



Model-based systems engineering for life-sciences instrumentation development

Patou, François; Dimaki, Maria; Maier, Anja; Svendsen, Winnie Edith; Madsen, Jan

Published in:
Systems Engineering

Link to article, DOI:
[10.1002/sys.21429](https://doi.org/10.1002/sys.21429)

Publication date:
2019

Document Version
Peer reviewed version

[Link back to DTU Orbit](#)

Citation (APA):
Patou, F., Dimaki, M., Maier, A., Svendsen, W. E., & Madsen, J. (2019). Model-based systems engineering for life-sciences instrumentation development. *Systems Engineering*, 22(2), 98-113. DOI: 10.1002/sys.21429

General rights

Copyright and moral rights for the publications made accessible in the public portal are retained by the authors and/or other copyright owners and it is a condition of accessing publications that users recognise and abide by the legal requirements associated with these rights.

- Users may download and print one copy of any publication from the public portal for the purpose of private study or research.
- You may not further distribute the material or use it for any profit-making activity or commercial gain
- You may freely distribute the URL identifying the publication in the public portal

If you believe that this document breaches copyright please contact us providing details, and we will remove access to the work immediately and investigate your claim.

Towards A Model-Based Systems Engineering Approach To Life-Science Instrumentation Systems Development

François Patou, Maria Dimaki, Anja Maier, Winnie E Svendsen and Jan Madsen

Abstract

Next-generation genome sequencing machines and Point-of-Care *in vitro* diagnostics devices are precursors of an emerging class of Cyber-Physical Systems, one that harnesses biomolecular-scale mechanisms to enable novel “wet-technology” applications in medicine, biotechnology and environmental science. Although many such applications exist, testifying the importance of innovative life-sciences instrumentation, recent events have highlighted the difficulties that designing organisations face in their attempt to guarantee safety, reliability and performance of this special class of Cyber-Physical Systems. New regulations and increasing competition pressure innovators to rethink their design and engineering practices, and to better address the above challenges. The pace of innovation will be determined by how organisations manage to ensure the satisfaction of aforementioned constraints while also streamlining product development, maintaining high cost-efficiency and shortening time-to-market.

Model-Based Systems Engineering provides a valuable framework for addressing these challenges. In this paper, we demonstrate that existing and readily-available model-based development frameworks can be adopted early in the life-sciences instrumentation design process. Such frameworks are specifically helpful in describing and characterizing Cyber-Physical Systems including elements of a biological nature both at the architectural and performance level. We present the SysML model of a smartphone-based Point-Of-Care diagnostics system designed for detecting a particular molecular marker. By modelling components and behaviours spanning across the biological, physical-non-biological and computational domains, we were able to characterize the important systemic relations involved in the specification of our system’s Limit-Of-Detection. Our results illustrate the suitability of such an approach and call for further work towards formalisms enabling the formal-verification of systems including biomolecular components.

Index Terms

Cyber-Physical Systems; Life-Science; Model-Based Systems Engineering; Model-Based Systems Design; SysML; Sensitivity analysis

I. INTRODUCTION

Many advances in health, sustainability, and security depend on our ability to integrate emerging life-science technologies into complex Cyber-Physical Systems (CPS). The personalization of medicine and the scaling-up of air, water and soil quality monitoring are examples of application domains where progress is conditioned by our capacity to interface with the molecular micro-environment. Advances in biochemistry and synthetic biology give rise to as many powerful applications as their compositions with distributed computing or Artificial Intelligence (AI) allow. From the sequencing and interpretation of our genome [1], to the automated synthesis of *de novo* biopolymers such as DNA, RNA or proteins [2], [3], the spectrum of possibilities offered by systems spanning life-science, mechatronics and information technologies is immense. Novel molecular diagnostic and genomic technologies, for instance, challenge the current *in vitro* medical testing (IVMT) paradigm by offering progressively decentralized and self-diagnostics capabilities to lay-users, thereby promoting disruptive care models where patients are empowered to contribute more directly to their own health management [4]–[6]. Meanwhile, new tools in synthetic biology make it continuously easier to translate digital information into biological entities, to (re-)program life, and to gradually blur the boundaries that have so far separated the Natural from the Artificial [2], [3], [7].

Yet, the disruptive potential of these applications seems to have brought as much hope and excitement as it has sourced concern. The pressing character of ethical issues related to the decentralization and democratization of DNA synthesis technologies, for instance, is widely agreed upon [8]. Likewise, recent scandals in the field of *in vitro* diagnostics testing have led to skepticism among experts and lowered public trust in manufacturers’ ability to guarantee the safety and efficacy of CPS systems that peek into our blood [9], [10]. These rising ethical and safety concerns will likely drive the tightening of current IVMT and biosynthesis equipment manufacturing regulatory frameworks, which may in turn hinder the pace of innovation in these areas so critical for both our economy and quality of life. Confronted with more stringent requirements of all kinds, designing organisations have no choice but to seek for better adapted engineering practices. Such practices should ensure the

François Patou is with the Engineering Systems Division (ESD) at the Department of Management Engineering, Technical University of Denmark, Lyngby, frpato@dtu.dk

Anja Maier is head of the Engineering Systems Division (ESD) at the Department of Management Engineering, Technical University of Denmark, Lyngby

Maria Dimaki and Winnie E Svendsen are with the Department of Micro- and Nanotechnology, Technical University of Denmark, Lyngby

Jan Madsen is with the Department of Applied Mathematics and Computer Science, Technical University of Denmark, Lyngby

development of safe, reliable and high-performing CPS based on life-science technologies, help these organisations demonstrate that development efforts were pursued according to best practices, and at the same time favour cost-efficiency and shorten time-to-market.

We will refer to this class of systems tightly interfaced with the biomolecular environment as Cyber-Biological and -Physical Systems (CBPS). As such, CBPS encompass *in vitro* medical testing equipment [4], [5], but also *in vivo* molecular sensing devices [11], [12] and DNA synthesizers [2], [3], [13].

Facing a dynamic, highly-regulated and competitive environment and challenged by an increasing level of product complexity, CBPS-developing organisations possess all the characteristic incentives that call for the adoption of Model-Based Systems Engineering (MSBE) practices. Model-Based Systems Design (MBSD) in particular, has been leveraged in many industrial domains to streamline the systems engineering effort from early analysis and specification to implementation, verification and validation by confining early system development *in silico*. MBSD thus aims to reduce the risks of implementation, to ensure requirement satisfaction, to promote overall value-efficiency, and to facilitate the management of and innovation within product-families [14].

We demonstrate in this paper that generic tools and frameworks of MBSD readily support holistic design and development of Cyber-Biological and -Physical Systems. More specifically, we demonstrate that readily-available model-based development frameworks can be used to model and analyse Cyber-Physical Systems including elements of a biological nature both at the architectural and performance level: we present the multi-domain modelling and simulation capabilities associated with System Modelling Language (SysML) and illustrate its relevance for assessing CBPS' performance metrics influenced by elements of biological, physical-non-biological, and computational nature. In particular, we discuss a molecular diagnostics system, engineered around the Silicon-Nanowire biological Field-Effect Transistor (SiNW-bioFET) technology. We build and harness a SysML model of this diagnostics system and carry out the parametric performance analysis of its Limit of Detection (LoD) for a specific biomolecular target.

II. CYBER-BIOLOGICAL AND -PHYSICAL SYSTEMS

A. Properties of Cyber-Biological and -Physical Systems

Cyber Physical Systems (CPS) are defined as systems offering integrations of computation, networking and physical processes [15]. CPS thus exhibit both elements of software and elements of a physical nature closely interacting with one another. Essential for their purpose is the ability of a CPS to encode the physical reality experienced by its physical structures into palpable information for its cyber- constituents, the latter being generally responsible for analyzing and supporting decision-making through digital computations. Reciprocally, some of the commands and computational results issued from the cyber-elements may be communicated and translated back to the physical elements of the system in order to influence the physical world in a prescribed manner. Computations and control are generally achieved with a high degree of automation, which in turn requires that CPS implement networking and cyber-physical integrations over multiple temporal and spatial scales [16]. Sensors and actuators are therefore pivotal to CPS: they provide the interfaces, i.e. the junctions that close the control loops that enable CPS to influence the physical world in the way they are intended to.

Cyber-Biological and -Physical Systems, like CPS, behave according to multiple physics. They are yet generally more heterogeneous than conventional CPS and their complexity space is often of higher dimensionality, the heterogeneity of the engineering domains they encompass often meeting additional socio-technical, regulatory, and ethics challenges. Importantly, CBPS form a specialized class of CPS for which sensing and actuation require the consideration of structures and processes at the biomolecular level, especially when they influence overall system functionality and performance in a significant manner. We elaborate on this particular attribute.

Chemical and biological sensing are usually at the core of CBPS functionality. Biological sensing (biosensing), more specifically, underpins all the molecular diagnostics techniques of *in vitro* biochemical analysis, genome sequencing, as well as a growing number of *in vivo* monitoring applications [12]. Biosensing mechanisms may be derived from a wide panel of biophysical principles, with the objective to efficiently transduce information of biophysical nature into an alternative form more easily readable by conventional instrumentation, e.g. optical or electrochemical to name a few. Actuation involving biological components represents the other pillar of CBPS specialization. CBPS actuators comprehend an increasingly wide range of technologies, still mostly based on engineering at the micro- or higher dimensional scales. There, their design and fabrication remain manageable while providing sufficiently accurate physical behaviours to accommodate the most advanced CBPS applications we know of today. Digital Microfluidics (DMF) for instance, allow the discrete manipulation of liquid droplets containing relevant biomolecules on a 2D electrode array by using high electric potentials [17]. The digital nature of the DMF enables the reconfiguration of fluid processing steps depending on the application at hand, for instance to program different reagents and sample mixing protocols, droplet splitting, dilutions, or washing [18]. DMF has demonstrated its potential in a wide range of life-science applications, including detection by immunoassay, Polymerase Chain Reaction (PCR), proteomics, sample preparation for single-cell studies [19], or single-molecule extraction and analysis [20].

Sensing and actuation are thus critical articulation nodes for Cyber-Biological and -Physical Systems and play a fundamental role in determining overall CBPS utility and value-effectiveness.

B. Vertical integration in Cyber-Biological and -Physical Systems

Cyber-Biological and -Physical Systems are essentially engineered via the aggregation and interfacing of components issued from chemistry, synthetic biology, nanotechnology, microfluidics, and optics, together with electronics, mechanics, embedded- and application-software, cloud computing, and AI. CBPS systems engineers may therefore need to address a deeper *vertical* integration for CBPS applications than for any other conventional CPS. Additionally, the emergence of synthetic biology is bringing a myriad of new opportunities and challenges for the development of CBPS and marks a cornerstone in the history of engineered systems. It does so by blurring the boundaries between the natural and artificial world and also from a system architecting perspective, opening up new functional allocation schemes for CBPS design: biosensing, for instance, can now be performed via the reengineering of bacterial genome rather than by the patterning of microstructures and immobilization of organic molecules on silicon substrates [21]. Another example is the ever-more realistic scenario of DNA becoming a viable digital information storage media [22]. Such revolutions clearly require new design frameworks and methodologies supporting the complexity inherent to the deep integrations that next-generation CBPS will exhibit. That complexity may be further increased by humans in the loop whenever CBPS operation is not fully automated, requiring the additional consideration of user-system interactions or work process flows. Central clinical laboratories currently constitute one of the best examples of an environment where this latter point is essential for ensuring overall system safety, efficacy and cost-efficiency.

III. MODEL-BASED SYSTEMS ENGINEERING FOR LIFE-SCIENCES INSTRUMENTATION DEVELOPMENT

Extending the practice of conventional Systems Engineering (SE), MBSE aims to formalize the development of systems through the use of models. Rumbaugh et al. suggest that any model defines a “representation of a selected part of the world, the domain of interest, that captures the important aspects, from a certain point of view, simplifying or omitting the irrelevant features” [23]. MBSE consists of a set of formalisms and practices that leverage these representations throughout the systems engineering life cycle in order to support the delivery of value-effective systems [24]. It does so essentially by enabling efficient management of system complexity, mitigation of risks and assessment of requirement satisfaction via virtual prototyping. Model-Based System Design (MBSD), which encompasses all MBSE design-related activities, intends to harness models from early system analysis and specification, to design, implementation and testing, verification, and validation. MBSE and MBSD commonly rely on graphical modelling capabilities, addressing the need for communication between stakeholders of various backgrounds.

MBSE practices have matured together with information technology, progressively enabling systems architects and engineers to abandon traditional document-based SE to embrace a model-based approach to system design and development. MBSE has thus followed the footsteps of some of the traditional engineering disciplines it spans, such as mechanical or electrical engineering. MBSE has been adopted in a variety of application domains, from defence and aerospace to energy systems and transportation where the scale and complexity of systems and infrastructures keeps growing [25]. MBSE has only relatively recently been acknowledged as a potential vector for the development of value-efficient systems in healthcare. In particular, MBSE appeals for its formalism and the potential for standardizing a number of healthcare system development processes and medical systems architectures. Ongoing research is for instance ascertaining the potential of MBSE for developing high-assurance system software, for favoring interoperability, context-aware intelligence, autonomy, security and privacy, and for supporting device certifiability of life-critical, context-aware networks of medical devices [26]. Khayal et al. also recently underlined the value of MBSE in clinical practice in general, and in functional medicine in particular [27].

We see great potential in using MBSD for the development of Cyber-Biological and -Physical Systems. Supporting our vision are the encouraging early demonstrations of applicability of existing system modelling tools to the life-science domain. Somekh et al. for instance, have shown that Object-Process Modelling (OPM), a language typically used for engineered system modelling, could be harnessed for hypothesis generation in systems-biology [28]). Such results suggest that the development of systems spanning life-sciences, mechatronics, and information technologies readily possesses constructs and semantics to describe the biological elements of CBPS. This in turn ties the successful embrace of MBSD for life-science instrumentation development to two main challenges: missing integrations between domain-specific modelling tools and the lack of MBSD methodologies adapted to the CBPS development context.

The objectives of MBSD for CBPS development remain the same as for conventional system design: to reduce development time and associated costs. The amplitude of these benefits could yet be substantially higher in the former case, since the sole development time and costs associated to the biological domain are usually significantly higher than those associated with hardware or software. One way MBSD can limit these expenditures is by enabling better identification and characterization of system-level interactions bridging the biological domain with the field of instrumentation, embedded systems and AI. As we discussed in section II-B, these interactions (especially those at the low biological-physical-hardware level) and the interfaces defining them usually play a pivotal role in determining overall system functionality, safety, efficacy and/or cost-efficiency. CBPS development, perhaps more than most other kinds of systems, thus requires the availability of holistic modelling frameworks supporting their vastly heterogeneous nature, the concurrence of their different cyber- biological- and physical processes, and their potential real-time requirements.

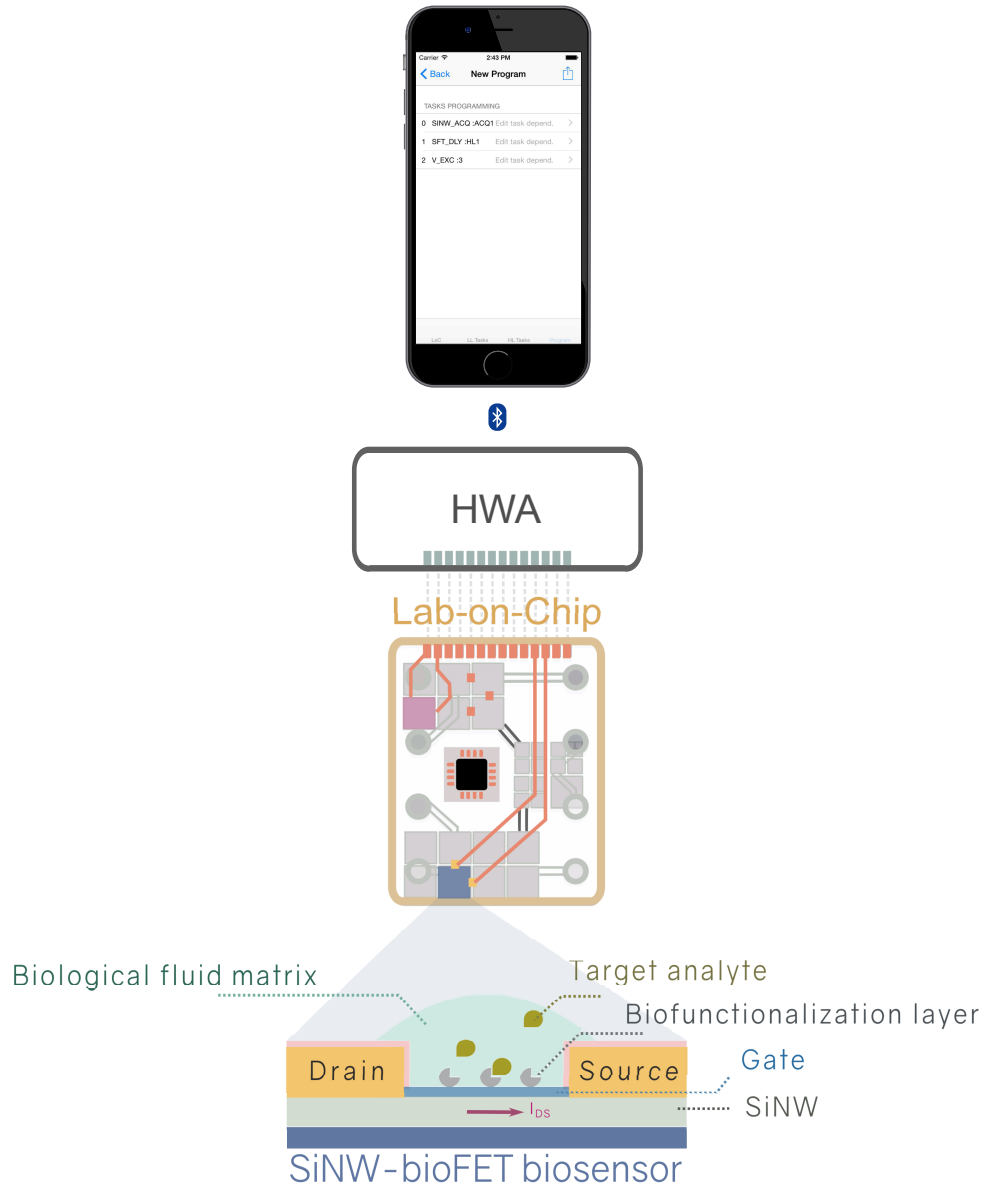


Fig. 1. Schematic of the Modular Diagnostic platform. The Hardware Accessory (HWA) is the pivotal element of the system, embedding the instrumentation and control units necessary to operate various Lab-on-Chips (LOC). Here it interfaces to an Apple iPhone 6 over Bluetooth. A LOC embedding a Silicon Nanowire biological Field Effect Transistor (SiNW-bioFET) is plugged to the front-end of the HWA. The gate of the SiNW-bioFET is coated with a ABL-kinase receptor, targeting ATP molecules in solution.

IV. SysML-BASED MBSD OF CYBER-BIOLOGICAL AND -PHYSICAL SYSTEMS

The System Modelling Language (SysML) is one of the most institutionalized systems modelling tools to this day. SysML is a general-purpose language developed by the Object Management Group (OMG) as an extension of the Unified Modelling Language (UML), the latter of which quickly became an industry standard for software design and analysis after the emergence of object-orientation in computing in the 1970's [24], [29]. SysML was meant to address the limitations of software-specific UML and to allow the modelling of multi-domain large engineering systems [30]. SysML is not bound to a specific system development framework, which has probably contributed to its institutionalization and growing acceptance.

Originally lacking clear semantics and being associated with a steep learning curve, SysML has suffered much criticism [31]. Although limitations of the OMG language encouraged the development of alternative systems modelling languages (e.g. Object-Process Modelling (OPM) [32]), many research institutions and industries have relied on SysML to assist the development of systems of various size and complexity. Many of these projects are still rooted in defence and aerospace [33]–[36]. As we will see in the ensuing section, more recent initiatives have demonstrated the further potential of SysML for the development and management of mechatronic or Cyber-Physical Systems (CPS). SysML recently benefited from the standardization of the foundational UML (fUML) specification, which has strengthened its execution semantics and hence enhanced its integration and simulation-related capabilities. SysML has been integrated both with domain-specific simulation environments (e.g. Matlab)

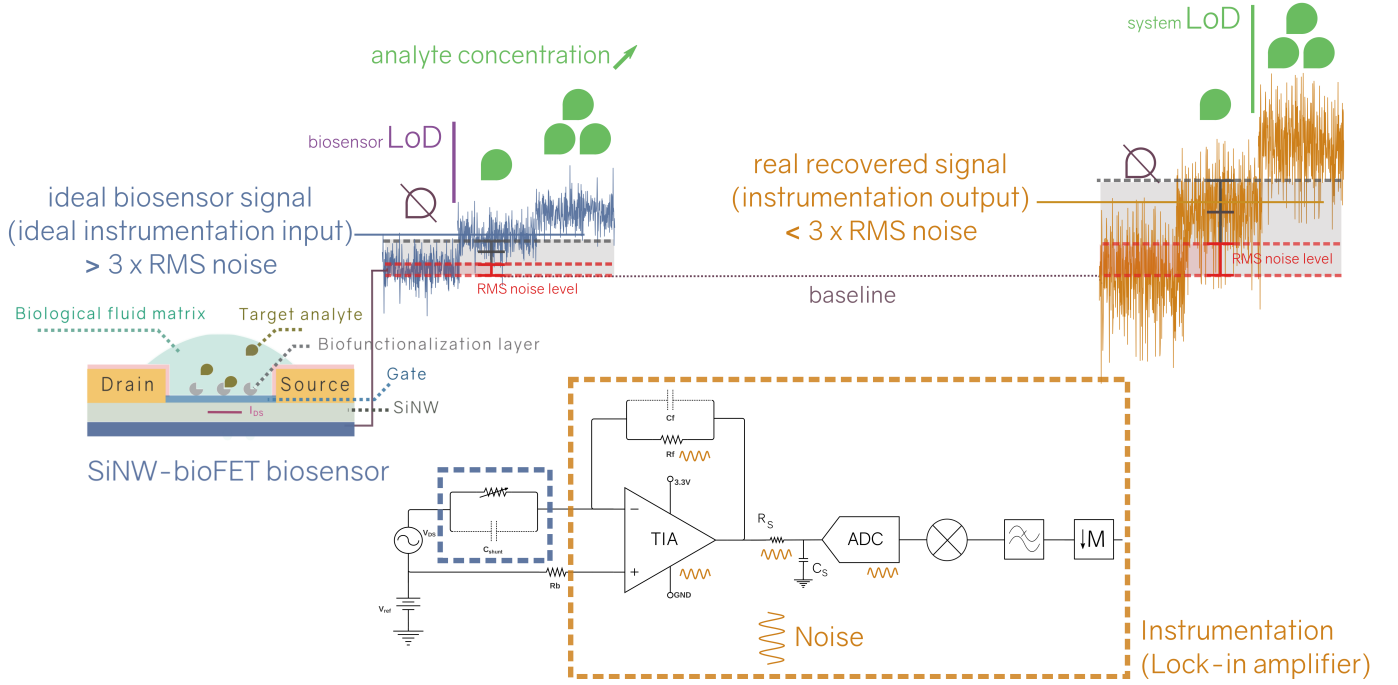


Fig. 2. SiNW-bioFET LoD and system-level LoD

and various model repositories (e.g. Product Lifecycle Management tools). Early SysML integration endeavours focused on establishing links between SysML abstract models on the one hand, and existing domain-specific executable models on the other hand (e.g. [37], [38]). More recent works have however strived towards the synthesis of executable domain-specific simulation code directly from abstract SysML models [39]. These integrations are possible thanks to the use of meta-modelling languages enabling the translation of domain-specific SysML profiles to specific simulation environments (e.g. Modelica, DEVS, etc.). These tools have allowed, in particular, purely discrete systems such as embedded real-time applications to be fully conceptualized at the abstract SysML level, to be translated to simulation code [40], to be formally verified [41], and eventually, in-part, to be synthesized to machine code [42], [43]. A review of the state of the art in executable SysML models is proposed in [39].

The MBSD of CPS also necessitates ways of representing the continuous laws that govern the behaviour of the physical elements of CPS. The biological processes pivotal to the functions and performances of CBPS, for instance, may demand the capacity to specify and resolve partial differential equations, or as an alternative, to circumvent that issue by abstracting time-dependent behaviours to simpler parametric relationships. Several MBSD approaches and tools have been proposed to handle the modelling and simulation of physical- or hybrid CPS sub-systems. Recently, Karban et al. carried out requirement verification for a large telescope using SysML [44]. The authors relied on parametric diagrams to establish the mathematical relationships between the system's most relevant variables, and on a variety of behavioral diagrams to establish an event-based model of all the discrete processes involved in the operation of the system. Leserf et al. [45] recently re-acknowledge the importance of comprehensive MBSE frameworks and modelling tools for exploring the CPS design space. The authors proposed a SysML-based multi-domain optimization tool which they used to model of drone-like system.

In the ensuing section we present how SysML can support the early design and analysis of CBPS. After briefly introducing a specific CBPS we developed in-house, we detail how SysML was used to support design choices. We specifically elaborate on our case to determine effective system configurations using a system-wide parametric study spanning across the biological, electronic and digital computation domains.

V. CASE: NANOWIRE BIOSENSOR AND INSTRUMENTATION SYSTEM FOR MEASURING ATP LEVELS IN SOLUTION

We undertook the MBSD of a biosensing platform introduced in [46]. Our Modular Diagnostics platform aims to allow the detection of various biological molecular markers at Point-of-Care (POC), i.e. field medical diagnostics. It is built around a Hardware Accessory (HWA) embedding several electronic instrumentation modules, and can be interfaced wirelessly to Apple mobile devices (e.g. iPhone, iPad). Different Lab-on-Chip (LOC) devices, embedding a variety of biosensors, can in turn be interfaced with the HWA (figure 1). This modular design theoretically allows for a wide panel of molecular targets to be addressable by the same platform via the use of disposable LOC devices. An essential requirement of the first prototype of this system was to accommodate for the Silicon Nanowire biological Field Effect Transistor (SiNW-bioFET) sensing technology.

We discussed extensively the SiNW-bioFET as well as the instrumentation technique we chose for recovering its signals in Patou et al. [47].

Derived from the common MOS-FET technology, the SiNW-bioFET supports the detection of specific biological targets by presenting a selective biofunctional molecular layer at the surface of its gate (left of figure 2). This interface layer enables the selective binding of circulating target molecules present in the biological sample (e.g. blood, saliva). The electric charges borne by these targets should in turn influence the conductivity of the semiconducting channel of the device. In this case example we consider the gate coated with the ABL-tyrosine-kinase receptor, specific to the ATP ligand. The ATP molecule has a pivotal role in cell metabolism. As ATP molecules bind to ABL tyrosine-kinase receptors at the gate, variations in conductivity within the semiconductor occur. This interaction principle is illustrated to the left in figure 2: the *baseline* current signal for the SiNW-bioFET corresponds to the current running through the SiNW when no analyte is present in the sample. Spikes of increasing concentrations of target biomarker should result in changes from that baseline, translating the building up of markers binding to the SiNW-bioFET gate surface. The effectiveness of the biochemical processes responsible for transducing the biochemical signal of targets at the gate into a form readable by the *instrumentation* determines the sensitivity of the *assay*.

Several electrical instrumentation techniques can be used to recover these signal variations. We consider the lock-in amplification method, also known as phase-sensitive detection [48]. The working principle of the lock-in amplifier is symbolically illustrated to the right of figure 2. In the ideal scenario, sensor and instrumentation are well matched so that the instrumentation can sensitively recover the signal variations at the sensor's terminals without degrading signal quality. This scenario corresponds to the illustration at the top-left of figure 2: an ideal instrumentation would allow the recovery of a concentration of target biomarker generating a signal change from baseline as low as three times the Root Mean Square (RMS) noise level present in the signal: this limit is called Limit-of-Detection (LoD). The LoD is an essential performance metric for *in vitro* diagnostics instrumentation as it defines the minimum quantity of target biomarker that can be detected with a given confidence level. The lower the LoD, the more likely one is to be able to ascertain the presence of low amounts of certain molecular disease markers, which in turn may help establishing a diagnosis earlier, initiate timely treatment and promote better odds of recovery. In the ideal (i.e. show to the left in figure 2) scenario, the LoD corresponds to one arbitrary unit of target biomarker.

The ideal scenario does not account for the intrinsic-noise generated by the instrumentation itself or by the extrinsic-noise the system may pick up from the environment. The lock-in amplifier, although specifically designed for high-noise rejection, will inevitably add some spurious components to the effective SiNW signal. Since SiNW-bioFETs generally output very low-amplitude signals, the noise added by the instrumentation may well represent a significant proportion of the overall signal, therefore impeding the overall LoD of the assay [47]. This realistic scenario is illustrated on the top-right corner of figure 2. The noise issued from the lock-in amplifier raises the overall noise level in the baseline signal. This means that a signal generated by a concentration of biomarker corresponding to the LoD in the ideal case would be drowned in noise in a real case scenario. Only signal changes larger than three times the RMS value of the inflated non-ideal case noise floor can effectively be detected: the system LoD will inevitably be higher than that of the sensor alone. This scenario is illustrated to the right in figure 2, where the LoD roughly corresponds to two arbitrary units of target biomarker, versus one where instrumentation would have been ideal.

Assay-instrumentation interactions must hence be established thoroughly in order to determine the trade-offs enabling satisfaction of the LoD requirements while striving for both design effectiveness and efficiency. These analyses have profound implications since they may, for instance, help determining whether engineering efforts and budgets should be allocated to the development of costly biochemical assays or rather to the design or upgrade of an instrumentation whose development costs may well differ by orders of magnitude. We present in the ensuing section how we pursued the early MBSD of our SiNW-bioFET/HWA/iPhone system. We used SysML for a sensitivity analysis of our LoD performance metric for the detection of ATP.

A. Methods

We used the NoMagic MagicDraw software suite to model our SiNW-bioFET/instrumentation system in SysML.

1) *Stereotypes*: Under the SysML profile, we started by defining stereotypes reflecting the various physical or engineering domains one can expect to be represented in CBPS. More specifically, we differentiated Biological sub-systems from Hardware (HW) sub-systems, Software (SW) sub-systems and from Mixed sub-systems, the latter relating to any combination or hybridization of the first three.

Using these stereotypes, we first modelled the system *structures* we assumed would play a role in determining the LoD specification (figure 3).

2) *Structures*: The biological sample, the LOC, and the HWA represent the three principal sub-systems involved in the determination of the system LoD. Out of those three sub-systems only the LOC and HWA are engineered: the biological sample is pre-existing and considered an input to the system. Yet, the abstraction of the biological sample leads to a hierarchy of elements just like the decomposition of the Lab-On-Chip and Hardware Accessory do. We thus strived to decompose each of these three sub-systems down to the highest level of abstraction that would allow capturing the most elementary properties influencing the system LoD.

TABLE I
INITIAL SYSTEM SPECIFICATIONS

Engineering Domain	Component	Specification	Value
Microfabrication	Silicon Nanowire	Length	$100 \times 10^{-6} \text{ m}$
		Width	$400 \times 10^{-9} \text{ m}$
Surface chemistry	Gate	Thickness	$\{20 : 90 \times 10^{-9} \text{ m}\}$
		Carrier mobility	$2 \text{ cm}^2/\text{V s}$
		Boron doping	$1 \times 10^{24} \text{ m}^{-3}$
		Stray capacitance	$1 \times 10^{-13} \text{ F}$
		Material	AlO_2
		Thickness	$\{2 : 5 \times 10^{-9} \text{ m}\}$
		Receptor	ABL Tyrosine-kinase
		Receptor projection area	$3 \times 10^{-17} \text{ m}^2$
		Receptor charge	—
		Receptor density	$\{6.5 : 100 \times 10^{14} \text{ m}^{-2}\}$
		Ligand	ATP
		Ligand projection area	$3 \times 10^{-17} \text{ m}^2$
		Ligand charge	$-3 e$
		Charge-surface distance	2.4 nm
—	Biological sample	Ionic strength	$1 \times 10^{-12} \text{ mol m}^{-3}$
		Temperature	298 K
		ATP concentration	VAR
	Excitation	Frequency	20 Hz
		Amplitude	0.3 V
	Transimpedance Amplifier	Opamp	AN8608
		GBW	$1 \times 10^7 \text{ Hz}$
		C_{cm}	$8 \times 10^{-12} \text{ F}$
		C_{diff}	$2.2 \times 10^{-12} \text{ F}$
		I_{noise}	$\{1 : 1000 \times 10^{-11} \text{ A}/\sqrt{\text{Hz}}\}$
		e_v	$8 \times 10^{-9} \text{ V}/\sqrt{\text{Hz}}$
		R_f	$\{1 : 10 \times 10^6 \Omega\}$
		C_f	$1.5 \times 10^{-11} \text{ F}$
	RC Driver	R_s	$1 \times 10^3 \Omega$
		C_s	$1 \times 10^{-9} \text{ F}$
Signal Processing	Analog-to-Digital Converter	Resolution	$\{12 : 14 \text{ bits}\}$
		Sampling frequency	$4 \times f_s$
	AC-Coupling	Input span	3.3 V
		Output offset error	—
	Demodulation	Frequency	20 Hz
		FIR Filter	$\{34 : 856 \text{ taps}\}$
	FIR Filtering		

Since the LoD is a function of the physico-chemical properties of the biosensor and of the interaction of the biosensor with the biological sample, we abstracted the biological entities present in the sample as well as those grafted to the sensor's gate. These entities here include the ATP nucleotide – our target biomarker – and its ABL tyrosine-kinase receptor. Although we did not require to develop a complete biomolecular taxonomy to classify these two molecules it is clear that the modelling of CBPS addressing hundreds or thousands of chemical and biological compounds would have compelled us to do to. As an illustration of what such a taxonomy may look like we derived the elementary classifications relevant to ATP and ABL-tyrosine kinase. ATP can be defined as a specialization of the *Ligand* class, and ABL-tyrosine kinase can be considered a specialization of the *Receptor* class (figure 3). Both of these generic classes fall under the same direct generalization class: *Molecule* (NB: ATP is not a protein-ligand, hence the most direct generalization goes to *Molecule* and not *Protein*).

In a similar fashion we abstracted the architecture of our LOC and HWA. We decomposed them into parts specified at gradually lower-level of abstraction We proceeded down to the level where the elementary properties affecting the LoD emerged. Examples of such properties are presented for the SiNW-bioFET sensor in figure 4. They include the SiNW length, width, etc. The components or aggregations of components (i.e. sub-systems) constituting the LOC and HWA were at first specified as what we call *generic* entities (see the *Generic* packages under LOC and HWA & Embedded SW in figure 3). These generic models made sense early on in the modelling process as the architectural details for the LOC and HWA were

unknown. We modelled the *specific* sub-systems or components once enough architectural details were known. We specified the generalization relationships existing between the generic and specific parts and then replaced generic parts by their specific counter parts. This is for instance illustrated in figure 3 with the Point-of-Care Hardware Accessory (POC HWA) aggregating a Bluetooth Low Energy module (BLE112), the latter itself representing a specific implementation of a HWA communication module.

3) *Functions*: We modelled the system's *functions* influencing the LoD specification using the same abstraction and decomposition steps we had followed for specifying the model's *structures*. The highest-level functional view of the system is provided by figure 4, which reveals the first-level functional decomposition of the SiNW-instrumentation system. The SiNW Chip Instrumentation engulfs the Biological Sample in which the target analyte is present, the SiNW-bioFET sensor, and the Lock-in amplifier (Lock-in amp) function. The scope of our analysis could thus be confined to the SiNW Chip Instrumentation block. Once all the structures and functions composing or nested in this block were defined, we could proceed to the *parametric specification* of all sub-systems and parts of interest.

4) *Parametric relationships*: We mathematically represented both the laws governing the physical interactions at the sample/biosensor level and the signal processing and computational steps influencing the system LoD using parametric diagrams. We started by defining these laws at the lowest levels (most fundamental level of abstraction: the component level followed by the sub-system level). Figure 5, for instance, represents the most elementary parametric relations governing the physical behaviour of the gate of the SiNW-bioFET sensor. Each constraint block calls a Mathematica function responsible for calculating the value of the fundamental properties derived from gate properties.

Using a bottom-up approach, we relied on these low-level parametric relations to progressively establish the mathematical laws defining the property values of sub-systems at higher abstraction levels. For instance, the parametric specification of the Root Mean Square (RMS) noise level at the output of the Current Amplifier Stage block, held in the `VnoiseOutRmsSigCond` property, could be defined by successively summing the individual noise contributions of the three main blocks of the Current Amplifier Stage (i.e. AD8608 amplifier, the RC filter and the ADC) (figure 6). The `VnoiseOutRmsSigCond` could similarly be leveraged one level up in the structural/functional hierarchy within the Lock-in amp function as the latter itself nests the Current Amplifier Stage block (figure 7), etc. This strategy ended with the specification of the parametric specification of the highest abstraction level, that of the SiNW Chip Instrumentation function (figure 8). There the LoD value property could be calculated, together with the signal amplitude values needed to ascertain that no signal saturation i.e. constraint violation would occur.

5) *Parametric study*: Once our model was completed, we set up a trade study using the Paramagic plugin by defining sets of specification values for parameters we deemed should be most relevant to investigate if we were to upgrade system components in isolation in an attempt to reach a lower system LoD specification. By isolation we mean that a component swap or upgrade would likely not cascade into further needed changes throughout the rest of the system. The parameters we selected span over all the engineering disciplines involved in the definition of the system-level LoD: surface chemistry, microfabrication, analog electronics and digital signal processing. These parameters are highlighted in bold in Table I. We considered 8 SiNW thickness alternatives, from 20 to 90 nm, 4 different SiNW gate thicknesses, 6 possible SiNW gate receptors surface coverage densities, 4 possible specifications for the input amplifier's current noise density, 2 possible gains for this input amplifier, 2 possible resolutions for the Analog to Digital Converter (ADC), 6 different Finite Impulse Response (FIR) digital filters. We therefore investigated a design space containing $8 \times 4 \times 6 \times 4 \times 2 \times 2 \times 6 = 18432$ points. The trade-study was set and executed within the MagicDraw environment, importing and exporting variable values from and to Microsoft Excel. We used Matlab to display the results presented in the following section.

VI. RESULTS

Adopting a systemic perspective on the SiNW-bioFET/instrumentation assembly turned out to be crucial in identifying which sub-systems, and thus engineering domains, influence the most the LoD specification. Our parametric study shows the relative influence of couples of parametric variables on the LoD. In figure 9, the LoD is investigated as a function of SiNW thickness and gate surface receptors density respectively. Here it is evident that the predominant influence on LoD is surface chemistry. A similar trend is seen in figure 10 where the LoD is plotted versus SiNW gate oxide thickness and gate surface receptors. The availability of such result should therefore encourage sensor fabrication specialists and surface chemists to agree on a design trade-off taking into consideration the relative difficulties associated with the thinning of sensor structures down to a few nanometers versus the small LoD performance enhancement one may hope to achieve from it.

Also, our system-wide investigation highlights limitations that could not be anticipated by the investigation of the biosensor alone: the apparent non-linear influence of the SiNW thickness in figure 11 is not predicted by existing analytical models for SiNW-bioFETs. Rather, this behaviour results from the complex interactions between SiNW-bioFET and instrumentation. Figure 11 highlights the balance between antagonists trends: towards greater sensor LoD performances on one end and poorer instrumentation LoD performances on the other end. Figure 11 also reveals some of the systemic configurations to avoid: when the gate oxide thickness is 2 nm no LoD can be computed, i.e. where there was no instrument configuration providing a sufficient Signal to Noise ratio.

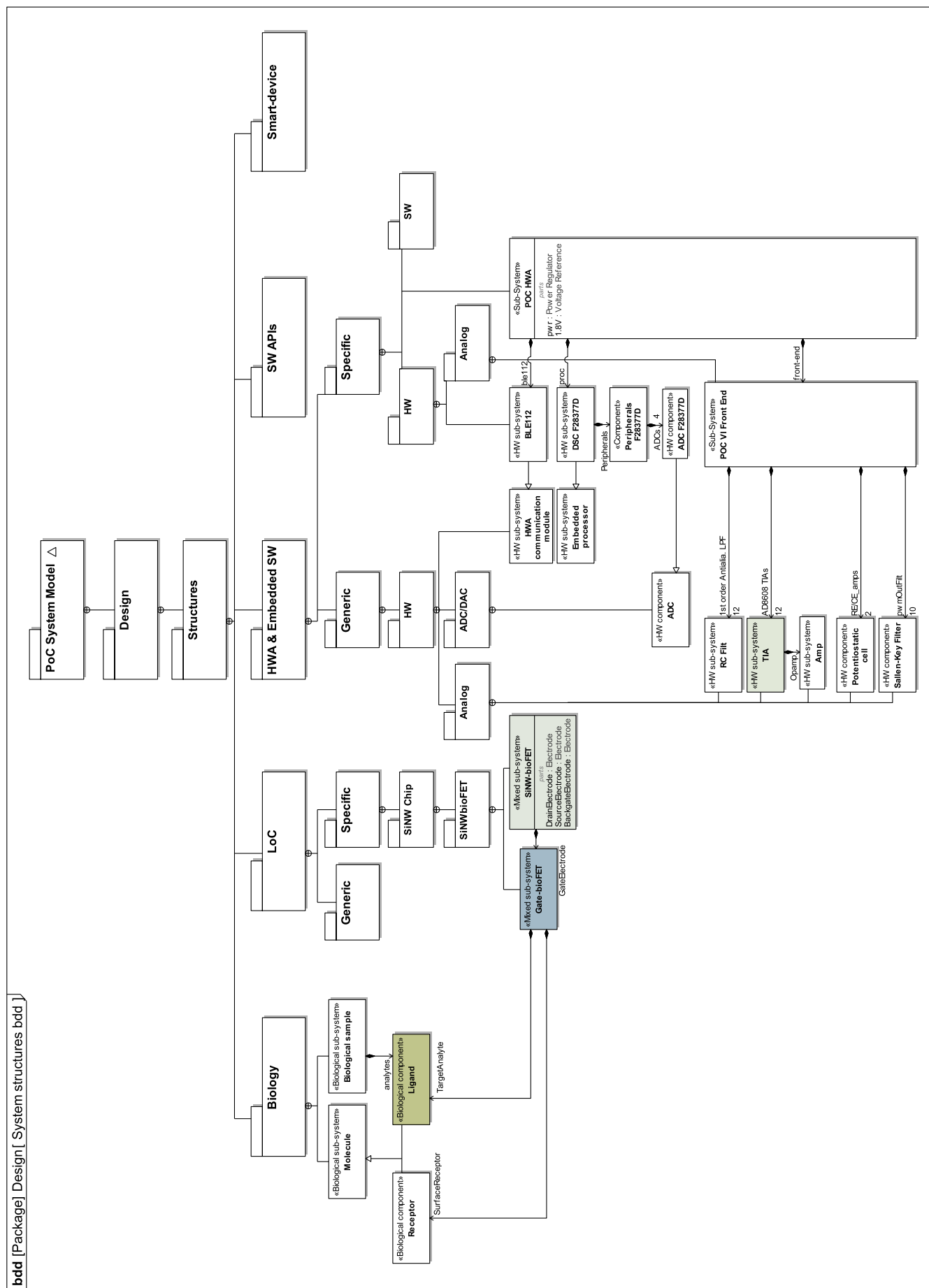


Fig. 3. Structures involved in the analysis

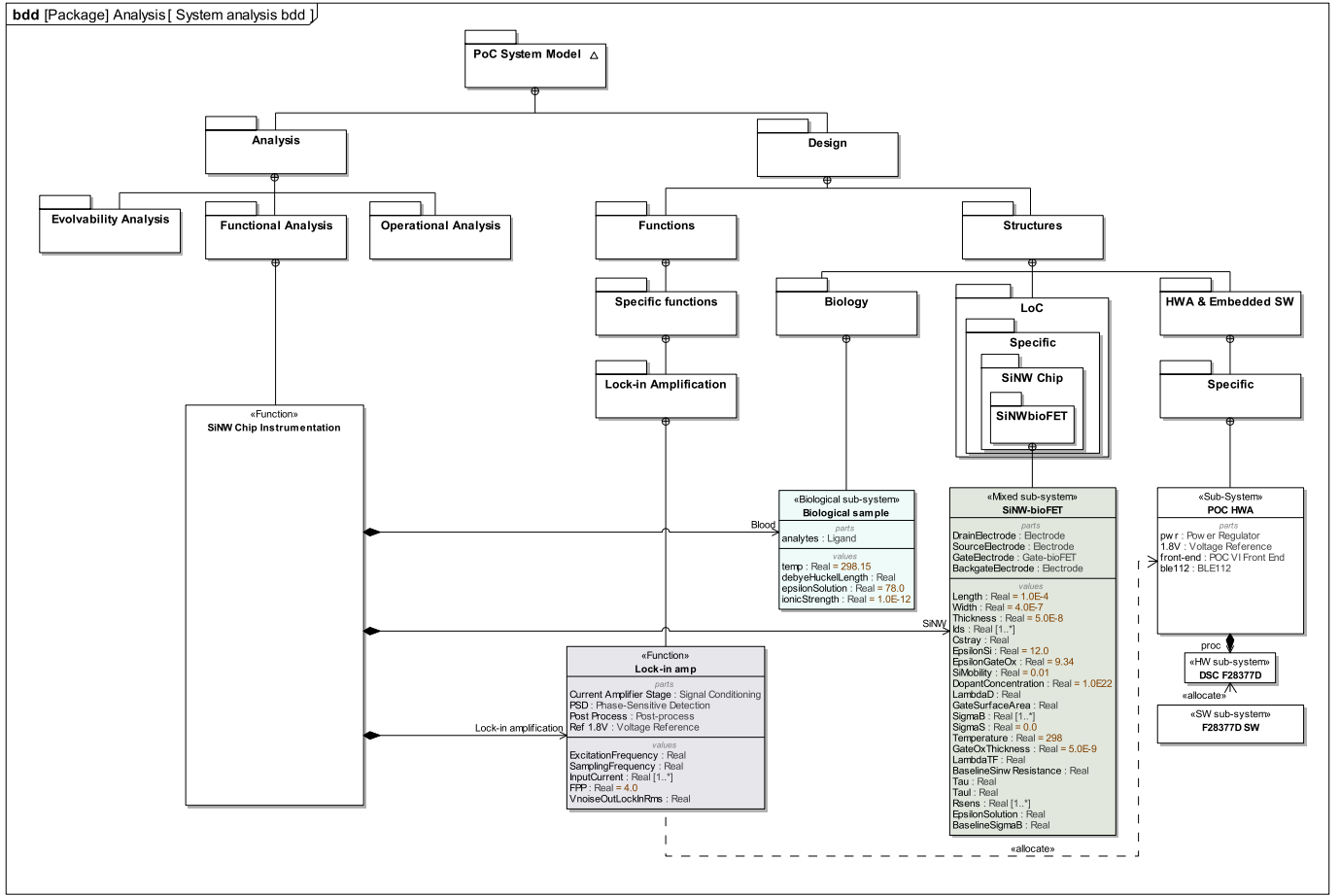


Fig. 4. SiNW instrumentation functional decomposition and function allocation

Beside the identification of emergent systemic behaviours, we were able to predict the extent of performance enhancement we thought we could obtain by changing the input amplifier for a variant specified with a lower current noise density. We thus expected a lower amount of noise injected by the amplifier to translate into better LoD performances. Figure 12 also reveals the negligible influence of the amplifier's current noise specification against the SiNW thickness. The latter parameter already playing a small role in LoD specification, the input amplifier current noise can be neglected.

Finally, and most importantly, figure 13 reveals the relative influence of the gate surface receptor density versus the influence of the efficiency of the digital filtering block, here represented by the number of taps of the various filters available in the Post-Process block (figure 7). This observation thereby allows us to link the two most remote engineering domains involved in the definition of the system-level LoD: surface chemistry on one side, and digital signal processing on the other. An important observation here is that there seem to be system configurations for which filter selection or filter re-design could help avoid the painstaking reengineering of the sensor's biofunctionalization layer. Indeed, it appears that among the available filters, selecting the 137-tap filter instead of any other can in some instances benefit the system-level LoD performance to a similar extent as to improving the gate surface coverage by half an order of magnitude. This characteristic can be explained by the design methods used to specify these filters [47] and will not be detailed here. The implications of this latter finding are substantial: contrary to the foreseeable difficulties in remodelling the gate surface chemistry, digital filters can easily be optimized at negligible costs and without any need for significant structural or behavioural alteration at the system-level.

VII. DISCUSSION AND CONCLUSION

The emergence of CPS harnessing biomolecular-scale components brings exciting opportunities for the advance of medicine and environmental-sciences. The translation of innovative concepts to successful applications will yet require designing organisations to address safety, efficacy and cost-efficiency challenges that concern both expert and public opinion. The adoption of appropriate MBSD frameworks can support designing organisations in that attempt, by enabling the design and analysis of CBPS spanning across the biological, physical-non-biological and computational domains, while streamlining product development.

Here, we demonstrated in particular that formalisms of the SysML language can be harnessed in the early phases of CBPS design by: 1– modelling a complete *in vitro* diagnostic system; 2– illustrating the possibility to carry out system-wide

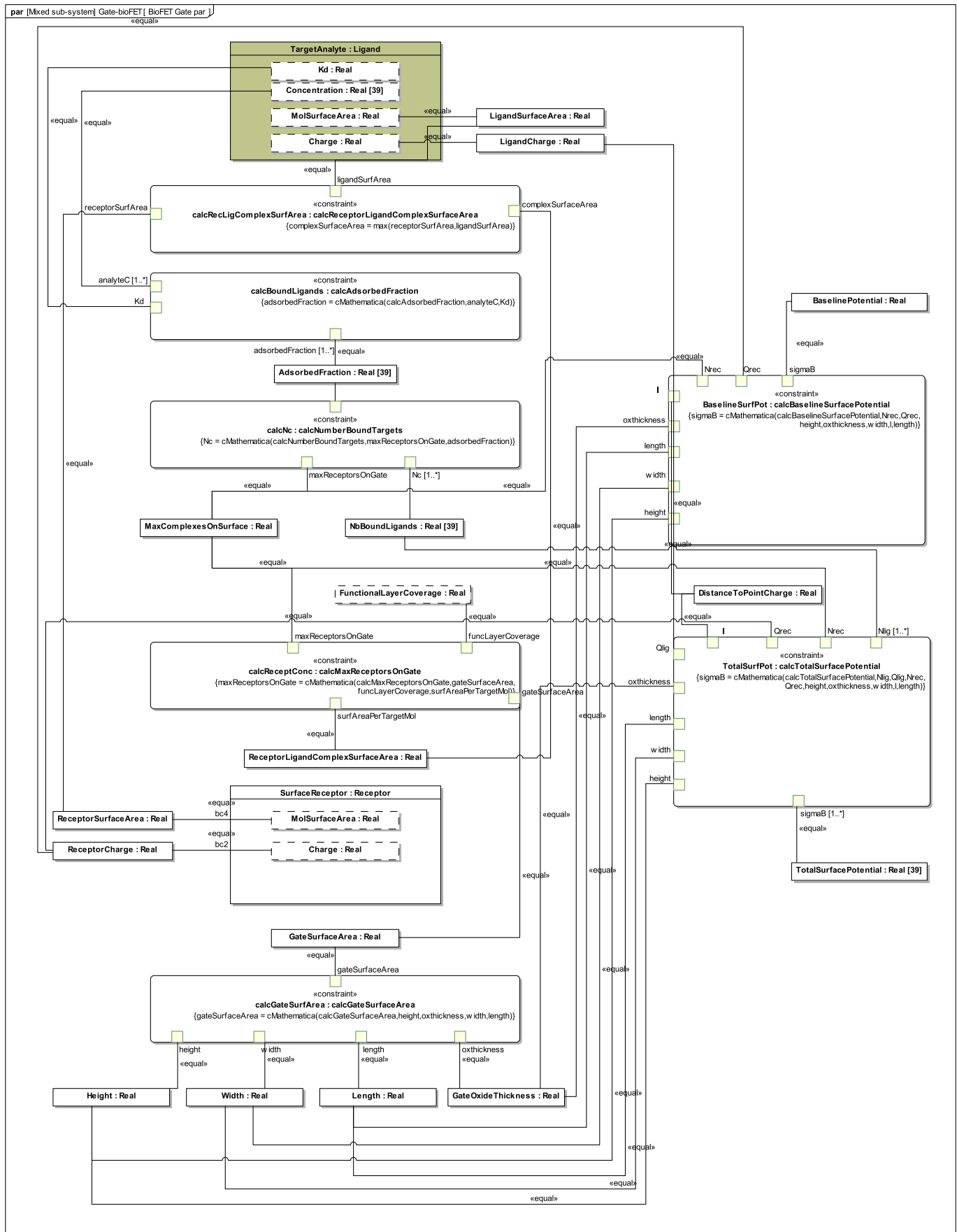


Fig. 5. Low-level parametric diagram for the gate of the SiNW-bioFET sensor

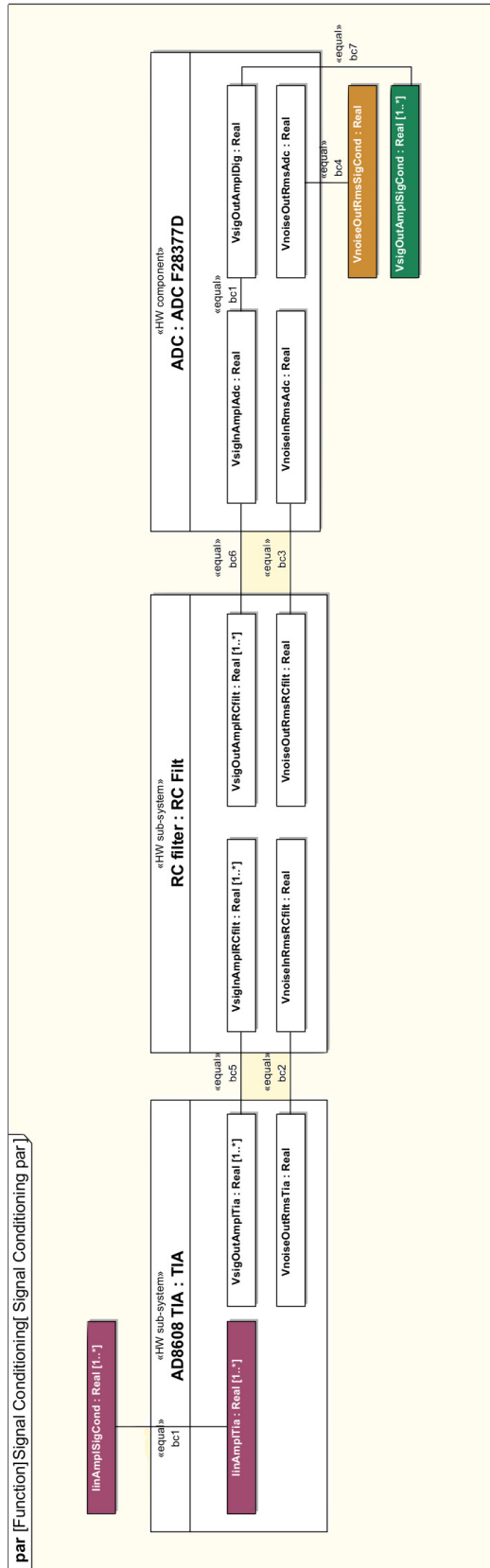


Fig. 6. Parametric diagram of the signal conditioning block (input of the lock-in amplifier)

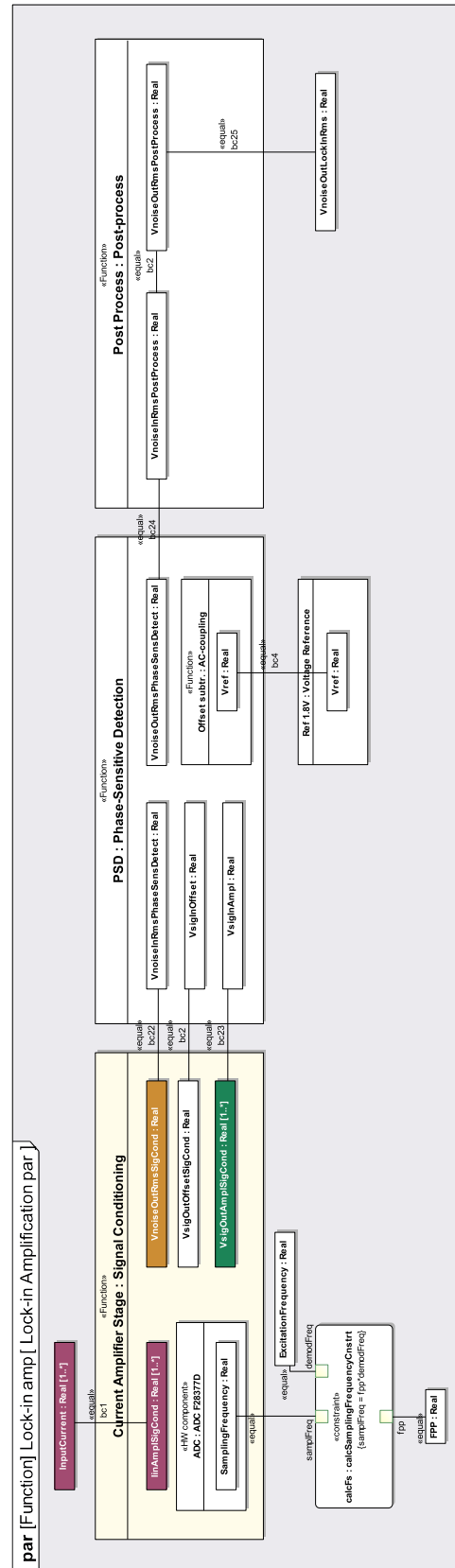


Fig. 7. Top-level parametric diagram of the lock-in amplifier

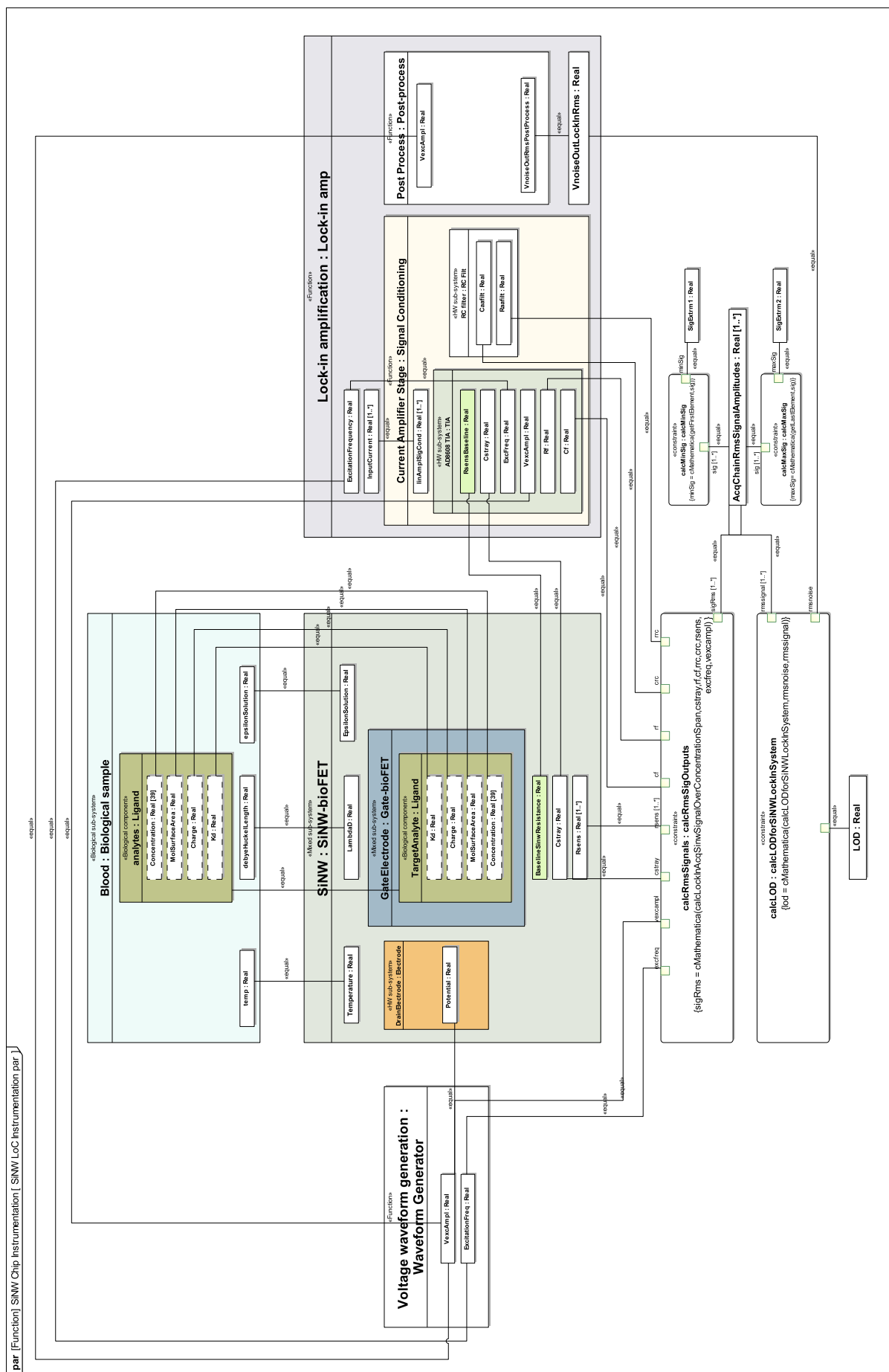


Fig. 8. Top-level parametric diagram of the SiNW-bioFET instrumentation system

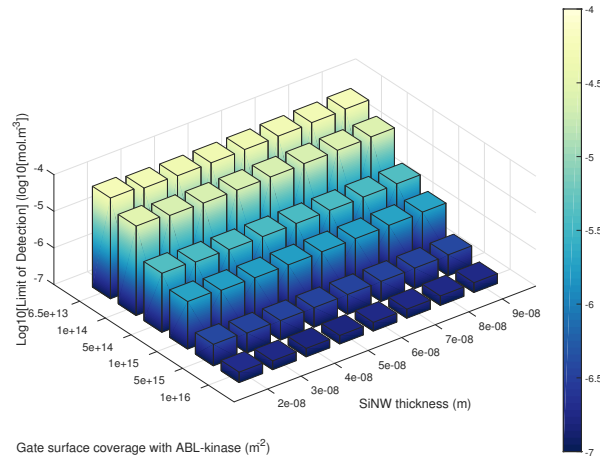


Fig. 9. Influence of the SiNW thickness versus gate surface receptors density on the system-level LoD performance. Specifications for the other variables investigated are those of the reference design: gate oxide thickness = 5 nm, amplifier's current noise density $I_{\text{noise}} = 1 \times 10^{-12} \text{ A}/\sqrt{\text{Hz}}$, ADC resolution = 12 bits, 856-tap FIR filter

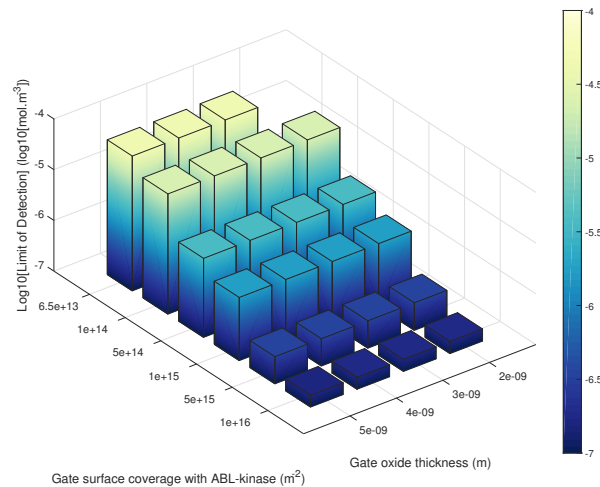


Fig. 10. Influence of the SiNW gate oxide thickness versus gate surface receptors density on the system-level LoD performance. Specifications for the other variables investigated are those of the reference design: SiNW thickness = 50 nm, amplifier's current noise density $I_{\text{noise}} = 1 \times 10^{-12} \text{ A}/\sqrt{\text{Hz}}$, ADC resolution = 12 bits, 856-tap FIR filter

performance analyses on that model and, from those: 3– identifying system-level bottlenecks to system performance indicating which system modules should be targeted first for optimization.

From such endeavours, it is also straightforward to assume the feasibility of formal performance requirements verification since SysML allows for requirements and specification traceability. Likewise, we may conjecture that other tools of MBSD may further strengthen the legitimacy of the approach: Design Structure Matrices and change-propagation analyses are becoming standard tools of SysML-based MBSD [49]–[51]. These can help trace dependencies, plan for system upgrade or redesign and perhaps support the re-thinking of functional allocation even for the largest of CBPS currently existing (e.g. bench-size clinical IVMT analyzers).

Questions now arise as to the extent to which available MBSD frameworks can support designing organisations throughout the remainder of the system development process. Although we showed that early modelling and analyses paved the way for formal verification methods, the integration of these practices into an engineering framework tightly coupled with quality management and regulatory affairs is another issue that will require further research. Also, even though the modelling capabilities offered by SysML supposedly allow the modelling and *in silico* analysis of CBPS of greater complexity (e.g. such as of those more closely associated with the low-level manipulation of biomolecules like automated synthetic biology instruments) we must reflect on the

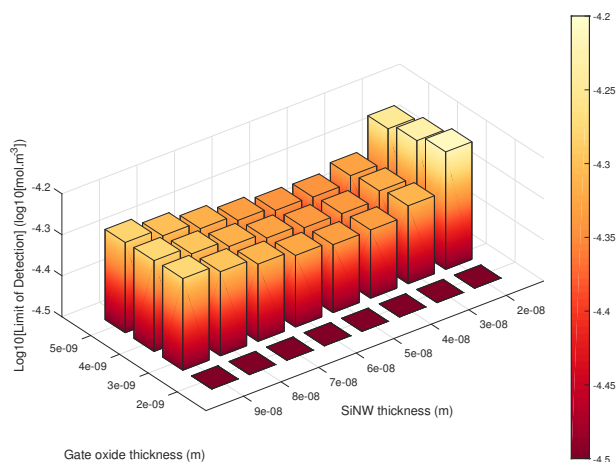


Fig. 11. Influence of the SiNW thickness versus SiNW gate oxide thickness on the system-level LoD performance. Specifications for the other variables investigated are those of the reference design: gate surface receptors density = $6.5 \times 10^{13} \text{ m}^{-2}$, amplifier's current noise density $I_{\text{noise}} = 1 \times 10^{-12} \text{ A}/\sqrt{\text{Hz}}$, ADC resolution = 12 bits, 856-tap FIR filter

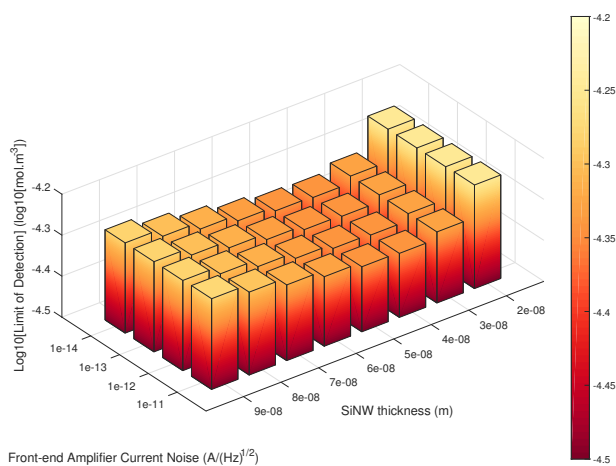


Fig. 12. Influence of the SiNW thickness versus amplifier's input current noise density on the system-level LoD performance. Specifications for the other variables investigated are those of the reference design: gate surface receptors density = $6.5 \times 10^{13} \text{ m}^{-2}$, gate oxide thickness = 5 nm, ADC resolution = 12 bits, 856-tap FIR filter

missing integrations between current SysML tools and design tools for hardware components and for chemical and biological synthesis. Only when such integrations are available will design synthesis of CBPS be made possible. Indeed, although code-generation from early abstract CPS SysML models has been demonstrated for computation-only embedded systems, there seems to be a long way until the same principles enable the specification of CBPS where the functions, performance and constraints imposed by a designer would be translated automatically into not only machine-code but also mechanical specifications and biopolymer sequences (e.g. DNA). This visionary portrait of fully synthesized CBPS therefore extends our current vision of the holy grail of CPS design.

Despite its current limitations, MBSD and in particular SysML provide designing organisations with a stepping-stone towards the design of safe and cost-efficient CBPS. Advances in CPS MBSE will keep on benefiting those organisations who may soon be capable not only to undertake software and hardware co-design but also to investigate the trade-offs involving elements of a biological nature. Such developments promise the streamlining of CBPS development and encourage researchers to work on the matter.

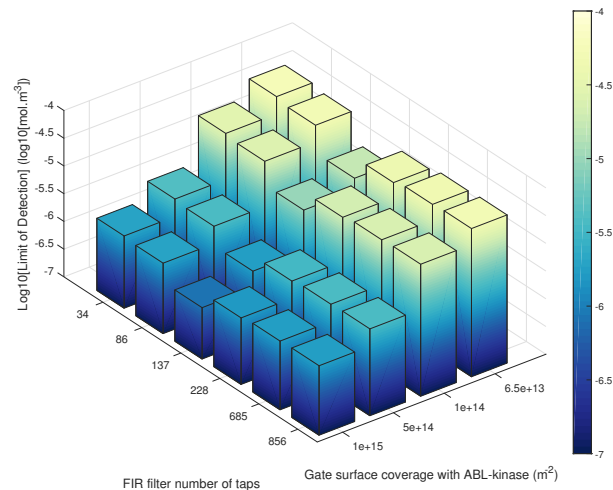


Fig. 13. Influence of the gate surface receptors density versus FIR filter on the system-level LoD performance. Specifications for the other variables investigated are those of the reference design: SiNW thickness = 50 nm, gate oxide thickness = 5 nm, amplifier's current noise density $I_{\text{noise}} = 1 \times 10^{-12} \text{ A}/\sqrt{\text{Hz}}$, ADC resolution = 12 bits

ACKNOWLEDGMENT

This project is a part of the EU Marie Curie Initial Training Networks (ITN) Biomedical Engineering for Cancer and BRAin disease diagnosis and therapy development: EngCaBra ; Project No. PITN-GA-2010-264417.

REFERENCES

- [1] S. Goodwin, J. D. McPherson, and W. R. McCombie, "Coming of age: ten years of next-generation sequencing technologies," *Nat Rev Genet*, vol. 17, no. 6, pp. 333–351, 2016. [Online]. Available: <https://www.ncbi.nlm.nih.gov/pubmed/27184599>
- [2] S. Kosuri and G. M. Church, "Large-scale de novo DNA synthesis: technologies and applications," *Nature methods*, vol. 11, no. 5, pp. 499–507, 2014. [Online]. Available: <http://www.ncbi.nlm.nih.gov/pubmed/24781323>
- [3] K. S. Boles, K. Kannan, J. Gill, M. Felderman, H. Gouvis, B. Hubby, K. I. Kamrud, J. C. Venter, and D. G. Gibson, "Digital-to-biological converter for on-demand production of biologics," *Nature Biotechnology*, vol. 1, no. May, 2017. [Online]. Available: <http://www.nature.com/doi/10.1038/nbt.3859>
- [4] L. J. Kricka, T. G. Polsky, J. Y. Park, and P. Fortina, "The future of laboratory medicine - A 2014 perspective," *Clinica Chimica Acta*, vol. 438, pp. 284–303, 2015. [Online]. Available: <http://dx.doi.org/10.1016/j.cca.2014.09.005>
- [5] S.-m. Park, A. Sabour, J. Son, S. Lee, and L. Lee, "Toward Integrated Molecular Diagnostic System (iMDx): Principles and Applications," *IEEE Transactions on Biomedical Engineering*, vol. 61, no. 5, pp. 1506–1521, 2014. [Online]. Available: http://ieeexplore.ieee.org/xpls/abs_all.jsp?arnumber=6775268
- [6] C. S. Bloss, N. J. Schork, and E. J. Topol, "Direct-to-consumer pharmacogenomic testing assessed in a US-based study," *Journal of Medical Genetics*, vol. 51, pp. 83–89, 2014.
- [7] D. E. Cameron, C. J. Bashor, and J. J. Collins, "A brief history of synthetic biology," *Nature reviews. Microbiology*, vol. 12, no. 5, pp. 381–90, 2014. [Online]. Available: <http://www.ncbi.nlm.nih.gov/pubmed/24686414>
- [8] P. Perez-Pinera, N. Han, S. Cleto, J. Cao, O. Purcell, K. A. Shah, K. Lee, R. Ram, and T. K. Lu, "Synthetic biology and microreactor platforms for programmable production of biologics at the point-of-care," *Nature Communications*, vol. 7, p. 12211, 2016. [Online]. Available: <http://www.nature.com/doi/10.1038/ncomms12211>
- [9] E. P. Diamandis, "Theranostic phenomenon: Promises and fallacies," *Clinical Chemistry and Laboratory Medicine*, vol. 53, no. 7, pp. 989–993, 2015.
- [10] J. P. A. Ioannidis, "Stealth Research and Theranos: Reflections and Update 1 Year Later," *Jama*, vol. 316, no. 4, pp. 389–90, 2016. [Online]. Available: <http://www.ncbi.nlm.nih.gov/pubmed/27191700>
- [11] B. S. Ferguson, D. A. Hoggarth, D. Maliniak, K. Ploense, R. J. White, N. Woodward, K. Hsieh, A. J. Bonham, M. Eisenstein, T. E. Kippin, K. W. Plaxco, and H. T. Soh, "Real-Time, Aptamer-Based Tracking of Circulating Therapeutic Agents in Living Animals," *Science Translational Medicine*, vol. 5, no. 213, pp. 213ra165–213ra165, 2013. [Online]. Available: <http://stm.sciencemag.org/content/5/213/213ra165>
- [12] T. T. Ruckh and H. a. Clark, "Implantable nanosensors: Toward continuous physiologic monitoring," *Analytical Chemistry*, vol. 86, no. 3, pp. 1314–1323, 2014.
- [13] C. H. Alvarez, "DNA assembly and cloning in an overnight run with the BioXp™ 3200 system," *Nature Methods*, vol. 12, no. 12, pp. v–vi, 2015. [Online]. Available: <http://dx.doi.org/10.1038/nmeth.f.390>
- [14] H. P. L. Bruun, N. H. Mortensen, and U. Harlou, "Interface diagram: Design tool for supporting the development of modularity in complex product systems," *Concurrent Engineering*, vol. 22, no. 1, pp. 62–76, 2014. [Online]. Available: <http://journals.sagepub.com/doi/10.1177/1063293X13516329>
- [15] S. K. Khaitan, S. Member, and J. D. McCalley, "Design Techniques and Applications of Cyberphysical Systems : A Survey," *IEEE Systems Journal*, vol. 9, no. 2, pp. 350–365, 2015.
- [16] L. Miclea and T. Sanislav, "About dependability in cyber-physical systems," in *Proceedings of IEEE East-West Design and Test Symposium, EWDTS'2011*, 2011, pp. 17–21.
- [17] P. Pop, M. Alistar, E. Stuart, and J. Madsen, *Fault-Tolerant Digital Microfluidic Biochips*. Springer International, 2015.
- [18] M. J. Jebrail, M. S. Bartsch, and K. D. Patel, "Digital microfluidics: a versatile tool for applications in chemistry, biology and medicine," *Lab on a Chip*, vol. 12, no. 14, p. 2452, 2012. [Online]. Available: <http://xlink.rsc.org/?DOI=c2lc40318h>
- [19] A. Rival, D. Jary, C. Delattre, Y. Fouillet, G. Castellan, A. Bellemine-Comte, and X. Gidrol, "EWOD-based microfluidic chip for single-cell isolation, mRNA purification and subsequent multiplex qPCR," *Lab on a Chip*, vol. 14, pp. 3739–3749, 2014. [Online]. Available: <http://pubs.rsc.org/en/Content/ArticleLanding/2014/LC/C4LC00592A>

- [20] D. Witters, K. Knez, F. Ceysens, R. Puers, and J. Lammertyn, "Digital microfluidics-enabled single-molecule detection by printing and sealing single magnetic beads in femtoliter droplets," *Lab on a Chip*, vol. 13, no. 11, p. 2047, 2013. [Online]. Available: <http://xlink.rsc.org/?DOI=c3lc50119a>
- [21] S. Slomovic, K. Pardee, and J. J. Collins, "Synthetic biology devices for in vitro and in vivo diagnostics," *Proceedings of the National Academy of Sciences of the United States of America*, vol. 112, no. 47, pp. 14429–35, 2015. [Online]. Available: <http://www.pnas.org/content/112/47/14429.long>
- [22] N. Goldman, P. Bertone, S. Chen, C. Dessimoz, E. M. LeProust, B. Sipos, and E. Birney, "Towards practical, high-capacity, low-maintenance information storage in synthesized DNA," *Nature*, vol. 494, no. 7435, pp. 77–80, 2013.
- [23] J. Rumbaugh, I. Jacobson, and G. Booch, *The Unified Modeling Language Reference Manual*, 1999. [Online]. Available: http://www.amazon.com/s/ref=nb_sb_noss?url=search-alias%3Daps&field-keywords=9780201309980
- [24] A. L. Ramos, J. V. Ferreira, and J. Barceló, "Model-based systems engineering: An emerging approach for modern systems," *IEEE Transactions on Systems, Man and Cybernetics Part C: Applications and Reviews*, vol. 42, no. 1, pp. 101–111, 2012.
- [25] C. Piaszczyk, "Model Based Systems Engineering with Department of Defense Architectural Framework," *Systems Engineering*, vol. 14, no. 3, pp. 305–326, 2011.
- [26] I. Lee, O. Sokolsky, S. Chen, and J. Hatcliff, "Challenges and Research Directions in Medical Cyber-Physical Systems," *Proceedings of the ...*, vol. 100, no. 1, pp. 75–90, 2012. [Online]. Available: http://ieeexplore.ieee.org/xpls/abs_all.jsp?arnumber=6051465
- [27] I. S. Khayal and A. M. Farid, "The Need for Systems Tools in the Practice of Clinical Medicine," *Systems Engineering*, vol. 20, no. 1, pp. 3–20, 2017.
- [28] J. Somekh, G. Haimovich, A. Guterman, D. Dori, and M. Choder, "Conceptual modeling of mRNA decay provokes new hypotheses," *PLoS ONE*, vol. 9, no. 9, 2014.
- [29] D. W. Oliver, J. F. Andary, and H. Frisch, "Model-based systems engineering," *Handbook of Systems Engineering and Management*, no. December, pp. 1361–1400, 2009.
- [30] S. Friedenthal, A. Moore, and R. Steiner, *A Practical Guide to SysML*, 2015. [Online]. Available: <http://www.sciencedirect.com/science/article/pii/B9780128002025000199>
- [31] P. Derler, E. a. Lee, and A. Sangiovanni Vincentelli, "Modeling cyber-physical systems," *Proceedings of the IEEE*, vol. 100, no. 1, pp. 13–28, 2012.
- [32] D. Dori, *Model-Based Systems Engineering with OPM and SysML*. New York, NY: Springer-Verlag, 2016.
- [33] M. Rao, S. Ramakrishnan, and C. Dagli, "Modeling and simulation of net centric system of systems using systems modeling language and Colored Petri-nets: A demonstration using the Global Earth Observation System of Systems," *Systems Engineering*, vol. 11, no. 3, pp. 203–220, 2008.
- [34] P. Shames, S. Anderson, S. Kowal, M. Levesque, O. Sindiy, K. Donahue, and P. Barnes, "NASA Integrated Network Monitor and Control Software Architecture," *The 12th International Conference on Space Operations*, pp. 1–21, 2012.
- [35] D. Kaslow, G. Soremekun, H. Kim, and S. Spangelo, "Integrated model-based systems engineering (MBSE) applied to the Simulation of a CubeSat mission," *IEEE Aerospace Conference Proceedings*, 2014.
- [36] R. Cloutier, B. Sauser, M. Bone, and A. Taylor, "Transitioning systems thinking to model-based systems engineering: Systemigrams to SysML models," *IEEE Transactions on Systems, Man, and Cybernetics: Systems*, vol. 45, no. 4, pp. 662–674, 2015.
- [37] T. Sakairi, E. Palachi, C. Cohen, Y. Hatsutori, J. Shimizu, and H. Miyashita, "Designing a control system using SysML and Simulink," *SICE Annual Conference (SICE), 2012 Proceedings of*, pp. 2011–2017, 2012. [Online]. Available: http://ieeexplore.ieee.org/xpls/abs_all.jsp?arnumber=6318343
- [38] S. Nakajima, S. Furukawa, and Y. Ueda, "Co-analysis of SysML and simulink models for cyber-physical systems design," *Proceedings - 18th IEEE International Conference on Embedded and Real-Time Computing Systems and Applications, RTCSA 2012 - 2nd Workshop on Cyber-Physical Systems, Networks, and Applications, CPSNA*, no. Figure 2, pp. 473–478, 2012.
- [39] M. Nikolaidou, G. D. Kapos, A. Tsadimas, V. Dalakas, and D. Anagnostopoulos, "Simulating SysML models: Overview and challenges," *2015 10th System of Systems Engineering Conference, SoSE 2015*, pp. 328–333, 2015.
- [40] G. D. Kapos, V. Dalakas, A. Tsadimas, M. Nikolaidou, and D. Anagnostopoulos, "Model-based system engineering using SysML: Deriving executable simulation models with QVT," *8th Annual IEEE International Systems Conference, SysCon 2014 - Proceedings*, pp. 531–538, 2014.
- [41] A. M. Khan, F. Mallet, and M. Rashid, "Combining SysML and Marte/CCSL to model complex electronic systems," *Proceedings - 2016 International Conference on Information Systems Engineering, ICISE 2016*, pp. 12–17, 2016.
- [42] J. Vidal, F. de Lamotte, G. Gogniat, P. Soulard, and J.-P. Diguët, "A co-design approach for embedded system modeling and code generation with UML and MARTE," *Proceedings of the Conference on Design, Automation and Test in Europe (DATE'09)*, no. APRIL 2009, pp. 226–231, 2009. [Online]. Available: <http://dl.acm.org/citation.cfm?id=1874620.1874674>
- [43] M. Hossein, A. Hemmat, O. A. Mohamed, and M. Boukadoum, "Towards code generation for ARM Cortex-M MCUs from SysML activity diagrams," *Proceedings - IEEE International Symposium on Circuits and Systems*, vol. 2016-July, pp. 970–973, 2016.
- [44] R. Karban, N. Jankevičius, and M. Elaasar, "ESEM: Automated Systems Analysis using Executable SysML Modeling Patterns," *INCOSE International Symposium*, vol. 26, no. 1, pp. 1–24, 2016. [Online]. Available: <http://dx.doi.org/10.1002/j.2334-5837.2016.00142.x>
- [45] P. Leserf, P. de Saqui-Sannes, J. Hugues, and K. Chaaban, "SysML modeling for embedded systems design optimization: A case study," *Model-Driven Engineering and Software Development (MODELSWARD), 2015 3rd International Conference on*, pp. 449–457, 2015.
- [46] F. Patou, F. Alatraktchi, C. Kjægaard, M. Dimaki, J. Madsen, and W. E. Svendsen, "Evolvable Smartphone-Based Platforms for Point-Of-Care In-Vitro Diagnostics Applications," *Diagnostics*, vol. 6, no. 3, pp. 1–18, 2016.
- [47] F. Patou, M. Dimaki, A. Maier, J. Madsen, and W. E. Svendsen, "System-level Sensitivity Analysis of SiNW-bioFET-based Biosensing Using Lock-in Amplification," *IEEE Sensors Journal*, vol. Submitted, 2017.
- [48] J. Leis, C. Kelly, and D. Buttsworth, "Sampling, Quantization and Computational Aspects of the Quadrature Lock-In Amplifier," in *Signal Processing and Communication Systems (ICSPCS), 2012 6th International Conference on*, 2012, pp. 1–7.
- [49] S. D. Eppinger and T. R. Browning, *Design Structure Matrix Methods and Applications*. Cambridge: The MIT Press, 2012.
- [50] E. C. Koh, "A study on the Requirements to Support the Accurate Prediction of Engineering Change Propagation," *Systems Engineering*, vol. 20, no. 2, pp. 147–157, 2017.
- [51] B. Hamraz, N. H. Caldwell, and P. J. Clarkson, "A Holistic Categorization Framework for Literature on Engineering Change Management," *Systems Engineering*, vol. 16, no. 4, pp. 473–505, 2013.