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Electronic systems for health management

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42.1 Introduction

Several important societal and economic world problems can be addressed by the smart use of technology. The past 40 years have witnessed the realization of computational systems and networks, rooted in our ability to craft complex integrated circuits out of billions of electronic devices. Nowadays, the ability to master materials at the molecular level and their interaction with living matter opens up unforeseeable horizons. Networking biological sensors through body-area, *ad hoc* and standard communication networks boosts the intrinsic power of local measurements, and allows us to reach new standards in health management. The Swiss Nano-Tera program addresses applications of nanotechnologies to health management, and it has been instrumental in fostering research and innovation in this domain.

42.2 The Nano-Tera program

Nano-Tera addresses system engineering research that leverages micro-, nano-, information, and communication technologies. The broad objectives of the program are both to improve quality of life and security of people across different levels of education, wealth and age, and eventually to create innovative products, technologies and manufacturing methods, thus resulting in job and revenue creation. Although the principal application domains are health and environment, energy and security issues are also investigated as support areas. The intrinsic value of the underlying research is to bridge traditional disciplines, including electrical engineering, micro/nano-mechanical systems engineering, biomedical sciences, and computer/communication sciences, with the objectives of (i) deepening the understanding of enabling technologies, (ii) reducing scientific concepts to practice, and (iii) mastering the novel challenges of designing large-scale complex systems.

The Nano-Tera program was launched by the Swiss government in 2008. After a first 5-year phase devoted to the search of enabling technologies, a second phase started in 2013 with a focus on applying new technologies to systems. The governmental funding rate is approximatively 15M USD/year. This funding is matched by an equal amount provided by the partner institutions and by third parties (e.g. industry). Nano-Tera has been established as a *simple partnership*, which enables universities and research centers to provide a neutral platform for collaboration and development.

Nano-Tera distributes money for funding projects on a competitive basis, and the Swiss National Science Foundation provides it with proposal reviews for quality control. Nano-Tera funded 19 large projects during the first phase, and 18 new large projects are starting under phase two in 2013. A similar number of small projects and education/dissemination events are also supported. More than 80% of the total funds are dedicated to the large projects, dubbed *Research, Technology and Development* (RTD) projects, which, by construction, involve multi-discipline, multi-institutional teams of researchers addressing cutting edge topics within the program scope. Typically, these

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projects require a strong investment which is not readily available from other funding sources. A total of about 700 researchers participate in the RTD projects and about 120 doctoral theses are supported by the program at the time of writing (Q1 2013). This chapter provides a glimpse of the current RTD projects addressing health management. A detailed description and statistics of these and other projects are available online [1], as well as citations to specific scientific work.

42.3 Health management technologies

Future health management systems will require an increasingly large presence of automation, information extraction, and elaboration, as well as control of the medical procedures. In essence, we can envision three major areas that require innovation: (i) real-time sensing and data acquisition of bio-chemical compound concentrations; (ii) information networking through a specialized physical layer; (iii) data elaboration, retrieval, and classification.

Sensing is a discipline that traditionally has been developed by communities related to fundamental sciences (e.g., physics, chemistry, and biology). Despite the large number of sensors available, their effective use is limited by size, power consumption, and lack of effective integration with electronic and information systems. In other words, sensing is still based on discrete components, in much the way that a transistor radio was assembled 50 years ago. The integration of sensing with electronics, and thus the merging of sensing and electronic design, is key to achieving miniaturized, low-power, low-noise data acquisition chains with detection limits in regions of interest for clinical studies. To date, only glucose monitoring has reached some form of maturity, and FDA-approved devices are available for diabetic patient monitoring.

The challenges of biomedical electronic systems are related to both data acquisition and communication. Indeed, sensors in the body need to communicate to external devices. Power delivery means can obviate the need for implanted batteries, which always present some risk factor. Sensors on the body communicate through *body-area networks* (BAN), a new technology with several challenges, including energy efficiency, bandwidth, and security. Biocompatibilty and the selection of materials and related technologies are also important topics of research.

Information systems for biomedical applications have been developed, but they are typically used offline. The need for fast responses and their secure interaction with electronics on the body and/or in the body is still an area of research. Nevertheless, the combination of networked databases with online data acquisition chains opens the door to better therapy as well as to promoting the autonomy of the patient and convalescent.

42.4 Sensing and diagnosis

42.4.1 Biosensing

Biosensors are used in the medical practice for *online* and *offline* diagnosis. Few systems for online monitoring are available on the market. Monitoring metabolism is a complex and expensive process, mainly because of the unavailability of accurate, fast, and affordable sensing devices that can detect and quantify multiple compounds in parallel and several times a day. To date, most medical systems available on the market for human telemetry use wearable devices (accelerometers, heartbeat monitoring system, etc.) but they do not measure molecular metabolites. The only available real-time, implantable/wearable systems for metabolic control are limited to glucose monitoring in diabetic patients. For other pathologies, molecules are monitored in daily hospital practice by means of blood sampling and offline analysis. This requires large and expensive laboratory equipment. Offline bio-measurements are achieved by a wide array of techniques. Still, there is a strong potential for improvement, by exploring various sensing mechanisms, using advanced electronic devices and materials, and tightly coupling electronic sensing to data acquisition chains.

The *i-IronIC* project (Figure 42.1) addresses an innovative, highly integrated, fully implantable and real-time monitoring system for human metabolism. The monitored metabolic molecules are lactate, cholesterol, ATP, glutamate, glucose, and others. The system to be realized consists of: (i) an implantable integrated sensor array and data acquisition electronic unit; (ii) a wearable station for remote powering and signal processing; (iii) a remote station for

Figure 42.1 The i-IronIC implantable sensor. Courtesy of S. Carrara.

data collection and storage. The main scientific challenge is related to fabricating the implant to be housed in a biocompatible cylinder of about 2 mm in diameter and 15 mm in length, to be placed in the interstitial tissue. The current prototype includes: a sensor array, a CMOS mixed signal chip, and a tridimensional integrated coil for receiving inductive power and transmitting data via backscattering. The sensor array is realized with an innovative technology, in which *carbon nanotube* (CNT)-nanostructured electrodes enable us to measure metabolites with increased sensitivity and lower detection limits as compared with the state of the art. The integrated electronic and sensor array requires 0.5 mW to operate: the electronic power is harvested by the coil. An electronic patch on the body produces the inductive field to power the implant, receives the backscattered data, and transmits it to a base station using the bluetooth standard.

The *NanowireSensor* project seeks to develop a modular sensor platform for the electronic detection of analytes in solution. The platform uses *silicon nanowire* (SiNW) field-effect transistors as a sensor array and combines them with state-of-the-art microfabricated interface electronics as well as with microfluidic channels for liquid handling. Such sensors have the potential to be mass manufactured at reasonable costs, allowing their integration as the active sensor part in electronic point-of-care diagnostic devices. The platform can be used for offline analysis of substances at very low concentrations. While promising biosensing experiments based on SiNW field-effect transistors have been reported, real-life applications still require improved control, together with a detailed understanding of the basic sensing mechanisms. For instance, it is crucial to optimize the geometry of the wire, a still rather unexplored aspect up to now, as well as its surface functionalization or its selectivity to the targeted analytes.

The *IrSens* project aims at building a platform based on optical spectroscopy in the near and mid-infrared range, by exploiting optical absorption properties of the analytes. The sensors probe the vibrational frequencies of the targeted molecules of gases and liquids. The sensing platform for gases under development is based on multipath absorption cells with various semiconductor light source and detector types. In particular the platform can detect *Helicobacter pylori*, a bacterium responsible for gastric ulcers, by means of isotopic ratio measurements in exhaled CO_2. The integrated sensing platform for liquids is based on wave-guiding and surface measurement technologies, and the same sources and detectors as for the gas sensing. The sources are coupled to a silicon-based optical module where the liquid analyte flows through a built-in microfluidic channel (Figure 42.2). This is intended to be used for the detection of drugs and doping agents in human fluids, such as cocaine in human saliva.

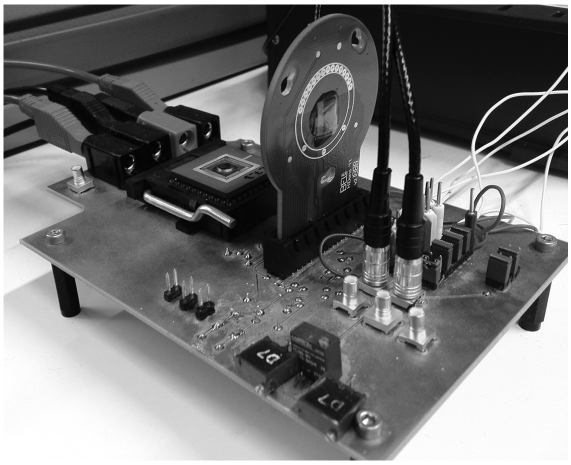

Figure 42.2 Printed circuit board to interface with fabricated CMOS chip and to connect it with the silicon nanowire chip. Courtesy of C. Schöneberger.

42.4.2 Advanced diagnosis tools

Advanced diagnosis relates to the design of new methods for probing the human body as well as making diagnosis tools portable and available at points of care. The miniaturization of diagnosis equipment often requires the use of new technologies, and opens the way to radically new procedures.

The *Nexray* project targets the development of novel small X-ray sources and detectors whose outputs will be combined to new image processing systems. The miniaturized X-ray sources are based on *multi-walled carbon nanotube* (MWCNT) cold-electron emitters. Unlike classical thermionic emission, field electron emission of the CNT is voltage-controlled, and thus enables high modulation frequencies up to GHz level. The X-ray direct detectors are based on crystalline germanium absorption layers grown directly on a CMOS sensor chip, yielding high-resolution and high-sensitivity X-ray detectors. Single photon detection enables a significant improvement of contrast. Moreover, the direct integration of germanium absorption layers into CMOS sensors results in on-pixel signal preprocessing capabilities, which can be exploited for various applications (Figure 42.3).

The outcome of this project relates to two radical new approaches to X-ray imaging. First, *X-ray time-of-flight* (XTOF) measurements can be used to probe the depth inside objects. This calls for an intensity-modulated X-ray signal in the MHz range which is not possible with conventional X-ray sources but can be achieved with CNT-based cold emitters. Second, we can achieve tomographic imaging by exploiting the fact that both the X-ray source and the X-ray detector are pixelated. Indeed, the X-ray source is built as a matrix of micro X-ray sources that can be

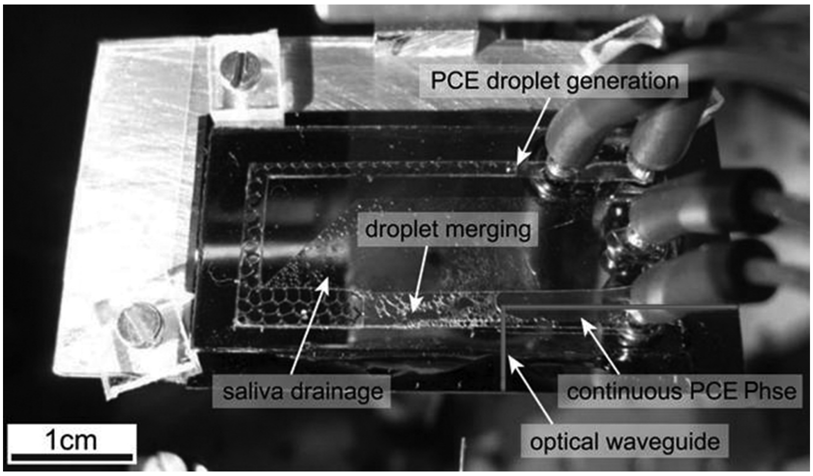

Figure 42.3 IrSens fluid detection: first fully integrated prototype for cocaine detection in saliva. Courtesy of J. Faist.

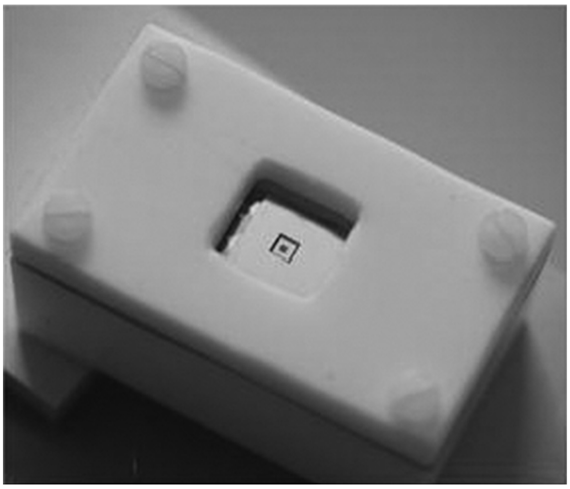

Figure 42.4 Test X-ray source. Courtesy of A. Domman.

addressed and controlled individually. The combination of pixelated X-ray sources and detectors opens up completely new imaging capabilities.

The *PATLiSCi* project aims at investigating diagnosis of tissues based on micromechanical sensing (Figure 42.4). Scanning force microscopy and related techniques enable high-resolution imaging e.g. of membrane proteins, offering unprecedented insights into their structure and their functioning. Interestingly, it has been shown recently that the stiffness of cancer cells affects the way they spread in the body. Equally important are the adhesion forces of cancer cells to other cells. The measurement of nanomechanical properties of cells as well as cell–cell interactions as a function of milieu parameters is thus of particular interest in cancer research. The nanomechanical properties of microcantilevers allow us to use them as highly sensitive probes for the detection of molecular species adsorbed to them. The additional mass and/or the surface stress exerted by the adsorbents changes the mechanical properties, such as their bending or their resonance frequency, and can be readily detected. This method is often described as a *mechanical nose*, since many of these cantilevers in parallel, each responsible for the detection of a specific target substance, detect an ensemble of substances. The nanomechanical nose mirrors the design of the human olfactory system, where mechano-transduction in olfactory cells is coupled to the biological neural network, i.e. the brain. The old medical art of diagnosing disease by its odor, limited by observer dependence, lack of quantitative analysis, and the limited sensitivity of the human nose, thus finds its correlation in nanomedicine, where nanomechanical olfactory sensors enable quantitative and objective analysis of carcinogenic diseases in point-of-care early diagnostics.

The *NutriChip* project aims at building an integrated lab-on-a-chip platform to investigate the effects of food ingestion by humans (Figure 42.5). The core of the system is an integrated chip, the NutriChip, which, as a demonstrator of an artificial and miniaturized gastrointestinal tract, will be able to probe the health potential of dairy food samples, using a minimal biomarker set identified through *in vivo* and *in vitro* studies. The project exploits innovative CMOS circuits at the nanoscale for high signal-to-noise ratio optical detection and proposes a special microfluidic system closely integrating cell-based materials within the chip. The NutriChip will be tested for screening and selection of dairy products with specific health-promoting properties.

42.5 Medical care support

42.5.1 Electronic textiles

Electronic textiles provide us with a very interesting functional material for realizing body-area networks. Moreover,

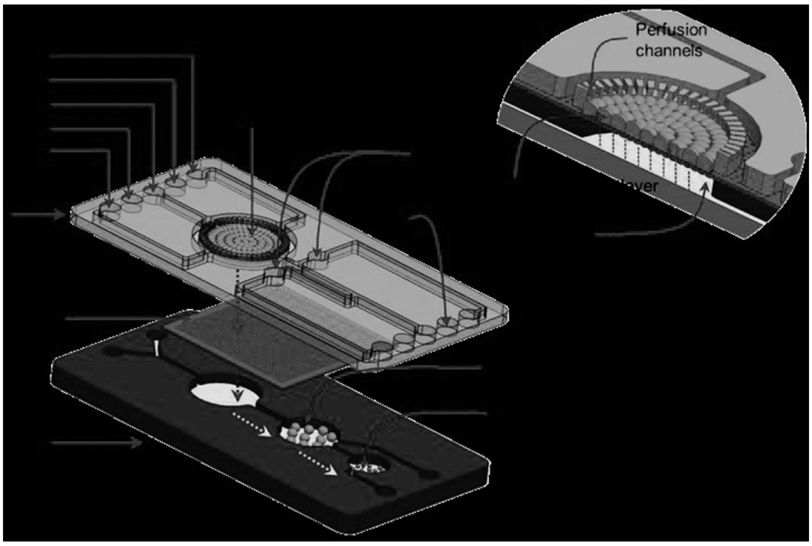

Figure 42.5 NutriChip principle: schematic of the microfluidic PDMS chip forming the microfluidic gastro-intestinal tract. Courtesy of M. Gijs.

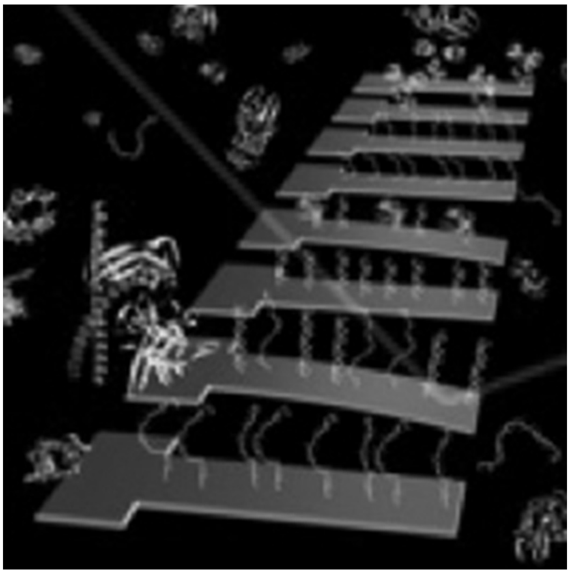

Figure 42.6 Microcantilevers of the PATLiSCi project. Courtesy of H. Heinzelman.

electronic textiles can merge both sensing and communication in the same medium.

The *TecInTex* project aims at the development of textile-based advanced (electrical/optical) fibers incorporating sensors, signal transmission, and other active nano-components (Figure 42.6). The research objectives are to devise both: (i) a family of new functional fibers, enabling *in situ* measurements of body functions like continuous *electrocardiograph* (ECG) monitoring and biological species in body proximity; and (ii) approved fabrication processes and working prototypes dedicated for healthcare, rehabilitation, and prevention. A demonstrator of this technology is embodied by electronic underwear for paraplegics, who typically suffer from pressure ulcers twice a year on average. With intelligent textiles, ulcers can be prevented, with an important reduction of pain and associated healthcare costs. The research includes development of biosensing optical fibers and the design of a prototype for testing the fibers. Biosensing fibers are obtained by modifying standard optical fibers with a sensitive, porous layer specific to relevant biomarkers. Detection is based on optical transmission changes: for example pH sensing fibers were developed by replacing the cladding of the fiber over a length of 2–6 cm with a porous sol-gel layer encapsulating pH sensitive dyes. pH changes result in color changes of the layer, which are detected by measuring absorbance changes at the wavelength of maximum absorbance. An optical source, a photodetector, and a trans-impedance amplifier are needed to convert light into photocurrent and eventually into a voltage for further signal processing. This trans-impedance amplifier is integrated into the textile, as close as possible to the photodetector, to reduce the noise influence.

42.5.2 Smart prostheses

Over one million hip and knee prostheses are implanted each year in the European Union and the United States. The expected lifetime for these prostheses is between 10 and 20 years, but premature failure is quite common (about 20% for people less than 50 years old). Prosthesis failures require revision surgeries that are generally complex and traumatic. None of these prostheses contains microchips, and few are analyzed based on motion analysis devices.

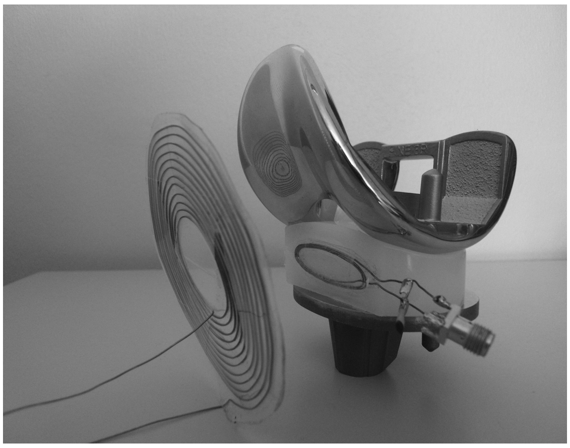

Figure 42.7 Configuration of implanted and external antennas. Courtesy of P. Ryser.

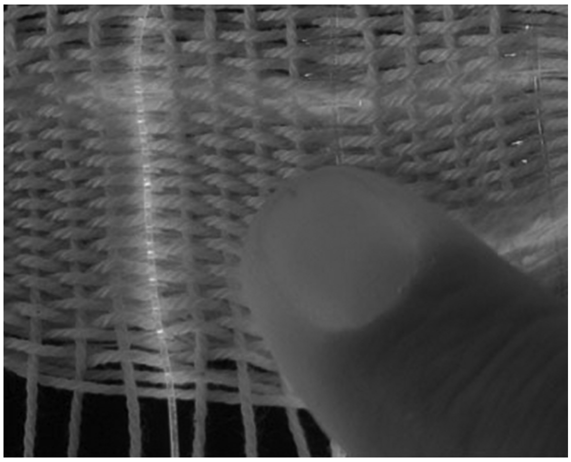

Figure 42.8 Electro-optical textile fabric. Courtesy of G. Troester.

The *SYmOS* project seeks to design innovative tools to measure *in vivo* biomechanical parameters of joint prostheses, orthopaedic implants, bones, and ligaments. These tools, partly implanted, partly external, will record and analyze relevant information in order to improve medical treatments. An implant module includes sensors to measure the forces, temperature sensors to measure the interface frictions, magneto-resistance sensors to measure the 3D orientation of the knee joint, and accelerometers to measure stem micro-motion and impacts. An external module, fixed on the patient's body segments, includes electronic components to power and to communicate with the implant, as well as a set of sensors for measurements that can be realized externally. This equipment is designed to help the surgeon with the alignment and positioning phase during surgery. After surgery, the prostheses will allow the surgeon to detect any early migration and potentially avoid failure by providing information on excessive wear and micromotion. During rehabilitation, it will provide useful data to evaluate *in vivo* joint functions. The tools provided can also be implanted during any joint surgery in order to give the physician the information needed to diagnose future disease such as ligament insufficiency or osteoarthritis, or prevent further accident. Although the scientific and technical developments proposed in this project can be applied to all orthopaedic implants, the technological platform which is being built as a demonstrator is limited to the case of knee prosthesis (Figure 42.8). In addition, by reaching the minimum size achievable thanks to clever packaging techniques and also by reducing, or even removing, the cumbersome battery, it paves the way for a new generation of autonomous implantable medical devices.

42.5.3 Drug delivery

Medical progress is increasingly improving the survival rate and life quality of patients affected by serious life-threatening conditions, such as HIV infection, disseminated cancers, and/or vital organ failure. These achievements rely significantly on new radical improvements in drug regimens and therapeutic protocols. Newly adopted treatments for such diseases require the daily administration of highly active therapies in the long term. The huge variability range in drug response poses strong limits and severe problems in drug treatment definition. The largest part of variability in drug response (roughly 80%) resides in the pharmacokinetic phase, i.e. in dose–concentration relationships.

The *ISyPeM* project aims at providing advanced technologies for assessing drug response by measuring drug concentrations and relevant biomarkers. In particular, it aims at providing drug treatment optimization based on processing of statistical and personal data, and to enable seamless monitoring and delivery by an ultra-low-power integrated system. Thus it is the purpose of the project to create new enabling technologies for drug monitoring and delivery control rooted in the combination of sensing, *in situ* data processing, short-range wireless communication, and drug release control mechanisms. These new technologies, in combination with currently available medical devices (micro-pumps, micro-needles, etc.) can significantly improve medical care and reduce the related costs. Targeted application domains are HIV infection, cancer diseases, and post-transplant therapies, which are currently addressed by the research in pharmacokinetics carried out at the regional hospital CHUV in Lausanne.

42.6 Summary and conclusions

Advances in sensing technology, nanoelectronics, data processing and communication enable the design of new health monitoring and management systems. Research in these area is multifaceted, and can only be achieved through the collaborative effort of various groups with diversified competences. The Nano-Tera.ch program has spearheaded some important challenges in these domains. It is unique as a research funding program because it creates a fabric of scientists and engineers whose combined effort can meet the various challenges.

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Reference

[1] www.nano-tera.ch