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Micro-nano-biosystems: An overview of European research

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Abstract
New developments in science, technologies and applications are blurring the boundaries between information and communications technology (ICT), micro-nano systems and life sciences, e.g. through miniaturisation and the ability to manipulate matter at the atomic scale and to interface live and man-made systems. Interdisciplinary research towards integrated systems and their applications based on emerging convergence of information & communication technologies, micro-nano and bio technologies is expected to have a direct influence on healthcare, ageing population and well being. Micro-Nano-Bio Systems (MNBS) research and development activities under the European Union's R&D Programs, Information & Communication Technologies priority address miniaturised, smart and integrated systems for *in-vitro* testing e.g. lab-on-chips and systems interacting with the human e.g. autonomous implants, endoscopic capsules and robotics for minimally invasive surgery. The MNBS group involves hundreds of key public and private international organisations working on system development and validation in diverse applications such as cancer detection and therapy follow-up, minimally invasive surgery, capsular endocsopy, wearable biochemical monitoring and repairing of vital functions with active implant devices. The paper presents MNBS rationale and activities, discusses key research and innovation challenges and proposes R&D directions to achieve the expected impact on healthcare and quality of life.

Keywords: *Micro-nano systems, micro-nano-bio technologies, information and communication technologies*

Introduction

Research and development at the interface between the micro, nano and living worlds is leading to a new class of technologies and systems able to detect pre-disposition to disease conditions or earliest possible signatures of emerging disease and support immediate, specific and highly targeted intervention (Figure 1).

Micro-nano systems and smart systems technologies targeting 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, are key for achieving the required ability to sense, detect, analyse, communicate, respond and monitor phenomena from macro to nano scale. Furthermore, micro-nano-bio systems (MNBS) exploit additional physical phenomena that involve single molecule interactions and only emerge at the nanoscale, such as surface-plasmon – resonance or solid-state photodetector sensing. Major examples of enabling concepts are integration of all steps of a complex biological protocol into a microsystem that delivers a fast, cheap, easy-to-use and reliable molecular diagnosis at the point of care, and, new miniaturised devices to interface with the skin or to operate safely inside the body. This area concentrates great R&D effort and is supported worldwide through different initiatives/programs such as nano/bio/cognitive technologies convergence (NBIC) (1), nanomedicine and Bio-ICT, driven either by exploration oriented topics (such as materials, tools and processes) or goal-oriented topics (e.g. micro/nano biochemical systems or medical microsystems). All programs serve major policies such as knowledge, technology innovation and industrialisation to address major societal needs.

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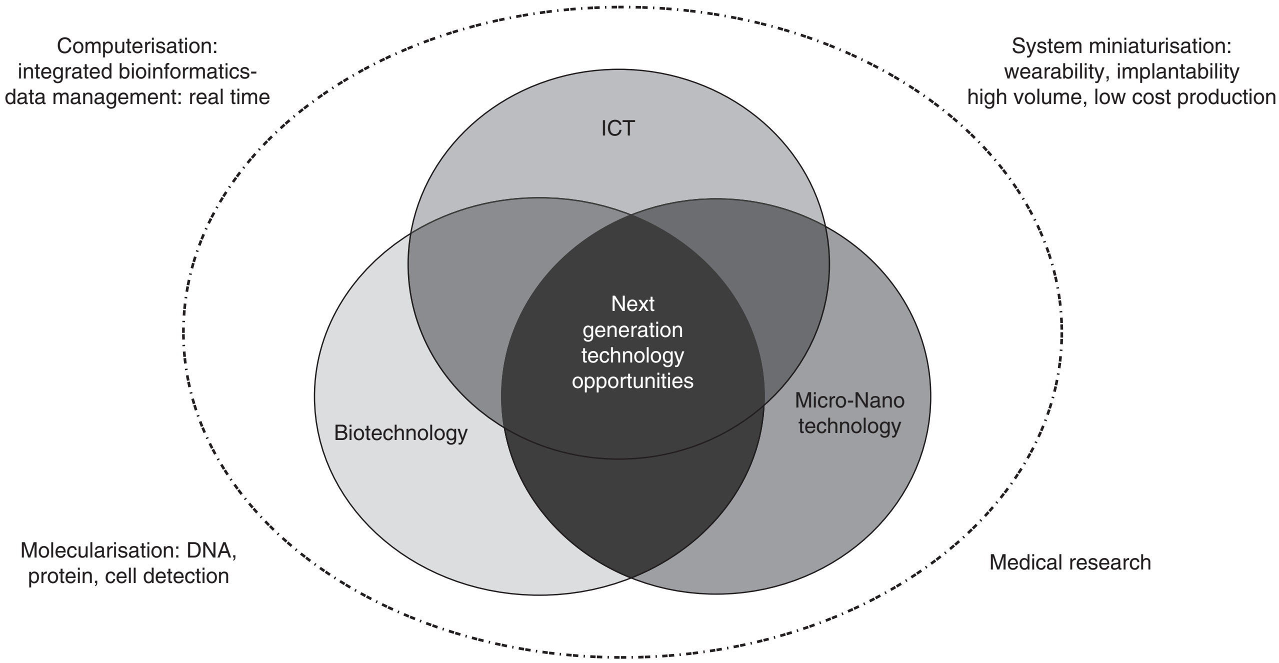

Figure 1. Research at the convergence of ICT, biotechnology and micro-nano technology: Advances driven by computerisation, miniaturisation, molecularisation and medicine.

Within the European Union (EU) R&D Programs, Information and Communication Technologies (ICT) priority (http://cordis.europa.eu/fp7/ict/), the current strategies focus on the achievement of substantial improvement on various aspects of system integration. This includes miniaturization and reduced power consumption, system quality & reliability, increased speed and shorter time-to-market. In addition, significant effort is put on advanced solutions and testing of building blocks such as molecular detection, biocompatibility and interfacing with tissues.

The MNBS group of projects (2), involving more than 350 private and public organisations from Europe and other regions of the world, currently includes advanced systems for

- *in vitro* molecular diagnosis & biochemical analysis and
- *in vivo* interaction with the human body.

Projects addressing the first subgroup focus on the development and testing of building blocks (e.g. miniaturisation and optimisation of microfluidics, sample preparation, chemistry process for molecular recognition and ultra sensitive detection) and their integration into reliable and low-cost systems, e.g. DNA & protein arrays, micro Total Analysis Systems (µTAS), Lab on Chip (LoC) and Lab on Card. Projects in the second subgroup focus on building blocs (e.g. biocompatible materials, sensing & actuation, power solutions and interfacing electronics with human tissues and cells) and their integration into reliable, minimally invasive and low-cost smart systems such as active implants, endoscopic capsules, robotics for minimally invasive surgery, drug delivery systems and wearable biomedical systems. Standardisation, clinical validation and strong involvement of end-users are essential elements of the projects in the process of pre-commercial system design and development.

Achievements and ongoing research

Microsystems technologies are considered today as the main miniaturisation and parallelisation approach for life sciences applications, leading to a number of significant achievements. Table I provides a summary of the major microsystems products (BIOMEMS 2008, Yole Development SARL, March 2008) available on the market and representative examples.

However, although these products demonstrate significant advances in biochemical testing, at cellular and molecular level, and in body monitoring, they do not fully address the large spectrum of application requirements in life sciences, pharmaceutical and healthcare. For example in the area of *in-vitro* testing, market products do not meet the requirements for fast, low-cost and high complexity sample analysis.

Table I. Major Microsystems products in Life Sciences, pharmaceutical research, diagnostics and therapeutics.

Type of Products	Applications	Product examples
Microarrays (or chips)	Life sciences & pharmaceutical research, *in-vitro* diagnostics	-Affymetrix-GeneChip^{R} -Roche-Amplichip CYP450
Microfluidic Devices	• Life sciences & pharmaceutical research (e.g. cell chips, electrophoresis chips, proteomic devices and microdispensers • Point-of-Care diagnosis (e.g. autonomous diagnostic systems) • Drug delivery (micropumps, atomisers, microneedles)	• Life Sciences - Silicon Biosystems- Smart Slide^{TM} chip. - IMT LifeMEMS^{TM} -Rare cell purification chip • Point-of-Care diagnosis - Abbott i-Stat device for blood gas & electrolytes - STmicroelectronics-in-Check system for sample preparation, PCR amplification and detection. - Siemens- Quicklab^{R} silicon La-on-chip • Drug Delivery - Boeringer MicroParts Respimat^{R} Inhaler for pulmonary diseases - Medtronic Minimed Inc.-Minimed 2007 Implantable insulin pump
Pressure Sensors	Blood and respiratory monitoring	• Motorola- Disposable micromachined blood pressure sensor • NovaSensor/GE- micro sensors for monitoring blood pressure during cardiac catheterisation
Accelerometers	• For pacemakers • For Blood pressure measurement	-ELA Medical- accelerometer for activity monitoring and adjustment of pacemaker action to activity level - Omron Healthcare- portable wrist blood pressure monitor allowing measurements only after the wrist is set at the right position.
Gyroscopes	For human motion analysis in case of movement disorders	ClevemED – Kinesia system to monitor upper extremity motion for diagnosis and therapy evaluation

In vitro testing and point of care systems

Cellular and molecular *in-vitro* analysis represents today a large R&D community, investment and market opportunities. The *in-vitro*-diagnostics (IVD) market (BIOMEMS 2008, Yole Development) (e.g. molecular biology, clinical chemistry and immunoassays) was evaluated at $ 34 billion in 2007 and presents an annual growth of 4–5%. Much cell-based microsystem research (3–11) takes place under a "Lab-on-Chip" or "micro-total-analysis-system", incorporating several steps for the analysis of the biochemical reactions in cells (including image-based analysis and techniques for gene and protein analysis of cell lysates) into a single system. However, despite the fact that typical unit operations have been demonstrated (e.g. sample processing, sensor arrays, development of bio-interfaces and protocols for DNA and protein detection, data analysis & read-out circuitry and specific biomarkers), robust approaches to fabrication, integration and packaging remain major areas of research. The major expected impacts from integrated, smart miniaturised *in-vitro* testing systems are related to reduction of time to diagnosis and treatment time; automatic storage of test results and provision of qualitative and quantitative fast results; potential shortening of the length of hospital stay by making test results available earlier and therapies more effective.

MNBS projects for in-vitro testing and diagnosis research and develop solutions to meet those challenges. As they have been selected through different calls for proposals of the *Information and Communication Technologies R&D program*, they tackle these issues through different and complementary targets, e.g.:

- Enhanced diagnostic capabilities meeting requirements of cost and disposability; radical improvement of sensitivity, accuracy, precision, stability, selectivity, reproducibility, reliability and cost.
- Integration of technological developments - in particular of biosensors and smart and hybrid materials that may interact with their surroundings, precision engineering, micro- and nano-fluidics, and opto/electromagnetic methods with greater knowledge of the interactions between biological and non-biological systems.

The projects target testing and validation in several applications such as allergen detection, circulating tumour cells detection for breast and prostate cancer, toxin detection, leukaemia, hepatitis B /liver cancer, cardiovascular diseases, cystic fibrosis and early detection of deep vein thrombosis. The types of biological compounds which interact in the bioanalysis process are DNA, protein, cell, DNA/protein, antibody-antigen (A-A) /DNA, A-A, A-A/Protein or DNA/mRNA.

Three different physical principles of biosensing have been applied: Optical (12,13), impedimetric (14) and inertial (15) (Table II).

The projects' objectives can be classified in four main types: Improved sensitivity, multianalyte capabilities, rapidity of the biosensing process and development of a fully integrated/miniaturised end-system/ prototype.

- *Sensitivity:* Improvements of the sensitivity of a MNB system are brought about by improved detection and/or improved labelling (16–18). Several projects achieve the former by refining existing detection methods, e.g. by using two incident polarizations instead of one in surface plasmon resonance or by developing interferometric techniques that utilize both phase and intensity. Ongoing improvements in the quantum efficiency of LEDs, organic light emitting diodes (OLEDs) and solid-state technology are likely to improve performances. Experimental work to determine better biolabels (18–20), as well as the optimization of chromatographic electrospray systems for mass spectrometry, complements the improvements in detector technology.
- *Multianalyte capabilities:* They refer to the ability to make parallel measurements of the same or different analytes or to devices designed for testing a range of biosamples (20). Significant results have been achieved through combination of advances in microfluidics (specifically analytic and numerical approaches to understand the phase transitions and dynamics of drops on patterned surfaces with the aim of improving microchannel design), in multiple parallel biomarkers (e.g. for several cancer types, hepatitis B and cytomegalovirus) and detector sensitivity.
- *Rapidity:* Some projects have pursued label-free technology to eliminate time-consuming sample pre-treatment (14,16). Multianalyte capabilities speed up bio-analysis by allowing e.g. the sampling of up to 100 allergens in parallel.
- *Integration and miniaturisation:* This is achieved by refining each stage of the bioanalysis process. Technological solutions include label-free methods, integrated wireless technology, disposable lab cards, increased detector sensitivity and multichannel detection and enhanced microfluidics management, especially the use of hydrophobic materials to allow smaller channel dimensions.

Recently started research by multidisciplinary teams aims to cope with interfacing and integration problems generic to microfluidics and smart miniaturised systems. It focuses on the achievement of reliable, fast, specific and cost-effective LoCs integrating the entire process flow from sample preparation to detection. Driving applications are early cancer detection and follow-up, food and water quality control for contamination & crisis management and

Table II. Sensing techniques applied by MNBS projects.

Sensing Method	Basic Principles	Features
Optical sensing	Measuring changes to the optical properties of a sample caused by the biological interaction of interest; Optical sensing includes Raman Spectroscopy, Photonic crystals, Waveguides, Interferometers, Optical fibers, and Surface Plasmon Resonance.	- label-free sensing i.e. the presence of a particular molecule alters the propagation constant in a waveguide, or, - involving markers such as fluorescing nanoparticles.
Impedimetric sensing	Measuring changes to the electrical properties of a sample caused by the biological interaction of interest	- Affinity-based sensing i.e. an immobilized capture probe selectively binding to the analyte (normally via an antibody-antigen interaction) so transferring the challenge of detecting a target in solution into detecting a change at a localized surface, and, - frequently label-free. Related amperometric sensing, measures DC current as a function of analyte concentration under an applied potential difference.
Inertial sensing	Relies on measuring changes to some inertial characteristic and typically involves biomarkers	A familiar example is mass spectroscopy.

detection of potentially dangerous substances through sweat analysis.

In vivo MNBS and wearable systems

In vivo interaction between micro-nano systems and the human body e.g. with body sensors, implantable systems, endoscopic probes, and wearable systems, targets several applications such as non-invasive long term monitoring, drug delivery, vital functions repair, targeted therapy, early diagnosis and well being support. Medical technology has significantly contributed to better healthcare through cardiac pacemakers, minimally invasive surgery, neuro-stimulators, prosthetics and instrumentation. Wireless sensors for body monitoring and wearable technology have greatly enlarged the application possibilities (21,22). However, despite recent progress, many challenges remain on the road to body sensors and systems.

MNBS projects in this area focus on research, development and validation of high-performance components and modules (e.g. micro/nano electrodes, sensors and 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 activities are on active smart implants (23–25). This requires key technologies development such as in power supply (e.g. implantable battery and biofull cell), wireless communication, biocompatible implant coating and system integration. EC funded project Healthy Aims (26) developed core implant technologies (e.g. biocompatible implant coatings, biofuel cell to power implant electronics and wireless communication), new medical 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)

The systems have been successfully evaluated in laboratory and through ethically approved animal and human trials.

Another project currently researches and develops implantable subcutaneous glucose biosensor for continuous monitoring of diabetic patients (http://www.pcezanneportal.co.uk). The measurement is based on glucose-binding proteins (developed by the project) with fluorescent characteristics that are affected by the level of occupancy with glucose (designated GBP-Fluo proteins).

The need for high temporal and spatial resolution brain studies is addressed by the Neuroprobes project through the development of arrays of multifunctional microprobes (27). The resulting array is modular, integrates electronic depth control to adjust the position of individual electrodes with respect to neurons, and enables recording and stimulation, both electrically and chemically. This is a powerful tool for brain disorders (e.g. epilepsy) and brain-computer interface applications.

Another important contribution is on diagnosis and therapy of gastrointestinal cancers through intelligent endoscopic capsules using innovations in micro- and nanotechnology (28). These capsules have unprecedented functions, e.g. advanced vision, magnetic and other navigation modes, localisation and wireless transmission capabilities and are capable of screening, diagnosis and therapy (manipulation of tissues).

Two other important projects have delivered intraoral microsystem drug delivery (http://www.intellidrug.org/link_solution) and ambulatory systems for attention, stress and vigilance monitoring (http://www.sensation-eu.org/).

ARAKNES (http://www.araknes.org/home.html) is a major activity in endoluminal, transluminal, and transabdominal robotic surgery. It integrates the advantages of traditional open surgery, laparoscopic surgery (MIS), and robotics surgery into a deeply innovative system for bi-manual, ambulatory, tethered, visible scarless surgery, based on an array of smart microrobotic instrumentation (29).

Non-invasive wearable smart systems such as smart fabrics and interactive textile (or e-textile) (30) offer, in addition to unobtrusiveness and comfort, the advantage of removing the task of placing the sensors by a professional as well as offering a natural interface with the body with accurate, reproductive positioning of the sensors. The sensors are enclosed in the layers of fabric (e.g. fiber optic), or it is the fabric itself which is used as sensor or distributed network of sensors. (e.g. piezo-resistive and conductive fabrics). These prototypes incorporate mainly electrocardiogram and respiration monitoring and accessorily other physiological and physical parameters (depending on the targeted applications) by implementing strain fabric sensors and fabric electrodes.

A very promising research activity is on wearable biochemical sensing though sweat analysis. Biotex project (31) developed and tested a textile patch comprising an integrated passive pump and pH sensor unit, built into the fabric itself. Additionally the patch is provided with a flexible polyimide substrate carrying a multi-sensor unit containing: A sensor for sweat conductivity, temperature and Na^+ concentration, a sweat rate sensor and an SpO_2 optical oximeter unit. Furthermore, the project has shown a portable system which optically measures pH and C-Reactive Protein (CRP) in wound exudates. Preliminary pilot trials on sportsmen, patients suffering from cystic fibrosis and on people suffering from diabetes showed promising results and identified issues for further development and testing.

Challenges and future R&D directions

The main challenges for the development of new generation MNBS are directly linked to three major "dimensions of progress" i.e. computerisation (employment of ICT), miniaturisation (decreasing size of devices, systems & components) and molecularisation (integration of molecular & cell biology) (Micro-Nano-Bio Systems: New Challenges and Future R&D, FP7 Consultation Workshop, Brussels, 3rd May 2006, WS Report, available online at http://www.cordis.europa.eu/ist/mnd/events.htm).

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

The impact of miniaturisation is on the application or the delivery of a given function. Advanced 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 to make a system is, also, a critical and very challenging task.

Major challenges of "molecularisation" include: The development of new marker molecules; the immobilization of active molecules on surfaces and in exact positions; new surface chemistry; 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 a laboratory tool to being commercial products in the full range of markets.

The nature and economics of healthcare has always been dynamic and has always responded dramatically to demographic change and technology development. Societal changes such as the ageing population, lead to increased demand for care. At the same time scientific progress is generating more opportunities to meet the demands for prevention and treatment. Progress needs to be channelled into new products, services and legislation in order to meet future demands growing in the marketplace. Micro-nano-bio systems are expected to impact in the next five to ten years the areas of imaging and sensing, minimally invasive surgery, healthcare IT, smart devices that correct deficient body functions and molecular medicine.

Micro & nano technologies (MNT) will change the way healthcare is organised, thus altering the cost base for healthcare and will diminish the boundaries between medical and pharmaceutical practice, between home care and test laboratories.

Major technology demands

MNBS require dedicated detection of multiple parameters. The development of new sensors and their integration into small smart systems are key for the achievement of reliability, robustness and limitation in price. Functionalities include the fields of physical sensing (such as pressure, motion, and heart contractibility), chemical & biochemical sensing (such as analysis of body fluids and breath) and biosensing (such as proteins, DNA, lipids and toxins in biological fluids). 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, photoactive materials, and materials combined with actuation (electrical, mechanical, chemical) 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:

- Low power micro/nano-electronics and micro/nano-systems fabrication.
- Flexible and robust electronics, inter-connects, and fluidic manifolds production.
- Heterogeneous wireless communication systems, with further attention to low power.
- Packaging and assembly for biocompatibility and compliance.

Particularly 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.

Lab on a chip remains a major area of activity in micro and nano technology research and attracts great interest for future developments. LoC is an effective technology at a research level, often developed in a specific lab for a specific purpose, commercially a specific chip is produced for a specific function. The next stage is to satisfy the demand for multifunction chips and reliable integrated LoC which will drive towards much wider application in a range of markets, such as environmental monitoring or food process. Therefore manufacturing and industrialization of technology are critical steps to reach the market. This is also the case for identification, development and application of new biomarkers.

Other outstanding issues

Robust standards will contribute to ensure scientific accuracy and probity, to address specific scientific, technical and ethical concerns in application. Strongly linked to standards and protocols, MNBS validation, evaluation and demonstration in real size trials in different applications fields like health, environment and safety are critical steps towards the implementation of MNBS applications.

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. Clearly 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.

MNBS have also to reach clinical acceptance by medical professionals and patients. Another important issue is liability of MNBS, like any new medical technology which inevitably becomes 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 relevant stakeholders.

An additional barrier to further exploitation of MNBS is regulation and health finances. Therapeutics, diagnostics and medical devices are all subject to extensive and complex regulatory regimes both in Europe and internationally. It is clear that micro- and nano- technologies will either fall under the aegis of the current regulations or require the development of additional regulatory legislation. New medical technologies also raise a wide range of ethical issues. For example many doctors believe that medical support and counselling is vitally necessary for difficult diagnoses. If a POC cancer diagnostic means a patient can self-test, the medical profession is concerned whether making such a product available is ethical. The ethical issues range from data protection, to insurance, criminal records and healthcare provision matters. Frameworks will have to be developed to address these issues if societies and governments are to sanction the application of these technologies.

Conclusion

Research and developments of micro-nano-bio systems such as biochip, biosensors, LoC, active implants and minimally invasive body sensors address significant issues in life sciences, pharmaceutical research and in healthcare. Apart from the technological research progress increasing physiological knowledge leads to possible new applications of smart integrated systems. These developments imply that interdisciplinary research and development involving medical, natural and engineering sciences will form the basis for innovative contributions to improve healthcare in the future.

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