Tuesday Afternoon, October 21, 2008

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).

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