The Whitesides Research Group

# Research

## Microfluidics

The Whitesides Group is very active in microfluidics. Our previous accomplishments in the field include work on laminar flow in microchannels (Figures 1,2), fabrication of three-dimensional channel topologies (Figures 3) and mixing by chaotic advection (Figure 4). We have also applied microfluidics to fabricate monodisperse polymer, hydrogel, and metal microparticles coated with thin, nylon-coated membranes (Figure 5). Currently, we are working on several projects related to microfluidics, including exploiting the behavior of bubbles and droplets for mixing and other applications, manipulating samples electrokinetically and probing the use of solder as electrodes in microchannels.

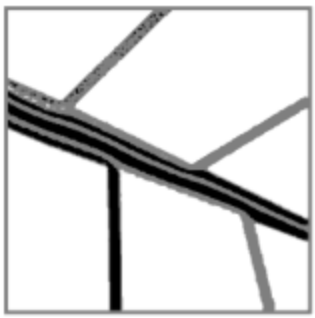

Figure 1

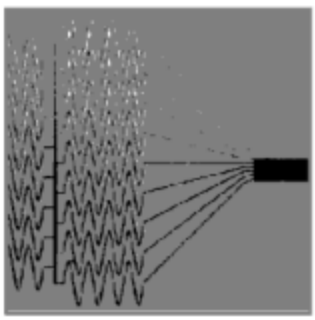

Figure 2

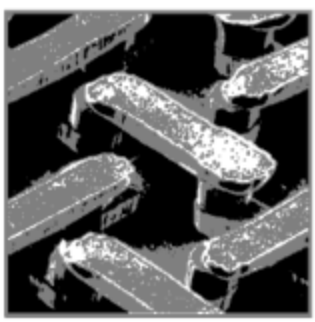

Figure 3

### Bubbles and Droplets in Microchannels

Our recent experiments in microfluidics include investigations into the behavior of bubbles and droplets in microchannels. Specifically, we are interested in four sub-areas: (1) enhanced mixing in microfluidic systems using bubbles; (2) the paths from monodisperse to chaotic bubbling in flow-focusing devices; (3) the production of bubbles with uniquely high periodicities in modified flow-focusing systems; (4) the path-selection process that bubbles demonstrate as they move through a network. Mixing in microchannels, in particular, is an important challenge in the microfluidics subgroup of our laboratory (the other areas introduced here are described further in the complexity section of the website).

Mixing between streams of fluid that flow in a laminar fashion is difficult to achieve. Previously, we have introduced a method to enhance mixing involving multiple lithographic steps. Our current work uses bubbles to facilitate the folding over of streams of fluid as they proceed through a network of microchannels (Movie 6). The bubbles partially block the channels in which they move, causing a portion of a stream of bulk fluid to cross over into the

channel in which the other stream moves. This process is repeated several times before the streams are mixed fully, with the final mixing device occupying an area of only a square millimeter on the chip.

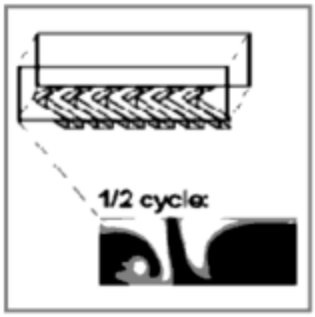

Figure 4

**Electrokinetic Flow in Microfluidic Channels**

We are exploring electrokinetically-driven microfluidic systems for separation of complex biological samples. Our ultimate goal is to provide a new sample handling method (femtomole/nL) for proteomic analysis and high-throughput biochemical assays. Currently, we are investigating geometrical designs, surface coatings and concentration techniques such as isotachophoresis.

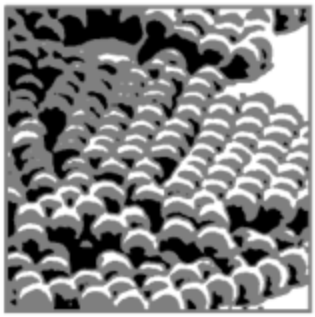
Figure 5

**TWIST Valves**

We have developed a new approach for controlling the flow of fluids in microfluidic channels. TWIST valves consist of small machine screws (500 um diameter) embedded in a layer of polyurethane cast above microfluidic channels fabricated in poly(dimethylsiloxane) (PDMS). The polyurethane is cured photochemically with the screws in place; on curing, it bonds to the surrounding layer of PDMS and forms a stiff layer that retains an impression of the threads of the screws (Figure 7). The valves are separated from the ceiling of microfluidic channels by a layer of PDMS, and are integrated into channels using a simple procedure compatible with rapid prototyping. Turning the screws actuates the valves by collapsing the PDMS layer between the valve and channel, controlling the flow of fluids in the underlying channels. These valves have the useful characteristic that they do not require power to retain their setting (on/off). They also allow settings between "on" and "off", resist large back pressures (>350 kPa) without failure, and can be integrated into portable, disposable microfluidic devices for carrying out biological assays (Figure 8).


Movie 6


Figure 7

**TWIST Pumps**

We have designed a system for storing and pumping fluids in microfluidic devices fabricated in poly(dimethylsiloxane) (PDMS) using TWIST valves. The method uses valves to isolate microfluidic reservoirs that are filled with solutions of reagents under pressure; the fluid is released, and the flow rate controlled, by opening one of the valves. Figure 9 shows a microfluidic pump fabricated using this approach.

**References**

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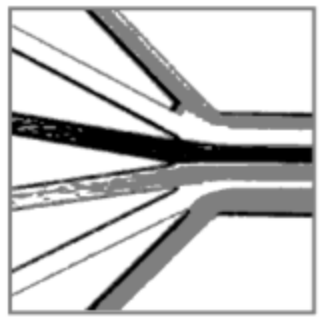

Figure 8

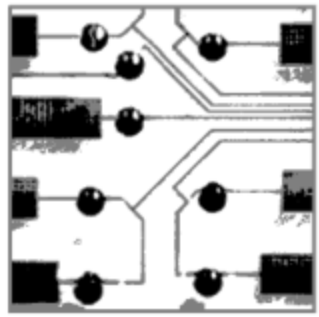

Figure 9

The Whitesides Research Group

# Research

## Fluidic Optics

Photonics deals with photons as a medium for transmitting information. Typically, photonic circuits either rely on passive devices with pre-designed optical functions, or use active components where application of external fields changes the optical properties of the materials (e.g. in electro-optical devices). Our projects in fluidic optics explore alternatives to application of external fields - in these projects we demonstrate the generation and reconfiguration of photonic devices in *real time* by manipulating flowing liquids.

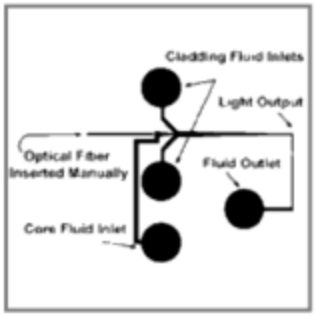


Figure 1

### Fluid Optical Waveguides

We take advantage of laminar flow in microscopic channels (i.e. microfluidic systems) and of diffusion. In the simplest demonstration, we sandwich a fluid of higher index of refraction between two streams of liquid with lower index of refraction (Figuire 1). In microchannels, the liquids flowing through the channel will not mix except by molecular diffusion; thus, the flow is laminar and the two liquids flowing side-by-side form an *optically smooth interface* [1,2]. This system acts as a waveguide (we call it a "liquid-liquid" or L2 waveguide).

Figure 2

Fluid optical waveguides are fabricated easily and rapidly in organic polymers using the convenient techniques for rapid prototyping developed in our group. The L2 waveguides are *dynamic* their structure and function depend on a continuous flow of the core and cladding liquids. They can be reconfigured, renewed (if damaged), and continuously adapted in ways that are not possible with solid-state waveguides. Manipulation of the rate of flow and the composition of the liquids (thus the optical properties) tunes the characteristics of these optical systems in real time. Currently, we are studying the design and operation of fluid analogs of several common optical elements: single- and multi-mode waveguides, optical switches, and evanescent couplers [3].

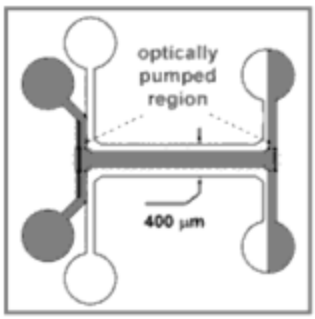


Figure 3

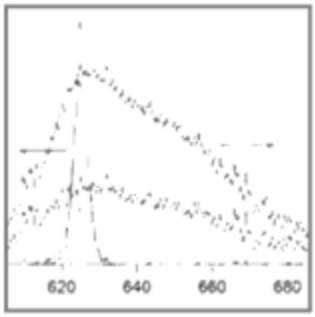

Figure 4

**Generation of Light in Microchannels**

We have also demonstrated that fluid waveguides can generate light in microchannels, thus simplifying the coupling of light from external sources to these fluidic devices [4]. When laminar streams of fluorescent organic dyes are separated by a low index fluid and illuminated by an incandescent light source (Figure 2), they each produce fluorescence of specific color that can be collected and propagated by a fluid waveguide. One can tune the wavelength (color), position, shape and intensity of these microfluidic light sources by making adjustments of the rate of flow or composition of individual streams. Such simple fluidic light sources could be important, for example, for microanalysis "on-chip" in integrated biophotonic microsystems.

**Microfluidic Dye Laser**

We used microfluidic technology to design a miniaturized waveguide dye laser, in which the laser cavity contained a liquid core-liquid cladding waveguide (Figure 3). The key feature of the laser is a long optical path length along the waveguide axis that allows us to achieve high gain in one pass and thus lower the threshold for lasing. By adding thin gold coatings on the surfaces of the T-junctions, we built the laser mirrors into flouresent L2 waveguide light source. Rhodamine 640 perchlorate dissolved in methanol served as the core stream, and pure methanol worked as the cladding stream. Optical pumping of the microlaser with a 532-nm frequency-doubled Nd:YAG laser at 50 Hz results in the bandwidth decrease by an order of magnitude at laser threshold (Figure 4). The fluid waveguide laser is readily tunable by continuously varying the composition of the mixed solvent (methanol-dimethylsulfoxide) while using the same concentration of the dye. The ability to easily change wavelength is critical for applications in spectroscopy and for various types of optical detection requiring different wavelengths.

**Select Publications**

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The Whitesides Research Group

# Research

## Simple Nanotechnology

"Nanofabrication" is the process of making functional structures with arbitrary patterns having minimum dimensions currently defined (more-or-less arbitrarily) to be ~100 nm. Microelectronic devices and information technologies have improved, and will continue to improve, as a result of large-scale, commercial implementation of nanofabrication. The motivation for these improvements is to increase the density of components, to lower their cost, and to increase their performance per device, and per integrated circuit. Methods used to generate nanoscale structures and nanostructured materials are commonly characterized as "top-down" and "bottom-up". The conventional top-down techniques include photolithography and scanning beam (or maskless) lithography (e.g., electron beam and focused ion beam lithography). The limitations of these conventional approaches when applied to innovative problems - high capital and operating costs, the difficulty in accessing the facilities necessary to use them, and their restricted applicability to many important classes of problems - motivate our exploration and development of new, or "unconventional" nanofabrication techniques. Unconventional techniques have the potential to be the ultimate, low-cost method for certain types of nanomanufacturing; approaches based on reel-to-reel processing are particularly attractive for low-cost processes. Unconventional approaches are also operationally much simpler to use than are conventional techniques, and thus help to open nanoscience and nanotechnology to exploration by a wide range of disciplines, especially those historically only weakly connected to electrical engineering and applied physics.

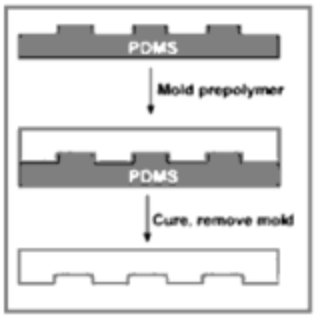


Figure 1

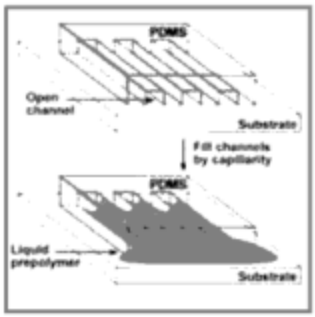


Figure 2

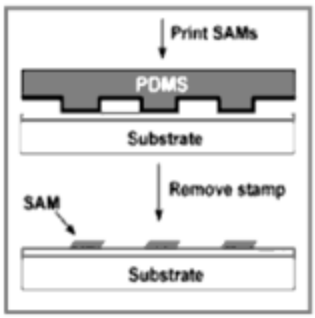


Figure 3

### Nanofabrication by Molding

The Whitesides group has developed four unique methods for fabricating nanostructures by molding (Figures 1, 2): (1) Replica Molding (RM) consists of three steps: i) creating a topographically patterned master (usually by conventional techniques; see, for example, ii) transferring the pattern of

this master into PDMS by replica molding; and iii) fabricating a replica of the original master by solidifying a liquid precursor against the PDMS mold. (2) Solvent-Assisted Micromolding (SAMIM) uses an elastomeric mold and an appropriate solvent to emboss polymer films. (3) Micromolding In Capillaries (MIMIC) uses capillarity to fill a series of channels in a topographically patterned PDMS stamp with a fluid, low-viscosity polymer or ceramic precursor. (4) Microtransfer Molding (μTM), prepolymer fills the recessed regions of the mold, and excess prepolymer is removed from the top surface using a flat edge. After placing the mold in contact with a rigid substrate, the prepolymer is cured by appropriate means.

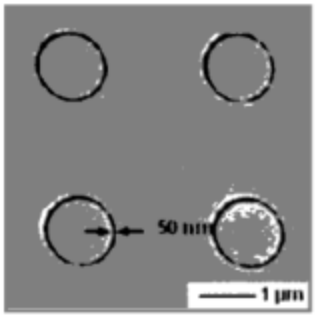

Figure 4

**Nanofabrication by Stamping**

We have developed two methods for patterning molecules on surfaces with high resolution (Figure 3). In microcontact printing (μCP), molecules are transfered from a patterned PDMS stamp to a substrate by the formation of covalent bonds. In electrical microcontact printing (e-μCP), a flexible electrode is used to pattern a thin film of electret-based material (i.e., that accepts and maintains an electrostatic potential), probably by injecting and trapping charges.

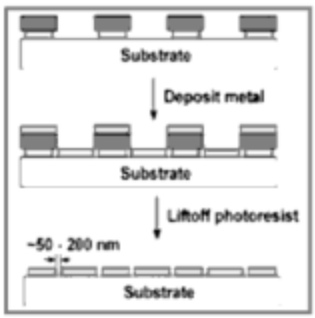

Figure 5

**Edge Lithography**

We are exploring several methods for creating nanostructures from using the topographical changes in the edges of patterns. One approach is to pattern nanostructures by selective removal or deposition of material at the edges of lithographically-defined topographic features, such as SAMs (Figure 4).

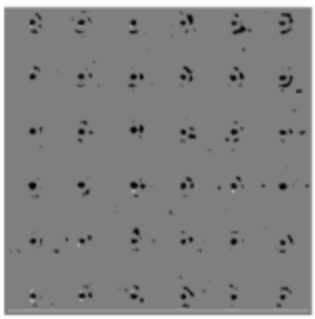
Figure 6

A second approach (Controlled Undercutting), patterns arrays of nanostructured trenches can be fabricated by the controlled undercutting of topographic features using isotropic wet etching, followed by deposition of a thin film (Figure 5).

A third approach is Phase-Shifting Photolithography (Figure 6). In this technique, the vertical edges of a transparent, topographically patterned substrate can induce changes in the phase of incident, collimated light to create narrow regions of constructive and destructive interference. Phase-shifting photolithography uses this phenomenon to project "dark or "bright" spots of incident light onto the surface of a photoresist.

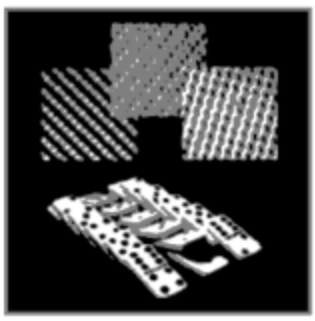
Figure 7

We and others have discovered that exposing the edge of a thin film can lead to the formation of nanostructure (Figure 7). This method of edge lithography takes advantage of the numerous methods that can grow thin films over large areas with a thickness between 1 and 50 nm. Converting these films - which are thin in the vertical direction - into structures that are thin in the lateral direction is an approach to fabricating nanostructures.

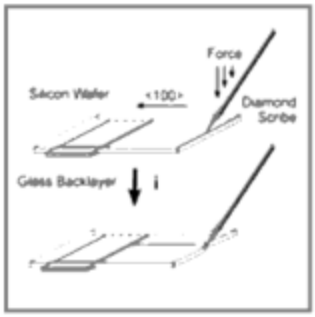


Figure 8

**Approaching Zero Through Crystalline Fracture (Cracking)**

We have demonstrated a convenient method to generate steps in a planar, surface with vertical dimension ranging from the microscale to the atomic ( less than 0.5 nm) scale (Figure 8). The process involves introducing a crack halfway into a wafer of single-crystal silicon. These cracks have the following attributes: i) they are continuous steps of smoothly decreasing height, which run in straight lines along crystal planes; ii) the step edges of the cracks are typically ~10 µm in height at edge of the wafer (where they initiate) and decrease to 0 nm at the "tip" of the crack (where they disappear into the atomically smooth surface of the silicon wafer; hence "approaching zero"); and iii) these steps are continuous and linear, thereby making them easy to find and characterize. We demonstrate the use of crystal fracture for metrology in nanoscience, by probing the limits of polymeric replication with 0.4 nm resolution (Figure 9).

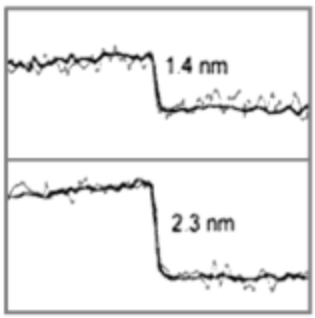


Figure 9

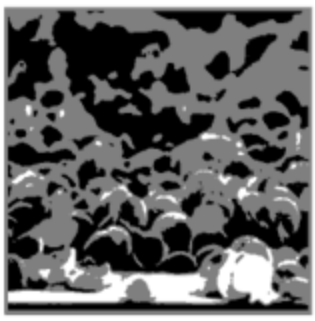

Figure 10

**Functional, Dispersable, Nanostructures from Templates**

*Metallic half-shells with submicron diameters:* We have demonstrated the use of spherical silica colloids on substrate as template on which metallic half-shells are formed. Dissolution of the template releases hollow metallic (Au, Pt, Pd) hemispheres with nanometric-scale dimensions (Figure 10).

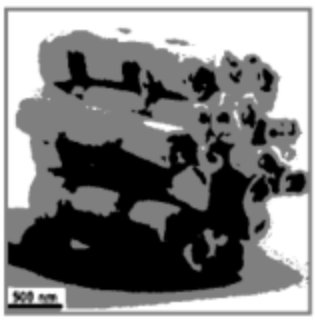


Figure 11

*Metallic rods with submicron diameters:* We use the method of Martin to perform sequential electrodeposition of multiple components with a porous template and to generate multi-functional nanostructures. For example, it is possible to generate nanorods with alternating sections of gold and nickel (Figure 11). The gold provides a surface that can be functionalized with thiol chemistry, while the nickel allows the nanorods to be manipulated with an external magnetic field. The rods naturally self-assemble into hexagonal bundles through magnetic interactions. The magnetic forces

polarize the disk-like section within the individual rods, perpendicular to the physical (long) axis of the rods and promote lateral interactions that direct the self-assembly of the rods.

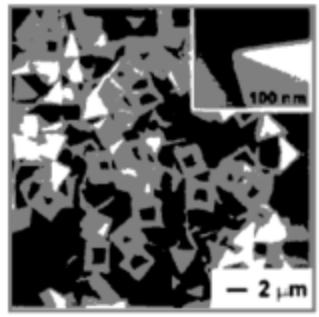

Figure 12

*Free-standing metallic pyramidal shells:* We fabricate metallic shells with a pyramidal structure where the tips have a radius of curvature of ~50 nm (Figure 12). The templates are formed by anisotropic etching of Si. The metal shells are formed by electrodeposition. The uniformity of the templates fabricated by photolithography or soft lithography ensures the uniformity in shape and size of the pyramidal shells.

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The Whitesides Research Group

# Research

## Science for Developing Economies

An important problem is to use first-world science to benefit the welfare of people in developing economies. The Whitesides group is using its competencies in materials science, engineering and biology to attack this type of global problem, with a focus on health diagnostics and local energy production. (Other problems include nutrition, sanitation, information technology, education, ecosystem management, and wealth creation.)

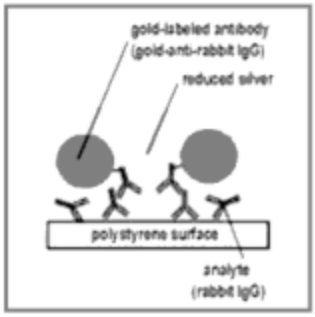



Figure 1

Our approach - what we call "simple solutions" - relies on a re-thinking to basic issues of design assumptions, from the ground up, to fit the technology to the socioeconomic constraints present in the developing world. Simple solutions are inexpensive to produce, easy to maintain or replace, simple to use, adaptable to local conditions, scalable for mass consumptions, and easily stored and transported. To the greatest degree possible, they are independent of first-world infrastructure (such as electricity and trained personnel).

Figure 2

### Health Diagnostics

A top priority for improving health in developing countries is technology for simple, affordable diagnosis of infectious diseases. We have developed new approaches that provide low-cost, simple, and reliable solutions for (1) signal amplification and detection in microfluidic devices, (2) reagent handling in microfluidics, (3) fabrication of microfluidic systems, and (4) valving. The work demonstrates the potential of simplifying high-performing devices (such as lab-on-a-chip devices) for use as diagnostic tools in developing economies.

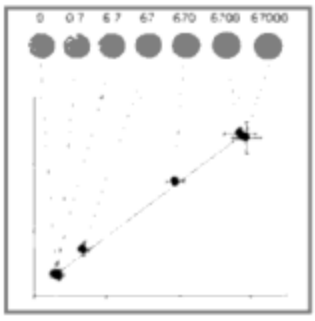



Figure 3

*POCKET Immunoassay:* The POCKET immunoassay "POCKET" is short for portable and cost-effective) is an integrated approach to a miniaturized immunoassay. It is inexpensive and operable with minimal equipment and technical skills, and shows an analytical performance approaching that of enzyme-linked immunosorbent assays

(ELISA).

The immunoassay (Figure 1) is performed in an inexpensive, miniaturized platform (made by soft lithography), in which the amplification chemistry is compatible with microfluidics and simple optics. The immunoassay functions with a portable and reusable detector was built from components costing less than $45 US and consists of an InGaAlP red semiconductor laser diode (654 nm) as the light source and an optical integrated circuit as the photodetector (Figure 2). The detector is powered using a single 9V battery and can be used outdoors in daylight without changes in background signal. Instead of enzyme-conjugated secondary antibodies in conventional ELISA, the system uses antibodies conjugated to 10 nm gold colloids; amplification of detection events is accomplished by electroless deposition of a silver film, whose opacity is a function of the concentration of the analyte (Figure 3). In sensitivity, limit of detection, and reproducibility, the POCKET immunoassay performs comparably to conventional ELISA, and within a factor of 10 of the most sensitive ELISA format - chemiluminescence (Figure 4). The POCKET immunoassay can also reliably distinguish the sera of HIV-1-infected patients from those of noninfected patients (Figure 5).

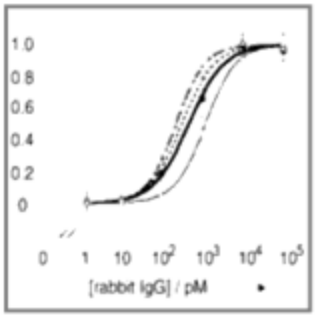



Figure 4

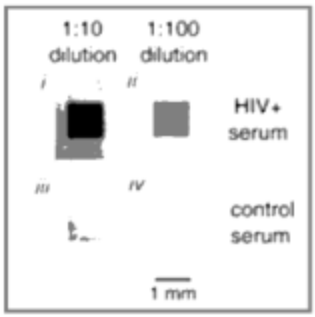



Figure 5

*Reagent-Loaded Cartridges:* Current techniques for automating fluid delivery in microfluidic devices, which include valves and electroosmosis, require sophisticated microfabrication of the chip, bulky instrumentation, or both. Reagent-loaded cartridges are a simple and reliable technique for storing and delivering a sequence of reagents to a microfluidic device (Figure 6). The technique is low-cost, requires minimal user intervention, and can be performed in resource-poor settings (e.g., outside of a laboratory) in the absence of electricity and computer-controlled equipment. In this method, cartridges made of commercially available tubing are filled by sequentially injecting plugs of reagents separated by air spacers (Figure 7). The air spacers prevent the reagents from mixing with each other during cartridge preparation, storage, and usage. As an example, we used this technology to complete an immunoassay with low-nanomolar sensitivity in a microchannel in 2 min; we demonstrated the diagnosis of HIV in 13 min.

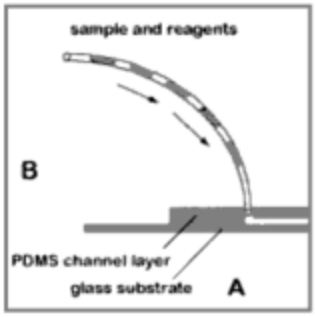



Figure 6

Figure 7

**Novel Energy Concepts**

Coal is a hugely abundant fuel source. We are exploring approaches to fuel cells in which powdered coal is the fuel.

We have developed a prototype coal fuel cell using a solution of sub-bituminous coal (SBC) partially oxidized by Fe-III (Figure 8). The rate of oxidation depended on the concentration of the iron and the surface area of the coal. At 100 deg C, the maximum current density in the cell was 5 A/L and the power density was 0.6 W/L. The cell operated without loss of performance for 1000 hours.

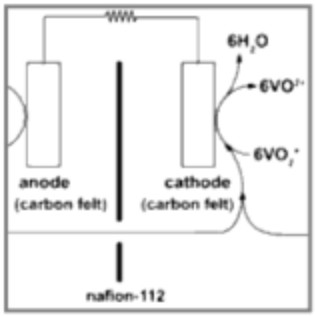


Figure 8

**Select Publications**

1. Sia, S.K. et al. "An Integrated Approach to Portable and Low-Cost Immunoassay for Resource-Poor Settings." Angew. Chem. Int. Ed. 43, 498-502 (2004).

2. Linder, V., Sia, S.K. and Whitesides, G.M. "Reagent-Loaded Cartridges for Valveless and Automated Fluid Delivery in Microfluidic Devices." Anal. Chem. 77, 64-71 (2005).

3. Weibel, D. B. et al "Modeling the Anodic Half-Cell of a Low-Temperature Coal Fuel Cell" Angew. Chem. 44 (35), 2005, 5682-5686.

The Whitesides Research Group

# Research

## Complexity and Emergence

We are exploring complex and emergent phenomena in several dynamically self-assembling systems. Systems that we have studied include disks spinning at liquid/liquid and liquid/air interfaces, metal beads rolling on polymer surfaces, and components moving autonomously on the surface of a hydrogen peroxide solution using bubble-based propulsion. Our recent work in this area focuses on systems in which bubbles and droplets in microfluidic networks are the primary components.

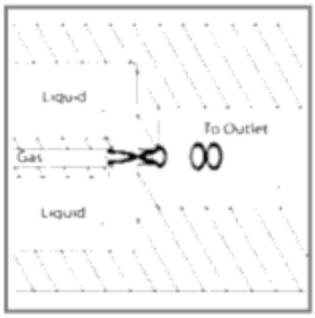



Figure 1

### Periodic and Chaotic Formation of Bubbles

We are exploring the formation of bubbles in a microfluidic flow-focusing device (Figure 1) in which the rate of flow of liquid and the pressure of gas are externally controllable. Over much of the flow rate/pressure phase space, the system produces monodisperse bubbles. We have shown that these bubbles can be used to generate flowing lattices and dynamically assembled foams (Figure 2). As one of the parameters is varied, however, the sizes of the bubbles produced become bi-disperse (Figure 3). Further variation of the parameter leads to periodic production of bubbles of four different sizes. The flow-focusing device can also be tuned to produce bubbles with a random size distribution. The system shows similar behavior to a dripping faucet, which also displays period-doubling bifurcations.

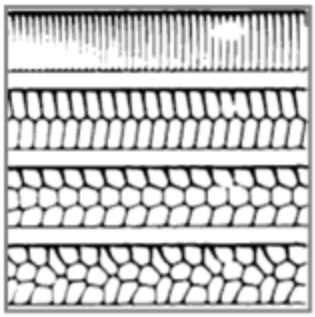


Figure 2

### Stable, Periodic Behavior in a Bubble-Making System

We have extended the flow-focusing device to include five inlets for liquid on either side of the gaseous thread. In a simple flow-focusing device, the gaseous thread advances into the orifice region where it is squeezed closed by the buildup of pressure in the liquid around it. In the five-inlet system, as the gaseous thread advances through the orifice region, it blocks the orifices sequentially, thereby increasing the rate of flow of liquid through the unblocked orifices. The advancing gaseous thread thus creates a mechanism of

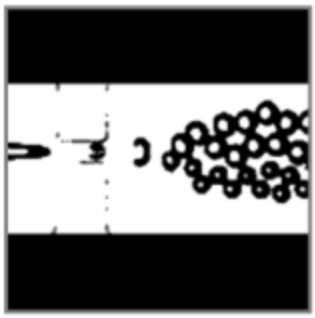
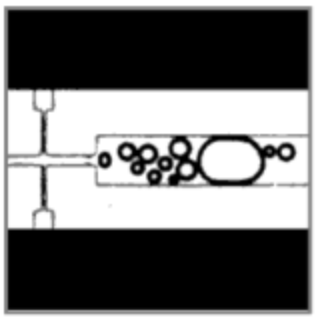


Figure 3

feedback in the system. Bubbles are squeezed off by the downstream orifices as the thread is slowly squeezed at the most upstream orifice, leading to the production of bursts of bubbles (Movie 4). By varying the pressure of gas in the system, for a constant rate of flow of liquid, we can tune the number of bubbles produced by the device in each burst from one up to 40 and back down to ~10. We observe highly stable periodic behavior over a range of pressures in which 29 bubbles are produced per period (Figure 5).



Movie 4

**Solving Mazes Using Bubbles in Microchannels**

Previously, we have shown that an advancing front of ink in a microfluidic network can elucidate the paths through the network. We are extending this research to incorporate bubbles that move in a continuous flow into the microchannels. The use of bubbles increases the potential utility of these systems as models for complicated networks, such as traffic patterns in a busy city.

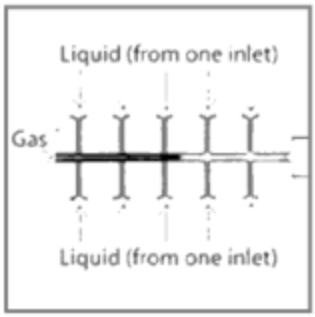



Figure 5

**Select Publications:**

1. Grzybowski, B. A., Stone, H. A. and Whitesides, G. M. Dynamics of self assembly of magnetized disks rotating at the liquid-air interface. Proceedings of the National Academy of Sciences of the United States of America 99, 4147-4151 (2002).

2. Garstecki, P., Gitlin, I., DiLuzio, W., Whitesides, G. M., Kumacheva E. and Stone, H. A. Formation of monodisperse bubbles in a microfluidic flow-focusing device. Applied Physics Letters 85, 2649-2651 (2004).

3. Wiles, J. A., Grzybowski, B. A., Winkleman, A. and Whitesides, G. M. A tool for studying contact electrification in systems comprising metals and insulating polymers. Analytical Chemistry 75, 4859-4867 (2003).

4. Fuerstman, M. J., Deschatelets, P., Kane, R., Schwartz, A., Kenis, P. J. A., Deutch, J. M. and Whitesides, G. M. Solving mazes using microfluidic networks. Langmuir 19, 4714-4722 (2003).

5. Grzybowski, B. A., Wiles, J. A., and Whitesides, G. M. Dynamic self assembly of rings of charged metallic spheres. Physical Review Letters 90, (2003).

6. Grzybowski, B. A. and Whitesides, G. M. Directed

dynamic self-assembly of objects rotating on two parallel fluid interfaces. Journal of Chemical Physics 116, 8571-8577 (2002).

7. Grzybowski, B. A. and Whitesides, G. M. Dynamic aggregation of chiral spinners. Science 296, 718-721 (2002).

The Whitesides Research Group

# Research

## Magnetics

The Whitesides group is pursuing several projects involving magnetism. In general we use magnetism as a handle for physical manipulation of objects that are too small to be easily manipulated directly (e.g. with tweezers or micromanipulators). Much of this work is in collaboration with Professors Donald Ingber (HMS) and Mara Prentiss (Physics).

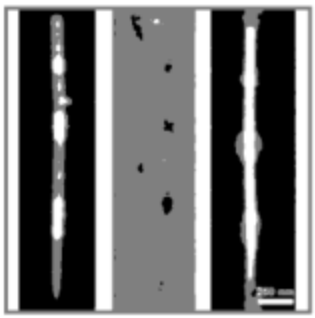


Figure 1

### Multifunctional Micro- and Nano-Rods

This project involves the fabrication of multifunctional anisotropic structures through electrodeposition inside porous templates. For example, we have demonstrated the synthesis of metallic rods with submicron diameters that contain disk-like ferromagnetic sections (Figure 1) [1]. The metallic sections of these nanorods can be easily functionalized using thiol chemistry, while the magnetic portions provide a handle for manipulation with external magnetic fields. These rods also self-assemble into highly stable, hexagonally close-packed arrays (Figure 2). This configuration minimizes the energy of the bundle and does not generate a net dipole for the structure. This work provides a simple demonstration that magnetic interactions between ferromagnetic objects can direct and stabilize the formation of ordered, 3D structures by self-assembly.


Figure 2

### Magnetic Spheres

We are currently developing methodologies for generating homogeneous ferromagnetic nanoparticles coated with a uniform thin layer of gold. Similar to the multifunctional rods, these core-shell structures could be easily modified with functional bio-molecules (e.g. proteins, DNAs, etc) and then manipulated with external magnetic fields. We are also exploring the synthesis and use of functionalizable metallic/magnetic spheres in the form of half-shells (Figure 3) [2]. We have demonstrated that it is possible to use spherical colloids (e.g. silica or polystyrene) as templates

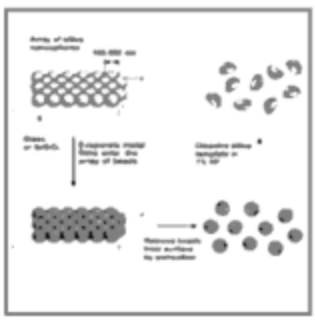


Figure 3

for vapor-phase metal deposition. In this case, we deposit colloids in a monolayer on a flat substrate and evaporate first a magnetic layer, then a metallic layer. The colloids can be either resuspended in solution to give half-coated spheres, or dissolved to give half-shells.

**Magnetic Separations**

We are actively examining the potential for using functional magnetic micro- and nano-structures in microfluidics [3,4]. One potential use for such structures is in microfluidic separations. We can use functional magnetic particles to bind to certain components of a mixture selectively. We can flow this mixture down a microfluidc channel with multiple outlets. Application of a magnetic field gradient across the channel can be used to direct the magnetic labeled components in the mixture into a specific outlet. The factors that determine the efficiency of this system include: strength of the magnetic field, magnetic susceptibility of the particles, viscosity of the liquid, and flow rate.

**Magnetic Traps**

This project involves the fabrication of three-dimensional magnetic traps for diamagnetic objects in an aqueous solution of paramagnetic ions [5]. We have demonstrated trapping of polystyrene spheres, and of various types of living cells: mouse fibroblast (NIH-3T3), yeast (Saccharomyces cerevisae), and algae (Chlamydomonas reinhardtii). The trapped particle and location of the magnetic trap can be translated in three dimensions by independent manipulation of the magnets that contribute to the overall magnetic field.

**Magnetic Tweezers**

We have recently begun a project to measure the rates of protein-ligand dissociation in a single-molecule format, using magnetic forces. We have been able to extrapolate to the rate constant for dissociation in the absence of an applied force and have obtained values that are in good agreement with rate constants from other techniques for a representative protein-ligand pair. We will extend this technique to protein-ligand complexes that exhibit complicated energy landscapes that cannot be followed adequately using ensemble averaging techniques and other interesting biological systems.

**Select Publications:**

1. Love, J. C. et al. "Three-Dimensional Self-Assembly of Metallic Rods with Sub-Micron Diameters Using Magnetic Interactions". Journal of the American Chemical Society 125, 12696-12697 (2003).

2. Love, J. C. et al. "Fabrication and Wetting Properties of Metallic Half-Shells with Sub-Micron Diameters. Nano Letters 2, 891-894 (2002).

3. Deng, T. Prentiss, M. and Whitesides, G. M. "Fabrication of magnetic microfiltration systems using soft lithography". Applied Physics Letters 80, 461-463 (2002).

4. Deng, T. et al. "Manipulation of magnetic microbeads in suspension using micromagnetic systems fabricated with soft lithography." Applied Physics Letters 78, 1775-1777 (2001).

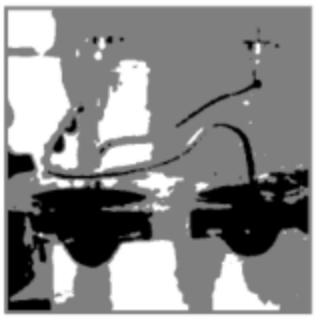
5. Winkleman, A., et al. "A magnetic trap for living cells suspended in a paramagnetic buffer". Applied Physics Letters 85, 2411-2413 (2004).

The Whitesides Research Group

# Research

## Electrets

Electrets are materials that contain permanent charges or permanently induced dipoles. They have a permanent electric field, just as permanent magnets have a permanent magnetic field. Electrets have been used for decades in audio and video equipment, telephones and microphones, photocopiers, printers, spray painters, and other technologies that depend on charged materials. We are examining the fundamental properties of electrets as materials. We use these materials for self-assembly and to understand the fundamental processes involved with producing (and preventing) charge on materials.



Movie 1

### Fluid Electrets

We are examining the mechanism of charging in pure protic and aprotic solvents. We systematically dope these solvents with various solutes; small changes in the concentration of these solutes affect the charging of the fluid as it flows through a capillary under an applied potential. It is easier to perform such a systematic study using fluids, rather than solids, because fluids can be doped in a readily well-controlled, quantitative manner. Understanding the mechanism of charging fluids is of fundamental importance for understanding electrochemical processes.

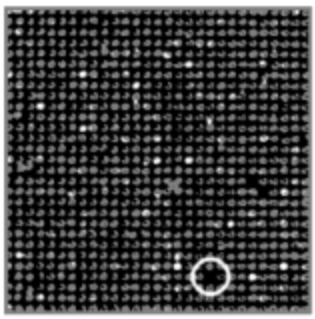


Figure 2

The motivation for this study originates from an attempt to understand the underlying mechanism for charging in a Kelvin electrostatic generator (Movie 1). In this movie, you can see the generator charge - dyed water droplets fly away from the collection (bottom) electrodes and coat the white backdrop - and discharge - the droplets fall straight into the collection electrodes.

### Self-Assembly of Microspheres

We have shown that glass microspheres self-assemble on a patterned electrode under the influence of an applied electric field (Figure 2). This process occurs for ordered arrays and

arbitrary patterns, over areas up to ~0.7 cm^2, with a defect rate (e.g., missing spheres, or extra spheres) of about 1%. These arrays of microspheres on the surface of the electrode can be transferred into polymeric matrices. This method employs reusable templates to guide components rapidly (less than 5 seconds) into ordered structures that cannot be made by traditional lithographic techniques.

**Select Publications**

1. Wiles, J. A., et al. "A Tool for Studying Contact Electrification in Systems Comprising Metals and Insulating Polymers." Analytical Chemistry 75, 4859-4867 (2003).

2. Grzybowski, B. A., et al. "Electrostatic Self-Assembly of Macroscopic Crystals using Contact Electrification." Nature Materials 2, 241-245 (2003).

The Whitesides Research Group

# Research

## Surface Science

### Microcontact Printing of Self-Assembled Monolayers

We are interested in organic surface science and its applications across science and technology. We have studied the conversion of alkanethiols into self-assembled monolayers (SAMs) on surfaces (Figure 1) and patterned SAMS for *microcontact printing*. In this technique, a PDMS stamp is constructed using soft-lithography. The stamp is then wetted with an alkanethiol and placed in contact with a gold (or other noble metal) for several seconds. SAMs form on the surface only in the areas that had been in contact with the stamp (Figure 2).

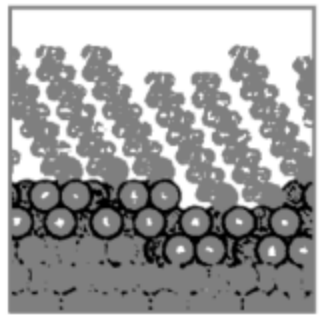


Figure 1

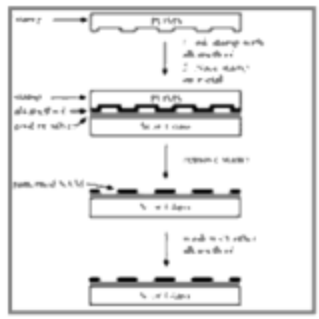


Figure 2

Microcontact printing of SAMs has a number of applications. By patterning one SAM with a hydrophobic terminus and then filling in the rest of the area with a SAM with a hydrophilic terminus, it is possible to create hydrophobic (or hydrophilic) patterns on surfaces with micron dimensions (Figures 3,4). Patterning specific areas with cell-friendly (protein terminated) and cell-unfriendly (polyethylene-glycol terminated) SAMs can be used to pattern endothelial cells on surfaces and to even force these cells to take on specific shapes (Figure 5).

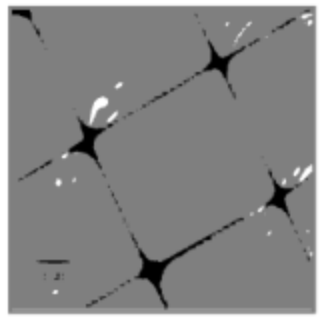


Figure 3

### Electrochemical Desorption of Self-Assembled Monolayers

We have also shown that alkanethiol SAMs can be released from surfaces when a small (less than 1 V) potential is applied across the surface; this process is called "electrochemical desorption" (Figure 6). In one application of electrochemical desorption, polyethylene-glycol terminated SAMs are pattered around islands protein-terminated SAMs. Applying the potential releases the polyethylene-glycol SAMs from the surface and allows the cells to spread out from confinement. This technique has allowed us to tune the inertness of surfaces in real time and to design cell motility assays (Movie 7).

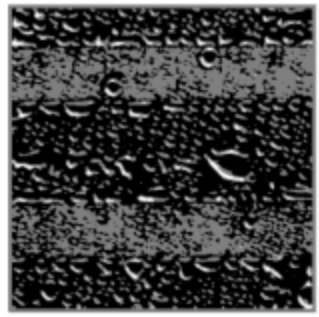


Figure 4

**Surface Analytical Techniques**

We also use a number of surface analytical techniques to characterize the surface coatings of PDMS and glass; such techniques include x-ray photoelectron spectroscopy (XPS), reflectance IR and ellipsometry. Controlling surface properties of these materials is important for biological applications. These properties are particularly important in the field of electrokinetic injections and separation, because they affect adsorption of proteins as well as surface charge, which determines the magnitude of electroosmotic flow (EOF). In turn, measurements of EOF allow us to infer the density of surface charge and its surface uniformity. Figure 8 shows an XPS signal describing the presence of nitrogen from polyacrylamide photopolymerized inside a sealed PDMS channel.

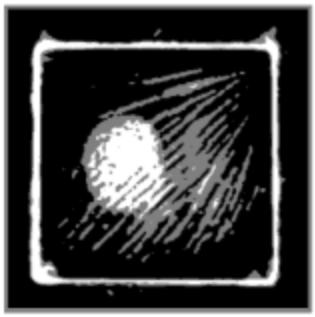


Figure 5

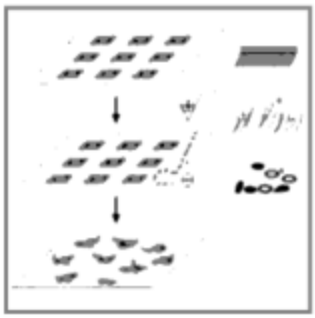
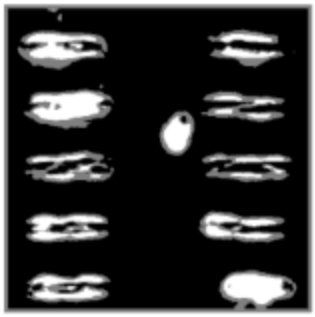


Figure 6



Movie 7

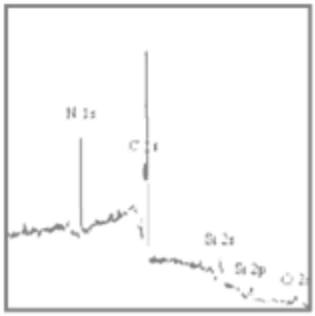


Figure 8

**Select Publications**

1. Laibinis, P. E. et al. "Orthogonal self-assembled monolayers: alkanethiols on gold and alkane carboxylic acids on alumina." Science (1989), 245(4920), 845-7.

2. Abbott, N. L., Folkers, J. P. and Whitesides, G. M. "Manipulation of the wettability of surfaces on the 0.1- to 1-micrometer scale through micromachining and molecular self-assembly." Science (1992), 257(5075), 1380-2.

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4. Wilbur, J. L. et al. "Microcontact printing of self-assembled monolayers: applications in microfabrication." Nanotechnology (1996), 7(4), 452-457.

5. Kane, R. S. et al. "Patterning proteins and cells using soft lithography." Biomaterials (1999), 20(23/24), 2363-2376.

6. Jiang, X. et al. "Electrochemical desorption of self-assembled monolayers noninvasively releases patterned cells from geometrical confinements." JACS (2003), 125, 2366-2367.

The Whitesides Research Group

# Research

## Self Assembly

In any living cell, nanoscale cellular machines spontaneously assemble themselves and drive the processes of life. Improvements in fabrication techniques are pushing the dimensions of electronic components to regimes beyond the reach of direct manipulation by human or machine. The functional self-assembly sub-group at the Whitesides Lab seeks to design self-assembling systems at a variety of scales, and to use these systems to form working devices that would be difficult (or practically impossible) to build with any other technique.

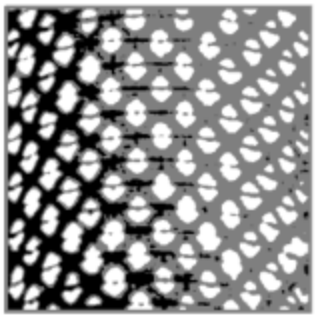

Figure 1

Self-assembly involves spontaneous organization of interacting components into an ordered aggregate or aggregates without direct human or mechanical interference. In the natural world, self-assembly occurs over a wide range of size-scales to create structures that display new properties not present in the original components. Self-assembly occurs both in systems at equilibrium - such as the crystallization of proteins or colloids - and in systems far from equilibrium - such as cellular replication of DNA. This work seeks to exploit the power of self-assembly to order small components into functional, three-dimensional structures in a parallel process.

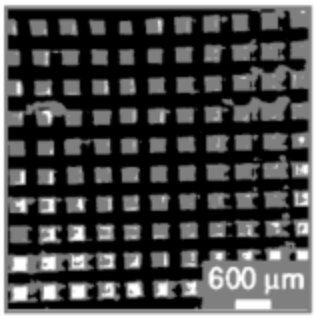


Figure 2

### Driving Forces

We have demonstrated the self-assembly of functional electronic devices with components as small as 100 microns on a side. Figure 1 describes a self-assembled GaAs display. Figure 2 describes 1560 silicon blocks self-assembled onto a flexible substrtate. To provide the interactions between components, our past work relied on the capillary interaction between menisci, drops of hydrophobic liquid, or pads of molten metal; more recent work has used electrostatic or magnetic interactions.

Figure 3

### Perfecting Self-Assembly

Two main problems complicate the design of self-assembling systems: *maximization of yield* and *fabrication of components.* To improve the yield of self-assembly, we have demonstrated templating of the self-assembly process. Templating can include constraining the aggregation in a container of a particular shape, and tethering the components together on a flexible ribbon or polymer sheet. The strategy of confining components to a flat sheet is particularly interesting to us, because we can use photolithography and other established methods to fabrication components in two-dimensions, and then allow the sheet to fold spontaneously by self-assembly into a functional three-dimensional shape. Once we have techniques to pattern components for function and self-assembly in parallel, it will be easy to decrease the size of the components even further. To date, most functional assemblies have been composed of either very simple components (e.g., silicon blocks) or relatively large ones (mm-scale). A "synthetic" approach to the fabrication of individual components will lead to greater understanding of the self-assembly process, and to smaller, better devices.

Figure 4


Figure 5

**Projects**

*Self-healing materials:* Wires and bonds made from low-melting conductive alloys can spontaneously heal upon heating. It is possible to fix devices based on self-healing materials from the outside, with no disassembly required. Figure 3 describes a self-healing "spine"; Figure 4 describes a composite of a flexible polymer and molten metal, tat spontaneously folds into a helix. We have also used these techniques to describe a functional 3D sphere folded from a sheet by magnetic forces (Figure 5).


Figure 6

*Folding tapes and sheets:* Capillary forces between patterns of molten metal (or other liquid with high surface free energy) lead to ordered folded structures. As with proteins, the primary structure of the precursor - that is, the sequence and spacing of "monomers" with various sizes, hydrophobicity, or other forms of patterning - determines the structure of the final product. Unlike the synthesis of proteins, we are free to begin with either linear chains or flat sheets of unfolded components.


Figure 7

*Passive electronic components:* Self-assembly offers a potential method for reducing the footprint of passive components (capacitors, inductors, and resistors) on microchips. In experiments we have shown that the same components can assemble into different devices when these components are placed in different containers.

*Plasticity and redundancy:* In these experiments, we show that designing components that self-assemble to different products under different macroscopic conditions, or components with redundant elements, will lead to reconfigurable devices. Specifically, Shape-complementarity can improve the yield of self-assembly (Figure 6)

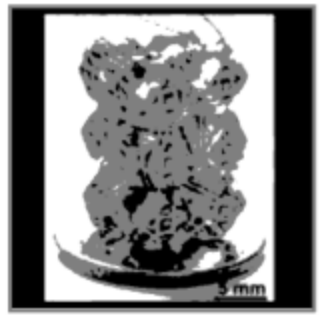

Figure 8

*Three-dimensional recognition:* Most photolithographic methods are optimized for the fabrication of two-dimensional patterns. Biological recognition depends on both chemical interactions and shape recognition. This work seeks to improve yield of self-assembly through improved design of high surface energy recognition patterns, and improved fabrication of three-dimensional components for shape-complementarity (Figure 7, Figure 8).

**Select Publications**

Boncheva, M. et al. "Magnetic Self-Assembly of Three-Dimensional Surfaces from Planar Sheets." PNAS 102, 3924-3929 (2005).

Boncheva, M., Bruzewicz, D. A. & Whitesides, G. M. "Millimeter-Scale Self-Assembly and Its Applications." Pure Appl. Chem. 75, 621-630 (2003).

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Boncheva, M. & Whitesides, G. M. "Self-healing systems having a design stimulated by the vertebrate spine." Angew. Chem. Int. Ed. 42, 2644-2751 (2003).

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The Whitesides Research Group

# Research

## Organic / Organometallic Electronics

We are interested in the electronic properties of organic and organometallic molecules, usually crystallized into self-assembled monolayers (SAMs). The simplest SAMs comprise alkanethiolates; more complex versions have a substituted end group at the non-binding end of the molecules. The electronic properties of a SAM are dependent on the metal substrate on which the SAM forms (Au, Ag, Cu, Pd, Pt, Hg), the head group that binds to the metal (commonly a thiolate), the chemical structure of the chain (alkane, aromatic), and the substituted end group (-COOH, -OH, -CN, etc).

Figure 1

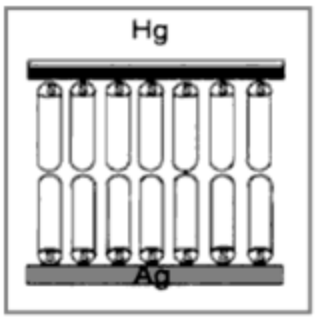



Figure 2

We study SAMs using a two-terminal junction, where one electrode is a mercury drop covered with a standard SAM (usually C12 alkanethiolate) and the other is a sample metal covered with one of a series of SAMs of interest (Figure 1). By using a series of related molecules, we can determine the ease of tunneling across a certain type of molecule (Figure 2). We are interested in understanding the features that will cause a molecule have an unusual current response, such as rectification or negative differential resistance, with the goal of being able to design systems with interesting electronic responses.

Related techniques in the field of organic electronics examine single molecules or molecules in self-assembled monolayers (SAMs) using break junctions, nanopores, conducting atomic force microscopy (cAFM), scanning tunneling microscopy (STM), and three-terminal junctions. The components of the systems vary widely, but there is widespread agreement on the ease of tunneling through a few key types of molecules. The understanding of these relatively simple systems paves the way for the field to broaden into more exploratory and novel systems. The mercury drop junction is an ideal tool for exploratory work due to its ease of use and quick sample preparation time.

**This site was designed by Adam Siegel, Paul Bracher and Demetri Moustakas** **Last Updated: March 10, 2008**

The Whitesides Research Group

# Research

## Proteomics and Protein Biophysics

We study general principles in proteomics and protein biophysics using carbonic anhydrase as our model protein. Our studies are directed towards understanding such issues as the role of surface charge in protein folding and surfactant denaturation, and the nature of enthalpy/entropy compensation in protein-ligand binding.

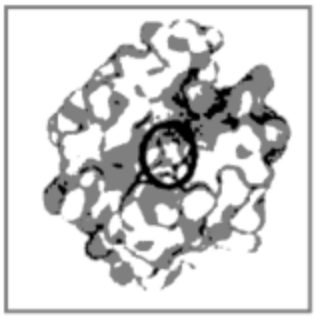


Figure 1

### Electrostatic Effects in Proteins

All proteins contain charged amino acids, both in the interior and on the surface, but the role(s) of these charges is not well described. We focus on the role surface charges, and study how the chemical modification of these residues affects the behavior of the protein. We have recently shown [1] that eliminating the 18 positive charges from the surface of carbonic anhydrase does not affect its folding characteristics. This highly-charge derivative of the protein is more stable to SDS, but less stable to heat, urea, and guanidinium, than is the native protein. We are currently using modeling and simulations to investigate the molecular details behind the reduced stability of the charged derivatives relative to the native protein.

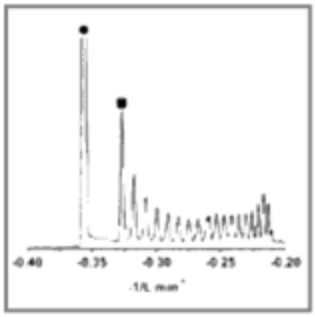



Figure 2

Our other approach to investigating the roles of charged residues on the surfaces of proteins is via protein charge ladders - derivatives of a protein with incremental changes in charge. We use capillary electrophoresis to separate mixtures of charged proteins into peaks of mixtures of regioisomers with equal charge. Using charge ladders, we can study the effects of charge on ligand binding,[2] proton binding, [3] and stability.

### Protein-Surfactant Interactions

SDS-PAGE is one of the most ubiquitous tools in proteomics and biochemistry, but the molecular mechanism of the interaction between SDS and proteins is incompletely understood. The relative importance of electrostatics and

hydrophobicity, the final structure(s) of the protein-SDS complex, and the reasons behind the fact that nearly all proteins bind SDS in the ratio of ~1 SDS molecule per 2 amino acids are not known. Our current focus is aimed at understanding importance of electrostatics and hydrophobicity of SDS binding to carbonic anhydrase - a model globular protein. We chemically modify the surface lysine residues of CA; each modification removes the charge from the lysine group and adds variable degree of hydrophobicity. We then study the behavior of denaturation of these derivatives in solutions of SDS. We find that removing the positive charge from the lysine groups makes the derivatives more stable to SDS up to some critical number of modifications; above the critical number each additional modification makes the derivatives less stable. Modifications with more hydrophobic groups render the protein less stable to SDS than less hydrophobic groups.

**Enthalpy / Entropy Compensation**

We have used the combination of carbonic anhydrase and benzenesulfonamides as a model system for understanding principles of drug design.[6-9] Our current interests are to use this well-characterized system to probe the nature of enthalpy/entropy compensation [10,11] in protein-ligand interactions, that is, the off-setting (often, perfectly) changes in binding enthalpy and entropy that accompany alterations in ligand structure. We are using a series of systematically varied sulfonamides and isothermal titration calorimetry for these studies.

**Select Publications**

1. Gudiksen et al "Eliminating Positively Charged Lysine-NH3+ Groups on the Surface of Carbonic Anhydrase Has No Significant Influence on Its Folding from Sodium Dodecyl Sulfate" J. Am. Chem. Soc., 127 (13), 4707 -4714, 2005.

2. Gitlin et al "Significance of Charge Regulation in the Analysis of Protein Charge Ladders" J. Phys. Chem. B, 107 (6), 1466 -1472, 2003.

The Whitesides Research Group

# Research

## Cell Biology

### Patterning Mammalian Cells

Soft lithography offers the ability to generate patterns and structures on the micron scale that are useful in examining cells. Using soft lithography, we have demonstrated the ability to control the molecular structure of surfaces, pattern the complex molecules relevant to biology, fabricate channels for the examination of cells, and pattern and manipulate cells. Poly(dimethylsiloxane) is a useful material for the study of cells because it is compatible with many cell types, it is optically transparent, and it is permeable to many gases.

Figure 1

Using microcontact printing, we form patterns of self-assembled monolayers (SAMs) on gold or palladium (SAMs). We can generate patterns of molecules that either promote or resist the binding of cells to the surface, which results in the patterning of cells to selected geometrical regions. We found that the adherent area available to cells determines the viability of cells. SAMs can be electrochemically desorbed from the gold surface, releasing cells from patterned regions. Using microcontact printing, we have recently created asymmetric, tear-drop-shaped patterned SAMs for cell adsorption. When cells adhere to these patterns, the cytoskeleton of the cells are polarized (Figure 1). When cells are electrochemically released from the surface, the initial polarization determines the direction of cell migration.

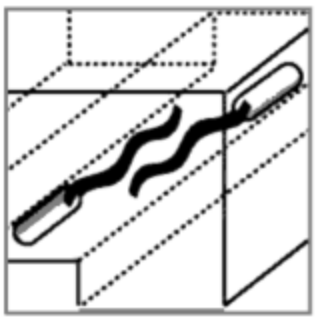


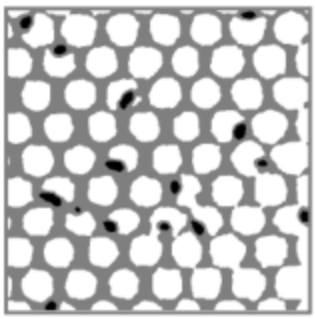
Figure 2

We have also patterned cells using elastomeric membranes fabricated using soft lithography. We have generated patterns and gradients within microfluidic channels and examined the behavior of cells to solution and surface gradient. We have partially treated cells in laminar flow to study the subcellular movement of microchondria and changes in cytoskeletal structure. Using a microfluidic gradient generator, we created substrate-bound gradients of laminin and found the neurons preferentially extended their axon towards increasing laminin concentration.

Movie 3

**Bacterial Swarming**

We are interested in using soft lithography techniques to study the behavior of microorganisms. Microchannels and microwells allow for the examination of single microorganisms in a chemically and mechanically controlled environment. We are interested in developing microdevices that utilize the motion of swimming microorganisms.



Movie 4

We have examined the behavior of *E. coli* swarmer cells in composite hydrogel/PDMS channels shown in Figure 2. We found that the agar surface affects the hydrodynamics of swimming cells more than the PDMS surfaces do. These different interactions bias the motion of cells in microchannels causing *E. coli* cells to "drive on the right" in rectangular microchannels. Movie 3 shows this traffic-like behavior of cells. This preferential movement could be used as a new strategy for directing cells in microdevices that would not require external pumping.

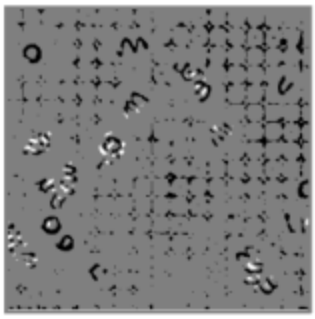


Figure 5

We have confined single bacterial cells in small, agarose microchambers, which allow for the continued growth of cells in a confined but nutritive environment. Movie 4 shows motile *E. coli* cells confined in these chambers. We have grown multinucleate, non-septate, filamentous cells in these microchambers (Figure 5). Filamentous cells still maintain the shape imposed by the chann□8el after their release. We have observed that even when molded into a long, spiral shapes, the cells are still capable of swimming. (Movie 6)

Movie 6

**Patterning Bacteria**

We have recently developed a technique for microcontact printing patterns of bacteria on growth media using topographically-patterned agarose stamps. This method produces patterns of multiple bacteria with feature sizes as small as 200 um over areas as large as 50 cm^2. Figure 7 shows different patterns of the luminescent bacteria, *Vibrio fischeri*, produced using this technique. Micropatterned agarose stamps inked once with bacteria can be used to create hundreds of replica patterns (Figure 8). The cells of bacteria thrive on the surface of agarose stamps containing media, making it possible to prepare stamps that "regenerate" their own ink. This technique can be used to pattern several different strains of bacteria using a single stamp (Figure 9). We are now using patterns of bacteria to explore organism-organism, organism-small molecule, and

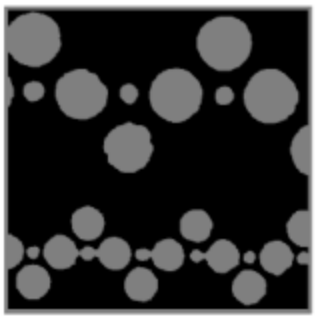


Figure 7

organism-surface interactions.

**"Microoxen"**

We have developed a conceptually new approach for harnessing the transduction of energy by microorganisms. We use the power produced by eukaryotic flagella in intact cells of the unicellular, photosynthetic algae *Chlamydomonas reinhardtii* to transport loads in microfluidic networks. These motile microorganisms -- which we refer to in this context as "microoxen" -- move microscale objects (1-3 um diameter beads) at velocities of ~100-200 um/sec and over distances as large as 20 cm. Cells carrying loads are steered using phototaxis (Movie 10). Controlling the surface chemistry of the loads allows us to attach them to cells; loads are detached from cells using photochemistry (Movie 11).

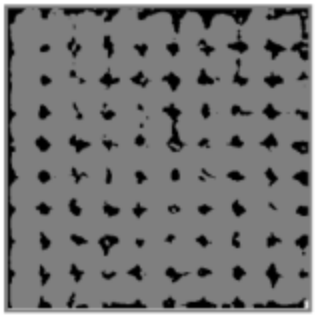


Figure 8

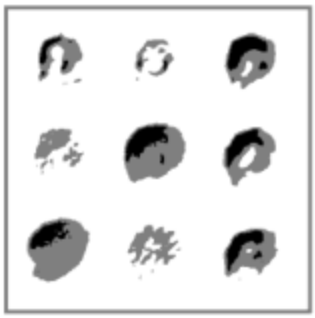
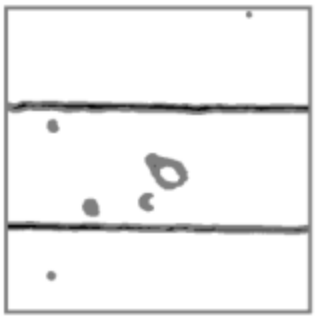
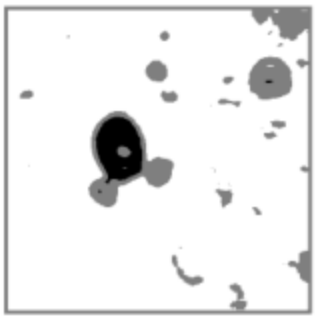


Figure 9



Movie 10



Movie 11

**Select Publications:**

1. Singhvi, R. et al. "Engineering cell shape and function". Science 264, 696-698 (1994).

2. Takayama, S. et al. "Patterning cells and their environments using multiple laminar fluid flows in capillary networks". PNAS 96, 5545-5548 (1999).

3. Ostuni, E. et al. "Patterning mammalian cells using elastomeric membranes". Langmuir 16, 7811-7819 (2000).

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5. Whitesides, G. M. et al "Soft lithography in biology and biochemistry." Annual Review of Biomedical Engineering 3, 335-373 (2001).

6. Dertinger, S. K. et al "Gradients of substrate-bound laminin orient axonal specification of neurons". PNAS 99, 12542-12547 (2002).

7. Takeuchi, S. et al. "Controlling the Shape of Filamentous Cells of Escherichia coli" Nano Letters; 2005; 5(9); 1819-1823.

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The Whitesides Research Group

# Research

## Polyvalency

Polyvalency is the simultaneous interaction of multiple ligands with multiple receptors (Figure 1). The objective of our research on this subject is to understand the characteristics of polyvalency in biochemical systems, and to use this understanding to develop new types of drugs, reagents, and procedures for use in medicine and biology.

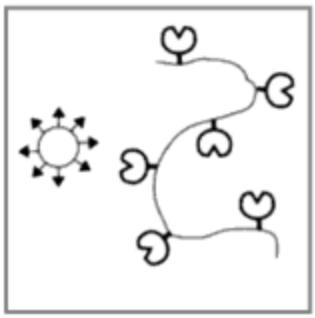

Figure 1

Much of biochemistry and medicinal chemistry has historically focused on the interaction of individual ligands (or substrates) with the active sites of individual proteins. It is, of course, widely understood that many important interactions in biology involve simultaneous interactions of multiple ligands and multiple receptors. Examples include antibodies interacting with ligands on the surfaces of viruses or virally infected cells, pathogens adhering to target cells, interaction of bacterial toxins with cell surfaces, assembly of the attack complex in complement activation, and the interaction of cell-surface receptors with hormones. If molecular recognition is the most fundamental molecular class of events in the cell, multivalent molecular recognition is the least understood part of this class. Our work in polyvalency is focused on three broad themes described below.

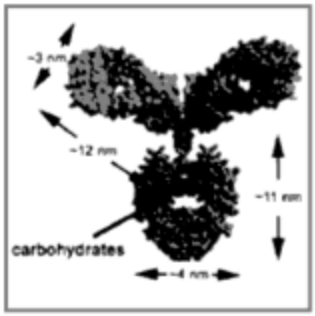


Figure 2

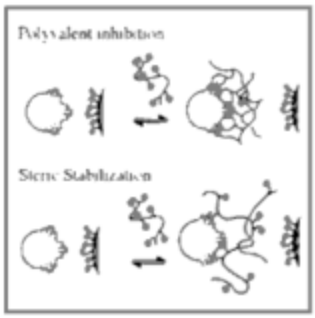


Figure 3

### Understanding and Using the Divalency of Antibodies

The first objective of this project is to understand why antibodies are (at minimum) divalent, how this divalency leads to enhanced avidity in binding, and how to use this understanding to manipulate them (Figure 2). The potential outcomes of the research are new methods of purifying antibodies, and optimizing antibodies for other uses. It may also provide improved methods of using antibody-based bioanalytical systems, and new approaches to modulating the activities of antibodies *in vivo.*

### Physics of Polymers Presenting Multiple Ligands

The second major focus of this research is the biophysics of polymers presenting multiple ligands and interacting with surfaces presenting multiple receptors (Figure 3). The emphasis in the work is on understanding the phenomena exhibited by polymeric polyvalency, and on using this understanding to test new concepts in managing bacterial and viral infectious disease.

**The Kinetic and Thermodynamic Basis for Polyvalency**

The third focus of the work is avidity - the affinity of polyvalent systems of receptors for polyvalent systems of ligands. Avidity in polyvalent systems is widely accepted to reflect some combination of the free energy of binding of individual ligands to individual binding sites, with an entropic advantage that comes with linking the ligands. The interplay of free energy, enthalpy, and entropy in these systems is not well understood. We will combine studies of relationships between structure and affinity in monovalent, divalent, oligovalent, and polyvalent systems with experimental measurements of relevant thermodynamic properties (especially using microcalorimetry), and theory (statistical mechanics and molecular mechanics); the objective of this work is to develop a *theory* of avidity. A useful theory will help us and others to design successful polyvalent systems, and will provide design rules that will help to apply an important emerging principle: that polyvalent presentation of a ligand, which is itself weakly bound as a monomer, can often lead to very strong biological effects. In this context, polyvalency can be a kind of amplifier of weak biological interactions.

The benefits of the work include: i) improved understanding of the mechanism of binding of antibodies; ii) the potential for modulating this binding, with the possibility for application in research and clinical immunology; iii) development of new approaches to management of infectious disease; iv) more efficient design of targeted ligands and drug leads, by improving understanding of polyvalency (broadly defined); v) new reagents and processes useful in research biochemistry and biology.

**Select Publications:**

1. Mammen, M., Choi, S. K. and Whitesides, G. M. "Polyvalent interactions in biological systems: Implications for design and use of multivalent ligands and inhibitors"; Angew. Chem., Int. Ed. Eng. 1998, 37, 2755.

2. Choi, S. K., Mammen, M., and Whitesides, G. M. "Generation and in situ evaluation of libraries of poly (acrylic acid) presenting sialosides as side chains as polyvalent inhibitors of influenza-mediated hemagglutination"; J. Am. Chem. Soc. 1997, 119, 4103.

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7. Qian, X. P. et al. "Measuring the inhibition of adhesion of lectins to the surface of erythrocytes with optically controlled collisions between microspheres and erythrocytes"; J. Phys. Chem. B 2002, 106, 9159.

8. Rao, J. H. and Whitesides, G. M. "Tight binding of a dimeric derivative of vancomycin with dimeric L-Lys-D-Ala-D-Ala"; J. Am. Chem. Soc. 1997, 119, 10286.

9. Rao, J. H. et al. "A trivalent system from vancomycin-D-Ala-D-Ala with higher affinity than avidin-biotin"; Science 1998, 280, 708.

10. Rao, J. H. et al. "Design, synthesis, and characterization of a high-affinity trivalent system derived from vancomycin and L-Lys-D-Ala-D-Ala"; J. Am. Chem. Soc. 2000, 122, 2698.

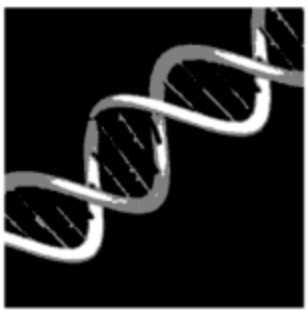
11. Yang, J. et al. "Self-assembled aggregates of IgGs as templates for the growth of clusters of gold nanoparticles"; Angew. Chem., Int. Ed. Eng. 2004, 43, 1555.

The Whitesides Research Group

# Research

## The Origin of Life

The Whitesides group is interested in fundamental questions related to the origin of life. What sources of free energy were available to drive the earliest proto-biochemical reactions? How was information first encoded? We believe that the prebiotic storage of energy and information are two of the most fascinating mysteries in science.




### Prebiotic Energetics

We are interested in exploring plausible mechanisms for the conversion and storage of free energy that were essential for the chemical origins of life. The ubiquity of concentration gradients in biology - for example, the intra- and extracellular concentration of potassium and sodium - represents one possible reservoir of free energy. How did these gradients arise and how can they be harnessed to power the machinery of life?

Phosphoanhydride bonds, such as those found in ATP and inorganic polyphosphate, are the energetic currency of modern biology. We, and others, believe that the accumulation of phosphoanhydride bonds was an important step that probably occurred early in the development of chemical systems for storing energy. The formation of polyphosphates from salts of inorganic phosphate and organic compounds - such as those that were likely to have been present on the early earth - represents a "simple" route to molecules capable of storing free energy.

### Prebiotic Mechanisms for Storing Information

Our interest in phosphates extends beyond energy, and includes chemical systems for storing information. We share a working hypothesis with others that DNA was probably not among the first molecules used in nature to store information. In this area, we are synthesizing and studying the chemistry of organophosphate polymers that may have preceded DNA.

The Whitesides Research Group

# Research

## Funding

The Whitesides Group receives funding from a variety of sources. This list includes current research grants awarded by public agencies:

**DOE DE-FG02-OOER45852**
"Dynamic Self-Assembly, Emergence and Complexity"

**NSF CHE-0518055**
"Micron-to-Millimeter-Scale Self Assembly"

**DARPA/ARO W911NF-07-0626**
"Study to Determine Targets for Development of Technology Using Fluidic Optics"

**DARPA/ARO W911NF-07-0647**
"Chemical Communications"

**DARPA/ARO W911NF-08-1-0040**
"Evolvable Matter"

**DARPA/ARO W911NF-08-1-0143**
"Programmable Matter"

**DARPA/ARO W911NF-04-1-0170**
"Design and Processing of Electret Structures"

**DARPA/ARO W911NF-07-1-0276**
"A High-Pressure Liquid Chromatography System for Synthetic and Biophysical Studies"

**NIH R01 GM051559**
"Capillary Electrophoresis and Protein Biophysics"

**NIH R01 GM30367**
"Multivalency: Mechanisms and Applications"

**NIH R01 ES016665**
"Nano-Scale Tools for Use in Cell Biology"

**Caltech/DARPA HR0011-04-1-0032**

"Center for Optofluidic Integration"

**Caltech/DARPA HR0011-04-1-0032**
"Optical Detection in Paper-Based Fluidic Systems"

**Caltech/DARPA HR0011-04-1-0032**
"Optofluidic Devices for Sensors Technology"

**Vertex Pharmaceuticals**
"3D Mammalian Cell Culture in Microstructured Collagen Gels"

**U.C.-Irvine/DARPA 5226551-01**
"Micro/Nano Fluidics Fundamentals Focus Center"