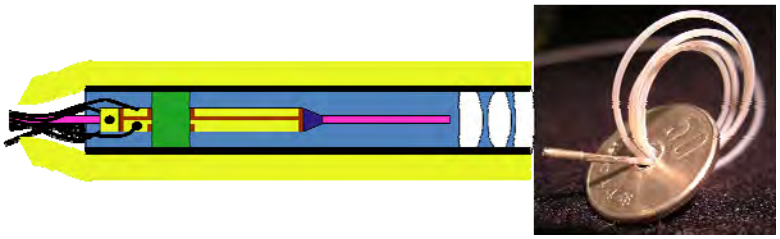
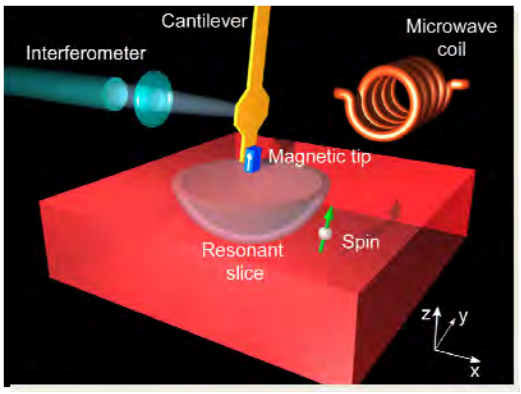
Health Related Research Expertise

Mechanical Engineering Department

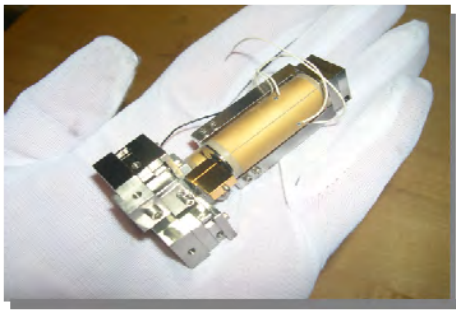
U. of Washington

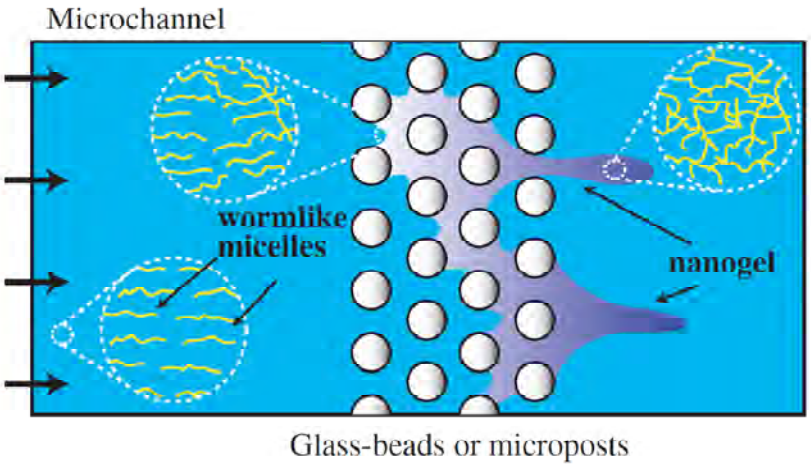


Scanning Single Fiber Endoscope (Eric Seibel)



Magnetic Resonance Force Microscopy (Joe Garbini)





Nanogel Fabrication (Amy Shen)

Nov 28th 2011

OVERVIEW OF INCLUDED FACULTY PROFILES

- **Amy Shen:** Soft matter and micro-fluids laboratory, complex fluids, morphologies and structures, nanotechnology, biotechnology, novel materials (biomaterials, nanomaterials).
- **Y. (Steve) Shen:** vibration, dynamics, sensing, and actuation. (a) piezoelectric thin-film devices (micro-actuators for hybrid cochlear implants and micro-sensors for totally implantable cochlear prostheses.) and (b) spindle and rotor dynamics.
- **Alexander Veress:** computational soft tissue and cardiacbiomechanics; finite element modeling of the heart; organ function; combination of numerical analysis and clinical imaging to study soft tissue mechanics in both the normal and pathological cases.
- **Dayong Gao:** Cryopreservation, cryobiology, Bio-heat-mass transfer and thermal stress, bio-sensors and BioMEMS, artificial organs, nano-technology/nano-fluid/membrane science, tissue engineering, cardiovascular and blood research.
- **Jae-Hyun Chung:** Nanoengineering, low cost disease diagnosis using a tip probe concentrator, immunofluorescence detection of bacteria (BCG) from saliva and sputum, microscale and nanoscale tips for concentration of biomarkers.
- **Junlan Wang:** mechanical reliability of nanoporous materials, thin film adhesion measurement, high strain-rate materials, mechanics of cells and biomaterials, ultrasonic and laser-based sensing, and size-dependent plastic behavior of nano and microstructures.
- **Nathan Sniadecki:** Cell biomechanics lab, biomechanics and mechanobiology, cardiovascular disease and cancer, single-cell and multi-cellular mechanics, mechanotransduction, migration
- **Wei-Chih Wang:** polymer based sensors and actuators for biomedical applications, electro optic polymers, conductive polymers, electro-optic and MEMS based endoscopes
- **Jiangyu Li**: Multifunctional materials laboratory, formation and evolution of microstructure, structure-property relationship, optimizing microstructures and processing.
- **Santosh Devasia**: Control of micro/nano bio-mimetic structures for fluidic devices; micro-mixing, cilia-based devices, nano-positioning, atomic force microscopy.
- **Per Reinhall**: biomedical sensors and actuators for prosthetic, diagnostic, and imaging, cardiac dynamics research, computational modeling of human heart, screening for high risk for ventricular fibrillation or sudden death from heart failure.
- **Joe Garbini:** Instrumentation/control systems, electromechanical analysis, embedded control systems, observe molecular structure nondestructively with angstrom-scale resolution, scanning probe microscopy.
- **Eric Seibel**: Scanning single-illumination optical fiber endoscope, 3D optical projection microscopic imaging of cells for disease diagnosis.

Research Description of Amy Shen

Soft Matter and Microfluidics Lab

Amy Shen's research program concerns complex fluids and the processing of these fascinating materials to create morphologies and structures that can find application in the nanotechnology, biotechnology, and novel materials (i.e. biomaterials, nanomaterials). Whether they are gels, polymeric liquids, surfactants and vesicles, or suspensions, this important class of soft materials is characterized by intermolecular/particle forces that give rise to time and length scale distributions that are easily accessed by processing flows. Consequently, external processing forces can create a host of nano-morphologies and bulk properties that are central to their end-use applications. Within this broad area, Shen's laboratory takes advantage of the

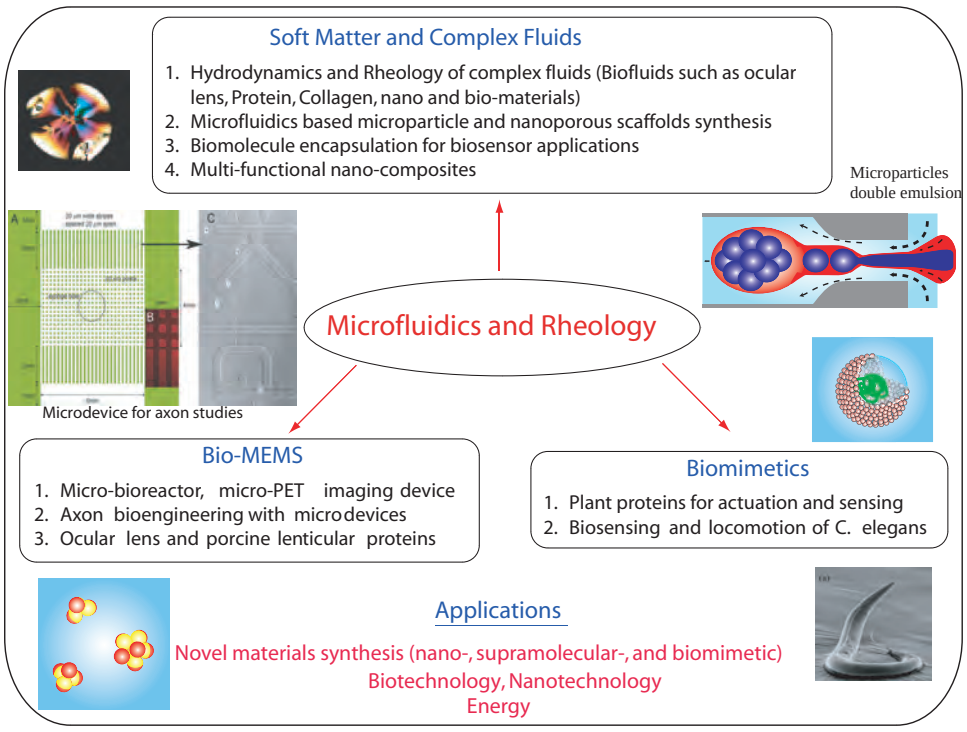


Figure 1: Overall research interests and interdisciplinary research projects.

coupling of complex fluid microstructures with the spatial confinement that is possible by using microfluidic flow methods, to offer exquisite morphological control of soft materials. These strategies are being used to address problems in three specific areas: flow-induced nano-materials synthesis in confined geometries, biomimetics and bio-sensors, and bio-MEMS (see Figure 1). The successes of this research program have been acknowledged by a NSF CAREER Award, a Ralph E. Powe Junior Faculty Enhancement Award, and recognition in the research community through numerous invited lectures.

The following sections summarize some ongoing research projects and describe the possible collaborations with UW's dental school.

Nanoporous scaffolds synthesis and biomolecule encapsulation

Biosensors play indispensible roles in disease diagnosis, drug screening, and forensic applications. One important area of biosensor research is the immobilization of biomolecules (i.e. enzyme, DNA) with retained or enhanced activities as it is critical to enhance biosensor performance. Nanoporous scaffolds hold an

enormous potential in improving the performance of biosensors as porous scaffolds can serve as excellent encapsulating matrix to various bioagents.

Shen's group recently demonstrated that irreversible flow-induced gelation could occur very rapidly when a dilute precursor solution of water/salt/soap mixture, were pumped through a microchannel containing a hexagonal array of cylindrical microposts (see Figure 2).

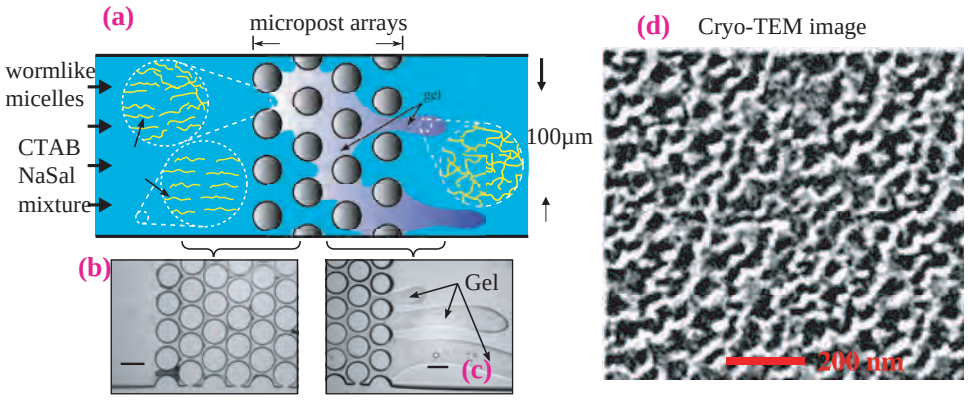


Figure 2: (a) Microposts are fabricated inside microchannels to achieve high shear and extension rates. Precursor of CTAB/ NaSal were injected through the microchannel and the gel is observed to jet out from tiny pores between microposts on the order of seconds. (b) A photo of the microchannel showing the start of the micropost array. (c) A photo of the microchannel showing gel production at the end of micropost array. (d) The generated gel sample was characterized by cryo-TEM.

The microfluidics approach offers an ideal encapsulating environment for enzymes and other biomolecules because it is rapid, simple, no harsh or reactive chemicals for possible deactivation of the enzyme, if a proper precursor can be identified. Proof-of-concept studies of horseradish peroxidase (HRP) enzyme immobilization in the nanoporous scaffolds has recently been performed in Shen's lab. Subsequently, we used the HRP immobilized nanoporous scaffolds to coat the electrode for a basic ITO based electrochemical H_2O_2 sensor. Our sensor showed high sensitivity, stability and selectivity in comparison to the existing sensors.

Possible collaboration: Use microfluidics based materials synthesis route to design simple, fast, biocompatible, and cost-effective process to synthesize biomimetic type, layer-by-layer smart materials, and collagen based porous materials. With our immobilization technique for enhanced glucose sensor (or other types) performance.

Bio-MEMs for biomedical applications

The ability to mimic the in vivo environment for cellular studies in vitro is a major engineering and biological challenge. Microfluidics provides a tool to recreate an in vivo-like environment with small reagent volumes, short reaction times, and the possibility of parallel operation.

Methanogens belong to the form of life known as Archaea. My group studied the methanogens attachment behavior in-situ by utilizing an *anaerobic micro-bioreactor*. The anaerobic micro-bioreactor is a portable, airtight chamber, filled with N_2/CO_2 gas, which houses a micro-fluidic chip used to culture the anaerobes (see fig. 3). The waste-water anaerobe methanothrix concilli was cultured for a period of 3 months inside the micro-bioreactor in a fluid network with varying channel widths to study the effects of shear-rate.

Possible collaboration: modifying our current micro-bioreactor design for use in microbial microreactors.

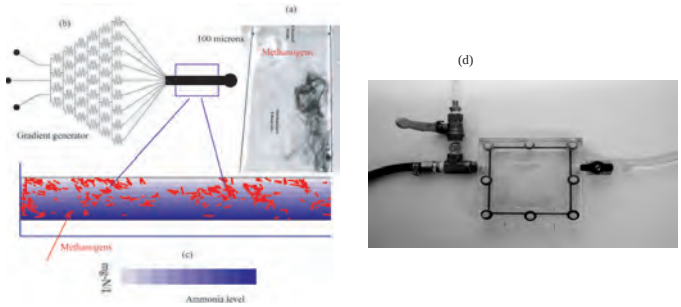


Figure 3: Chemical gradient presentation in vitro using microfluidic devices. (a) Dense methoanogen filaments grown inside microchannels after 3 months. (b) Microfluidic gradient generator. (c) Overlay of filament density with ammonia gradient. (d) Anaerobic box containing the microdevice.

Using microfluidics for small droplets formation

The production of emulsion droplets from two immiscible fluids is influenced by hydrodynamic conditions such as: the flow rates of the continuous and dispersed phase fluids, the ratio of the phase viscosities, the interfacial tension between the fluids, and flow geometry. We study the influences of device wall surface energy and complex fluids rheology on droplet formation. By using microfluidics, we can choose proper continuous and dispersed phase, adjust the rheology of the fluids, and flow rates to generate micron size (or smaller) droplets or particles (see Figure 1).

Possible collaboration: Explore the validity and potential utility of micron and nanometer size emulsion droplets or particles for drug delivery and novel material synthesis.

Oriented lipid tubule synthesis

Phospholipids self assemble into bilayered lipid vesicles in aqueous solution, and these vesicles can further self assemble into secondary structures including reversible aggregates, vesosomes, entangled tubules, and tubular networks. We have developed a new technique (see Fig. 4) to produce oriented tubules that can grow to be as long as 13 mm. Our technique does not require externally imposed flow, temperature control, or bio-incompatible catalyzing agents.

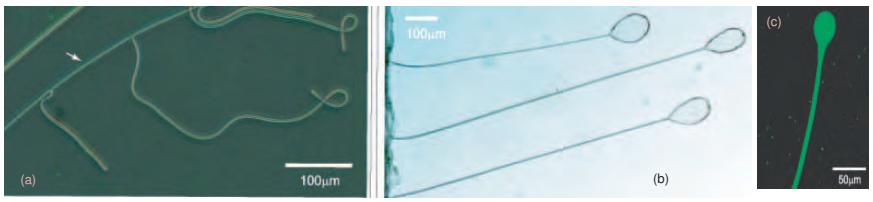
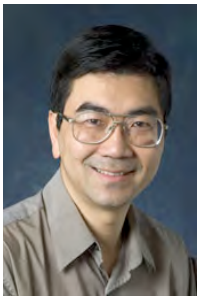


Figure 4: The self-assembly of lipid vesicles into oriented tubules. (a) Tubule branching recorded at 22°C during thermal quenching. (b) UV-polymerized diacetylene tubules showed structural stability and flexibility. (c) Oriented tubules assembled from lipid vesicles entrapping a green aqueous dye.

Possible collaborations: We hope to manipulate the tubule size, orientation, and growth-rate in a more controllable fashion. We are developing encapsulated siRNA tubules, inter-digitated branching tubules, and polymerized solid tubules in a single-throughput self-assembly process for possible nanocomposite materials synthesis and drug delivery applications.

Research Profile of Professor I. Y. (Steve) Shen



Professor Shen's research expertise includes vibration, dynamics, sensing, and actuation. Currently, his research focuses on the following two subjects: (a) Piezoelectric thin-film devices and (b) spindle and rotor dynamics.

Piezoelectric Thin-Film Devices. This research is to develop lead-zirconium-titanium oxide (PZT) thin-film sensors and actuators. Being a piezoelectric material, PZT generates charge as it deforms, thus making it an ideal sensor. PZT also deforms when it is subjected to an electric field, making it an ideal actuator. For tiny sensors and actuators, PZT must appear in the form of thin films to maintain proper aspect ratios of the devices. Current research topics include (a) micro-actuators for hybrid cochlear implants and (b) micro-sensors for totally implantable cochlear prostheses.

Our micro-actuator takes the form of a probe with 1 mm wide, 10 mm long, and 0.4 mm thick; see Fig. 1. At the tip of the probe, there is a piezoelectric diaphragm serving as an acoustic actuator; see Fig. 2. When a voltage is applied, the piezoelectric diaphragm deforms to generate acoustic stimuli serving as an actuator. The designed diaphragm has a size of 0.8 mm by 0.8 mm, and is able to deflect at least 200 nm. The same platform can also be used as a micro-sensor. Figure 3 shows an SEM photo of our prototype, and Fig. 4 shows a measured response.

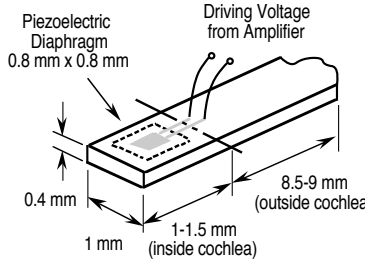


Fig. 1 PZT sensor & actuator probe

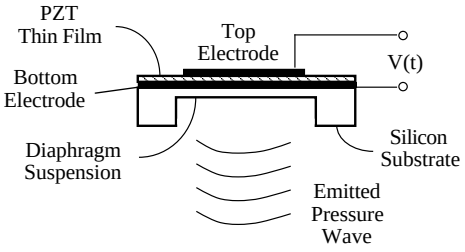


Fig. 2 Principle of operation

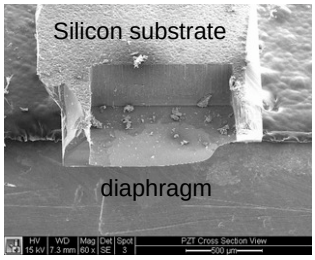


Fig. 3 SEM of prototypes

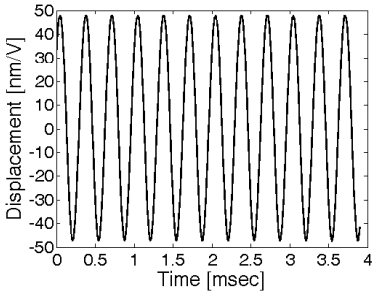


Fig. 4 Measured response

Aside from fabrication and instrumentation, we also aim to overcome fundamental challenges encountered in the design of these devices. For example, we perform finite element analysis to design top electrodes that maximize actuator displacement. We develop feasible ways to alleviate residual stresses to improve actuator sensitivity. We developed accurate and yet cost-effective methods to measure piezoelectric coefficient of PZT thin films. We are experimenting with nano-technology-based electrodes and PZT composites to enhance performance.

Opportunities for Collaboration: PZT is a material widely used for sensors and actuators. It has large piezoelectric coefficients (i.e., very sensitive), high bandwidth, large energy density and large actuation force. Miniaturization of PZT in the form of thin films will find various new killer applications in sensors (e.g., microphones, gyroscopes, shock/force/pressure sensing, accelerometers, and viscosimeter) and actuators (e.g., hearing aids, scanners, mixers, pumps, resonators, and nano-positioners).

Spindle and Rotor Dynamics. In this area, Professor Shen is developing computational algorithms to predict vibration and understand the physics of complex rotating machines, such as disk drives and turbines. Specific research topics include (a) vibration of spinning cyclic symmetric rotors (e.g., wind turbines), (b) interaction of spinning rotors with bearings and housing, (c) vibration of spinning mistuned rotors, and (d) health monitoring, damage detection and machine diagnostics.

Traditional rotor dynamics analyses focus on individual components (e.g., blade-disks or rotor shaft) using a *rotor-based* formulation. As a result, they do not completely describe interactions among all components in a rotating machine (e.g., wind turbine blades interacting with their tower). Nor do traditional analyses lead to a *ground-base* formulation, which can be more feasible for monitoring health of the rotary machines.

The approach we used is called component-mode synthesis (CMS). The idea is to analyze each component using finite element models to accommodate arbitrary and complex geometry of each component. After the finite element analyses, vibration characteristics of each component are distilled into a small number of "modes." Then the modes from all components are synthesized to give ground-based response of the entire rotary machine at the system level.

We have successfully used CMS to analyze vibration encountered in hard disk drives (HDD). We have been the world leader in HDD vibration research since 1995. In particular, we identify the cause and mechanism of rocking vibration in HDD spindle motors that often cause read-write errors in HDD. We establish experimental techniques to measure spindle motor vibration accurately. We have also developed simulation software to predict HDD spindle response. Our current effort in HDD research is to extract fluid-dynamic bearing coefficients of spindle motors from experimental data.

We have also applied CMS to spinning cyclic symmetric rotors, such as propellers and wind turbines. We find that cyclic symmetric rotors present both primary and secondary resonances for a ground-based observer. The former is often observed in rotor-base coordinates, but the latter is not. The presence of secondary resonances provides a brand new avenue to monitor the health of a spinning cyclic symmetric rotor. We have also found that a cyclic symmetric rotor will selectively interact with its housing through bearings. Some rotor vibration modes will couple their vibration with the housing, but others will not. These coupling modes can be predicted accurately via our mathematical formulations.

Opportunities for Collaboration: The method of CMS has more applications than spinning rotors. It can be used to predict vibration of complex structures subjected to prescribed motion. One example is deformation of flapping wings of insect flight. The method can predict wing deformations under Coriolis forces for biologists to understand sensori-motor coordination of movement in insects. It can also bear importance in future design of micro-aerial vehicles.

Alexander Veress

Overview

The focus of the research done by Dr. Alexander Veress and his students primarily involves computational soft tissue and cardiac biomechanics. This involves finite element modeling of the heart in order to better understand normal function as well as how certain pathologies affect the organ function. This is accomplished through the combination of numerical analysis methods and standard clinical imaging to study soft tissue mechanics in both the normal and pathological cases. The focus of our work has been the study of cardiovascular diseases such as ischemia, infarction and heart failure.

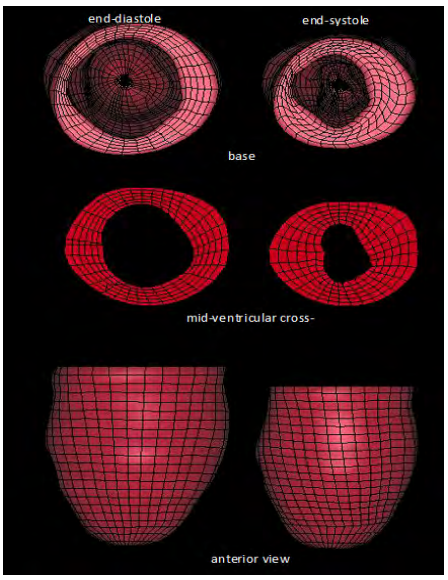


Figure 1: Finite element model of the left ventricle.

Research

Finite Element Modeling of the Left Ventricle. Finite element based (FE) computational models (Fig. 1) of the heart have been developed to gain a greater understanding of the regional mechanics of the normal heart compared with hearts that have regions of compromised function due to ischemia and infarction. These models have been able to reproduce the altered function found in the native heart[1, 2]. For example the aneurismic bulging found in ischemia is reproduced by the finite element model (Fig. 2)

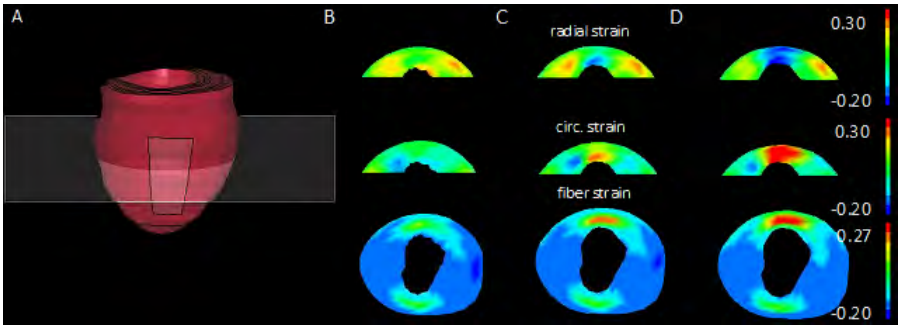


Figure 2. Transmural and subendocardial ischemic regions was defined in the anterior section of the LV model (top of LV cross-section). (A) Location of cross-section. (B) Normal LV strain distributions. (C) Sub-endocardial ischemia strain distributions. (D) Transmural ischemia strain distribution.

These studies indicate that the transmural ischemic region bulges out during systole resulting in dyskinetic motion and circumferential elongation of the ischemic tissue. This bulging tissue represents a loss of efficiency for the cardiac pump as less volume can be pumped out of the heart.

The FE models are then incorporated into the image phantom software such as the 4D NURBS-based Cardiac-Torso (NCAT). This allows the NCAT to realistic ischemic regions in synthetic PET and SPECT images. Figure 3 illustrates a synthetic SPECT image based upon the transmural ischemia finite element model. The bulging tissue can be seen at the top of the LV (arrow).

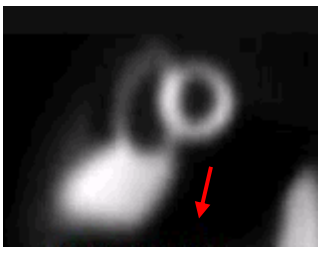


Figure 3. The 4D NCAT produced SPECT image based upon the transmural ischemia FE model. The red arrow indicates the location of the ischemic region which is undergoing bulging.

Finite Element based Image Registration. Nuclear cardiac imaging software packages are commonly included in commercial nuclear imaging equipment in order to provide functional information of the left ventricle. These software packages can be used to obtain estimates of ejection fraction (EF), wall motion and wall thickening. However, these are indirect measures of left ventricular tissue contraction and dilation. A direct measure of systolic and diastolic cardiac function is regional myocardial deformation as quantified by strain. We make use of image registration to determine the strain distributions documented in standard clinical medical imaging to determine of the deformation the left ventricle undergoes during the cardiac cycle.

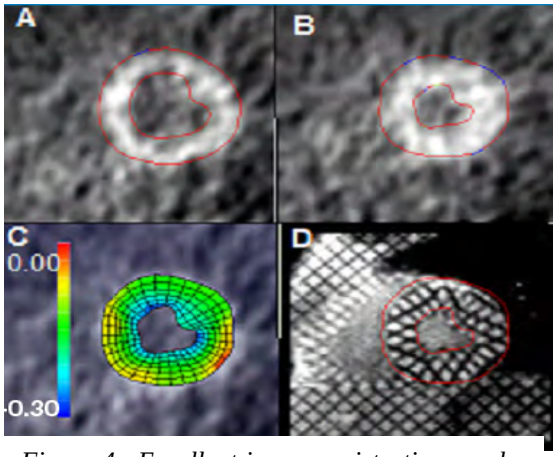


Figure 4. Excellent image registration can be achieved as demonstrated by the analysis of a (A) template PET image (end-diastole) and (B) target PET image (end-systole). (C) The registered FE model circumferential strain results superimposed on target PET image, and (D) registered epi- and endocardial wall outlines predicted by the Warping FE model superimposed on the co-registered, end-systolic, tagged MRI image of the same patient.

Image registration is the deformation map necessary for the template image (Fig 4A) to look like the deformed target image (Fig. 4B). We make use of a finite element based image registration system known as Hyperelastic Warping. The general approach to Hyperelastic Warping is that the local image intensity differences between the template and target images produce forces that deform a finite element representation of the template image into alignment with the target image(s). The technology has been successfully used to determine the strain distribution using intravascular ultrasound[3], cine-MRI[4] and PET[5]. A realistic material model of the myocardium complete with realistic myofiber distribution are incorporated into the FE element models that are used to regularize the image registration process. These realistic material properties limit the types of deformations possible to those of the native LV can undergo.

Dayong Gao, Ph.D.

Professor of Mechanical Engineering and Adjunct
Professor of Bioengineering, University of Washington

Professor Dayong Gao graduated (with B.Sc. degree) from University of Science and Technology of China in 1982, and obtained Ph.D. in Mechanical Engineering and Biomedical Engineering in 1992 from Concordia University, Montreal, Canada. His research has been focused on the problems in Bio-thermal/fluid science and biomedical engineering with funding supports from NIH, NSF, DoD, Whitaker Foundation, American Cancer Society, American Heart Association, Bill-Melinda Gates Foundation, Industries, and research institutions. Before joining University of Washington, he was Professor and Baxter Healthcare Chair of Engineering in University of Kentucky, Lexington, KY, USA. He has published over 300 original full manuscripts and obtained 12 US patents in the following research areas:

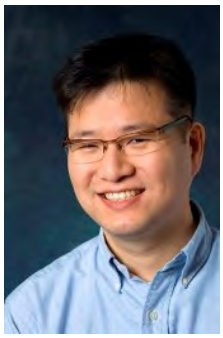
- Cryopreservation and fundamental cryobiology (mechanisms of cell cryoinjury and cryoprotection) of cells and tissues including: human and mammalian sperm, oocytes, embryos, pancreatic islets, bone marrow stem cells, umbilical cord blood derived stem cells, human platelets, skin, blood vessels/arteries, red blood cells, fatty cells, ovary tissues, and cornea.
- Bio-heat-mass transfer and thermal stress in cells/tissues during cryopreservation: permeability of cell and artificial porous membranes, micro-heat and mass transfer across cell/artificial membranes and its activation energy, solidification/vitrification of biomaterials, intracellular ice formation and growth, thermal and mechanical properties of biomaterials, thermal stress and its-induced fracture in tissues/organs during cryopreservation processes, directional solidification of biomaterials.
- Bio-sensors and BioMEMS: Developing biosensors through micro and nano-fabrication for various application in (a) early and rapid diagnosis of diseases; (b) detection and collection of macromolecules (e.g. DNA and proteins); (c) determination of physical and biological properties of biomaterials; and (d) detection and evaluation of function of cells (e.g. human platelets), etc.
- Artificial Organs: (a) investigating and developing a new generation of artificial kidney (including home-based, portable and mobile artificial kidney systems) to treat the End Stage Kidney Failure disease. (b) Inventing and developing a novel artificial liver replacement system and modeling to treat liver failure patients.
- Nano-technology/nano-fluid/Membrane Science: investigating and developing novel ceramic porous membranes with uniformly-distributed and identical nano-scale pores (nano-scale fabrication) for the blood purification (mass transfer) and the separation of bio-macromolecules (nano-scale). Developing novel technology for manufacturing porous membrane hollow fibers (polymer) by "Wet spinning technology" (nano-scale fabrication) for use in artificial kidney and artificial liver.

- Development of optimal technology and equipment (e.g. cell micro-perfusion chamber, automated perfusion-washing machine for addition and removal of cryoprotectants in cells, directional solidification machine for freezing of biological cells and tissues) for cryopreservation and banking of cells and tissues as well as re-engineered tissues for transplantation.
- Novel-microwave-irradiation-enhanced vitrification/glassification and rapid-uniform re-warming of biological systems.
- Tissue engineering: (a) developing a novel bio-reactor (cell-foam) to expand hematopoietic stem cells derived from human bone marrow or umbilical cord blood for use in bone marrow transplantation and potential gene therapy; (b) developing a bio-reactor for use in the bio-functional artificial kidney.
- Cardiovascular and blood research: (a) development of novel MRI imaging techniques to investigate the blood flow in blood vessels and its interaction with blood vessels, a well as blood flow in the porous membrane hollow fibers in the artificial kidney; (b) cryopreservation and micro-surgical implantation of arteries in bypass surgery (animal models); (c) blood coagulation and wound healing; and (d) freeze-drying of human red cells and platelets for transfusion.
- Major clinical research collaborations with physicians and surgeons (for 15 years) to treat diseases: cryopreservation of pancreatic islets for pancreatic islet transplantation (treating diabetes), cryopreservation of sperm/oocytes/ovary tissues for artificial insemination/in vitro fertilization (treating infertility or for cancer patients before chemotherapy), cryopreservation of small elastic artery for coronary artery bypass surgery (treating heart disease), cryopreservation of bone marrow and umbilical cord blood for hematopoietic stem cell transplantation (treating cancers), cryopreservation of blood cells (red cells and platelets) for blood transfusion/banking (surgery, trauma, cancer treatment), cryopreservation of fatty cells and bones (plastic surgery), and development optimal hemodiafiltration conditions and a new generation of artificial kidney (treating end stage renal failure disease).

UNIVERSITY OF WASHINGTON
COLLEGE *of* ENGINEERING

Mechanical Engineering

Jae-Hyun Chung
Assistant Professor
UW, ME Bldg, Box 352600
Seattle, WA 98195
206.543.4355
Jae71@uw.edu
depts.washington.edu/nlab



Low cost disease diagnosis using a tip probe concentrator

The main focus of Chung's research is in 'nanoengineering for low cost, rapid diagnosis of diseases'. The research fields cover from the discovery of fundamental sciences for a tip enrichment method using an electric field to the development of a biomedical device for low cost, rapid diagnosis of diseases'. The major funding sources for my research projects are National Science Foundation (NSF), Center for Disease Control and Prevention (CDC), and Bill and Melinda Gates Foundation. The major technical outcomes are as below.

Major performance of a tip sensor and future

- Immunofluorescence detection of bacteria (BCG) from saliva and sputum in 15 minutes with a sensitivity of 100 cfu/mL
- Nonspecific enrichment of human genomic DNA from saliva in 5 minutes. (PCR-ready sample preparation of DNA)
- Nonspecific concentration of human genomic DNA from human cell lines and buccal swab samples in 20 minutes.
- Sequence-specific detection of BCG genomic DNA with sensitivity of 1000 copies/mL
- Concentration of 100nm-diameter Au nanospheres with sensitivity of 10,000 particles/mL

Microscale and nanoscale tips for concentration of biomarkers: The enrichment of low abundance molecules is a crucial step toward disease diagnosis, drug- delivery and discovery, and environmental monitoring. However, the efficiency of current molecular enrichment methods is very limited due to extremely small mass and dimension. *The innovation of the tip enrichment system* is in the specific concentration mechanism of target analytes to the terminal end of a tip using an electric field, binding affinity, and capillary action. In particular, to enhance the sensitivity, the enrichment is conducted in a 1 mL sample volume through the multiscale enrichment mechanism.

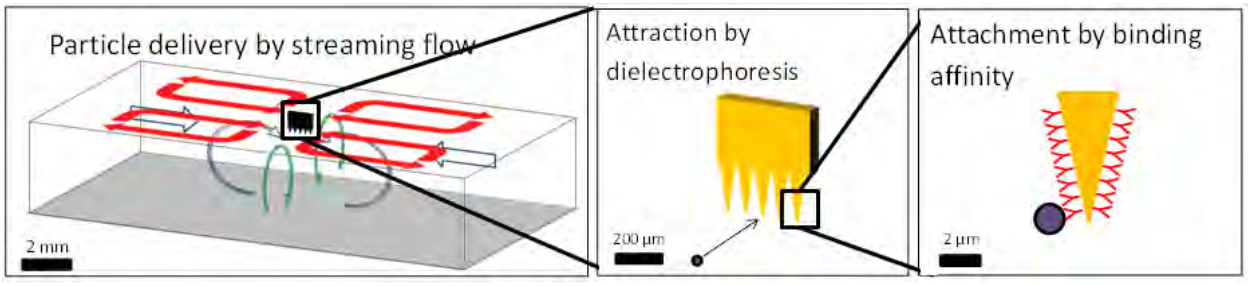


Fig.1 Multiscale enrichment mechanism using streaming flow, dielectrophoresis, and binding affinity.

UNIVERSITY OF WASHINGTON
COLLEGE of ENGINEERING

Mechanical Engineering

Jae-Hyun Chung
Assistant Professor
UW, ME Bldg, Box 352600
Seattle, WA 98195
206.543.4355
Jae71@uw.edu
depts.washington.edu/nlab

Fig. 1 shows the working principle of the multiscale enrichment, which includes (1) target delivery in 10 millimeter scale by streaming flow [Fig. 1(a)], (2) dielectrophoretic enrichment to a microtip in hundreds of micrometers [Fig. 1(b)], and (3) specific binding by antibodies within a few micrometers [Fig. 1(c)]. The captured targets are assayed by fluorescence or other detection methods.

Due to the superior enrichment mechanism, amplification-free and culture-free detection can be achieved. The three-dimensional circulation of the sample suspension using the streaming flow enables the enrichment of targets within two minutes. Targets in solution are attracted to a tip by electrical polarizability, which offers selective enrichment according to electrical properties. The capillary and viscous forces on tip surface in the withdrawal step yield size-selective enrichment of targets. This sample-friendly process replaces aggressive centrifugation and microfiltration steps. Specificity due to binding affinity is conferred by probe molecules decorated on a tip surface. In spite of the highly complex enrichment mechanism, the device operation is very straightforward, namely "*dipping and withdrawal of tips*".

Future development:

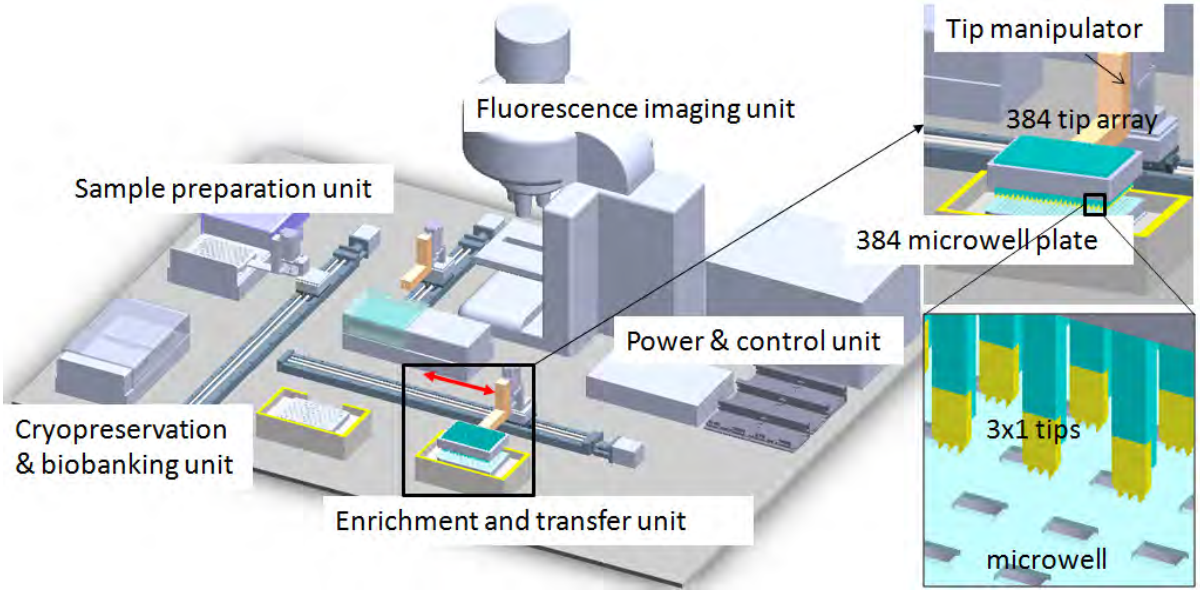


Fig. 2 Disease diagnostic station for enrichment, transfer, biobanking and analysis of targets.

We envision this tip enrichment system (Fig. 2) as a fundamental tool to provide solutions for early disease diagnostics and biomarker discovery. Due to the scalable approach, 384- or 1536 microwell plate format can be manufactured for high throughput enrichment of targets. The major functions of this system are (1) high throughput enrichment and transfer of cells, nucleic acids, proteins, and other biomarkers (2) multiplexing platforms for fluorescence microscopy, electron microscopy, mass spectrometry, etc. and (3) preservation and biobanking of targets.

Cell-Substrate Adhesion Study using a Laser-induced Stress Wave Technique

Junlan Wang

Department of Mechanical Engineering, University of Washington
Phone: 206-543-4601; Email: junlan@u.washington.edu; Http://nanomech.me.washington.edu/
October, 2010

Prof. Wang's research is in the area of mechanics of complex material systems. In particular, we are interested in developing novel experimental techniques complemented by numerical and analytical approaches to study the mechanics and physics of materials and structures at small spatial and temporal scales. Our current focus is in these sub-areas: 1) mechanical reliability of nanoporous materials as low-dielectric constant and wear-and-corrosion-resistant coatings; 2) thin film adhesion measurement and high strain-rate materials behavior study using laser-induced stress waves; 3) mechanics of cells and biomaterials, and ultrasonic and laser-based chemical and biological sensing; and 4) size-dependent plastic behavior of surface nano and microstructures.

In the health area, one of the projects we have been working on is the cell-substrate adhesion measurement using laser-induced stress waves. The adherence of cells to relevant substrates is a fundamental property of living cells. It influences a wide range of cell behaviors such as proliferation, differentiation, gene expression, migration and apoptosis. It is a critical issue in the successful development of biomedical implants, and diagnostic and drug delivery devices. Traditionally, techniques such as the hydrodynamics flow, centrifugation and micromanipulation methods have been used for evaluating cell-substrate adhesion. While the first two techniques tend to be more qualitative and can work with certain types of cells, the micromanipulation technique tends to be more invasive causing the cells to remodel before true adhesion can be evaluated. In our group, using pulse laser-induced stress waves as a loading means, we extended our previously developed laser spallation technique for thin film adhesion measurement to measure the adhesion strength of a cell-substrate interface. Within the nanoseconds duration of the stress wave, the cells under loading do not have time to respond or remodel thus true cell-substrate adhesion can be measured.

Figure 1 (left) is a schematic of our laser spallation setup for cell-substrate adhesion study. The sample configuration consists (from bottom to top) of a transparent glass confining layer, a thin metallic energy-absorbing layer such as aluminum, a substrate of interest, a glass petri dish with a pre-cut central hole sealed on top of the substrate, surrounding liquid medium for cell culture and the cells of interest contained in the petri dish. Once the cell-substrate adhesion is established, a high-energy infrared Nd:YAG laser pulse of 5 ns duration is launched from the YAG laser and steered toward the bottom of the multilayer sample. Upon absorbing the YAG laser energy, the exfoliation of the confined energy-absorbing layer generates a compressive stress wave (i.e., a pressure pulse) which propagates through the substrate toward the cell. Due to the large property mismatch between the substrate and the medium, a significant amount of the stress wave will be reflected at the solid/medium interface into a tensile wave, which will load the cell-substrate interface in tension. Given sufficiently high energy in the laser pulse, the cells will be detached from the substrate. Figure 1 (top-right) shows a computer simulation of

the propagating stress wave in the substrate toward the cell. The stress wave has an essentially planar wave front thus providing a uniform loading toward the entire cell-substrate interface. Figure 1 (bottom-right) shows a case study we did on neuron cells derived from hippocampi dissected from embryonic day 17 Holtzman rat embryos and immortalized by retroviral transduction. After applying the laser-induced press pulse, the majority of the cells in the tested region were removed.

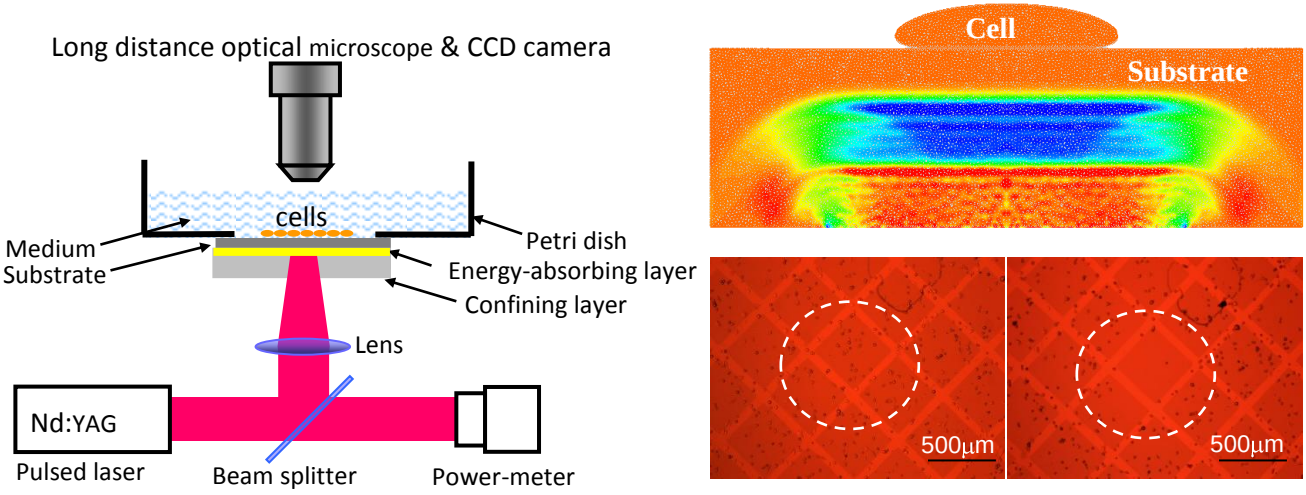


Figure 1. (left) Schematic of the Laser spallation setup for cell-substrate adhesion study. Note: this drawing is not to scale. The YAG laser beam is generally much larger than the multilayer sample thickness and the cell dimension. (top-right) Computer simulation of stress wave propagating towards the cell. (bottom-right) Neuron cells on Si substrate before (left) and after (right) laser spallation testing; cells in the tested region were removed.

Comparing with other existing cell-substrate adhesion measurement techniques, our technique has several unique advantages: 1) since the separation force is provided uniformly across the loading area by the planar stress pulse, the technique can measure the adhesion between either a single cell or a layer of cells (e.g. biofilm, biocoating) and the relevant substrate; 2) since this is a non-contact technique, the cells are undisturbed before they are detached and they do not have time to react to the nanosecond duration detachment force, which guarantees that real adhesion between the cell and substrate surface be measured; 3) the amplitude of the stress wave can be easily varied to obtain the adhesion information of the whole cell growth cycle. With the efficacy of technique validated, we are interested in extending this technique to some real case studies and to evaluate/measure the effect of various control factors in the cell-substrate adhesion development.

In addition to the above cell-substrate adhesion study, our group is also developing laser curvature interferometry based techniques for studying the cell-cell adhesion and laser-induced surface acoustic wave technique for chemical and biological sensing. Collaboration opportunities in all these areas are highly welcome!

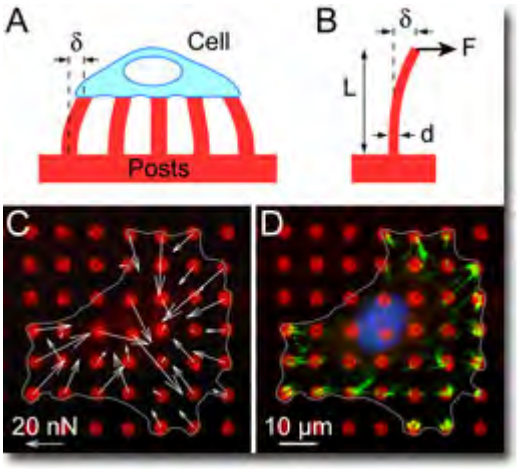
Cell Biomechanics Lab

Research Focus

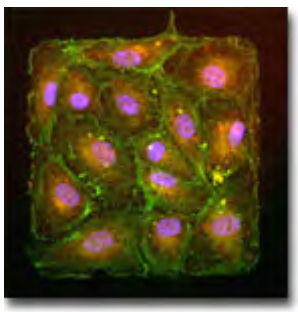
Nathan J. Sniadecki (Asst. Professor)

The Cell Biomechanics Lab investigates how cells are influenced by mechanical interactions at the micro and nanoscale. To pursue these goals, we are developing new tools - micro- and nano-devices, quantitative image analysis, and computational models - that we use to understand the underpinnings of biomechanics and mechanobiology. The greater impact of our work is to delineate how cell mechanics affects cardiovascular disease and cancer in order to catalyze new strategies for their treatment. By working at the intersection of mechanics and biology, we are also developing an increased understanding on the theories of soft, active, and multifunctional materials. Specifically, we are interested in how biophysical forces, adhesivity, spatial organization, internal structure, and material properties affect the behavior of cells. Since cells are the basic building blocks of organisms, if we can better understand cellular mechanotransduction processes, which are how cells detect and recognize these mechanical factors, then it would be possible to integrate, simulate, and study these interactions at larger scales, e.g. tissue or organ systems. For example, fluid shear stress can affect vascular endothelial permeability and gene expression, tensile strain can drive them to reorient, and matrix elasticity can dictate how much adhesion area cells cover. These changes can be detrimental to the function of the walls of the arteries and veins and can cause cardiovascular disease like hypertension and stroke. Cells also use their internal actin-myosin forces to transmit these mechanical signals to each other (cell-cell) or to the surrounding matrix (cell-matrix) during tissue remodeling events such as angiogenesis, wound healing, scaffold implantation, and inflammation. Our current research focuses can be grouped into three broad categories:

I. Cell Mechanics Measurements



Single cell mechanics: By their dynamic nature, cells are active materials that are difficult to measure with traditional characterization techniques. Instead, innovative tools are needed that are biocompatible, biofunctional, and as small as cells, or smaller. One set of tools we use to measure cell mechanics are arrays of micro or nano-posts. Cells plated onto these array attach to the tips of the posts and generate traction forces that deflect the posts like a cantilever beams $\delta = (L^3 / 3\pi E d^4) F$ (Sniadecki, et al. 2007). Cells generate forces through the interaction of myosin motor proteins on actin filaments in the cytoskeleton. They use these forces to migrate from one location to the next or to develop internal contractility or pre-stress that defines the shape of cells and tissue and helps to hold them together. Cells are responsive to mechanical cues and modulate their pre-stress with respect to the elasticity and adhesivity of the underlying matrix. To measure traction forces, the posts behave like simple cantilever beams, in which the deflection of the tips directly reports the traction forces of the adherent cell on the array. Since each force sensor is mechanically decoupled, this system can generate maps of subcellular traction forces. With this tool, we can measure how forces are generated and transmitted within the cytoskeleton and by observing cells on the microposts over time, we can also capture how these forces are dynamically coordinated during migration or contraction. *Current Funding*: NSF CAREER, NIH-NHLBI R21.



Multicellular mechanics: In addition to studying single-cell mechanics, we are investigating the mechanical interactions that cells have with neighboring cells in a monolayer. We can spatially control the space that cells occupy with micro-contact printing. This technique controls the placement of matrix proteins and blocks cellular adhesion from all other locations. We can stamp matrix areas of different shapes, e.g. squares, rectangle, circles, etc., and thereby control the spatial interactions that cells have with their neighbors. We have used this in conjunction with the microposts arrays to measure how traction forces and the adhesivity of adherens junctions that connect cells are coordinated within different shapes of monolayers (Nelson, et al. 2005). We can also measure the retraction forces of many platelets within a clot (Liang, et al. 2010), the tugging force between pairs of cells (Liu, et al. 2010), and the heterotypic interactions between monocytes and monolayers of endothelial cells (Liu, et al. 2010). We see that cells have different levels of participation in multi-cellular mechanics and can vary their traction forces and cell-cell contacts to collectively

regulate their structure-function relationships. *Current Funding*: NIH-NHLBI R21, NIH-NIBIB F32, *Past Funding*: NIH-NHBLI T32, UW RRF.

II. Mechanotransduction

Focal adhesions: One technique we have developed uses nanofabricated magnetic nanowires in the micropost array to create a sensor-actuator system for cell mechanics. The nanowires are embedded into the silicone microposts to create a robust tool that can apply piezomagnetic forces and simultaneously measure traction forces at the focal adhesions of cells. Focal adhesions are "spot-weld" structures (100-2000 nm) that transduce internal and external forces into biochemical responses. Focal adhesion growth and signaling increases with the application of external force and we found that a local force leads to an increase in local FA protein accumulation at magnetic microposts, but not at nearby, nonmagnetic microposts. We have also seen that cells respond to external force at focal adhesions through the dynamic regulation of their own internal traction forces showing that the mechanics of cells is coordinated with respect to mechanical factors outside the cell (Sniadecki, et al. 2007). *Current Funding*: NSF CAREER, NIH-NHLBI R21, *Past Funding*: NIH-NHLBI T32.

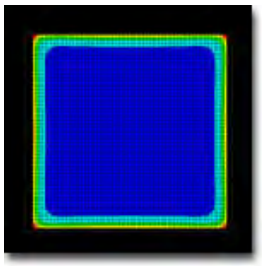
Shear flow: We are also developing fluidic approaches to apply shear stress to cells to mimic the fluid mechanics of the cardiovascular system. We use the same microfabrication techniques of the micropost arrays to build shear flow bioreactors in which cells are cultured. Using various pumping schemes we can stimulate cells with the identical fluid forces that they would encounter *in vivo*. We can then assay their response to various biochemical factors and fluid shear stress levels in order to screen therapeutic agents to cardiovascular disease. *Current Funding*: NIH-NIBIB F32, *Past Funding*: UW RRF.

Matrix stiffness: Cells also rely on their cytoskeletal tension to interpreting mechanical factors in the extracellular microenvironment. Matrix stiffness and the spread area of a cell can spread strongly influence how cytoskeletal tension is delivered to the focal adhesions of a cell, but it has been uncertain if these factors were intrinsically linked. To decouple the factors, we used arrays of posts that were fabricated with different heights, diameters, and densities and printed with patterned areas of available matrix ligand. We have found that matrix stiffness and spread area are independent factors of contractility, but the spatial distribution and density of focal adhesions underneath a cell greatly influence cytoskeletal tension. These findings led us to consider the effective shear modulus of the substrate, derived from the density and flexibility of the posts underneath a cell, which we confirmed to be a factor of cytoskeletal tension. Our viewpoint is that cells modulate their traction forces not only in response to the local stiffness at their focal adhesions, but also in response to the effective stiffness of their microenvironment. On the other hand, spread area increases the contractile work of a cell, which in turn is transferred to the substrate in a spatially dependent manner as traction forces. *Current Funding*: NSF CAREER.

III. Cell Mechanics Models

Migration: We are developing mathematical models of the coordination of cell mechanics during migration. Specifically, we are interested in mathematically expressing the dynamic events of migration and contraction and how the many *small* parts come together (myosin, actin, focal adhesions, etc.) and spatiotemporally coordinate their activity to produce cellular function. We use multi-physics finite element analysis to model the generation of traction forces during cell migration that incorporates elasticity and biochemical activity within a cell. *Current Funding*: NSF CAREER.

Monolayers: We have also used finite element analysis to model the generation and transmission of stress within monolayers of cells. This approach is matching to cellular mechanics because individual cells in a monolayer act like finite elements within a sheet. We have found that the traction forces observed within monolayers matches well with the predicted stresses (Nelson, et al. 2005). We seek to further develop these models from a "bottom-up" approach that utilizes what we know about mechanotransduction and cell mechanics at the single cell level to articulate what is observed during morphogenesis and adult tissue structures. *Past Funding*: NIH-NHBLI T32.



Summary

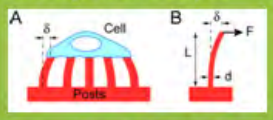
Cells use mechanical factors from the *outside* and *inside* to guide their collective function, but there is a lack of appropriate tool-sets with which to study these phenomena. Our micro- and nanofabrication techniques and modeling approaches can allow us to measure these mechanical factors, manipulate the physical interactions, and verify our mathematical predictions. By controlling mechanical interactions at the small scale, we strive to build up a working knowledge of biomechanics that guides new approaches in treatment and prevention of diseases.

Cell Biomechanics Lab

Investigating the Role of Cell Mechanics in Biology and Disease

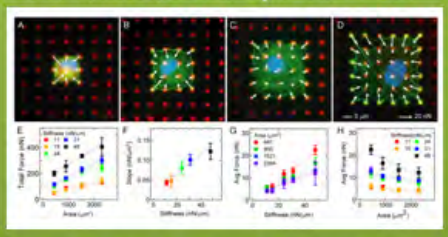
CELL TRACTION FORCES

Micropost Arrays:

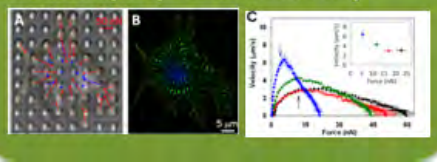


$F = (3\pi E d^4/L^3)\,\delta$

Post Stiffness and Spread Area:

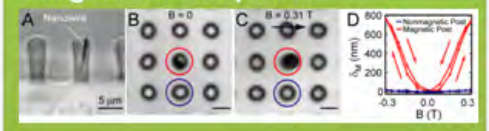


Cardiomyocyte Contractility:

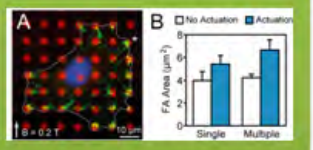


FORCE TRANSDUCTION

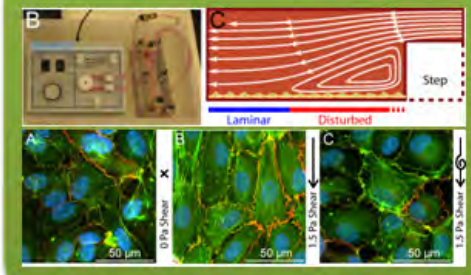
Magnetic Microposts:



Adhesion Mechano-Growth:

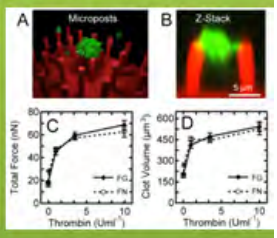


Endothelial Shear Response:

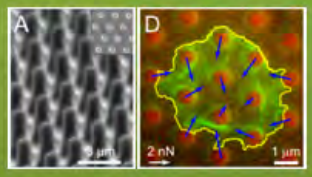


PLATELET BIOMECHANICS

Micro-Clotting Mechanics:



Single Platelet Mechanics:



ACKNOWLEDGEMENTS

S. Han, L. Ting, X. Liang, S. Feghhi, J. Jahn, B. Shuman

Wei-Chih Wang

In last five years, my research has been mainly focused in the area of **developing polymer based sensors and actuators for biomedical and industrial applications**. Due to the fact that these polymer devices require special manufacturing processes, my research also involves the development of new fabrication techniques.

My primary sources of funding have been from government and private sectors such as VA, NIH, Taiwan NSC International Collaboration Fund, and venture capitalists. The amount or research support from these sources over last five years is over 1.3 millions dollars. Most of the applications for my sensor and actuator research are in the area of medical device development. The developed principles and technology, however, can easily be expanded into industrial and military applications. Many of the active materials and devices that I have developed are associated with patent pending applications and several have received US and world patents.

About ten years ago, it became clear to me that the development of sensors needed a change in direction. All micro and distributed sensors were made of stiff semiconductor materials. This made it impossible to accurately measure the state of strain and stress in flimsy materials such as human tissue due to the fact mismatch in mechanical impedance. A large stiffness mismatch between the system of interest and the sensors is not desirable since it will affect what one is trying to measure. My research has therefore been focused on soft polymer based sensors and actuators development. The materials are flexible, lightweight, inexpensive, and durable. Furthermore, they can be configured into any shape and their properties can be tailored to satisfy a broad range of requirements. New founded polymers can also be photonically or electromagnetically activated to create physical and/or material property changes. Since 2000, I have worked on various forms of these active polymers, or so called "smart materials", using polymer composites, electro optic polymers and conductive polymers to create new types of sensors and actuators for medical applications. By advancing sensor and transducer technology from current stiff semiconductors to polymer materials and developing new fabrication techniques, I aim to create a new class of biocompatible sensors with associated new diagnostics tools. My current research projects using polymer based sensors and actuators include polymer based optical sensors for distributive pressure/shear sensing, force sensor glove for surgical procedures, active prosthetic liner system, scanning endoscope and micro display, vibrating resonance viscometer, liquid crystal based Fourier transform micro spectrometer, dialysis monitoring sensor, central venous catheter sensor, wound stress monitoring patch sensor (>60% strain measurement), and new rapid prototyping system for manufacturing electromagnetic polymers.

The success of my research is reflected by my research funding, publications, filed patents, and interest from venture capitalists. I have been successful in attracting research funding from NIH. To date I have received two NIH R21 and one R01 grants. One of my major

projects is developing a novel distributive pressure and shear sensor for foot ulceration studies on patients with diabetes. The project received NIH R21 funding in 2003 denoting myself as PI. The project is in collaboration with the Veteran Affair Puget Sound Health Care System R&D Center in Seattle where the project was initially funded under a VA research grant that initiated in 2002. I received another NIH R21 grant in 2006 to develop an ultra small electro-optic based scanning endoscope. This project is an interdisciplinary project that includes collaborative venture with Dr. Alex Jen of UW Material Science Department and Dr. Sum Lee of UW Medical School. Initial funding for this project was obtained from a Technology Gap Innovation Fund from UW Office of Technology Transfer. More recently, I jointly received a NIH RO1 funding with four other investigators from the Departments of Bioengineering, Electrical Engineering, Medicine, and Pathology at the University of Washington and John Hopkins. The objective is to develop and validate two new MEMS based scanning endoscopes and molecular contrast agents for improving early detection of cancer in luminal organs. Furthermore, the shear sensor and both electro-optic and MEMS based endoscopes also have received 5 US and world patents and have resulted in 10 journal publications respectfully.

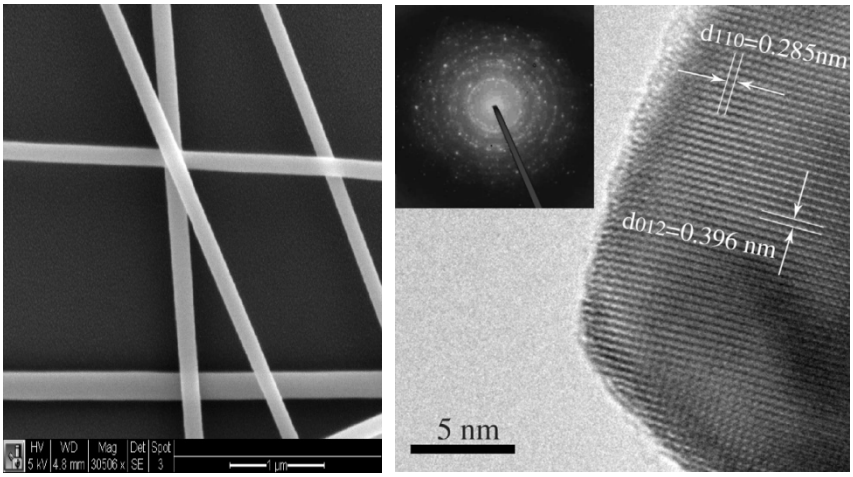
Aside from government funding, I have also been involved in getting private funding from industry and venture capitalists to develop devices and systems (including endoscope technology, active prosthetic liner, and smart shoe) for licensing and for a potential company start-up. In 2002, my collaboration with the Human Interface Laboratory at the Washington Technology Center to develop a microfabricated scanning endoscope contributed to an optional licensing agreement with PENTAX Corporation and also resulted in another US and world patent filing. Currently, UW is in negotiations with venture capitalists who are interested in forming a startup company to use our polymer based sensors and actuators in prosthetic and rehab applications. Dr. Nuckley of University of Minnesota and I are also in the process of forming a company called Lite Touch which we are exploring potential orthopedic and surgical applications using an optical force sensing glove developed in the lab. UW has also filed a US provisional patent on this. More recently, HD+ Oregon based biomedical company which is interested in our Fourier transform NIR spectrometer is in the process of signing a license agreement and finance a multi-years sponsor research on noninvasive NIR biosensor

My immediate research plan will mainly focus on utilizing polymers and polymer composites and developing new 3D printing techniques for electromagnetic and optical device manufacturing. I am especially interested in meta materials and advance material and structure development. I am also interested in applying existing technology for more practical applications such as creating and improving the environment around us. My current research focuses on applications using polymer sensors and actuators for medical applications; however I want to expand its application to other areas. For a future plan, I also like to develop a lab or center for doing a collaborative research for toy development which involves exploring different aspects of toy development with pedagogical emphasis. My research interests are broad and driven by a desire to seek and produce innovative ideas. I intend to continue collaborating with other departments, schools, and companies in the US as well as abroad to maximize novel technology development for the enhancement of the health and quality of life.

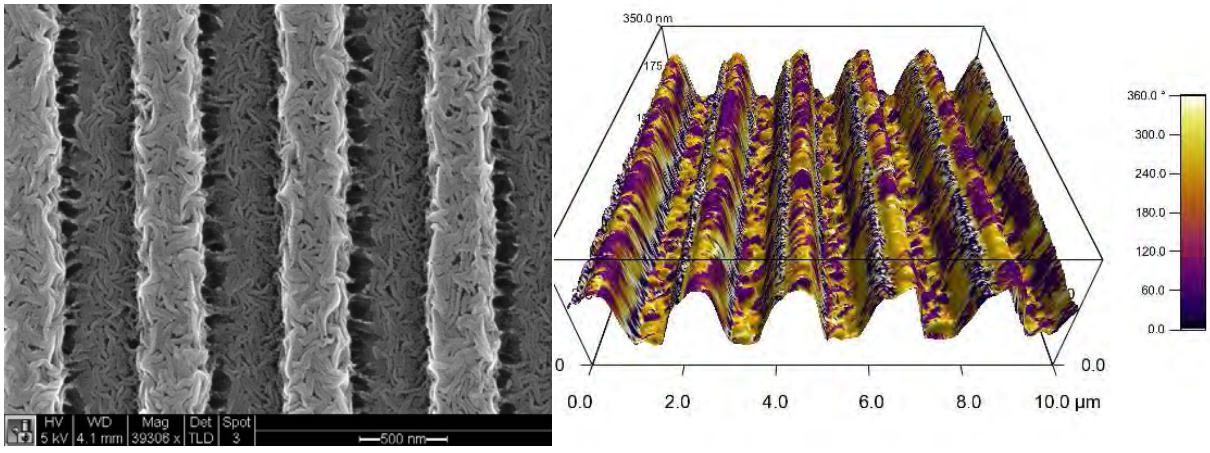
Multifunctional Materials Laboratory
University of Washington
Director: Jiangyu Li
206-543-6226; jjli@uw.edu; http://mfml.me.washington.edu/

The Multifunctional Materials Laboratory at University of Washington is devoted to investigating the mechanics and physics of multifunctional materials, using tightly combined theoretical, numerical, and experimental investigations. We are interested in understanding the formation and evolution of microstructure in materials, clarifying their structure-property relationship, and optimizing microstructures and processing conditions for superior functional properties. We have been working on ferroelectrics, ferromagnetic materials, multiferroics, thermoelectrics, and electro-active polymers and composites, and we are currently focusing on global energy need through multifunctional materials design and synthesis. Some of our current activities are summarized below:

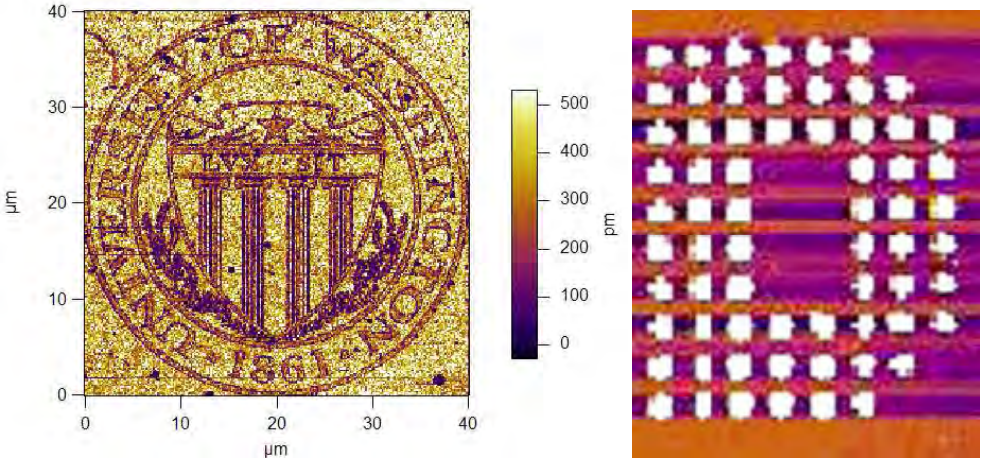
Synthesis of multifunctional nanofibers for sensing, actuation, and energy conversion



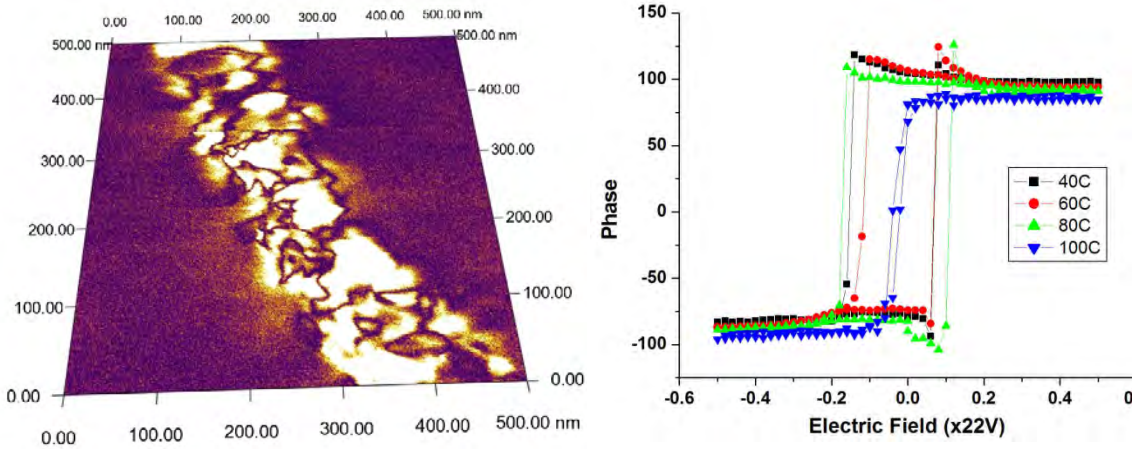
Patterning multifuncitonal nanostructures by nanoimprint- and soft-lithography



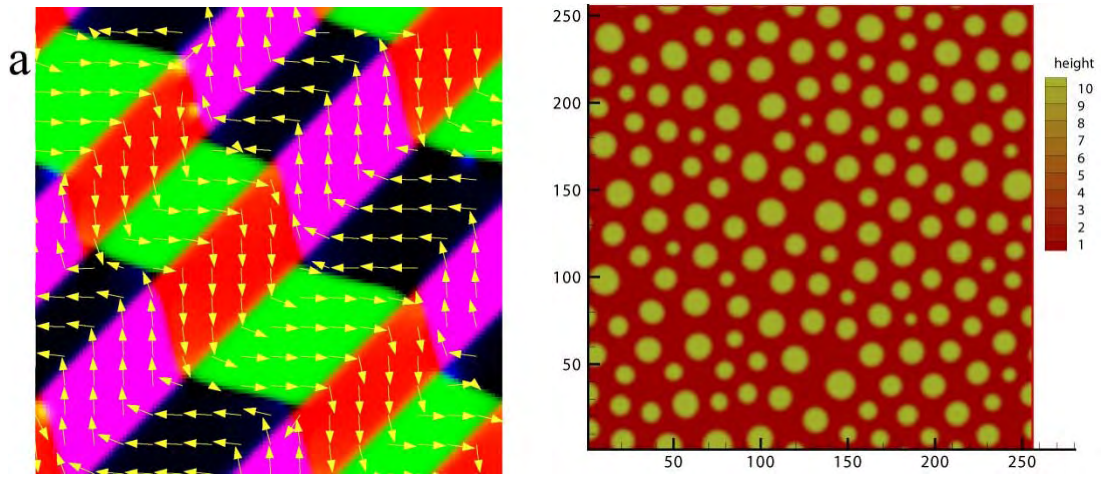
Scanning probe microscopy based nanolithography and nanofabrication



Nanoscale characterization by advanced scanning probe microscopy and nanoindentation



Modeling and simulation of active microstructures and multifunctional properties



Santosh Devasia

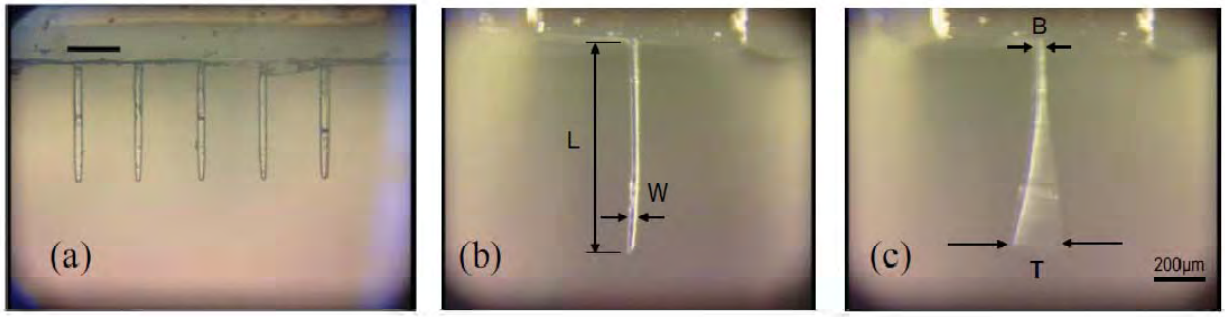
Santosh Devasia received the B.Tech. (Hons) from the Indian Institute of Technology, Kharagpur, India, in 1988, and the M.S. and Ph.D. degrees in Mechanical Engineering from the University of California at Santa Barbara in 1990 and 1993 respectively.

He is a Professor in the Mechanical Engineering Department at the University of Washington, Seattle where he joined in 2000. From 1994 to 2000, he taught in the Mechanical Engineering Department at the University of Utah, Salt Lake City.

His current research interests include high-precision positioning systems, Atomic Force Microscopy and Scanning Tunneling Microscopy used in nanotechnology, and biomedical applications such as the imaging of human cells to investigate cell locomotion and micro-mixing.

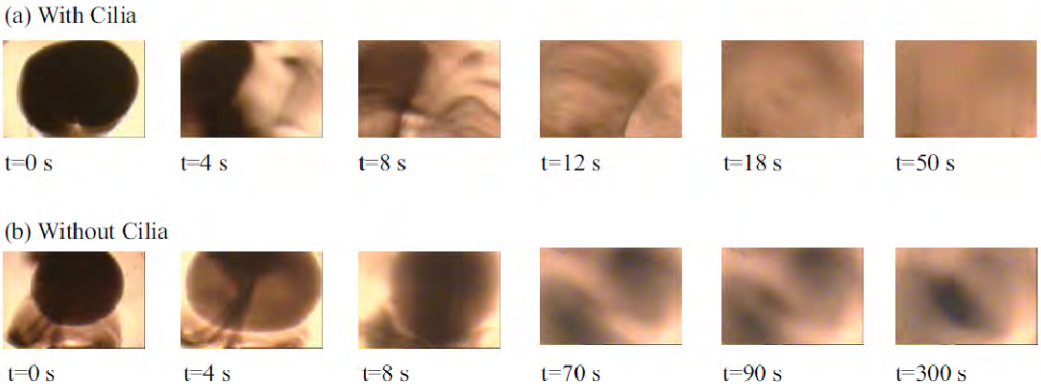
Control of Micro/Nano Bio-mimetic Structures for Fluidic Devices, NSF-funded work*,*
S . Devasia was principal investigator (P.I.) with Prof. J.Chung and Prof. J. Riley as co-P.I.s.

Research effort: The goal of the project was to study minimal energy control of novel cilia-based devices for handling micro/nano-scale fluid flows. The major accomplishments of this work were: (i) the design and fabrication of Polydimethylsiloxane (PDMS or Silicone) cilia and demonstrating substantial resonance excitation in an oscillating fluid-chamber, ; (ii) analytically and experimentally showing that an added mass effect can be used to explain the substantial reduction in the resonance frequency of the cilia; (iii) characterizing the mixing of fluids with the cilia; and (iv) analytically and experimentally demonstrating models of the fluid-structure to explain the large-amplitude cilia vibrations and improvements in mixing performance, as illustrated in example results on mixing, with and without cilia. Additionally, we have used control techniques to precisely control the driving waveforms and experimentally choose the best waveforms for mixing.

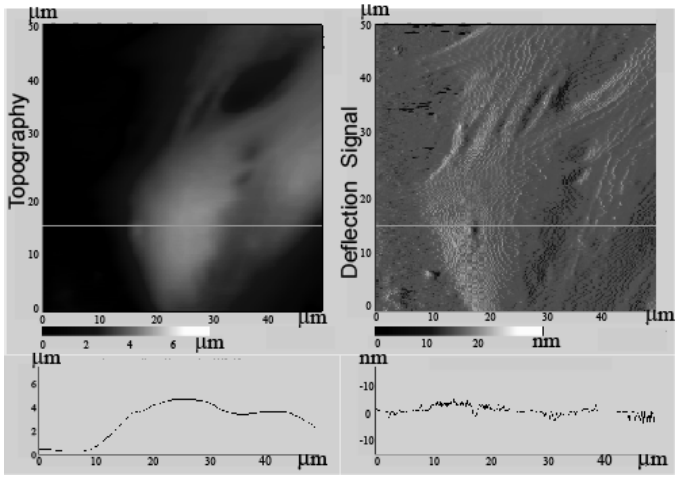


*Images of PDMS cilia by Kieseok Oh (a) PDMS cilia in water without collapse (*10μm × 75μm ×400 μm *with 200 m spacing. Scale bar is* 200μm*). (b) Single cilium in deionized (DI) water in a PDMS well.*

Length (L) is 800µm *and width (W) is* 10µm*. (c) Resonance of a cilium in DI water at* 90Hz *with a large peak-to-peak response T. Note that the motion of the base of the cilium (i.e., vibrational excitation of the cilia chamber) is relatively small compared to the tip motion.*



Mixing with and without cilia – Images by Jiradech Kongthon. Time-lapse images of the mixing process at different time instants t: (a) Top row with cilia; and (b) Bottom row without cilia. The cilia-chamber is oscillated at 98Hz *with an amplitude of* 10µm *for both cases. The sloshing-based vibration of the cilia is larger than the sloshing itself, which leads to relative motion between the cilia and the fluid and improved mixing with cilia when compared to the case without cilia. The dimensions of cilia for these experiments were* 800 × 45 × 10µm*. Some of the cilia are visible in the top image (at t =* 50s*). The initial dark region is black drawing ink: the change in the ink pattern is used to characterize mixing.*



Nano-scale Bio-Imaging: High-Speed Atomic-Force-Microscopy for Imaging of Cells: Biomedical applications like high-speed imaging of human cells to investigate cell migration. The key goal is to improve the temporal resolution of Atomic Force Microscopes when imaging soft samples such as human cells with high resolution and small forces (as seen to the right; images by Szu-Chi Tien).

Nanotechnology: Increasing the Throughput of Scanning Probe Microscopes Emerging technologies such as nano-fabrication require precision positioning systems with nano-scale resolution. During high-speed positioning, say with piezo-actuators, one of the critical challenges is to overcome motion-induced vibrations. This current effort (funded by NSF), aimed at vibration compensation in such high-speed nano-positioning systems, seeks to develop positioning techniques to control Atomic Force Microscopes (AFMs) and Scanning Tunneling Microscopes (STMs) with sub-angstrom-level precision. It is noted that the AFM and STM are key enabling tools in the nano area; therefore the current work aimed at increasing their throughput will have a significant impact on the real-time investigation and manipulation of nano-scale and sub-nano-scale phenomena.

Per Reinhall

Chair, ME Department
(206) 543-5628
reinhall@uw.edu

Professor Reinhall is currently conducting research on the development of biomedical sensors and actuators for prosthetic, diagnostic, and imaging applications. He is also interested in the dynamics of the human heart including the computational modeling of human heart valves and the development of methods to screen for high risk for ventricular fibrillation or sudden death among patients suffering from heart failure. His research is supported by National Institutes of Health. Non-medical research includes sensor and actuators, noise and vibration control of structures, fluid structure interaction, nonlinear dynamics, and noise control.

Biomedical sensors and actuators

We are interested in developing new prosthetic technologies. This includes the development of new materials that can be used between the prosthetic socket and the below knee residual limb. The goal of our work is to improve prescription and design of interface liner materials for patients with limb amputation so as to create prostheses that are mechanically stable and resist soft tissue injury during ambulation; and a novel tool for prosthetic liner prescription that shifts clinical thinking to evidence-based practice rather than exclusively experience-based practice.

We are also developing flexible sensors and actuators that can be incorporated into the prosthetic system to sense and react to changes in the interface between the soft tissue and the prosthesis. Specifically, research is ongoing in:

- Distributed and flexible sensors for the measurement of shear and pressure on soft tissue
- Active soft materials capable of stiffness change.

We are also developing ultra-thin endoscopes that can be used for the early detection of cancer. Projects in this area with Professor Eric Seibel include:

- The development of steerable guidewire with eyes for image-guided intervention in the upper urinary tract
- Automated bladder surveillance system using an ultrathin laser imaging probe and active distal steering
- Development of an automated steering mechanism for bladder urothelium surveillance
- Optimization of the dynamics of a scanning fiber endoscopes

Other biosensor projects include:

- Implantable viscosity sensors
- Ultra compact based endoscopic imaging using electro-optic scanning
- A bio inspired ultra compact acoustic vector sensor

Cardiac Dynamics Research

Cardiovascular disease is the leading cause of death in the United States claiming over 900,000 lives per year. In addition to the cost in terms of lost lives, the dollar cost of cardiovascular diseases in 2004 is estimated to be $314 billion, according to the American Heart Association and the National Heart, Lung, and Blood Institute.

Screening for the risk of sudden tachycardiac death.
The onset of a seemingly chaotic heart dynamics called ventricular fibrillation can lead to a rapid decrease in blood pressure and death. The ability to predict and screen for this arrhythmia is being developed in our laboratory. We have shown that the fractal content of the ECG provide insights into differences in cardiac behavior and can predict mortality where traditional techniques of data analysis have shown not to be sufficient.

Heart valve dynamics
The dynamics of the heart valves result from the synergy of heart geometry, local blood flow and soft tissue integrity. By constructing nonlinear coupled fluid-structure finite element models of the mitral and aortic valves we aim to aid in the development of new surgical valve repair techniques. Research in this area includes a finite element investigation of hemodynamic determinants of the mitral valve closure sound and a nonlinear fluid-coupled computational model of the dynamics of the mitral valve.

Prof. Joseph L. Garbini
(Joe)

MEB 216
Office: 206-543-5399
Email: garbini@u.washington.edu

Broad Research Interests:

- Instrumentation and control systems.
- Engineering systems research and design.
- Extensive work in systems analysis and control, dynamics and instrumentation.
- Background includes electromechanical analysis, embedded control systems, and
- Scanning probe microscopy.

Current Research:
In Professor Garbini's principal research he applies his background in controls and instrumentation to the development of a special-purpose micro-electromechanical system: Magnetic Resonance Force Microscopy (MRFM).

One of the oldest and most enduring dreams of the scientific community is to directly observe molecular structure nondestructively, in situ, in three dimensions, with Angstrom-scale resolution. Such an imaging technology would immediately address urgent needs in nanoscale engineering, materials science, molecular biology, and medicine. The objective of Magnetic Resonance Force Microscopy research is to create such a technology.

The interdisciplinary UW MRFM group, housed in the Department of Mechanical Engineering, offers research opportunities in dynamic systems, controls and instrumentation.

Undergraduate Design Projects:
The ME department offers a guided undergraduate curriculum in mechatronics, consisting of these required and option courses, additional electives, and culminating in a special mechatronics capstone design course. These senior-level group design efforts are often excellent venues for collaborative projects.

Mechatronics is the term originally coined to describe the integration of mechanical, electrical, and computer technologies into the design of complex products. Although products have long included all three components, traditional design methods viewed them as separate, independently realized aspects of the design.

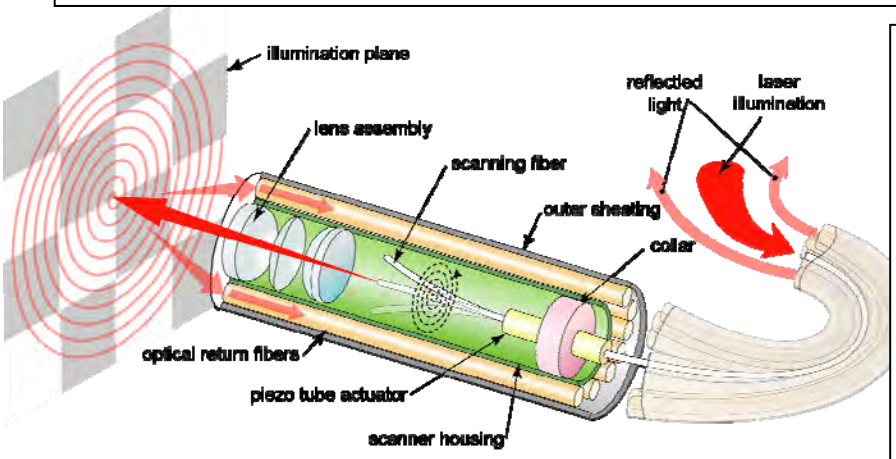
Mechatronics emphasizes global optimization by integrating these three components of the design process.

Past medical-related Projects

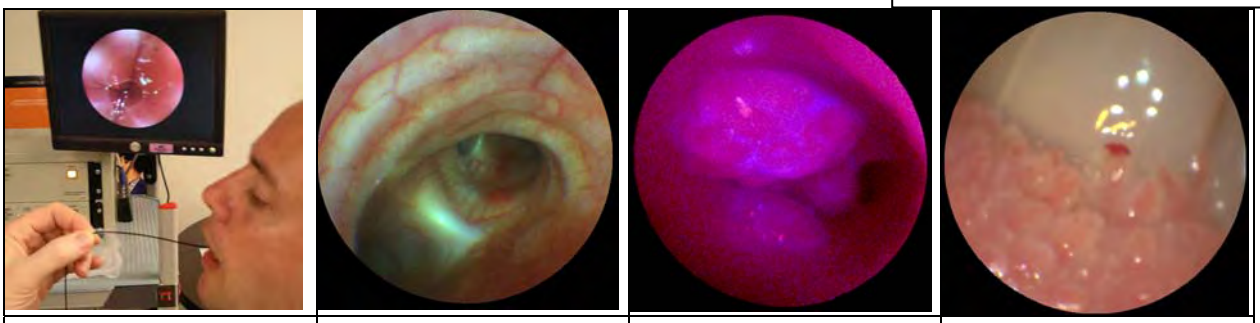
- Medical Doppler ultrasound
- Robotic surgery

ERIC SEIBEL

Scanning single-illumination optical fiber endoscope (1.5 mm diameter)



Laser illumination is combined, (white light is made up of red, green, and blue narrow band emissions), then enters the single illumination optical fiber which is guided to the distal tip for scanning within a flexible sheath. Within the 10-mm rigid tip is a tubular piezoelectric actuator which electro-mechanically drives the free fiber end in mechanical resonance in a spiral pattern. A lens assembly seals the tip of the scope which focuses the scanned beam of light across a wide field of view. Backscattered and fluorescence emission from this scanned illumination are collected in a ring of optical fibers that sends this back to the detectors in the base station. Example images are shown.



Imaging unsedated human's esophagus	Live pig airways	Live mouse colon polyp (fluorescence biomarker)	Human tooth & gum

Endoscopes are used to see inside the human body at video rates and at high resolution (sub-cellular). Current endoscopes form images using cameras that require a physical space for each display pixel. Small size and high resolution are not possible using this camera technology, so a new technology was invented. This new type of laser endoscope provides features never before possible in medicine, such as:

- 1-mm imaging catheterscopes with high resolution color imaging at wide fields of view
- Imaging regions of the body previously inaccessible, e.g. pancreas and fallopian tube
- Imaging from ultraviolet to visible to infrared wavelengths of light
- Laser diagnostics for more sensitive disease detection
- Fluorescence biomarker imaging (wide-field, confocal, multiphoton)
- Optical spectroscopies (Laser-induced fluorescence, Raman, etc)
- Laser therapies (e.g. laser surgery and photodynamic therapy)
- Image-guided interventions (biopsy and surgery)
- 3D imaging and 3D mosaicing

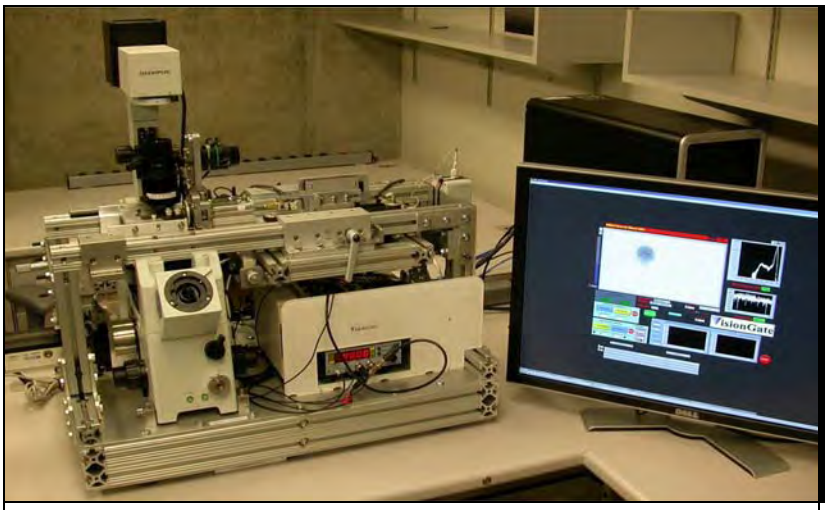
New concepts being explored in minimally-invasive medicine/dentistry and engineering

- Guidewire with Eyes (instead of metal guidewires with x-ray imaging)
- Eyes on Tools (instead of tools through endoscope channels)
- Low cost endoscopy with unsedated patients (versus sedated patients)
- Integrated imaging, diagnosis, therapy, and monitoring with same device
- Pixel-accurate laser therapies in endoscopy and real-time dosimetry
- Long term dynamic monitoring of human chronic conditions

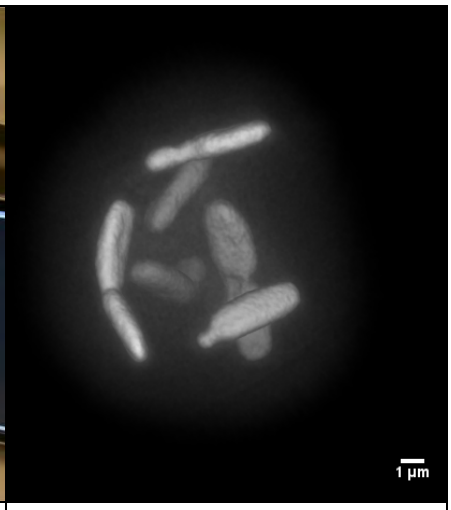
- Fluorescence biomarker imaging of pre-cancer (dysplasia) and early cancer
- Low cost advancements in screening & surveillance of cancers
- Advanced medical device design, manufacturing, and human testing
- Dynamics and control of amplitude-modulated resonance scanners

For further details, please see recent review by Lee, Engelbrecht, Soper, Helmchen, and Seibel, Journal of Biophotonics, May/June 2010, No. 5-6, pg. 385-407.

3D optical projection microscopic imaging of cells for disease diagnosis



Optical Projection Tomography Microscope (OPTM) co-developed by VisionGate Inc. and the University of Washington (Seibel's lab)



Single cell chromosomes imaged with OPTM (absorbance & fluor.)

Optical microscopes are used to diagnose disease, and absorbance stain using hematoxylin is used in a majority of all cancer diagnoses. The analysis of single cells for disease diagnosis is cytological analysis. The ability of imaging cells in 3D will increase sensitivity of early cancer diagnosis, however, there are no commercial 3D microscopes that can image the clinical useful stains (e.g. hematoxylin). A new type of microscope was invented and co-developed by a start-up company within Seibel's Human Photonics Lab which is called Optical Projection Tomography Microscope (see OPTM photo above). Current research is expanding the features of the OPTM by adding fluorescence 3D images that co-register with absorbance 3D images of the same cell (see figure above of single mutjac cell, chromosomes in metaphase). See reference Miao et al., Journal of Biomedical Optics, Nov/Dec 2009, 14(6): 064035.

Future work is developing a more quantitative 3D microscope with isometric resolution and photometric calibration to measure sub-cellular concentrations of biomarkers. In addition, multi-cellular images are being acquired that preserves tissue microstructure for multimodal disease diagnosis by pathologists.

Engineering design, analysis, and instrumentation is required for the unique method of optical scanning that creates a high-resolution projection of the cell. Future work is required for modeling the imaging process to reduce artifacts in the 3D images, calibration to achieve absolute concentration measures, and automated sample preparation and scanning for high-throughput cell analysis for clinical use.