Tuesday Morning, October 21, 2008

BioMEMS Topical Conference
Room: 309 - Session BM+MN+BI+BO-TuM

MEMS/NEMS for Biology and Medicine

Moderator: E. Meng, University of Southern California

8:00am **BM+MN+BI+BO-TuM1 Microfluidic Systems for Cell Growth and Analysis**, ***K.F. Jensen***, *A. Adamo, L. Ye, Z. Zhang*, Massachusetts Institute of Technology **INVITED**

We present microfluidic systems for cell growth, including instrumented microbioreactors in which the main process parameters (e.g., optical density, dissolved oxygen and pH) are monitored optically and controlled. The system accommodates bioreactors in different operational modes, batch and continuous. The systems are disposable and consist of layers of poly(methyl methacrylate) for structural integrity and poly(dimethyl siloxane) (PDMS) layers for aeration. We also combine cell growth with analysis of protein responses underlying cell signaling. Analysis of these potentially fast transient events requires very short treatment times and well-controlled and reproducible stimulus conditions. Consequently, such pathways can be difficult to probe reproducibly with conventional laboratory techniques that are susceptible to small fluctuations in manual handling – in particular at short times. Microfluidic systems provide for reproducible and automated analysis with excellent control over experimental conditions. We describe microfluidic based methods for investigating signaling pathway ways of adherent cells with the overall aim of controlling cell culture, cell stimulation, and the subsequent protein analysis. The devices, which are fabricated in PDMS by soft lithography, enable dynamic studies of cell signaling by taking advantage of the equivalence between distance travelled along a microfluidic channel and treatment time. They perform all the necessary steps needed in stimulus-signal response analysis of signaling pathways by a fluorescent immunocytochemical assay including cell culture, cell stimulus, cell fixation, and antibody analysis. Average cell population data are obtained by scanning and imaging the entire device, while high resolution microscopy moving along the channel allows responses to be collected at the single cell level. Finally, we present microfluidic devices for quantitative microinjection of macromolecules and nanoparticles into living cells. These approaches overcome limitations with traditional manual manipulation of microinjection needles.

8:40am **BM+MN+BI+BO-TuM3 High-Throughput pMHC Microarrays for Characterizing Diverse T Cell Populations**, ***M. Paulaitis***, Ohio State University and Johns Hopkins University, *C. Yue, N. Guzman,* Ohio State University, *J. Schneck, M. Oelke*, Johns Hopkins School of Medicine **INVITED**

We are developing protein microarrays for rapidly scanning and screening diverse T cell populations to characterize human adaptive immune responses. An important early molecular recognition event that triggers an immune response is the interaction of a T cell receptor (TCR) on the surface of the T cell with its complementary major histocompatibility complex (MHC) on the surface of antigen-presenting cells. This interaction is mediated by a small peptide (the antigen) 8-10 amino acids in length bound to the MHC, such that the amino acid sequence of the peptide antigen determines the specificity of the TCR/peptide-MHC (pMHC) interaction. Surface plasmon resonance studies of TCR/pMHC interactions have established that the overall range of binding affinities of stimulatory pMHC ligands is low relative to that for anti¬body-antigen interactions. Yet, these interactions have remarkably high specificity/sensitivity leading to T cell activa¬tion and different immune responses depending on the nature of the peptide. Individual T cells are also characterized by a unique TCR; therefore, pMHC microarrays printed with peptides having different amino acid sequences serve to distinguish T cells by their characteristic TCR/pMHC interactions. In addition, co-printing antibodies against cytokines secreted by the captured T cells enables an antigen-specific functional analysis of T cell activation across this population. We show that pMHC microarrays can selectively capture and enumerate antigen-specific T cells in diverse populations at high sensitivity, and that this information provides insights into the general principles governing early molecular recognition events in human immune responses. Results on the functional diversity of the human immune response will also be presented. This work is supported by the National Science Foundation (BES-0555281) and the National Institute of Allergy and Infectious Diseases of the National Institutes of Health (1R21AI077097-01).

9:20am **BM+MN+BI+BO-TuM5 Tunable Microeddies for Microfluidics: Non-contact Single-cell Trapping using Gentle Fluid Flow**, ***B.R. Lutz***, *J. Chen, D.T. Schwartz,* University of Washington, *D.R. Meldrum*, Arizona State University

Cells that normally live in suspension typically exhibit strong biological responses to physical contact. Microfluidic devices have been very successful for studying single adherent cells in controlled chemical environments, but tools for manipulating single cells in suspension are extremely limited. We developed a non-contact microfluidic single-cell trap that creates strong trapping forces using only gentle fluid flow. The traps are based on steady streaming flow, which is the steady flow generated when oscillating fluid interacts with any boundary that causes the fluid to turn (e.g., obstacles, cavities, bends). Steady streaming was first identified over a century ago, but its remarkable ability to trap cells was not known. A key feature of this approach is that traps are insensitive to differences in cell shape, cell density, and fluid medium. We demonstrate the ease of trapping for bubbles, spheres, rod-like debris, non-spherical motile phytoplankton, macrophages, and monocytes in different fluid media. The approach is remarkably simple to implement and control, in fact, early work used hand-built flow channels and a home stereo amplifier. The flow is created by audible-frequency fluid oscillation in a microchannel containing a cylindrical post. The back-and-forth motion creates four eddies around the cylinder, and each eddy traps a cell and holds it in place at a predictable location within the fluid. We use capture and release of swimming phytoplankton to estimate the trap strength; strong trapping forces capable of holding the strongest swimmers are easily generated (>30 picoNewtons), while gentle shear conditions in the traps are comparable to arterial blood flow. By using flow to displace trapped spheres under different conditions, we determine a simple scaling relationship that quantitatively describes the trapping force for common cell sizes (5-50 microns). The traps withstand net flows as large as 1 cm/second, which enables medium exchange and chemical treatment of single cells in suspension. Posts can be arrayed with little effect on trapping behavior, providing the potential for high-throughput screening of suspension cells based on dynamic measurements. The combination of strong, tunable trapping forces and gentle trapping environment makes this an appealing new alternative for manipulating single cells in microfluidic devices.

9:40am **BM+MN+BI+BO-TuM6 Automated on-Chip Rapid Microscopy, Phenotyping, and Screening of C. elegans**, ***H. Lu***, Georgia Institute of Technology

Microscopy, phenotyping, and visual screens are critical methods frequently applied to model organisms in combination with genetics. Although widely used, these techniques for multicellular organisms have mostly remained manual and low-throughput. We report the complete automation of sample handling, high-resolution microscopy, phenotyping, and screening of C. elegans using a custom-designed microfluidic system. The engineered system, coupled with customized software, enables high-throughput diffraction-limited imaging and sorting of samples with no human intervention with any microscopy setup. The robustness and automation of our system relies greatly on integrated closed-loop control software as well as engineered hardware design of the microchip. The chip has six salient features that ensure a consistent and reliable operation for an extended period of time. First, it automatically self-regulates the loading of nematodes by a simple passive loading-regulator design. Constant pressure drives the flow, so that no feedback or intervention is necessary for the microchip to allow one and only one animal to occupy the imaging area at a time. Second, the setup automatically positions the samples in an identical position in the chip, so as to minimize the travel of the motorized stage and thereby reduce the processing time and increase the throughput. Third, the device has an integrated local temperature control system whereby animals are cooled to ~4 °C and completely immobilized briefly (~ a few seconds) for imaging and manipulation without the use of anesthetic drugs. Cooling provides an alternative to anesthetics, potentially minimizing the adverse developmental effects. Fourth, the microchip and the setup are compatible with any standard microscopy setup with no modification necessary, including simple compound epifluorescence microscopy, as well as more expensive multiphoton or confocal microscopy. Fifth, the microchip has no permanent small features (<20 μm), and therefore is easy to fabricate, less likely to be clogged by debris, and can operate very robustly. Lastly, losses through our system are minimal (~3%,) and the device design is gentle on the animals as the viability of all the sorted animals is ~100%. We show that compared to standard manual operation, time for phenotyping and visual screens can be reduced by ~2 orders of magnitude in our system with no human intervention, which has not been demonstrated before. Moreover, we show the ability to perform multiple sensitive and quantitative genetic

screens with real biological samples based on cellular and subcellular features with over 95% accuracy per round.

10:40am **BM+MN+BI+BO-TuM9 BioMEMS Challenges and Opportunities – A Department of Defense Perspective**, *D. Polla*, Defense Advanced Research Projects Agency, ***S. Barker***, System Planning Corporation **INVITED**

Considerable progress has been made over the last 15 years in realizing a great variety of BioMEMS devices and systems. The field of BioMEMS can be approximately subdivided into three categories: (1) bioanalytical systems, (2), surgical systems, and (3) therapeutic systems. All three areas have numerous commercial and defense applications, but in many cases progress is inhibited by fundamental scientific and technological challenges. This paper presents the authors' perspective on the top 10 challenges facing BioMEMS today. Bioanalytical systems, which are also commonly referred to as "lab-on-a chip," have not realized their full potential for numerous reasons: (1) Autonomous sample processing with minimal human intervention has yet to be achieved. (2) Sample clean-up and pre-processing pose significant challenges that often limit the performance of a bioassay. (3) The ability to take a biological sample and obtain a result or set of results is still a long process, often taking several hours; obtaining a microfluidics-based PCR bioassay result in less than one minute persists as a grand challenge for the BioMEMS community. (4) The development of size-scaled microinstruments for bioanalysis presents an enormous opportunity toward the realization of remote site-derived information that can be conveniently communicated to a physician's office and correlated with a patient's stored medical record. The potential of surgical MEMS has often meant "micro-invasive" surgery that provides significant benefit to the patient. (5) But non-invasive surgery enabled by MEMS has the potential for providing even better patient outcomes. (6) Both sensors and actuators with the capability for more accurately and more reliably reproducing the skill of a surgeon's hands still need to be realized. (7) Developments that enable in vivo imaging of cells and organs using MEMS devices may also play an important role in enabling more effective precision surgeries. Therapeutic systems based on MEMS technology have yet to be made smart. (8) This means effectively integrating sensors, electronics, and actuators in a controlled feedback system designed to provide therapy only when the body needs it. These systems are often implantable and are limited by (9) battery size and lifetime. And finally, (10) neural prosthesis represents an exciting new domain where MEMS may provide an effective interface between nerves and electronics.

11:20am **BM+MN+BI+BO-TuM11 CD Based Sample Preparation and Pathogen Screening**, ***M.J. Madou***, Unversity of California, Irvine **INVITED**

We have demonstrated the feasibility of a multiplexed microfluidic CD apparatus for sample preparation of a wide variety of clinical samples and the subsequent detection of viruses, bacteria and fungi through fast DNA hybridization on the same platform. As the CD slowly rotates, a free moving magnetic disc in a lysis chamber is moved back and forth in the radial direction by the magnetic force of stationary magnets located below the rotating CD. The movement of the magnetic disk causes mechanical shear that disrupts cell membranes. This CD does not only process multiple samples simultaneously, but can also be used for the centrifugal precipitation of solids from each sample liquid. After precipitation, the resulting clarified liquid is transferred through a solid phase extraction membrane to capture the DNA. This step is followed by subsequent automated washing, elution, and detection by hybridization and fluorescence detection on an embedded DNA array. Recent sample to answer results and modeling of ice valves and coriolis valves will be detailed.

BioMEMS Topical Conference
Room: 309 - Session BM+BI+BO+NC-TuA

Microfluidics/Lab-on-a-Chip

Moderator: L. Rieth, University of Utah

1:40pm **BM+BI+BO+NC-TuA1 Interfacing Silicon, Biology, and Medicine at the Micro and Nanoscale: Opportunities and Prospects**, ***R. Bashir***, *Y.-S. Liu*, University of Illinois, Urbana-Champaign, *D. Akin*, Stanford University Medical School, *O. Elibol*, *B. Reddy*, University of Illinois, Urbana-Champaign, *K. Park*, Purdue University **INVITED**

Nanotechnology and BioMEMS will have a significant impact on medicine and biology in the areas of single cell detection, diagnosis and combating disease, providing specificity of drug delivery for therapy, and avoiding time consuming steps to provide faster results and solutions to the patient. Integration of biology and silicon at the micro and nano scale offers tremendous opportunities for solving important problems in biology and medicine and to enable a wide range of applications in diagnostics, therapeutics, and tissue engineering. In this talk, we will present an overview of our work in Silicon-Based BioMEMS and Bionanotechnology and discuss the state of the art and the future challenges and opportunities. We will review a range of projects in our group integrating micro-systems engineering with biology, focused towards developing rapid detection of biological entities and developing point of care devices using electrical or mechanical phenomenon at the micro and nano scale. Towards this end, we will present our work on developing silicon-based petri dishes-on-a-chip, silicon based nano-pores for detection of DNA, silicon field-effect sensors for detection of DNA and proteins, and use of mechanical sensors for characterization of living cells.

2:20pm **BM+BI+BO+NC-TuA3 Chemical Imaging of Surface Immobilization Chemistry: Mapping NHS with Protein and Cell Immobilization**, *F. Cheng*, University of Washington, *H. Takahashi*, University of Utah, *M. Dubey*, University of Washington, *K. Emoto*, Acclerys Technology Corporation, *L.J. Gamble*, University of Washington, ***D.W. Grainger***, University of Utah, *D.G. Castner*, University of Washington **INVITED**

N-hydroxysuccinimide (NHS) esters are widely used to activate covalent coupling of amine-containing biomolecules onto surfaces in academic and commercial surface immobilizations in many applications. However, their intrinsic hydrolytic instability is well-known and limits this reactive surface chemistry. No methods are known to quantify this chemistry conveniently. We have used x-ray photoelectron spectroscopy (XPS) and time-of-flight secondary ion mass spectrometry (ToF-SIMS) to investigate surface hydrolysis and spatial reactivity in NHS-bearing thin films.[1] Principal component analysis (PCA) of ion ToF-SIMS data correlates changes in the NHS chemistry as a function of conditions. NHS ester oligo(ethylene glycol) (NHS-OEG) monolayers on gold and commercial polymer films have been compared after surface treatments. From PCA results, multivariate peak intensity ratios were developed to assess NHS reactivity, thin film thickness and oxidation of the monolayers during surface hydrolysis. Aging in ambient air up to seven days results in some NHS hydrolysis and thiol oxidation. Overnight film immersion under water completes hydrolysis and NHS removal. The same PCA peak intensity ratios for surface coupling of amine-terminated molecules confirmed that NHS surface regeneration methods re-establish bound NHS concentrations approximately 50% of that on freshly prepared NHS-OEG monolayers. The chemometrics were then extended to commercial poly(ethylene glycol) (PEG)-based polymer film-coated glass slides.[2] Reactive NHS and methoxy-capped (MeO) regions (used for non-fouling) were co-patterned onto these slides using photolithographic methods. NHS patterns are easily imaged with ToF-SIMS/PCA, resolved at high sensitivity.[3] NHS-specific protein coupling was imaged and correlated to NHS images by specific coupling of streptavidin on the surface though NHS chemistry. Specific NHS-mediated cell adhesion peptide (RGD) grafting could be imaged, and prompted fibroblasts in serum to attach and proliferate only on the NHS regions. Longer-term cell culture retains high cell-pattern fidelity correlating with chemical imaging of both the NHS and RGD patterns and also lack of cell adhesion to MeO regions. High cross-correlation between various ion-derived ToF-SIMS images is observed, providing sensitive chemical corroboration of pattern chemistry and biological reactivity in complex milieu. This method is unique with important practical impacts for application of new ToF-SIMS surface imaging tools to track and validate pattern fabrication and performance.

[1]X-ray photoelectron spectroscopy, time-of-flight secondary ion mass spectrometry, and principal component analysis of the hydrolysis, regeneration, and reactivity of N-hydroxysuccinimide-containing organic thin films Fang Cheng, Lara J. Gamble, David W. Grainger, David G. Castner, Anal. Chem. 2007, 79, 8781-8788

[2]Functionalized poly(ethylene glycol)-based bioassay surface chemistry that facilitates bio-immobilization and inhibits nonspecific protein, bacterial, and mammalian cell adhesion Gregory M. Harbers, Kazunori Emoto, Charles Greef, Steven W. Metzger, Heather N. Woodward, James J. Mascali, David W. Grainger, Michael J. Lochhead, Chem. Mater. 2007, 19, 4405-4414

[3]Imaging surface immobilization chemistry: correlation with cell patterning on non-adhesive hydrogel thin films Hironobu Takahashi, Kazunori Emoto, Manish Dubey, David G. Castner, David W. Grainger, Adv. Funct. Mater. In press

3:00pm **BM+BI+BO+NC-TuA5 Nanoscale Determination of Conformation of a Polymeric Coating on Layered Surfaces**, ***A. Yalcin***, Boston University, *F. Damin*, CNR, Milan, Italy, *E. Ozkumur*, Boston University, *G. di Carlo*, CNR, Milan, Italy, *B.B. Goldberg*, Boston University, *M. Chiari*, CNR, Milan, Italy, *M.S. Unlu*, Boston University

With microarrays becoming a main tool in genetics and proteomics research, advancement of microarray technology through optimization of surface chemistries and probe-target interactions has become a major research area. Ideally, surface chemistries should provide functional groups for probe attachment, minimal nonspecific adsorption, stability to environmental changes, and probe activity after immobilization for efficient target capture. Among existing surface chemistries, three-dimensional coatings are the most promising in meeting these criteria. One such 3-D polymeric coating, copoly(DMA-NAS-MAPS), has been introduced previously for use in DNA and protein microarrays. The polymer self adsorbs to the surface and forms a hydrophilic coating, where each monomer has a specific function: Dimethylacrylamide(DMA) provides self-adsorption, 3-(trimethoxysilyl)propyl methacrylate(MAPS) increases the strength of the binding through covalent attachment to the surface with silane functionalities, and acryloyloxysuccinimide(NAS) provides functional groups to covalently bind the probes. Earlier studies with copoly(DMA-NAS-MAPS) have shown an improved performance in DNA hybridization efficiency when compared to existing organosilanization-based surface chemistries. With the aim of understanding the effect of the conformation of the polymer on the obtained results, we use an interferometric technique, Spectral Self-Interference Fluorescence Microscopy (SSFM) for characterization of the conformation, specifically swelling, of the polymer on oxide surfaces. SSFM is used in combination with a standard white light reflection spectroscopy technique, which allows for measuring the average optical thickness of a biolayer on the oxide surface, as well as the axial position of fluorescent markers with sub-nanometer accuracy. In this study, we covalently attach short strands of fluorescently labeled DNA (23mers) to the functional groups of the polymer and use them to probe conformational changes. Fluorophore heights obtained at single-stranded DNA spots indicate an axial increase of 8nm upon hydration. No increase, indicating no swelling, is measured on the epoxysilanized control surface. Furthermore, we measure the swelling using different probe molecules, and report interesting results that reveal information about the size dependent probe penetration in the polymer and the dependence of hybridization efficiency to the axial position of the probes with respect to the surface.

4:00pm **BM+BI+BO+NC-TuA8 Analysis and Diagnostics based on Nanomechanics**, ***C. Gerber***, University of Basel, Switzerland **INVITED**

In recent years we have taken AFM technology well beyond imaging, exploring new frontiers in bio analyses and diagnostics. Micro-fabricated silicon cantilevers arrays offer a novel label-free approach where ligand-receptor binding interactions occurring on the sensor generate nanomechanical signals - like bending or a change in mass - that is optically detected in-situ. We report the detection of multiple unlabelled biomolecules simultaneously down to picomolar concentrations within minutes. Differential measurements including reference cantilevers on an array of eight sensors enables sequence-specific detection of unlabelled DNA and is suitable to detect specific gene fragments within a complete genome (gene fishing). Expression of detection of inducible genes and the detection of total RNA fragments in an unspecific background will be shown. Ligand-receptor binding interactions, such as antigen recognition will be presented. Antibody activated cantilevers with sFv (single chain fragments) which bind to the indicator proteins show a significantly improved sensitivity which is comparable with the SPR (Surface Plasmon Resonance) technique. In addition, this technology offers a brought variety of receptor molecule applications such as e.g. membrane protein recognition, micro-organism detection, and enantiomeric separation. New coating procedures, enlargement of the active surface area by dendritic molecules as well as improvement of the receptor-cantilever chemical bond will be presented. These new findings may lead to a novel individual diagnostic assay in a combined label-free GENOMICs and PROTEOMIC biomarker sensor (COMBIOSENS). We foresee this novel technology being used as a tool to be applied in the upcoming field of systems biology

and preventive medicine to evaluate treatment response efficacy for personalized medical diagnostics.

4:40pm **BM+BI+BO+NC-TuA10 MEMS for Implantable Medical Applications**, ***S. Roy***, Cleveland Clinic Foundation **INVITED**

The application of MEMS technology to biomedical problems (bioMEMS) has attracted great attention over the last decade. This awareness in the potential of bioMEMS has resulted in a flurry of research activities, which, in turn, have culminated in some commercialization successes such as microarrays and lab-on-chip in vitro diagnostics. Furthermore, the feasibility of a variety of implantable bioMEMS devices for drug delivery, physiological monitoring, and tissue engineering, has been demonstrated within a research context. Unfortunately, their translation into the clinical environment has been largely limited due to technical, cultural, and economic challenges. The talk will present the state of clinical bioMEMS today, and provide examples of on-going research projects addressing unmet clinical needs, such as development of microtextured scaffolds for bone regeneration, nanoporous membranes for ultrafiltration, wireless pressure sensors for in vivo biomechanics, and microtransducers for intravascular ultrasound (IVUS) imaging.

5:20pm **BM+BI+BO+NC-TuA12 Microfabrication of MEMS-Based Neural Probes From a Bio-Inspired, Mechanically Dynamic Polymer Nanocomposite**, ***A. Hess***, Case Western Reserve University, *J. Dunning*, Louis Stokes VA Medical Center, *J. Harris*, Case Western Reserve University, *J.R. Capadona*, Louis Stokes VA Medical Center, *K. Shanmuganathan*, *D. Tyler*, *S. Rowan*, *C. Weder*, *C.A. Zorman*, Case Western Reserve University

The development of advanced micromachining techniques for polymers has enabled the fabrication of mechanically flexible, MEMS-based neural probes from polyimide, PDMS, parylene and similar materials. The mechanical properties of these polymers can often be "tuned" during synthesis, but cannot be dynamically controlled once the material is formed. Members of our team have recently described the development of novel nanofiber-based polymer composites that exhibit reversible chemoresponsive mechanical behavior.[1] These materials consist of a low modulus polymer that is reinforced by stiff cellulose fibrils. The stiffness of the nanocomposite is dependent on the interactions between these fibrils, which can be regulated chemically. Inspiration comes from the sea cucumber, which can modify the stiffness of its dermis by chemical regulation of collagen fibers. One of these nanocomposites, a poly(vinylacetate) (PVAc), exhibits a reduction in tensile modulus from 4.2 GPa to 1.6 MPa upon exposure to water, making it particularly well suited for penetrating neural probes that must be rigid during insertion and highly compliant during deployment. This paper describes the first effort to micromachine MEMS structures from such a material. The PVAc nanocomposite consisted of a dispersion of cellulose nanofibers (~16% v/v) extracted from sea creatures known as tunicates using the process described in Ref. 1. Neural probe designs similar to the well known "Michigan Probe" were selected for the first prototypes. These probes consist of a 50 μm-thick substrate micromachined into 280 um-wide by 3000 um-long shanks using a 50 W CO2 laser and a two-step process designed to minimize damage to the polymer. Both uncoated and Au-coated substrates were micromachined using this process. A process was developed to remove 300 nm of Au while only partially damaging the underlying PVAc nanocomposite, thereby enabling the fabrication of multi-electrode structures. No delamination of the Au films was observed throughout simple soak tests in PBS for 9 days. The presentation will detail the laser-based micromachining process and describe the challenges associated with PVAc micromachining, describe devices that incorporate parylene films to electrically insulate and passivate the electrodes, and review the performance of the neural probes.

[1] J. R. Capadona, K. Shanmuganathan, D.J. Tyler, S.J. Rowan, and C. Weder, Science, 319, 1370 (2008).

BioMEMS Topical Conference
Room: Hall D - Session BM-TuP

BioMEMS

BM-TuP1 Electrowetting Using Probe of Atomic Force Microscope as Mobile Electrode, ***X. Ling***, *B. Bhushan*, The Ohio State University

The wetting behavior of liquid droplet on nanostructured surface can be dynamically tuned using electrowetting technique. A conductive AFM probe is used as a mobile electrode to replace the normally fixed electrode in conventional electrowetting setup. The forces involved in the electrowetting process are quantitatively measured from the deflection of AFM cantilever. The AFM tip geometry is precisely determined using SEM and calibration standard. The force between the AFM tip and the droplet is modeled and quantitatively compared with experimental results. By actuating the AFM probe vertically and laterally using the integrated piezo-driver, the droplet is actuated on the nanostructured surface in a fully controllable way due to the capillary force between the AFM tip and the droplet. The actuated droplet is used as a nano-vehicle to effectively transport and/or arrange other nano-objects on surface with capillary-induced manipulation, which opens a new way to integrate nanometer-sized building-blocks that were not movable with other methods.

BM-TuP2 Nanoscale Adhesion, Friction and Wear Studies of Biomolecules on SAM-Coated Silicon Based Surfaces, *B. Bhushan, **K.J. Kwak**, S. Gupta, S. Lee*, The Ohio State University

Protein layers are deployed over the surfaces of microdevices such as bioMEMS and bioimplants as functional layers that confer specific molecular recognition or binding properties or to facilitate biocompatibility with biological tissue. When a microdevice comes in contact with any exterior environment, like tissues and/or fluids with a variable pH, the biomolecules on its surface may get abraded. Silicon based bioMEMS are an important class of devices. Adhesion, friction and wear properties of biomolecules (e.g., proteins) on SAM coated silicon based surfaces are therefore important. These studies have been carried out on protein biomolecules using tapping mode AFM. Based on this study, adhesion, friction and wear mechanisms of biomolecules on SAM-coated silicon based surfaces are discussed.

BM-TuP3 Measurement of the Slip Length of Water Flow on Hydrophilic, Hydrophobic and Superhydrophobic Surfaces, *Y. Wang, **B. Bhushan***, The Ohio State University

The growing interest of boundary slip at liquid-solid interface in micro/nano scale is an important issue in microfluidics systems, where lower liquid flow friction is generally desirable. Recent studies have shown that the no-slip boundary condition is not always valid on micro/nano scale, especially on hydrophobic. Theoretical and experimental studies suggest that at the liquid-solid interface, the presence of gas bubbles is responsible for the breakdown of the no-slip condition for hydrophobic surfaces. The degree of boundary slip at liquid-solid interfaces is usually quantified by a parameter called slip length, which infers a distance between a liquid-solid interface and a virtual no-slip interface. Atomic force microscopy is a powerful tool to measure slip length. It has also been used to image nanobubbles in tapping mode. Although the slip length has been reported on both hydrophilic and hydrophobic surfaces, the direct experiment evidence has not been given between nanobubble and apparent slip on hydrophobic surfaces, as well as the relationship between bubbles' properties and slip length. In this study, the colloidal probe techniques is used to measure hydrodynamic force on hydrophilic, hydrophobic and superhydrophobic surfaces with AFM. The slip length is obtained based on a model proposed in the literature. By combining nanobubble images on hydrophobic and superphdrophobic surfaces, the contribution of nanobubbles to boundary slip is studied with known bubble properties, such as size and distribution density. A model is presented for nanobubbles' friction reducing mechanisms.

BM-TuP4 Electrical Assay for Real-Time Monitoring Cardiomyocyte Apoptosis, ***Y. Qiu***, *X. Zhang*, Boston University

Deregulated cardiomyocyte apoptosis is a critical risk factor in a variety of cardiovascular diseases. Though enzymatic DNA fragmentation is most commonly used criteria of apoptosis at the level of individual cardiomyocytes, the capability of detecting cell detachment will provide instant information at early phase of apoptosis. Furthermore, the assays used to detect DNA fragmentation are all invasive to living cells, which disables real-time monitoring of the whole process. In this work, we developed an impedance-sensing assay for real time monitoring cardiomyocyte apoptosis induced by tumor necrosis factor alpha (TNF-alpha) based on recording the change in cardiomyocyte adhesion to extracellular matrix (ECM). Electrochemical impedance spectroscopy (EIS) was employed in impedance to process the impedance spectra, followed by manual calibration with electrical cell-substrate impedance sensing (ECIS) technique. Adhesion profile of cardiomyocytes undergoing cell death process was recorded in a time course of equivalent cell-substrate distance. Multiple concentration levels of TNF-alpha (from 10 to 80 ng/mL) were applied to the cultured cardiomyocytes and the concentration-related adhesion profiles were recorded for the cell death process. An optimal concentration of TNF-alpha (20 ng/mL) was determined to induce cardiomyocyte apoptosis rather than necrosis because of its mild slope of developing cell detachment in 24-hour real-time monitoring. It was also observed in the Trypan blue exclusion (TBE) results that a gradual and significant increment in cell death rate was achieved with a concentration level of 20 ng/mL. Treat with optimal concentration of TNF-alpha, the cardiomyocytes first experienced a transient drop in cell-substrate distance followed a sustained cell detachment. The equivalent cell-substrate distance increased from 59.1 to 89.2 nm within 24 hours. The early change of cell adhesion was proven related to cardiomyocyte apoptosis with the following TUNEL test in which the treated cardiomyocytes suffered an apoptotic percentage of 21.1 ± 5.5 % (vs. 5.9 ± 2.5 % in the control sample). This novel assay has the potential to become a valuable high-throughput experimental approach in studying in vitro cardiomyocyte apoptosis research.

BM-TuP5 Parylene Electrothermal Valves for Rapid In Vivo Drug Delivery, ***P.-Y. Li***, *D.P. Holschneider, J.-M.I. Maarek, E. Meng*, University of Southern California

Two single-use electrothermal valves featuring low power (mW) and rapid operation (ms) were designed, modeled, fabricated, and tested. They share a common layout consisting of a composite membrane (Parylene/Pt/Parylene) situated in the flow path between two catheter segments. Current applied to the Pt thermal element initiates Joule heating that leads to thermal degradation or melting of the membrane and causes the valve to open. Compared to previous work employing metal membranes, Parylene enables low power operation (thermally degraded (125-200°C) or melted (290°C) at much lower temperatures). Parylene also enables large robust membranes for larger effective valve opening area (in this case, 330-500 μm). Membrane designs were mechanically modeled to assess performance using a large deflection (Parylene only) and nonlinear FEM models (composite). The nonlinear model indicates 1.53GPa maximum stress of the Pt element under 1 atm pressure (peak under normal operation) which is less than its tensile strength (1.83GPa); modeling and load deflection experiments showed good agreement. Transient thermal FEM modeling and video microscopy were used to investigate thermal events leading to valve opening; simulation and experimental results were in close agreement. The temperature coefficient of resistivity of the Pt element and the resistance change as a function of applied current were obtained. These results allowed prediction of the temperature of the Pt thermal element and determination of the appropriate operating current. For the prototype valve having a serpentine Pt element spanning the valve area, 25-50 mW was required to open the valve under constant current operation in air and a current ramping rate of 0.1 mA/sec was the optimal condition for valve opening for use with water. The best opening time achieved with this design was 100 ms in air but several seconds in water. The optimized valve further improves the opening speed; the Pt element (straight and serpentine) was defined only at the perimeter of the valve except for a small gap where the element connects to contact pads. Preliminary results indicate that the optimized valve can be opened in water in the millisecond range (100 mW). We also demonstrate successful application of our valve in a wirelessly operated minipump that allows bolus drug infusion in animals.

BM-TuP6 Mapping Smooth Muscle Cell Contractile State Regulated by Contractile Proteins using a Novel BioMEMS Moire Mapping Sensor, ***X.Y. Zheng***, *X. Zhang*, Boston University

Abnormal vascular smooth muscle cell contractility plays an important role in the pathogenesis of hypertension, blood vessel spasm, and atherosclerosis. This paper presents the mapping of smooth muscle cell contractility using a novel optical moiré method. We utilized coherent laser beams to illuminate periodic polymeric substrates where isolated cells were cultured. The diffraction phenomena of coherent laser beams through the polymeric periodic substrates where living cells were cultured introduces moiré patterns and can be used to real-time mapping the cell-substrate traction forces. The PDMS micropillar arrays were embedded between large sidewalls for cell guidance. A polycarbonate flow perfusion chamber is

sealed under the chip. The same chip with imbedded pillars with aspect ratio of 1:3 was mounted on a rotational stage parallel to the first substrate. Diffraction moiré patterns can be generated by illuminating coherent beam via two parallel grating lines or grids. The grating lines served as reference gratings for diffraction moiré pattern generation in (0,1,0) or (1,0,0) direction whereas two-dimensional moiré fringes can be formed via two paralleled imbedded pillars. Therefore, contraction of the vascular smooth muscle cells can be real time "magnified" and "mapped" through moiré pattern evolutions. For contractility mapping of vascular smooth muscle cells, we considered the cell total area, cell length and width. On the other hand, we measured the distortion area of the moiré patterns, moiré pattern length and width. In the experiment, these two factors were shown to be consistent. Further, vascular smooth muscle cells were cultured on substrates with serum media to develop focal adhesion, and then the cells were relaxed on serum free media for another 48 hours followed by treating SMCs with contractile agonist lysophosphatidic Acid. We found that the area of the distorted moiré patterns produced on two overlapped periodic substrates were inversely correlated with the distortion of the moiré patterns, thereby indicating that the contraction of vascular smooth muscle cells were inversely correlated with the initial spreading developed in serum. We anticipate that this method will increasingly provide more applications and cell biological insights in vascular cell contraction mechanism study.

BM-TuP7 Toward a Selective Optical Biosensor for Integrated Biofilm Detection, ***M.T. Meyer***, *S.T. Koev, R. Fernandes, W.E. Bentley, R. Ghodssi*, University of Maryland

Certain types of bacteria regulate gene expression through quorum-sensing, the detection of extracellular levels of bacterial signaling compounds. Once bacteria sense their population is sufficiently large to overwhelm a host's immune system, they will aggregate and form a pathogenic matrix of bacteria, or biofilm. While this phenomenon is not fully understood, it is of interest to study biofilms to gain knowledge toward developing new antibacterial treatments. We have developed a platform for examining bacterial biofilm growth and response in a microfluidic environment using optical monitoring of selectively deposited Escherichia coli. Bacterial growth over time was quantified via optical absorbance using an external photodiode; the use of an optical sensor isolated from the fluidic environment allows for more reliable sensor operation as well as increased sensitivity. Two bacterial adhesion layers were investigated, including the amino-polysaccharide chitosan and a fusion protein (E72G3), consisting of a hydrophobic domain and an antibody-binding protein G domain, bound to antibodies against E. coli. E. coli cells were immobilized on electrodeposited chitosan, and biofilms were grown over a period of 48 hours. While chitosan can be selectively deposited and promotes bacterial adhesion, results show that material irregularities impede optical observation of the progression of biofilm growth. E72G3 was also used to immobilize E. coli by depositing the proteins on a patterned hydrophobic surface, then immobilizing antibodies against E. coli on E72G3. This method of bacterial deposition can be extended to numerous other pathogens by virtue of the fusion protein's antibody-binding properties. Optically detectable biofilm formation was confirmed on this spatially and biologically selective surface. The platform can be used to quantify normal biofilm formation in addition to biofilm formation in response to external stimuli. Detailed device fabrication and testing parameters as well as experimental results will be presented. Our goal is to develop this platform into a fully integrated, compact device with highly parallel throughput for applications in discovering new antibacterial agents.

BM-TuP8 In-vitro Comparison of Activated and Sputtered Iridium Oxide Neural Microelectrodes, ***S. Negi***, *R. Bhandari, L. Rieth, R.A. Normann, F. Solzbacher*, University of Utah

To provide low impedance electrical connection between the neural electrode and the nerve, the electrodes are coated with conductive material like Iridium oxide (IrO_x) due to its higher charge injection capacity and resistance to corrosion.[1] In this report, IrO_x is deposited by two methods; activation of iridium to form activated iridium oxide film (AIROF), and reactive sputtering to form sputtered iridium oxide film (SIROF) on similar shape and size neural electrodes. The AIROF and SIROF properties are studied and the results are compared. Utah Electrode Arrays (UEAs), were used for this study.[2] To fabricate AIROF coated UEA, 99.8 % pure Ir was DC sputter deposited on to the UEA tips using an Ar pressure of 20 mTorr, and 5W power for 12 minutes to achieve 1000 Å thickness. The Ir electrodes were activated by cyclic voltammetry (CV), sweeping between -0.8 to +0.8 V versus Ag/AgCl in phosphate buffered saline (PBS) solution at the rate of 1 Hz. The SIROF films were deposited on the UEA tips by pulsed-DC reactive sputtering with 50%:50% ratio of Ar and O_2 in the ambient, keeping the chamber pressure at 10 mTorr. Ar and O_2 flow rates were both 100 sccm. The pulse frequency was at 100 kHz, the duty-cycle was 30 percent, and a power of 100 W was used to achieve thickness of 1000 Å after 20 minutes of deposition. Charge storage capacity for AIROF and SIROF coated UEAs was found to be 10 and 38 mC/cm^2, respectively. The electrochemical impedance at 1 kHz was measured for AIROF and SIROF as a function of the exposed UEA tip. At 100 µm tip exposure, AIROF and SIROF impedance were 36 and 6 kΩ respectively, while, at 20 µm tip exposure the AIROF and SIROF impedance were 200 and 50 kΩ respectively. The results indicate that decreasing the tip exposures increases impedance exponentially. SIROF coated electrodes have lower impedance and, potentially, will offer higher neural selectivity without compromising on the electrode sensitivity. The higher charge storage capacity and lower impedance makes SIROF a promising material for stimulating and recording neural signals.

[1] W. F. Agnew and D. B. McCreery (Eds), Neural Prostheses: Fundamental Studies, Prentice Hall Biophysics and Bioengineering series.

[2] K. E. Jones, P. K. Campbell, and R. A. Normann, A glass/silicon composite intracortical electrode array, Ann. Biomed. Eng., vol. 20, no., pp 423-37, 1992.

BM-TuP9 Capillary Electrophoresis Electrochemical Detector using Capacitometric Method for Endocrine Disruptor Detection, ***J.W. Yoo***, *K. Ha, Y.S. Kim, C.J. Kang, Y.J. Choi*, Myongji University, Korea

Interests in the use of polymeric materials such as polydimethylsiloxane (PDMS) and polymethylmethacrylate (PMMA) have increased over the past few years. PDMS has been widely discussed due to fine optical transparency for detection, curability at low temperatures, easily replicable molding and fine adhesion. In past, PDMS substrate based capillary electrophoresis-electrochemical detection (CE-ECD) microchips have been developed for separation and detection of endocrine disruptors. We also developed systems and measured bisphenol-A (BPA) and butylphenol as well as dopamine and catechol with various electrode structures such as ITO, Au as well as Prussian blue modified ITO and Au. Whereas, because of the sensitivity and structural dependence of measurement, capacitance based detection of these chemicals have not been attempted much so far. The strong point of the capacitometric method is that the electrode doesn't need to be contacted with a sample or electrolyte, resulting in reproducible and more reliable results than those from the amperometric detection. Thus, as long as high sensitivity of capacitance can be achieved with a suitable detection system, we can apply it to even a flowing channel system. To do that, we used a high frequency cavity resonator and measured dC/dV with a resolution of better than 10-18 F/V. A device including microchannels built using PDMS mold was also fabricated on glass substrate. In this work, we studied capacitometric detection of BPA. The separation of BPA was carried out using a 7 cm long capillary. A solution containing MES of pH 6.5 was used as separation buffer. A field of 60 V/cm was applied to a channel for separation and the same field for injection for 10 seconds. With a time evolutional monitoring of dC/dV, 100 µM to 10 mM BPA could be detected.

BM-TuP11 Microcantilever Grafted with Responsive Polymer Brushes for Glucose Sensing, ***T. Chen***, Duke University, *R. Desikan, R.H. Datar, R.P. D, T.G. Thundat,* Oak Ridge National Laboratory, *S. Zauscher*, Duke University

There is considerable interest in microcantilevers grafted with stimulus-responsive polymer brushes for sensor applications in aqueous environments, as they potentially provide a much larger cantilever bending response to changes in stimuli, such as temperature, light, chemical, and pH compared with cantilevers decorated with self-assembled monolayers (SAMs). To engineer sensitivity to specific stimuli, functional monomers can be incorporated into polymer brushes via copolymerization and functional moieties can be introduced through subsequent chemical modification. As boronic acid can bind diols through reversible boronate ester formation, incorporation of boronic acid into linear copolymers such as latex and polymer gels for the detection of glucose has been shown. Herein, we show the synthesis of novel glucose-responsive poly(N-isopropylacrylamide)-co-poly(acrylic acid)-(3-aminophenylboronic acid) (pNIPAAM-co-pAA-PBA) polymer brushes, and explore their use in a prototypical example for their potential as polymer brushes-functionalized microcantilevers firstly for the detection of blood glucose at physiologically relevant concentrations. We evaluated the stimulus-response of the polymer brushes to changes in glucose concentration and solution pH by measuring concomitant brush height changes. Glucose-responsive pNIPAAM-co-pAA-PBA brushes show a large, reversible swelling response in presence of free glucose at physiologically relevant concentrations. The deflection and surface-stress response of microcantilevers, functionalized with PBA-brushes, is substantially larger and faster than that for PBA-SAM functionalized levers. This shows the promise of pNIPAAM-co-pAA-PBA brushes for microcantilever glucose sensing applications, and demonstrates, more generally, the potential of responsive polymer brushes to sense and transduce changes in a solution environment efficiently.

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