CHAPTER 7

EMERGING APPLICATIONS RESEARCH IN JAPAN—MICROFLUIDICS AND BIO-MEMS

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MICROFLUIDICS AND BIO-MEMS AS EMERGING FOCUS AREAS IN MEMS

The apparent, perhaps as well as hidden, messages from our visits to cutting-edge academic MEMS research labs and leading-edge industries engaged in MEMS in Japan unequivocally created rapid flashbacks and reassuring reminders. We were pleased to see some of *what we had heard about*, *what we had talked about*, and *what we had thought about* in the United States, already being under development, working as a prototype, or available as actual products in Japan.

At many of the sites the WTEC panel visited, a significant shift in the long-term applications focus had occurred explicitly towards bio-MEMS and microfluidics, which seemed to be receiving active funding and support. Notably the research includes microfluidic MEMS development for chemical analysis (e.g., DNA analysis, protein analysis/proteomics, environmental analysis, etc.), integration into Lab-On-A-Chip and a variety of bio-MEMS (e.g., microTAS, modular microfluidic components, etc.), and medical devices (e.g., diagnostic, a point-of-care, etc.).

Cross-discipline MEMS research *en route* to innovative microfluidics and bio-MEMS development was prominent in Japan, especially in taking new approaches such as inorganic/bio-organic interfaces and hybrids as well as biomimetic engineering. The panel encountered highly sensitive molecular detection, mixing and controlling of micro-volume fluids and a multi-phase flow, and highly integrated and/or highly parallelized on-chip processing for chemical analysis.

In contrast, the panel did not observe much indication of RF MEMS-related activities and plans, or even discussions about them among the researchers during the visits. The only hint of RF MEMS activities in Japan we identified seems to be a casual mention of a potential interest in "switches" by Murata and the "switch project" in Prof. Esashi's lab at Tohoku University. For now, we have to conclude that RF MEMS activities in Japan are either invisible/hidden or just low profile, being tentatively expressed as "no plans."

The following report, therefore, recollects some interesting technological highlights from MEMS research labs we visited in Japan, specifically focusing on the microfluidics and bio-MEMS areas of current research activities.

HITACHI (IBARAKI)—MECHANICAL ENGINEERING RESEARCH LABORATORY

Hitachi Mechanical Engineering Research Laboratory indicated that the main motivation of microfluidics and bio-MEMS activities there mainly came from the needs of environmental issues and rapid medical diagnostics applications. Hitachi has commercialized a compact water quality analysis system (Type AN-530), based on a MEMS microfluidic chip to measure such parameters as residual chlorine content, turbidity, and chromaticity, integrated with an associated reagent mixing chip and an integrated optical spectrophotometric sensor chip (Okumura et al. 2001; Miyake et al. 2001). Hitachi has plans for several components for development for MicroTAS and microfluidic devices for chemical processes, including pneumatically-actuated Si diaphragms, micropumps based on piezoelectric disks, multi-stack laminated flow channels with valves, and siloxane-based separation microchannels (Yahamakawa et al. 2001). Their chemical processing systems effectively integrate micro-absorption modules, micro-extraction modules, and/or micro-concentration modules for on-site monitoring, or in medical diagnosis for point-of-care and proteomics systems. Hitachi also has a plan to further increase efforts in microfluidics and bioanalysis such as DNA analysis and DNA sequencing in addition to proteomics analysis. In response to the question, "Why do more sequencing after human genome has been sequenced?" Hitachi indicated the need for further long-term DNA sequencing of rice, plants, and other foodstuffs. The Japanese population is reportedly sensitive to genetic modifications (GMs) of foodstuffs found abroad. In particular, the identification of GMs in rice crops seems to be an integral part of the screening processes used by grain importers/traders and in government regulatory operations.

KANAGAWA ACADEMY OF SCIENCE AND TECHNOLOGY (KANAGAWA)—*PROFESSOR KITAMORI (UNIVERSITY OF TOKYO)*

Professor Kitamori's Integrated Chemistry Project at the Kanagawa Academy of Science and Technology focuses on standard MEMS fabrication techniques to form microfluidic platforms with highly innovative and integrated chemistry for disease diagnosis. These projects include microfluidics devices for 1) a cancer marker (e.g., "CEA") detection system with reduced assay time from 2-3 days to 30 minutes; 2) environmental protection such as water quality assurance by detecting heavy metal (e.g., cobalt); 3) cell-based biochemistry; and 4) combinatorial chemistry, focusing on chemical synthesis using the multiplexing microflow systems to overcome the conventional limitations of capillary electrophoresis-based approaches to the aqueous environment with ionic species and fluorescence-based detection methods. The group uses glass as a substrate, with vertically stacked, interconnected chips to increase the number of flow inputs and outputs in channels of 10-200 μm in diameter. In particular, the group is exploring "nanocapillaries" where the behavior of water clusters constrained by the capillary walls becomes unconventional, leading to a longer decay constant for fluorescence. In order to connect the microflow chips to conventional microtubing, very small, precisely machined reusable plastic connectors are used. A small local company machines them nearby.

Professor Kitamori has also developed microfluidic structures to support micro-unit operations and continuous flow chemical processing. Micro-diffusion mixers have been implemented by guide structures of ~5 μm in height etched into the microchannel to maintain separation of flow streams. *In situ* fabrication of a nylon membrane was demonstrated by polymerization at a flow interface between two streams. A particularly impressive demonstration was the co-axial flow of an air stream surrounded by fluid in a microchannel driven by a syringe pumps with a pressure of several atmospheres at the inlets.

Professor Kitamori has also developed a thermal lens microscope (TLM) as a complement to fluorescence-based detection of molecules, with its refinement being capable of detecting on the order of 1-10 molecules (Uchiyama et al. 2000). TLM is based on the physical principle that molecules emit heat to the surrounding fluid when they absorb optical energy, creating a temperature profile in the fluid that causes a change in the refractive index and a transient optical lens. The change in focus can be detected using a confocal microscope at a different wavelength, thereby indirectly sensing the molecule of interest. The technique is non-specific, so the microfluidic system must be used to select the molecule of interest, and temperature sensitivities of ~1 μK are needed to detect single molecules. Special lenses for the TLM are provided in the glass chip, and these lenses are Selfoc™ optical communications components made by Nihon Sheet Glass.

MICROMACHINE CENTER (TOKYO)

The project areas related to microfluidics and bio-MEMS activities at the Micromachine Center were presented as the Intraluminal Diagnostic & Therapeutic System, one of the three conceptual systems explored as the only proposed areas of study in the first phase (of two phases, each 5 years long) initiated in 1991. However, the budget for this area was not significant: only the elemental technologies were funded, but not the system development.

OLYMPUS OPTICAL (TOKYO)

Olympus researchers at the Corporate R&D Center described their goal as being to establish the elemental technology for realizing a micromachine (i.e., MEMS) that can work in “restricted” areas, e.g., diagnosis and treatment within the human body. Their core applications and developments during the past decade have included medical applications such as endoscopes, catheters, tactile sensors, and chips for DNA testing along with associated microfluidics. The endoscopes and catheters have been developed for medical and industrial use where both have common functional features such as actuators for manipulation and control, piezoelectric contact sensors for navigation, light/vision devices to measure important parameters, and devices for repairing damaged parts.

Olympus's views of micromachines features are as follows: 1) working in tight, complicated areas for minimally invasive diagnosis and treatment and creating thinner, more sophisticated endoscopes; 2) enhanced portability such as a smaller information system; and 3) micron-level control such as cell or DNA manipulation, including a device integrating microfluidics with electro-osmotic flow for chemical analysis. For DNA analysis and proteomics, bio-chips for DNA and chemical testing/analysis based on free-flow electrophoresis for rapid sample preparation have been developed and prototyped.

OMRON (KYOTO)

Omron focuses on industrial and automotive pressure sensing and acceleration sensing and on medical devices. Since the piezo-resistive pressure sensors were first produced in 1981, followed by a capacitive pressure sensor (1994) and a “glass-silicon-glass” capacitive accelerometer (1995), the major applications have been blood pressure monitoring, leak detection, and suspension control for automotive. Finger-type blood pressure sensors are Omron’s current MEMS medical products. Their future product interests are motion sensors, RF MEMS, DNA chips, microTAS, the components for game applications, IT, and biology markets.

TOHOKU UNIVERSITY (SENDAI)—*PROFESSOR ESASHI*

Professor Esashi’s group has a long history of successful technology transfer dating back to the 1970s and of the productization of his research outcome such as the portable pH sensor based on an ion-sensitive FET. A capacitive pressure sensor developed at Tohoku University was the basis of several products of the Toyoda Machine Works. Another commercial development was an immobilized enzyme based biosensor for detecting “pylori” bacteria, which is the cause of many stomach ulcers. Olympus and Nihon Kohden already have products based on this device. Recently, shape-memory actuators (e.g., coil and spring) were used to make a steerable catheter with 0.5 mm outer diameter. Dr. Yoichi Haga, a medical doctor working at NICHE (described in Chapter above), is launching a spin-off company to commercialize the active catheter.

WASEDA UNIVERSITY (TOKYO)—*PROFESSOR SHOJI*

Professor Shoji’s research focuses on microfluidics, using a variety of substrates such as polymer, silicon, Teflon, and glass. A particularly unique development is the use of a Teflon-like membrane in bio-MEMS. This Teflon-like membrane is deposited by spin-coating at Asahi Glass Company (“Cytop membrane” is the brand name). Professor Shoji has developed a microfluidic check-valve based on PDMS soft lithography, which was presented in the recent MicroTAS conference. His group is developing a modular approach to enable System-On-Chip ASIC-style microfluidics. A library of building blocks of pumps, valves, reactors, separators, and sensors is being designed and tested. His group has also integrated an antibody array as a surface coating on a PDMS substrate, permitting high throughput antibody-based screening of biological fluids as they flow through a microchannel, primarily for protein detection applications. Professor Shoji, collaborating with Professors Ikuta and Kitamori of Kanagawa Academy of Science and Technology, is also interested in chemical synthesis applications for the system based on the microfluidic building block library.

Professor Shoji also collaborates actively with Olympus in the such bio-MEMS areas as the development of an on-chip bioreactor, which is a PCR chamber on a chip funded through the Japanese government's Bioinformatics Initiative (mostly for DNA analysis). He commented that Olympus seemed to work with many universities on bio-applications of MEMS.

Professor Shoji also presented cell sorters using a thermal sol-gel transition where a laser-driven microfluidic valve developed in collaboration with Olympus. The valve works through laser-based heating that is used to trigger gelation of methylcellulose, which in turn blocks a microchannel. The gelation is reversible by cooling, permitting the valve to be turned on and off repeatedly by laser beam. When the gelation site is placed at a T-intersection, a multiplexor-style switch is formed.

UNIVERSITY OF TOKYO (TOKYO)—*PROFESSOR ANDO*

Professor Ando's lab focuses on the "entire" sensing system. MEMS miniaturizations of subcomponents as well as an integration of biomimetic principles bring novel functionality in the bio-MEMS projects.

Based on the human eye's involuntary eye movement to extract correlation signals, Professor Ando has developed a correlation image sensor in which the relative magnitude of adjoining pixel is measured (Ando 2000). Coupled with a vibrating mirror (at 240 Hz), this system simulates the effect of involuntary eye movement to accomplish real-time image processing such as edge detection, ranging, and spectral image matching. The latest sensing chip integrates the image sensors directly with the correlation processing circuitry with the further aim to integrate the vibration actuators with the sensors.

Inspired by the human cochlea, the Fishbone sensor (Tanaka, Abe, and Ando 1998), mechanically separates an audio signal into its frequency components (1998). Used in conjunction with a logarithmic spiral reflector, this decomposition of the audio signal could be used to accomplish sound source localization. If used in reverse by actuating the "bone" fingers, in turn, the structure could be used to generate a single impulse. The cochlea has also been the inspiration for auditory scene analysis algorithms based on decomposition of volume, pitch, and timbre. Finally, other types of direction-sensitive audio detectors have been demonstrated that mimic the ears of a barn owl and a fly.

The group also has developed a number of robust tactile sensors that take various approaches to sensing the deformation of a layer of silicone, which would be applied to the surface of the sensing appendage. The latest sensor principle achieves six-axis deformation sensing by launching ultrasonic waves from a 2 x 2 transmitter array and measuring the waves with a similar receiver after they have traversed the medium (Ando et al. 2001).

Extending the work in tactile sensing, the group is now investigating methods of generating tactile feedback. In one device, a SAW device is used to modulate the stick-slip behavior of a slider on its surface. As the slider is pushed around by the user, the perceived surface roughness can be modulated by changing the SAW frequency. Another device launches ultrasonic waves at the user's finger under water to produce tactile (Nara et al. 2001).

MICROFLUIDICS AND BIO-MEMS PROJECTS IN OTHER LABS

At Ritsumeikan University (Professor Sugiyama), among a number of applications of the LIGA, the bio-MEMS application was a Lab-On-A-Chip DNA analysis demonstrated in a PMMA micro capillary array. In addition, a device with tunable acoustic absorption characteristics was created using an array of Helmholtz resonators with mechanically adjustable cavity lengths, which potentially could lead to some biosensor applications.

At the Laboratory for Integrated Micro-Mechatronic Systems of the University of Tokyo's Center for International Research on MicroMechatronics, Professor Fujita briefly described several on-going bio-MEMS and microfluidics projects such as biomicrosystems for cells manipulation, MEMS applications to the gene transfer, a neural growth biomicrosystem, and the design and realization of a robotics device for depositing pico-liter volumes of liquid.

In response to our inquiry, Mr. Matsumoto of Sony Corporation mentioned "ePrint company" as their external collaboration on a microfluidics project with Professor Esashi (Tohoku University). No other microfluidic or bio-MEMS projects were mentioned.

CONCLUSIONS

The WTEC panel found no big surprises during the visits, but found many quality innovations in emerging MEMS applications research in the microfluidics and bio-MEMS areas with increasing funding and support in Japan. We identified a big push to advance basic microfluidics MEMS technologies toward the highly integrated, modularized, and/or parallelized platforms for chemical and bio-analysis, microTAS, and diagnostic medical devices with innovative new approaches as described above. Microfluidics and bio-MEMS are no longer subsumed as ancillary applications of MEMS, but are gradually becoming a mainstream enabler for MEMS applications research in Japan. In contrast, current RF MEMS activities in Japan seem to be invisible/hidden or potentially at the "getting ready stage."

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