

MEMS FOR CELLULAR FORCE MEASUREMENTS AND MOLECULAR DETECTION

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MEMS technology and devices have proven their importance in facilitating single cell studies by providing quantitative information on cellular and sub-cellular levels. This paper reviews existing techniques for cellular and sub-cellular force measurement and molecular detection using MEMS-based devices. Literature on these techniques and sample devices is reviewed. The significance and limitations of various approaches are analyzed.

Keywords: MEMS; molecular biology; cell membrane forces; bio-agent detection.

1. Introduction

The ability to analyze individual cells rather than averaged properties over a population is a major step toward understanding the fundamental elements of biological systems. Studies on individual cells are a key component in the development of highly selective cell-based sensors, the identification of genes, and the bacterial synthesis of specific DNA. MicroElectroMechanical systems (MEMS) devices can play important roles in facilitating single cell studies because they can provide not only qualitative, but also quantitative information in the cellular and sub-cellular level. To illustrate the importance of microsensor measurements in cell studies,

intracytoplasmic injection (cell injection) can be taken as an example. Intracytoplasmic injection, shown in Fig. 1, is a method for introducing foreign genetic materials into cells. In Fig. 1, a holding pipette holds a cell and an injection pipette performs the injection task. A successful cell injection operation depends on the control of force and speed of the injection pipette [Sun & Nelson, 2002]. Quantitative force measurements are needed for improved success rates. However, few quantitative measurements of cell membrane forces are available due to the difficulties in developing sensors for this scale.

As in cell injections, but not limited to this application, accurate measurement of forces is

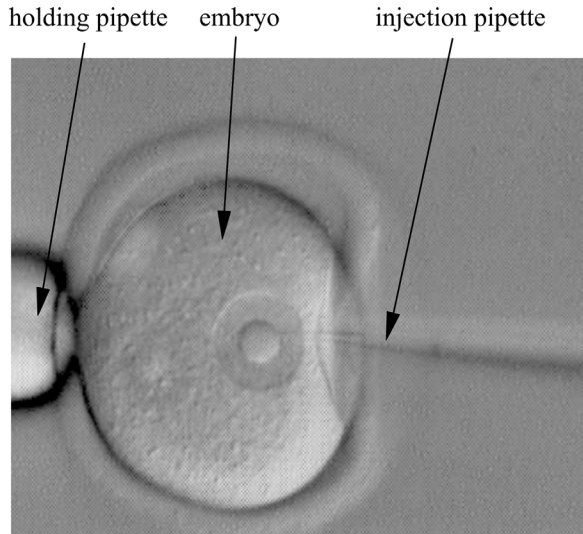


Fig. 1. Cell injection of a mouse embryo.

fundamental in many biological research and applications. Investigations into the functions and behaviors of various biological structures often require that the biomembranes isolating these structures from their immediate surroundings are characterized, in which precise cellular force measurements must be obtained. The forces in the cellular and sub-cellular level are on the scale of pN and μ N [Charras *et al.*, 2001; Needham & Nunn, 1990]. Conventional cellular force measurement techniques include laser traps [Conia *et al.*, 1997; Wright *et al.*, 1990] and ultra fine glass needles [Ishijima *et al.*, 1996; Kishino & Yanagada, 1988]. In laser trapping the high dissipation of visible light in aqueous solutions requires the use of high energy light close to the UV spectrum, raising the possibility of damage to the cell and inducing abnormalities in the cell's genetic material, though some researchers claim that such concerns could be overcome by using wavelengths in the near infrared (IR) spectrum [Conia *et al.*, 1997; Ponelies *et al.*, 1994]. The glass needle technique also has major limitations. Firstly, force measurements using glass needles are not consistent enough to make reliable one-time measurements. In order to have reliable data, multiple measurements should be taken and averaged. This is more time consuming and requires data analysis. Secondly, each needle must be

calibrated individually because of large manufacturing variations. Because of these limitations in conventional techniques, researchers of single cell studies are turning to MEMS transducers.

This paper reviews existing cellular force measurement techniques and recent development. Besides the application in cellular force measurements, MEMS-based transducers have also been recently developed and widely applied to biological agent detection at the molecular level, which is another focus of this paper. Example MEMS devices are used to illustrate individual measurement mechanisms. According to various definitions of biosensors [Fraser, 1994; Guilbault & Luong, 1989; Higson, 1994; Judy, 2000; Kovacs, 1998], some of these devices discussed in this paper can be categorized as biosensors. This paper, however, is not meant to be a thorough survey on biosensors or provide detailed fundamental microfabrication processes including biosensor fabrication issues that have been discussed extensively in [Fauver *et al.*, 1998; Hierlemann *et al.*, 2003; Kovacs, 1998; Madou, 1997; Sze, 2002].

2. Cantilever — A Versatile Structure for Biological Measurements and Detection

2.1. Cellular force measurements with cantilevers

Cantilevers are the most frequently implemented MEMS devices. The main sensing mechanisms used with cantilevers are optical, piezoresistive, and piezoelectric methods. Table 1 summarizes the main characteristics of each mechanism.

Cantilever-based optical force sensors and piezoresistive force sensors have been reported for cellular force measurements [Charras *et al.*, 2001; Fauver *et al.*, 1998; Guilbault & Luong, 1989; Lin *et al.*, 1995, 2000]. Cantilever-based optical force measurement often uses atomic force microscopy (AFM) techniques. Figure 2 illustrates the typical AFM's optical deflection setup. The displacement of the cantilever is amplified and sensed by the photo diode. Force is then calculated by multiplying the optically sensed displacement by the cantilever

Table 1. Comparison of optical, piezoresistive, and piezoelectric cantilevers for microforce measurement.

Method	Optical	Piezoresistive	Piezoelectric
force nature	dynamic and static	dynamic and static	dynamic
typical resolution	easily reach 10^{-12} N	can reach 10^{-9} N, careful circuit design required	can reach 10^{-9} N, careful circuit design required
measurement range	small	medium	large
temperature sensitivity	low	high, can be compensated	high, difficult to compensate
intrinsic noise	mechanical, vibration, laser point stability, shot noise	Johnson noise (1/f noise), thermal noise	thermal noise, transmission noise
multi-axis measurement	complex setup required	possible	difficult
adjustment requirement	high	low	low
signal conditioning	medium, position sensitive	high	high
instrument requirement	detector		
integration potential	poor	good	medium

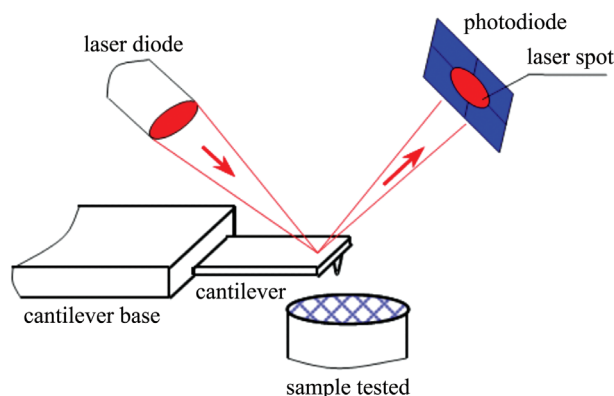


Fig. 2. Optical cantilever deflection AFM setup.

spring constant. An error analysis demonstrated that the major noise sources include mechanical vibration, laser pointing stability and shot noise for modulation frequencies beyond 10 kHz [Meyer & Amer, 1988]. The system is ultra sensitive and higher resolution can be achieved by using cantilevers with lower stiffness.

There are three limitations restricting AFM use in cellular force measurement. First, a major requirement in AFM measurement is that a complex transmit-receive setup is required. This setup places a high demand on optical alignment and adjustment. The surface of the cantilever must also be sufficiently reflective to achieve high accuracy. Second, an important system limitation is that for commercially available systems the photodiode can only detect a small range of deflection. This constrains the force measurement range. Third, when an AFM is

used in aqueous medium where biological cells survive, the reflection and refraction of the transmitted light make the accuracy of cellular force measurements problematic. These limitations must be considered in the application of AFM to cellular force measurements.

2.2. Resonant cantilevers for biological agent detection

Cantilever array sensors belong to the resonant sensor family. The basic mechanism employs a sensitive molecule attached to the surface of a resonating cantilever. The subsequent binding of analyte molecules adds mass and causes a shift in the resonant frequency. Bacteria detection has been reported using such a cantilever array sensor [Illic *et al.*, 2000], where the array of cantilevers was coated individually with a distinct antibody or a selective surface, which enables the device to detect multiple molecules simultaneously within minutes. Figure 3(a) shows a cantilever array sensor developed by IBM Zurich. Figure 3(b) illustrates the selective binding of a molecule to the cantilever surface. These cantilever array sensors have been demonstrated to be capable of detecting proteins [Arntz *et al.*, 2003].

3. Capacitive Cellular Force Sensors

Even though widely used, almost all existing cantilever-based cellular force sensors are only

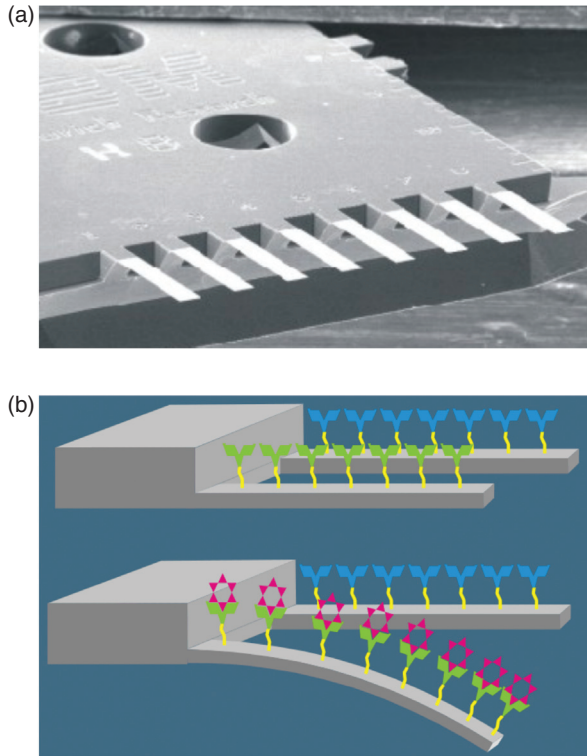


Fig. 3. (a) IBM cantilever array sensor. (b) Selective binding of a molecule to cantilever surface.

capable of measuring forces perpendicular to the sensor plane. To provide multi-axis force information and avoid the limitations of atomic force microscopy, a multi-axis capacitive cellular force sensor has been developed [Sun *et al.*, 2002].

The MEMS-based two-axis cellular force sensor shown in Fig. 4 is capable of resolving normal forces applied to a cell as well as tangential forces generated by improperly aligned cell probes. A high-yield microfabrication process

was developed to form the 3-D high aspect ratio structure by using Deep Reactive Ion Etching (DRIE) on Silicon-On-Insulator (SOI) wafers. As shown in Fig. 4, the constrained outer frame and the inner movable structure are connected by four curved springs. A load applied on the probe causes the inner structure to move, changing the gap between each pair of interdigitated comb capacitors. Consequently, the total capacitance change resolves the applied force. The interdigitated capacitors are orthogonally configured to make the force sensor capable of resolving forces in both the x and y directions. The two-axis cellular force sensors are capable of resolving forces up to $490\ \mu\text{N}$ with a resolution of $0.01\ \mu\text{N}$ in x , and up to $900\ \mu\text{N}$ with a resolution of $0.24\ \mu\text{N}$ in y .

By integrating these cellular microforce sensors into a microrobotic system, biomembrane mechanical property characterization was conducted on mouse zona pellucida (ZP) [Sun *et al.*, 2003]. ZP is composed of proteins called ZP1, ZP2, and ZP3, which is different from more common biomembranes of a lipid-protein structure. Upon fertilization, the ZP surrounding the oocyte undergoes a “hardening” process in order to prevent subsequent sperm from penetrating. The experimental results quantitatively describe the mechanical property changes during the ZP hardening process. Besides being a first in molecular biology, this research also provided insight into ZP protein structure development, justifying that an increase in the number of cross links of protein ZP1 between ZP2-ZP3

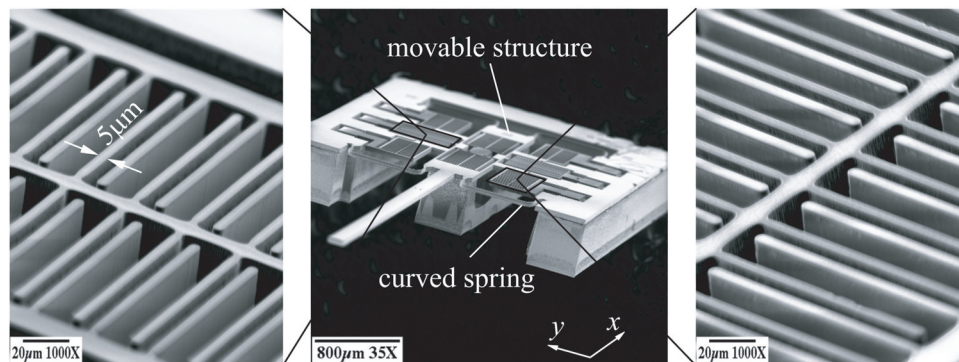


Fig. 4. SEM of a two-axis capacitive cellular force sensor.

units is responsible for ZP stiffness increase [Sun *et al.*, 2004].

To resolve pN forces on biomembranes of a lipid-protein structure, such as cytoplasm membranes, the sensitivity of these capacitive sensors needs to be further improved. The nonlinearity drawback can be overcome by adopting a trivial comb drive configuration such as the one described in [Sun *et al.*, 2004].

4. Magnetic Bead Assisted Cellular Force Measurements

Cell responses to mechanical forces are different according to which receptor is being stressed. Using the magnetic bead force application (MBFA) technique, controlled mechanical forces can be applied to specific cell surface receptors using ligand-coated microfabricated ferromagnetic beads. As shown in Fig. 5, a cell surface-attached magnetic bead is subjected to a high gradient magnetic field generated by the sharpened pole piece of an electromagnet. By controlling the current passing through the electromagnet, the magnetic bead is capable of accurately applying a specified force in the pN scale to specific cell receptors of the cell so that the resulting behavior can be observed. This technique has been applied to mechanical property studies of cells [Alenghat *et al.*, 2000] and lipid vesicles [Heinrich & Waugh, 1996] and neuron studies [Fass & Odde, 2003].

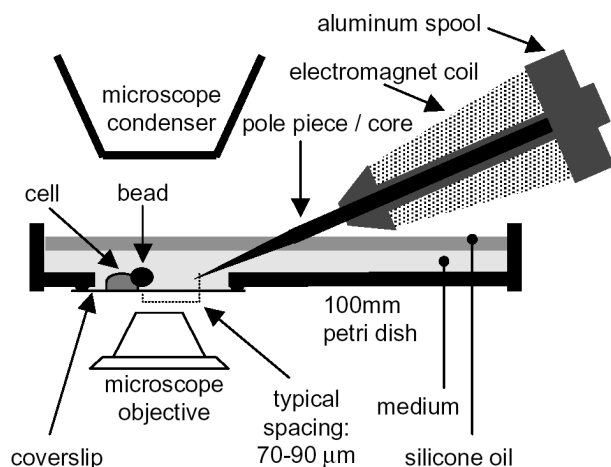


Fig. 5. Magnetic bead force measurement setup (from [Fass & Odde, 2003]).

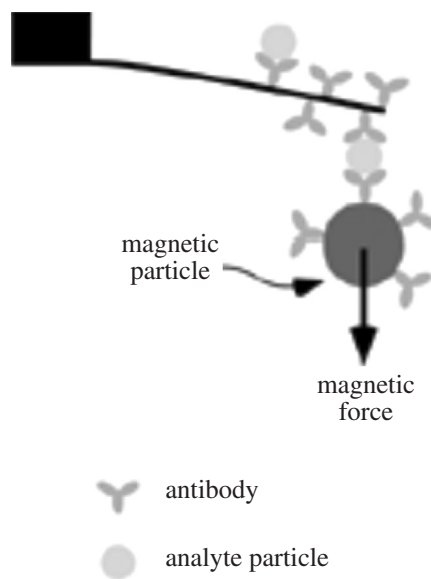


Fig. 6. Detection of antibody-antigen interaction with a magnetic bead and a cantilever (redrawn from [Baselt, *et al.*, 1997]).

Microfabricated magnetic beads coated with antibody have also been used for antigen detection. As shown in Fig. 6, a magnetic field pulls the antibody-derivitized magnetic bead to deflect the cantilever. The cantilever resolves the antibody-antigen binding force with piezoresistors. The authors claim that this system setup eliminates the need to manually position a tip and sample next to each other with pm positioning precision and stability as required for atomic force microscopy (AFM) [Baselt, *et al.*, 1997].

5. Acoustic Wave Sensors

Microfabricated acoustic-wave-based devices use various acoustic waves, such as the surface acoustic wave, shear transverse wave, Love wave, and Lamb wave [Grate *et al.*, 1993; Luginbuhl *et al.*, 1997]. This section discusses biological agent detection using surface acoustic waves (SAW). The mechanism of SAW sensing is illustrated in Fig. 7. An alternating voltage is applied to the input comb capacitors. The material between the fingers of the interdigitated electrode pattern deforms because of the piezoelectric effect. This periodic deformation gives rise to an acoustic wave propagating both

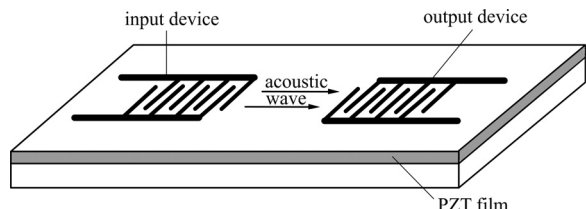


Fig. 7. MEMS surface acoustic wave device for biological agent detection.

toward the second electrode pattern, and in other directions where it can be damped at the edges of the substrate to prevent interference with the preferred wave. By virtue of the reverse piezoelectric effect, the acoustic wave can be detected at the other end of the substrate. When biological agents such as antigens or antibodies are present in the propagation course of the acoustic wave, the frequency spectra of the acoustic wave is changed. Thus, the biological agents are detected [Baca *et al.*, 1999; Hierlemann *et al.*, 1999; Welsch *et al.*, 1996].

The main advantages of the SAW sensor technology include the rugged planar design of the devices, the suitability of polymer-coated devices for use in arrays with pattern recognition, fast response, and the flexibility of the array approach to be adapted to many detection problems. The biological agents to be detected by a SAW sensor array system can be changed merely by the selection of the polymer coatings and the pattern recognition algorithm used. The main drawback of SAW sensors for biological agent detection is that the typical dimensions of the substrate are 50 mm long by 10 mm wide, which is too large to be integrated into a complete system. The other problem is that SAW sensors are traditionally fabricated on quartz substrates that are difficult to integrate with microelectronics. To overcome these drawbacks, Sandia National Laboratories recently developed SAW sensors for biological agent detection on gallium arsenide (GaAs) substrates instead of the usual quartz. Having the same property as quartz, GaAs is piezoelectric, which is necessary to produce the surface acoustic waves for sensing. Furthermore, GaAs is suitable for fabricating high frequency microelectronics. It is reported that Sandia's newly developed device is only 2 mm long and 0.5 mm wide,

which is dramatically smaller than typical SAW sensors.

6. Micro Patch Clamps

Patch clamps are used for electrophysiological measurements of cell membrane activities and recording bioelectrical signals in cells. In patch clamp techniques, a low-resistance electrode filled with saline solution is placed onto a patch of cell membrane in such a way that a giga-ohm resistance seal forms between the electrode and the membrane. Either current or voltage is measured. The patch clamp technique allows the recording of the activities of a single membrane channel. The technique imposes high requirements upon the micromanipulator. During operation the electrode is not permitted to drift during the recording process in order to avoid breaking the giga-ohm seal, which is likely to result in the failure of the measurement. High fidelity patch clamp measurements require a tight electrical connection between the cell membrane and the surface of the recording electrode. To fulfill these requirements and also to improve throughput and ease of use, MEMS-based patch clamps have been developed [Klemic *et al.*, 2002; Okandan, 1997].

In the micro patch clamp shown in Fig. 8, the 400 μm thick oxidized PDMS partition is sealed onto the chamber bottom with vacuum grease. The chamber bottom contains an array

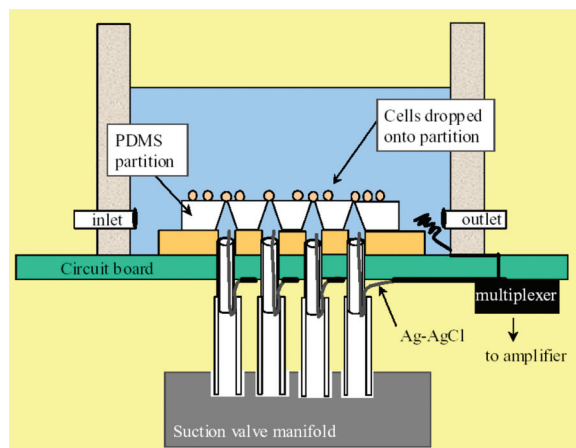


Fig. 8. Schematic of MEMS patch electrode array recording system (from [Klemic *et al.*, 2002]).

of openings, each containing tubing and a Ag-AgCl wire. The tubing connects to a suction manifold and the Ag-AgCl wire connects to a multiplexer chip on the circuit board under the chamber bottom. The multiplexer connects each contact to the amplifier electronics. Another Ag-AgCl wire in the bath solution connects to the ground of the amplifier. Bath solution is exchanged through solution lines into and out of the bath chamber. Cells are dropped onto the aperture to make a patch clamp recording [Klemic *et al.*, 2002].

7. Calorimetric MEMS Devices

Micro calorimeters have been developed for monitoring physiological states of biological cells [Verhaegen *et al.*, 2000; Zhang & Tadigadapa, 2003]. The power-conduction calorimeter [Verhaegen *et al.*, 2000] is capable of measuring activities of living cells, such as basal metabolism. Detection is based on thermopiles using the Seebeck effect. A thermopile is a self-generating device with no offset because the heat flowing through it supplies the power for the output signal. The ability to directly measure temperature differences enables it to reject common-mode thermal noise with a high efficiency, allowing measurements of very small amounts of heat without requiring complicated temperature control.

As shown in Fig. 9, the cells are placed in the measurement channel which is filled with 100 μ l of medium. The reference channel contains an equal amount of culture medium without cells. The thermopile voltage, corresponding to

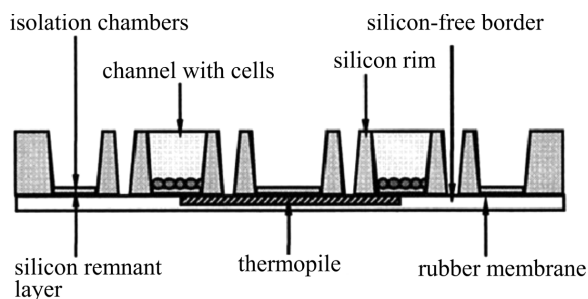


Fig. 9. Micro calorimeter measuring cellular metabolism (from [Verhaegen *et al.*, 2000]).

the temperature difference between both channels, reflects the basal physiological state of the animal cells in the measurement chamber. Kidney cell testing has been reported [Verhaegen *et al.*, 2000].

To increase the sensitivity, the thermal isolation of the device needs to be increased. This was accomplished by material and dimensional optimization. The areas had to be thermally isolated from each other and from the environment to obtain a high thermal resistance. This was done by post processing etching techniques that removed the thermally conductive bulk silicon to fabricate silicon-free membranes. Taking all considerations into account, the size of the thermopile membrane is large at 10–20 cm^2 . The large size of the device makes integration into a complete detection system difficult.

8. Gene Chips

MEMS technology has been applied to fabricating gene chips/DNA microarrays for determining DNA coding, which allows massively parallel gene expression and gene discovery. The method exploits the highly selective hybridization process allowing DNA fragments to bind only to their complementary sequence. In order to test for many specific sets of DNA sequences, a large number of unique oligonucleotide probes are constructed and compared to the amplified DNA from polymerase chain reaction (PCR). DNA amplification using the PCR process is for synthesizing more copies of sample DNA for testing [Watson *et al.*, 1992]. One method of constructing such oligonucleotide probes employs photolithography. For example, Affymetrix, Inc. produces gene chips in this way to construct large arrays of unique combinations of nucleotide [<http://www.gene-chips.com/>]. After tagging the ample DNA with a fluorescent probe, it is then distributed over the array of oligonucleotide probes. DNA strands with known identity are used to determine complementary binding, thus allowing massively parallel gene expression and gene discovery. Subsequent optical inspection of the distribution of fluorescence indicates which oligonucleotides

in the array match with a section of the sample DNA. The intensity and color of each spot encode information on a specific gene from the tested sample. Besides fabricating gene chips photolithographically, companies including Agilent Technologies are introducing the ink-jet technique [Kovacs, 1998; Nielsen, 1985] (as in ink-jet printers) into the construction of oligonucleotide probes.

9. Discussions

Besides MEMS devices for cellular force measurements and molecular detection, many other MEMS devices have been developed to facilitate biological studies by enabling complex cell manipulation strategies, such as MEMS devices for cell transportation using dielectrophoretic forces [Lee & Fu, 2003] and devices for cell sorting [Li & Bashir, 2002].

Recently, a concept that is the so-called lab-in-a-cell is proposed as lab-on-a-chip further downscales. For example, measurements of Ca^{2+} concentration is important for an understanding of many biological processes, such as protein secretion, cell death, cell development, and cell signaling. The capability of continuously monitoring calcium concentration inside a single biological cell throughout developmental stages will provide further insight into cell development studies. To realize intracellular monitoring, nanoelectromechanical systems (NEMS) are promising. For example, when a nanowire (NW) is fixed between the drain and source of a nanoFET, and by immobilizing calmodulin onto the SiNW surfaces, the conductance of the SiNW changes with Ca^{2+} concentration variation, which has been demonstrated in [Cui *et al.*, 2001]. Nano materials such as nanowires and nanotubes are especially suitable for intracellular measurements because of their small size and large surface to volume ratio. NEMS devices have the potential to extend extracellular studies to intracellular monitoring.

10. Conclusions

MEMS technology has been used to provide valuable tools for single cell studies. This

paper reviewed recent development and existing techniques for cellular and sub-cellular force measurement and molecular detection using MEMS-based devices. MEMS will continue to contribute to biological studies, which promises a deeper understanding on the cellular and sub-cellular levels.

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