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- 6 Devices Jacopo lannacci, Fondazione Bruno Kessler (Italy)
- 7 Characterization Erwin Peiner, Technische Universität Braunschweig (Germany)
- 8 Systems José L. Sánchez-Rojas, Universidad de Castilla-La Mancha (Spain)
- 9 Chemical Sensors Jürgen Wöllenstein, Fraunhofer-Institut für Physikalische Messtechnik (Germany)

Part B Cyber Physical Systems

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- Energy Harvesting and Low Power Design Alessandro Bertacchini, Università degli Studi di Modena e Reggio Emilia (Italy)
- 11 Embedded Systems Applications Florian Hammer, Linz Center of Mechatronics (Austria)
- 12 Networking and Embedded Computing Valerio Frascolla, Intel GmbH (Germany)

Introduction to Part A: Smart Sensors, Actuators, and MEMS VII

The conference 'Smart Sensors, Actuators and MEMS' took place in Barcelona, Spain, from 4 May to 6 May, 2015. The interdisciplinary spirit of the event was displayed by a wide range of topics based on the latest research results on the frontiers of microtechnology. Therefore, sessions focused on design, material and fabrication aspects, on micromachined sensors and actuators for the determination of biological, physical and chemical quantities as well as on reliability issues. Moreover, optical and RF MEMS have been presented and more application oriented topics such as energy scavengers, and low power management systems, were discussed. Due to this broad range of topics, researchers coming from academia and industry, with their specific backgrounds, created a very stimulating atmosphere for the exchange of new ideas.

Besides the high quality of the oral and poster presentations, I would like to highlight the three invited talks, the first given by Stephen P. Beeby, from University of Southampton (United Kingdom), on miniaturisation and applications in vibration energy harvesting, the second by Reinoud F. Wolffenbuttel, from Technische Universiteit Delft (Netherlands), on MEMSbased optical microspectrometers, and last, but not least, by Uwe Brand, from, Physikalisch-Technische Bundesanstalt (Germany), focusing on calibration standards for high precision metrology.

I would like to thank all participants for their individual contributions which made the conference a successful event in the international conference calendar. Special thanks go to Ulrich Schmid, Thomas Becker, Jacopo lannacci and Carles Cané, for organising the symposium, to SPIE staff and the Co-chairs Erwin Peiner (Technische Universität Braunschweig, Germany) and José Correia, (Universidade do Minho, Portugal). Finally, I would like to thank the members of the Technical Programme Committee for reviewing the abstracts, especially those who served as session chairs.

José L. Sánchez-Rojas

Introduction to Part B: Cyber Physical Systems

It is with great pleasure we met you at the 1st SPIE Conference on Cyber-Physical Systems. It has been a very interesting event in which authors both from industry and academia had the chance to get in touch and exchange ideas. We really hope they were able to broaden their network of contacts while hopefully finding new ways to cooperate or new market chances.

We are living in one of the most exciting moments in the history of communication and embedded computing, the rise of the Internet of Things. With a forecast of 30 billion connected devices in the next few years, market and research opportunities are growing day by day. With this in mind we tried to shape the Cyber-Physical Systems Conference stressing both the communication and self-sufficiency needs of these distributed systems. By letting wireless links to meet CPSs, new and unpredictable ways of interaction between smart-objects and the surrounding environment will be enabled.

Let me personally thank all participants and authors that, with their contributions, made this conference a great beginning. We are now working on the next edition of the Cyber-Physical Systems Conference, and we are eager to meet you all there, making this event the preferred meeting for a new and sparkling CPS community!

It has been a real pleasure and an honor to work with Alessandro Bertacchini (Università degli Studi di Modena e Reggio, Italy) and Florian Hammer (Linz Center of Mechatronics, Austria) while organizing this event. Their commitment and dedication have been the driving force of this conference. Special thanks go to Valerio Frascolla (Intel, GmbH, Germany) serving as Session Chair in an exemplar way. Together with them, I would also like to thank our entire Programme Committee, which allowed us, with its invaluable work, to meet quality standards this first SPIE Conference on Cyber-Physical Systems deserved.

Riccardo Brama

Measuring life: sensors and analytics for precision medicine

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ABSTRACT

The first industrial revolution focused on machines, the second one was data-centric – a third revolution combining the power of devices and information has just started and transforms our understanding of life itself. Thereby novel sensors and networks from wearable biometric devices to lab-on-a-chip platforms for exploratory fundamental research on single-biomolecule characterization and design occupy a key role. In combination with recent advances in big data analytics for life sciences, healthcare and genomics such sensors are essential tools for moving from fast and cheap personalized DNA-sequencing via smart genomics towards one-off prevention and treatment plans. Replacing state-ofthe-art, one-fits-all approaches, this paradigm shifting individual "assess & response" scheme commonly referred to as precision medicine merges biomedical engineering, systems biology, systems genomics, and information technology. Integrated sensors for isolating, investigating and eventually manipulating single biomolecules are important experimental tools for developing next-generation DNA-sequencing platforms and for conducting 'omics research which is a defining part of systems biology. In that context resistive pulse sensing has emerged as a powerful technology at the intersection of biotechnology and nanotechnology allowing electrical, label-free screening of biological compounds such as proteins or DNA with single-molecule, single-nucleotide and even single binding site resolution. Resistive pulse sensing technology has been at the center of recent commercial \$100Ms investments in the next-generation DNAsequencing sector. While next-generation sequencing platforms based on resistive pulse sensing techniques will mature further, the technology is also increasingly used for screening other biomolecules such as for example proteins. This allows for developing novel diagnostics and ultra-high throughput pre-clinical drug screening systems which might help to transform the pharma pipeline similarly to how the \$1000-genome has revolutionized DNA-sequencing.

Keywords: resistive pulse sensing, precision medicine, systems biology, systems genomics, single molecule sensing, label-free, DNA-sequencing, drug screening, protein screening, nanopore, nanochannel

1. INTRODUCTION

A conventional engine control unit for commercial cars gathers dozens of data points per second. State-of-the-art flight data recorders collect around 3000 data points per second storing several gigabytes of data per flight. The so called APGAR test was developed in 1952 and to-date still is the most comprehensive check of a newborn's organism: it is performed once in a baby's life and collects a total of 5 data points. Why is it that we are monitoring and controlling systems which we entrust our lives to with such diligence, but do not do the same with our life itself? The answer lies in the complexity of the human organism: operating a car engine or flying an airplane is trivial compared to grasping the complexity of physiological interactions in the human body which shape every second of our life. Ever since the doublehelix structure of DNA was discovered in 1953 we have investigated its role as the carrier of the code of life. It was a multi-\$B effort over more than 10 years until a complete human genome had been fully sequenced for the first time in 2003. Being able to read the manual of human life was of course a breakthrough but information could not be derived from it. In order to make sense out of sequencing data it has to be individually contextualized with biomedical metadata (such as for example healthcare and medical records, medical family history, scientific publications). Being able to do this in a meaningful way requires three things: firstly, a statistically relevant number of reference cases needs to be compared to narrow down the physiological function of a specific gene, therefore secondly, DNA-sequencing needs to be fast and affordable for everyone, everywhere, and thirdly, given the size and inhomogeneity of the data to be correlated in a reasonable time, novel big data analytics technologies are needed.

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2. NOVEL SENSORS FOR PRECISION MEDICINE APPLICATIONS

Advancing DNA-sequencing from the \$1000-Genome to the \$1-Genome is a bionanotechnology hardware challenge residing in the field of biomedical device engineering. Setting up large-scale human genome studies to create and analyze sequencing and contextual medical data of an ever increasing number of individuals is a complex joint operational effort in the hands of patients, medical practitioners, scientists as well as regulatory and funding bodies. Developing platforms to process and analyze big data packages of unprecedented size and diversity is a software challenge calling for novel cognitive analytics techniques. The last 3 years have seen substantial advancements in all these areas: the size/cost footprint of DNA-sequencing tools is decreasing fast bringing cheap and portable DNAsequencers into reach^{1, 2}. At the same time performance of high-throughput state-of-the-art sequencing techniques has improved at a pace that led to the abandonment of the X-Price for demonstrating the \$1000-Genome as various teams are currently approaching and likely blazing through that milestone with the \$100-Genome in sight. Building on these enhanced sequencing capabilities multiple private, commercial and government institutions have initiated large scale genome studies: ranging from a recent landmark study performed on the population of Iceland³ via the Genomics England Initiative⁴ and Craig Venter's newly founded Human Longevity⁵ enterprise to the Precision Medicine Initiative of the US government⁶, current studies aim to collect whole genome information on patient pools consisting of several thousands to 100,000 genomes. At the same time advanced cognitive big data analytics tools like for example IBM's Watson technology have emerged and mature showing first indications of early-stage commercial practicability⁷. Finally, in order to be able to respond to the findings of personalized genome analysis we need to develop faster and cheaper technologies for discovering novel drugs, for improving existing drugs, and for their intelligent use in an increasingly complex and customized environment transforming the pharma pipeline much like the \$1000-Genome has revolutionized DNA-sequencing. First cases of all building blocks working in sync towards successful individual treatments have been reported recently^{6, 8}, but at this point these examples constitute encouraging, yet isolated efforts rather to proof that the concept can be moved from hype to impact, than demonstrating population-wide availability of precision medicine services.

Precision medicine is a story about data. Figure 1 schematically projects key data sources and corresponding sensor types onto the 'omics canvas of precision medicine. While some data is readily available or can be extracted using existing techniques, other data has to be generated individually and from scratch requiring novel and improved sensing platforms. Besides biometric data creation through wearable sensors, this is naturally the case for sequencing data and also applies to data which we collect in the pre-clinical drug discovery phase to test the impact of drug compounds on physiological intra- and intercellular activities. It is our fragmentary understanding of the nature of these biomolecular cross functionalities that we mean when we talk about the complexity of the human organism. Investigating which proteins our body builds and why, how these proteins interact with each other and to which end, and finally how these interactions can be impacted by introducing drug compounds to the cellular environment is key to understanding, monitoring and eventually controlling our body with the same level of detail that we control a driving car or flying plane with. This task forms the backbone of systems genomics, systems biology and in particular 'omics research. It covers the entire spectrum of the biomatrix from investigating biophysical characteristics and interaction dynamics of single molecules to analyzing the behavior of complex many-biomolecule systems in the context of the environment an individual lives in and the lifestyle it pursues. In that context resistive pulse sensing technology (often also referred to as nanopore/nanochannel translocation technology) has emerged as a predestined technique for single-molecule isolation, investigation and eventually manipulation⁹.

Resistive pulse sensing is a label-free, single-molecule screening technology allowing electrical detection and characterization of single particles in aqueous solutions. Thereby, location, speed and direction of motion of single target molecules can be controlled at the same time. Alternative sensing technologies include surface plasmonic/waveguide sensors, resonator-based sensors, and nanowire devices. While these technologies also offer label-free, single-molecule sensing capabilities, location control at the time of detection is low, and more sophisticated nanofabrication and integration processes are required to incorporate these types of sensors in lab-on-a-chip platforms. Instead of employing custom-labelled biological assays, resistive pulse sensing is performed purely electrically in a nanofluidic chip which contains at least one integrated nanochannel connected to two reservoirs. The system is wetted with an aqueous electrolyte solution, and a sample containing the target molecules is pumped into one reservoir. After creating a potential drop between the two reservoirs an ionic current begins to flow through the nanochannel forming the baseline current signal and creating a hydrodynamic drag force close to the channel openings. As single target molecules are pulled into the nanochannel and translocate through it one at a time, they partially block the channel and thus modulate the baseline

current signal. This produces an individual electrical fingerprint for each translocation event whose distinct features can be correlated with the biophysical properties of the translocating molecule that created it. Resistive pulse sensing can be used to investigate a broad variety of molecular biological systems with single-particle, single nucleotide and even single-binding site resolution. It is explicitly powerful to perform next-generation nanopore-based DNA-sequencing¹⁰⁻¹⁶ and to investigate target-ligand interactions in the pre-clinical compound-to-hit, hit-to-lead, and lead optimization stages of the pharma pipeline¹⁷⁻²².



Figure 1. Precision medicine contextualizes data from genome to exposome (left). Thereby genomic, transcriptomic, proteomic, metabolomic and microbiomic data is biomolecular by nature while epigenomic and exposomic data also takes environmental, biometric and medical metadata sources into account (center). On one hand, environmental and biometric data is highly diversified but often readily available and can be collected and processed through smart sensor networks which are incorporated into novel mobile platforms such as wearables, smart phones or smart watches. Such platforms then communicate directly to analytical tools for point-of-care monitoring and diagnostics (top). On the other hand collecting biomolecular data from intra- and intercellular systems on the genome to microbiome scale is a biophysical challenge in the field of experimental systems biology requiring the design of highly customized tools for screening biomolecules with single particle and single binding site resolution (bottom).

3. OUTLOOK

Highlighting the extraordinary current relevance of resistive pulse sensing technology for next-generation DNAsequencing and drug discovery and giving a perspective onto the resulting impact of this technology on precision medicine applications, a comprehensive technical and commercial review has recently been published elsewhere²³. Integrated bionanosensors utilizing resistive pulse sensing technology are uniquely suitable to characterize the smallest units of the human organism and to help understand their complex interplay. While resistive pulse sensing-based nextgeneration sequencing platforms will mature further, the technology will also increasingly be used for developing novel diagnostics and ultra-high throughput pre-clinical drug screening systems. This could contribute to transforming the pharma pipeline similarly to how the \$1000-Genome has revolutionized DNA-sequencing, thus making resistive pulse sensing an essential part of precision medicine, the next big thing emerging at the intersection of biotechnology, nanotechnology and big data.

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