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The era of micro and nano systems in the biomedical area: bridging the research and innovation gap

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Abstract— The area of Micro and Nano systems (MNS) focuses on heterogeneous integration of technologies (e.g. electronics, mechanics and biotechnology) and implementation of multiple functionalities (e.g. sensing, processing, communication, energy and actuation) into small systems. A significant amount of MNS activities targets development and testing of systems enabling biomedicine and personal health solutions. Convergence of micro-nano-bio and Information & communication technologies is being leading to enabling innovative solutions e.g. for in-vitro testing and in vivo interaction with the human body for early diagnosis and minimally invasive therapy. Of particular interest are smart wearable systems such as smart textiles aiming at the full integration of sensors/actuators, energy sources, processing and communication within the clothes to enable non-invasive personal health, lifestyle, safety and emergency applications. The paper presents on going major R&D activities on micro-nano-bio systems (MNBS) and wearable systems for pHealth under the European Union R&D Programs, Information and Communication Technologies (ICT) priority; it also identifies gaps and discusses key challenges for the future.

Keywords: Micros & nano systems, nano-bio convergence, Information and communication technologies, wearable systems, Smart textile

I. Introduction

Research and development at the interface of micro-nano systems (MNS) and biology combining information and communication technologies, has the potential to provide the necessary technological platforms and enhanced ability to sense, detect, analyse, communicate, respond and monitor phenomena from macro to nano scale. This currently leads to the development of new medical technology fields and applications e.g. molecular imaging, point of care testing (POC), gene therapy and bionics, which are expected to revolutionise future healthcare delivery and quality of life.

However, to achieve such complex systems, substantial improvement is required on various aspects of system integration e.g. miniaturization, power consumption, as well as on product quality and reliability.

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Micro- nano systems are potent facilitators of heterogeneous integration targeting low cost and shorter time-to-market.

Two of the most important MNS activities of the ICT program[2] supported by the European Union are driven by biomedicine and personalised health (pHealth) applications: *Micro-Nano-Bio technologies' convergence* systems (MNBS) [1] and *Wearable Smart Systems* (WSS) like smart textiles systems [2].

MNBS is a rapidly growing market[3] (relating to BIOMEMS[4] and Nanobiotechnology) where Europe (33%) is with USA (42%) and Japan (10%) in leading position. New emerging markets are China and Korea. The average annual growth for all BIOMEMS applications is 17%.

The R&D group[5] addresses:

a) *In vitro molecular diagnosis and biochemical analysis systems*, such as DNA & protein arrays, micro-total analysis systems (μTAS), lab-on-chip and cell-on-chip systems to enable early diagnosis and therapy follow-up, e.g. in cancer, infections and vein thrombosis.

b) *Integrated systems interacting with the human body,* such as active implant devices, neuro-electrode arrays, capsular endoscopes, minimally invasive robotic surgery systems and other minimally invasive diagnostic systems.

Wearable smart systems area achieved great advances over the last ten years, in terms of miniaturisation, seamless integration of multiple functions (e.g. sensing, data & power management and networking) and comfort, providing an attractive response to the strong need for affordable, comfortable and ubiquitous pHealth solutions at the point of need. The effort is currently focusing on further enhancement of the development of WSS and in particular SFIT (Smart Fabrics and Interactive Textile) systems through integration of regular electronics into textiles and integration of fibred devices into textile and fabric to allow robust and low cost manufacturable devices.

Use of standards, clinical validation and strong involvement of end-users are essential elements of the projects in the process of pre-commercial system's design and development.

[2] http://cordis.europa.eu/fp7/ict/micro-nanosystems/projects_en.html

[3] The BIOMEMS market is expected to reach 2.3 B$ in 2012 from roughly 800 M$ in 2008 (*BIOMEMS 2008, March 2008, Yole Development)*.
The Nanobiotechnology market was estimated at $20b in 2010 and expected to reach $70b in 2015 (*Nanobiotechnology Applications, Markets and Companies: A Jain Pharmabiotech Report, 2006*)

[4] Bio-Micro-electro-mechanical systems

[5] http://cordis.europa.eu/fp7/ict/micronanosystems/projects_en.html#Micro-Nano-Bio%20Convergence

II. MNBS FOR PHEALTH: ACHIEVMENTS AND ONGOING R&D

A. In vitro MNBS

Research focuses on building blocks (e.g. biosamples' preparation, microfluidics, sensing, detection, surface functionalisation, biomarkers and signal processing) and system integration and testing in several biomedical and healthcare applications such as cancer diagnosis and disease recurrence [3], diabetes monitoring and deep vein thrombosis early detection[6].

Most common objectives of the projects are linked to the improvement of sensitivity, of multi-analyte capabilities and rapidity of the biosensing process as well as to the development of fully integrated/miniaturised end-system/prototype.

Some of the major achievements of label free LoC (Lab on a Chip) are:

- Portable and label-free analysis of proteins and DNA mutations with high sensitivity and dynamic range with PCR integration;
- Multiple mutations analyzed in a label-free manner;
- Increasing sensitivity without compromising dynamic range

The main outstanding issues consist e.g. on the integration of sample pre-treatment; chip stabilization of immobilized immunoreagents (antibodies); reliability and repeatability if results in label-free detection.

Major achievements on LoC for cell and bacteria analysis are:

- Use of flexible printed circuit board technology;
- Application in immunology (cell therapy) and drug screening (identification of resistant tumour cells);
- Integration of complex microfluidics control system and of imaging system;
- Single analysis or continuous monitoring

The main outstanding issues consist on system integration (e.g. compatibility of flow rates), on relatively low sensitivity and on robustness of biological reactions on chip.

Other LoCs projects achieved promising results in interfacing with patients, doctors and hospitals; demonstrating the proof of principle on sweat analysis for detecting diabetic hypo- or hyper-glycaemia episodes; sample preparation for PCR from whole blood and novel cartridges which include a hybridization chamber.

However, despite these great advances, the clinical validation of the systems has not been achieved. Very few real samples have been tested so far and there is an urgent need to involve more end users in the whole value chain of the LoC systems.

B. In vivo MNBS and Wearable Systems

In vivo interaction between micro-nano systems and the human body (e.g. body sensors, implantable systems, endoscopic probes and wearable systems) target several applications such as non-invasive long term monitoring, drug delivery, vital functions' repairing, targeted therapy, early diagnosis & well being support. MNBS projects in this area focus on research, development and validation of high-performance components & modules (e.g. micro/nano electrodes, sensors & actuators, power supply and wireless telecommunication) and on integrated multifunctional miniaturised systems and devices. All projects are tested and validated in, at least, one biomedical / healthcare application.

Major development, performed by project Healthy Aims, [4] is on core implant technologies (e.g. biocompatible implant coatings, biofuel cell to power implant electronics and wireless communication), active smart implants and diagnostic equipment for:

- Restoration of sight (retina implant);
- Diagnosing glaucoma (glaucoma sensor);
- Monitoring intra-cranial pressure (intracranial pressure sensor);
- Restoration of hearing (cochlear implant);
- Restoration of upper-limp motion bladder & bowel control (functional electrical stimulation).

In addition, stimulation & recording of brain activity and disorders (e.g. epilepsy) has been achieved through modular probes arrays by project Neuroprobes [5] which integrate electronic depth control to adjust the position of individual electrodes with respect to neurons. Finally, significant results have been achieved in blood glucose monitoring[7] with the development of subcutaneous glucose biosensor based on glucose binding proteins.

Other major advances have been made in capsular endoscopy for gastrointestinal tumour screening, diagnosis and therapy (e.g. manipulation of tissues) [6]. The capsules, currently under clinical experimentation with animals, integrate sensors, advanced vision, magnetic and other navigation modes, localisation and wireless transmission capabilities (project Vector).

Integrated prototypes have been also achieved in drug delivery[8] (through intraoral Microsystems, project Intellidrug) and ambulatory systems for attention, stress and vigilance monitoring[9] (project Sensation).

Another promising research activity is at the interface of micro-nano-bio and wearable technologies, such as smart textile [7, 8, 9][10]. New concepts have been recently tested and proved by project Biotex [10], e.g. wearable biochemical sensing through body fluids (e.g. sweat) analysis. It includes textile patch with an integrated passive pump and pH sensor unit, built into the fabric itself. Additionally the patch is provided with a flexible substrate carrying a multi-sensor unit containing: a sensor for sweat

[6] http://www.diagnosingdvt.com

[7] http://www.pcezanneportal.co.uk/

[8] http://www.ibmt.fraunhofer.de/fhg/Images/SM_ms_IntelliDrug_en_tcm266-80609.pdf

[9] http://www.sensation-eu.org/

[10] Existing prototypes incorporate mainly electrocardiogram and respiration monitoring, and accessorily other physiological and physical parameters by implementing strain fabric sensors and fabric electrodes.

conductivity, temperature and Na^+ concentration, a sweat rate sensor and a SpO_2 optical oximeter unit. Preliminary testing on sportsmen and diabetes patients showed promising results and identified issues for further development and testing.

The above prototype systems either have been recently finalized and tested or are currently going through testing and validation. The large majority of these devices require further improvements, testing and validation to reach the medical device label, meet the regulatory framework (s) and identity sustainable market opportunities.

III. CHALLENGES AND FUTURE R&D DIRECTIONS

The main challenges for the development of new generation MNBS are directly linked to three major "dimensions" i.e. computerisation, miniaturisation and "molecularisation" (integration of molecular & cell biology)[11].

Computerisation will enable for example integrated bioinformatics medical data management, increasing data rates, storage power and tele-transmission of patient data.

The impact of miniaturisation is on the delivery of a given function as well as on mass production and cost of the final system. Future micro-nano systems will consist of integrated smart systems able to sense and diagnose a situation, to interface, interact and communicate with the environment and with other systems, as well as to predict, act and perform multiple tasks. Integration into the fabrication sequence ready for industrialization and especially, integration with other devices is, also, a critical and very challenging task.

Major challenges of "molecularisation" include e.g. the development of new biomarkers, the immobilization of active molecules on surfaces and in exact positions, new surface chemistry, as well as biocompatibility and multiplexing techniques to ensure powerful and accurate signal output. A further key issue is to develop reliable and reproducible engineering, chemistries and bioprocesses at the molecular level that can be manufactured, in bulk, in mass production systems to take nanotechnologies from the status of laboratory tools into commercial products in the full range of markets.

Additionally, the development of new biological & biochemical sensors (e.g. for analysis of DNA, proteins and toxins in body fluids and breath) and their integration into small smart systems are key for the achievement of dedicated multi-parametric detection, for reliability, robustness and limitation in price. To meet these requirements adaptive materials capable of changing their physical and/or chemical properties in response to a change in conditions are necessary e.g. conducting polymers, and materials combined with actuation to generate local responses. New and more effective materials are also required for energy generation/storage/supply such as photoelectric cells, piezoelectric and micro-fuel cells. Other major demands relate to, flexible and robust electronics, inter-connects, and fluidic manifolds production; heterogeneous low power wireless communications systems; and, packaging and assembly for biocompatibility and compliance.

In particular for in vivo applications, a challenging issue is the miniaturisation of long-life power supplies and signal coupling from inside the body to local body networks.

The effort towards a fully comfortable, multifunctional, reliable, low-power consumption and cost-effective wearable systems should focus more on the achievement of high added value products in the next five to ten years. Several issues, technical as well user-oriented, societal and business, remain to be solved. More robust and certified core modules/technologies should be achieved for e.g. interfacing, packaging, conformability (e.g. stretchable and flexible electronics), and layers interconnexion[12, 13]. Manufacturing, usability and better collaboration between designers, engineers and users are key issues for success. More knowledge on biophysical issues such as biophysical expertise on skin-sensor interaction models, electrochemical aspects and skin physical-chemical properties (e.g. age, gender and race) is necessary to optimise these systems.

Reliability of MNBS is a critical issue. Major advances in micro and nano fabrication have delivered failure rates of less than one in a thousand, ten thousand or a million but by the time these components are applied in a system in a biological setting these rates may raise significantly, quite possibly to a level unacceptable in medical reliability terms. It is clear that in some applications there is the possibility with micro and nano systems for massive parallel processing with a high degree of redundancy actually raising reliability levels.

Micro-nano-bio and wearable systems have also to reach clinical acceptance by medical professionals and patients. Another important issue is liability of these systems, like any new medical technology which inevitably become a barrier to technology development and application as a result of the cost, time and manpower that is necessary to invest to address and offset potential liabilities.

New technologies bring new approaches to medicine and these can often be seen as more costly because they imply system changes. Early phase technologies are often very expensive and it is only when the technology is industrialised that costs drop. Reimbursement systems vary from country to country and between healthcare providers. Different regimes operate for, pharmaceuticals, diagnostics, devices and services. The classification and reimbursement regime for nano and micro-technology solutions in healthcare will have to be addressed with all stakeholders.

[11] Micro-Nano-Bio Systems: New challenges and Future R&D, FP7 Consultation Workshop, Brussels, 3rd May 2006, WS Report, available on line at http://cordis.europa.eu/ist/mnd/events.htm

[12] http://www.place-it-project.eu/

[13] http://www.pasta-project.eu/

IV. Conclusion

MNBS and wearable smart systems hold great hope for addressing cost-effectively major pHealth needs. Advances in micro and nano systems will enable better treatment and monitoring of patients at the point of need. In combination with better medical and biochemical knowledge of the individual, these systems will constitute one of the pillars for an integrated approach of tomorrow's healthcare.

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