How fabrication services can aid CMOS and MEMS use in biomedical designs

By Bernard Courtois

Universities need to have access to technology for teaching their students who can be trained at least on the most up to date technology processes. Research Laboratories usually need to have high performance technologies to validate new concepts.

The quality of the research results depends mostly on the quality of the technologies. It is also vital that industrial users have access to the latest technologies as the development of a product is usually long – more than 1 or 2 years – and up to date process improve product life.

The basic idea of a multi-project chip is to collectively process circuits that are different and dissimilar enabling high fabrication costs to be shared. The fabrication yield must be good and consistent as circuits cannot usually be tested before being sent back to the designer. Multi-project chip / multi-project wafers techniques (MPC/MPW) – see figure 1 – are designed to provide lower cost, and a efficient turn-around time. CMP aims to provide a turn-around time of about 12 weeks from layout to packaged chip .

Non profit service

CMP has been providing this type of service for prototyping as well as for low volume production since 1990. It is a non profit service, reporting to CNRS (the French National Council for Research) and to Universities in Grenoble.[1] It started work with a NMOS process in 1981 and has continued development until it introduce a 45nm CMOS process earlier this year. Its can provide processes aligned with those from Austriamicrosystems, STMicroelectronics, OMMIC and CSMC.

To support development design kits and libraries are distributed by CMP for most of the processes and most commonly used CAD tools. The design kits are sometimes developed in cooperation with the manufacturers and the CAD vendors and it also offers special CAD software conditions from a few CAD vendors. About 40 design kits are available for each process and the main CAD tools.

Packaging and testing services are also offered with support including DIL, SOIC, CQFP, JLCC, and PGA. While prototype test is usually done by the final user CMP can, especially for low volume production, take over testing together manufacturing.

For biomed applications, ICs are necessary but additional mechanical features are required. These are usually provided by micro-electromechanical systems (MEMS).

There are two families of MEMS. Firstly bulk micromachining also called volume micromachining in which the substrate is etched in the depth, with a wet or a dry method, front side or back side. These kinds of MEMS are mostly used for beams, bridges and thin structures.

Secondly the surface micromachining method uses sacrificial layers, grown during the fabrication process and then removed during the post process to let structures movable. These kinds of MEMS are often used for capacitive devices.

Several types of MEMS are available from CMP, classified in two categories. Bulk micromachining MEMS, based on standard CMOS and BiCMOS processes, for which structures are released with a post process step and without any additional mask. This process/post process enables the integration of both electronics and mechanical structures on the same circuit. The second category are specific MEMS processes such as the MUMPs family from MEMSCAP and SUMMiT V from Sandia, which are either surface or volume micromachining. On these processes, very advanced systems can be created on moveable platforms.

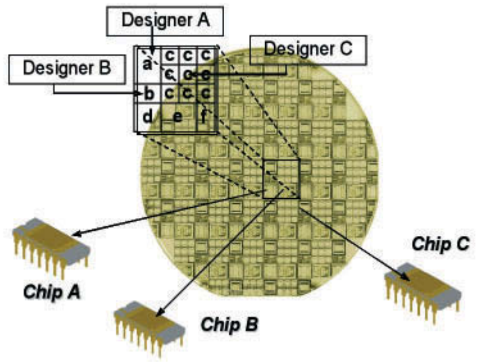

Fig. 1: Multi-project chip/multi-project wafers (MPC/MPW) techniques

Bulk micromachining MEMS

CMP can fabricate MEMS on a low-cost 0.6μ CMOS process, from CSMC, which has two poly and two metal layers. Structures are released after the circuit fabrication with a humid TMAH solution to etch the silicon. Systems like bridges, micro mirrors, comb drives or sensors can be made.

The second bulk micromachining possibility is based on the 0.25u BiCMOS process from STMicroelectronics. This BiCMOS7RF process has five metal layers with top thick metal, vertical NPN with F_t = 55 GHz and is convenient for RF designs. It includes MIM capacitors, inductors and bipolar components. The associated post process is called application-specific integrated MEMS Process Service (ASIMPS) and is made at the Carnegie Mellon University (CMU). Mechanical structures are released by reactive ion etch (RIE) and then by deep reactive ion etch (DRIE).

Potential devices to be designed and fabricated in the process include accelerometers, gyroscopes, radio frequency (RF) MEMS communication systems (with resonator oscillators, RF filter and High-Q inductors), infrared sensors and imagers, electro thermal converters and force sensors.

Some researches are currently developing a 'bioacoustic membrane' gravimetric biosensor. This is a chip-based biosensor that is aimed at macromolecular targets. The technology enables integration of multiple devices on the same chip. For example, high-Q inductors and micromechanical resonators can be combined for CMOS RF application. In another example, multiple accelerometers are integrated on chip to create a 3-axis inertial measurement system. Furthermore, both the communications and accelerometer systems can be combined to form a wireless micro sensor system.

Two complementary design kits are provided by CMP, one from STMicroelectronics for the electronic part and one from CMU for the MEMS part.

Processes supplied by CMP and dedicated for MEMS include the multi-user MEMS processes (MUMPs) family with PolyMUMPs, which is a polysilicon / gold surface micromachining, using sacrificial layers to suspend structures and SOIMUMPs, which uses the DRIE on silicon on insulator (SOI). This process enables to etch front side and back side of the wafer to completely suspend the structures. Also available is MetalMUMPs, which uses thick nickel electroplated layer. On these last two processes the substrate is etched.

For all MUMPs processes, CMP provides Cadence and Tanner design kits, with technology files and DRC implementation.

The Sandia Ultra planar Multi level MEMS Technology V (SUMMiT V) is also available and this process uses five polysilicon layers, all planarized providing flexibility and a mechanical robustness in the devices.

Systems like comb actuators, meshing gears and transmissions dynamometers, laminated support springs, steam engines, micro engines and micro machines, motors, mirrors and optical encoders, micro sensors, RF MEMS and linear racks can be fabricated.

In biomed applications some work is focused on a system that may allow large samples to be handled and processed in micro channel devices that are made in sheet and rolled or stacked. Also, a component that separates nucleic acids by size has already been made. Two design kits are available through CMP. MEMS Pro from SoftMEMS and Autocad 2000. Both enable DRC verification, 2D and 3D visualization.

The portfolio of MEMS processes should be large enough to provide a solution fabrication of very complex mechanical structures. The designs can be complex either with the electronics management and control of the MEMS or in the movable structures.

Biomed applications that use electronics and MEMS range from implant devices to biosensors, DNA-based systems analytical protein arrays and cell based systems[2]. Two basic technological prerequisites are micro-fluidic platforms and separation based tools on chips. Here we will provide examples of biomed applications that can be produced using standard process like those supplied by CMP. Users do not need specific custom process developments, they only need to design, they do not need to care about the manufacturing.

Electrons and holes in semiconductors and ions in cells are the information carriers. Neurons transmit information along nerves through the action potential that is the depolarisation of their membrane. Due to differences in ion concentration between sides of the cell membrane, neurons present a negative potential inside the membrane. When membrane proteins open ions channels, a depolarisation occurs and propagates along the nerve, it is the propagation of the action potential. By placing a metallic or insulator/semiconductor structure in the vicinity of a neuron membrane, it is possible to measure the depolarisation and thus to access the electrical activity of cells.

The idea of trying to build an electrical connection between a living cell and an electronic circuit has started in the 70's. This idea is based on the measurement of the extracellular potential instead of the intracellular potential thus being a non-invasive method for accessing the electrical activity of cells. Micro electrode arrays (MEAs) have then been developed and succeeded in not only measuring the electrical activity of neurons and tissues (the spikes) but also to interfere and initiate action potentials in neurons. Needle shaped microelectrodes have also been developed in order to be implanted in vivo in cerebral tissue and then to record its electrical activity.

Despite these remarkable results, MEAs were suffering from limitations in

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terms of signal / noise ratio and integration possibilities.

In 1991, Peter Fromherz[3] was working on silicon/neuron junction and then developed the first real connection between a neuron and an integrated circuit. These works have been pursued toward a greater integration and soon a real communication between an IC and a neuron [4-5] has been shown. By communication we mean initiation of an action potential in a neuron, propagation to other neurons and then reading of the signals in these other neurons through other microelectrodes in the IC.

The integration of real neuron networks with integrated circuits is a very promising technique for neuroscience. However some specific care must be taken for the coupling. For biocompatibility reasons, it is not possible to directly connect a culture medium to the surface of an integrated circuit. The aluminum as an example of metal present in ICs connection pads is not compatible with neurons. Several techniques have been develop to overcome this problem including the use of capacitive electrodes (silicon dioxyde is biocomptabile) or the covering of metal electrodes with noble metals such as platinum – see figure 2.

Apart from an electrical interface with electrically active cells, ICs have been used in several other bio applications such as the measure of ion concentration in the vicinity of cells. This has been done in the purpose to study ionic activity of cells (through membrane proteins) regarding the presence of drugs in the culture medium. In this case, several studies report the use of ion sensitive field effect transistors to measure ionic concentration. Another application in cell biology has been to use an IC for localization and immobilization of cells. For instance an array of photodiodes / electrodes included in a microfluidic system[6],. Once a cell is detected through the array of photodetectors it is kept trapped by means of a vertical dielectrophoretic well. This system allows the control of cells population on top of an IC.

The previously described applications have been developed to establish a measure of electrical or ionic activity of living neurons. On another hand, there is an intense research activity on the field of mimicking the behaviour of neurons and synapses in the goal of building artificial analog neuron networks. Neuron networks have been intensively studied and modelled using computers. In the case of neuromorphic ICs [7], a physical implementation of a neuron is made on silicon. It has the advantage of being real time and could be used both for the study of computing techniques and also in the goal of hybridization with a real neuron network. Figure 3 shows an example of such an analog neuron network, it has been made by researchers in University of Bordeaux.

This chip emulates neurons electrical activity using a biophysical model (Hodgkin-Huxley formalism). Five neurons have been integrated and are fully tunable. Their model cards are stored in an analog memory cell array. Such ASICs, as shown in Figure 3, form the computation core of a complete simulation system dedicated to the investigation of the dynamics of biomimetic neural networks.

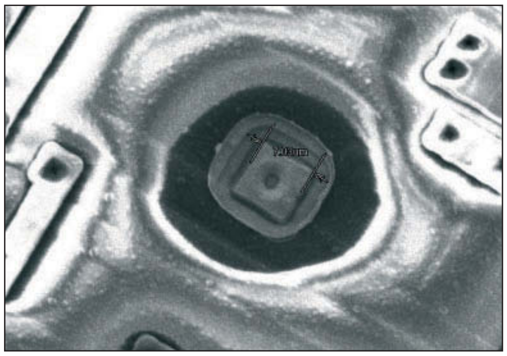

Fig. 2: SEM picture of the grid electrode of an ISFET covered with a platinum layer. This electrode is a part of an ISFET sensor matrix implemented on CMOS.

Bulk micromachining allows the fabrication of various types of sensors for biomed applications including an acoustic sensor for ORL surgery. This project is being jointly carried out at the TIMA Laboratory in Grenoble and at the Hopital Nord in Grenoble.

In Oto-Rhino-Laryngology (ORL), the middle ear surgery aims at correcting certain types of hearing loss or in treating certain diseases. Among different kinds of techniques, the ossiculoplasty attempts to re-establish a connection between the tympanic membrane and the oval window. This surgery involves ossicular chain reparation or reconstruction with appropriate replacement prosthesis. Three elements of the ossicular chain (stapes, incus, and malleus), the smallest bones of the human body, provide the sound energy transfer between the tympanic membrane and the inner ear.

Successful surgery can lead to the correction of hearing loss due to tympanic membrane anomalies or to a discontinuity or fractures of ear bones. There exists a number of different techniques leading to the ossicular chain reconstruction using either biomaterials or various other materials such as titanium, gold or ceramics. In spite of all this progress, the surgical act in the middle ear remains difficult because of a large number of factors influencing its success.

Moreover, there is no available means enabling per-operatory monitoring and thus giving necessary feedback to the surgeon.

The project is aimed at the development of a micromachined vibration sensor working in the audible frequency range from 1 to 5 kHz is required by ORL surgeons. Such a sensor, used during a surgery, will make easier to a surgeon to take a decision whether the realized ossiculoplasty is providing an optimal transfer of the acoustic signal from the tympanic membrane to the inner ear.

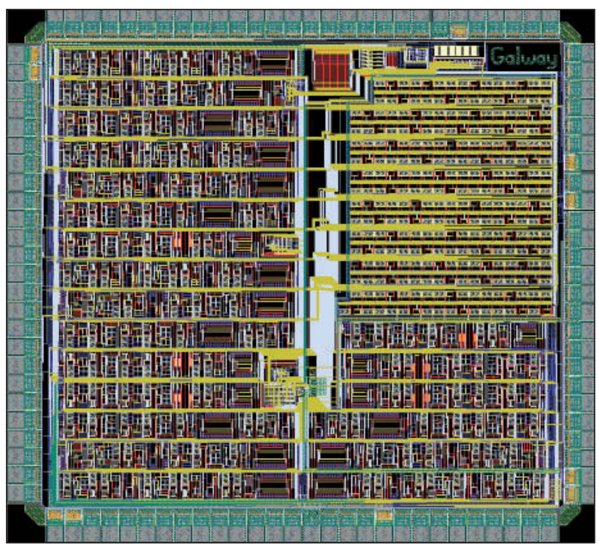

Fig. 3: A neuromimetic and modular ASIC: integration of biomimetic neurons

A sound source located in front of the patient's outer ear generates a test signal that propagates through the external ear to the tympanic membrane. The movement of the tympanic membrane is transferred via the ossicular chain to the input of the inner ear represented by the oval window. The vibration sensor put in contact with any part of the ossicular chain will thus provide real-time information about its degree of mobility and about the quality of the propagated sound signal.

The MEMS-based approach to the sensor design is motivated by the small size and low mechanical impedance of the ossicular chain. A micro-machined sensor tip will provide a possibility of the vibration measurement by a physical contact with no side effects to the ear function. A careful design of the sensor is required in order to overcome the ultra-low level of vibrations.

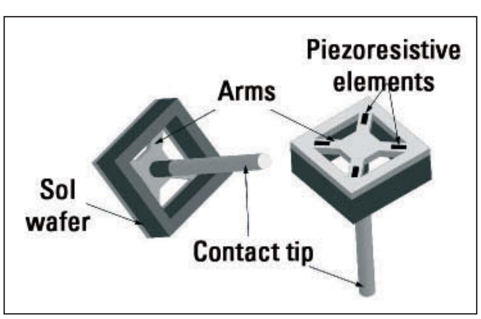

Fig. 4: Principle of the sensor structure.

Different possible arrangements of the sensor have been investigated. The sensor with a contact tip placed perpendicularly to the sensitive element composed of four arms equipped with piezoresistive gauges – see figure 4.

The sensitive element of the sensor is made from the silicon-on-insulator (SoI) wafer. This kind of substrate facilitates the fabrication of arms with uniform thickness. The silicon arms are made by the front side micromachining. The whole sensitive structure is suspended on the cavity obtained with the deep reactive ion etch (DRIE) from the back-side of the wafer. The contact tip is formed by a glass fiber attached with a central stem obtained after the patterning and the etching of the bulk silicon layer.

Attention must be paid to the resulting characteristics of the mechanical structure. Especially, the mechanical impedance at the end of the tip must match that of the middle ear ossicular chain. Too high value of the mechanical impedance may result in affecting the function or even in damaging the structure of the ear; too low impedance value would not ensure the optimal transfer of the tip movement towards the piezoresistive gauges.

Another important issue consists in piezoresistive gauges optimization. Extremely low displacement values require high signal-to-noise ratio achieved by optimal geometry and placement of the gauges, by proper doping of the silicon layer and by low-noise electronics applied at the front-end.

Research applications

MUMPS is also used for the manufacturing of devices in various biomed applications. Canadian Microelectronics Corporation (CMC) provides a similar to CMP, servicing the Canadian Universities. CMC has worked with Karan Kaler and Martin P. Mintchev at the University of Calgary. The project team have developed a device would extract blood like a mosquito would, electronically analyze the sample and then transmit it to a wireless device to monitor and control the insulin infusion pump so that the glucose balance in the body of a diabetic patient is maintained throughout the day – see figure 5.

The very small volume of blood (<1ml) delivered by the sampling process is stored in a miniature blood compartment, where the microsensor converts the blood element of interest (for example, the glucose level) into an electrical signal. This automated and self-calibrated procedure is performed by a microsensor integrated inside the blood compartment.

An array of single-use and individually actuated e-Mosquito cells form the disposable patch and a matrix of 180 e-Mosquito cells can provide periodic blood sampling for up to one week, assuming that blood monitoring is required every hour.

An other example comes from Dalhousie University, Mechanical Engineering Department, where Ted Hubbard and his team have developed a microgripper for mechanical testing of cells and bacteria, cell manipulation, medical screening. Initial designs were made on MUMPS, they next moved to Micragem, a SOI MEMS technology from Micralyne, that is available from CMC. An electrothermal microgripper is used and typical displacements for chevron actuators are in the range of a few micrometres, so mechanical amplifiers are needed to increase the motion. [8]

Figure 6 shows a chevron actuator with a set of two closed-toggle-style amplifiers, one for each jaw of the gripper. A small displacement downward (along the y- axis) at the centre of the chevron actuator (3) draws in the gripper jaws (6) significantly. The amplifiers (5) are mechanically connected to the actuators (3), and therefore current also flows through them. This means that they will also heat up and thermally expand. To take advantage of his current, the amplifiers are designed to act as hot/cold-arm-type thermal actuators, where the thin-finned hot arm of the actuator is on the outside, contributing to the inward, closing motion of the jaws (6). The gripper is able to grasp 5 μm spheres.

Commercial applications

MUMPS have served as test vehicles to test various components which have gone on to be manufactured using more commercial methods. A pressure sensor MEMSCAP is manufacturing for CardioMEMS has a wireless pressure sensor is inserted during the minimally invasive repair of abdominal aortic aneurysms (AAA) or thoracic aortic aneurysms (TAA), via a catheter into a patient's aneurysm sac. The small size, durability, and lack of wires and batteries enable system to last for, and transmit data over, the lifetime of the patient without requiring repeated procedures.

A second example is a wireless imaging system made for Given Imaging in view of endoscopy. The tiny camera contained in a capsule captures images of the gastrointestinal tract as it travels through the body and transmits the images to a computer so a physician can view them and make a diagnosis see www.eetimes.eu/192200168.

ASIMPS from Carnegie-Mellon University has been used for a project involving clinical management of skeletal trauma and disease which relies on radiographic imaging to infer bone quality. However, bone strength does not necessarily correlate well with image intensity. There is a need for a safe and convenient way to measure bone strength in situ. The goal is to present a new technique to directly measure bone strength in situ at a micro-level scale through a MEMS sensor. The proposed MEMS stress imager comprises an array of piezoresistive sensor 'pixels' to detect stress across the interfacial area between the MEMS chip and bone with resolution to 100 Pa, in 1 sec averaging.

The sensors are integrated within a textured surface to accommodate sensor integration into bone. From initial research, surface topography with 30-60 μm features was found to be conducive to guiding new cell growth. Finite Element Analysis (FEA) has led to a sensor design for normal and shear stress detection[9].

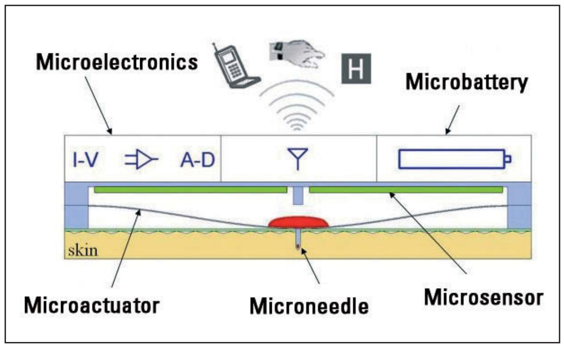

Fig. 5: The e-Mosquito cell [courtesy from the University of Calgary]

Figure 7 shows the MEMS device that includes the piezoresistive sensor array, and a coil antenna for RF power and telemetry. The interest for clinicians is that if they had a practical means to directly measure and quantify biomechanical properties of healing or diseased bone in situ, within bone, this capability could provide improved and timely information for treatment management

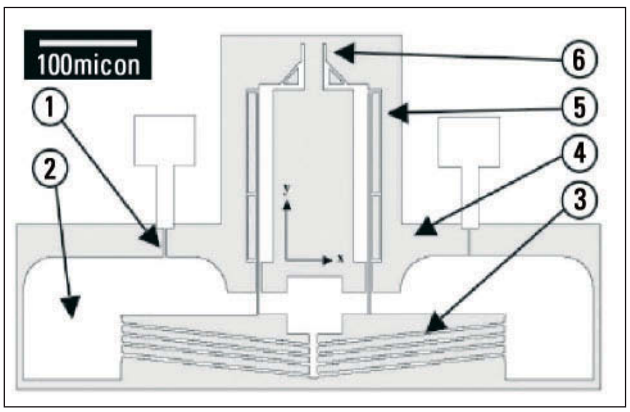

Fig. 6: Design of an off-chip gripper: (1) breakable tether; (2) bonding pad; (3) chevron actuator; (4) cavity; (5) amplifiers; (6) jaws [8]

options, including drugs, fixation adjustments, rehabilitation regiments, or preemptive surgical intervention.

In contrast to the local nature of the validation in single sensor experiments, an array of piezoresistive elements offers the possibility of global data over an entire surface on the order of 1-4 mm^2.

System approach

IntuiSkin, a wholly owned subsidiary of the MEMSCAP Group has worked on a whole system including various kinds of sensors, ASICs for signal processing, data acquisition, and expert systems. IntuiSkin is focused on innovative, technology based skin care solutions. These solutions provide an answer to the new and strong consumer demand for technology based cosmetology. They allow to characterize the skin in general, in order to recommend suitable cosmetic treatments.[10]

Various MEMS sensors are grouped into two probes measuring many basic parameters of the skin. The Visio probe uses its sensors to capture with an extreme precision the skin images. The system enables many measurements including wrinkles, sebum, hairiness, dark spots and clogged pores/bacterial infection.

The Physio probe contains sensors and extracts in vivo the key characteristics of the skin. This probe measures, among other parameters, the hydration, the trans-epidermal water loss (TEWL), and the skin temperature. Different products have been derived by IntuiSkin to address various needs. The Skin Evidence is addressing the medical market. It is an answer to the practician needs in cure and detection as well as in specific treatments (peeling, injection, fillers,...) as well as to the clinician in pre and post surgical support.

It is expected that the system will be used by skin specialists, dermatologists, dermato-cosmeticians, plastic surgeons in their clinics or in their office. The other market addressed by the general concept of intuiSkin is the beauty market. The IOMA Beauty Diag is measuring the seven main dysfunctions of the skin: hydration and UV damage, fine lines, wrinkles and elasticity, redness, bacterial infection, sebum, dark spots. It is expected that aestheticians will use the equipment to recommend the best treatments.

The last exemplified systems are portable systems for consumer use: the Sensicards which optimizes the use of cosmetic products to check evolution of skin evolution to enjoy the sun benefits with no constraints. SensiCards are systems equipped with sensors, micro-electronics, data displays, batteries, communications interface and data analysis and management.

They are custom made and integrated in a light and resistant packaging the size of a credit card. The UV-SensiCard is expected to be used for skin protection against the sun. Once the sun protection factor (SPF) of the available sun cream is selected, this card enables to measure and display the intensity of the ambient UV, and to recommend for each skin type the time to reapplication of this sun cream. Other SensiCards have been developed along the same general concept.

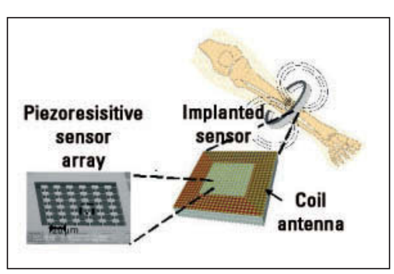

Fig. 7: Bone Implantable Stress Sensor [9]

CMP believes it will be important for the BioMed education and research should take advantage of these infrastructures, in the same way as their microelectronics colleagues have taken advantage of these infrastructures in the 80s.

Various CMOS and MEMS processes can allow students, teachers, researchers to focus on biomed applications but not all possible applications can be reached by standard processes offered by service organizations like CMP, but these service organizations are continuously expanding their portfolios.

CMC from Canada recently introduced, for example, access to a microfluidics platform. In addition to fixtures for custom fluidic microchips, it gains advantage from multiple technologies--photonics, electronics and embedded software, and pushes further the set of BioMed applications targeted by teachers, researchers and students. ■

REFERENCES

[1] "MPC Services available worldwide", B. COURTOIS invited paper, APCCAS'94 IEEE Asia-Pacific Conference on Circuits and Systems, December 5-8 1994, Grand Hotel, Taipei, Taiwan.

[2] "BioMEMS", Edited by G. URBAN, Springer, 2006.

[3] "A Neuron Silicon Jonction : A Retzius Cell of the Leech on an Insulated Gate Field Effect Transistor", P. Fromherz et al., Science n° 1952, pp. 1290-1293, 1991.

[4] "Silicon-Neuron Junction: Capacitive Stimulation of an Individual Neuron on a Silicon Chip", P. Fromherz, A. Stett, Physical Revue Letter, n° 75, pp. 1670à 1673, 1995.

[5] "A 128x128 Bio-sensor array for extracellular recording of neural activity", P. Fromherz et al. International Solid State Circuits Conference (ISSCC), 2003.

[6] "A CMOS Chip for Individual Cell Manipulation and Detection", N. Manaresi et al. IEEE Journal of Solid-State Circuits, Vol.38, n°12, 2003.

[7] "Neuromimetic ICs with analog cores: an alternative for simulating spiking neural networks ", S. Renaud et al. in Proceedings of the IEEE 2007 International Symposium on Circuits And Systems, (ISCAS'07), New-Orleans, USA, 2007, pp. 3355-3358.

[8] "Theoretical and experimental analysis of an off-chip microgripper", J. Fraser, T. Hubbard, M. Kujath, Can. J. Elect. Comput. Eng., Vol.31, No.2, Spring 2006.

[9] "BioImplantable Bone Stress Sensor", F. Alfaro et al, Proc. of the Int' Conf. of IEEE Engineering in Medicine and Biology Society (EMBS), Shanghai, China, Sept. 1-4, 2005.

[10] "Panel on success stories in MEMS-based systems", J.M Karam, Design, Test, Integration and Packaging of MEMS and MOEMS Conference, Nice, France, 9-11 April 2008.