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Publications:

Engineering Value-Effective Healthcare Solutions: A Systems Design Perspective
Our modern healthcare systems commonly face an important dilemma. While they depend on innovation to provide
continuously greater healthcare value, they also struggle financially with the burden of adopting a continuous flow of new
products and services. Although several disruptive healthcare models, i.e. decentralised, personalised, pervasive,
connected, and stratified, promise to relieve some of this tension, they do not per se guarantee optimal value generation.
We argue that systems thinking and engineering design can remedy this limitation. We support this claim by making the
case of Design for Evolvability and by elaborating on two examples: MRI systems and Point-of-Care in-vitro diagnostics
solutions. We specifically argue that Design for Evolvability can realign the agendas of various healthcare stakeholders,
serving both individual and national interests. We finally acknowledge the limitations of current engineering design
practices and call for new theoretical and empirical research initiatives taking a systems perspective on healthcare product
and service design.

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Systems
Authors: Patou, F. (Intern), Maier, A. (Intern)
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In-situ doped junctionless polysilicon nanowires field effect transistors for low-cost biosensors
Silicon nanowire (SiNW) field effect transistor based biosensors have already been proven to be a promising tool to detect
biomolecules. However, the most commonly used fabrication techniques involve expensive Silicon-On-Insulator (SOI)
wafers, E-beam lithography and ion-implantation steps. In the work presented here, a top down approach to fabricate
SiNW junctionless field effect biosensors using novel in-situ doped polysilicon is demonstrated. The p-type polysilicon is
grown with an optimum boron concentration that gives a good metal-silicon electrical contact while maintaining the doping
level at a low enough level to provide a good sensitivity for the biosensor. The silicon nanowires are patterned using standard photolithography and a wet etch method. The metal contacts are made from magnetron sputtered TiW and e-beam evaporation of gold. The passivation of electrodes has been done by sputtered Si3N4 which is patterned by a lift-off process. The characterization of the critical fabrication steps is done by Secondary Ion Mass Spectroscopy (SIMS) and by statistical analysis of the measurements made on the width of the SiNWs. The electrical characterization of the SiNW in air is done by sweeping the back gate voltage while keeping the source drain potential to a constant value and surface characterization is done by applying liquid gate in phosphate buffered saline (PBS) solution. The fabricated SiNWs sensors functionalized with (3-aminopropyl)triethoxysilane (APTES) have demonstrated good sensitivity in detecting different pH buffer solutions.

General information
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System-Level Sensitivity Analysis of SiNW-bioFET-Based Biosensing Using Lockin Amplification
Although Silicon Nanowire biological Field-Effect Transistors (SiNW-bioFETs) have steadily demonstrated their ability to detect biological markers at ultra-low concentration, they have not yet translated into routine diagnostics applications. One of the challenges inherent to the technology is that it requires an instrumentation capable of recovering ultra-low signal variations from sensors usually designed and operated in a highly-resistive configuration. Often overlooked, the SiNWbioFET/instrument interactions are yet critical factors in determining overall system biodetection performances. Here, we carry out for the first time the system-level sensitivity analysis of a generic SiNW-bioFET model coupled to a custom-design instrument based on the lock-in amplifier. By investigating a large parametric space spanning over both sensor and instrumentation specifications, we demonstrate that system-wide investigations can be instrumental in identifying the design trade-offs that will ensure the lowest Limits-of-Detection. The generic character of our analytical model allows us to elaborate on the most general SiNW-bioFET/instrument interactions and their overall implications on detection performances. Our model can be adapted to better match specific sensor or instrument designs to either ensure that ultra-high sensitivity SiNW-bioFETs are coupled with an appropriately sensitive and noise-rejecting instrumentation, or to best tailor SiNW-bioFET design to the specifications of an existing instrument.

General information
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Authors: Patou, F. (Intern), Dimaki, M. (Intern), Kjærgaard, C. (Intern), Madsen, J. (Intern), Svendsen, W. E. (Intern)
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Evolvable Smartphone-Based Platforms for Point-Of-Care In-Vitro Diagnostics Applications

The association of smart mobile devices and lab-on-chip technologies offers unprecedented opportunities for the emergence of direct-to-consumer in vitro medical diagnostics applications. Despite their clear transformative potential, obstacles remain to the large-scale disruption and long-lasting success of these systems in the consumer market. For instance, the increasing level of complexity of instrumented lab-on-chip devices, coupled to the sporadic nature of point-of-care testing, threatens the viability of a business model mainly relying on disposable/consumable lab-on-chips. We argued recently that system evolvability, defined as the design characteristic that facilitates more manageable transitions between
system generations via the modification of an inherited design, can help remedy these limitations. In this paper, we discuss how platform-based design can constitute a formal entry point to the design and implementation of evolvable smart device/lab-on-chip systems. We present both a hardware/software design framework and the implementation details of a platform prototype enabling at this stage the interfacing of several lab-on-chip variants relying on current- or impedance-based biosensors. Our findings suggest that several change-enabling mechanisms implemented in the higher abstraction software layers of the system can promote evolvability, together with the design of change-absorbing hardware/software interfaces. Our platform architecture is based on a mobile software application programming interface coupled to a modular hardware accessory. It allows the specification of lab-on-chip operation and post-analytic functions at the mobile software layer. We demonstrate its potential by operating a simple lab-on-chip to carry out the detection of dopamine using various electroanalytical methods.

**Evolvable Smartphone-Based Point-of-Care Systems For In-Vitro Diagnostics**

Recent developments in the life-science -omics disciplines, together with advances in micro- and nanoscale technologies offer unprecedented opportunities to tackle some of the major healthcare challenges of our time. Lab-on-Chip technologies coupled with smart-devices in particular, constitute key enablers for the decentralization of many in-vitro medical diagnostics applications to the point-of-care, supporting the advent of a preventive and personalized medicine. Although the technical feasibility and the potential of Lab-on-Chip/smart-device systems is repeatedly demonstrated, direct-to-consumer applications remain scarce. This thesis addresses this limitation. After identifying system evolvability as a key enabler to the adoption and long-lasting success of next-generation point-of-care systems by favoring the integration of new technologies, streamlining the reengineering efforts for system upgrades and limiting the risk of premature system obsolescence. Among possible strategies, platform-based design represents a particularly suitable entry point to the development of evolvable systems. One necessary condition, is for change-absorbing and change-enabling mechanisms to be incorporated in the platform architecture at initial design-time. Important considerations arise as to where in Lab-on-Chip/smart-device platforms these mechanisms be integrated, and how to implement them. Our investigation revolves around the silicon-nanowire biological field effect transistor, a promising biosensing technology for the detection of biological analytes at ultra low concentrations. We discuss extensively the sensitivity and instrumentation requirements set by the technology before we present the design and implementation of an evolvable smartphone-based platform capable of interfacing lab-on-chips embedding such sensors. We elaborate on the implementation of various architectural patterns throughout the platform and present how these facilitated the evolution of the system towards one accommodating for electrochemical sensing. Model-based development was undertaken throughout the engineering process. A formal SysML system model fed our evolvability assessment process. We
introduce, in particular, a model-based methodology enabling the evaluation of modular scalability: the ability of a system to scale the current value of one of its specification by successively reengineering targeted system modules. The research work presented in this thesis provides a roadmap for the development of evolvable point-of-care systems, including those targeting direct-to-consumer applications. It extends from the early identification of anticipated change, to the assessment of the ability of a system to accommodate for these changes. Our research should thus interest industrials eager not only to disrupt, but also to last in a shifting socio-technical paradigm.

**General information**
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Authors: Patou, F. (Intern), Svendsen, W. E. (Intern), Dimaki, M. (Intern), Madsen, J. (Intern)
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Publication: Research › Ph.D. thesis – Annual report year: 2016

**Model-Based Evaluation Of System Scalability: Bandwidth Analysis For Smartphone-Based Biosensing Applications**
Scalability is a design principle often valued for the engineering of complex systems. Scalability is the ability of a system to change the current value of one of its specification parameters. Although targeted frameworks are available for the evaluation of scalability for specific digital systems, methodologies enabling scalability analysis of multidomain, complex systems, are still missing. In acknowledgment of the importance for complex systems to present the ability to change or evolve, we present in this work a system-level model-based methodology allowing the multidisciplinary parametric evaluation of scalability. Our approach can be used to determine how a set of limited changes to targeted system modules could affect design specifications of interest. It can also help predict and trace system bottlenecks over several product generations, offering system designers the chance to to better plan re-engineering efforts for scaling a system specification efficaciously.

We demonstrate the value of our methodology by investigating a smartphone-based biosensing instrumentation platform. Specifically, we carry out scalability analysis for the system’s bandwidth specification: the maximum analog voltage waveform excitation frequency the system could output while allowing continuous acquisition and wireless streaming of bioimpedance measurements. We rely on several SysML modelling tools, including dependency matrices, as well as a fault-detection Simulink Stateflow executable model to conclude on how the successive re-engineering of 5 independent system modules, from the replacement of a wireless Bluetooth interface, to the revision of the ADC sample-and-hold operation could help increase system bandwidth.

**General information**
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Organisations: Department of Micro- and Nanotechnology, Nano Bio Integrated Systems, Department of Applied Mathematics and Computer Science, Embedded Systems Engineering
Authors: Patou, F. (Intern), Madsen, J. (Intern), Dimaki, M. (Intern), Svendsen, W. E. (Intern)
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**Smartphone-based biosensing platform evolution: implementation of electrochemical analysis capabilities**

Lab-on-Chip technologies offer great opportunities for the democratization of in-vitro medical diagnostics to the consumer-market. Despite the limitations set by the strict instrumentation and control requirements of certain families of these devices, new solutions are emerging. Smartphones now routinely demonstrate their potential as an interface of choice for operating complex, instrumented Lab-on-Chips. The sporadic nature of home-based in-vitro medical diagnostics testing calls for the development of systems capable of evolving with new applications or new technologies for Lab-on-Chip devices. We present in this work how we evolved the first generation of a smartphone/Lab-on-Chip platform designed for evolvability. We demonstrate how reengineering efforts can be confined to the mobile-software layer and illustrate some of the benefits of building evolvable systems. We implement electrochemical capabilities on our platform prototype and carry out cyclic voltammetry to measure dopamine concentrations over several orders of magnitude.

**General information**

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The early diagnosis and monitoring of chronic diseases still constitutes today one of the major healthcare challenges in our society. Advances in nanotechnology and microfluidics have been increasingly empowering researchers and engineers with tools to develop integrated biosensing solutions helping to address this challenge. Specifically, Lab-on-Chip (LoC) devices have a key role to play in the advent of Point-of-Care (PoC) medical applications, driving a shift of the medical diagnostics paradigm and the transition from a centralized, technical, high-throughput biological sample analysis process to a diagnostician and patient-oriented field decision-making support system.

The success of such systems requires the development of highly sensitive and specific biosensors to reliably detect small amounts of relevant biological markers. Nevertheless, the socio-technical complexity of the PoC medical diagnostics context necessitates considering broader requirements, notably in terms of usability, flexibility, and integration capabilities. These characteristics call for multi-disciplinary design methodologies inspired from the field of systems engineering and constitute the motivations for this work.

We present a mobile-device based, PoC biosensing instrumentation platform, designed for multiplexed high-impedance sensing and the electrochemical detection of biological species on a LoC. The proposed system is thus designed as a flexible, user-friendly hardware and software platform allowing programmable electrical readout from LoCs potentially comprehending varied transducers addressing different targeted biological markers. A smart-phone/tablet docking-station embeds the hardware interface necessary for the implementation of a smart-phone digital lock-in amplifier. The platform is tested with high-impedimetric measurements from Silicon-nanowire Field Effect Transistors embedded in a LoC.

Programmable firmware and flexible hardware will in turn allow for standard voltammetry and electrical impedance spectroscopy to be performed. The design of a mobile app and standard mobile software libraries will ensure system evolvability, enabling application-specific biosensors readouts and adapted user interfacing.
A novel single-step, multipoint calibration method for instrumented Lab-on-Chip systems

Despite recent and substantial advances in biosensing, information and communication, and Lab-on-Chip (LoC) technologies, the success of Point-of-Care (PoC) diagnostics and monitoring systems is still challenged by stringent requirements for robustness, cost-effectiveness, and system integration.

The pitfalls of PoC system adoption can be addressed early in the system design phase. They require a multidisciplinary design approach supported by systems engineering tools and methods. Considering this, we here present both a model and an implementation of a simple and rapid calibration scheme for instrument-based PoC blood biomarker analysis systems. Motivated by the complexity of associating high-accuracy biosensing using silicon nanowire field effect transistors with ease of use for the PoC system user, we propose a novel one-step, multipoint calibration method for LoC-based systems. Our approach specifically addresses the important interfaces between a novel microfluidic unit to integrate the sensor array and a mobile-device hardware accessory. A multi-point calibration curve is obtained by generating a defined set of reference concentrations from a single input. By consecutively splitting the flow perpendicular to the diffusion interface only one mixing step is required for each of the generated calibration solutions. This results in a compact design with a very small footprint of the microfluidic layout.

Translating silicon nanowire BioFET sensor-technology to embedded point-of-care medical diagnostics

Silicon nanowire and nanoribbon biosensors have shown great promise in the detection of biomarkers at very low concentrations. Their high sensitivity makes them ideal candidates for use in early-stage medical diagnostics and further disease monitoring where low amounts of biomarkers need to be detected. However, in order to translate this technology from the bench to the bedside, a number of key issues need to be taken into consideration: Integrating nanobiosensors-
based technology requires to overcome the difficult tradeoff between imperatives for high device reproducibility and associated rising fabrication costs. Also, the translation of nano-scale sensor technology into daily-use point-of-care devices requires acknowledgement of the end-user requirements, making device portability and human-interfacing a focus point in device development. Sample handling or purification for instance, should be addressed in an automated way. Here, we present the concept of a polysilicon nanoribbon sensor array integrated with multiplexed microfluidic functionalization, automated calibration and sample handling for flexible diagnostics from finger prick blood samples. Functionalization of the sensor surface is performed in a controlled microfluidic environment and can be monitored in real-time to ensure reproducible results. In a simple temporary PDMS device, multiple parallel pathways enable straightforward selective functionalization for different biomarkers. Common diagnostic essays, which require a specific set of biomarkers to be identified and quantified simultaneously, can thus be readily translated onto this platform. After hydrogen termination of the silicon surface, an alkyne monolayer is formed based on a hydrosilylation process. Antibodies and other receptor proteins can then be immobilized in a parallel manner without the use of a spotting system using various chemistries depending on the chosen headgroup in the monolayer. The system is designed to work with a single tube at the outlet and is able to mix and deliver immobilization reactants and antibody solution as well as washing buffer to the sensor surface.

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Publication date: 2013

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Projects:

Healthcare Design for Patient Engagement and Collaborative Care

Department of Management Engineering
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Number of participants: 4
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Supervisor: Dominguez, Maria Helena (Ekstern)
Main Supervisor: Maier, Anja (Intern)

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Source: Internal funding (public)
Name of research programme: Samfinansieret - Andet
Project: PhD

Evolvable Smartphone-based Point-of-Care Systems for In-Vitro Diagnostics

Department of Micro- and Nanotechnology
Period: 01/02/2013 → 02/11/2016
Number of participants: 7
Phd Student: Patou, François (Intern)
Supervisor: Dimaki, Maria (Intern)
Main Supervisor: Madsen, Jan (Intern)
Main Supervisor:
Svendsen, Winnie Edith (Intern)
Examiner:
Pop, Paul (Intern)
Romano-Rodriguez, Albert (Ekstern)
Shah, Pranjul Jaykumar (Intern)

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Relations
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Activities:

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François Patou (Speaker)
Department of Micro- and Nanotechnology
Nano Bio Integrated Systems
Department of Applied Mathematics and Computer Science

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Oral presentation

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