiabatic techniques because of the low frequency of operation and the ease with which we can reclaim energy from discharging the capacitors. Building on the application, the integrated capacitor acting as a local supply allows us to reclaim energy without having to design any energy-recovery circuitry.

Ultra-low Power, Energy-efficient Platform for Biomedical Implants

... To make medical implants more attractive, there is a need to reduce their size and power consumption. Small medical implants would allow for less invasive procedures and greater comfort for patients. Reductions in power consumption translate to longer battery life. The two primary limitations to the size of small medical implants are the batteries that provide energy to circuit and sensor components and the antennae that enable wireless communication to terminals outside of the body.

This research looks to explore and combine unconventional approaches to ultra-low power and adiabatic techniques, ultracapacitor-based energy sources, RFID links, and fractal geometry antennas to achieve the goals of micro-miniaturization and ultra-low power operation. http://www-mtl.mit.edu/~jldawson/research_group/group_projects.html#micro

PROF. JOHN V GUTTAG

Professor Guttag does his research in the Laboratory for Computer Science, where he is co-leader of the Networks and Mobile Systems Group. This group studies issues related to computer networks, applications of networked and mobile systems, and advanced software-based medical instrumentation systems. Professor Guttag has also done research, published, and lectured in the areas of software engineering, mechanical theorem proving, hardware verification, compilation, software radios, and medical computing.

Enhancing a Patient-Specific, Scalp-EEG Seizure Onset Detector
Entry Date:  01/29/09, Department of Electrical Engineering and Computer Science

* Abstract unavailable *
**Finding Medically Relevant Patterns in Lengthy Streams of Physiological Data**

Date: 03/13/09, Harvard-MIT Division of Health Sciences and Technology; Center for Integration of Medicine & Innovative Technology (CIMIT)

* Abstract unavailable *

**PROF. IAN W HUNTER**


**BioInstrumentation Laboratory**

Modern experimental research requires the combination of many traditional disciplines including biology, optics, mechanics, mathematics, electronics and chemistry. The BioInstrumentation Laboratory is uniquely placed to bring together these areas of research with its broad array of students and postdoctoral research scientists from diverse fields. In addition, the lab maintains extensive laboratory facilities to allow our researchers to move quickly from a device concept to a prototype and rapidly iterate their designs. Research at the BioInstrumentation Laboratory includes a number of fields including conducting polymer chemistry, medical devices, wireless instrumentation, and actuator design. [http://bioinstrumentation.mit.edu/mediawiki/index.php/Main_Page](http://bioinstrumentation.mit.edu/mediawiki/index.php/Main_Page)

**Measurement, Instrumentation, Control, and Automation (MICA) Project**

Principal Investigator: Prof. Ian W Hunter
Other Investigators: Dr. Nora Catherine Hogan (Cathy), Dr. Lynette A Jones, Serge R LaFontaine, Bryan P Ruddy
Date: 03/02/10

The MICA (Measurement, Instrumentation, Control, and Automation) Project is a research and development project aimed at producing a line of sensors and generators, linked together wirelessly and controlled from a laptop. The system is intended to be a high level, minimal configuration system that is both simple to use and extend, while powerful and accurate enough for laboratory research.

**PROF. SANG-GOOK KIM**


His research and teaching at MIT has addressed issues in bridging the gap between scientific findings and engineering innovations, developing novel manufacturing processes for newly-
developed materials, and designing and realizing new product at micro- and nano-scales, which include carbon nanotube assembly, muscle inspired actuators and MEMS energy harvesters.

Self-Powered Systems for Autonomous Sensing for Biomedical and Other Applications
Principal Investigator: Prof. Sang-Gook Kim
Other Investigators: Prof. Anantha P Chandrakasan, Prof. Martin A Schmidt
Date: 11/23/09, Microsystems Technology Laboratories

Researchers are developing technologies that would enable autonomous sensing for biomedical and other applications. Energy for autonomous sensors can be harvested from environmentally available vibration and processed via intelligent, low-power control circuitry. Working closely with researchers who are creating energy storage devices to buffer energy from the scavenging device, they will develop systems capable of collecting information for either continuous broadcasting or periodic read out. Example of application: A self-powered sensor system that can be used for remote wireless sensing (i.e., self-powered accelerometer). Packaging will be explored for integrating MEMS and CMOS devices (fabricated in a standard off-the-shelf technology) together.

PROF. JOSEPH A PARADISO
Sony Corporation Career Development Associate Professor of Media Arts and Sciences; Head, Responsive Environments Group, http://www.media.mit.edu/people/jeop

Joseph Paradiso is the Sony Career Development Associate Professor of Media Arts and Sciences at the MIT Media Laboratory, where he directs the Responsive Environments group, which explores how sensor networks augment and mediate human experience, interaction, and perception. In addition, he co-directs the Things That Think Consortium, a group of industry sponsors and Media Lab researchers who explore the extreme fringe of embedded computation, communication, and sensing.

sportSemble
Date: 04/14/09, MIT Media Laboratory

A high-speed wearable wireless sensor network that enables direct measurement and analysis of the extreme forces that an athlete’s body experiences during activity. These measurements allow sports medicine doctors to understand, treat and prevent sports injuries... Sportsemble bypasses these issues by directly measuring the extreme acceleration and rotational forces acting on an athlete ten times faster than standard camera systems, and can be used anywhere with minimal setup time.

The data from our system provides the ability to understand the forces and torques that an athletes joints and body segments undergo during activity. It also allows for precise biomechanical modeling of an athletes motion. These two married together give the ability to recognize and analyze different styles of athletic gesture...
http://www.media.mit.edu/resenv/sportSemble/
PROF. ROSALIND W PICARD
Professor of Media Arts and Sciences; Head, Affective Computing Group; Co-Director, Things That Think (TTT) Consortium,  http://www.media.mit.edu/people/picard

The author of over 140 peer-reviewed scientific articles in multidimensional signal modeling, computer vision, pattern recognition, machine learning, and human-computer interaction, Picard is known internationally for envisioning and conducting research in affective computing—computing that relates to, arises from, or deliberately influences emotion or other affective phenomena—and, prior to that, for pioneering research in content-based image and video retrieval... She and her students have designed and developed a variety of new sensors, algorithms, and systems for sensing, recognizing, and responding respectfully to human affective information, with applications in human and machine learning, health, and human-computer interaction.

Heartphones
Date: 01/11/10, MIT Media Laboratory

We are developing wearable sensors that measure cardiovascular parameters such as heart rate and heart rate variability (HRV) in real time. HRV provides a sensitive index of autonomic nervous system activity. These sensors will be capable of communication with mobile devices such as the iPhone and iPod Touch.  http://affect.media.mit.edu/projects.php?id=2594

Infant Monitoring and Communication
Date: 01/11/10, MIT Media Laboratory

We have been developing comfortable, safe, attractive physiological sensors that infants can wear around the clock to wirelessly communicate their internal physiological state changes. The sensors capture sympathetic nervous system arousal, temperature, physical activity, and other physiological indications that can be processed to signal changes in sleep, arousal, discomfort or distress, all of which are important for helping parents better understand the internal state of their child and what things stress or soothe their baby. The technology can also be used to collect physiological and circadian patterns of data in infants at risk for developmental disabilities. http://affect.media.mit.edu/projects.php?id=2769

Passive Wireless Heart-Rate Sensor
Date: 04/14/09, MIT Media Laboratory

We have developed a low-cost device that can wirelessly detect a beating heart over a short distance (1m) and does not require any sensor placed on the person's body. This device can be used for wireless medical/health applications as well as security and safety applications, such as automobile/truck drivers as well as ATM machines. We have also created a small battery-powered version of this sensor that can be worn on a person's clothing but does not require touching the person's skin. http://affect.media.mit.edu/projects.php?id=2684

Sensor-Enabled Measurement of Stereotypy and Arousal in Individuals with Autism
Date: 04/14/09, MIT Media Laboratory

A small number of studies support the notion that there is a functional relationship between movement stereotypy and arousal in individuals with ASD, such that changes in autonomic
activity either precede or are a consequence of engaging in stereotypical motor movements. Unfortunately, however, it is difficult to generalize these findings since previous studies fail to report reliability statistics that demonstrate accurate identification of movement stereotypy start and end times, and use autonomic monitors that are obtrusive and thus only suitable for short-term measurement in laboratory settings. The current investigation further explores the relationship between movement stereotypy and autonomic activity in persons with autism by combining state-of-the-art ambulatory heart rate monitors to objectively assess arousal across settings and wireless, wearable motion sensors and pattern recognition software that can automatically and reliably detect stereotypical motor movements in individuals with autism in real time. http://affect.media.mit.edu/projects.php?id=2640

PROF. CHARLES G SODINI

Professor Sodini’s principal fields of interest are electronics and integrated circuit design and technology. More specifically, his research concerns technology intensive integrated circuit and systems design, with application toward sensory interface electronics and wireless communication emphasizing analog signal processing and RF integrated circuits.

A Leadless, Long-Term ECG Monitor for In-Home Use
Date: 10/19/09, Microsystems Technology Laboratories

With the escalating costs of hospital visits, clinicians are opting to use at-home monitoring devices to diagnose patients. Current ECG Holter monitoring devices typically have 24 - 48 hour memory and battery capacity. With many patients experiencing intermittent heart problems that can occur once every week -- month, the Holter monitor is not a good solution and an event recorder or loop recorder is required. However, each of these recorders can only save up to a few minutes of ECG recordings. This leads to the loss of most of the data, which could be very important in alerting the user for the onset of future episodes. Therefore, we have developed a Holter monitor prototype with the goal of battery and memory capacity of two weeks.

We based the long-term monitor prototype around a Texas Instruments MSP430 low-power microcontroller which enables high computing power with very low power consumption. The prototype monitor, which is currently being designed, will be mounted on standard 3M 2560 Red Dot electrodes and fabricated on a flexible PCB substrate. Mounting the PCB directly to the electrodes will improve the SNR by an estimated 40 dB compared to using wired leads. The monitor will be ‘L’ shaped with rounded corners and placed on the patient’s chest. The ‘L’ shape will enable several mounting sites to be placed on the board which will allow the doctor to choose which measurement he would like to record. The monitor will have 320 Mbytes of FLASH memory which is enough to store two weeks of data sampled at 250 Hz continuously. Total power consumption of the system is estimated to be less than 8mW.
SPECTROPHOTOMETRIC DIAGNOSTIC METHODS

Biomedical physics; medical spectrophotometry; optical coherence tomography

PROF. GEORGE B BENDEK
Alfred H Caspary Professor of Biological Physics and Physics; Professor of Health Sciences and Technology, http://web.mit.edu/physics/people/faculty/benedek_george.html

An experimental physicist, Benedek has published over one hundred and sixty research papers in a variety of fields including high pressure physics, nuclear magnetic resonance, quasielastic light scattering spectroscopy, phase transitions and critical phenomena in ferromagnets, simple fluids, micelles and microemulsions. His work focuses on the connection between aggregation, phase separation and self-assembly of biological macromolecules and cataract disease, Alzheimer's disease, and cholesterol gallstone formation.

The Benedek Group
The research of the Benedek group centers on phase transitions, self-assembly and aggregation of biological molecules. These phenomena are of biological and medical interest because phase separation, self-assembly and aggregation of biological molecules are known to play a central role in several human diseases such as cataract, Alzheimer's disease, and cholesterol gallstone formation. A combination of experimental work, theoretical analysis, and computer simulations is used to understand the connection between the basic interactions amongst the molecules and the resulting condensed phases. http://web.mit.edu/physics/benedek/index.html

PROF. JAMES G FUJIMOTO
Professor of Electrical Engineering, http://www.rle.mit.edu/rleonline/People/JamesG.Fujimoto.html

Professor Fujimoto's area of research involves the development and application of femtosecond laser technology, studies of ultrafast phenomena, and laser medicine and surgery. His research group in Research Laboratory of Electronics (RLE) and collaborators invented optical coherence tomography and pioneered its development.

Laser Medicine & Medical Imaging Group
Optical coherence tomography (OCT) is an emerging medical imaging and diagnostic technology developed by our research group and collaborators in 1991... OCT is attractive for biomedical research and clinical imaging for several reasons. Imaging can be performed in real time, allowing tissue microstructure to be visualized without the need to excise and process specimens as in conventional biopsy and histopathology. Image resolutions are 1 to 15 microns, enabling visualization of tissue architectural morphology. OCT can be performed with a wide range of instruments including ophthalmoscopes, small endoscopes, catheters, probes, needles, or other surgical instruments.... http://www.rle.mit.edu/lmmi/index.htm

Optical coherence tomography (OCT)
Optical coherence tomography (OCT) is an emerging imaging modality which can generate high resolution, cross-sectional and three dimensional images of microstructure in biological systems.
OCT in Ophthalmology

OCT has become a standard diagnostic tool in ophthalmology, enabling more sensitive diagnosis of disease, elucidating disease pathogenesis, progression, and response to treatment.

OCT Endoscopic Imaging

Our group has developed an endoscopic imaging system capable of acquiring OCT data at unprecedented speeds and at three-dimensional resolutions, enabling the detection of small structures.

Optical coherence microscopy (OCM)

Optical coherence microscopy (OCM) can dramatically enhance image penetration compared to confocal microscopy, while significantly improving transverse resolution in OCT to enable cellular-level imaging.

Functional Brain Imaging with OCT

OCT provides depth-resolved, cross-sectional images of functional brain activation, and has the potential to become a new method for basic and applied neuroscience research.

PROF. MEHMET FATIH YANIK

Robert J Shillman (1974) Career Development Assistant Professor of Electrical Engineering; Associate Member, Broad Institute; http://www.rle.mit.edu/rleonline/People/MehmetF.Yanik.html

Yanik’s work on high-throughput technologies, ultrafast optics, microfluidics, neuronal regeneration, coherent photonics is recognized by NIH Director's Innovator Award, Packard Award in Engineering and Science, Alfred Sloan Award in Neuroscience, NIH Eureka (Exceptional Unconventional Research Enabling Knowledge Acceleration) Award, Shillman Career Award, NSF Career Award, Silicon Valley Innovator's Challenge Award, Technology Review Magazine's "World's top 35 innovators under age 35", Junior Chamber International's "Outstanding Young Person", and Technology Research News Magazine's "Top ten advances of the year". His studies have been highlighted in ABC, The Economist, Scientific American, Nature, New Scientist, Biophotonics International, Popular Mechanics, Genome Technology, and others.

“On peer inside a living cell: An electron microscope image of a butterfly's wings”

Quantum mechanics could help build ultra-high-resolution electron microscopes that won't destroy living cells, according to MIT electrical engineers.

Anne Trafton, MIT News Office, October 6, 2009

Electron microscopes are the most powerful type of microscope, capable of distinguishing even individual atoms. However, these microscopes cannot be used to image living cells because the electrons destroy the samples.
Now, MIT assistant professor Mehmet Fatih Yanik and his student, William Putnam, propose a new scheme that can overcome this limitation by using a quantum mechanical measurement technique that allows electrons to sense objects remotely. Damage would be avoided because the electrons would never actually hit the imaged objects.

Such a non-invasive electron microscope could shed light on fundamental questions about life and matter, allowing researchers to observe molecules inside a living cell without disturbing them... More at http://comm-cms-1.mit.edu/newsoffice/2009/electron-microscope.html

High-Throughput Neurotechnology Group
Our Lab is working on development and applications of high-throughput technologies for probing and engineering neural processes. Both in vivo and in vitro neural regeneration and complex wiring of central nervous system is studied using femtosecond laser nano-surgery and on-chip multi-photon imaging as well as microfluidic in vitro and in vivo high-throughput screening technologies using the model organism C. elegans, primary mammalian neurons as well as human embryonic stem cell derived neurons. We are also developing non-invasive electron microscopy technologies using interaction-free quantum measurements for imaging live biological specimen at molecular resolution. http://www.rle.mit.edu/bbng/

http://www.rle.mit.edu/bbng/research.htm
http://www.rle.mit.edu/bbng/publications.htm

Paper: “Sub-cellular precision on-chip small-animal immobilization, multi-photon imaging and femtosecond-laser manipulation”

GEORGE R. HARRISON SPECTROSCOPY LABORATORY: RESEARCH IN BIOMEDICAL OPTICS AND SPECTROSCOPY
Biomedical applications of lasers and laser spectroscopy are changing the face of medicine as it is currently practiced. The mission of the Laser Biomedical Research Center (LBRC), an NIH-sponsored research resource center, is to develop the scientific understanding required for advancing the applications of lasers in medicine and biology. Research projects are developed from the ground up: fundamental studies involving biochemicals, cells, ex vivo tissue are undertaken to advance understanding, spectral models are developed and instrumentation refined, before these methods are tested in clinical trials at medical centers and hospitals.

Biomedical initiatives within the LBRC have resulted in the development of new spectroscopic methods to diagnose disease through minimally invasive procedures using absorption,
fluorescence, Raman and intensity-based light scattering techniques; novel technologies for spectroscopic imaging of disease, in particular field-based light scattering techniques such as low-coherence interferometry; and improved understanding and modeling of light transport in tissue. Basic studies in biophysics and biochemistry are also pursued to support the development of novel spectroscopic methods of disease diagnosis.

http://web.mit.edu/spectroscopy/research/biomedicaloptics.html

George R. Harrison Spectroscopy Laboratory: Research in Physical Science

Atomic and molecular spectroscopy has a venerable history at MIT, in large part nurtured by the Spectroscopy Laboratory. Researchers using the Laboratory’s facilities develop novel laser-based spectroscopic techniques to explore the fundamental properties and interactions of atomic, molecular and material systems through research conducted in the MIT Laser Research Facility (LRF). Research programs conducted in the LRF seek to observe and quantify physical, chemical and biological systems with high resolution and sensitivity using a diverse collection of laser systems and spectroscopic techniques.

http://web.mit.edu/spectroscopy/research/physicalscience.html

Core Projects examples:

Interferometric Measurement of Neural Activity
http://web.mit.edu/spectroscopy/research/phys_research/lrf_01_yen.html

Interferometry of Red Blood Cells
http://web.mit.edu/spectroscopy/research/phys_research/lrf_02_popescu.html

Paper: “Metabolic remodeling of the human red blood cell membrane”


NANOMATERIALS USEFUL IN DIAGNOSTICS

INSTITUTE FOR SOLDIER NANOtechnologies

Integrated Amplifying Fluorescent Polymer Biosensory Systems
Principal Investigator: Prof. Karen K Gleason
Other Investigators: Prof. Klavs F Jensen, Prof. Timothy M Swager, Prof. Steven R Tannenbaum
Date: 02/25/10

This project proposes pre-symptomatic detection of infection and poisoning of a Soldier using integrated physiological monitoring to detect the relative concentrations of multiple biomarkers. The goals are to allow for rapid administration of treatment and for timely evasive measures which can prevent further exposure. This proposal will determine the critical biosensory signatures of inflammatory reaction. These biomarkers include protease inhibitors, proteins, and metabolites associated with the liver and also small molecules in the blood. Amplified fluorescent polymers (AFPs) with specific and ultrasensitive responses to a number of biological and chemical
analytes (Swager, ISN-1 Project 3.6) will be integrated into a multiplexed sensing system of microfluidic devices with nanosensory elements with advanced cell manipulation and optical coupling capabilities (Jensen, ISN-1 Project 5.4). From the first phase of ISN funding, TNT sensitive AFPs were transitioned as key enabler of Nomadics/ICX FIDO platform. Functional sensory polymeric nanocoatings deposited by chemical vapor deposition (CVD) (Gleason, ISN-1 Project 5.4) will be studied to provide broad flexibility in tethering AFPs and for creating tunable, adhesive, reactive hydrogel layers for binding specific proteases.

http://web.mit.edu/isn/research/sra02/project02_03_03.html

Low-Power, Portable Electro-microfluidic Devices for Real-time Medical Monitoring
Principal Investigator: Prof. Saman P Amarasinghe
Other Investigator: Prof. Martin Z Bazant
Date: 02/25/10

This project proposes research on nanoscale fluid manipulation by “induced-charge electro-osmosis” (ICEO), using small AC voltages applied at microelectrodes, to enable rapid, real-time medical monitoring of the Soldier for exposure to toxic agents. Building on the team’s successful development of ICEO microfluidics in ISN-1 Project 6.3, specific objectives are to: automate blood analysis with ICEO pumps and mixers in a lightweight, portable “lab-on-a-chip” device for rapid detection and monitoring of genetic signals of exposure (Thorsen); develop and implement novel control software for automated on-chip sample processing and data reporting (Thorsen, Amarasinghe, new ISN PI); and use modeling and simulation to continually develop next-generation ICEO components with better performance metrics, e.g., lower power consumption, faster pumping and mixing, and extended range of solvent compatibility, and new capabilities, e.g. rapid electroporation of cells (Bazant). Key Soldier benefits will include improved sensitivity in detecting exposure, with an ability to non-invasively monitor Soldier physiology by sampling only a few cells (nanoliters of body fluids such as blood, sweat, saliva); more rapid turn around time, with assay results available in tens of minutes rather than tens of hours; low electric power consumption and portability – ICEO-driven pumps will require only a few volts from a watch battery. The ICEO lab-on-a-chip device will evolve from a hand-held device toward a lightweight medical monitoring “badge”, which shows promise for straightforward incorporation into the battle suit and more near term Soldier protection garments.

http://web.mit.edu/isn/research/sra02/project02_03_04.html

Non-Invasive Delivery and Sensing
Principal Investigator: Prof. Robert S Langer Jr
Date: 02/25/10

This project seeks to develop non-invasive transdermal approaches for the detection of analytes and for the delivery of injury intervention agents, eliminating the use of needles for the physiological monitoring of Soldiers or for administering pharmaceutical agents. Specifically, ultrasound has been discovered as a non-invasive way to safely, and temporarily, disorder lipids in the outermost area of the skin, the stratum corneum, which is the primary barrier to transdermal transport. Transient cavitation events near the skin surface are primarily responsible for the structural perturbations in skin exposed to low-frequency ultrasound, leading to the formation of localized transport regions (LTRs) and to the observed enhancements in transdermal permeabilities. Models will be developed to predict transdermal transport in the
intercellular regions of the stratum corneum when LTR’s are present and to predict the range of molecules that can be delivered or sensed through LTR’s. Experimental investigations will focus on observing the localized regions of highly permeability in skin and investigating the transdermal transport pathways and transport mechanisms in skin treated using two-photon microscopy. Transdermal detection and delivery is a key need for developing remote and local wound and injury triage and emergency treatment systems to enhance Soldier survivability and for developing novel detection schemes for chemical and biowarfare threats. http://web.mit.edu/isn/research/sra02/project02_03_02.html

**Smart Quantum Dot Sensors**

Principal Investigator: Prof. Moungi G Bawendi
Other Investigator: Prof. Daniel G Nocera
Date: 02/25/10

This project seeks to design, develop and demonstrate QD-dye constructs that are reversible and self-referencing molecular sensors. The goal is to turn QD fluorophores as active reporters of their molecular micro-environment. These QD-dye constructs will exploit FRET between a QD donor and dye acceptors, with the FRET signal modulated by binding of analyte to the dye or to a linking group between the QD and dye. The use of modulated FRET allows for molecular sensors that have the powerful property that they are ratiometric and hence self-referencing and quantitative. A QD-dye construct for sensing will be demonstrated to be a general platform for sensing a wide variety of analytes, from the biomedically relevant such as pO2 and glucose, to molecular toxins. Nocera (new ISN PI) and Bawendi have demonstrated the validity of the concept with a reversible, self-referencing pH sensor built around a dye molecule synthesized in the Nocera laboratory. The project seeks to capitalize on this initial demonstration with optimized coupling strategies between sensing dye constructs designed in the Nocera laboratory with QD synthesized in this theme. http://web.mit.edu/isn/research/sra01/project01_02_03.html

**PROF. ROBERT S LANGER JR**

Institute Professor; Professor of Mechanical, Chemical and Biomedical Engineering and Health Sciences and Technology; http://web.mit.edu/cheme/people/profile.html?id=18, http://web.mit.edu/langerlab/research/index.html

Research Interests: drug delivery; biomaterials; tissue engineering; biotechnology; immobilized enzymes; biomedical engineering

**Novel Fluorescent Substrates Used in the Detection of Prostate Cancer In Vivo**

Date: 09/30/08, Department of Chemical Engineering

Prostate cancer has become the most commonly diagnosed cancer in men in the United States. Clinical diagnostic procedures currently include prostate-specific antigen (PSA) screening, digital rectal exam, and prostatic needle biopsy. However, these methods lack the sensitivity to detect small lesions that occur in the early stages of cancer and metastasis. We propose a molecular imaging modality that provides a biochemical characterization of localized regions of prostate tissue. Using fluorescence quenching, several peptide substrates have been designed to respond to varying concentrations of PSA with a concomitant increase in fluorescence. In the near-infrared
wavelength range, these fluorescent substrates can be imaged through thin sections of tissue to allow surface volume imaging of biochemical function, and thus, to provide additional insight into prostate cancer localization and progression.

“LAB-ON-A-CHIP” TECHNOLOGY

Cell manipulation on a chip; microfluidic logic and controls; integrated micro-chemical/sensor systems

PROF. PATRICK S DOYLE
Associate Professor of Chemical Engineering;
http://web.mit.edu/cheme/people/profile.html?id=11

Research Interests: Microfluidics, complex fluids, polymer physics, rheology and transport phenomena

Doyle Group: Dynamics of Biopolymers & Complex Fluids

Our research focuses on understanding the dynamics of single polymers, biomolecules and colloids under forces and fields. We utilize both experimental and computational approaches in our research in order to understand fundamental issues in a wide variety of applications ranging from lab-on-chip separations to polymer rheology. http://web.mit.edu/doylegroup/research.html

Current & Past Research Areas:
- DNA electrophoresis in microfluidic devices
- Single DNA molecule mapping
- DNA dynamics in nanofluidic devices
- Superparamagnetic colloids in microfluidic devices
- Brownian Dynamics simulations of complex molecules
- Microrheology of extracellular matrices and biopolymers
- Microparticle synthesis using microfluidics
- Multiplexed biomolecule detection using barcoded particles

PROF. JOEL VOLDMAN
Associate Professor of Electrical Engineering
http://www.rle.mit.edu/rleonline/People/JoelVoldman.html
http://csbi.mit.edu/people/voldman.html

Professor Voldman’s current research interests focus on BioMEMS, applying microfabrication technology to illuminate biological systems, especially at the cellular level. Specifically, he investigates technologies that enhance or enable the acquisition of information from cells. His research builds upon various disciplines: electrical engineering, microfabrication, bioengineering, surface science, fluid mechanics, and mass transport. His group takes a quantitative approach to designing technology, using both analytical and numerical modeling to gain fundamental understanding of the technologies that we create. He then takes designs through microfabrication to packaging and testing and to biological assay.
Biological Microtechnology and BioMEMS Group

The RLE Biological Microtechnology and BioMEMS Group performs research on microfluidics applied to fundamental and applied problems in cell biology. Our interests are specifically in cell sorting and stem cell biology. We take a quantitative approach to technology design, and take projects all the way from engineering design to fabrication to elucidating biological information with our technology. http://www.rle.mit.edu/biomicro/research.htm

Publication: “Surface-Patterned Electrode Bioreactor for Electrical Stimulation”
More at: http://www.rle.mit.edu/biomicro/publications.htm

Enabling Technologies for Stem Cell Biology

We are interested in understanding what extrinsic factors control stem cell phenotype, specifically as it pertains to embryonic stem cell (ESC) self-renewal and differentiation. While biologists understand many aspects of self-renewal, especially in mouse ESCs, the effects of cell-secreted autocrine and paracrine factors are not well understood. Cell Patterning: One technology that we have been developing allows us to place single ESCs in defined locations, giving us excellent control over cell microenvironment. This technology uses DEP traps to create potentially energy wells for cell patterning. We have used quantitative modeling to develop a simple yet surprisingly strong planar DEP trap for single-cell patterning... More at http://www.rle.mit.edu/biomicro/stemcells.htm

Cell Micropatterns for Studying Autocrine Signaling

Date: 10/09/09, Microsystems Technology Laboratories

Autocrine signaling plays a key role in tumorigenesis and in the maintenance of various physiologic states. Due to its intrinsic, closed-loop nature, autocrine signaling is, however, difficult to investigate experimentally. Research involves the use of cell-patterning techniques to investigate the role of autocrine signaling during in vitro maintenance of embryonic stem cells, stem cell differentiation, and uncontrolled expansion of cancer cells.

First we use stencil cell patterning to examine the spatial distribution of autocrine systems. Typical techniques to quantify autocrine signaling rely on bulk measurement of autocrine pathway activation using randomly plated cells. Such random cell positioning usually masks the effects of local ligand concentration gradients, reducing the chance to observe spatially varying cell responses. We fabricated regular arrays of cell patches with varying colony size and spacing and generated graded levels of autocrine ligands in space while maintaining the same global ligand concentration. Using the TGF/EGFR paradigm in A431 cells as our model, we have determined the effective length scale where autocrine signaling contributed to promote growth of adjacent cell patterns. We are applying the developed platform to determine the contribution of autocrine signaling in preserving a homogeneous population of mouse embryonic stem cells (mESCs) in vitro.

Expanding on our previous work on Bio Flip Chips, we have used them to create patterns of single cells at varying densities. We then studied the effects of plating density on the colony-forming efficiency of mESCs and found that the colony-forming efficiency increases with density. We have confirmed this result by performing growth assays in a traditional well-plate format and in a
defined medium. In this second set of assays, we found that the growth of mESCs increases with density (for a certain range), both in the first 24 hours and in the next 24 hours after plating of cells. Finally, we checked that medium that has been conditioned by cells enhances the growth of mESCs. Together, these results prove that mESCs produce at least one diffusible factor that aids survival.

In addition to localization of a single cell type on the substrate, we have also developed a novel technique to fabricate complex heterotypic patterns-within-patterns. Stencil-delineated electroactive patterning (S-DEP) combines dielectrophoresis (DEP) and stencil patterning to create cell clusters with customizable shapes, positions, and internal cell organization. Stencils define overarching tissue-like construct geometries, and negative-dielectrophoretic forcing guides subgroupings of cells to desired positions within constructs. The S-DEP enables correlation of cells’ cluster location to phenotype and provides avenues for creating mosaic tissue-like constructs of phenotypically or genetically distinct cells. Such diversified chimeric cell clusters help us evaluate the impact of diffusive signaling on stem-cell differentiation.


Image-Based Sorting of Cells
Date: 10/09/09, Microsystems Technology Laboratories

This research involves the development of architectures for screening complex phenotypes in biological cells. We augment microscopy with the ability to retrieve cells of interest. This capability will permit cell isolation on the basis of dynamic and/or intracellular responses, enabling new avenues for screening. Currently, such sorts require expensive, specialized equipment, widely prohibiting such sorts.

We have explored microfabricated/microfluidic approaches to cell sorting. These approaches employed purely dielectrophoretic (DEP) trap arrays, passive hydrodynamic trap arrays with active DEP-based cell release, and passive microwell arrays with optical cell release to permit sorting of non-adhered cells. We recently developed a photolithography-inspired method that allows sorting of adherent cells without the use of microfluidics. Here we plate adherent cells in a dish and assay them, identifying the locations of cells of interest. We then use a computer and standard office printer to automatically generate a transparency mask. After alignment of the transparency mask to the back of the cell culture dish, opaque mask features reside beneath desired cells. We then add a prepolymer to the dish, containing cell culture media, a UV-photoinitiator, and poly(ethylene glycol) diacrylate (PEGDA) monomer. Next we use a standard fluorescence lamp to shine UV light through the mask, crosslinking a hydrogel over all unmasked locations and encapsulating all undesired cells. Desired cells can be enzymatically released and re-captured. Our sorting process requires standard equipment found in biology labs and inexpensive reagents (<$10 per experiment), simplifying widespread adoption.

We have demonstrated cell release from 500 µm-diameter wells, as well as the isolation of perfectly pure, viable target cells from a background population of undesired cells. Further efforts will reduce well size, enabling the sorting of denser cell populations. The simplicity and inexpensiveness of our method will allow for widespread dissemination and new cell sorting paradigms. http://mtlweb.mit.edu/research/annual_reports/2009/files/ms.pdf

See also: http://www.rle.mit.edu/biomicro/cytometer.htm
Measuring the Effects of Electric Fields on Cell Phenotype
Entry Date: 10/09/09, Microsystems Technology Laboratories

One overarching goal of our research group involves using electric fields to manipulate, position, and ultimately sort living biological entities. To enable such exquisite control over living organisms, we leverage a technique called dielectrophoresis (DEP), which uses spatially non-uniform electric fields to “push” or “pull” cells towards or away from electrodes. The processing of biological samples is more readily achieved using systems on the length-scale of the samples themselves. Such biological microelectromechanical systems, or BioMEMS, enable integrated sample preparation and analysis; they leverage techniques such as DEP to enable cell manipulation. Hence, it is imperative that we understand the effects of DEP manipulation on cell physiology to determine whether DEP manipulation itself can alter particular phenotypes of interest and confound downstream biological assays. To this end, we have developed a microfabricated, high-content screening (HCS) platform that can apply a large number of different electrical stimuli to cells and then monitor the molecular effects of those stimuli using automated fluorescence microscopy. The platform consists of a chip with individually addressable arrayed electrodes and support electronics to generate the desired waveforms. Mammalian cells are seeded on the chip and then the entire assembly is clamped and placed in a standard cell culture incubator, where a computer-controlled custom-designed switch box automatically and autonomously applies arbitrary stimulation waveforms (varying voltage, frequency, and duration) to individual electrode sites. Since this platform uses transparent electrode structures, it can equally be used with both inverted and fluorescent microscopy techniques.

Using this HCS platform, we have been able to elucidate the response of cells to electric fields using a custom-designed live-cell stress sensor. This stress sensor was designed using transfection and cloning techniques, and it forms the basis for the read-out of our biological assay. Stressful events in the environment around the cells, such as temperature elevation (due to Joule heating) and the generation of oxygen radicals are sensed by our stress sensor and reported as a distinct fluorescence level. These fluorescent signals are collected for individual cells using automated microscopy and quantified using image-processing algorithms. This HCS platform enables the molecular-level biological assays across a very wide range of electric field conditions, a feat challenging to accomplish with previously developed systems or assay platforms.


PROF. RALPH WEISSLEDER
Visiting Professor of Biology; Professor, Harvard Medical School (HMS);
http://csb.mgh.harvard.edu/weissleder

Dr. Weissleder is a world leader in applying molecular imaging tools to the study of complex human diseases. He has made fundamental discoveries in early disease detection, development of nanomaterials for sensing and systems analysis. His research has been translational and several of his developments have led to advanced clinical trials. Dr. Weissleder is currently the principal investigator of several RO1 NIH grants, a P50 Center grant, a U24 grant, and a U01 consortium focusing on nanotechnology.
Development of Novel Miniaturized Sensing Technologies (Chips) for Real-Time High-Throughput Analysis

Principal Investigator: Prof. Ralph Weissleder, Visiting Professor of Biology; Professor, Harvard Medical School (HMS); Director, Center for Molecular Imaging Research; Director, Center for Systems Biology
Date: 07/21/08, Koch Institute for Integrative Cancer Research (KIICR)

Multiplexed, platform independent and rapid analysis of biological specimen remains a major bottleneck in unravelling complex biological phenomena. A number of established techniques provide accurate measurements, facilitate early disease detection and have been used to gain valuable insights into biology at the systems level. However, many of the techniques rely on extensive and time consuming purification of samples, typically followed by a set of amplification strategies and often do not allow rapid multiplexed measurements required in complex diseases. We have recently developed a chip based micro-NMR (µNMR) system to perform highly sensitive measurements in complex biological samples. NMR devices allow measurements in turbid samples, characterization of chemical species and form the basis of clinical imaging systems. Using microfabrication technology we miniaturized elements of an NMR system to perform proton T2 measurements of aqueous biological samples. Using readily available magnetic nanoparticles as sensors for proximity assays the technique allows parallel measurements of nucleic acids, proteins, peptides, metabolites and cells. Importantly, the spatial proximity of two nanoparticles by an analyte of choice results in large-scale amplification allowing rapid, parallel detection of biological targets in unprocessed samples. The integration of the sensor with microfluidic system allows facile control and manipulation of small volumes of liquid, and additional magnetic separation and concentration of targets from a complex parent specimen. In this project we apply the chip for parallel measurements of cellular proteins.
http://web.mit.edu/ki/research/approaches/detection.html

COMPUTATION, MODELING, ANALYSIS

Computational biophysics

PROF. COLLIN M STULTZ
W M Keck Career Development Associate Professor of Biomedical Engineering
Associate Professor of Health Sciences and Technology
http://www.rle.mit.edu/leonline/People/CollinM.Stultz.html
http://www.csail.mit.edu/user/934

Stultz's research is interested in conformational changes in macromolecules and the effect of structural transitions on common human diseases. Since conformational transitions in biomolecules are typically difficult to observe experimentally, we use novel methods to gain insights into the role that molecular structure plays in the progression of human disease. We employ an interdisciplinary approach that utilizes techniques drawn from computational chemistry, signal processing, and basic biochemistry.
Computational Biophysics Group

The RLE Computational Biophysics Group is focused on understanding conformational changes in biomolecules that play an important role in common human diseases. The group uses an interdisciplinary approach combining computational modeling with biochemical experiments to make connections between conformational changes in macromolecules and disease progression. By employing two types of modeling, molecular dynamics and probabilistic modeling, hypotheses can be developed and then tested experimentally. http://www.rle.mit.edu/cbg/research.htm

ECG Markers to Predict Cardiovascular Death
Principal Investigator: Prof. Collin M Stultz
Other Investigator: Prof. John V Guttag
Date: 04/28/09

ECG parameters such as heart rate variability (HRV), deceleration capacity (DC) and morphologic variability (MV) may help identify patients at high risk post-ACS. These techniques measure specific aspects of cardiac health. HRV studies sympathovagal modulation of heart rate, DC extends heart rate turbulence by measuring acceleration-deceleration patterns, and MV quantifies variability in the shape of the ECG signal associated with myocardial instability. We are assessing the relationship among HRV, DC and MV, and cardiovascular (CV) death after NSTEACS. We have explored the effect of different ECG based risk scores on predicting patients who are at high risk of death following NSTEACS.

Symbolic Analyses of Cardiovascular Signals
Date: 11/03/08, Research Laboratory of Electronics

In collaboration with the data-driven medicine group, we have helped to developed automatic techniques for analyzing large amounts of cardiovascular data. In contrast to traditional medical expert systems, this technique incorporates no a priori knowledge about disease states and therefore facilitates the discovery of unexpected events that are difficult to predict. The ultimate goal is to use these methods to uncover novel patterns with prognostic significance from databases containing large amounts of clinical information. http://www.rle.mit.edu/cbg/research.htm

The Mechanism of Collagenolysis: A Substrate-Centric View
Date: 04/28/09, Research Laboratory of Electronics

Collagenolysis (collagen degradation) is a critical process in the progression of cancer metastasis, atherosclerosis, and other diseases. Despite considerable efforts to understand the steps involved, the exact mechanism of collagenolysis remains unknown. One proposed mechanism for collagenolysis suggests that the enzymes that degrade collagen, collagenases, physically unwind the triple-helical structure of collagen to gain access to the peptide bond that is cleaved. This unwinding mechanism would have large energetic requirements, but neither ATP nor other energy-rich molecules are necessary for collagenolysis. An alternative mechanism is that collagen exists in multiple states, some featuring structures that are unwound in the vicinity of the collagenase cleavage site, and that collagenases preferentially bind to and stabilize the unwound structures before degradation occurs. The focus of this work is to investigate several aspects of
this alternative mechanism using both experimental and computational methods. In particular, we used molecular dynamics simulations to explore the structure of human type I collagen in the vicinity of the collagenase cleavage site. Since posttranslational proline hydroxylation is an important step in the synthesis of collagen chains, we used the DNA sequence for the alpha-1 and alpha-2 chains of human type I collagen with the known amino acid sequences for bovine and chicken type I collagen, to determine which prolines are hydroxylated in the vicinity of the collagenase cleavage site.

Simulations of type I collagen in this region suggest that partial unfolding of the alpha-2 chain is energetically preferred relative to unfolding of the alpha-1 chains. Localized unfolding of the alpha-2 chain leads to a metastable structure that has disrupted hydrogen bonds N-terminal to the collagenase cleavage site. The data suggest that this disruption in hydrogen bonding pattern leads to increased chain flexibility, thereby enabling the alpha-2 chain to sample different partially unfolded states. Surprisingly, our data also imply that alpha-2 chain unfolding is mediated by the non-hydroxylation of a proline residue that is N-terminal to the cleavage site in alpha-1 chains. These results therefore suggest that hydroxylation on one chain (alpha-1) can affect the structure of another chain (alpha-2), and point to a critical role for the non-hydroxylation of proline residues near the collagenase cleavage site.

**The Role of Unfolded States in Collagen Degradation**

**Date:** 04/28/09, Harvard-MIT Division of Health Sciences and Technology, Research Laboratory of Electronics

The hypothesis of this work is that collagen can undergo local unfolding near the cleavage site and that collagen degradation is the result of the interaction of preformed locally unfolded states in collagen and MMPs.

Using molecular dynamics as a tool, the particular structural features around the actual cleavage site of type III collagen were studied. It was shown that, out of the 5 potential cleavage sites in type III collagen, the actual cleavage site is the most vulnerable, locally unfolded and flexible of all. Moreover, under the hypothesis of locally unfolded states, the structural basis of a series of existing sequence rules that a cleavage site a series needs to accomplish in order to be degraded were established.

In order to obtain a model of collagen bound to MMP, both catalytic domain and full enzyme. Crystallography was initially chosen as the technique of use. The inactive catalytic domain of MMP8 (ICAT) was engineered out of the MMP8 sequence, purified and crystallized. A structure of the ICAT was obtained to a resolution of 1.75Å.

A rigid body docking methodology was developed in order to dock the lowest energy structures of collagen obtained in AIM1 into the ICAT structure. The best dock, corresponding to the actual cleavage site of type III collagen, can be then refined and molecular dynamics can be used in order to generate contact maps. Such contact maps constitute a dynamical model of collagen-MMP binding that can be tested in AIM3.

In order to initially validate the docking model of ICAT and type III collagen, degradation experiments involving the catalytic domain of MMP8 and type III collagen were carried out. The results showed unequivocally, and for the first time, that type III collagen can be degraded by the
catalytic domain of MMP8 in the absence of the binding domain. These results support the use of the docking model as a starting structure to generate contact maps. Finally, mutants of MMP8 that eliminate the most important contacts with collagen will be tested for binding and degradation in order to validate the developed model.

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4/2008
Principal Investigator: Frank Moss, Director, MIT Media Lab,
http://newmed.media.mit.edu/people/index.php

The New Media Medicine research group believes that it’s time for a power shift in health care. As a society, we have dramatically underestimated the power of ordinary people to transform the system, to take care of their own health, to help develop therapies, and to help solve massive public health problems. We are working on technologies that will enable radical new collaborations between doctors, patients and communities... New Media Medicine's work is rich and varied, but all projects are based on the following principles:

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SOCIAL HEALTH LIVING LABORATORY
Directed by: Prof. Alex (Sandy) Pentland, Dr. Frank Moss, MIT Media Lab; 7/2009

Instead of building on a reactive health-care system centered around treating disease rather than preventing it, the Lab’s new Social Health Living Laboratory is focused on developing a proactive, social health system: a network of organizations and tools to give people the knowledge and support they need to maintain health, vitality, and happiness throughout their entire lives. This involves developing devices such as mobile phones that record our daily patterns and smart exercise equipment that knows our personal patterns and life-style goals. This initiative will integrate: persuasive technologies, to help us make better decisions and adopt better behaviors;
personal sensing, to increase our awareness of our bodies; personal collective intelligence, for
collect knowledge from our peers; and socially aware computation and communication systems
that are aware of us as social beings.  http://www.media.mit.edu/research/social-health-living-
laboratory

“REVOLUTIONIZING MEDICINE, ONE CHIP AT A TIME”
MIT News, March 11, 2010

Low-power computer chips allow engineers to design wearable and implantable devices to
monitor patients.

In the past several decades, microchips have transformed consumer electronics, enabling new
products from digital watches and pocket-sized calculators to laptop computers and digital music
players.

The next wave of this electronics revolution will involve biomedical devices, say electrical
engineers in MIT’s Microsystems Technology Laboratory (MTL) who are working on tiny, low-
power chips that could diagnose heart problems, monitor patients with Parkinson's disease or
predict seizures in epileptic patients. Such wearable or implantable devices could transform the
way medicine is practiced and help cut the costs of expensive diagnostic tests, says Dennis Buss,
former vice president of silicon technology development at Texas Instruments...