SYMPOSIUM N

Biomicroelectromechanical Systems (BioMEMS)

April 22 – 25, 2003

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* Invited paper

SESSION N1: DRUG DELIVERY AND THERAPEUTICS I
Chairs: John T. Santini, Jr. and Tejal Ashwin Desai
Tuesday Morning, April 22, 2003
Salon 12/13 (Marriott)

8:30 AM *N1.1
MEDICAL THERAPY USING BIODEGRADABLE AND BIOACTIVE FORMS OF SILICON. L.T.Canham, R.S. Saffie, N. Torabi-Pour, J. Dormer, C.H. Lau, D.Wakelin, M.Anderson, D. Petty, S. Connor, R. Aston, pSiMedica Ltd, Malvern Hills Science Park, Malvern, Worcs., UNITED KINGDOM.

The commercial development of bioMEMS is currently focussed on in-vitro "biochip" diagnostic applications. The next stage of development will be its utilisation on and in the human body ie "therapeutic MEMS". Here biocompatibility issues are of paramount importance. Research during the 1990's has shown that the semiconductor silicon can be made much more biocompatible than previously imagined. Certain nanostructured forms of poly-Si and porous silicon can even be made biodegradable, releasing silicic acid that is readily excreted by the kidneys. This talk will survey some of the perceived clinical applications facilitated by biocompatible silicon: namely controlled drug delivery, bracytherapy,orthopaedics,bioMEMS implant packaging and in-vivo diagnostics.

9:00 AM *N1.2
IMPLANTABLE BIOMEMS FOR DRUG DELIVERY. Scott A. Uhland, MicroCHIPS, Inc., Bedford, MA.

As pharmaceutical drugs become more potent, targeted, and complex, the importance of systems designed to precisely control the delivery of those drugs to the body increases. Therefore, much research is focused on developing materials and devices that can release combinations of multiple drugs, provide control over the timing of drug release, and increase patient compliance with prescribed drug regimens. Designing systems that increase the long-term stability of protein-based therapeutics is another challenge faced by those developing new drug delivery systems. Microfabrication technology has enabled the creation of intelligent drug delivery systems that meet these needs. Microchip devices (bio-micro-electro-mechanical systems or BioMEMS) containing an array of sealed, drug-filled reservoirs have been developed and can be implanted in the body. Release of drug from the microchips reservoirs is controlled by pre-programmed microprocessors, wireless telemetry, or biosensors. Our group was the first to demonstrate the storage and in vitro release of multiple chemicals from a microchip, and recently, we achieved in vivo chemical release from subcutaneously implanted microchip devices. This presentation will review recent progress in the development of these implantable bioMEMS devices for drug delivery applications.

9:30 AM *N1.3
MEDICAL INNOVATIONS IN DRUG DELIVERY: ARTIFICIAL MUSCLE AND 'SMART' SENSORS FOR RELEASE OF MEDICATIONS WITH PRECISION. Marc J. Madou, Dept of Mechanical and Aerospace Engineering, University of California, Irvine, CA.

Si micromachined chambers for drug storage and release were introduced in the early nineties. Liquid drugs were put into micromachined Si chambers and a metal cover (a single-use valve) was opened electrochemically to release the drugs stored in those micromachined chambers. Using an array of these chambers, different compounds can be released at different times, and by opening more chambers, the rate can be adjusted. In a further improvement it is found that the metal valves could be featured in a polymer micromachined embodiment and that the valves can be made reversible by replacing the metal cover with polymer. The latter are so-called artificial muscle valves and they are based on blends of hydrogels and redox-polymers attached to voltage addressable valve seats. In addition, simple fluidic structures in the smart device will enable not only sample dissolution and reconstitution but also dilution and mixing of multiple reagents to provide constantly fresh sample. This approach is ideal for delivery of reagents and/or drugs in long-time implants and discrete measurements. In the case of responsive drug delivery systems, the sensor(s) may monitor disease marker molecule(s), the dispensed drug(s) itself, or drug metabolites. In this way, the smart device forms a closed loop delivering the right amount of drug based on the individual patients need. The sensing results will be interpreted by an on-board micro-processor switching on the required voltage from the battery to open the valve of the storage chamber. The activation of the drug delivery may also be initiated from outside the body via a telemetric link. This feature could be used as a safety or override and for physicians intervention. As is clear from above, it may also be possible to combine multiple sensing reagents and a variety of drugs in micromachined chamber arrays. This would be especially useful in the treatment of a disease that requires administration of a drug cocktail as well as in the treatment of individuals with multiple clinical conditions, who must carefully manage administration of multiple therapeutics on a daily basis.

10:15 AM N1.4
IN VIVO RELEASE FROM MICRORESERVOIR DRUG DELIVERY MEMS. Rebecca S. Shawgo, MIT, Dept. of Materials Science and Engineering, Cambridge MA; Betty Tyler, Paul P. Wang, Phillip B. Storm, Henry Brem, Johns Hopkins School of Medicine, Dept. of Neurological Surgery, Baltimore, MD; Michael J. Cima, MIT, Dept. of Materials Science and Engineering, Cambridge MA; Robert Langer, MIT, Dept. of Chemical Engineering, Cambridge MA.

Implantable drug delivery devices have been developed based on substrates containing micro-reservoirs that can be filled with individual doses of drug. Each reservoir is capped with a gold membrane that can be selectively removed by the application of an anodic voltage to allow the drug dose to be released. Devices were used for the delivery of model compounds in vivo in a flank model. Radiolabeled carmustine (BCNU) was released from several devices and release monitored by the concentration of 14C in the urine or serum. Excreted carmustine exhibited mass balance but poor temporal resolution while blood levels showed greater sensitivity to initial carmustine release but poor mass balance. Device release was compared with both in vitro controls and subcutaneous injections of carmustine. Carmustine pharmacokinetics were found to be important for data interpretation. Fluorescent dye was also released from devices to model the spatial profile of a small molecule after device activation.

10:30 AM *N1.5
OPTICALLY ENCODED MICROBEADS FOR MULTIPLEXED ANALYSIS OF GENES, PROTEINS, AND CELLS. Shuming Nie, Departments of Biomedical Engineering, Chemistry, Hematology, Oncology, and the Winship Cancer Institute, Georgia Institute of Technology and Emory University School of Medicine, Atlanta, GA.

The integration of nanotechnology with biology and medicine is expected to produce major advances in molecular diagnostics, therapeutics, molecular biology, and bioengineering. Recent advances have led to the development of functional (electronic, optical, magnetic, or structural) nanoparticles that are covalently linked to biological molecules such as peptides, proteins, and nucleic acids. Due to their size-dependent properties and dimensional similarities to biomacromolecules, these biomolecular nanoconjugates are well suited as contrast agents for in-vivo optical and magnetic resonance imaging, as smart carriers for drug delivery, and as structural scaffolds for tissue engineering. In this talk, we report the development of a multiplexed optical coding technology for throughput applications in genomics, proteomics, and cytomics. This technology is based on the novel optical properties of semiconductor quantum dots (QDs) and our abilities to incorporate multicolor quantum dots into micrometer-sized beads at precisely controlled ratios. A surprising finding is that the embedded QDs are spatially separated from each other and do not undergo fluorescence resonance energy transfer (FRET). In comparison with planar DNA chips, this encoded bead technology is expected to be more flexible in target selection (e.g., adding new genes or single nucleotide mutations), faster in binding kinetics (similar to that in homogeneous solution), and cheaper in production.

11:00 AM *N1.6
ULTRASONICALLY ENERGIZED MINIATURE IMPLANTS. Avi Penner, Remon Medical Technologies Ltd., Caesarea, ISRAEL.

Miniaturization of sensors and actuators using MEMS technology, the advances in chip design, as well as manufacturing and development of minimally invasive procedures, open a new era of smart, interactive, miniaturized medical implants. Different clinical applications call for various, sometimes contradicting, technological characteristics. A permanent implant should be miniature, have a long operating life, be biocompatible, and, preferably, interactive with the external world. One of the major obstacles in developing such devices is the need for electrical power with years of operation in a miniature casing. Batteries provide challenges both in terms of size and life span. The obvious alternative is to energize the implant wirelessly, from outside the body. However, all the conventional means of remote energizing attenuate and ultimately fail to perform as the device is implanted deeper inside the body. Remon Medical Technologies has developed an acoustic based technology that allows energy transfer to an implant, independent of the depth of the implant in the body. Remons unique energy converter is capable of transforming ultrasonic to electrical energy at very high efficiencies, enabling the development of extremely small implants. The same energy converter also provides excellent bi-directional acoustic communication between the implant and an external trans-receiver ultrasonic transducer. Since Remons energy converter (approximately 2 mm) is far smaller than the ultrasonic wavelengths used (several centimeters), the implant is

insensitive to the direction of the external exciting field. The technology can be applied to remote monitoring of various physiological parameters - such as pressure, temperature, flow, impedance, or concentration of bio-chemical compounds such as blood gases, glucose, or potassium. Another discipline of applications is in the remote actuating, communicating and programming of active medical implants, such as local drug delivery systems, drug activation (i.e. photodynamic therapy) and nerve stimulators.

11:30 AM N1.7
NETWORK FORMATION, SURFACE PATTERNING AND SIEVING PERFORMANCE OF SELF-ASSEMBLING HYDROGELS. Julia A. Kornfield, Rob Lammertink, Chemical Engineering, California Institute of Technology, Pasadena, CA.

Self-assembling hydrogels have been synthesized and studied for use as sieving media in capillary gel electrophoresis applications. In order to fill capillaries and microchannels with self-assembling solutions, their rheological behavior is of extreme importance. To meet the requirement for materials with tunable rheology and sieving characteristics, we explore fluoroalkyl ended poly(ethylene glycols) that form networks in water via aggregation of the hydrophobic end groups. These hydrogels are extremely interesting for applications in need of hydrogel materials that readily form in situ. More specifically, entangled polymer solutions that are frequently used as sieving media in capillary electrophoresis poses extremely high viscosities and therefore require high pressures to be transported into small capillaries and channels. We examine the effects of PEG length and fluoroalkyl length on rheological properties and separation performance for DNA electrophoresis. In addition, facile means to disrupt the physical network offer routes to conformal hydrogel layers on teflon surfaces of interest in biomedicine, facile injection into capillaries in labs on a chip, and generation of functional hydrogel arrays on surfaces.

11:45 AM N1.8
MODEL OF AN APPROACH TO EMBOLOTHERAPY BASED ON UNIFORM MAGNETIC FIELDS. Zach G. Forbes and Kenneth A. Barbee, Drexel University, Biomedical Engineering; Benjamin B. Yellen and Gary Friedman, Drexel University, Department of Electrical Engineering.

New materials for embolotherapy are being investigated for applications in occluding blood flow to tumors, clotting arteriovenous malformations, and minimizing blood loss during surgery. The main limitations to currently used embolic agents, including compressible microspheres and polymerizing gels, are both that the blockages are irreversible and that the agents must be applied through catheterization, which limits their application to relatively large blood vessels. An alternative approach to embolotherapy is using superparamagnetic microspheres, which undergo reversible phase transformation in the presence of external magnetic fields. Previous attempts to use magnetic microspheres to target specific areas in the vascular system, however, have not enjoyed marked success because they have relied on high gradient external magnetic fields, which apply relatively small and insufficiently local forces on microspheres. We propose a method for inducing highly localized phase transformation in the vascular system by applying uniform magnetic fields to an injected superparamagnetic colloidal fluid. The proposed design involves seeding magnetic particles onto blood vessel walls at designated sites through specific receptor-ligand recognition, followed by the use of anchored particles as magnetic traps for an injected magnetic colloid. A simplified model of the trapping process will be presented, which predicts the net force on a single chain of magnetic particles anchored perpendicular to flow in a fluidic channel. This idealized model will determine rough approximations of the balance between the drag force on a chain of spherical particles in Poiseuille flow and the magnetic force due to interactions between particles in the chain. The results will be used to predict the equilibrium curvature of the chain and the critical magnitude of flow required to separate the chain from the anchored particles. Theoretical models will be tested with microfluidic and *in vitro* biological experiments, which will evaluate the strength of the chain-anchor attachment in varying flow conditions.

SESSION N2: DRUG DELIVERY AND THERAPEUTICS II
Chairs: Sadik C. Esener and Joel Voldman
Tuesday Afternoon, April 22, 2003
Salon 12/13 (Marriott)

1:30 PM *N2.1
NANOPORE TECHNOLOGY FOR MEDICAL THERAPEUTICS. Mauro Ferrari, Edgar Hendrickson, Dorothy M. Davis Heart and Lung Research Institute, The Ohio State University, Columbus, OH.

The state of the applications of sacrificial layer silicon nanopore (SLSN) membranes to medical therapeutics will be reviewed.Passive and active controlled release of therapeutic agents will be presented, as well as 'stealth implantable bioreactor' technology. In the latter application, nanopore membranes are employed as immunoisolators to prevent or minimize rejection phenomena against therapeutic cell xenografts. New results will be presented, that pertain to the use of osmotic pressure theory at high concentrations for the purpose of quality control of nanopore thicknesses.

2:00 PM *N2.2
BIOMOLECULE-COATED QUANTUM DOTS FOR IN VIVO MEDICAL APPLICATIONS. Warren C.W. Chan, University of Toronto, Institute of Biomaterials and Biomedical Engineering (IBBME), Toronto, ON, CANADA.

Organic/inorganic hybrid nanoparticles have attracted widespread interest in the last ten years. Inorganic nanoparticles have unique optical, electronic, and dimensional properties that are advantageous over traditional organic-only systems. The ability to integrate these nanoparticles with sophisticated recognition molecules can lead to the emergence of new technologies for high-throughput drug screening, clinical diagnostics, and in-vivo monitoring of gene expression and enzyme activity. This talk describes the use of bimolecule-coated semiconductor nanoparticles, also known as quantum dots, as an optical detection probe for in vivo medical applications. Organic probes are limited by photobleaching, environmental quenching, broad and asymmetric emission spectra, and the inability to excite more than 2-3 colors at a single wavelength. These problems can be overcome by exploiting the unique optical properties of semiconductor nanoparticles (e.g., quantum dots are estimated to be 20 times brighter and 100 times more stable against photobleaching than organic reporter molecules). We demonstrate the feasibility of selectively targeting inorganic nanoparticles inside living mammals. Specifically, we coated green and red luminescent ZnS-capped CdSe quantum dots with vascular targeting peptides obtained by phage display, and showed the accumulation of quantum dots coated with tumor homing peptides in the blood or lymphatic vessels of human breast carcinoma MDA-MB-435 xenograft tumors after intravenous injection. This work provides a first step towards the use of nanomaterials (e.g. optically-active metallic colloids, near-infrared emitting nanocrystals, magnetic nanoparticles) as in vivo optical and magnetic probes for non-invasive imaging of diseases (e.g., cancer or HIV) or the use of peptides to target drug carrying nanostructures (such as those composed of fullerenes or dendrimers). This work was recently published in Proc. Natl. Acad. Sci, (2002), 99, 12617-12621 with co-first author M. Akerman and authors P. Laakkonen, S. Bhatia, and E. Ruoslahti.

2:30 PM N2.3
BIOCOMPATIBILITY OF CARBON NANOTUBES AND POTENTIAL APPLICATIONS IN CLINICAL MEDICINE. Huajian Gao, Daxiang Cui, Yong Kong, Max-Planck Institute for Metals Research, Stuttgart, GERMANY; Cengiz Ozkan, Department of Mechanical Engineering, University of California, Riverside, CA.

Carbon nanotube may have great potential for clinical medicine applications. Its application prospect depends on its biocompatibility. We have designed a series of experiments to explore the interaction of DNA, RNA and protein molecules with carbon nanotubes and the effects of these bio-nano-complexes on cellular functions. The experiments involve observation of target molecules such as As-myc, BMP2 and AF10 under confocal microscopy, SEM, TEM. Computer simulations are used to simulate the bio-nano system interaction. HL-60 cell line is selected to study the effect of nanotubes on cellular function, signal transduction and cell apoptosis.

2:45 PM N2.4
STAINLESS STEEL MICROSYSTEMS FOR INTRAVASCULAR THERAPEUTIC DELIVERY. Whye-Kei Lye and Michael L. Reed, University of Virginia, Department of Electrical and Computer Engineering, Charlottesville, VA.

We have developed a novel coronary stent with deployable microbarbs for intravascular therapeutic delivery, and will present in vivo data from acute animal trials. Despite manifesting a restenosis as high as 30%, percutaneous transluminal coronary angioplasty in conjunction with stent deployment is still the treatment of choice for most patients with coronary atherosclerosis. While stents conventionally function as mechanical supports for the blood vessel, there is great interest in using them for therapeutic delivery. Drug eluting stents are currently in development to lower restenosis rates by delivering anti-proliferative agents to the atherosclerotic lesion. These devices rely on drug diffusion from polymeric coatings to deliver therapeutics into the vessel wall. Diffusive transport limits the selection of therapeutic agents to low molecular weight, lipophilic agents; and obviates the use of larger molecules such as DNA or more hydrophilic

compounds. Additionally, both the atherosclerotic plaque and the internal elastic lamina serve as barriers to the transport of therapeutic agents. The concept of a stent with integrated microstructures has previously been proposed as a means for breaching these barriers to effect the delivery of therapies into the media and adventitia where much of the etiology of restenosis resides. In vitro cell culture studies and ex vivo tests on filleted rabbit iliac arteries using bulk micromachined silicon microprobe arrays have demonstrated the potential of this approach for both mechanical gene transfection and vessel wall transection. In vivo animal studies require a device in which the microprobes that are presented to the vessel wall only at the time of stent deployment. To this end, we have developed a novel stainless steel micromechanical stent with a nanoporous coating for therapeutic retention. We will discuss device design and fabrication and present results of the acute in vivo animal trials.

SESSION N3: BIOSENSING DEVICES AND SYSTEMS I
Chairs: Marc J. Madou and Murat Okandan
Tuesday Afternoon, April 22, 2003
Salon 12/13 (Marriott)

3:30 PM *N3.1
NANOMECHANICS OF INDIVIDUAL CELLS. Krystyn van Vliet, Subra Suresh, Dept of Materials Science and Engineering; Ram Sasisekharan, Division of Biological Engineering, Massachusetts Institute of Technology, Cambridge, MA.

We outline the application of new experimental capabilities for high-resolution force spectroscopy (HRFS) measurements in three dimensions (approximately 1 pN force and approximately 0.3 nm displacement resolution) in fluid or air environments. Such an approach is well-suited for measurement of surface forces in fluids on biological and soft polymeric samples, and can easily be employed for higher force nanoindentation and nanoscratching measurements on hard materials such as metals, ceramics, and bone. Our goal is to use simultaneous imaging and application of a well-known distribution of (pico- to nano-Newton) forces to a single cell in vitro, in order to elucidate the interdependence of the mechanical stress state, chemical signals, and morphology at the molecular and single cell level. Using model cell systems, we apply different types of forces (constant, monotonically increasing, and cyclic), and then study the effects of these forces on cellular signaling as mapped by a variety of intracellular signaling molecules. We investigate several cell types in order to identify the appropriate model system for a more detailed investigation. In parallel, we present results on the spatial distribution of cell signaling molecules on the surface of cells. Such surface molecules can be correlated with cell phenotype, but the current interpretation of this correlation has been limited to average compositions from samples comprising over a million cells.

4:00 PM N3.2
FABRICATION AND SIMULATION OF AMORPHOUS CARBON CANTILEVER STRUCTURES. L.J. Yu, D. Sheeja, B.K. Tay, School of Electrical and Electronic Engineering, NTU, SINGAPORE; D.H.C. Chua and W.I. Milne, University of Cambridge, Engineering Dept, Cambridge, UNITED KINGDOM.

In view of the superior bio-compatibility of amorphous carbon (a-C) coatings, an investigation has been carried out to fabricate and simulate free-standing amorphous carbon structures. The cantilever assembly was fabricated by a single photolithography step. A micro-meter thick, medium as well as low stress, smooth (Rrms $\sim$0.75nm) a-C films were deposited by filtered cathodic vacuum arc deposition (FCVA) system, in conjunction with high substrate pulse biasing. Undercutting of the cantilever structures was carried out by anisotropic wet (Si) etching (in 40% KOH) method. The maximum deflection of the free-standing cantilever structures were carefully measured by using SEM. Simulation of the cantilever assembly was carried out to obtain the deflection and stress distribution. The stress in the a-C cantilever structures was also independently calculated from the deflection equation, by assuming uniform loading with a fixed end. This stress value is compared with the actual stress in the film measured by the radius of curvature technique. The simulated parameters and results are compared with the experimental results.

4:15 PM N3.3
EFFECT OF BIO FUNCTIONALIZATION ON CONDUCTIVITY OF CARBON NANOTUBES. Tao Zhan, Cengiz Ozkan, Univ of California Riverside, Dept of Mechanical Engineering, Riverside, CA; Satyajith Ravindran, Mihri Ozkan, Univ of California Riverside, Dept of Chemical and Environmental Engineering, Riverside, CA.

Carbon Nanotubes (CNT) has received special interest in the field of nanotechnology due to its outstanding physical, mechanical and electrical properties and this makes them promising candidates in nanoscale device fabrications, gas sensing, bio scaffolding etc. For all the above-mentioned applications the controlling factors are the placement, orientation, and the manipulation of these nanotubes. Here, we describe a technique for electrical measurements across multi walled carbon nanotubes (MWCNTs). Oxidized MWCNTs were distributed on a SiO_2/Si substrate. A MWCNT is located and electrical contacts are given by E-Beam lithography for electrical measurements. Then the MWCNTs are immobilized with proteins and the electrical conductivity change is investigated.

4:30 PM N3.4
UREA SENSOR USED HYDROGEN-TERMINATED POLYCRYSTALLINE DIAMOND. Kwang-Soup Song, Toshikatsu Sakai, Hirofumi Kanazawa, Naoki Fuzihara, Yusuke Nakamura, Shouta Kawamura, Hitoshi Umezawa, Minoru Tachiki, Hiroshi Kawarada, Waseda Univ, Dept of Communication Engineering, CREST, Japan Science and Technology Corporation (JST), Tokyo, JAPAN.

The urea sensor used hydrogen-terminated (H-terminated) polycrystalline diamond has been introduced for the first time. We used the electrolyte-solution gate diamond field effect transistor (SGFET) as urea sensor. The diamond SGFET meets the requirements as biosensors because of its physical/chemical stability, wide potential window, high mobility, high response and biocompatibility, etc. The as-grown CVD diamond surface terminated by hydrogen exhibits the surface p-type conductivity, which is used in the p-channel SGFET. Urease is immobilized with BSA (Bovine Serum Albumin) on diamond surface channels where the surface is partially oxygen-terminated (O-terminated) or aminated (NH2-terminated). We have checked the change in the drain-source current and the threshold voltage of SGFET to examine the sensitivity of urea on the diamond channel surface. As urea density increases, the absolute value of the drain-source current decreases at about 40μA/decade and the threshold voltage increases at about 20 mV/decade in a FET with 500μm gate length in solution. It is expected that the sensitivity of urea on polycrystalline diamond surface can be increased by the miniaturization of gate length. The 5μm gate SGFET exhibits more sensitivity by 50 times in the halogen ion detection of the 500μm gate SGFET.

4:45 PM N3.5
INVESTIGATION OF THE INFILTRATION OF DNA MOLECULES IN POROUS SILICON AS FUNCTION OF THE PORE MORPHOLOGY. M.J. Archer, M. Christophersen, P.M. Fauchet, Center for Future Health, University of Rochester, NY.

Several biosensors based on porous silicon have recently been developed. A critical issue for sensor development using porous silicon is the infiltration of the probe and target molecules into the structure. Most bio-sensing applications of porous silicon are based either on mesoporous or macroporous layers exhibiting different pore morphologies (pore diameter and wall roughness). As opposed to the characteristics with aqueous electrolytes, mesopores with smooth walls can be obtained by processing with chromium-trioxide based solutions. This can be obtained in highly doped n- and p-type material. The structure size of the mesoporous layers can be varied from several nm up to 0.5 μm by changing the chromium-trioxide concentration in the electrolyte and the anodic etch current. In this study we present a systematic investigation of the infiltration dynamics of liquids with different densities and with probe and target DNA molecules, as a function of the underlying pore morphology. The morphology is studied by scanning electron microscopy and the infiltration by the electrical response of different molecules in mesoporous, smooth mesoporous and macroporous silicon layers. The electrical measurement system is described elsewhere [1]. In general pores with smooth and straight pore walls promote fast infiltration. A more uniform distribution of the probe molecules inside the pores can be achieved by reducing the pore wall roughness and enhancing infiltration. Our results give general guidelines for the structural design of the pore morphology required to enhance infiltration in porous silicon bio-sensor and the underlying etch conditions. [1] M.J. Archer, P.M. Fauchet, Electrical sensing of DNA hybrid-ization in porous silicon, Phys. Stat. Sol. (a), in press.

SESSION N4: CELL ARRAYS AND TISSUE ENGINEERING I
Chairs: Cengiz Sinan Ozkan and Gang Bao
Wednesday Morning, April 23, 2003
Salon 12/13 (Marriott)

8:30 AM *N4.1
CELL-BASED APPLICATIONS OF MEMS IN BIOLOGY AND MEDICINE. Mehmet Toner, Center for Engineering in Medicine, Massachusetts General Hospital, Harvard Medical School, Shriners Hospital for Children, Boston, MA.

Biomedical applications of microfabricated devices is no longer limited to non-living systems as genes-on-a-chip or lab-on-a-chip, recent advances in the understanding of cellular behavior in micro-environments have started to pave the way toward living micro-devices. These emerging devices are expected to become key technologies in the 21st century of medicine with a broad range of applications varying from diagnostic, tissue engineered products, cell-based drug screening tools, and basic molecular biology tools. They will also include multiple cell types and/or genetically engineered cells to investigate complex interactions between cells from different tissues. These sophisticated devices will contain micro-engineered tissue units coupled to each other by complex microfluidic handling network. Microfluidic mixing systems will also precisely regulate the composition and concentration of drugs to be tested. This presentation will briefly review the early historical literature on the use of microtechnologies in cellular systems and then focus on fundamental aspects of integrating cells into micro-devices. Several emerging areas of applications will also be discussed including liver and skin tissue engineering using microfabrication, the use of dielectropheresis to create cellular arrays for rapid screening, and microfluidic cellular chemotaxis assays.

9:00 AM *N4.2
MICROFLUIDIC PATTERNING OF 3D BIOPOLYMER MATRICES FOR CARDIOVASCULAR TISSUE ENGINEERING. Tejal A. Desai, Boston University, Dept of Biomedical Engineering, Boston, MA.

Microfabrication techniques, which permit the creation of multifunctional platforms that possess a combination of structure, mechanical, and biochemical features, may surmount several challenges associated withe the conventional delivery of cell-based therapy, including tissue engineered constructs. The potential advantages of such microsystems lie in the ability to create more physiologtically relevant models of cell and tissue with precise feature size, surface characteristics, and porosity for cell ingrowth and spatial control. Microengineered interfaces may be further optimized for biomolecular recognition and surface bioactivity. In this talk, in vitro and in vivo cellular delivery concepts are presented which capitalize on the strenghts of microfabrication. Current work on microtextured and microfluidically patterned biopolymers for cardiovascular tissue engineering will be discussed as examples of efforts to extend microtechnology to the field of tissue engineering. Such approaches can allow for not only spatial control over cells on 3D substrates, but compositional control over the construct itself. Microtechnology can allow us to move closer to in vivo tissue models in the laboratory for drug screening, therapeutic delivery, and ultimately tissue replacement.

9:30 AM *N4.3
MICROSCALE DIELECTROPHORETIC TRAPS FOR POSITIONING MANY SINGLE CELLS. Joel Voldman, Massachusetts Institute of Technology, Dept of Electrical Engineering and Computer Science, Cambridge, MA.

This presentation will discuss the use of dielectrophoretic forces to viably position many individual cells at the microscale. Dielectrophoresis refers to the force on polarizable particles, such as cells, in non-uniform electric fields. By using suitable microelectrode geometries it is possible to create stable traps for individual cells that are scalable, addressable, and reversible. When combined with the power of microfabrication and strong fundamental quantitative modeling, this allows us to create structures that manipulate single cells for applications ranging from cell-based genetic screens to investigations of fundamental cell biology.

10:30 AM *N4.4
OPTICALLY ASSISTED SORTING AND SELF ALIGNMENT OF SMALL OBJECT IN FLUIDS. Sadik Esener, Jacobs School of Engineering University of California, San Diego, CA.

One of the many engineering challenges encountered in heterogeneously integrating sub-systems and components that consist of many types of small micron size objects is the sorting and alignment / patterning of these objects on suitable substrates. In many cases, sorting by size may suffice. But in most cases sorting by materials characteristics such as dielectric properties independent of size is more desirable. Similarly, in some cases robotic pick and place techniques may be sufficient to position a few small objects with limited accuracy in desired locations. However, more complex systems often require larger number of small objects to be handled and aligned or patterned in parallel with much smaller tolerances and higher throughput than what can be achieved with present pick and place techniques. Over the last few years, our group has put forward and demonstrated photonics based powerful solutions for sorting objects in a fluidic environment based on their dielectric properties. Our group has also proposed and demonstrated the feasibility of using DNA strands and hydrogen bond assisted massively parallel assembly techniques. In this presentation, we will review these techniques and describe their applications in various engineering fields ranging from sorting and characterization of biological cells for therapeutic and diagnostics applications to the fabrication of optoelectronic array components that enable micro-lenses and pinholes to be self-aligned to desired light sources in an array format.

11:00 AM N4.5
BIOMOLECULAR ARRAYS FORMED BY DIP-PEN NANOLITHOGRAPHY (DPN). Ki-Bum Lee and Chad A. Mirkin, Northwestern University, Department of Chemistry and Institute for Nanotechnology, Evanston, IL; Jennifer C. Smith and Milan Mrksich, University of Chicago, Department of Chemistry and the Institute for Biophysical Dynamics, Chicago, IL.

There is considerable interest in developing methods for the fabrication of protein microarrays comprised of different proteins because of their potential applications in proteomics, cell research, and pharmaceutical screening processes. Herein, we demonstrate the ability to construct arrays of proteins and viruses with 100 nm features using the ultrahigh resolution patterning technique, Dip-Pen Nanolithography (DPN). These nanoarrays exhibit little detectable non-specific binding of proteins to their passivated array portions, even when exposed to complex mixtures of proteins. Therefore, reactions involving the protein features and antibodies in such solutions can be screened by atomic force microscopy (AFM). We also apply this strategy to the immobilization of Cowpea Mosaic Virus (CPMV) particles as well as to the selective detection of mutant CPMV, which display cysteine residues on their surface capsids. These novel arrays can be used to study other surface-mediated biological processes such as cell adhesion. Significantly, arrays of 200 nm Retronectin^{TM} dots have been used to demonstrate that cell adhesion can be manipulated on the nano- rather than micrometer length scale. The ability to make protein or virus nanoarrays with well-defined feature size, shape, and spacing will enable researchers to ask and answer more detailed questions regarding the interactions between biological structures (cell, complementary proteins, and viruses), and surface patterns.

11:15 AM N4.6
ARTIFICIAL BRAIN-ON-A-CHIP. Shalini Prasad, Mihri Ozkan, Univ of California Riverside, Dept of Electrical Engineering, Riverside, CA; Mo Yang, Xuan Zhang, Cengiz Ozkan, Univ of California Riverside, Dept of Mechanical Engineering, Riverside, CA; Lynell Gutierrez, Univ of California Riverside, Dept of Chemical and Environmental Engineering, Riverside, CA.

It is estimated that about 18 million people worldwide suffer from dementia and it is projected to increase to about 35 million by 2025. All types of dementia occur due to an aberration in memory retention and development, caused by malfunctioning neurons. Experimental investigation of the dynamics of biological networks is a fundamental step towards understanding how the nervous system works. Activity-dependent modification of synaptic strength is widely recognized as a cellular basis of learning, memory, and developmental plasticity. There is an enormous need to develop novel ways for assembly of highly controlled neural networks. To this end, here we propose the use of a 4x4 multiple microelectrode array system to form spatially arranged neural networks, formed by combination of applied DC and AC fields. Our test platform is composed of electrically addressable planar Pt electrodes with a diameter of 80 micrometers (and 200 micrometer spacings). During the assembly of the network, the major consideration is the establishment of a single connection among the processes of adjacent neurons in order to eliminate signal crossover and signal loss due to the adjacent glia cells. For this, we use DC electric field and highly localized proteins to control axon growth direction within the network. Applied electric field direction is found as an important parameter for axon growth. Hence, we characterized electric field distribution inside our test platform by using 3-dimensional finite element modeling. Finally, the stability of this network and its response to long term potentiation and long term depression input stimuli is studied and compared with responses from spontaneously assembled networks in culture and in-vivo networks.The potential application of this research is to develop a diagnostic tool whereby case-by-case analysis of electrical characterization of neurons can be performed and the healthy neurons can be stimulated to communicate circumventing the affected neurons.

11:30 AM *N4.7
BIOCOMPATIBILITY OF MICROSYSTEMS MATERIALS. Shuvo Roy and Aaron J. Fleischman, Department of Biomedical Engineering, The Cleveland Clinic Foundation, Cleveland, OH.

The biocompatibility of common microsystems materials - single crystal Si, SiO_2, polysilicon, Si_3N_4, polysilicon, SiC, Ti, and SU-8 - have been evaluated by tests based on internationally recognized ISO

10933 standards. Previous efforts on biocompatibility testing of microsystems materials were usually limited to specific applications and often relied on non-standard testing protocols. While this approach might be suitable for screening purposes within a research context, it is not sufficient for microsystems that will be subject to regulatory scrutiny as medical devices. Consequently, a biocompatibility evaluation of microsystems materials using the ISO 10933 test matrix should enhance the ability of designers to select appropriate materials for the development of microsystems for medical applications. Starting substrates were 100 mm-diameter, 450-480 μm-thick, $<100>$-oriented, prime grade, p-type Si wafers with a resistivity of 1-50 Ω-cm. Thin films of candidate microsystems materials were formed on some of these Si wafers by various standard processes. Afterwards, the wafers were sterilized twice by either, steam at 121°C for 25 minutes, or, gamma radiation of 2.5 Mrad. Samples of the microsystems materials were subjected to cytotoxicity, implantation, and physicochemical tests. All microsystems materials passed the cytotoxicity tests and performed as well as the negative control. Visual and histopathological examinations of the tissue around the implanted strips for both acute and chronic cases revealed that the microsystems materials performed as well as negative control with respect to inflammation, fibroplasia, and fibrosis. Consequently, microsystems materials are classified as non-irritants. The water extracts revealed the absence of heavy metals for all microsystems materials and negligible quantities of non-volatile residue except for Si_3N_4, and SU-8. Furthermore, the buffering capacity and residue on ignition were also significantly higher for SU-8 extracted in water. The isopropanol extract of SU-8 exhibited significantly higher quantities of non-volatile residue and residue on ignition than other microsystems materials extracted in isopropanol.

SESSION N5: CELL ARRAYS AND TISSUE ENGINEERING II

Chairs: Mehmet Toner and Huajian Gao
Wednesday Afternoon, April 23, 2003
Salon 12/13 (Marriott)

1:30 PM *N5.1
MICROSYSTEMS TECHNOLOGY DEVELOPMENT FOR BIOMEMS AND MICROFLUIDICS. Murat Okandan, Paul Galambos, Conrad James, Ron Manginell, Seethambal S. Mani, Sandia National Laboratories, Albuquerque, NM.

Throughout the last decade, polysilicon surface micromachining has demonstrated its capability to generate very intricate and complex microsystems. SUMMiT(TM) (Sandias Ultra-planar Multi-layer Micromachining Technology) offers five polysilicon layers and allows independent design of features on each layer. Current technology development efforts have concentrated on further enhancement of this technology through the incorporation of silicon nitride insulating layers that allow intimate integration of microfluidic, mechanical, optical and electrical/electrochemical components on the same substrate. The devices that are created using this technology are intended to utilize the highest level of integration to achieve functionality that is not possible with other techniques or fabrication methods. Most of the biomedical and sensing applications require the manipulation and analysis of very small fluid volumes that necessitate incorporation of the sample handling and analysis in a seamless manner. An example of such a system is the monolithically integrated micro-chem-lab, which has sample preconcentration, separation and analysis components on the same silicon substrate. Another device, the patch clamp array, is designed to address some of the same requirements: capture, manipulation of and (optical and electrical) measurements on a single cell or a group of cells. In order to facilitate a modular approach, we have been fabricating and testing common modules such as valves, flow channels and pumps that are used in these systems. Integration of these microsystems and their access to the macro-world is enabled by hybrid assembly of multiple chips using polymers, glass and other packaging techniques. This approach offers a wide range of material selection and design options for different applications. Our approach has been to enable unique functions on a microsystem level and facilitate its integration into a system, since the overall function is provided by the integrated system for that specific application.

2:00 PM *N5.2
INTEGRATED HIGHTHROUGHPUT CELLULAR ARRAYS WITH OPTICAL MANIPULATORS. Mihrimah Ozkan, Dept of Electrical Engineering, Riverside, CA; Sangeeta Bhatia, Dept of Bioengineering, San Diego, CA; Sadik Esener, Dept of Electrical and Computer Engineering, San Diego, CA.

Advancements in micro-electro-mechanical-systems and biotechnology lead to fabrication of highly integrated chip platforms that can enable multi-processing within the same chip environment. To this end, we have developed a highly integrated chip-based bio-system that can spatially arrange live cells in the form of large arrays and also can simultaneously micromanipulate the cells via integrated micro-light tweezers. The platform we describe here is an electro-optical method that employs two complementary processes: 1) electrophoretic arraying of cells in a DC field due to their intrinsic negative surface charge and 2) remote optical manipulation of individual cells by vertical cavity surface emitting laser driven infrared optical tweezers. Finally, due to accessible hightroughput processing capability this integrated chip-based bio-system can be applied for applications in drug discovery, functional genomics and tissue engineering.

2:30 PM N5.3
A METHOD FOR PRINTING HETEROGENEOUS CELL PATTERNS. B.B. Yellen[a], Z.G. Forbes[b], G. Gallo[c], K.A. Barbee[b], G. Friedman[a], Drexel University, Philadelphia, PA, Department of Electrical Engineering[a], School of Biomedical Engineering[b], College of Medicine[c].

Cell separation based on high gradient magnetic fields provides an attractive alternative to centrifugation methods because high-speed separations can be performed with only a large ferromagnet and superparamagnetic beads that recognize and bind to specific cells. An interesting modification of this technique is using a substrate patterned ferromagnetic film to trap cells from suspension. Ferromagnetic traps are easily patterned on glass or Silicon substrates with micrometer resolution using standard photolithographic methods. The advantage to using ferromagnetic traps to print cells is that the highly non-linear behavior of magnetic materials can be exploited to generate both attractive and repulsive forces on colloidal particles. The ability to generate repulsion, in particular, allows for the possibility of printing heterogeneous patterns of cells.
The magnetic printing method is used to print neuronal cells next to skeletal muscle cells with highly defined spatial precision for the purpose of building and analyzing neuromuscular circuits. Various different experimental arrangements have been studied. In one arrangement, a single neuronal cell is patterned next to a single muscle cell. In another arrangement, a single neuronal cell is patterned next to a row of muscle cells that fuse together to form a muscle fiber. In experimental investigations, a thick film photoresist is photographically defined with openings aligned over the ends of Cobalt islands, patterned with conventional lift-off techniques. Application of external uniform magnetic fields perpendicular to the substrate can bias the traps to attract cells labeled with magnetic beads to one end of the island and repel them from the opposite end. In these experiments, the bias is used to attract muscle cells to one end of the island. The solution is rinsed, and then the bias is reversed to attract neuronal cells to the opposite end of the island.

2:45 PM N5.4
PARALLEL TRAPPING AND MANIPULATION OF CELLS USING A HIGH-DENSITY OPTICAL FIBER-BASED TWEEZER ARRAY. Jenny M. Tam, Israel Biran, David R. Walt, Tufts University, Medford, MA.

By coupling a laser beam to an optical imaging fiber bundle, we have created an optical tweezer array, a device capable of trapping a multitude of cells and other dielectric microparticles simultaneously. A laser beam is directed into an optical fiber bundle, and the light energy is distributed across the face of the fiber. Each individual fiber in the bundle carries a light signal to the distal end of the bundle. Light focusing elements at the end of each fiber focus the laser light and form optical traps, creating a dense array (10^5 traps per mm^2) of optical tweezers able to capture thousands of cells in parallel. An array of trapped cells can be used for assaying many individual cells simultaneously and can obtain information about complex cellular responses. Manipulating a large number of cells can be valuable for many biological applications such as drug discovery and diagnostics.

3:30 PM *N5.5
TAILORED INTERFACES TO INTEGRATE CELLS WITH ELECTRONICS. Milan Mrksich, University of Chicago, Department of Chemistry and Institute for Biophysical Dynamics, Chicago, IL.

This presentation will outline the opportunities for bridging biology and engineering to realize devices that combine biological and electrical components. It will describe a chemical approach to integrating mammalian cells and electrical components. The strategy is based on self-assembled monolayers of alkanethiolates on gold that are modified with peptide ligands which promote cell adhesion. The monolayers are then engineered with electroactive moieties such that application of an electrical potential to the gold film results in modulation of the activities of immobilized ligands. In one example, an electroactive monolayer could turn on the migration of fibroblast cells that were originally confined to circular patterns on the substrate. This example, which was based on a monolayer that could be switched from an inert state to a state that promotes cell adhesion, establishes the feasibility of engineering active interfaces that can

translate electrical signals into biological signals. A second example demonstrated an active monolayer that could selectively release immobilized ligands, and even individual cells. The lecture will describe these and several other strategies for creating functional interfaces between cells and electronics, and will address the opportunities for applying these strategies to creating hybrid devices comprising electrical and cellular components.

4:00 PM *N5.6
VISUALIZING SOLID STATE SIGNAL TRANSDUCTION IN LIVING CELLS WITH MICROFLUIDICS. Philip LeDuc, Chia-Chi Ho, Debajyoti Datta, Childrens Hospital/Harvard Medical School, Dept of Pathology and Surgical Research, Boston, MA; Stephanie Betancourt, Han Htun, UCLA, Dept of Molecular and Medical Pharmacology, Los Angeles, CA; George Whitesides, Dept of Chemistry and Chemical Biology, Harvard University, Cambridge, MA; Donald E. Ingber, Childrens Hospital/Harvard Medical School, Dept of Pathology and Surgical Research, Boston, MA.

A microfluidics system was used to create a chemical gradient of steroid hormone across the width of a single mammalian cell expressing glucocorticoid receptor linked to green fluorescent protein. Only receptors in regions of the cytoplasm that were exposed to steroid became activated, however, they first circumnavigated the nucleus into the non-stimulated regions of the cytoplasm before entering the nucleus. A sustained gradient is not only created but also established effectively for long time periods in the cytoplasm and in the nucleus. Further, compartmental modeling effectively defeats passive transport theories of free cytoplasmic diffusion for these steroid receptors. Active transport thus appears to induce gradients and may therefore contribute to the mechanism by which cells sense chemical gradients and transduce hormonal signals into changes in gene expression by locally modulating translocation of activated receptors into the nucleus.

4:30 PM N5.7
IMMOBILISING MICRON AND NANOMETER SCALE FEATURES OF PROTEINS ON POLYMERIC SUBSTRATES FOR NERVE CELL GROWTH. Sunil M. Bhangale, Tan Le-Shon, L. Wu, Melissa Sander, Peter M. Moran, Institute of Materials Research and Engineering (IMRE), SINGAPORE.

The study of cell growth/cell response to various substrates is currently receiving considerable attention. In order to study nerve cell and axon growth, we are aiming to form a gradient of proteins in the form of varying densities of micro/nano features (i.e. Digital or Pixelated format) over a region on polymer substrate. To achieve this, we have developed methods of immobilising micron size patterns of proteins on polymer substrates. In the first method, an aqueous solution of reactive monomer was trapped in the microwells of a silicon stamp using a method similar to that described in reference 1. The stamp was clamped against a plasma treated polymer substrate and was irradiated with UV light in order to selectively graft the entrapped monomer on the polymer surface. Proteins were then selectively conjugated on the regions where the monomer had grafted. Using this method, 5μm to 50μm features were made. In our second method, a pattern of metal (generally gold or nickel) was stamped onto a polymer substrate (one method for doing this is described in Ref. 2). The exposed region of polymer was subjected to protein conjugation. Thus micron-sized (2μm to 10μm) features of protein surrounded by metal lines were formed. Stamps containing nanoscale features are currently being fabricated in order to reduce the dimensions of the protein dots. Another method being explored is the use of nanoporous alumina templates to achieve nanodots of protein on the polymer surface. The methods of micro- & nano-printing will be optimised in order to form a digital gradient of protein on polymer substrates. (1) P.M. Moran and C. Robert, "Microstamping of freestanding bipolymer features", App. Phys. Lett. 78 (23), 3741-3743 (2001). (2) W.K. Ng, L. Wu and P.M. Moran, "Microcontact printing of catalytic nanoparticles for selective metallization of non planar polymeric substrates", in press App. Phys. Lett. (2002).

4:45 PM N5.8
MULTI-SITE, NEUROTRANSMITTER-BASED RETINAL PROSTHETIC INTERFACE. Mark C. Peterman, Department of Applied Physics, Stanford University, Stanford, CA; Harvey A. Fishman, Department of Ophthalmology, Stanford University Medical Center, Stanford, CA.

Nearly all retinal prosthetics have focused on electrical stimulation of the nervous system. We are developing a novel prosthetic interface for the retina based on neurotransmitter delivery. In the past, we have demonstrated the ability to stimulate individual rat pheochromacytoma cells (PC12 cell line) using microfluidic delivery through micron-sized apertures. This delivery was highly reproducible, very controllable, and quantifiable. But this early stage device was limited to a single stimulation site and crude microfluidics. Here, we present the next stage in microfluidic retinal prosthetics with a multi-stimulation site device that incorporates more advanced control over the microfluidic delivery. We created an array of apertures in a thin silicon nitride membrane, to which we can deliver neurotransmitters in an addressable manner. Excitable cells (PC12) are seeded on the device and imaged using Ca^{2+}-sensitive dyes with a confocal microscope. We can then excite the cells at an array of multiple precise locations near the apertures, demonstrating the next step in neurotransmitter-based retinal prosthetics.

SESSION N6: POSTER SESSION
Chairs: Cengiz Sinan Ozkan and Huajian Gao
Wednesday Evening, April 23, 2003
8:00 PM
Salon 1-7 (Marriott)

N6.1
ANALYSIS AND CONTROL OF MICROCANTILEVER DEFLECTIONS IN BIO-SENSING SYSTEMS. Mo Yang, Xuan Zhang, Joe Reinbold, Cengiz Ozkan, University of California, Riverside, Dep of Mechanical Engineering, Riverside, CA; Mihri Ozkan, University of California, Riverside, Dep of Chemical and Environmental Engineering, Riverside, CA.

The main causes for the deflection of microcantilevers, which are the main, constitute of biochips with mechanical detection systems are analyzed. First, the primary deflection due to the chemical reaction between the analyte molecules and the receptor coating, which produces surface stresses on the receptor side, is analayzed. Bimaterial effects on the microcantilever, which influence the deflection, are established analytically. Oscillating flow conditions, which are the main source of turbulence, are found to produce substantial deflections in the microcantilever at relatively large frequency of turbulence. Bimaterial effect is found to be prominent at relatively low frequency of turbulence. In the absence of bimaterial effects, turbulence increases the deflection due to chemical reactions at relatively large frequency of turbulence yet it increases the noise due to the increased dynamical effects of the flow on the microcantilever. Finally, different microcantilever assemblies are proposed that can increase the deflection due to chemical reaction while decreasing those due to flow dynamical effects.

N6.2
TRANSIMPEDANCE-MODE CMOS MICROELECTRODE ARRAY FOR IN VITRO NEURONAL ACTIVITY RECORDING. Jacob S. Wegman, Dept. of Electrical and Computer Engineering, Univ. of Virginia, Charlottesville, VA; Amar Dwarka, Dept. of Electrical and Computer Engineering, Univ. of Virginia, Charlottesville, VA; Matthew Holzer, Dept. of Electrical and Computer Engineering, Univ. of Virginia, Charlottesville, VA; Whye-Kei Lye, Dept. of Electrical and Computer Engineering, Univ. of Virginia, Charlottesville, VA; Michael Reed, Dept. of Electrical and Computer Engineering, Univ. of Virginia, Charlottesville, VA; Erik Herzog, Dept. of Biology, Univ. of Washington, St. Louis, MO; Travis N. Blalock, Dept. of Electrical and Computer Engineering, Univ. of Virginia, Charlottesville, VA.

We have developed a post-processed CMOS integrated circuit for in-vitro electrical monitoring of large numbers of mammalian neurons. The new chip offers scalability and array densities greater than traditional glass-plate based thin-film electrode recording systems. The scalability is achieved by on-chip preamplification and multiplexing of the relatively low bandwidth (3 KHz) neuron action potentials. Unlike other neuronal recording systems, we have employed a low input impedance transimpedance amplifier directly under each electrode to accurately control the DC bias of the neuron interface while providing low-noise amplification of the neuron charge displacement currents. The 0.5 um CMOS chips arrive from the foundry with aluminum recording electrodes. The recording array is made bio-compatible by a postprocessing procedure which includes sequential metallization steps that deposit Ti/Pt/Au on the electrode surfaces. The prototype chip electrodes are 10 um x 10 um and arranged in an 8 x 8 array. The 3 KHz bandwidth neuron signals are amplified on-chip and multiplexed column-wise at a 100 KHz rate, providing approximately 4X oversampling of each site. Simulations indicate that the multiplex rate can be increased significantly, thereby providing scalability to much larger arrays while still limiting the interconnect required to continuously monitor all of the array locations. We have tested the new chips and verified functionality of the preamplifier and multiplex systems. The transimpedance preamplifier approach is sensitive to device mismatch related offset errors. Methods to correct this sensitivity include gated offset sampling and correction as well as low-frequency feedback to stabilize the DC output. External circuitry and packaging required to implement in-vitro testing will also be presented.

N6.3
FABRICATION OF NANOSCALE HYDROPHOBIC REGIONS ON ANODIC ALUMINA FOR SELECTIVE ADHESION OF BIOLOGIC MOLECULES. X. Lin, A.S.W. Ham, N.A. Villani, W.K. Lye, Q. Huang, M. Lawrence, B.P. Helmke, M. L. Reed, Univ. of Virginia, Dept. Biomedical Eng. and Dept. Electrical and Computer Eng., Charlottesville, VA.

Studies of selective adhesion of biological molecules provide a path for understanding fundamental cellular properties. A useful technique is to use patterned substrates, where the pattern of interest has the same length scale as the molecular bonding sites of a cell, in the tens of nanometer range. We employ electrochemical methods to grow anodic alumina, which has a naturally ordered pore structure (interpore spacings of 40 to 400 nm) controlled by the anodization potential. Cells are introduced into a flow chamber and their velocity measured as they pass over the sample surface. The pore spacing has a direct effect on the spatial density of adhesion sites. Through these measurements it is possible to estimate the length scale of receptor clusters on the cell surface. This information is useful in understanding mechanisms of leukocyte adhesion to endothelial cells; the method also has applications in tissue engineering, drug and gene delivery, cell signaling and biocompatibility design. In this work we have developed methods to selectively fill the alumina pores with materials with contrasting properties. Thin films of gold, for example, are deposited over the entire surface, and the excess material is removed mechanically (by lapping), chemically (wet etching), or physically (backsputter etching). The result is a patterned surface with closely separated islands of material with different chemical properties, surrounded by hydrophilic alumina. When this patterned surface is exposed to biological molecules, they selectively adhere to the isolated sites. We have performed experiments with adhesive molecules P-selectin, VCAM-1, and fibronectin. Rolling characteristics (velocity versus time) of the HL60 cell have been observed on alumina coated with these molecules, functionalized polyethylene glycol and control surfaces. Differential cell adhesion has been observed for the various surface preparations. This work is supported by the UVa/NSF MRSEC for Nanoscopic Design.

N6.4
COVALENT IMMOBILIZATION OF TRANSFERRIN ON CARBON NANOTUBES FOR BIOLOGICAL APPLICATION.
Sathyajith Ravindran, Mihri Ozkan, Univ of California, Riverside, Dept of Chemical and Environmental Engineering, Riverside, CA; Sumit Chaudhary, Univ of California, Riverside, Dept of Electrical Engineering, Riverside, CA; Cengiz Ozkan, Univ of California, Riverside, Dept of Mechanical Engineering, Riverside, CA.

The chemical inertness of Carbon Nanotubes along with their nanoscale dimensions has rendered them as potential candidates for Bio-related application. Current research is underway to investigate the biocompatibility of carbon nanotubes by immobilization of biopolymers and proteins on the nanotube sidewalls. In this paper, we report our work on the immobilization of transferrin (an iron transport protein) tagged with a FITC fluorescent label on carbon nanotubes. The immobilization process takes place by a covalent amide bond formation between the oxygen containing groups on the nanotubes and the amines in the residues of the protein. 1-ethyl-3-(3-dimethylaminopropyl) Carbodiimide HCl (EDC) in the presence of sulfo-N-Hydroxysuccinimide (sulfo-NHS) is utilized for this amide bond formation between the -COOH and the -NH2 groups. Characterizations using atomic force microscopy (AFM), thermal gravimetric analysis, Raman, FTIR and confocal microscopy indicated the successful conjugation and that the protein is intimately associated with the nanotubes. Transferrin is an endocytosis mediating protein and this functionalization can be extremely promising in the in-vivo applications of carbon nanotubes.

N6.5
A MICROFLUIDIC DEVICE WITH INTEGRATED IMPEDANCE DETECTION FOR λ-DNA. Myung-Il Park, Jongin Hong, Chong-Ook Park, Korea Advanced Institute of Science and Technology, Dept of Materials Science and Engineering, Daejeon, REP. OF KOREA; Dae Sung Yoon and Geunbae Im, Biochip Project Team and MEMS Laboratory, Samsung Advanced Institute of Technology, Suwon, REP. OF KOREA.

The large optical detection systems that are typically utilized at present may not be able to reach their full potential as portable analysis tools. Accurate, early, and fast diagnosis for many diseases requires the direct detection of biomolecules such as DNA, proteins, and cells. In this research, a glass microchip with integrated microelectrodes has been fabricated, and the performance of electrochemical impedance detection was investigated for the biomolecules. We have used label-free λ-DNA as a sample biomolecule. By changing the distance between microelectrodes, the significant difference between DW and the TE buffer solution is obtained from the impedance-frequency measurements. In addition, the comparison for the impedance magnitude of DW, the TE buffer, and λ-DNA at the same distance was analyzed.

N6.6
SURFACE DIFFUSION AND REACTION OF ADSORBED ENZYMES MEASURED BY MICROFLUIDIC PATTERNING OF SUBSTRATE SURFACES. Shaunak Roy, Channing Roberston, Stanford Univ, Dept of Chemical Engineering, Stanford, CA; Alice Gast, MIT, Dept of Chemical Engineering, Cambridge, MA.

Enzymatic reactions with surface bound substrates present an interesting problem in biomolecular surface science as they require us to consider traditional enzyme kinetics in the context of protein adsorption. These reactions are important in such applications as detergent enzyme additives, food processing and contact lens cleaners. We have previously shown (Kim et al., *Langmuir*, 18(16), 6312-6318) that the kinetics of proteolytic cleavage of surface bound substrates are controlled by the surface properties of the adsorbed enzyme. Here, we specifically study one important, potentially rate-determining surface property: lateral diffusivity. Utilizing microfluidic patterning techniques, we are able to decorate a region of the bovine serum albumin substrate surface with a subtilisin protease without the use of physical barriers. Any spreading of the enzyme from this initial region is indicative of surface diffusion, while removal of the substrate provides a measure of reactivity. This simultaneous measurement, in conjunction with our previous study, allows us to assess the relative impacts of the three processes: adsorption, surface diffusion, and reaction, on the kinetics of substrate removal. By varying the ionic strength of the system and studying several single point mutations of subtilisin, we additionally study the influence of electrostatic interactions on the system.

N6.7
DEVELOPMENT OF A HEAT SENSOR USING MSCL.
Sharon E. Jones, Rajesh R. Naik, Gunjan Agarwal, John Cuppoletti[a], and Morley O. Stone, US Air Force Research Laboratory, Materials & Manufacturing Directorate, Wright-Patterson Air Force Base, OH; [a] Molecular and Cellular Physiology, University of Cincinnati, Cincinnati, OH.

The Mechanosensitive channel of Large conductance (MscL), a homopentameric membrane-bound channel protein, allows bacteria to rapidly adapt to changing environmental conditions such as osmolarity (Sukharev, S.I. *et. al. Nature* 1994:368:265-268; Chang, G., *et. al. Science* 1998 282:2220-2226; Sukharev, S.I., *et. al. J. Membr. Biol.* 1999 171:183-193). The MscL channel opens in response to increased membrane tension allowing for efflux of cytoplasmic constituents into the extracellular environment (Ajouz, *et. al. J. Biol. Chem.*1998 273:26670-26674; Berrier, *et. al. J. Bacteriol.* 2000 182:248-251). It has been previously demonstrated that MscL gates in response to heat shock (Jones, S.E. *et al. Biochem. Biophys. Res. Comm.* 2000 279:208-212). These findings have significant biosensor implications, especially for exploring the use of channel proteins in biosensor applications. In the present study, the feasibility of using MscL as a biosensor was examined. The MscL protein was purified and reconstituted into liposomes, which were then incorporated into a solid supported membrane (SSM) similar to those previously described (Seifert, K., *et. al. Biophys J.* 1993. 64:384-391). Charge translocation was then studied at different temperatures with SSM alone, SSM treated with buffer, SSM treated with phospholipid vesicles, and SSM treated with phospholipid vesicles containing MscL. The use of new SSM materials for incorporation of MscL was explored. Such materials must allow measurement of MscL activity in an environment unaffected by modest increases in heat. Candidate materials include two-part epoxies, UV-curable positive photoresist and highly rigid polymers.

N6.8
MODELING AND OPTIMAL DESIGN OF HIGH-SENSITIVITY PIEZORESISTIVE MICROCANTILEVERS FOR BIOSENSING APPLICATIONS. Xuan Zhang, Mo Yang, Joe Reinbold, Cengiz Ozkan, Univ of California, Riverside, Dept of Mechanical Engineering, Riverside, CA; Satyajith Ravindran, Univ of California-Riverside, Dept of Chemical and Environmental Engineering, Riverside, CA.

The mechanical design and optimization of piezoresistive cantilevers for biosensing applications is studied via finite element analysis. Models are described for predicting the static behavior of cantilevers with elastic and piezoresistive layers. The high-sensitivity cantilevers can be used to detect changes in surface stress due to binding and hybridization of biomolecules. The silicon based cantilevers have thicknesses typically on the order of a few microns and are doped to introduce their piezoresistive characteristics. Parametric modeling based on the finite element method is used to help determine the optimum parameters of cantilever design. Chemo-mechanical binding

forces have been analyzed to understand issues of saturation over the cantilever surface. Furthermore, the introduction of stress concentration regions during cantilever fabrication has been discussed which greatly enhances the detection sensitivity through increased surface stress. Finally, novel microcantilever assemblies are presented for the first time that can increase the deflection due to chemical reaction.

N6.9
PATTEREND CARBON NANOTUBE SUBSTRATES FOR DIRECTED NEURONAL GROWTH. Satyajith Ravindran, Mihri Ozkan, University of California Riverside, Dept of Chemical and Environmental Engineering, Riverside, CA; Shalini Prasad, University of California Riverside, Dept of Electrical Engineering, Riverside, CA; Brooke Colburn, Cengiz Ozkan, University of California Riverside, Dept of Mechanical Engineering, Riverside, CA.

Carbon Nanotubes have come under the limelight of Nanotechnology because of its superior physical, mechanical and electrical properties. Lately, we have started comprehending the potential of Carbon Nanotubes in nanoscale device fabrication, chemical sensing and bio related applications. CNTs for neuronal growth research is a new area. Here, we report the use of patterned Carbon Nanotubes modified with neuron growth factors for building neural networks. Silicon substrate was patterned with iron (Fe) catalyst using E-Beam lithography followed by annealing at 300°C to oxidize the Fe catalyst patterns. The Carbon Nanotubes are grown using the catalytic chemical vapor deposition technique (CCVD) preferentially over the iron patterns. Growth factor-4-Hydroxynonenal (4-HNE) is immobilized on the Carbon Nanotubes by simply incubating the substrate in a 4-HNE solution to make them more biocompatible. Neurons are plated on the substrate and the directional growth and activity was investigated. The neurons used for this study were eighteen-day rat embryo neurons from the visual cortex. The synaptic connections and synaptic strength of the neurons grown on the substrate is monitored and measured and the behavioral efficiency of this network is compared with that of the in-vitro networks on standard microelectrode arrays. Similar studies are carried out with silicon substrates with patterned Anodic Aluminum Oxide (AAO) lines. The AAO pores are also filled with the growth factor 4-HNE. The stability of the neural network formed on these patterned substrates was comparable with the results achieved from standard in-vitro studies. The long term response is still being investigated.

SESSION N7: BIOSENSING DEVICES AND SYSTEMS II
Chairs: Mauro Ferrari and Warren C.W. Chan
Thursday Morning, April 24, 2003
Salon 12/13 (Marriott)

8:45 AM N7.1
FUNCTIONALIZED BIOMEMS CANTILEVERS FOR CANCER CELL DETECTION. Steve Mwenifumbo, Chris Milburn, Seyed Allameh, and Winston Soboyejo, Princeton Univ, Princeton Materials Institute and Dept of Mechanical and Aerospace Engineering, Princeton, NJ; Michael Carolus and Jeff Schwartz, Princeton Univ, Dept of Chemistry, Princeton, NJ.

This paper presents the results of recent efforts to produce a functionalized bioMEMS sensor for specific cancer cell detection. The Ti-coated surfaces of Si micro-cantilevers are functionalized with alkane-phosphonic based molecular structures that bind selectively to cancer cells. Possible cell/device interactions are investigated by culturing human osteosarcoma (HOS) cells onto coated and functionalized surfaces. The initial spreading of the HOS cells is studied using fluorescence and scanning electron microscopy. The adhesion between the HOS cells and the coated surfaces is also investigated using cell lift-off and shear assay techniques. Finally, frequency changes due to cell attachment (on functionalized micro-cantilevers) are measured using an atomic force microscopy platform.

8:45 AM N7.2
Abstract Withdrawn.

9:00 AM N7.3
MICROMACHINED MAGNETIC ULTRASOUND TRANSDUCER IN POST-PROCESSED CMOS. Rohit Viswanathan[a], Nicholas Jankowski[a], Whye-Kei Lye[a], Gregory Petit Dufrenoy[a], Michael J. Harrison[a], John A. Hossack[b], Travis N. Blalock[a], and Michael L. Reed[a,b]; University of Virginia, [a]Department of Electrical and Computer Engineering, [b]Department of Biomedical Engineering, Charlottesville, VA.

We have designed and fabricated a prototype ultrasound transducer, using a standard CMOS process and minimal post processing, which operates on electromagnetic rather than electrostatic interactions. This mode facilitates low voltage operation compatible with advanced CMOS electronics and is considerably safer for biomedical imaging applications. Piezoelectric materials such as lead zirconate titanate (PZT) are often the choice for fabricating imaging ultrasound transducers. However, it is difficult to integrate these materials with standard CMOS process flows. In contrast, post-processing of CMOS electronics is a straightforward and well-established method for fabricating complex MEMS structures. The ultrasound transducers we have designed comprise two concentric spiral coils: a fixed stator and a movable flapper. The flapper is tethered to the substrate by a cantilevered beam. DC current is passed through one coil to establish a static magnetic field oriented out of the plane of the substrate. A modulated current through the other coil establishes a time-varying magnetic field in the same direction. The force arising from the interaction of the coupled magnetic fields induces a mechanical vibration of the flapper structure. Ultrasound transmit pulses are generated by operating the flapper as an actuator. The device also operates as a sensor: applying a modulated pressure displaces the inner coil, which induces an alternating current proportional to the ultrasound echo amplitude. The actuation/sensing elements are integrated with on-chip electronics and are operated in current mode. The use of high voltages, necessary for PZT transducers, is thus avoided. This simplifies insulation requirements and allows large arrays of transducers to be multiplexed onto a single output line. Imagers employing integrated CMOS technology can thus be deployed in otherwise inaccessible locations, (e.g., a biopsy needle). We have investigated two flapper designs with 2 micron gap coils. Our paper will detail the electrical and mechanical behavior of these transducers.

9:15 AM N7.4
DEVELOPMENT OF FUNCTIONALIZED SEMICONDUCTOR NANOCRYSTALS AS SELECTIVE COLORIMETRIC SENSORS FOR BIOLOGICAL CONTAMINANTS. Megan A. Hahn, Todd D. Krauss, Benjamin L. Miller, Univ of Rochester, Center for Future Health, Depts of Chemistry and Dermatology, Rochester, NY.

Drinking water contamination and food poisoning due to pathogens such as *Escherichia coli* (*E. coli*) are urgent issues plaguing today's world. Laboratory cultures used to detect the presence of these organisms can take days to perform; in some cases, this time can mean the difference between life and death. One solution to this problem is to develop a simple and sensitive biological sensor for the detection of common types of infectious bacteria. We hope to achieve this goal through the use of highly stable and fluorescent CdSe nanocrystals (NCs): judicious derivatization of the nanocrystal surface with receptors for a target pathogen can initiate binding to this antigen, which can provide the basis for a simple colorimetric sensor. Due to quantum-size effects, CdSe NCs exhibit size-tunable fluorescence that spans the visible spectrum. Their narrow emission spectra, broad absorption spectra, and high photostability versus traditional organic fluorophores make these materials attractive for biological applications because the simultaneous detection of multiple antigens is possible. We will present our initial efforts concerning the development of a nanocrystal-based colorimetric sensor for *E. coli*. CdSe NCs with diameters of ~3 nm have been derivatized with receptor molecules that are specific for certain components of the bacterial cell wall, such as O antigen and lipid A. When incubated with *E. coli*, these functionalized nanocrystals bind to the microorganism, as determined by fluorescence microscopy of individual bacterial cells. The sensitivity and selectivity provided by these methods should prove useful for the rapid detection of common pathogens.

9:30 AM N7.5
OBLIQUE-INCIDENCE REFLECTIVITY DIFFERENCE AND FLUORESCENCE IMAGING OF PROTEIN MICROARRAYS. James P. Landry, X.D. Zhu and X.W. Guo, Univ of California at Davis, Dept of Physics, Davis, CA; J. Gregg, University of California at Davis, Dept of Molecular Pathology, Davis, CA.

Biomolecular interactions can be assayed simultaneously by exposing target molecules to an array of probe molecules immobilized on a solid substrate. Typically, the target molecules are labelled with fluorescent dyes and their binding affinity to the probe molecules is detected using some form of fluorescence-based optical scanner. However, in many applications it is desirable to detect the binding of target molecules to probe molecules without using fluorescent dyes. This not only eliminates labeling steps in target preparation, but more importantly, removes the potential effect of fluorescent tag molecules on the affinity of a target molecule to a probe molecule, particularly when protein molecules are involved.
We show that an oblique-incidence reflectivity difference (OI-RD) ellipsometer is capable of detecting the binding of target molecules to probe molecules on a microarray without fluorescent labeling. In OI-RD ellipsometry, a polarization-modulated laser beam is reflected from a surface containing a microarray at an oblique angle of incidence. This results in a reflected beam with a periodically varying

polarization state that is subsequently analyzed. The key property of our OI-RD ellipsometry arrangement is that we directly measure the difference in fractional reflectivity change between s-polarization and p-polarization components of the incident beam in response to minute changes in optical constants as the light beam is scanned across the microarray-covered surface. The optical constant change comes from the change in the molecular density and conformation as a result of target molecules binding to probe molecules.
We have constructed a scanning OI-RD microscope for detecting protein microarrays printed on functionalized glass slides. We present our preliminary images of antibody microarrays obtained with our OI-RD microscope and a commercial fluorescence-based scanner. We found that the binding affinity of goat antibodies to their corresponding antigens significantly changes when the antigen is labeled with Cy5 or Cy3 fluorescent molecules.

9:45 AM N7.6
POTENTIAL-SENSITIVE DETECTION OF CHARGED BIOMOLECULES ON FUNCTIONAL DIAMOND SURFACE.
Hitoshi Umezawa, Minoru Tachiki, Yu Kaibara, Toshikatsu Sakai, Kwang Soup Song, Hiroaki Ishizaka, and Hiroshi Kawarada, School of Science & Engineering, Waseda University, Tokyo, JAPAN, CREST, Japan Science and Technology Corporation (JST), JAPAN.

The properties of hydrogen-terminated (H-terminated) diamond surfaces contrast with those of oxygen-terminated (O-terminated) surfaces. The surface hydrogenation induces p-type surface conduction even in undoped diamond, though O-terminated diamond is insulative. In the previous study, we have performed nanoscale local anodic oxidation on H-terminated diamond surface using atomic force microscope (AFM) and fabrication of in-plane-gated single-electron transistors has been demonstrated based on this technology. On the other hand, we also developed diamond solution gate field-effect transistors (SGFETs), which can operate in the electrolyte solutions. To apply these diamond surface devices to the biosensing technology, electrical characterization of the locally modified diamond surface is crucial. In the present study, we perform the surface potential and the surface charge characterization of local areas on the CVD diamond surface by using a Kelvin force microscope (KFM). From KFM images of the locally oxidized area on the H-terminated diamond surface, surface potential of the H-terminated area is observed to be 0.1 V higher than that of the O-terminated area. This potential difference is attributed to the positive surface charging of the H-terminated diamond due to the surface dipole caused by the electronegativity difference between carbon and hydrogen. These surface charge difference can be used for the immobilization or detection of the charged biomolecules such as deoxyribonucleic acid (DNA). We also investigate the hydrophobic fluorinated and amino-group-terminated diamond surface by KFM. Based on the surface potential measurement, we performed adsorption control of DNA molecules on locally modified diamond surface. We also examined the potential-sensitive detection of biomolecules by KFM and SGFET the for the nanoscale biosensor applications.

10:30 AM N7.7
LONG-TERM MULTIPLE COLOR IMAGING OF LIVE CELLS USING QUANTUM DOT BIOCONJUGATES.
Jyoti K. Jaiswal, Sanford M. Simon, The Rockefeller University, New York, NY; Hedi Mattoussi, J. Matthew Mauro, U.S. Naval Research Laboratory, Washington, DC; Division of Optical Sciences and Center for Bio/Molecular Science and Engineering.

Colloidal luminescent semiconductor nanocrystals (quantum dots, QDs) are a promising alternative to organic dyes for a variety of fluorescence-based applications. We have previously developed an approach to conjugate biotinylated or non-biotinylated antibodies to CdSe-ZnS core shell QDs via molecular adaptor proteins that have been electrostatically linked with dihydrolipoic acid (DHLA)-capped nanocrystals.1,2 These QD-antibody conjugates exhibit high specificity and stability in immunoassays.2,3 In the present work we have used these bioconjugates in live cell labeling. For this, we developed approaches for using the QD-conjugates in generalized and specific labeling of both mammalian (HeLa) and Dictyostelium discoideum cells. In particular, we showed that QD-antibody conjugates can selectively label cells and regions within cells that express proteins of interest, and that they can be used for generalized labeling of any cell type (driven by endocytic uptake of QDs). These approaches enabled the use of luminescent QDs for simultaneously studying growth and development of multiple cells over extended time periods. Hence, we have imaged and tracked mixtures of developing cells for periods of hours to days using multiple colored QDs. We have also found that labeling of cells with QDs using either approach did not interfere with cellular growth and differentiation. Our approach demonstrates the utility of using luminescent QDs for cellular imaging. 1. H. Mattoussi et al., J. Am. Chem. Soc. 122, 12142 (2000). 2. E.R. Goldman et al., J. Am. Chem. Soc. 124, 6378 (2002). 3. E.R. Goldman et al., Anal. Chem. 74, 841 (2002).

10:45 AM N7.8
SILICON TECHNOLOGIES FOR BIOLOGICAL DETECTION.
Adrian Horgan, Lei Jin, Patrick Johnson, Rastislav Levicky, Gang Shen, Columbia Univ, Dept of Chemical Engineering, New York, NY; George Patounakis, Kenneth Shepard, Columbia Univ, Dept of Electrical Engineering, New York, NY.

Detection of biological analytes in complex sample environments is often implemented by capturing them, via specific molecular interactions, to appropriately functionalized solid supports. Most commonly, passive solid supports are used, such as a glass slide or a polymer membrane bearing appropriate capture molecules (e.g. proteins, nucleic acids, carbohydrates) whose function is to bind analytes of interest. In the context of nucleic acid diagnostics, the talk will summarize our efforts to develop "active" supports that contain integrated circuitry for on-command control and detection of hybridization between surface-tethered and free strands. A physical picture of mixed-phase hybridization will be presented, as will novel approaches for fabricating robust DNA-functional surfaces and prototype silicon (CMOS) microarrays with feature density compatible with whole-genome analysis. This effort seeks to provide accessible, low cost diagnostic platforms that minimize need for macroscopic external equipment and that enable instant tuning of the thermodynamics and kinetics of sensing events.

11:00 AM N7.9
CdSe-ZnS QUANTUM DOT BIOCONJUGATES AS FLUORESCENCE RESONANCE ENERGY TRANSFER DONORS.
Aaron R. Clapp, Igor L. Medintz, Ellen R. Goldman, George P. Anderson, J. Matthew Mauro, and Hedi Mattoussi, Optical Sciences Division and Center for Bio/Molecular Science and Engineering, U.S. Naval Research Laboratory, Washington, DC.

Colloidal semiconductor quantum dots (QDs) such as those made of CdSe-ZnS core-shell are highly luminescent nanocrystals with size-specific optical and spectroscopic properties, and they exhibit high resistance to chemical and photo-degradations. They offer a promising alternative to organic dyes in a variety of biological tagging applications. We have previously demonstrated a useful method for attaching engineered and naturally occurring proteins to CdSe-ZnS QDs using dihydrolipoic acid (DHLA) surface capping groups and electrostatic self-assembly in an aqueous environment. The resulting QD bioconjugates exhibit high specificity and stability in immunoassays. We have used this conjugation strategy to build solution-based QD-conjugate sensors based on fluorescence resonance energy transfer (FRET) between QD donors and dye-labeled protein acceptors. Specific binding between the QD-ligand donor and dye-labeled receptor was achieved, for example, via the avidin-biotin interaction. In this scheme, the donors were QD-avidin conjugates formed using previously developed approaches based on electrostatic self-assembly, while the organic dyes, attached to a short oligonucleotide sequence with biotin at the opposing end, served as the acceptors. The ligand-receptor complex was optically excited in a region where absorption of the dye is negligible compared to that of the nanocrystals. We observed a continuous decrease of the QD emission accompanied by a steady and pronounced increase of the acceptor emission as the ratio of dye to QD was increased. Other aspects such as donor-acceptor separation distance and degree of overlap between absorption of the dye acceptor and the emission of the QD donor have been investigated. The results of these experiments suggest efficient resonance energy transfer between the QD donor and the dye acceptor upon ligand-receptor binding. Other aspects such as reverse FRET (upon ligand-receptor release) in a reversible assay will also be discussed.

11:15 AM N7.10
ENGINEERING OF MOLECULAR BEACONS FOR EXTENDED LIFE TIME AND STRONGER SIGNALS.
Joong Hyun Kim and Mihri Ozkan, University of California, Dept of Chemical and Environmental Engineering, Riverside, CA.

Molecular beacons (MBs) have been used as DNA probes since 1996 after the work presented by Tyagi and Kramer. Then, further developments followed to improve the performance of MBs by modifying the structure of fluorophores and quenchers. Yet, due to photobleaching and instability of organic dyes, the use of MBs especially for in vivo applications remains as a limitation. Hence, there is an immediate need to further engineer MBs for extended life time and stronger signals. Here, we present quantum dot conjugated MBs that offer these advantages. For this, conventional organic dyes are replaced with colloidal quantum dots. Our most recent studies with modified MBs show signal to noise ratio greater than 4. It is being determined that the signal to noise ratio is decided by fraction of the materials conjugated with molecular beacons and thus we are investigating various fractions of mixtures for higher signal to noise ratio. Finally, our engineered molecular beacons can be applied to in

vivo applications for detection of single nucleotide polymorphism, mutation, pathogenic and RNA detection

11:30 AM N7.11
BIOSENSING IN MICROFLUIDIC DEVICES USING FLUORESCENCE POLARIZATION. Vamsi K. Yadavalli and Michael V. Pishko, Penn State University, Dept. of Chemical Engineering, University Park, PA.

Microfluidic devices provide useful platforms for sensing and conducting immunoassays for high throughput screening and drug discovery. Here, fluorescence polarization has been used as a technique for probing binding events within 500 micron and smaller microfluidic channels fabricated in poly(dimethyl siloxane) (PDMS). The binding of acetylcholinesterase to concanavalin A has been used to demonstrate the homogeneous, ratioing format of fluorescence polarization for the quick and accurate determination of extremely low (nanomole) concentrations. Polarization has also been used to sense for a poly-aromatic hydrocarbon (PAH) within a microfluidic channel using binding to an antibody. We have also demonstrated a simple pH sensor based on the change in anisotropy of a pH sensitive fluorophore. The ease of fabrication and measurement using such polarization-based devices make them extremely suitable for micro-sized sensors, assays and total analysis systems.

11:45 AM N7.12
MONITORING OF STEM CELL DIFFERENTIATION USING A PERMITTIVITY RESPONSIVE BIOINTERFACE.
P.O. Bagnaninchi[a], M. Dikeakos[b], T. Veres[b], M. Tabrizian[a]; [a]Department of Biomedical Engineering, McGill university, QC, CANADA; [b]IMI-National Research Council Canada, Boucherville, Qc, CANADA.

In-vitro bone engineering relies on the use of stem cells and microporous scaffolds to promote bone formation. During this process, stem cells attach to the scaffold, proliferate and differentiate into bone tissue. In order to assess quickly and non-destructively the various stages of bone formation, microporous scaffolds acting as bio-interfaces are utilized with permittivity-responsive sensors. By enabling the detection of Complex Permittivity (CP) variation in their host medium, this concept will lead to dielectric biosensors designed especially for tissue-engineering interests. The aim of this study is to monitor and characterize growth and differentiation of stem cells in microporous biointerfaces by CP measurements. Measurements are taken throughout the entire process of the stem cells culture, growth, and differentiation using a dielectric probe in conjunction with a network analyzer under sterile conditions. Cells are seeded in the microporous host and cultured until evidence of bone formation is observed. Control scaffolds are used for scanning electron microscopy analysis and cell-counting. An effective medium model is implemented in order to parameterize the heterogeneous host medium. By establishing the relationship between the latter parameters and those obtained previously from the scaffold characterization (porosity), it is possible to monitor the growth and differentiation of cells by CP variation. Dramatic changes in the medium properties following the transformation of stem cells to bone tissue are translated into variations of both complex permittivity and relaxation frequency. This method yields the number of stem cells and the volume fraction of bone tissue formed in the microporous scaffold. These permittivity-responsive biointerfaces in combination with the dielectric probe will lead to sensitive biosensors especially adapted for tissue engineering.

SESSION N8: BIO-NANO SYSTEMS I
Chairs: Mihrimah Ozkan and Viola Vogel
Thursday Afternoon, April 24, 2003
Salon 12/13 (Marriott)

1:30 PM *N8.1
GENETICALLY-ENGINEERED PROTEINS FOR SELF-ASSEMBLED FUNCTIONAL NANOSTRUCTURES. Mehmet Sarikaya, D. Heidel, C. Tamerler, H. Zareie, S. Dincer, B.W. Reed, University of Washington, Materials Science and Engineering, Seattle, WA.

Assembly and order in biological organisms in producing functional materials and systems are accomplished through protein/macromolecular interactions that are highly specific. The biological systems could be particulates (magnetic particles of magnetotactic bacteria), thin films (surface layer proteins), and three-dimensional ordered, hierarchical structures (mollusk shells, bone, and dental tissues). Using this scheme, and inspired by Mother Nature, we are engineering proteins with specific affinity to inorganic surfaces and use them as molecular "erector sets" to assemble functional hybrid materials and systems. We select (7-14 amino acid long) polypeptides (via combinatorial biology protocols, e.g., phage and cell-surface display) from a large library of random sequences, which have strong affinity to inorganic surfaces. Through experimental and theoretical approaches, we find unusual conformation schemes of these polypeptides on selected surfaces with varying binding characteristics. For example, a 42 amino-acid long repeated gold-binding polypeptide binds to Au surface via polar OH-groups, and self assembles onto Au{111} forming a single molecular layer-thick film (a self-assembled monolayer) that conforms into a 3-fold symmetrical network. These genetically engineered proteins for inorganics (GEPIs) offer three solutions to the development of heterofunctional nanostructure problems simultaneously. i. GEPIs are templates designed at the molecular level (and through genetics) ensuring the "bottom-up" processing for nanostructural control at the lowest dimensional scale possible; ii. GEPIs are linkers that bind to synthetic entities, including nanoparticles, functional polymers, or other nanostructures onto molecular templates. And, finally; iii. GEPIs self- and co-assemble into ordered secondary and nano-structures, ensuring a robust assembly process for achieving complex nanostructures, similar to those found in Nature. The areas of strong interest are wide ranging and include biomaterials and tissue engineering, drug delivery, biosensors, proteomics, and molecular biomimetics. We thank our collaborators, F. Baneyx, B. Traxler, S. Brown, J. Evans, and K. Schulten, and ARO through a DURINT Project.

2:00 PM *N8.2
NANOSCALE BIOPOLYMERS WITH TUNABLE PROPERTIES FOR BIOMEDICAL AND ENVIRONMENTAL APPLICATIONS. Hana Stiborova, Giridhar Prabhukumar, Jan Kostal, Wifred Chen, Ashok Mulchandani, Department of Chemical and Environmental Engineering, University of California, Riverside, CA.

Nanoscale biopolymers based on elastin-like polypeptide (ELP) have been engineered with novel properties that suitable for a wide range of biomedical and environmental applications. Unlike the statistical nature of step and chain polymerization reactions, biopolymers are specifically pre-programmed within a synthetic gene template that can be precisely controlled over chain length, composition, sequence, and most importantly properties. In one study, biopolymers with both metal-binding and tunable properties were created for the selectively removal of heavy metals from dilute solutions. By simple environmental triggers such as pH and temperature, reversible network formation between the individual biopolymers enables the recovery of the sequestered metals by precipitation. In another study the controlled drug delivery by engineering novel ELP-based hydrogels with tunable properties has been investigated. Unlike conventional chemical crosslinking, novel hydrogels engineered by coordinated ligand-bridging that allow reversible swelling in response to a specific target molecule in addition to temperature and pH has been employed.

2:30 PM *N8.3
SPATIALLY ENCODED AND MOBILE ARRAYS OF TETHERED LIPID VESICLES. Chiaki Ishii and Steven G. Boxer, Stanford University, Department of Chemistry, Stanford, CA.

Lipids have been prepared with a relatively short DNA oligonucleotide covalently attached to the head group. These oligolipids can be displayed on the surface of a fluid supported lipid bilayer. When vesicles displaying oligolipids with the complimentary sequence are flowed over such a supported bilayer surface, the vesicles become tethered to the lipids on the supported bilayer. Tethering is sequence specific. Once tethered, vesicles are laterally mobile in the plane of the supported bilayer. Upon application of an electric field parallel to the plane of the supported bilayer, the tethered vesicles are observed to move rapidly in the direction of electoosmotic flow. Using techniques developed for patterning supported bilayers [Accts. Chem. Res. 35, 149 (2002)], corrals displaying different oligolipids can be prepared. These arrays of corrals can be used to tether and sort vesicles displaying the complimentary sequence, and different vesicles can have different contents, lipid composition and/or membrane-associated proteins encoded by the corresponding oligonucleotide sequence. Because the vesicles are laterally mobile, individual vesicle-vesicle interactions, mediated by different components on the vesicle surface or in solution, can be observed directly.

3:30 PM *N8.4
SINGLE MOLECULAR BIOPHOTONICS MEMS. Luke Lee, Berkeley Sensor & Actuator Center, Department of Bioengineering, University of California, Berkeley, CA.

In order to create ultrasensitive $in-vivo$ detection or ultrafast lab-on-a-chip, we have been developing various Biophotonic MEMS called BioPOEMS*. As an example of BioPOEMS, microscale Confocal Imagining Arrays (μCIAs) with microfluidic networks and self-aligned integrated microfluidic optical systems (SiMOS), and integrated microfluidic arrays with total internal reflection system are

realized. The μCIAs have capabilities of single cellular detection and manipulation within microfluidic chips. Compact, multi-functional, self-aligned μCIAs have several advantages in comparison to conventional systems: size, cost, and sensitivity. The μCIAs utilize the precise control of the micro-optical motion and multiple optical trapping capabilities for various biomedical applications. The μCIAs will have applications in non-invasive real-time single molecule detection in living cells that allows dynamic monitoring of individual molecules $in-vivo$ in the highly complex cellular environment. Disposable SiMOS are ideal for biophotonic chips since it eliminates optical alignment with microfluidic devices. The integrated microfluidic arrays with a total internal reflection fluorescence system is presented utilizing an integrated silicon micromirror multilayer chip for single molecule detection. The hybrid integration of biophotonic devices, optical MEMS, and microfluidics will be useful for future ultrafast biochips for single molecules detections, functional genomics, and proteomics.
*Bio-Polymer-Opto-Electro-Mechanical-Systems.

4:00 PM N8.5
MODELLING CARBON-NANOTUBE BASED BIO-NANO-SYSTEMS. Huajian Gao, Yong Kong, Daxiang Cui, Max-Planck Institute for Metals Research, Stuttgart, GERMANY; Cengiz Ozkan, Department of Mechanical Engineering, University of California, Riverside, CA.

Advances in understanding behaviour and mechanics of bio-nano-structures will ultimately lead to a new generation of nano-scale biological/chemical devices including probes and sensors. Recently, Hummer et al. (Nature **414**, 188-190 (2001)) has reported that single-walled carbon nanotubes can be realized as molecular channels for water by computer simulation. Here we present our theoretical study on SWNT based bio-nano-system. The primary objective is to understand the interfaces and interactions between nanotube and biological molecules. Using classical molecular dynamics method, we study dynamical behaviours and properties of bio-SWNT systems in solvent and discuss effects of temperature, pressure, solvent pH value and size (diameter and length) of SWNT.

4:15 PM N8.6
MOLECULAR SHUTTLES BASED ON MOTOR PROTEINS: A NANOSCALE TRANSPORT SYSTEM. Henry Hess, John Clemmens, Robert Doot, Robert Tucker, and Viola Vogel, University of Washington, Dept. of Bioengineering, Seattle, WA; Jonathon Howard, Max-Planck-Institute of Molecular Cell Biology and Genetics, Dresden, GERMANY.

Active transport in cells, utilizing molecular motors like kinesin and myosin, provides the inspiration for the integration of active transport into miniaturized devices, replacing fluid flow driven by pressure or electroosmosis. Hybrid devices, utilizing motor proteins in a synthetic environment, allow us to explore the benefits of active transport in the absence of advanced synthetic molecular motors.
We have designed a nanoscale transport system, termed a Molecular Shuttle, for the controlled transport of molecular cargo. Applications of molecular shuttles can be envisioned e.g. in the field of Nano-Electro-Mechanical-Systems (NEMS), where scaling laws favor active transport over fluid flow, and in the bottom-up assembly of novel materials. Our shuttle system utilizes surface-adsorbed kinesin motor proteins to move functionalized microtubules, which have a diameter of 30 nm and a length of several micrometers.
The key problems for the construction of a molecular shuttle are guiding the direction of the motion, controlling the speed, and loading and unloading of cargo. Various techniques, relying on surface topography and chemistry as well as flow fields and electric fields, have been developed by us and others to guide the movement of molecular shuttles based on motor proteins. The control of ATP concentration, acting as fuel supply, can serve as a means to control the speed of movement. The loading process requires the coupling of cargo to the shuttle, ideally by a strong and specific link.
Recently, we developed an in-depth understanding of the mechanisms responsible for the guiding of a Molecular Shuttle along a chemically or topographically defined track on a surface. The mechanical properties of the shuttle as well as the presence of Brownian forces play a major role in the guiding process. We apply these insights to the design of novel NEMS devices, which integrate molecular shuttles.

4:30 PM *N8.7
BIOMATERIALS FOR REMOTE MANIPULATION: *IN VIVO* ADJUSTABLE INTRA-OCULAR LENS. Julia A. Kornfield, Chemical Engineering, California Institute of Technology, Pasadena, CA.

To achieve optimal outcomes with medical implants it is necessary to account for the body's inherently unpredictable wound healing response. A prevalent example is the implantation of lenses in the human eye, to provide refractive correction after cataract surgery: over 13 million lenses are implanted annually worldwide. The final position of the lens and the ultimate shape of the eye are not precisely known until wound healing has stabilized; consequently, most patients require spectacles to correct residual refractive errors. Here we describe a material that possesses a latent ability to change shape, which can be triggered in a spatially resolved manner using light to non-invasively adjust an implanted lens. The physics of diffusion and swelling in elastomers are applied to create a transparent silicone suitable for making a foldable intraocular lens that can be reshaped using near ultraviolet light. A crosslinked silicone matrix dictates the initial shape of the lens, while "macromers" short silicone chains with polymerizable end groups and photoinitiator enable shape adjustment using light: polymerization of the macromer in the irradiated regions, followed by diffusion of free macromer causes local swelling. In addition to correcting defocus and astigmatism, customization of the irradiation beam profile can compensate for higher order optical aberrations in the eye. Patients implanted with light-adjustable intraocular lenses may therefore potentially achieve levels of visual acuity that are inaccessible with current technologies.

SESSION N9: BIO-NANO SYSTEMS II
Chairs: Philip R. LeDuc and Luke P. Lee
Friday Morning, April 25, 2003
Salon 12/13 (Marriott)

8:30 AM *N9.1
FROM BIOMEMS TO BIONANOTECHNOLOGY: INTERFACING BIOLOGY WITH MICRO/NANO-SYSTEMS. Rashid Bashir, School of Electrical and Computer Engineering, Department of Biomedical Engineering, Purdue University, West Lafayette, IN.

The merger of life-science and engineering, specially at the micro and nanoscale, can bring about some very exciting and practical possibilities for the development of "integrated systems". Micro and nanoscale engineering can be used to solve important problems in life-sciences such as detection of biological organisms, while concepts from life sciences such as bio-inspired assembly can be used to meet significant engineering challenges such as novel techniques for material synthesis and manufacturing. Future integrated systems will utilize nano-scale phenomena, and micro-scale components used to interface the nano-scale components to the macro-world. This talk will present the interdisciplinary work in progress in our group in these exciting research areas including; Detection of microorganisms and the determination of their viability within micro-scale bio-chips and bio-reactors, fabrication of ultra thin silicon cantilevers for high sensitivity detection of molecular byproducts of cells, and exploration of DNA and protein based assembly of micro and nano-particles and silicon devices.

9:00 AM *N9.2
BIOMOLECULAR MATERIALS THAT TALK AND LISTEN IN NANOSPACE. Patrick S. Stayton and Allan S. Hoffman, University of Washington, Dept of Bioengineering, Seattle, WA.

One of the hallmarks of biological systems is their ability to change important physical properties in response to environmental cues. "Smart" or "intelligent" materials have the analogous ability to reversibly change their structural, mechanical and/or functional properties in response to environmental signals such as a change in temperature, pH or light irradiation. We have been working to develop "smart" hybrid polymer-biomolecular materials for BioMEMS applications, where the environmentally responsive changes in "smart" polymer structure and physical properties are directly coupled to the control of protein biofunctionality. The polymers serve as environmental sensors and differentially control access of ligands or substrates to binding or catalytic sites as a function of their expanded or collapsed states. The collapse of the smart polymers can also result in allosteric regulation of ligand affinity to turn protein activity on or off. The smart polymers thus provide "listening" elements that reversibly modulate protein (or other biomolecule) activity in the device setting. These hybrid systems merge the impressive recognition and biofunctional properties of biomolecules, with the impressive responsiveness and chemical versatility of "smart" polymers.

9:30 AM *N9.3
INTEGRATING MOTOR PROTEINS INTO NANODEVICES AND HYBRID MATERIALS. Henry Hess, John Clemmens, Robert Doot, Robert Tucker, Viola Vogel, University of Washington, Dept of Bioengineering, Seattle, WA; Jonathon Howard, Max-Planck-Institute of Molecular Cell Biology and Genetics, Dresden, GERMANY.

Motor proteins are unique nanoscale machines, converting chemical energy into mechanical work by hydrolyzing ATP. In nature, motors like kinesins and myosins perform a wide variety of functions, ranging

from active transport of nanoscale objects to the contraction of muscles. In our research, we integrate these advanced molecular motors into synthetic devices in order to explore the potential of molecular motors in nanotechnology. Examples for this approach are the "molecular shuttle", a nanoscale transport system, "Monte-Carlo imaging", a surface imaging method based on the random sampling of a surface by nanoscale probe-robots, and a piconewton forcemeter for the measurement of the strength of intermolecular bonds. In the fabrication of these hybrid devices we combine protein-patterning, soft-lithography, and microfluidics with biomolecular techniques in order to control protein-surface and protein-protein interactions. Due to their nanometer dimensions, motor proteins can be either integrated into novel materials, where they dynamically modulate material properties in response to external stimuli, or aid the assembly of molecular building blocks into a non-equilibrium configuration, e.g. by transporting them against a concentration gradient. These hybrid materials will be discussed further.

J. Clemmens, H. Hess, J. Howard, and V. Vogel: "Analysis of microtubule guidance by microfabricated channels coated with kinesin." Langmuir (in print)
H. Hess, J. Howard, and V. Vogel: "A Piconewton Forcemeter assembled from Microtubules and Kinesins." Nano Letters 2(10), 1113-1115 (2002)
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H. Hess, J. Clemmens, C.M. Matzke, G.D. Bachand, B.C. Bunker, and V. Vogel: "Ratchet patterns sort molecular shuttles." Appl. Phys. A 75, 309-313 (2002)
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H. Hess and V. Vogel: "Molecular shuttles based on motor proteins: Active transport in synthetic environments." Reviews in Molecular Biotechnology 82, 67-85 (2001).

SESSION N10: MICROFLUIDICS I
Chairs: Mehmet Sarikaya and Julia A. Kornfield
Friday Morning, April 25, 2003
Salon 12/13 (Marriott)

10:30 AM *N10.1
OPTICALLY ACTUATED MICROFLUIDIC DEVICE BASED ON OPTO-ELECTROWETTING. Pei Yu Chiou, Zehao Chang, Ming C. Wu, University of California at Los Angeles, Department of Electrical Engineering, Los Angeles, CA.

A light-actuated microfluidic device has been successfully fabricated to inject, move, separate, and merge liquid droplets with nano-liter volumes. This is based on a new mechanism proposed by our group, called opto-electrowetting (OEW). It is realized by monolithically integrating a photoconductor with a dense array of electrowetting electrodes. OEW enables local control of surface wettability by a light beam. Illumination of light reduces the contact angle of liquid interface. Scanning of light beam therefore drags the droplet along the light path. Liquid droplets with volumes of 10 ~100 nl are injected from a reservoir, and then transported or separated by scanning optical beams. A droplet transport speed of 78 mm/s is observed in this new device. Electrowetting is very effective for driving liquids in microscale, particularly in droplet forms. Several microfluidic functions (injection, transport, mixing, and separation) have been demonstrated. Generally, 2-D droplet movement requires N^2 electrodes (and therefore wires) for N × N grid. The OEW mechanism we proposed completely eliminates the wiring problem. Only two bias lines are needed for the entire device. In this paper, we report, for the first time, optical injection, separation, merging, and transport of multiple droplets using two computer-controlled scanning laser beams.

11:00 AM N10.2
MICROREACTORS WITHOUT MICROFABRICATION: USING MICROSCALE STEADY-STATE KINETIC ANALYSIS (MICROSKA) TO STUDY BIOLOGICAL INTERACTIONS. Nathaniel J. Gleason and Jeffrey D. Carbeck, Princeton University, Department of Chemical Engineering, Princeton, NJ.

Limited mixing at low Reynolds numbers, as well as the difficulties associated with microfabrication, limit the applicability and accessibility of microfluidic systems to the analysis of biochemical reactions. In traditional microreactors, the effects of mass transport often limit the observed rates of chemical reactions. For reactions at surfaces, a concentration boundary layer depleted in reactants can form adjacent to the surface. Once developed the rate of diffusion across the boundary layer determines the observed rate of reaction. We present a new technique - microscale steady-state kinetic analysis (MicroSKA) that employs this concentration boundary layer to effectively create microscopic reaction volumes in macroscopic systems without the need for any microfabrication. Steady state analysis of the formation of this boundary layer provides kinetic parameters. We create a microchemical system with boundaries defined by relative rates of reaction and transport, not by the imposition of microfluidic channels or micropatterned surfaces. The combined effects of reaction and diffusion restrict reactions to a thin layer of fluid (~1 - 10 microns) adjacent to a reactive surface. For enzyme-catalyzed reactions, complete conversion in this volume occurs over microscopic distances (~10 - 100 microns). By monitoring the development of this concentration boundary layer at an interface, we can determine the kinetics of the underlying chemical reaction. We have developed analytical solutions to a simplified reaction-transport model to illustrate the microscopic dimensions of the reacting system. A complete model, based on the coupled reaction, diffusion and convection equations, has also been solved numerically; these solutions allow quantitative kinetic data to be extracted from spatial variation in conversion under steady state operation. We demonstrate these ideas with a model system composed of the enzyme alkaline phosphatase immobilized on a surface; this enzyme converts a non-fluorescent substrate to a fluorescent product. Epifluorescence microscopy measures the spatial variation of conversion under steady state conditions. Fitting of the model to the data provides the kinetic parameters for the reaction. This system is readily adapted to parallel analysis of multiple enzyme and/or substrates. This method of analysis is broadly applicable to a wide range of interactions in biology (protein - ligand, protein - protein and protein - DNA) and to different modes of detection, such as total internal reflectance and surface plasmon resonance.

11:15 AM N10.3
THERMOCAPILLARY ACTUATION OF LIQUIDS USING PATTERNED HEATER ARRAYS. Joseph P. Valentino, Princeton Univ, Dept. of Electrical Engineering, Princeton, NJ; Anton A. Darhuber, Sandra M. Troian, Princeton Univ, Dept. of Chemical Engineering, Princeton, NJ; Sigurd Wagner, Princeton Univ, Dept. of Electrical Engineering, Princeton, NJ.

We demonstrate a new method for active manipulation of nanoliter volumes of liquid on a glass or silicon surface by integrating chemical surface patterning with electronically addressable microheater arrays. This actuation method is especially suited to applications that require direct accessibility to liquid samples for handling and diagnostic purposes. An induced temperature gradient locally induces a gradient of the liquid surface tension leading to the generation of a thermocapillary stress. This stress propels the liquid toward cooler regions. Temperature maps can be programmed which enable liquids to move in a straight line, split, and turn corners. Droplet velocity is determined by the liquid viscosity, height, and thermal gradient. Droplets were split and propelled along 1mm wide hydrophilic stripes by supplying power of up to 40 mW to 140 Ω resistors, which corresponds to a temperature gradient of 1.5°C/mm. By varying the applied temperature gradient, bulk droplet velocities ranging between 50 μm/s and 1 mm/s can be achieved. For completely wetting surfaces, a very thin liquid residue may be left behind due to the diminutive receding contact angle. Making the surface partially wetting may eliminate this liquid residue. The liquids used in this study were polydimethylsiloxane silicone oil, dodecane, di(ethylene glycol) and tetra(ethylene glycol) in volumes of 150 to 300 nL.

11:30 AM N10.4
DISPERSION CONTROL IN MICROFLUIDIC BIO-CHIPS BY LOCALIZED ZETA-POTENTIAL VARIATION. R.-J. Yang, C.-C. Chang, L.-M. Fu, Dept of Engineering Science, National Cheng Kung University, Tainan, TAIWAN.

The paper proposes a new technique, which varies the zeta potential along the channel walls in the vicinity of the microchannel corners in such as a way as to minimize the effects of turn-induced dispersion within U-shaped separation channels. The effects of the separation channel geometry, the fluid velocity profile, and boundary control of the zeta potential on the band distribution in the detection area are all discussed within this paper. The results for a single square U-shaped separation channel indicate that boundary control of the zeta potential significantly reduces the band dispersion induced by the turns. Meanwhile, it is determined that the folded square U-shaped channel with boundary control of the zeta potential provides improved miniaturization and simplification benefits. Finally, the results confirm that application of the proposed localized zeta potential variation method results in a correction of the band tilting phenomenon and a reduction in the racetrack effect.

11:45 AM N10.5
ELECTRIC FIELD PULSE ASSISTED COVALENT IMMOBILIZATION AND HYBRIDIZATION OF DNA IN THE NANOSECOND TIME SCALE. F. Fixe[a,b], R. Cabeca[a], D.M.F. Prazeres[b], V. Chu[a] and J.P. Conde[a,c]; [a]INESC Microsistemas e

Nanotecnologias, Lisbon, PORTUGAL; [b]Biological Engineering Research Group, Instituto Superior Tecnico, Lisbon, PORTUGAL; [c]Department of Materials Engineering, Instituto Superior Tecnico, Lisbon, PORTUGAL.

The field of DNA microarrays can potentially revolutionize the acquisition and analysis of genetic information. Microarray technology bridges fields such as materials science, microelectronics, biochemistry and physics. In these devices, hybridization may occur in parallel with different capture probes immobilized at specific sites.
In this work we present the use of a single square voltage pulse resulting in selective covalent bonding of DNA probes to a functionalized thin film surface (silicon dioxide) at significantly higher rates. This technique is also used to enhance the kinetics and yield of hybridization of complementary strands to immobilized DNA molecules. The pulse is applied to an integrated metal electrode placed below the functionalized thin film surface. The duration and magnitude of the voltage pulse are compatible with silicon microelectronics circuits. For immobilization, covalent bonding occurs with only 100 ns of pulse duration, representing more than 10 orders of magnitude decrease in immobilization time from the 2 hours needed without electric field. Successful hybridization with a complementary strand was achieved on probes immobilized using this technique, confirming that the probe molecules were correctly oriented and were not damaged during the immobilization process. These results open the way for the electronic addressing of a microarray to immobilize, selectively and automatically, a large number of different probe molecules at specific sites as well as increasing the speed of biological data acquisition. A systematic study of the effects of the duration, magnitude and rise/fall times of the voltage pulse on the immobilization of DNA probe molecules is described. The effects of the electric field on hybridization kinetics will also be described.

SESSION N11: MICROFLUIDICS II
Chairs: Patrick S. Stayton and Gang Bao
Friday Afternoon, April 25, 2003
Salon 12/13 (Marriott)

1:30 PM N11.1
OSCILLATORY BEHAVIOR AND PATTERN FORMATION IN BINARY FLUIDS FLOWING IN PATTERNED MICROCHANNELS. Olga Kuksenok, Chemical Engineering Department, University of Pittsburgh, Pittsburgh, PA; David Jasnow, Physics Department, University of Pittsburgh, Pittsburgh, PA; Julia Yeomans, Theoretical Physics, Oxford University, Oxford, UNITED KINGDOM; Anna Balazs, Chemical Engineering Department, University of Pittsburgh, Pittsburgh, PA.

Through computer simulations, we probe the behavior of a binary fluid that consists of two partially miscible components, A and B, which are driven through a chemically patterned, three-dimensional microchannel. Two different arrangements of chemically distinct patches on the surface of the microchannels were investigated. We found that the behavior of the confined fluid strongly depends on the arrangement of the patches. In the first study, the top and bottom of the microchannel are decorated with a checkerboard pattern. Each checkerboard is composed of two A(B)-like patches, which are preferentially wetted by the A(B) fluid. The first B patch is placed in the way of the A stream and correspondingly, the first A patch is located in the path of the B fluid. The most interesting behavior occurs neat the sidewalls, where we observed the simultaneous, periodic formation of A-in-B and B-in-A droplets. Furthermore, the system bifurcates between time-independent behavior and different types of regular, non-decaying oscillations in the structural characteristics. We plot a bifurcation diagram that shows surprisingly complex behavior, including "memory" effects in the system. In the second study, we consider just two patches, that is, one A and B patch–on the top and bottom of the substrate. In this case, complex morphological instabilities give rise to spatiotemporal periodic patterns in the center of channel. We isolate conditions where this structure is similar to "plug" flow. In both examples, the morphological instabilities and complex behavior is observed even in the absence of hydrodynamic interactions and arises from the interplay between the fluid flow and patterned substrate.

1:45 PM N11.2
CAPACITIVE SENSING OF LIQUID FILMS IN "OPEN" MICROFLUIDIC DEVICES. Jian Z. Chen[†], Anton A. Darhuber[‡], Sandra M. Troian[‡] and Sigurd Wagner[†]; [†]Dept. of Electrical Engineering; [‡]Microfluidic Research and Engineering Laboratory, Dept. of Chemical Engineering, Princeton University, Princeton NJ.

There is increasing demand for micro- total analysis systems (mTAS) that can serve as miniature chemical laboratories on a chip. Aside from novel schemes for liquid pumping and mixing, further device development requires detection and feedback techniques for monitoring the location, composition and volume of liquid samples. The high sensitivity inherent in capacitance based sensors make these an ideal choice for liquid detection in "open" fluidic devices i.e. systems in which liquid streams or droplets move along the surface of a glass or silicon chip. We have developed a coplanar capacitance technique which can successfully distinguish between different liquid samples of known film thickness or which can determine the film thickness for samples of known dielectric constant. The variation in capacitance is monitored by the output frequency of an RC relaxation oscillator consisting of two inverters, one resistor and one capacitor. At a prescribed frequency of 370 kHz, the sensitivity of this capacitive sensor is 0.07 pF. Integration of this capacitive sensor with a thermocapillary based microfluidic device developed in our laboratory can be achieved with a double layer design. The performance of this coplanar sensor is controlled by the electrode width, length and spacing. These geometric variables determine the field penetration depth within the liquid, which in our cases ranged from 100 to 450 μm. Numerical solutions for the capacitance corresponding to the exact fabricated geometry agree very well with experimental data. An approximate analytic solution, which ignores fringe field effects, however, provides a simple but excellent guide for design development.

2:00 PM N11.3
LARGE AREA, HIGH ASPECT RATIO MICROELECTRODE ARRAYS. Charles D. Merritt, Paul L. Falkenstein, Brian L. Justus, US Naval Research Laboratory, Optical Physics Branch, Washington, DC.

A method is described for the fabrication of arrays of conducting, high aspect ratio microwires for use as electrodes. The electrode arrays are fabricated by electrochemical deposition of metals, including Ni, Pt, Ag, Au and Rh, in channel glass templates having parallel, uniform, hollow channels with diameters that range from sub-micrometer to over 100 micrometers. The metals completely fill the hollow channels, yielding highly uniform electrodes with aspect ratios on the order of 1000 or more. The electrodes are electrically insulated from one another by the glass template. The electrode array wafers are cut and polished to a thickness ranging from about 100 to 2000 micrometers. The overall surface area is as large as 1 square centimeter. Alternatively, the wafers can be partially etched with acid to remove some of the glass matrix surrounding the electrodes, exposing an array of bare, solid wire stubs. The high aspect ratio microelectrode arrays were initially fabricated in order to provide the electrical interface for an intraocular retinal prosthesis, but have additional applications including biological and chemical sensing. Results of fabrication using different metals will be presented. Arrays with different channel sizes, different electrode spacing (with pitch from approximately 3R to 20R, where R is the electrode radius), and different geometrical arrangement will be shown. Measurements of the impedance and corrosion resistance of electrodes in saline solution as a function of size, spacing and electrode material will be presented.

2:15 PM N11.4
ULTRANANOCRYSTALLINE DIAMOND-BIOMOLECULE COMPOSITES: TOWARDS BIOMEMS. Nicole M. Haralampus Grynaviski, Jennifer E. Gerbi, John A. Carlisle, Orlando Auciello, Dieter M. Gruen, and Millicent A. Firestone, Materials Science Division, Argonne National Laboratory, Argonne, IL.

Research on the surface functionalization of ultrananocrystalline diamond (UNCD) films to develop biocomposite materials for use as BioMicroElectroMechanical systems (BioMEMS) will be presented. Prior work in this Laboratory has demonstrated that UNCD thin films can span the range of insulator (undoped) to semiconductor (doped with nitrogen). These films feature excellent electrochemical properties, including low background current, a wide electrochemical window, corrosion resistance and biocompatibility. In addition, we have developed techniques to fabricate MEMS components based on UNCD, which can be used to produce cantilever and/or resonator-based devices with potentially high sensitivity mass sensing capability to enable MEMS biosensors. An important first step toward exploitation of these materials as biocompatible electrodes for use in devices (e.g., BioMEMS) is surface functionalization to render them amenable to coupling with biological macromolecules. To this end UNCD films, which feature (3-5 nm) grains sizes, have been synthesized using a microwave plasma chemical vapor deposition technique. Surface functionalization by covalent attachment of halo-terminated alkenes provides a means for the subsequent attachment of a wide variety of biological macromolecules (e.g., proteins, biomembranes). The UNCD-biomolecule composites have been characterized using scanning probe microscopy and a variety of surface-sensitive spectroscopies. In this presentation, the fabrication and characterization of these materials will be described and preliminary studies using them to both probe and control fundamental biochemical functions of electron and charge transport will be discussed. This work was performed under the auspices of the Office of

Basic Energy Sciences, Division of Materials Sciences, United States Department of Energy under contract number, W31-109-ENG38.

2:30 PM N11.5
MEMS TACTILE SENSORS FOR SURGICAL INSTRUMENTS.
Keith J. Rebello, Kyle S. Lebouitz, and Michele Migliuolo, Verimetra, Inc., Pittsburgh, PA.

The development of sophisticated endoscopic tools and the recent introduction of robotics are expanding the applications of minimally invasive surgery. The lack of tactile feed-back in the currently available endoscopic and robotic telemanipulation systems however represents a significant limitation. A need has arisen for the development of surgical instruments having integrated sensors. Current efforts to integrate sensors into or onto surgical tools has focused on fabrication of sensors on silicon, polyimide, or some other substrate and then attaching the sensors to a tool by hand or machine with epoxy, tape, or some other glue layer. Attaching the sensor in this manner has certain deficiencies. In particular, this method of attaching sensors to a surgical tool limits the sensors size, increases its thickness, and further constrains where the sensor can be placed. A method of fabricating tactile sensors on surgical instruments that addresses these deficiencies is discussed.

2:45 PM N11.6
NEW MICROELECTRODE ARRAYS FOR 2D ACCURATE POSITIONING OF NEURONS AND 3D SEPARATION OF GLIAS.
Mo Yang, Xuan Zhang, Cengiz Ozkan, Univ of California, Riverside, Dept of Mechanical Engineering, Riverside, CA; Shalini Prasad, Mihri Ozkan, Univ of California, Riverside, Dept of Electrical Engineering, Riverside, CA.

Dielectrophoresis (DEP) can be applied for cell separation that eliminates the need for fluorescent tagging of cells which induces toxicity. In addition, it helps to preserve cell characteristics, which makes it as a suitable technique for long term study of separated cells. Here, we have developed a new multifunctional micro fluidic chip system for 2D accurate cell positioning and 3D cell separation that can separate about four cell types. This system employs DEP and DEP field flow fractionation (DEP-FFF) simultaneously to obtain the cell separation. For this, a 2X2 electrode array system is used. The chip system consists of an electrode array coupled with a single input and multiple output fluidic channels. It is possible to control the output flow with specific cell type into a certain channel via switches. The input and output channels are 20μm in diameter and the output channels are at different levels to provide an outlet to the cells separated by DEP-FFF. To maintain sterility an outer chamber with a volume of about 750μL made of PDMS is fabricated. The culture medium consists of a mixture of 18 day rat embryo visual cortex cells suspended in 250mM sucrose/1641 RPMI. Positive and negative DEP forces are used to achieve the separation and positioning of neurons from glial cells. The glial cells are further separated using DEP-FFF, as different levities can be achieved based on the density and the dielectric properties of the cell. As a result, the chip design permits the collection of the various sub groups of glial cells via means of channel switches. This allows us with the scope of analysis of various components of glial cells. The internal electric field distribution is simulated by using 3-D finite element model. Finally, high fidelity in the cell positioning and separation is achieved.