MEMS / Nanotechnology Integration for Bio-Medical Applications

Klaus Schadow
Schadow Technology
2896 Calle Heraldo
San Clemente, CA 92673

E-mail: schadowkc@cox.net

The integration of MEMS and nanotechnologies has resulted in new capabilities for environmental monitoring and bio-nano sciences. The capabilities are enabled through a new type class of gas sensors and novel techniques for identifying and manipulating biological cells. After a brief introduction into micromachining, the lecture will discuss three examples each of (1) a new generation of gas sensors with higher sensitivity, lighter weight, and lower power consumption, (2) ultra-sensitive molecular detection and characterization devices, and (3) manipulation techniques for singles cells.

1. Gas Sensors

The first sensor example is the use of nanoparticles for conventional tin-oxide gas sensors (Ref. 1). To improve the long-term stability of gas sensors, MicroChemical Systems (MiCS) is manufacturing silicon micromachined gas sensors that combine silicon microstructures with nanomaterials. MiCS deposits precise amounts of nanoparticle metal oxide material as the sensitive layer on a micro-hotplate. Due to the very small grain size, such sensors have high stability and sensitivity. Key elements of the sensor include a sensitive metal oxide layer whose resistance/conductivity changes upon exposure to the gas of interest, a heater that keeps the sensitive layer at a specific temperature, and a thin dielectric membrane with low power consumption. These novel sensors avoid drawbacks of conventional tin/metal oxide semiconductor gas sensors that include compromised selectivity and long-term drift, and temperature/humidity dependence.

In the second example, Forschungszentrum Karlsruhe (Ref. 2) has developed a compact electronic nose (KAMINA – KArlsruhe MIcroNOse) based on a highly integrated gradient microarray chip. All segments respond to nearly all gases (except rare gases or nitrogen) with a gradually different sensitivity, even at concentration of less than 1 ppm. The heart of the KAMINA device is a chip consisting of several gradually different gas sensors. The chip carries only one single metal oxide film (tin dioxide or tungsten trioxide) with its electric conductivity at higher temperatures (about 300C for tin oxide) sensitively and reversibly depending on the composition of the ambient gas. The chip is fabricated by partitioning the oxide film with parallel electrode strips, to form an array of individual gas sensor segments. These segments differentiate their sensitivity spectrum by both varying temperature (through individual heating elements) and varying thickness (between 2 and 20 nm) of a gas permeable membrane coating on the oxide layer. The electronic nose can be trained for a variety of applications, to identify chemical

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fingerprints of processes by detecting a wide range of gases, such as CO, NO_2, NH_3, H_2S, organic gases, other.

In the third gas sensor example, single walled carbon nanotubes (SWNTs) and metal oxides nanobelts or nanowires are used by NASA Ames on a pair of micromachined interdigitated electrodes (IDE) (Ref. 3). The nanotube based sensing material changes its conductivity with exposure to a variety of organic and inorganic gases & vapors. Great selectivity can be achieved by loading the nanotubes with catalytic metal, nano clusters and coating polymers. The electronic molecular sensing of the nanotubes can be understood by electronic modulation of the nanostructured devices and analytes in terms of charge transfer mechanism. Carbon nanotube-based chemical sensors have the following properties and advantages compared to current systems: (1) high sensitivity with potentially single molecule sensitivity due to large surface to volume ratio (SWNTs have all the atoms on the surface that are exposed to the environment), (2) fast response due to the one-dimensional quantum wire nature that makes its electronic properties very sensitive to gas absorption, (3) lower power consumption (at least 100 times less than current systems), because of a low surface energy barrier and a much lower operation temperature of around 150C compared to 500C for conventional metal oxide sensors, and (4) high thermal and mechanical stability because of a single crystalline structure and well organized molecular structure. NASA Ames is currently developing a sensor module that has a sensor chip containing 32 sensing channels using different nanostructurered materials, a complete electronic system for sensing signal acquisition, and a pneumatic pathway for gas sample delivery.

2. Molecular Detection and Identification

The use of MEMS technology for exploring the bio-nano space has resulted in ultra-sensitive molecular detection at much reduced weight and footprint for health monitoring (and also bio warfare agent surveillance). As examples, two devices, developed at the Institute for Cell Mimetic Space Exploration (CMISE)/UCLA, and a third device, a miniaturized gas chromatograph, developed at CALTECH, will be discussed.

The UCLA devices are used for DNA detection (Ref. 4). If a known probe-DNA merges with an unknown target-DNA (hybridization process), both DNA chains have complementary shapes and characteristics. If two similar DNA strains do not merge, the target DNA may have a mutation defect (for example one single misplaced “letter” in the DNA intertwined chains). The goal of the emerging detection devices is to detect mutation down to one base pairing (from 3 billion bases in the human genome), since a single misplaced letter is sufficient to cause disease. Different hybridization detection techniques are possible with pairing of the probe-DNA (tagged with signal enzymes) and the target-DNA producing fluorescence, electrons, or radioactivity.

The first detection example for exploring the bio-nano space with MEMS is the electrokinetic molecular focusing technique, that significantly enhances the detection efficiency for confocal laser induced fluorescence (LIF) based molecular sensing (Ref. 5). In this technique the probe-DNA is tagged on one end with a fluorophore and on the other end with a quencher. When hybridization between the probe-DNA and target-DNA

occurs, fluorescence is produced and photons for optical sensing are generated by LIF. For efficient detection electrodes in a micro channel concentrate fluorescence labeled molecules in a tiny probe region. The generated electric field is able to focus flowing DNA molecules to a width as narrow as 3 microns in a 120 microns wide channel with a probe volume of only 28 femto liter. The electrodes were designed to produce electric field towards the probing region by applying the proper potential between two side electrodes and a middle electrode. Before molecules pass through the LIF probe region, they are concentrated towards the middle electrode for detection by the applied electric field. Since the molecules are precisely focused to the downstream end of the middle electrode, which is designed as the focal region of the LIF, more individually passing molecules can be sensed. This new technique reaches one molecule and one base pair mutation level.

The second example is an enzyme based electrochemical biosensor for rapid detection of DNA (Ref. 6). This sensor combines the hybridization event with a signal enzyme, which activates chemical reaction. Generated electrons are transferred to an electrode and measured. A reusable DNA sensor array has been fabricated on a silicon chip. A micro-fabricated reaction well for the working electrodes (Gold) contains the drop of the solution to be investigated. Hybridization occurs and a signal is detected, when the probe-DNA, which is anchored to the electrode, is connected to the target-DNA with the enzyme. The DNA detection device is microfabricated on a MEMS lab-on-a-chip, with cell lysis, peristaltic pump, and micro valve. The output of the sensor is current proportional to the number of target cells in the solution. Because the DNA-based probes target the DNA sequence of the analyte instead of indirect probing using antibodies, it is not necessary to make copies of DNA for analysis and the entire protocol with solution preparation and enzymatic reaction is completed in 40 minutes. The device is also used for detection of bacteria, virus, or biological species. Down to 1000 E.coli bacteria cells can be detected using this sensor array.

The third example is a High Pressure Liquid Chromatograph (HPLC)-on-a-chip (Ref. 7). All the essential micro-fluidics and ESI components are from the same material and fabricated on a single chip to minimize dead volume. The separation of the gaseous components is achieved through surface characteristics in micro-channels. The chip performance is as good as commercial system.

3. Single Cell Manipulation

The ability to manipulate biological cells plays an important role in many biological and colloidal science applications. The presentation describes three techniques based on the use of electrokinetic forces, namely electrowetting, electroosmosis, and optical image driven dielectrophoresis, as examples of MEMS enabled bio-nano techniques (Ref. 8).

With electrowetting techniques fluidic operations are performed in droplet based digital fluidic circuits, instead of driving the bulk fluid inside microchannels or electrokinetic pumps. Among several mechanisms electrowetting on dielectric (EWOD) has been studied most extensively due to the low power consumption, high reversibility,

and wide applicability to different fluids (Ref. 9). EWOD enables the manipulation of liquid by electrically controlling surface wettibility, manifested by the contact angle between the liquid and a dielectric surface coating, which is used to cover the electrodes. The change in contact angles with applied voltage depends on surface tension at the liquid-vapor interface and the permittivity & thickness of the insulating dielectric layer. By applying an electric voltage asymmetrically between the two ends of a droplet inside the hydrophobically coated microchannel, corresponding asymmetric changes in contact angles induce the necessary pressure difference to move droplets. By energizing the driving electrodes embedded under the dielectric layers selectively, the droplet can be manipulated as programmed by the user. The droplet operations can be done on a single chip. It is envisioned that an entire biological analysis can be performed in these digital circuits.

Electroosmosis can occur due to the formation of an electric double layer at charged surfaces (Ref. 8). The double layer is formed by an electric potential, which causes charges to accumulate on the surface and results in changes of the charge density near surface. The electrical double layer interacts with the tangential component of the electric field, generates a net force, and causes fluid movement. When using an alternating electric field (ac electroosmosis), the sign of charges in the electrical double layer changes with the applied electric field and the tangential component. Therefore, the direction of the driving force for the fluid remains the same in alternative electric potential.

Optical image-driven dielectrophoresis technique permits high-resolution pattering of electric fields on a photoconductive surface for manipulating single particles (Ref. 10). This technique, which requires 100,000 times less optical intensity than conventional optical tweezers, has demonstrated parallel manipulation of 15,000 particles trapped on a 1.3 x 1.0 mm2 area. Two application examples are described, namely an integrated virtual machine and the selective collection of live and dead cells. The optoelectronic tweezers (OET) utilize direct optical images to create high-resolution dielectrophoresis (DEP) electrodes for parallel manipulation of single particles. The DEP force results from interaction of the induced dipoles in the particles subjected to a non-uniform electric field. The magnitude of the force depends on the electric field gradient and the polarizability of the particle, which is dependent on the dielectric properties of the particle and the surrounding medium. In the MEMS OET structure the liquid containing the cells of interest is sandwiched between an upper transparent, conductive glass and a lower photoconductive multi-layer glass. These two surfaces are biased with an a.c. signal. When projected light illuminates the photo-conductive layer, it turns into virtual electrodes, creating non-uniform electric fields and enabling particle manipulation via DEP forces. Particle can be attracted by or repelled from the illuminated areas, depending on the a.c. electric field frequency and the particle’s internal and surface forces. Using direct imaging, sophisticated virtual electrodes can be easily patterned and reconfigured to create dynamic electric field distribution for continuous particle manipulation without assistance of the fluidic flow. Using an optical manipulator that combines functions of optical conveyors, sorters, wedges, and joints, particles can be transported through different functional areas in a light-patterned circuit. By exploiting the dielectric differences between different particles or cells, DEP techniques have been

able to discriminate and sort biological cells that have different in membrane properties, internal conductivity, and size. With OET a selective concentration of live human cells from a mixture of live and dead cells was demonstrated. Live cells experience positive OET and are attracted to the illuminated regions, while dead cells experience negative OET and are not collected.

Many applications of electrokinetic manipulations in microdevices are being considered, including fluid delivery, cell positioning, mixing, separation, and concentration of biomolecules. Direct manipulating molecules and cells has provided a link to study the complex biological systems micro to nano scale and new potential for bio-nano sciences research (Ref. 8).

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