Micro- and nano-systems for chemical/bio-medical analysis and diagnostics

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Abstract

This paper reports selected results of the MNS-DIAG research project. The project is aimed at facilitating access of research teams coming from academia to fully equipped CMOS/MEMS R&D and manufacturing line and thus allowing for inflow of innovative microdevice concepts and development of demonstrators. To address the important grand societal challenges related to well-being and health in the ageing society, the project has been focused on application of micro- and nano-systems for chemical/bio-medical analysis and diagnostics. Out of five demonstrators elaborated within the MNS-DIAG, three are shortly described here, namely, Lab-on-a-chip for oocytes characterization, Micromechanical biosensors array and Integrated MEMS detector for dynamic humidity measurement in medical applications.

Keywords: microsystems; Lab-on-a-chip; biosensor array; humidity sensor.

1. Introduction

Enormous progress of silicon based micro- and nanotechnologies, aimed at development of increasingly complex integrated circuits according to a Moore’s law, brought us numerous, extremely refined process technologies. This in turn, created vast opportunities for development of much broader range of highly innovative micro- and nano-scale devices utilizing a knowledge gathered in virtually all branches of
physics, chemistry, biology, medicine, material sciences and other areas of science. Important features characterizing this new, “More-than-Moore” domain are – much lower cost of the technology, as compared to advanced IC’s manufacturing and much broader diversity of required expertise, knowledge, materials etc. Thus, MtM domain, in particular the area covering microsystem and sensor technologies became a field of research of choice for many academic research communities collecting pools of well-educated innovative minds with diversified expertise and knowledge. However, despite of the lower technology cost, difficult access to Clean Room facilities and non-standard micro-processing constitute an important barrier hindering research for many academic teams. Furthermore, as emphasized by the EC High Level expert Group (HLG) extension of the research towards industrial application requires that the bridge is built to pass across the “valley of death” along the road from basic observations and technology concepts, through technology development and validation up to demonstrator, prototype development and finally, mature product [1]. As recommended by HLG, this bridge has to be composed of three pillars: technological facilities, pilot lines and manufacturing facilities. While the second and third pillars are of strategic importance for industrial players, the first – referring to access of researchers to unique, advanced and non-standard processing facilities constitute a weak point and thus, it has to be supported through public funded research programs. With this in mind a research project named MNS-DIAG has been launched in Poland to support access of academic research teams to advanced micro/nano-technology facility, aimed at investigation of ten new device concepts and development of five innovative demonstrators. To address the important grand societal challenge related to well-being and health in the ageing society the project has been focused on application of micro- and nano-systems for chemical/bio-medical analysis and diagnostics. The MNS-DIAG is a structural funds supported project coordinated by Instytut Technologii Elektronowej (ITE) of Warsaw, Poland where fully equipped CMOS/MEMS R&D facility is located. The consortium is composed of 16 research teams coming from academia. In this paper a selected research undertaken within this project and achieved results are being reported.

2. Lab-on-a-chip for oocytes characterization (APOZAR sub-project, leader J.Dziuban, WRUT)

At the age of microfluidic techniques, lab-on-a-chip (LOC) instruments have been also used for enhancing the reproduction techniques. Labs-on-a-chip have been successfully applied for single oocyte or embryo manipulation, cumulus oocyte complex removal, test and selection of sperm, in vitro fertilization, embryo culture or single embryo barcodes codification.

Fig. 1. Scheme of the instrumentation and enlarged schematic top view of the lab-on-a-chip for spectrophotometric characterization of oocytes (left image), and view of the instrumentation ready to work (right image)
However, non-destructive and on-chip characterization of a reproductive cell, with a special attention paid to oocytes, is still a challenging technique. A novel methodology and lab-on-a-chip for optical characterization of single living porcine and bovine oocytes and embryos has been developed under MNS-DIAG/APOZAR project (Fig. 1). The developed LOC enables loading and on-chip long-distance transport of the cell into a measurement area, as well as safe uploading of the cell for further operations. Some differences in recorded and analyzed absorbance spectra obtained for different porcine oocytes collected from different follicle were observed. A set of objective, numerical parameters describing single porcine oocyte has been proposed. Thus, the spectrophotometric characterization of porcine oocytes utilizing LOC technique has been carried out for the first time.

3. Micromechanical biosensors array (SUBNANO sub-project, leader T.Gotszalk, WRUT)

A family of novel micromechanical array biosensors has been designed, fabricated, and applied to detect endotoxins of Gram-negative bacteria. The described devices enable detection of molecular adsorption in static and resonance mode. In these techniques sensor bending and shift of sensor’s resonance frequency occur due to the biomolecule adsorption on the cantilever surface. The enhanced detection selectivity is obtained by functionalization of receptor areas, which reduces crosstalk between adsorption induced stiffness modification and mass loading. Additionally, components for sensing of electrical impedance spectra and conductivity of the adsorbed layers are integrated with the mechanical transducers. In this way, not only mechanical response to the biomolecule adsorption but also electrical and electrochemical properties of the layer formed on the transducer surface can be recorded and investigated. Dual-mode operation in static and resonance mode of entire cantilever array was conducted by monitoring the intrinsic thermomechanical noise of sensor [2].

![Measurement examples: (a) thermal noise measurements in air and in methanol; (b) thermal noise resonance peaks of 4 microcantilevers are acquired at the same time.](image)

Application of low noise, high frequency and multi section photodetectors enabled analysis of flexural and torsional vibrations of the cantilevers in higher eigenmodes [3]. Developed system is capable of simultaneously measuring up to 8 microcantilevers, recording their static bending as well as flexural and torsional resonance mode parameters (frequency, quality factor, damping coefficient, amplitude).
4. MEMS detector for dynamic humidity measurement (MED-MEMS sub-project, leader R.Jachowicz, WUT)

In contrary to most of industrial application humidity measurements in medical diagnostics require hygrometer instruments with fast response. In particular to measure TEWL factor (TransEpidermal Water Loss) at dermatology test and to measure humidity changes in human breath, in nose and throat (nasal cavity, nasopharynx, pharynx and tracheotomy) during regular breathing in otorhino-laryngology tests, the time constant of humidity measurement should be less than 0.5s. To meet such a needs the integrated MEMS structure made on silicon substrate working as a dew point temperature detector has been elaborated. It contains the capacitive interdigitated sensor working as a dew detector, the thermoresistor (thermometer) and a heater located underneath both mentioned sensors and separated from them with thin dielectric layers. Small thickness (1.4 \textmu m) and low mass of these sensors as compared to total silicon substrate thickness of 400 \textmu m allows for fast response of the measurement. While in conventional hygrometer construction the measurement time constants are in the range of few seconds to minutes, in our structure up to 40 detections per second may be obtained which means that the developed device is up to 1000 times faster than conventional dew point hygrometers.

3. Cross-section of the sensor (left) and microscopic image of the sensor structure (right)

Conclusions:
The MNS-DIAG project considerably facilitated development and demonstration of new microdevice concepts addressing important societal needs in the biomedical application domain. This project, besides of the clear technical achievements allowed for closer collaboration of specialists coming from different scientific disciplines and from different research institutions. Furthermore, basing of the academic research on the professional, stable micro-manufacturing line considerably facilitate future transfer of the development from the academic research stage up to industrial manufacturing.


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