Habilitation à diriger la recherche

SYSTEMES HETEROGENES : OUTILS CAO ET APPLICATIONS A LA BIOLOGIE

Morgan MADEC

Document provisoire présenté au jury en vue
d'une soutenance le jeudi 27 juin 2019

Composition du Jury

Garant	Christophe LALLEMENT	ICube, Strasbourg, FR
Rapporteur	Mohammad SAWAN	Polytechnique Montréal, CA
Rapporteur	Ian O'CONNOR	INL, Lyon, FR
Rapporteur	Daniel RIVELINE	IGBMC, Strasbourg, FR
Examinateur	François PECHEUX	LIP6, Paris, FR
Examinateur	Jean-Michel SALLESE	EPFL, Lausanne, CH
Examinateur	Winfried RÖMER	BIOSS, Freiburg, DE
Examinateur	Luc HEBRARD	ICube, Strasbourg, FR

TABLE OF CONTENTS

GLOSSARY

Biosensor	Device that combines one or several physicochemical detection methods in order to measure biological signals.
Boolean function	Mathematical function defined by binary variables (*true* or *false*) and logical operators (*and*, *or*, *not*).
Carbon-Nanotubes Field-Effect Transistor (CNFET)	Transistor for which the conduction channel is achieved by one or several carbon nanotubes.
CMOS technology	Standard technological process used for the realization of most of the integrated circuits in microelectronics.
Compact models or design-oriented models	Computationally efficient description of the behavior of a device compatible with standard electrical circuit simulators.
Computer-Aided Design (CAD) tool	Software used to assist a system designer in several tasks: dimensioning, optimization, simulation, performances analysis, layout, etc;
Deoxyribonucleic Acid (DNA)	Molecule that encodes the genetic information.
Design Kit	Database of elementary devices achievable with a given technology with, for each, different views corresponding to the schematic, the layout, the models, the performances, etc.
Digital synthesizer	Tool of the electronic design automation environment that generates digital circuits from a high-level specification (truth table, state diagram, etc.)
Electrical impedance spectroscopy (EIS)	Detection technique for living matter based on the monitoring of the variations of the impedance of the tissues.
Electronic design automation (EDA)	Set of computer-aided design software used all along the design process of an electrical system and/or a microelectronic circuit.
Enzyme and enzymatic reaction	Biochemical reaction which consists in the transformation of a molecule (the substrate) into another (the product) under the assistance of a third one (the enzyme).
Enzyme-linked immunosorbent assay (ELISA)	A commonplace analytical biochemistry assay used for the detection of a protein by the binding on its associated antibody.
Finite difference / Finite element method	Two methods used for the numerical resolution of partial differential equations.
Gene	Small strand of the DNA molecule that encodes for one protein.
Gene regulatory networks (GRN)	Set of genes in interaction (the expression of a gene is controlled by a molecule synthesized from another gene) that achieve a biological function.
Hardware description language (HDL)	Computational language dedicated to the description of hardware, initially developed for microelectronics but now extended to cover most of the domains.
Hill's equation	Mathematical model used to describe the effect of a third-party activator or inhibitor on a biochemical reaction.
Ion-sensitive field effect transistor (ISFET)	Electrochemical sensor that behaves like a transistor which characteristics depend on the pH of a solution confined between the transistor gate and a counter-electrode.

Lab-on-chip	Autonomous devices that integrate sensors and microfluidic channels to perform a complete biochemical assay in a single chip.
Larmor frequency	Frequency at which the precession of the spin occurs for a given external magnetic field in NMR applications.
Messenger ribonucleic acid (mRNA)	Molecule synthesized from DNA by the transcription process and that is translated to synthesize proteins.
Metal-oxide-semiconductor field effect transistors (MOSFET)	Elementary 4-pin electronic device which basically behaves as a resistance or a conductance between two contacts (drain and source) which value is controlled by the voltage across the two other contacts (gate and bulk).
Michaelis-Menten	Mathematical model used to estimate the rate of most of the enzymatic reactions.
Nuclear magnetic resonance (NMR)	Physical phenomenon which is commonly used as a spectroscopy method for the analysis of the composition of matter.
Ordinary differential equations (ODE)	Differential equations for which all the terms only depend on the time.
Partial differential equations (PDE)	Differential equations for which at least one term depends both on the time and on the space.
Pulsed amperometry detection	Detection technique used in biochemistry based on impedance variation of living matter excited by current pulses.
Quorum sensing	Biological mechanisms used by several microorganisms to sense their environment and more particularly their local density.
Simulation program with integrated circuit emphasis (SPICE)	A general-purpose open-source language dedicated to the description and the simulation of analog electronic circuits.
Stochastic differential equations (SDE)	Differential equations for which at least one term corresponds to a stochastic (random) process.
Stochastic optimization algorithms	Class of optimization algorithms that proceed by trial-and-error and use random stochastic processes to generate new solutions from the previous ones.
Synthetic biology	Research field at the interface of biology and engineering sciences that aims at the design and the integration in living cells of artificial biological functions.
System biology	Research field at the interface of biology and computer sciences that aims at modeling complex biological systems to better understand their mechanisms.
System biology markup language (SBML)	Computational language dedicated to the description of biological systems.
SystemC-AMS	Open-source C++ class used for the modeling of heterogeneous systems
Transcription / Translation	Two biological mechanisms involved in the synthesis of proteins from DNA. The transcription is the synthesis of mRNA from DNA whereas translation is the synthesis of a protein from mRNA.
Verilog-A	Hardware description language (HDL) used for the description of the behavior of analog and mixed electronic circuits.
VHDL-AMS	Hardware description language (see HDL) used for the description of the behavior of heterogeneous circuits and systems.

GENERAL INTRODUCTION

In electrical engineering, heterogeneous systems are, by definition, systems that couple electronics with one or several other domains of physics: mechanics, electromagnetism, optics, thermal physics, etc. The design of such a system implies several challenges. First, the coordination of multidisciplinary teams composed of researchers/engineers with different background, different vocabularies and different habits is required. Second, the coupling between domains is definitively the major scientific bottleneck. The more coupling in the system, the trickier the design. To reduce risks of failure, transdisciplinary couplings have to be taken into account in the early staged of the design process. Third, deciding *a priori* what would be the best technologies for each part of the system is also tricky. Understanding the basics of the respective technologies, communicating efficiently between partners, anticipating of potential interferences and major coupling effect is required to take these decisions reliably.

For electrical systems, design-oriented modeling and computer-aided design environments are good fellows to tackle such challenges. Generally speaking, a model is a computer code written in a formal language. There are different levels of modeling. In our case, the focus is put on design-oriented models, *i.e.* models of elementary parts of the system that take first-order effects into account and that can be easily combined in order to obtain a predictive model of a complete system. Such models, often called virtual prototype, form an unambiguous description of the studied device or system, which reduces the risk of misunderstanding between project partners. Moreover, models might involve interactions that actually occur between parts of the system. By this way, prediction can be made and incompatibilities can be revealed early in the design process. Finally, fast and inexpensive *in silico* tests on several variations of a system can be made. The prerequisite for that is the availability of a database of models for the different devices achievable with a given technology. Modeling and virtual prototyping have been efficiently used in the context of microelectronics for decades. Since the 2000s, investigations have been made to integrate other domains of physics within electronics in a single language called Hardware Description Language. VHDL-AMS, Verilog-AMS or SystemC-AMS are the most common example of such language [Vachoux, Grimm and Einwich, 2003; Pecheux, Lallement and Vachoux, 2005].

Over the last 20 years, biology joined the big family of domains in interaction with electronics. Each day, a handful of papers describing new bioelectronic devices are published. Transducers which convert biological information into an electrical one are some examples. They can be made of different technologies and are widely used for biological signal monitoring [Luo *et al.*, 2004], DNA sequencing [Rothberg et *al.*, 2011] or point-of-care diagnosis [Wang, 2006].

By the same way, BioMEMS are devices coupling at least mechanics, electronics and biology. They can be used as sensors and/or as actuators in several applications encompassing tissue engineering, cell sorting, fluid separation and mixing, genetics, drugs delivery, biosensing, etc [Badilescu, Packirisamy and Packirisamy, 2016]. Sometimes, cells are used as a biological transducer to convert the signal of interest into a measurable one. Their main advantages compared to commonplace biosensors are their built-in selectivity to biochemical compound and their ability to react with analytes in a physiologically relevant way [Taniguchi, 2010].

Sometimes, the measurement of a biological signal requires a complete protocol (reagent mixing, incubation at a controlled temperature, etc). In this case, microfluidic circuits are used to perform the elementary operations of a biochemical protocol on a single device. When the biosensor is integrated within this microfluidic circuit, we speak about lab-on-chips or micro total analysis system. This kind of device can be used both for diagnosis and therapy (*e.g.* drug delivery) [Abgrall and Gué, 2007; Riahi *et al*., 2015]. By the same way, organs-on-chip is another killer application born from the coupling of lab-on-chips and living-cell applications. They are low-cost, more efficient and more ethical than *in vitro* cell-based assays or *in vivo* studies on animals [Huh *et al*., 2012; Chan *et al*., 2013].

_____

I have been working on modeling and electronic design automation tools for about 15 years. Besides, I discovered the fantastic world of applications emerging from the coupling between electronics and life sciences, mostly by participating in international conferences and having valuable discussions with colleagues in biology and biotechnologies. Thus, I started learning to better understand the "*Secrets of Life*" and initiated investigations on the interest to extend electronic design automation tools to the biological context. My long-term goal is to provide a computer-aided design environment dedicated to heterogeneous systems and more specifically systems that embrace biology. Moreover, I also would like to go beyond computational tools and realize actual biosystems for specific applications. Of course, going from end-to-end is much more attractive. However, I also believe that it is necessary in order to grasp the assets and the limitation of the software environment.

These ideas are discussed in this manuscript which is divided into three parts. PART ONE is a description of my research activities since my appointment in 2008. In CHAPTER 1, the focus is put on the compact modeling of integrated heterogeneous devices. CHAPTER 2 gives an overview of my investigations on the adaptation of electronic design automation tools to biology. Then, the research perspectives, briefly summarized in the previous paragraph, are detailed in PART TWO. First, upcoming projects and mid-term goals on the computer-aided design environment for heterogeneous systems are described in CHAPTER 3. Besides, concrete applications are discussed in CHAPTER 4. Finally, PART THREE (CHAPTER 5) summarizes my teaching and tutoring activities, as well as my involvement in research administration.

PART ONE -
RESEARCH ACTIVITIES

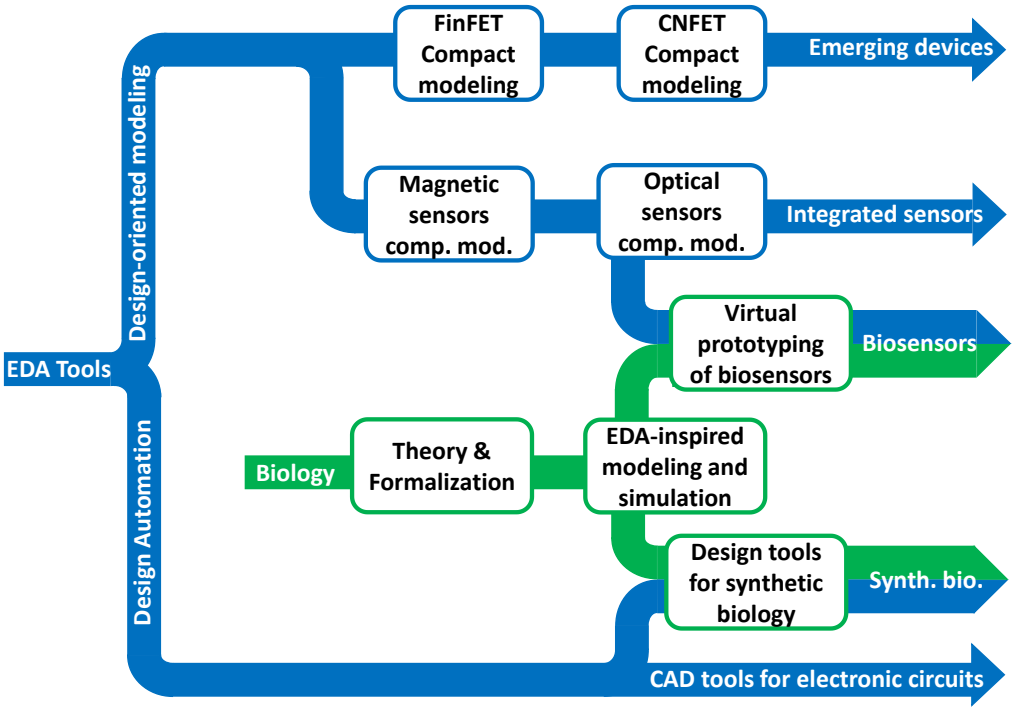

FIGURE 1 – THE GUIDING THREAD OF MY RESEARCH ACTIVITIES.

The first part of this manuscript is an overview of my research activities over the past 15 years. The guiding thread is summarized in FIGURE 1. The story began with my Ph.D. project in 2003. I was in charge of the evaluation of the performances of optoelectronic processors dedicated to tomographic image reconstruction. It was already a highly transdisciplinary project. It gave me a first experience on the aspects related to the system-level and design-oriented modeling of the multi-physic systems, on the concept of levels of abstraction and on the computational tools associated with this problematic. In particular, I used some of the computational tools that compose the electronic design automation environment. After the Ph.D., I was recruited as an associate professor in the *Heterogeneous Systems and Microsystems* research team. My first task was to bridge the gap between two important research activities of the team: the compact modeling of microelectronic devices on the one hand and the design of integrated sensor on the other.

CHAPTER 1 of the manuscript summarizes my activities in this scope. Three kinds of devices are considered: the emerging technologies of field-effect transistors (multiple-gate and carbon nanotubes), the integrated magnetic sensors and some optoelectronic devices. Regarding magnetic sensors, two families of devices have been modeled. The first is the fluxgate based on magnetic tunnel junction sensors. We released a compact model for such a device that encompasses both the magnetization reversal of the ferromagnetic layers as well as the tunnel conductance within the structure. The second kind of sensors is the Hall-effect sensors made in standard CMOS technology. In particular, we studied sensors that measure small variations of the magnetic field in the plane of the chip and sensors that measure the magnetic field in the direction perpendicular to the chip. Finally, we also developed compact models for two optoelectronic devices: a laser diode and a spatial light modulator based on ferromagnetic liquid crystal.

Since 2010, we have established collaborations with colleagues from the biological domain. We took advantage of a favorable geographical context since we share the same campus with the Biotechnology School of Strasbourg (ESBS) and its associated research lab (Laboratory of Biotechnologies and Cell Signaling, UMR7242), the Faculty of Pharmacy of the University of Strasbourg and the Institute for Genetics and Molecular and Cellular Biology (IGBMC). I first had to appropriate the theoretical concepts of biology in order to fully understand the ins and the outs of their projects. Then, we successfully linked electronics and biology by extending electronic design automation tools from one field to the other. This approach is retraced in CHAPTER 2 of the manuscript. BB-SPICE and BB-SPICE 3D, two software based on an electronic simulation environment and extended to the biochemical context are described. This first result enabled new investigations in the field of biosensors and synthetic biology. For instance, we demonstrated the interest of virtual prototyping for the design of biosensors. Besides, we successfully coupled theories on gene regulatory networks and design automation tools to provide innovative solutions in the field of synthetic biology.

CHAPTER 1 – DESIGN-ORIENTED MODELING

1. ADVANCED AND EMERGING DEVICES

1.1. MULTIPLE-GRID MOSFET

CONTEXT

Since a couple of years, the miniaturization of standard *Metal-Oxide-Semiconductor Field Effect Transistors* (MOSFET) has dropped off. For the last generation of MOSFET, gate thickness corresponds to a few dozens of atoms. At this scale, quantum mechanics come into play and performances of the transistors are drastically reduced. To get around these issues, the design of transistors with alternative geometries has been considered, with the main idea to wrap the gate around the transistor channel (FIGURE 2). Such devices have been given the generic name of Multigate MOSFET (MuGFET) or FinFET.

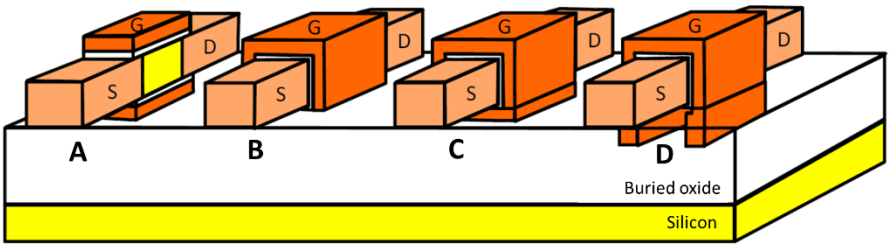

FIGURE 2 – STRUCTURES OF THE MOST COMMON MULTIGATE MOSFET. (A) IS A DOUBLE-GATE MOSFET. (B) IS THE TRIPLE-GATE MOSFET. (C) IS THE QUADRUPLE-GATE MOSFET. (D) IS THE PI-GATE MOSFET.

The design of FinFET-based circuits relies on the existence of compact models for such devices. During the 2000s, several models have been published. The equations describing the behavior of a FinFET are generally more complex than the equations for a conventional MOSFET because FinFET cannot be reduced to a 1-D problem, by opposition to the conventional MOSFET. In 2-D, the Boltzmann-Poisson equation, which is used to calculate the electrostatic potential in the transistor structure, does not have an analytical solution, except for symmetric double-gate MOSFETs [Sallese *et al.*, 2005]. Thus, most of the existing models use arbitrary smoothing functions and empirical parameters to fit the measured characteristics [Yu *et al.*, 2008; Ritzenthaler *et al.*, 2011]. Although effective, these approaches lead to models that lose their physical meaning.

MODEL

To obtain a physical compact model of a FinFET, we suggested an alternative strategy which consists of "planarizing" multigate MOSFET. By this way, it can be considered as a symmetric Double-Gate (DG) MOSFET (FIGURE 2A) having the same Si/SiO2 interface perimeter ensuring consistency with strong inversion, and also the same volume of silicon to match weak inversion characteristics. Under this assumption, we obtained a closed-form charge-potential relationship.

Details of the calculations used to derive the model are given in [Chevillon *et al.*, 2012]. In the end, we demonstrated that a FinFET can be modeled with the equations of planar DG-MOSFET by replacing the

silicon thickness and the silicon capacitance by an equivalent silicon thickness and equivalent silicon capacitance which depend on geometrical parameters of the FinFET.

Model Validation

The model was validated by comparison with numerical simulation on the Quadruple-Gate (QG) MOSFET with a cross-section of 40 nm x 40 nm and a channel length of 1 µm. In this case, the equivalent silicon thickness and channel width were respectively 20 nm and 80 nm. Numerical simulations were performed with Silvaco. Results are given in Figure 3. Regarding the drain current dependence on the gate voltage (Figure 3A), the fitting is good, both in linear and log scales and without the need to introduce any empirical parameter. Similarly, the matching is very good for the output characteristics, as shown in Figure 3B. Therefore, the transformation of the QG-MOSFET into a DG-MOSFET based on the equivalent geometrical parameters definitions is totally justified.

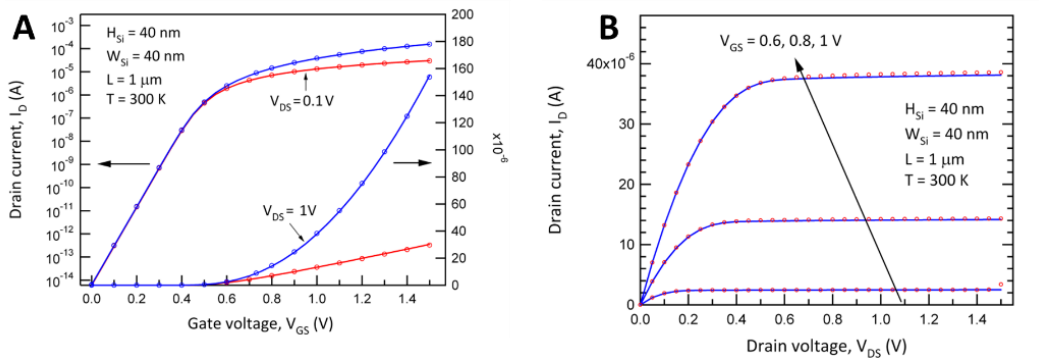

Figure 3 – Drain current of the QG-MOSFET with a square cross-section as a function of gate voltage (A) and drain voltage (B) in linear and saturation regimes. Symbols correspond to numerical simulation and lines to the model. On (A), red and blue curves corresponds respectively to the drain-source voltages of 0.1V and 1V. On (B), three different gate-source voltages have been tested: 0.6V, 0.8V and 1V.

Gate-Level Modeling of FinFET-based Digital Circuits

The use of the compact model is suitable for circuits with a reduced number of transistors. For the design of large-scale digital circuits involving dozens of transistors, a description at a higher level of abstraction is required. Typically, digital gates are often described as black boxes achieving a Boolean function and which behavior is summarized by a handful of parameters such as the minimal/maximal output voltage when the output is high or low, the minimal/maximal required input voltage to be sure that the gate interprets the voltage as a '1' or a '0', the maximal current consumed or supplied by the gate when the output is high or low, the propagation time (*i.e.* the maximal delay between a change at the input and a change at the output) and the rise/fall time of the output.

A design kit of the most common FinFET-based digital circuit, *i.e.* NOT, NAND and NOR, was realized, based on simulations of the compact model. Static characteristics (voltages and currents) were extracted from the closed-form static model whereas dynamic characteristics were estimated from the transcapacitance. Details are given in [Chevillon, Madec and Lallement, 2012]. Finally, gate-level models of FinFET-based digital gate with geometry-dependent parameters were established.

Then, digital circuits were simulated both with the gate-level model and the compact model for validation purpose. The use case was a D-latch and a frequency divider. We pointed out that differences between performances evaluated with the gate-level model on the one hand and with the

compact models on the other are less than 10%, but the computation time is reduced by a factor of 100.

Moreover, we also addressed the question of the dispersion of parameters. Three geometrical parameters were considered: the length of the transistor, the width of the silicon and the thickness of the oxide. For each gate, we simulated 100 circuits described at the transistor level for different parameters sets (allowing the nominal parameter to vary within a 5%-variance Gaussian distribution) and gather the results. It turned out that the variation of gate-level parameters is very low (less than 5%), which proved the robustness of the model.

OUTCOMES

This project took place within the FP7 European project COMON FP7 coordinated by Benjamin Iniguez (Universitat Rovira I Virgili, Tarragona, Spain) and involving 15 partners. Investigations were conducted by Nicolas Chevillon during his Ph.D. project that I co-supervised with Christophe Lallement (50%) and Fabien Prégaldiny (40%). This work gave me a first experience in compact modeling of nano-electronic devices as well as in the interfaces between the different level of abstraction for a single model (physical model, compact model, gate-level model). It also gave me good practices in model validation, robustness checking, and reliability estimation. The outcome results of the project are published in an IEEE Transaction on Electron Device review article as well as in two international IEEE conference (MIXDES in 2010 and NanoArch in 2012).

> N. CHEVILLON, J-M. SALLESE, C. LALLEMENT, F. PRÉGALDINY, M. MADEC, J. AGHASSI, J. SEDLMEIR, *GENERALIZATION OF THE CONCEPT OF EQUIVALENT THICKNESS AND CAPACITANCE TO MULTIGATE MOSFETS MODELING*, IN IEEE TRANSACTIONS ON ELECTRON DEVICES, PAGES 60--71, VOLUME 59, N° 1, JANUARY 2012, DOI:10.1109/TED.2011.2171347

1.2. CARBON-NANOTUBES FET

CONTEXT

Carbon-Nanotubes Field-Effect Transistor (CNFET) is another emerging alternative of standard MOSFET transistors. CNFETs use a single carbon nanotube or an array of carbon nanotube as a channel instead of the silicon bulk (FIGURE 4A and FIGURE 4B). The ability of the nanotube to conduct the current can be modulated by another voltage applied on the gate. As for the FinFET, the design of large-scale circuits using CNFETs requires a compact model. Although several models for such devices have already been published, even for radiofrequency (RF) applications (a state of the art is given in [Saberkari *et al.*, 2018]), none are composed of a simple user-friendly I-V equation depending on CNFET parameters and that could be used for the first step of integrated circuit design. Thus, the goal of this project was to establish and validate such an I-V closed-form equation suitable for analog/RF applications.

MODEL

Our model combines an existing HSPICE model of CNFET, namely the Stanford model [Deng and Wong, 2007], and the ballistic transport I-V relation of single-channel CNFET [Akinwande *et al.*, 2008]. The first does not provide a closed-form equation. The second is too rough to be used as it is in the model. To combine both approaches, we added some fitting parameters in the ballistic transport equation and use the Stanford model as a golden reference to fit these parameters. The IC-CAP characterization software [Keysight Technologies, 2019] was used for that purpose: simulation results of the Stanford model are used to emulate experimental results. The analysis was performed for different geometries and CNFET parameters (FIGURE 4C, FIGURE 4D and FIGURE 4E). Moreover, simulation results obtained

with the closed-form were been compared with experimental data extracted from [Ali Javey *et al.*, 2005] (FIGURE 4F).

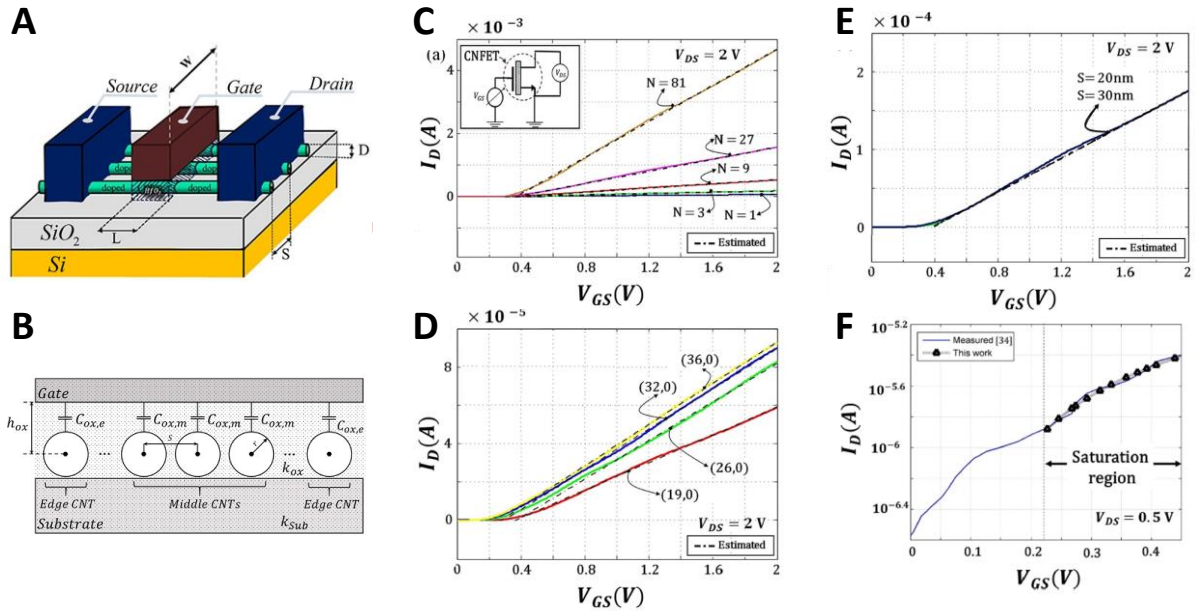

FIGURE 4- (A) 3D VIEW OF THE MULTICHANNEL CNFET. (B) FRONT-VIEW OF THE CNFET. (C) DRAIN CURRENT VERSUS GATE-SOURCE VOLTAGE CHARACTERISTICS FOR DIFFERENT NUMBERS OF CHANNELS. (D) DRAIN CURRENT VERSUS GATE-SOURCE VOLTAGE CHARACTERISTICS FOR DIFFERENT CHANNEL DIAMETER. (E) DRAIN CURRENT VERSUS GATE-SOURCE VOLTAGE CHARACTERISTICS FOR 3 NANOTUBES AND DIFFERENT DISTANCES BETWEEN NANOTUBES. FOR (C), (D) AND (E), LINES CORRESPOND TO STANFORD MODEL SIMULATIONS WHEREAS DASHED LINES CORRESPOND TO OUR I-V CLOSED-FORM EQUATION. (F) IS THE COMPARISON BETWEEN SIMULATIONS OBTAINED WITH THE CLOSED-FORM EQUATION AND EXPERIMENTAL DATA EXTRACTED FROM [ALI JAVEY *ET AL.*, 2005].

OUTCOMES

The model was enriched with noise sources and used for the design of a broadband CNFET-based low noise amplifier. Details are given in [Saberkari *et al.*, 2018]. The results of this work are published in IEEE Transaction on Nanotechnologies.

> A. SABERKARI , O. KHORGAMI , J. BAGHERI , M. MADEC, S. HOSSEINI-GOLGOO , E. ALARCÓN-COT, *DESIGN OF BROADBAND CNFET LNA BASED ON EXTRACTED I–V CLOSED-FORM EQUATION*, IN IEEE TRANSACTIONS ON NANOTECHNOLOGIES, VOLUME 17, N° 4, JULY 2018, DOI:10.1109/TNANO.2018.2822599

Moreover, this project initiated a collaboration with Dr. Alireeza Saberkari from the University of Guilan (Iran), which is in partnership with the University of Strasbourg. Since then, we successfully applied for an Idex Mobility grant and hosted a Master student for a 6-month internship on the design of a power amplifier. This student, Mohammadreza Dolaptoor, is now starting a Ph.D. in our team.

2. MAGNETIC SENSORS

The principle of design-oriented modeling, described in SECTION 1 on emerging microelectronic devices, can be extended to microsensors integrated into CMOS technology. Having accurate compact models for such devices enables the simulation of the complete sensor chain (*i.e.* sensing element, conditioning signal, analog front-end, and signal processing) within a unique software environment.

First, the focus is put on magnetic sensors, and more specifically magnetic tunnel junction and Hall-effect devices.

2.1. MAGNETIC TUNNEL JUNCTION

CONTEXT

Magnetic Tunnel Junctions (MTJs) are spintronic devices mostly used as memories in Magnetic Random Access Memories (MRAMs) [Tehrani *et al.*, 2003] or as highly sensitive magnetic sensor in MTJ-based fluxgate sensors [Kammerer *et al.*, 2004]. Basically, an MTJ consists of two layers of ferromagnetic metals such as cobalt, iron, or nickel, separated by a thin layer of insulator, typically alumina oxide or magnesium oxide with a thickness of about 1 nm (FIGURE 5A). The insulating layer is so thin that electrons can tunnel through the barrier if a bias voltage is applied between the two metal electrodes. Thanks to the electrode spin polarization, the conductance of the junction depends on the relative direction of the magnetic moments of each layer. When parallel, the conductance is high whereas when antiparallel, the conductance is low.

Most of the time, both electrodes are made of different ferromagnetic materials that have a different coercive field (*i.e.* the external magnetic field required to flip the magnetization orientation). The typical resistance versus external magnetic field characteristics is represented in FIGURE 5B. H_{cs} and H_{ch} are respectively the coercive fields of the soft and the hard layer. For memory application, H_{ch} is high enough to be unreachable under standard usage conditions. Thus, the hard layer, also called pinned layer, never flips and the state of the soft layer (leading to high or low conductivity) encodes for the data. In sensing application, the MTJ is subjected to an oscillating field ranging from a value below $-H_{ch}$ to a value above H_{ch}. Without any external field the characteristic is symmetrical. Under an external field, the characteristic is shifted to the left or to the right. This shift is measured in order to quantify this external field.

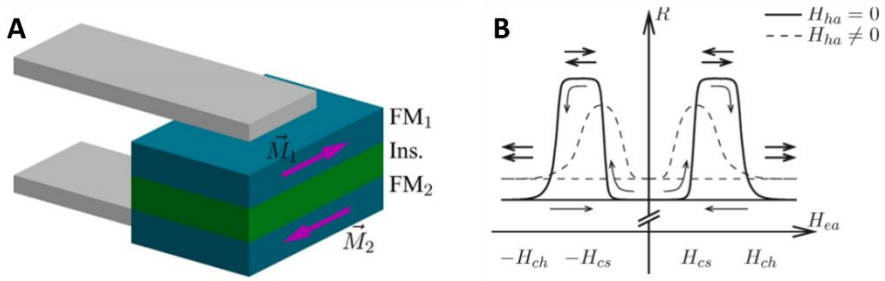

FIGURE 5 – (A) 3D STRUCTURE OF A MAGNETIC TUNNEL JUNCTION. (B) TYPICAL TUNNEL RESISTANCE VERSUS EXTERNAL MAGNETIC FIELD CHARACTERISTICS OF AN MTJ EXHIBITING A DOUBLE-HYSTERESIS SHAPE.

MAGNETIZATION MODEL

The compact model of the MTJ is composed of two parts: the model of layer magnetization and the I-V model of the tunnel junction. For the magnetization, we used the micro-magnetic formalism [Du Trémolet de Lacheisserie, Gignoux and Schlenker, 2005]. According to this theory, the magnetization vector $\mathbf{M}$ of a layer can be computed by the Landau-Lifschitz-Gilbert (LLG) equation. A modified version of this equation is implemented in VHDL-AMS in the layer magnetization model. Details are given in [Kammerer, Madec and Hébrard, 2010]. The model only depends on physical parameters, namely the saturation magnetization of the material, the direction of the easy axis of the ferromagnetic thin layer,

the damping factor of the material and the anisotropy constant of the material. Transient simulations, given in FIGURE 6, highlight the precession of the magnetization vector during the reversal. The results obtained in simulation match very well with experimental results found in the literature and results obtained with the numerical simulation performed on a dedicated tool, namely OOMMF (Object Oriented MicroMagnetic Framework) simulator [Donahue, 1999].

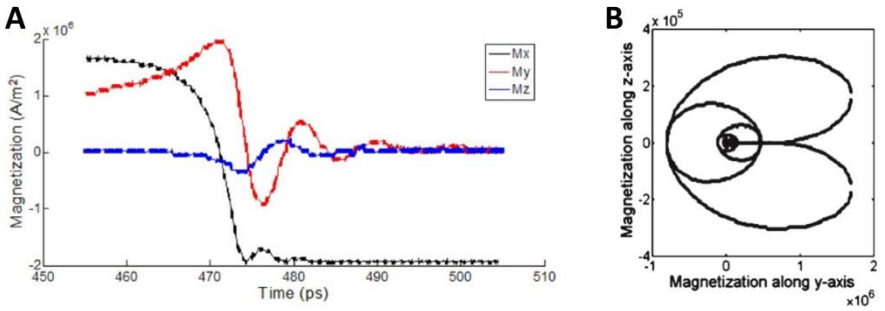

FIGURE 6 – TRANSIENT SIMULATION OF THE LAYER MAGNETIZATION MODEL DURING REVERSAL. (A) SHOWS THE TRANSIENT EVOLUTION OF THE THREE COMPONENT OF THE MAGNETIZATION VECTOR WHEREAS (B) IS A PROJECTION OF THE MAGNETIZATION VECTOR IN THE *Y-Z* PLACE

TUNNELING RESISTANCE MODEL

The closed-form I-V equation of the tunneling resistance as a function of the MTJ configuration and its physical parameters is a combination of several existing models. The approach is summarized in the following. Details of the calculation are given in [Madec, Kammerer and Hébrard, 2010].

1. Slonczewski's model is used to calculate the conductance of the parallel and the antiparallel states without external bias [Slonczewski, 1989] as a function of the geometry of the junction, the physical parameters of the insulator (thickness and the relative permittivity) and the physical parameters of ferromagnetic layer (thickness, Fermi energy, polarization and the extraction work);
2. The mean tunneling conductance over all possible configurations as a function of the voltage across the MTJ structure is derived from Brinkman's model [Brinkman, Dynes and Rowell, 1970];
3. One of the main characteristics of an MTJ is the tunnel magnetoresistance rate (TMR) defined as the relative difference between parallel and anti-parallel conductance. Li's models are then used to compute the variation of the TMR with respect to the applied voltage across the MTJ. Unfortunately, it does not give directly a closed-form equation. Thus, we look for a fitting function for the $TMR(V)$ equation and used a MATLAB implementation of Li's model as a reference to extract the associated empirical parameters (FIGURE 7A);
4. Equations provided by the three first steps are combined to obtain a closed-form equation for the tunneling conductance as a function of voltages and electrodes magnetization direction. This equation is integrated in order to obtain the I-V equation of the model.

COMPLETE MODEL OF MTJ

The complete model of an MTJ is composed of two instantiations of the magnetization model and five equations:

1. The equation giving the effective magnetic field seen by the top ferromagnetic layer, which obviously depends on the external field but also on the magnetization of the bottom layer due to coupling effects [Slonczewski, 1989; Kools *et al.*, 1999; Dubowik *et al.*, 2003; Hehn *et al.*, 2008];
2. By symmetry, the equation giving the effective magnetic field seen by the bottom layer;
3. The equation computing the angle θ formed by the relative orientation of both layers;

4. The closed-form I-V equation of the tunneling model established above;
5. The computation of the capacitance formed by the insulator and both ferromagnetic electrodes, in order to enable dynamic simulations.

Simulation Results

The VHDL-AMS model of the MTJ was simulated with Mentor's ADVance-MS 2004.1. The test device was a Fe(100 nm)/Al2O3(2 nm)/Ni(100 nm) MTJ biased by a 100-mV external voltage source and subjected to a sinusoidal magnetic field, along with the anisotropy direction of the ferromagnetic layer with a 100-kA/m amplitude and a 100-kHz frequency. Simulation results are given in Figure 7B for a well-aligned (*i.e.* easy-axis of both layers are parallel) and misaligned MTJ. They are qualitatively and quantitatively in accordance with measurements on a real MTJ that can be found in the literature.

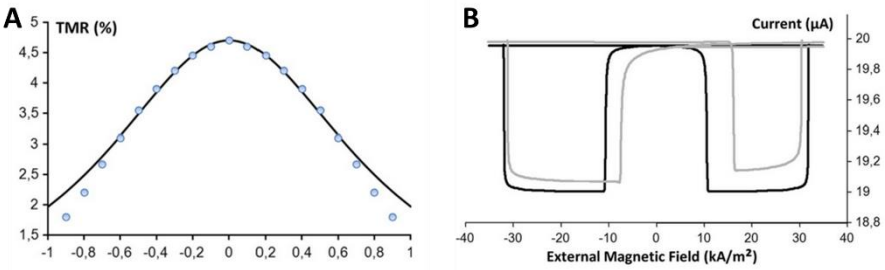

Figure 7 – (A) Fitting function found for the TMR-vs-V characteristics. Blue dots correspond to an implementation of Li's model whereas black curve if the fitted empirical law. (B) .DC simulation of the complete MTJ model for a well-aligned (black) and misaligned (grey) MTJ.

Outcomes

These investigations have been conducted within the scope of the ANR NTIF (New Technologies for Sensor Integration) coordinated by Luc Hebrard in cooperation with a team of the Institut Jean Lamour in Nancy (Michel Hehn, Demis Lacour, and François Montagne). The model has been published in a two-part IEEE Transaction on Electron Device paper. These papers have been cited about 20 times each, mostly by other papers dealing with MTJ compact modeling. Unfortunately, MTJ activities have not been pursued beyond this ANR project.

J-B. Kammerer, M. Madec, L. Hébrard, *Compact modeling of a magnetic tunnel junction - Part I: Dynamic magnetization model*, in IEEE Transactions on Electron Devices, pages 1408--1415, Volume 57, June 2010. DOI: 10.1109/TED.2010.2047070.

M. Madec, J-B. Kammerer, L. Hébrard, *Compact modeling of a magnetic tunnel junction - Part II: Tunneling current model*, in IEEE Transactions on Electron Devices, pages 1416--1424, Volume 57, June 2010. DOI: 10.1109/TED.2010.2047071

2.2. Horizontal Hall-Effect Device

Context

Horizontal Hall-Effect Devices (HHDs) are magnetometers realized in planar CMOS technology and sensitive to the component of the magnetic field perpendicular to the plane of the chip. They have a large detection range (typ. from 1mT to 10T) with an intermediate resolution (10 µT). The sensing element, *i.e.* the Hall plate, is generally at the heart of a larger integrated circuit in charge of biasing and signal processing [Pascal, Hebrard, *et al.*, 2008]. However, the design of such a system remains

challenging because the sensing element lacks in a design kit of standard devices. The goal of this project is to overcome this limitation by developing a compact model of HHDs.

The principle of the Hall effect is well known since 1879: when a conductor, biased by a current along one direction of the space, is immersed in a magnetic field **B** along a perpendicular direction (here the normal of the chip plane), an electrical field, called Hall field appears along the third direction. The magnitude of the electrical field is proportional to the product of the magnetic field and the applied current. In the past, several geometries of Hall sensors realized in CMOS technology have been explored [Popović, 2004]. Among them, the most efficient is the cross-shaped HHD (FIGURE 8A). Its main asset is to be symmetric by 90-degree rotation. Thus, Hall voltage can be estimated with four different configurations (depending on which contact are used for biasing and measurement). The spinning-current technique, described in the following, exploits this redundancy to reduce sensor noise [Popović, 2004].

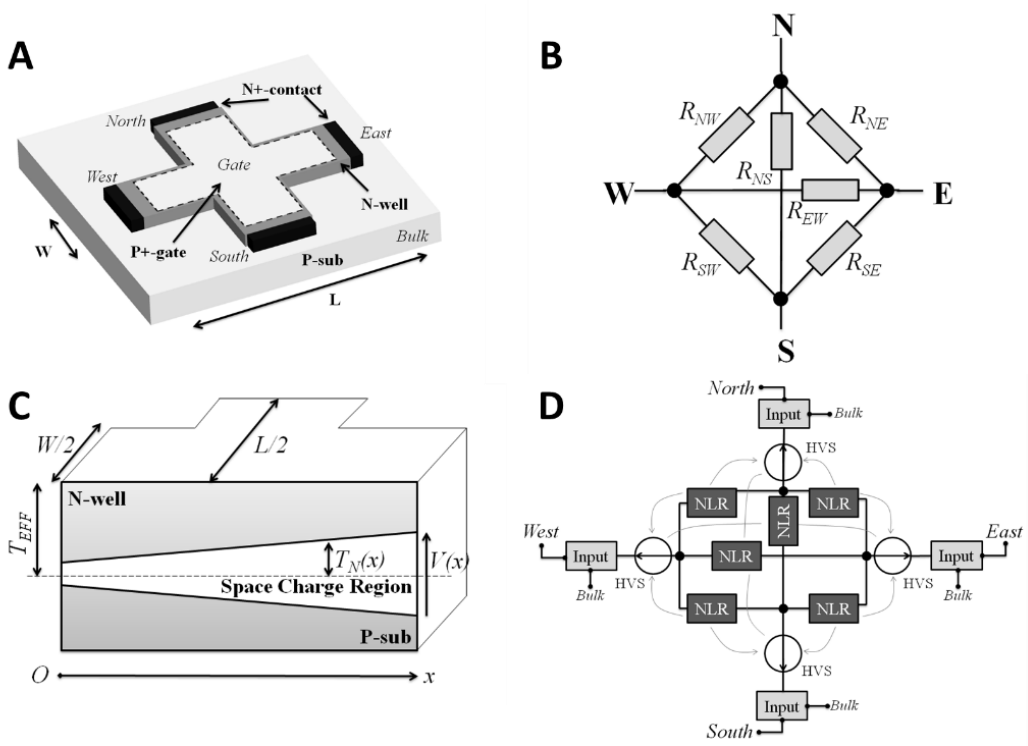

FIGURE 8 – (A) 3D VIEW OF THE CROSS-SHAPED HALL-EFFECT DEVICE. (B) THE BASIC 6-RESISTOR MODEL. (C) ILLUSTRATION OF THE MODULATION OF THE CONDUCTION CHANNEL THICKNESS. (D) THE IMPROVED MODEL WITH HALL VOLTAGE AND NON-LINEAR RESISTORS.

MODEL DESCRIPTION

First, let us consider the cross-shaped HHD without the P+-gate. The HHD has 4 contacts (in addition to the Bulk). Thus, from an electrical perspective, it can be modeled as a network of 6 non-linear resistors (FIGURE 8B). The modeling approach is described in the following. Details of the calculation are given in [M. Madec *et al.*, 2011]:

1. First, the effective resistance values Z_A seen between two adjacent contacts and Z_O between two opposite contacts are estimated. Our analysis relies on numerical simulation with COMSOL. An empirical law giving these values as a function of the conductivity of the semiconductor and geometrical parameters has been established;

2. The equivalent resistance transforms are used in order to link the values of R_{xy} (x and y being the contact N, S, E, W) with Z_A and Z_O.;
3. The modulation of the channel thickness is introduced. The thickness of the conduction channel depends on the thickness of the space charge region which itself depends on the voltage drop between the surface of the semiconductor and the bulk (FIGURE 8C). To take this effect into account, nonlinearities, based on semiconductor physics equations, has been added in the equation of Z_A and Z_O. The series-parallel resistor transform rules are not impacted by this non-linearity. Thus, relationships established in 2. are still valid;
4. Mismatches have been introduced on the resistor in order to break the device symmetry. They are required to simulate the systematic offset that appears on an actual device. Mismatches are empirical parameters encompassing distortions due to manufacturing imperfection, *e.g.* the variation of semiconductor conductivity within the silicon wafer, contact misalignment, shear stress induced by the packaging;
5. A series voltage source is added at each contact in order to model the Hall effect (FIGURE 8D). The Hall voltage for each source is computed as a function of the external field, the current that flows through the 6 non-linear resistors and a correction factor depending on the geometry [Versnel, 1981].

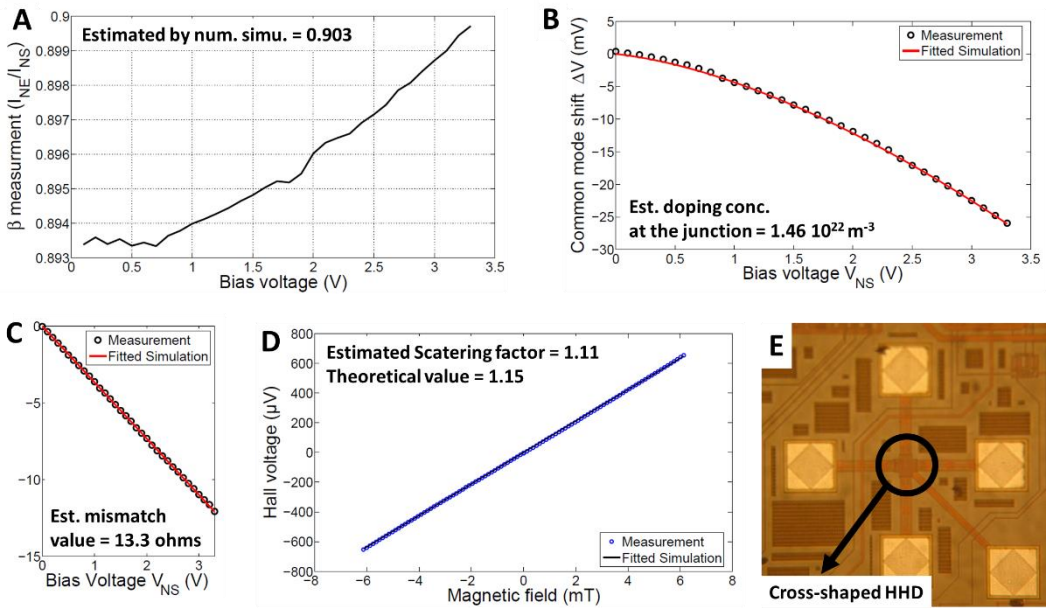

FIGURE 9 – (A) EXPERIMENTAL MEASUREMENT OF A PARAMETER USED IN THE ESTIMATION OF Z_A AND Z_O $\boldsymbol{Z_A}$ AND $\boldsymbol{Z_O}$. THE EMPIRICAL EQUATION USED IN THE MODEL GIVES A VALUE OF 0.903 WHEREAS THE EXPERIMENTAL ESTIMATION IS BETWEEN 0.8935 AND 0.8995, DEPENDING ON THE BIASING VOLTAGE. (B) INFLUENCE OF THE MODULATION OF THE CONDUCTION CHANNEL. BEST FIT BETWEEN EXPERIMENTAL RESULTS AND SIMULATION IS OBTAINED FOR A DOPING CONCENTRATION AT THE JUNCTION OF 1.46 20^{22} M^{-3}. (C) MEASUREMENT OF THE SYSTEMATIC OFFSET AS A FUNCTION OF THE BIASING VOLTAGE. THE BEST FIT BETWEEN EXPERIMENTAL RESULTS AND SIMULATIONS IS OBTAINED BY INTRODUCING A MISMATCH OF 13.3 OHM BETWEEN THE NORTH-WEST AND SOUTH-EAST RESISTOR ON THE ONE HAND AND NORTH-EAST AND SOUTH-WEST ON THE OTHER HAND. (D) MEASUREMENT OF THE MAGNETIC RESPONSE OF THE SENSOR. LINEAR REGRESSION BETWEEN SIMULATIONS AND EXPERIMENTAL RESULTS LEAD TO A SCATTERING FACTOR OF 1.11 WHICH IS VERY CLOSE TO THE VALUE COMMONLY USED IN THE LITERATURE [POPOVIĆ, 2004]. (E) MICROGRAPH OF THE CHIP HHD USED FOR THE VALIDATION.

VALIDATION AND PARAMETER EXTRACTION PROCEDURE

The model is implemented in Verilog-A. It was validated in comparison with experimental results obtained on a 40 µm × 20 µm cross-shaped HHD (FIGURE 9E) designed in a 0.35µm technology provided by Austria MicroSystems (AMS). For the electrical aspects, acquisitions were made with an HP4156 parameter analyzer under the Agilent IC-CAP environment which is able to drive in parallel with the common stimuli both the measurement device and the circuit simulator. This software environment also includes a parameter optimizer that computes the set of parameters that best fits the experimental results. For magnetic aspects, the device has been characterized with a calibrated Helmholtz's coil. Beyond validation, this work leads to the establishment of a complete procedure for the extraction of model parameters from experimental results. This procedure is described in [Morgan Madec *et al.*, 2011].

The matching between experimental results and the fitted model is convincing (FIGURE 9A to FIGURE 9D). Later, we used the same model and successfully applied the same procedure on HHDs realized in another technology, *i.e.* AMS 0.18µm, proving that the core of the model does not depend on the technology.

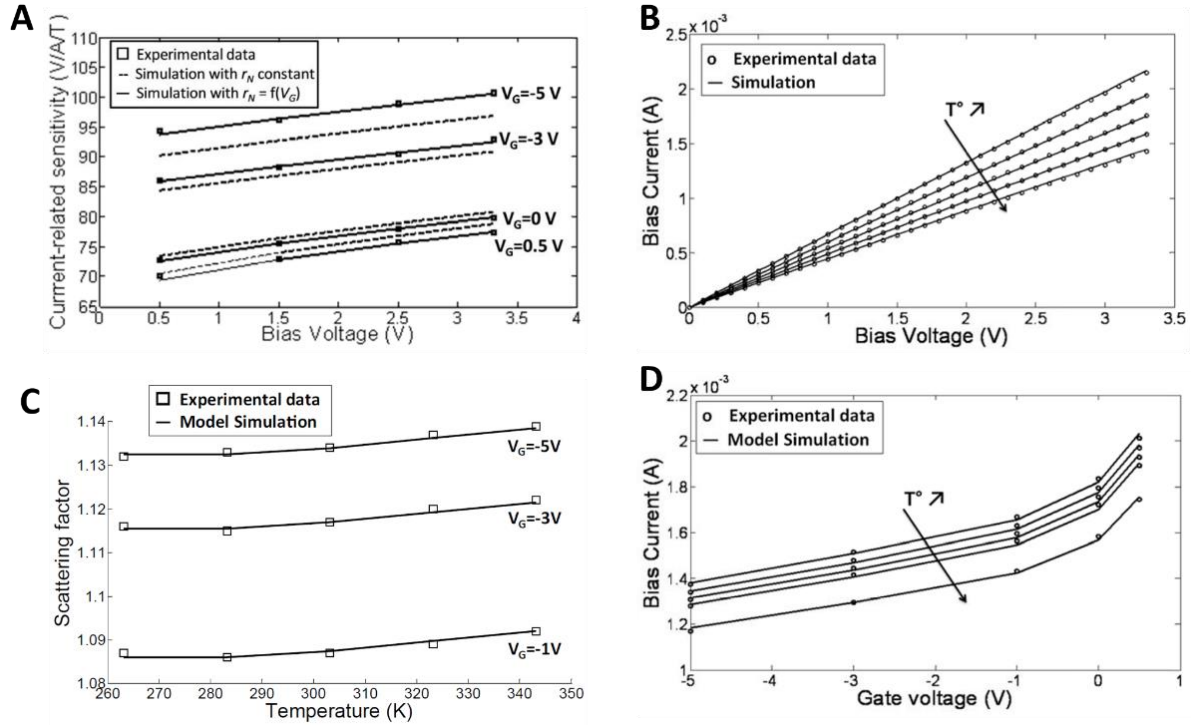

FIGURE 10 – SIMULATION OF THE IMPROVED MODEL. (A) IMPACT OF THE P+-GATE ON THE CURRENT-RELATIVE SENSITIVITY WITH AND WITHOUT THE EMPIRICAL CORRECTION OF THE SCATTERING FACTOR. (B) IMPACT OF THE TEMPERATURE ON THE RESISTIVE MODEL. (C) IMPACT OF THE TEMPERATURE ON THE SCATTERING FACTOR. (D) IMPACT OF THE TEMPERATURE AND THE GATE VOLTAGE ON THE BIASING CURRENT.

MODEL IMPROVEMENTS

In [Madec, Kammerer, *et al.*, 2012], we published two improvements to our model. First, the P+ gate (described in FIGURE 8A) is taken into account. The main role of this gate is to reduce the thickness of the conduction channel and thus increase the current-related sensitivity [Popović, 2004]. The P+-gate / N-well interface is comparable with the N-well / P-sub interface modeled in the initial version of the

model. Thus, the non-linear resistance is modified in order to take both contribution to channel width modulation effects into account. Simulation results of this new model match with measurement except on the current-relative sensitivity (FIGURE 10A). An extra empirical correction of the scattering factor with respect to the gate voltage is required to obtain a good fit.

Second, we also addressed the impact of the temperature on the response of the sensor. We first identify the most temperature-sensitive parameters, *i.e.* the electron mobility, the carrier density, the diffusion potential, the scattering factor, and the mismatch resistances. Influence of the temperature on these parameters has been introduced in the model by a combination of physical and empirical laws. The temperature-sensitive model has been experimentally validated by placing the sensor chip into an ESPEC thermal chamber allowing a temperature range between -70°C and 180°C. The equation introduced in the model lead to a good fitting between experimental measurements and simulations (FIGURE 10B to FIGURE 10D).

OUTCOMES

The work was published in two papers: in Sensors and Actuators in 2011 for the basic model and in Analog Integrated Circuits and Signal Processing in 2012 for the enhanced version. The compact model was also used to assess the efficiency of the spinning current technique [Madec and Kammerer, 2011].

> M. MADEC, J-B. KAMMERER, L. HÉBRARD, C. LALLEMENT, *AN ACCURATE COMPACT MODEL FOR CMOS CROSS-SHAPED HALL EFFECT SENSORS*, IN SENSORS AND ACTUATORS A: PHYSICAL, PAGES 69-78, VOLUME 171, NOVEMBER 2011. DOI: 10.1016/J.SNA.2011.05.027

> M. MADEC, J-B. KAMMERER, L. HÉBRARD, C. LALLEMENT, *AN IMPROVED COMPACT MODEL FOR CMOS CROSS-SHAPED HALL-EFFECT SENSOR INCLUDING OFFSET AND TEMPERATURE EFFECTS*, IN ANALOG INTEGRATED CIRCUITS AND SIGNAL PROCESSING, PAGES 719-730, VOLUME 73, DECEMBER 2012. DOI: 10.1007/S10470-012-9872-1

2.3. VERTICAL HALL-EFFECT DEVICES

CONTEXT

Vertical Hall-Effect Devices (VHDs) are also magnetometers realized in a planar CMOS technology but sensitive to the magnetic field in the chip plane, by opposition to HHDs. The structure of a VHD is depicted in FIGURE 11A. The sensor is biased by the contact C3 whereas contacts C1 and C5 are grounded. In this configuration, current lines go under contacts C2 and C4 and are almost parallel to contact alignment. When submitted to a perpendicular magnetic field, current lines are subjected to the Laplace force, and a vertical Hall electrical field appears. As current lines are in opposite directions under contacts C2 and C4, the Hall field is also opposite. Consequently, a Hall voltage can be picked-up between contacts C2 and C4 [Popović, 2004]. As for HHDs, this voltage is proportional to the amplitude of the magnetic field and to the biasing current. In 2008, Pascal *et al.* described an alternative biasing method with C2 and C4 grounded and the Hall voltage measured across the external contacts C1 and C5 (FIGURE 11B) [Pascal, Hébrard, *et al.*, 2008]. With this method, the sensitivity is slightly lower but the offset and the noise are drastically reduced in comparison with the conventional biasing methods.

The aim of this project is to establish a compact model for the VHD that can be instantiated in an electrical simulator in order to design and simulate the sensing element within its electronics.

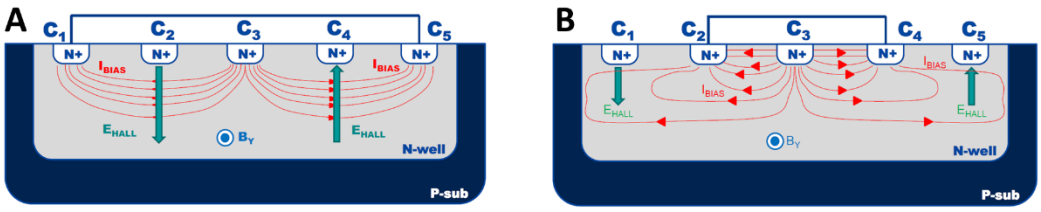

FIGURE 11 – THE 5-CONTACT VERTICAL HALL-EFFECT DEVICE. (A) CORRESPONDS TO THE CONVENTIONAL BIASING CONFIGURATION WHEREAS (B) IS THE EXTERNAL-CONTACT SENSING CONFIGURATION.

MODEL DESCRIPTION

To be used with both biasing configurations, 5 terminals (plus 1 for the bulk) are required, even if two of them are always short-circuited. First, the focus is put on the electrical model of the device. The modeling approach is quite similar to the one used for HHDs, except that the model is now composed of 10 non-linear resistors (one for each pair of contacts) and 5 Hall voltage sources. Up to now, only the electrical aspects of the model have been tackled. The key points are discussed in the following. Details of the calculation are given in [Madec, Schell, *et al.*, 2012]:

1. The equivalent resistance transforms are used in order to link the values of the resistor R_{xy} in the model network (x and y being the contact number) with resistance Z_{xy} measured between each pair of contact. These relationship are much more complicated than in the case of the HHD. A simple closed-form equation giving R_{xy} as a function of Z_{xy} can only be established under the assumption of a symmetric device;
2. Then, a first-order model for the calculation of Z_{xy} is set. Basically, the value of each Z_{xy} corresponds to the resistance of a semiconductor well with an effective inter-contact distance L'. This parameter corresponds to the actual distance L lengthen by a constant correction factor that corresponds to the vertical path of the current lines, and shorten by the length of all the contacts placed between the two contacts under consideration. The coherence of this empirical equation has been demonstrated theoretically and validated with COMSOL simulations;
3. Second-order effects are then integrated into the model: the resistances mismatch and the modulation of the conduction channel are treated as for the HHD. In VHD, another effect, namely the saturation of carriers velocity occurs for close contact [Sze and Ng, 2007]. Again, this effect is added in our model as a lengthening of L' by a term proportional to the current. The proportionality coefficient depends on the actual inter-contact distance L. Moreover, still for close contacts, current lines do not go deeply into the N-well. Thus, the effective conduction channel is reduced. In the model, actual thickness $t$is replaced by an effective thickness t' computed by an empirical law depending on L and obtained from COMSOL simulations.

EXPERIMENTAL VALIDATION

Our model was validated in comparison with experimental results obtained on a 25.4µm-long 6µm-wide VHD designed in the 0.35µm high-voltage technology provided by AMS (see the layout in FIGURE 12A). The set-up for electrical characterization is the same as for the VHD. The matching between experimental results and the fitted model is convincing (FIGURE 12B to FIGURE 12D).

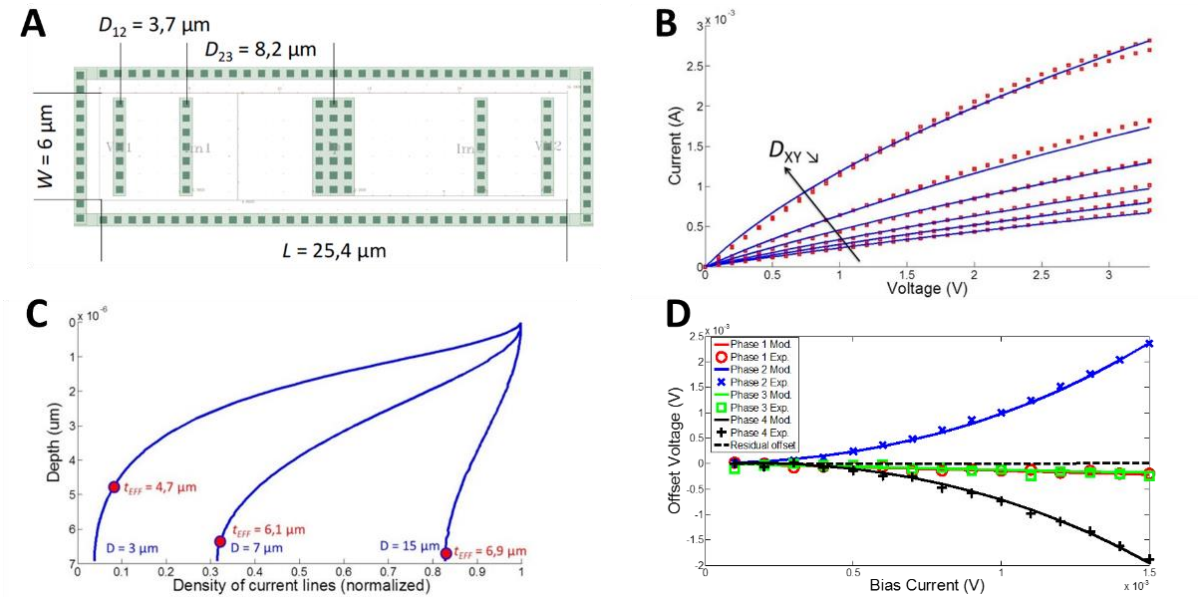

FIGURE 12 – (A) LAYOUT OF THE VHD USED FOR THE EXPERIMENTAL VALIDATION. (B) I-V CHARACTERISTICS FOR THE 10 PAIRS OF CONTACTS. RED DOTS CORRESPOND TO EXPERIMENTAL RESULTS WHEREAS THE BLUE CURVES ARE FOR THE FITTED MODEL. (C) COMSOL SIMULATION RESULTS HIGHLIGHTING THE LIMITATION OF THE REDUCTION CHANNEL. THE FIGURE SHOWS THE DISTRIBUTION OF CURRENT LINES AS A FUNCTION OF THE DEPTH FOR DIFFERENT INTER-CONTACT DISTANCES. FOR SPARSE CONTACTS, THE REPARTITION IS ALMOST UNIFORM. FOR CLOSE CONTACTS, MOST OF THE CURRENT LINES FLOW ON THE TOP OF THE DEVICE. THE EFFECTIVE CONDUCTION CHANNEL IN THIS FIGURE CORRESPONDS TO THE DEPTH ABOVE WHICH 95% OF THE CURRENT LINES FLOW. (D) OFFSET AS A FUNCTION OF THE BIASING CURRENT FOR THE FOUR BIASING CONFIGURATIONS. MARKERS CORRESPOND TO EXPERIMENTAL RESULTS WHEREAS CURVES CORRESPOND TO SIMULATIONS.

OUTCOMES

The model is published in two consecutive papers in Analog Integrated Circuits and Signal Processing: a first version of the model with an emphasis on the equivalent resistance transform and the reverse relationship between the R_{xy} and Z_{xy} in 2013 and an improved version including the second order effects in 2014. Moreover, the model was presented during the IEEE NEWCAS Conference at Montreal in 2012 and received the best paper award [Madec, Schell, *et al.*, 2012]. As for the HHD, the compact model was used to assess the efficiency of the spinning current techniques [Madec, Osberger and Hébrard, 2013].

> M. MADEC, J-B. SCHELL, J-B. KAMMERER, C. LALLEMENT, L. HÉBRARD, *COMPACT MODELING OF VERTICAL HALL-EFFECT DEVICES: ELECTRICAL BEHAVIOR*, IN ANALOG INTEGRATED CIRCUITS AND SIGNAL PROCESSING, PAGES 183-195, VOLUME 77, NOVEMBER 2013. DOI: 10.1007/S10470-013-0112-0.

> M. MADEC, J-B. SCHELL, J-B. KAMMERER, C. LALLEMENT, L. HÉBRARD, *AN IMPROVED COMPACT MODEL OF THE ELECTRICAL BEHAVIOR OF THE 5-CONTACT VERTICAL HALL DEVICE*, ANALOG INTEGRATED CIRCUITS AND SIGNAL PROCESSING, PAGES 677-691, VOLUME 81, N° 3, DECEMBER 2014. DOI: 10.1007/S10470-014-0438-2.

So far, the modeling of Hall-effect sensors has been very rewarding and has led to interesting questioning about how the sensor works and how to optimize its design. The step forward would be the integration of a predictive model for the Hall voltage sources. This is much more complicated than in the case of HHD. Basically, the Hall voltage is the product of four terms: the magnetic field, the

current that flows under the measurement contacts, the scattering factor which depends on the material and can be extracted by measurements and a geometrical correction factor which depends on the sensor geometry. The challenges to face are to establish equations for: i) the contribution of the current in each resistor of the model to the current that actually participates to the Hall effects and ii) the equation of the geometrical correction factor as a function of the sensor geometry. We have investigated different alternatives but, up to now, we still fail in establishing a predictive model for these parameters.

The compact models of the HHD and VHD are currently used by our team for a project with the University of Applied Sciences Western Switzerland aiming at designing a chip for a 3D magnetic camera.

3. Optoelectronic Devices

3.1. Liquid Crystal Display

Context

The topic of my Ph.D. was to evaluate the potential of optoelectronic processors for the reconstruction of tomographic images [Madec *et al.*, 2008]. We pointed out several bottlenecks that limit the performances of such an approach. Among others, the optoelectronic processor requires a high-speed spatial light modulator (SLM) that encodes images on at least 8 bits. At the time, none of the available technologies met our requirement [Efron, 1995]. One the one hand, nematic liquid crystal SLM generates greyscale images but was too slow. On the other hand, ferroelectric liquid crystal (FLC) SLM is fast-switching but bistable. Greyscale images could only be obtained with an FLC-SLM by temporal multiplexing, which was not suitable for our purpose [Madec *et al.*, 2007]. We had the idea to generate greyscale images with an FLC-SLM by maintaining the liquid crystal into an intermediate state with an appropriate driving signal. For that purpose, we first established a compact model of a single pixel of an FLC-SLM.

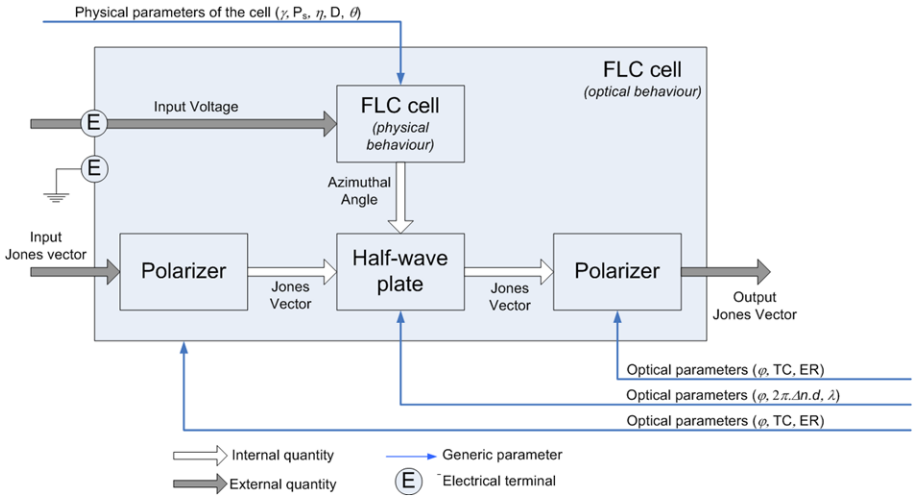

Figure 13 – Overview of the complete FLC-cell compact model.

Model

The main equation of the compact model is an ordinary differential equation (ODE) giving the FLC orientation as a function of the applied electrical field. This model, based on the so-called uniform

theory, also depends on physical parameters such as the FLC viscosity, their spontaneous polarization, the anchoring of the FLC cell and the geometry of the FLC cell [Pauwels *et al.*, 1989].

The complete model is described in FIGURE 13. In addition to the main equation, it encompasses:

1. The optical model of the complete modulator, *i.e.* the FLC cell and the two polarizers. The model relies on the Jones matrix formalism [Huard, 1997];
2. Because dynamic simulation is targeted, an accurate electrical is required to estimate the electric field seen by the liquid crystal as a function of the applied voltage. The electrical model is given in FIGURE 14A. It is composed of a series resistor that models the resistance of contact electrodes, the capacitor of the FLC-cell (the liquid crystal mixture playing the role of a dielectric), a parallel leakage resistor and the current source modeling the energy required to switch the molecules;
3. The dynamic of FLCs highly dependents on the temperature. In particular, 3 physical parameters of the FLC are temperature-sensitive: the viscosity of FLC, the spontaneous polarization and the pretilt angle used in the optical model. Equations found in the literature have been implemented [Escher, Geelhaar and Bohm, 1988; Spruce and Pringle, 1988; Essid *et al.*, 2005]. Additionally, a thermal model of the complete modulator has been established in order to take the self-heating into account;
4. Last but not least, we also include in the model the ion transport, a parasitic effect that introduces a non-linearity on the leakage resistor (which decreases while the electric field increases) and induces the ion trapping at the electrodes. Ion trapping creates a reverse persistent electric field inside the FLC cell. A complete model of ion transport has been developed by Maximus *et al.*, but it is composed of partial differential equation [Maximus *et al.*, 1991]. In our model, we use Maximus' model to derive an empirical closed-form equation.

Simulation Results and Model Validation

Simulation results are given in FIGURE 14B to FIGURE 14E. The impact of the polarization current during the FLC switching FLC (FIGURE 14C) and the influence of the temperature on the contrast ratio and the switching time (FIGURE 14D) can be noticed. Moreover, we also assessed the impact of the thermal noise on the switching process. High energy is required to take the FLC out of their stable steady state and flip them to the other steady state. Thermal agitation of FLC provides a fraction of this energy, reducing the quantity of external energy required for the switching, and thus decreasing the switching time (FIGURE 14E). Falling to gather experimental results on an actual FLC, our model has been only partially validated with results found in the literature.

Outcomes

The model was used to validate in simulation a new driving method which aims at maintaining the FLC in an intermediate state for a short time (typ. 100 µs) with an appropriate driving signal. Such signal is composed of an initial pulse followed by a high-frequency oscillating signal. Simulations prove the feasibility of this approach but also highlight some limitations. The most critical is the thermal drift of the response (FIGURE 15). The complete model, as well as the *in silico* proof of concept of the driving method has been published in Analog Integrated Circuits and Signal Processing in 2008. If we could do it all over again, we might change the title of the paper in order to put the emphasis on the compact model of the FLC (which could be of great interest for liquid crystal display designers) rather than on the new driving method.

M. MADEC, W. UHRING, Y. HERVÉ, *ANALOGUE-DRIVEN BISTABLE FERROELECTRIC LIQUID CRYSTALS*, IN ANALOG INTEGRATED CIRCUITS AND SIGNAL PROCESSING, PAGES 187-196, VOLUME 57, DECEMBER 2008. DOI: 10.1007/S10470-008-9171-Z.

Finally, the driving method has never been tested on an actual FLC cell. The conclusion of the Ph.D. work is that, although tomographic image reconstruction with optoelectronic processors is possible, the speed-up in comparison with fully-numeric architectures is not enough to compensate the cost and the complexity of the system. Moreover, the need for a high-speed greyscale display that operates without temporal multiplexing or pulse width modulation is very specific to this application. For these reasons, this project has not been pursued.

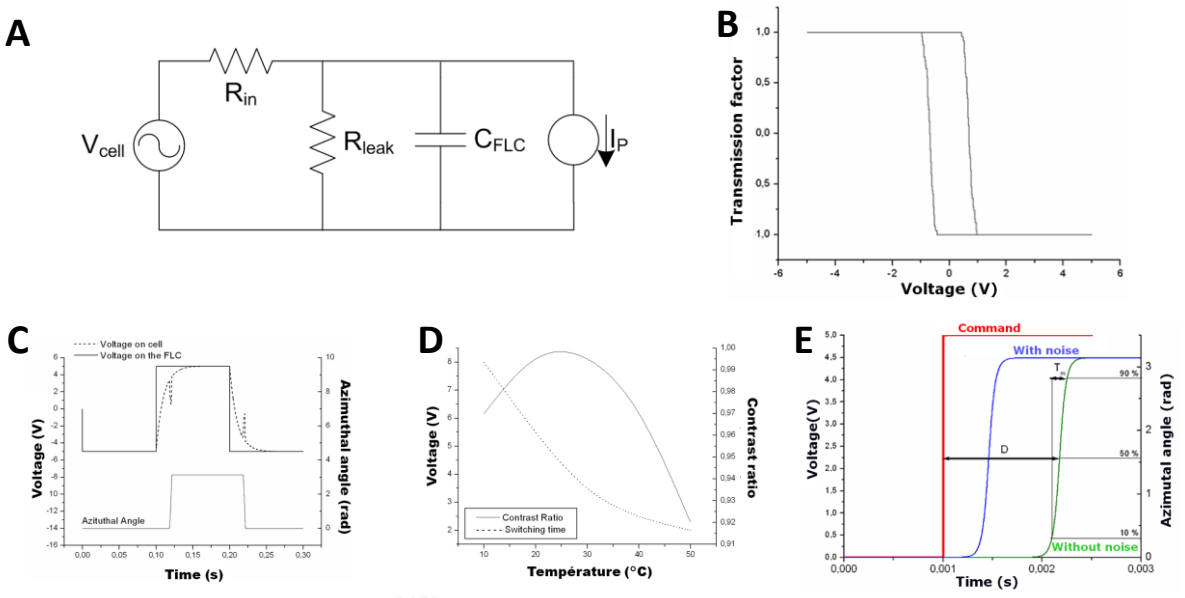

FIGURE 14 – (A) ELECTRICAL MODEL OF THE FLC-CELL. (B) DIRECT-COUPLING SWEEP SIMULATION SHOWING THE BISTABILITY OF FLC AS WELL AS THE HYSTERESIS. (C) TRANSIENT SIMULATION OF THE FLC-CELL MODEL COUPLED WITH THE ELECTRICAL MODEL. THE IMPACT OF THE POLARIZATION CURRENT ON THE EFFECTIVE FIELD SEEN BY LIQUID CRYSTAL DURING THEIR SWITCH IS WELL MARKED. (D) EFFECT OF THE TEMPERATURE ON THE SWITCHING TIME AND THE CONTRAST RATION OF THE FLC CELL. (E) IMPACT OF THE THERMAL NOISE ON THE FLC SWITCHING.

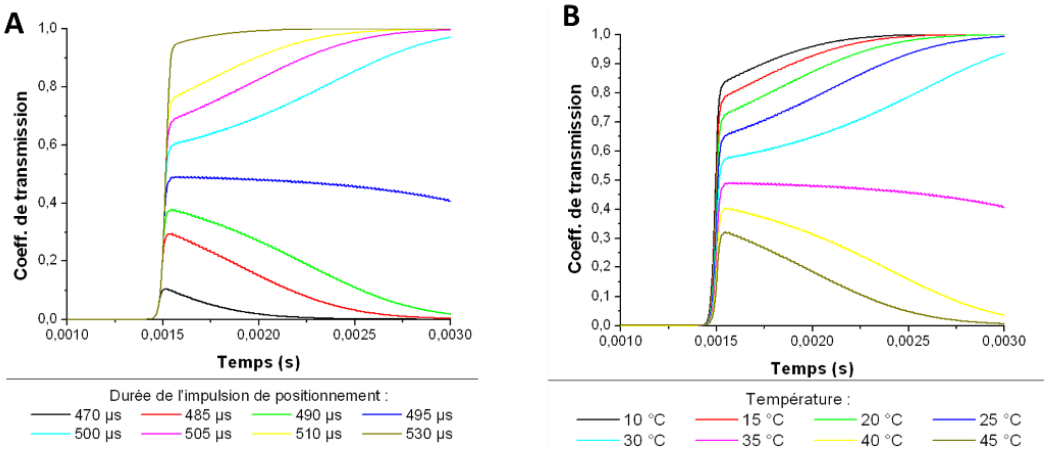

FIGURE 15 – SIMULATION OF THE FLC-CELL WITH DRIVING SIGNAL UNDER INVESTIGATION. (A) TRANSIENT SIMULATION FOR DIFFERENT INITIAL PULSE TIME AT 25°C. (B) TRANSIENT SIMULATIONS FOR THE SAME INITIAL PULSE (500 µS) TIME AT DIFFERENT TEMPERATURES.

3.2. LASER DIODE

We also developed a compact model of laser diodes. The model is composed of two parts: the common electrical model of a P-N junction and the optoelectrical model which consist of two coupled rate equations giving the dynamics of the number of electrons and the number of photons in the cavity [Deb and Agrawal, 1995]. Several variations of this model were implemented in VHDL-AMS. For instance, we completed the model by integrating second-order effects such as spontaneous emission (non-coherent light) [Yokoyama and Brorson, 1989], the saturation of the laser gain and an improved electrical model of the P-N junction that takes the temperature and the self-heating of the diode into account [Byrne and Keating, 1989; Desgreys *et al.*, 2002].

The final version of the model involves 27 parameters. Some of them (electrical and thermal parameters) can be easily extracted from electrical characterization or are given in the datasheet for commercial laser diodes. Some are much more challenging to obtain and require an optical characterization of the diode. We identified the four main parameters that have an impact on the optical response of the diode (*i.e.* the gain saturation constant, the transparency threshold, the dynamic gain of the cavity, the external temperature) and, of course, the electrical signal used to drive the diode. They seem to be highly coupled and deciphering the way each parameter changes the optical response is very complicated. Thus, it is almost impossible to establish a systematic parameter extraction.

The project is still in progress and has not been published yet. The issue of parameters extraction from optical characterization has not been solved. Given the complexity of the problem, stochastic optimization methods will probably be considered [Marti, 2015].

4. SUMMARY

In this chapter, we gave an overview of our projects on design-oriented compact modeling at the device level. We worked both on purely electronic devices, but also in multi-physics sensors including electromagnetic and optic aspects. Models were written both in VHDL-AMS and in Verilog-A. We also established systematic procedures for the extraction of model parameters, considering that a compact model is only interesting if its parameters are easy to obtain from experimental results and/or numerical simulation (COMSOL). A good compact model is also simple, fast-simulating and able to predict the behavior of a component according to several adjustable primitives such as the device material or the device geometry. These requirements have been met for most of the published models.

All these investigations led to the development of a library of design-oriented models that can be used as building blocks and coupled with models of electronic devices for the virtual prototyping of more complex integrated instrumental systems. Beyond the model itself, the modeling process puts some interesting question on the table, leading to a better understanding of the modeled devices and new ideas about their optimization. Moreover, these projects also give us a strong experience in modeling techniques, computer-aided design (CAD) tools, languages and electronic circuit simulators, etc. This experience has been reinvested to address another domain which has only sparsely been covered by multiphysics CAD tools: the biology.

CHAPTER 2 – EDA TOOLS APPLIED IN BIOLOGY

1. THEORY

1.1. REPRESENTATION OF A BIOLOGICAL SYSTEM

GRAPH REPRESENTATION

From a modeling perspective, a biological system is as a set of biochemical reactions that turn biological signals into others. The behavior of the system can be controlled by external biological and/or physical signals (temperature, pressure, etc). To illustrate the purpose, let us consider the biological system given in FIGURE 16. In this cartoon, blue bubbles are the biochemical species. Black arrows correspond to the biochemical reaction. The arrow starts from the reactants and points towards the products. A reaction rate v_i is associated with each reaction. For instance, the arrow labeled #1 means that R2 is converted into X2 at the rate v_1. Sometimes, one end of the arrow is not connected. This means that the reactant (or the product) is in excess. Thus, its concentration is considered to be constant and becomes a fixed parameter of the system. Finally, red and green arrows represent respectively the positive and negative regulations. For instance, the top left green arrow indicates that the presence of I2 increases the reaction rate v_1.

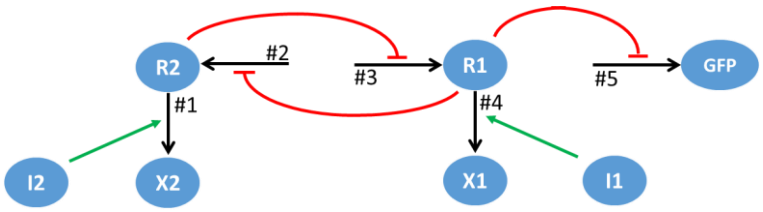

FIGURE 16 – GRAPHICAL REPRESENTATION OF A BIOLOGICAL SYSTEM. THIS SYSTEM CORRESPONDS TO A GENETIC TOGGLE SWITCH INSPIRED BY [GARDNER, CANTOR AND COLLINS, 2000].

SBML DESCRIPTION

The System Biology Markup Language (SBML) is a standard for the description of a biological system. An SBML model aggregates the information represented in FIGURE 16 in a text file. The language has been introduced in 2003 by M. Hucka who led a consortium of researchers in the domain of bioinformatics [Hucka, 2003]. A SBML is a XLM file composed of markups describing the elements of the system, *i.e.* the involved species, the list of reactions with, for each, the reactants, the products, the modifiers and the equation of the reaction rate, the parameters of this equation, events that should be applied when simulating the model, etc. More details on the syntax and features of the last SBML version are given in [Hucka *et al.*, 2018]. This language has emerged in recent years and has established itself as a standard in system biology. It is supported by a large amount of software and a multi-language open-source API has been developed to facilitate models manipulation whatever the context [Bornstein *et al.*, 2008]. In addition, the SBML standard is also used in several databases that record biological system descriptions, such as BioModel [Le Novère *et al.*, 2006].

DYNAMICS OF BIOLOGICAL SYSTEMS

The dynamics of a system composed of N species and M reactions can be computed by a set of coupled ordinary differential equations (ODE). Each equation states that the variation of the concentration of a given chemical species is the sum of the rates of reactions that produce this species, minus the sum of the rates of the reactions that consume it and minus a natural degradation term proportional to the concentration. The obtained ODE set can be written in a matrix form as following:

$$\frac{\mathrm{d}\mathbf{X}}{\mathrm{dt}} = \mathbf{S} \times \mathbf{V} - \mathbf{d} \cdot \mathbf{X} \qquad \text{Eq. 1}$$

where $\mathbf{X}$ is a column vector of the concentration of each species, $\mathbf{S}$ is the stoichiometry matrix (*i.e.* the term s_{ij} is the number of the i-th molecule produced if positive, or consumed if negative, each time the j-th reaction occurs), $\mathbf{V}$ is a column vector of the rate of each reaction, and $\mathbf{d}$ is a column vector of the natural degradation constant for each species.

1.2. COMMON MODELS OF REACTION RATE

FIRST-ORDER MODEL

Most of the time, the reaction rate of a biochemical reaction is modeled by a first-order equation. In this case, the reaction rate is proportional to the products of reactants concentration:

$$v = k \cdot \prod_i R_i^{S_i} \qquad \text{Eq. 2}$$

where R_i is the concentration of the i-th reactant and S_i is its associated stoichiometric coefficient. Equations Eq. 1 and Eq. 2 are sufficient to model the dynamics of every biological system. However, taking each elementary reaction into account leads to very large models with a high number of parameters. Additionally, the value of most of these parameters cannot be estimated by any experiment. Such models do not make sense in the scope of system-level modeling. To avoid such a pitfall, a model reduction can be done by grouping several mechanisms into subsystems and establishing, under several assumptions, simple macro-models for these subsystems.

MICHAELIS-MENTEN

The model of Michaelis and Menten [Michaelis and Maud Menten, 1913] is an example of such macro-model applicable for enzymatic reactions, *i.e.* the transformation of a molecule (the substrate S) into another (the product P) under the assistance of a third one (the enzyme E). Such a reaction encompasses three elementary mechanisms: i) the binding of S on E, ii) the transformation of the ES complex into the EP complex and iii) the releasing of P and E, E being available again for another reaction. Modeling the complete mechanism by Eq. 1 would lead to 4 species, 3 rate equations, and 4 parameters. Michaelis-Menten model requires only 3 species, one single rate equation, and 2 parameters:

$$v = \frac{dP}{dt} = -\frac{dS}{dt} = V_m \cdot E \cdot \frac{S}{K_M + S} \qquad \text{Eq. 3}$$

where V_m is maximal reaction rate and K_M is the Michaelis constant, defined as the concentration of substrate at which the reaction rate is half od the maximal reaction rate. Another benefit of the Michaelis-Menten equation is the use of parameters that can directly be extracted from experiments (FIGURE 17A and FIGURE 17B).

REGULATION MECHANISMS RULED BY HILL'S EQUATION

Hill's equation is also a simplified model applicable to regulation processes in biology [Konkoli, 2011]. This equation encompasses all the elementary mechanisms (binding, conformational change, etc) that occur when a molecule modifies the rate of a given reaction. Hill's equation is a phenomenological law with empirical parameters that can be extracted from the dose-response curve. In the case of a positive regulation (activation), this equation is:

$$v = V_m \cdot \frac{R^n}{K_R^n + R^n} \qquad \text{EQ. 4}$$

where V_m is maximal reaction rate, R is the concentration of the regulating molecule, K_R is an apparent binding constant defined as the concentration of regulating molecule (here, an activator) required for the reaction rate to reach half of V_m and n is Hill's number, which models the steepness of the transition between active and inactive states FIGURE 17C. In the case of negative regulation (inhibition), the reaction rate is given in a very similar way:

$$v = V_m \cdot \frac{K_R^n}{K_R^n + R^n} \qquad \text{EQ. 5}$$

The $v(R)$ curve exhibits a sigmoid shape in the log scale (FIGURE 17D), which is characteristics of Hill-like regulations.

A GENERIC FORMULATION FOR BIOLOGICAL MACRO-MODELS

If Hill and Michaelis-Menten are the most common macro-models, they do not apply for all cases. Thus, we formalized a generic framework in order to obtain such macro-models. The main steps of the framework are described in the following. Details of calculations are given in [Haiech *et al.*, 2014].

1. Identification of species and reactions that compose the macro-model;
2. Listing of accessible states of the system;
3. Drawing of the graph representing the transitions between the system's states. Nodes of the graph are the states and are linked by the reactions constants;
4. Estimation of the normalized concentration for each state by solving the complete model at the steady-state;
5. Calculation of the apparent reaction rate by averaging the contribution of each state to the reaction rate, weighted by the normalized concentration of the state.

We demonstrated in [Haiech *et al.*, 2014] that both the Michaelis-Menten model and Hill's equation are particular cases of this generic framework.

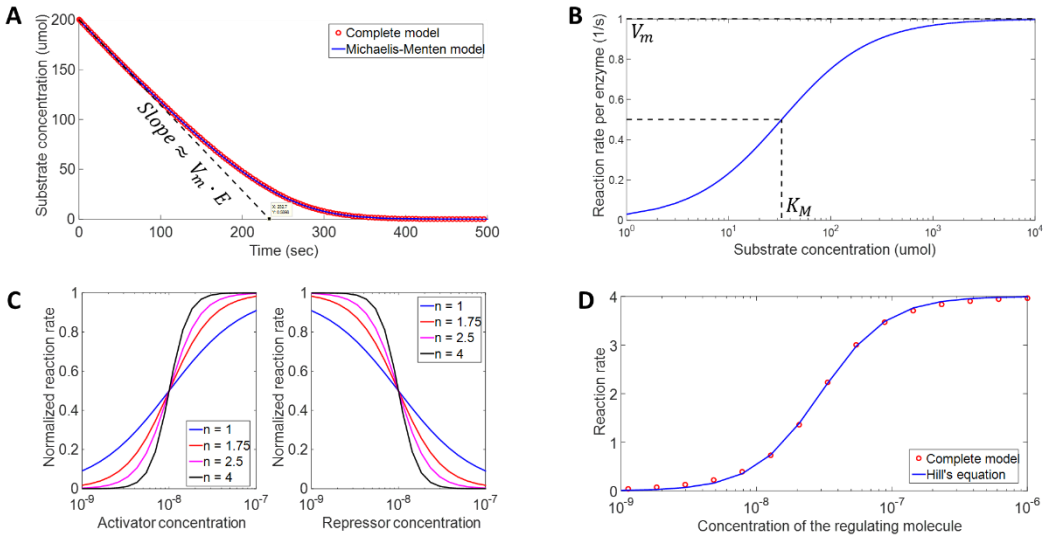

FIGURE 17 – EXAMPLE OF MACRO-MODELS USED IN SYSTEMS BIOLOGY. (A) IS A COMPARISON BETWEEN THE TRANSIENT RESPONSES OF AN ENZYMATIC SYSTEM DESCRIBED BOTH WITH THE COMPLETE MODEL AND WITH THE EQUATION OF MICHAELIS-MENTEN. THE SLOPE AT THE ORIGIN IS GIVEN A GOOD APPROXIMATION OF THE MAXIMAL REACTION RATE (EXPECTED -1 IN THIS CASE). HERE, THE INITIAL CONCENTRATION OF THE SUBSTRATE IS NOT LARGE ENOUGH TO HAVE $V=V_M$ AT T=0, WHICH EXPLAINED THE GAP. (B) IS ANOTHER REPRESENTATION OF THE SAME DATA. THE REACTION RATE PER ENZYME IS GIVEN WITH RESPECT TO THE SUBSTRATE CONCENTRATION. THIS CURVE IS SUITABLE FOR THE EXTRACTION OF THE TWO MICHAELIS PARAMETERS. (C) IS A GRAPHICAL REPRESENTATION OF HILL'S EQUATION IN THE CASE OF ACTIVATION AND OF REPRESSION. THE IMPACT ON HILL'S NUMBER ON THE STEEPNESS OF THE TRANSITION IS OBSERVABLE. (D) IS A COMPARISON OF THE COMPLETE MODEL OF AN INDUCIBLE PROMOTER WITH 4 COOPERATIVE BINDING SITES AND EQUIVALENT HILL'S MODEL. HILL'S NUMBER IS ABOUT 1.75.

1.3. SIMULATORS

DETERMINISTIC VS STOCHASTIC

The simulation of biological systems can be done in two ways. When EQ. 1 is solved by numerical methods such as Runge-Kutta [Dormand, 2017], we speak about deterministic simulation. On the other hand, ODEs can be transformed into stochastic differential equations (SDEs) to perform stochastic simulations. In this case, a concentration is a number of molecules and becomes a discrete value and reaction rate is interpreted as a probability for the reaction to occur. Each time it happens, the number of each molecule is updated according to the stoichiometry of the reaction. Gillespie's algorithm is the most common simulation algorithm to solve SDE [Gillespie, 2007].

A deterministic simulation can be seen as the limit of a stochastic simulation when the number of each molecule is large. This is not always the case in biology, especially for intracellular systems. Most of the time, deterministic simulation results can be retrieved from stochastic simulations by averaging on a large number of runs of the same simulation. However, sometimes, stochasticity of biological phenomena can lead to behaviors unexpected by deterministic simulation [Stamatakis and Mantzaris, 2009]. Conversely, we demonstrated that stochasticity can be retrieved from a deterministic simulation by adding shot noise (Poisson noise) when evaluating the reaction rate. [Gendrault *et al.*, 2017]

Dimensionless

Dimensionless systems can be defined as systems for which concentrations, reaction rates, and parameters are uniform inside the reaction volume. In this case, they can be described by Eq. 1. Several tools exist for the simulation of such systems. We can notably cite COPASI, one of the most common software used for metabolic network simulation [Hoops *et al.*, 2006]. It provides a graphical user interface to describe the system but can also import directly SBML files. Time course and steady-state simulations can be performed. For time course simulations, deterministic or stochastic algorithms can be applied. Moreover, COPASI offers other types of simulations like parameter scan and flux balance analysis, widely used in metabolomics.

In the same vein, BioCham can also be mentioned. BioCham is also able to read SBML files as well as ODEs written in a specific format [Calzone, Fagès and Soliman, 2006]. BioCham shares similar features to COPASI in terms of simulations and plotting but is a scripting language and does have a user-friendly GUI. Beside steady state and transient simulations, COPASI and BioCham also provide a furnished set of qualitative analysis of the network. Virtual Cell or VCell is also a very common tool for simulating biological systems, with a GUI and a comprehensive set of analyses [Loew and Schaff, 2001]. Finally, SBML descriptions can also be simulated directly with Matlab [Schmidt and Jirstrand, 2006] or Python [Lopez *et al.*, 2013] via dedicated toolbox or modules.

Space-dependent Problems

For space-dependent problems, at least one term of Eq. 1 depends on the location inside the reaction volume. In this case, Eq. 1 becomes a set of partial differential equations (PDE):

$$\frac{d\mathbf{X}}{dt} = \mathbf{D} \cdot \vec{\nabla} \cdot \left(\vec{\nabla}\mathbf{X}\right) + \mathbf{S} \times \mathbf{V} - \mathbf{d} \cdot \mathbf{X} \qquad \text{Eq. 6}$$

with $\boldsymbol{D}$ a column-vector giving the diffusion constant associated with each species. In this equation $\mathbf{X}$, $\mathbf{D}$, $\mathbf{S}$ and $\mathbf{d}$ now depend on space and time**.** Basically, there are two main approaches to tackle such issues. On the one hand, each molecule is modeled individually: its position and its interactions are computed at each time step. This approach is called entity-centered (or particle-centered) [Amar and Paulevé, 2015]. Alternative implementations of this approach use cellular automata [Ermentrout and Edelstein-Keshet, 1993]. In this case, space is divided into cubes and, at each time step, transfers of molecules from one cube to another and/or reactions between two molecules inside the same cube are computed according to probabilistic laws.

The alternative consists in solving the PDE with a numerical method. COMSOL Multiphysics is undoubtedly a golden reference in this domain. However, it is very expensive. Open-source alternatives exist, such as FreeFEM [Hecht, 2012] or Fell++ [Prud'homme *et al.*, 2012]. The last version of Virtual Cell also includes a PDE solver. Whatever the tool, the resolution always relies on space discretization. Thus, high accuracy can be reached with a very tight lattice but the price to pay is always an increase in the number of equations to solve, the size of the data to store and the complexity of the equations.

1.4. Outcomes

The understanding of the concepts briefly described in this section (as well as several others related to genetics, cells biology and biotechnologies) were for me an essential prerequisite to develop the

research activities I will describe in this chapter. With this newly acquired background, I feel more comfortable to discuss with researchers from the field of biology, to understand their issues and to teach these concepts to student and attendees from different level and different scientific communities.

For instance, I have been invited to give two tutorials on this topic, one for the microelectronic community during the IEEE NEWCAS 2018 conference in Montreal, and one for the life science community during the European Summer School on the Physics of Living Matter at Strasbourg in 2016. Moreover, I am the author of a book chapter on molecular interactions and their modeling in a book entitled “Engineering of Micro/Nano Biosystems: fundamentals and applications”.

> M. MADEC, *BIOMOLECULAR INTERACTIONS*, IN *ENGINEERING OF MICRO/NANO BIOSYSTEMS: FUNDAMENTALS AND APPLICATIONS*, G. BARBILLON, A. BOSSEBOEUF, K. CHUN, R. FERRIGNO, O. FRANÇAIS (EDS.), CHAPTER 2.1, SPRINGER, 2018, ISBN: 978-981-13-6548-5. DOI: 10.1007/978-981-13-6549-2.

I also participated with Pr. Jacques Haiech to the establishment of the general framework described in SECTION 1.2. This work has been published in 2014 in Biochimica et Biophysica Acta.

> J. HAIECH, Y. GENDRAULT, M-C. KILHOFFER , R. RANJEVA , M. MADEC, C. LALLEMENT, *A GENERAL FRAMEWORK IMPROVING TEACHING LIGAND BINDING TO A MACROMOLECULE*, BIOCHIMICA ET BIOPHYSICA ACTA - MOLECULAR CELL RESEARCH, PAGES 2348-2355, VOLUME 843, OCTOBER 2014, DOI:10.1016/J.BBAMCR.2014.03.013.

2. MODELING BIOLOGY WITH HARDWARE DESCRIPTION LANGUAGES

Hardware Description Languages (HDLs) are, by definition, languages dedicated to the description of electronic devices, or more generally any system ruled by Boolean statements and/or transfer functions and/or ODEs. HDLs are commonly used in electronics. Their potential extension to biology is described in this subsection.

2.1. ELECTRONIC EQUIVALENT CIRCUIT

DATA FLOW APPROACH

The set of ODEs describing the biological system (EQ. 1) can be directly written in a VHDL-AMS model and simulated. By this way, we obtain similar results as with any other ODEs solver (COPASI, MATLAB, etc.). However, this naive approach suffers from two main drawbacks. First, the model is not composable. Each time a new species and/or a new reaction is added to or suppressed from the system, the model has to be rewritten. It would be more suitable to describe a system as a set of elementary reactions connected together, as it is the case for instance with COPASI. Second, the conservative modeling feature of HDLs is not exploited.

BIOLOGICAL TRANSISTOR AND CURRENT KIRCHHOFF'S LAWS IN BIOLOGY

To overcome these limitations, we changed our approach and introduced the notion of biological transistors and biological Current Kirchhoff Law (CKL). In electronics, CKL states that the algebraic sum of the current arriving at a single node is equal to zero. To obtain an equivalent law for biology, we have to consider molecules as electrons. With this in mind, a positive or negative source of molecules can be seen as a positive or negative source of current in electronics. Moreover, the local concentration

can be interpreted as the accumulation of molecules in the reaction volume. This behavior corresponds to a capacitor in electronics. Finally, from a kinetic viewpoint, any chemical reaction can be considered as positive or negative sources of molecules, which value is equal to the production or the consumption rate and may depend on the concentration of other involved molecules. Thus, biochemical reactions are equivalent to transconductances (or voltage-controlled current sources, VCCSs) and thus modeled by a kind of biological transistor.

The main difference between electronics and biology circuits is that the information carrier is unique in electronic but multiple in biology (each species carries information). As a consequence, the ports of biological device models are tagged by the species name. The concept of natures in VHDL-AMS enables such operations. With this approach, we defined one or several biological transistors per reaction and connect them all together to describe the system. The ODEs set obtained by applying the CKL on each node of the system corresponds exactly to the EQ. 1.

To illustrate the purpose, let us go back to the biological system of FIGURE 16. The electric equivalent circuit of this system (excluding X1 and X2) is described in FIGURE 18. Blue, green and red nodes and devices correspond respectively to the molecules R1, GFP, and R2. Transistor labels correspond to the reaction number in FIGURE 16. Thus Q1 is a transistor that consumes R2 with a conductance controlled by I2, etc.

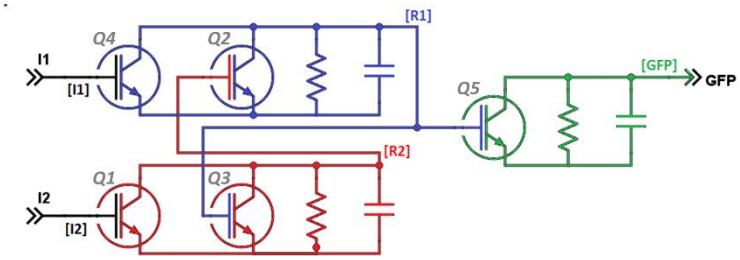

FIGURE 18 – ELECTRONIC EQUIVALENT CIRCUIT OF THE BIOLOGICAL SYSTEM DESCRIBED IN FIGURE 16. BIOLOGICAL TRANSISTORS' LABELS CORRESPOND TO THE REACTION NUMBER IN FIGURE 16.

OUTCOME

The formalism described in this section made the cover of an issue of IEEE Transaction on Biomedical Engineering in 2014. Preliminary works have been published in 5 international conferences, both in biology and in microelectronics. They caught the eye of the electrical engineering community. We have been invited to present this work as a keynote speaker in MOS-AK 2015 in Graz (Austria), in the Cadence Europe workshop CDN-Live 2016 in Munchen (Germany) where the presentation has been awarded by the best academic presentation, and for the 4th Thematic School in Compact Modeling in 2016 at Tarragona (Spain).

> Y. GENDRAULT, M. MADEC, C. LALLEMENT, J. HAIECH, *MODELING BIOLOGY WITH HDL LANGUAGES: A FIRST STEP TOWARD A GENETIC DESIGN AUTOMATION TOOL INSPIRED FROM MICROELECTRONICS*, IN IEEE TRANSACTIONS ON BIOMEDICAL ENGINEERING, PAGES 1231-1240, VOLUME 61, N° 4, JANUARY 2014. DOI:10.1109/TBME.2014.2298559.

2.2. MODELING WITH VHDL-AMS

MODEL GENERATOR

Within this formalism, a C ++ graphical user interface has been developed to prevent the user from having to encode manually the model of each reaction. The user is invited to fill the input interface with a list of involved species and a list of reactions both with some associated parameters. Then the model generates a VHDL-AMS model for each reaction and a top-level model that instantiates the elementary reactions. Results obtained with this approach match quantitatively with the one obtained with COPASI [Gendrault, Madec, Lallement, *et al.*, 2014].

SBML TO VHDL-AMS MODEL CONVERTER

Then, being aware that the data to provide to the graphical interface can also be found in an SBML file, we developed on an automatic SBML-to-VHDL-AMS translator. The role of this tool is to map different language constructs from SBML to VHDL-AMS. The most challenging mapping concerns equations described as MathML instances in an SBML file and that has to be converted into a VHDL-AMS concurrent statements.

The translator is written in Java. The current version supports standard SBML description, including initial assignments and algebraic rules. Events are not yet supported but this limitation comes from our software and not from the language capabilities. Moreover, the translator generates a single model for the whole system and does not yet exploit the concept of biological transistors described hereabove. The translator has been tested by importing different models described in SBML and comparing the simulation results obtained with COPASI and the generated model in VHDL-AMS [Rezgui *et al.*, 2015].

OUTCOME

Investigations on this topic have been a part of Yves Gendrault's Ph.D. project. Early developments and preliminary results have been published in the Biotechnology Journal in 2011. Later, the modeling of biological systems with VHDL-AMS according to the electronic equivalent formalism has been published together with the formalism itself in the IEEE Transaction on Biomedical Engineering paper described above.

> Y. GENDRAULT, M. MADEC, C. LALLEMENT, F. PÊCHEUX, J. HAIECH, *SYNTHETIC BIOLOGY METHODOLOGY AND MODEL REFINEMENT BASED ON MICROELECTRONIC MODELING TOOLS AND LANGUAGES*, BIOTECHNOLOGY JOURNAL, PAGES 796--806., VOLUME 6, JUNE 2011, DOI:10.1002/BIOT.201100083.

Moreover, the development of the VHDL-AMS model generator has been realized by two undergraduate students of Telecom Physic Strasbourg. With this project, they participated in the iGEM contest (International Genetically Engineered Machine, a worldwide annual inter-university contest in bio-engineering organized by the MIT) in the software track. For that works, they were awarded by a bronze medal at the European jamboree and qualified for the final of the contest in Boston. This result gave us worldwide exposure, in particular toward the American university which is very active in this field. Moreover, the work has also been presented at the IEEE EMBC conference in San Diego in 2012.

2.3. Modeling in SystemC-AMS

Timed Data Flow

We also explored the feasibility and the interest of the implementation of biological models in SystemC-AMS. SystemC-AMS in a C++ class for modeling heterogeneous systems [Vachoux, Grimm and Einwich, 2003]. The language is open-source and does not require dedicated simulator, which is an important asset in comparison with VHDL-AMS. Moreover, the programming language is C++, which is more likely to be used and adopted by biologists than VHDL-AMS. Two SystemC-AMS models of computation (MoC) can be compared. The Timed DataFlow (TDF) can be used for complex non-conservative (signal flow) behaviors. It can be seen as an equivalent of MATLAB Simulink. With this MoC, the model consists of encoding ODEs of Eq. 1, without any additional features.

Electrical Linear Networks

The second SystemC-AMS MoC that has been tested is Electrical Linear Network (ELN). As indicated by its name, this MoC is for the description of electronic networks, including transconductance. Thus, it is suitable for the description of an electronic equivalent circuit for any biological systems. Examples of code and simulation results are also given in [Pecheux, Madec and Lallement, 2010].

Outcomes

The results of this project were published at the 2010 IEEE ISCAS conference [Pecheux, Madec and Lallement, 2010]. Moreover, this project was the opportunity to establish a collaboration with Pr. François Pecheux (Laboratory of Computer Science, Paris 6, France) on the application of open-source EDA tools in biology. This collaboration leads to another project on gene regulatory network design automation that will be described in Subsection 4.2.

2.4. Modeling in SPICE: BB-Spice

Motivation

We demonstrated the suitability of HDLs for the description of biological systems. However, we also highlighted some shortcomings. First, HDLs are not very accessible for people that are not accustomed to this language. Even if a user interface generates automatically the VHDL-AMS code, fine-tuning of the model would require code manipulations which are not straightforward. Second, biological models are, from the mathematical perspective, quite simple and do not require the advanced features of VHDL-AMS or SystemC-AMS. Thus, it seemed interesting to consider using SPICE instead of HDLs. The BB-SPICE (SPICE for Biology and Biochemistry) environment described in this part has been established for that purpose. BB-SPICE consists of a SPICE-like formalism for the description of biological systems and of parsers and translators that produce SPICE descriptions of the electronic equivalent circuits.

Description of the Environment

The BB-SPICE environment is described in Figure 19. It is composed of six modules:

1. A biological netlist formalism to describe a biological system into a text file in a very compact way;
2. A parser that generates a Python dictionary which contains the list of species, the list of reactions, the reaction parameters, etc;
3. An SBML file reader which also generates a Python dictionary for a given biological system;
4. An SBML file generator, which takes as input the Python dictionary and generates an SBML description;

5. A SPICE circuit generator which takes as input the Python dictionary described hereabove and generates a SPICE netlist;
6. An open-source SPICE circuit simulator, namely NGSPICE [Nenzi and Vogt, 2011].

More details on the building blocks and on the parsers and translators are given in [Madec, Lallement and Haiech, 2017]. The software is available on an Open Science Framework repository: osf.io/8d269.

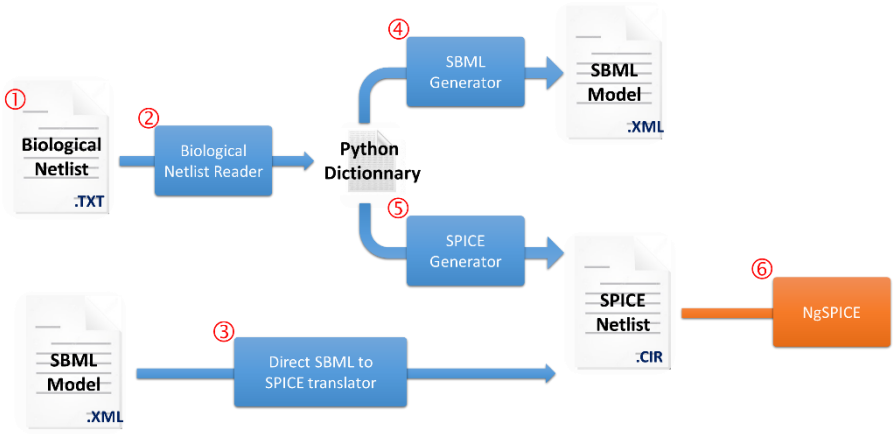

FIGURE 19 – DESCRIPTION OF THE BB-SPICE ENVIRONMENT

BB-SPICE NETLIST FORMALISM

We have devised a language for the description of biological systems that meets the three following constraints: i) being as compact as possible to be accessible for people that are not accustomed to microelectronics CAD tools, ii) looking like SPICE to make it accessible for people that of the engineering science community and iii) containing all the information required for the description of the system.

A BB-SPICE description is composed of 4 sections: the definition of the parameters, the declaration of involved species, the description of reactions and the simulation directives. Inside each section, descriptions are made according to a SPICE-like format, *i.e.* raw text with one line per instance and argument separated by blank characters. For each parameter, a name, a value, and an optional comment are required. For each species, a name followed by up to two arguments, *i.e.* the initial concentration (default 0) and the natural degradation rate (default 0) is required. For each reaction, the user gives a reaction name which first letter indicates its type. Then user also provides up to 4 arguments: the list of substrates (consumed by the reaction), the list of products (produced by the reactions), the list of modifiers (not consumed nor produced but which concentration has an impact on the reaction rate) and a list of parameters. Finally, the simulation directives give a syntax to specify the stimuli, the type of analysis and the species to monitor.

The current version of BB-SPICE includes 10 pre-defined reaction types with an associated generic reaction rate. Details are given in [Madec, Lallement and Haiech, 2017]. Moreover, the user can add a custom reaction. The list of reactants, products, and modifiers has to be specified during the instantiation in the netlist. FIGURE 20 gives an idea of a BB-SPICE netlist and of its translation into a SPICE netlist for the system depicted in FIGURE 16.

BB-SPICE netlist

```
#PARAMETERS
Ktr 1e-3
KR  1e-2
nR  2
Vm  1e-2
KM  1e-2

#SPECIES
R1  1e-3 0
R2  1e-3 1
I1  1e-3 0
I2  1e-3 0
X1  1e-3 0
X2  1e-3 0
GFP 1e-3 0

#REACTIONS
E1 R2 X2 I2 {Vm,HM}
T2 0 R1 R2 {Ktr,KR,nR}
T3 0 R2 R1 {Ktr,KR,nR}
E4 R1 X1 I1 {Vm,HM}
T5 0 R1 GFP {Ktr,KR,nR}

##SIMULATION
PULSE I2 1e-3 5000 100000 10000
PULSE I1 1e-3 5000 100000 60000
```

NGSPICE netlist

```
.param Ktr = 1e-3
.param KR = 1e-2
.param nR = 2
.param Vm = 1e-2
.param KM = 1e-2

C_R1  R1  0  C='1'
R_R1  R1  0  R='1/1e-3'
C_R2  R2  0  C='1' ic='1'
R_R2  R2  0  R='1/1e-3'
C_I1  I1  0  C='1'
R_I1  I1  0  R='1/1e-3'
C_I2  I2  0  C='1'
R_I2  I2  0  R='1/1e-3'
C_X1  X1  0  C='1'
R_X1  X1  0  R='1/1e-3'
C_X2  X2  0  C='1'
R_X2  X2  0  R='1/1e-3'
C_GFP GFP 0  C='1'
R_GFP GFP 0  R='1/1e-3'

G_E1_R2 R2 0  Value='Vm*V(I2)*V(R2)/(KM+V(R2))'
G_E1_X2 0 X2  Value='Vm*V(I2)*V(R2)/(KM+V(R2))'
G_T2_R2 0 R2 Value='Ktr/(1+(V(R1)/KR)**nR)'
G_T3_R1 0 R1 Value='Ktr/(1+(V(R2)/KR)**nR)'
G_E4_R1 R1 0  Value='Vm*V(I1)*V(R1)/(KM+V(R1))'
G_E4_X1 0 X1  Value='Vm*V(I1)*V(R1)/(KM+V(R1))'
G_T3_GFP 0 GFP Value='Ktr/(1+(V(R1)/KR)**nR)'

I_I2_1 0 I2 PULSE(0 1e-3 10000 0 0 5000 100000)
I_I1_1 0 I1 PULSE(0 1e-3 60000 0 0 5000 100000)
```

FIGURE 20 – EXAMPLE OF BB-SPICE NETLIST AND ITS CORRESPONDING NG-SPICE NETLIST FOR THE SYSTEM DEPICTED IN FIGURE 16. FIVE PARAMETERS ARE DEFINED IN THE FIRST SECTION. THEN, 7 SPECIES ARE DECLARED. FOR EACH SPECIES, A UNITARY CAPACITOR AND A RESISTOR ARE DEFINED. FOR THE R2 CAPACITOR, AN IC CONDITION IS ADDED TO TAKE THE INITIAL CONCENTRATION INTO ACCOUNT. THE VALUE OF THE RESISTORS IS THE INVERSE OF THE VALUE OF THE DEGRADATION RATE FOR EACH SPECIES. THIRD, 5 REACTIONS ARE DESCRIBED. REACTIONS STARTING BY E ARE ENZYMATIC REACTIONS. ARGUMENTS TO PROVIDE ARE THE SUBSTRATE, THE PRODUCT, THE MODIFIER AND, AS PARAMETERS, THE MAXIMAL RATE, AND THE MICHAELIS CONSTANT. EACH ENZYMATIC REACTION IS TRANSLATED BY TWO TRANSCONDUCTANCES IN THE NGSPICE NETLIST, ONE WITH A REVERSE CURRENT VALUE ASSOCIATED WITH SUBSTRATE AND ONE WITH A POSITIVE CURRENT ASSOCIATED WITH THE PRODUCT. REACTIONS STARTING BY T ARE THE DNA TRANSCRIPTION, ASSOCIATED WITH A HILL-LIKE REGULATION. ARGUMENTS TO PROVIDE ARE THE ACTIVATOR ('0' MEANS NO ACTIVATOR IN OUR CASE), THE REPRESSOR, THE SYNTHESIZED MOLECULE AND THE THREE PARAMETERS OF THE HILL EQUATION. EACH DNA TRANSCRIPTION IS TRANSLATED INTO A TRANSCONDUCTANCE IN THE NGSPICE NETLIST ASSOCIATED WITH THE SYNTHESIZED MOLECULE. THE LABEL (1 TO 5) OF THE REACTION CORRESPONDS TO THE REACTION NUMBER IN FIGURE 16. FINALLY, SIMULATION DIRECTIVES ARE GIVEN. HERE THE TEST VECTOR IS COMPOSED OF TWO PULSES, ONE FOR I2 AFTER 10,000 SECONDS AND ONE FOR I1 AFTER 60,000 SECONDS.

VALIDATION

First, we compare NGSPICE and COPASI simulations on a benchmark of 20 different biological systems, which cover all the mechanisms and the analysis capability of BB-SPICE. Models have been written in BB-SPICE and converted in a SPICE netlist and in an SMBL model. Both output files have been simulated with NGSPICE on the one hand and COPASI on the other hand. Results are always very close. For instance, the comparison of COPASI and NGSPICE simulation results on the circuit of FIGURE 16 is given in FIGURE 21.

Second, we validated the SBML-to-SPICE converter by comparing COPASI and SPICE simulations results over 25 models picked up in the BioModel database [Le Novère *et al.*, 2006]. Again, models have been chosen in order to cover all the features implemented in the current version of the converter. For all of them, simulations obtained with both software are in good accordance. The complete list of models used for this validation is given in [Madec, Lallement and Haiech, 2017].

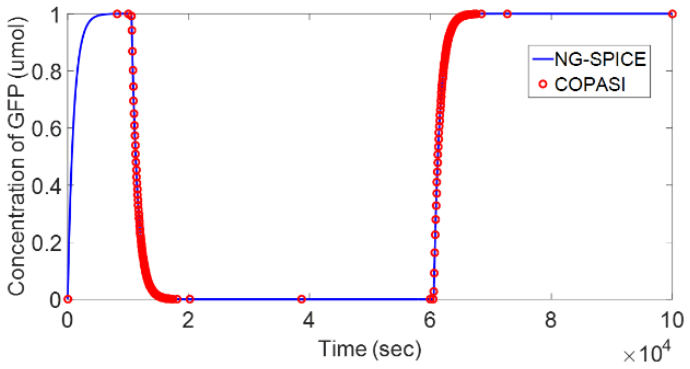

FIGURE 21 – COMPARISON OF SIMULATION RESULTS OBTAINED WITH SPICE AND WITH COPASI ON THE SYSTEM DESCRIBED IN FIGURE 16. HERE, THE TRANSIENT EVOLUTION OF GFP IS SHOWN. STIMULI ARE DESCRIBED IN THE NETLIST. IN THE BEGINNING, THE CONCENTRATION OF R2 IS HIGH. THUS R1 IS INHIBITED AND GFP IS, IN TURN, PRODUCED. AT 10,000 SECONDS, I2 IS PRODUCED. THUS, R2 IS CONSUMED AND THE INHIBITION OF R1 IS RELEASED. GFP IS NO MORE PRODUCED AND ITS CONCENTRATION DECREASES. AT 60000 SECONDS, I1 IS PRODUCED. THUS R1 IS CONSUMED AND THE INHIBITION OF R2 IS RELEASED. GFP IS PRODUCED AGAIN AND ITS CONCENTRATION INCREASES AGAIN.

BENCHMARK: COMPUTATION TIME

We also compared the computation time for both approaches. Two benchmarks composed of artificial biological systems have been generated for that purpose. The first one is composed of a set of metabolic reaction with N species and M reactions, each of them being catalyzed by one of the N species (randomly drawn) according to a Michaelis-Menten model. Operating point simulations are performed on these models. Comparison of computation time between NGSPICE and COPASI is given in FIGURE 22A and FIGURE 22B. The nodal analysis performed by NGSPICE is much more efficient that COPASI algorithm. A speed-up of 50 is observed between 50 and 1,000 reactions (pathways with more than 1,000 species have not been tested with COPASI because models failed to compile) without any loss in term of accuracy: the steady state concentration obtained by both tools is comparable with a mean square error of less than 10 ppm.

The second benchmark is composed of an oscillating gene regulatory networks (GRN) based on the principle of the repressilator [Elowitz and Leibler, 2000]. It involves an odd number of genes going 3 to 4,999 genes (for a total of 8 to 10,000 reactions). The transient simulation is performed and the compilation and computation time are compared for three different tools: COPASI, NGSPICE, and a commercial SPICE simulator optimized for multi-core processing, SPECTRE®. Results are given in FIGURE 22C.

The CPU time for NGSPICE and COPASI are comparable for GRN with up to 500 genes. Over this value, compilation and simulation time take off with COPASI while it remains linear with the number of genes with NGSPICE. With 10,000 reactions, the speedup offered by NGSPICE is about 30. Moreover, we also observe a speedup of 40 for SPECTRE® over NGSPICE simulation results for large systems. It should be noticed that computation time for SPECTRE® is always dominated by the compilation step, which can hardly benefit from parallelization, unlike simulation.

OUTCOME

BB-SPICE has been published in PloS One and presented during an international IEEE conference. This work also opened the prospect of using BB-SPICE for virtual prototyping of biosensors, as we will see in SECTION 3 of this chapter.

M. MADEC, C. LALLEMENT, J. HAIECH, *MODELING AND SIMULATION OF BIOLOGICAL SYSTEMS USING SPICE LANGUAGE*, PLOS ONE, 2017, DOI: 10.1371/JOURNAL.PONE.0182385

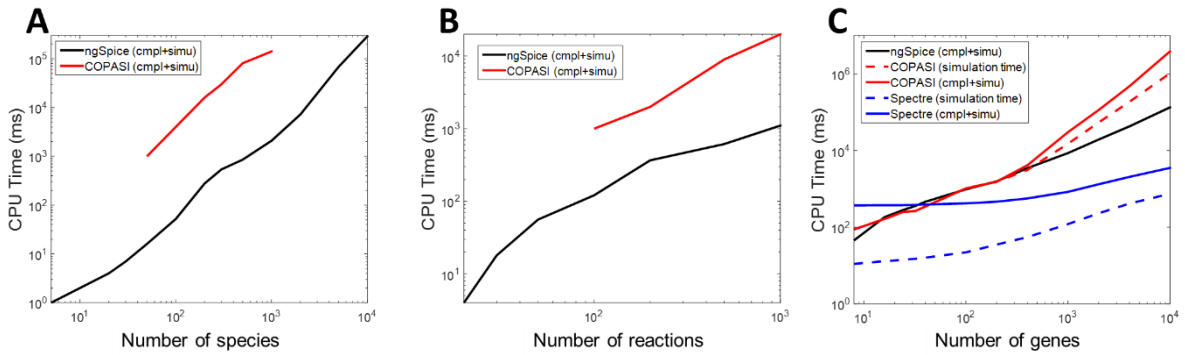

FIGURE 22 – COMPARISON OF COMPUTATION TIME BETWEEN THE COPASI AND NG-SPICE SIMULATION. (A) CORRESPONDS TO THE FIRST BENCHMARK FOR WHICH EACH REACTION CONVERTS THE SPECIES *K* INTO THE SPECIES *K*+1 AND IS CATALYZED BY ANOTHER INVOLVED SPECIES RANDOMLY DRAWN. (B) CORRESPONDS TO THE FIRST BENCHMARK WITH N=100 AND M REACTIONS FOR WHICH SUBSTRATE, PRODUCT, AND ENZYME ARE RANDOMLY DRAWN. (C) CORRESPONDS TO THE SECOND BENCHMARK.

2.5. BB-SPICE 3D

MOTIVATION

Dimensionless problems represent only a small fraction of the systems that are likely to be encountered in biology. Drugs diffusion in tissues [Arifin, Lee and Wang, 2006], intercellular communication [Basu *et al.*, 2005; Tamsir, Tabor and Voigt, 2011] or intracellular signaling [Somogyi and Stucki, 1991; Borghans, Dupont and Goldbeter, 1997] are some applications for which space- and time-dependent models are unavoidable. Thus, they are not directly compatible with the electronic equivalent circuit approaches described in SUBSECTION 2.1.

In this project, we investigated a way to simulate molecular diffusion on a mesoscopic scale still based on HDL. Our team recently developed an environment based on Verilog-A for the electro-thermal simulation of integrated circuits [Krencker *et al.*, 2014]. Considering the analogies that can be drawn between biology on the one hand and electronics (see SUBSECTION 2.1) and thermal physics on the other (similarities between EQ. 6 and the heat equation), we adapted this environment to the biological context.

TOOL DESCRIPTION

The tool is composed of four main elements:

1. A mesher that discretizes space into small parallelepipeds according to user-defined refinement requirement. The meshing algorithm is described in Figure 23A. Basically, it is composed of three steps: i) a coarse discretization at the higher accepted refinement degree over all the volume, ii) a refinement in zones in which high gradients are expected (these zones are defined by the user) and iii) a smoothing checking that ratio of side size between two adjacent parallelepipeds is 2 at the most. We use parallelepipeds in place of the traditional tetrahedron to simplify the generation of mesh as well as the model of the elementary mesh;
2. A generic model of the elementary mesh composed of up two 26 terminals, 12 being always connected and 14 which existence depends on the size of neighboring mesh Figure 23B. The model is composed of resistors and capacitors (Figure 23C). The value of these components are generic and adapt themselves depending on the configuration. They are computed so as to retrieve exactly

the equation of finite-difference discretization scheme when Kirchhoff's law is applied on each node of the lattice. More details on the model of the elementary mesh are given in [Rosati, Madec, Kammerer, *et al.*, 2018] for the 2D case and in [Madec *et al.*, 2019] for the 3D case;

3. A Python script that calls the mesher, reads the mesher output file, creates a SPICE netlist, instantiates in the netlist one elementary mesh model for each mesh of the lattice and treats the initial and boundary conditions;
4. A SPICE simulator that compiles the netlist and computes the results. The tool has been validated with NGSPICE but, most of the time, SPECTRE® is used to reduce the computation time.

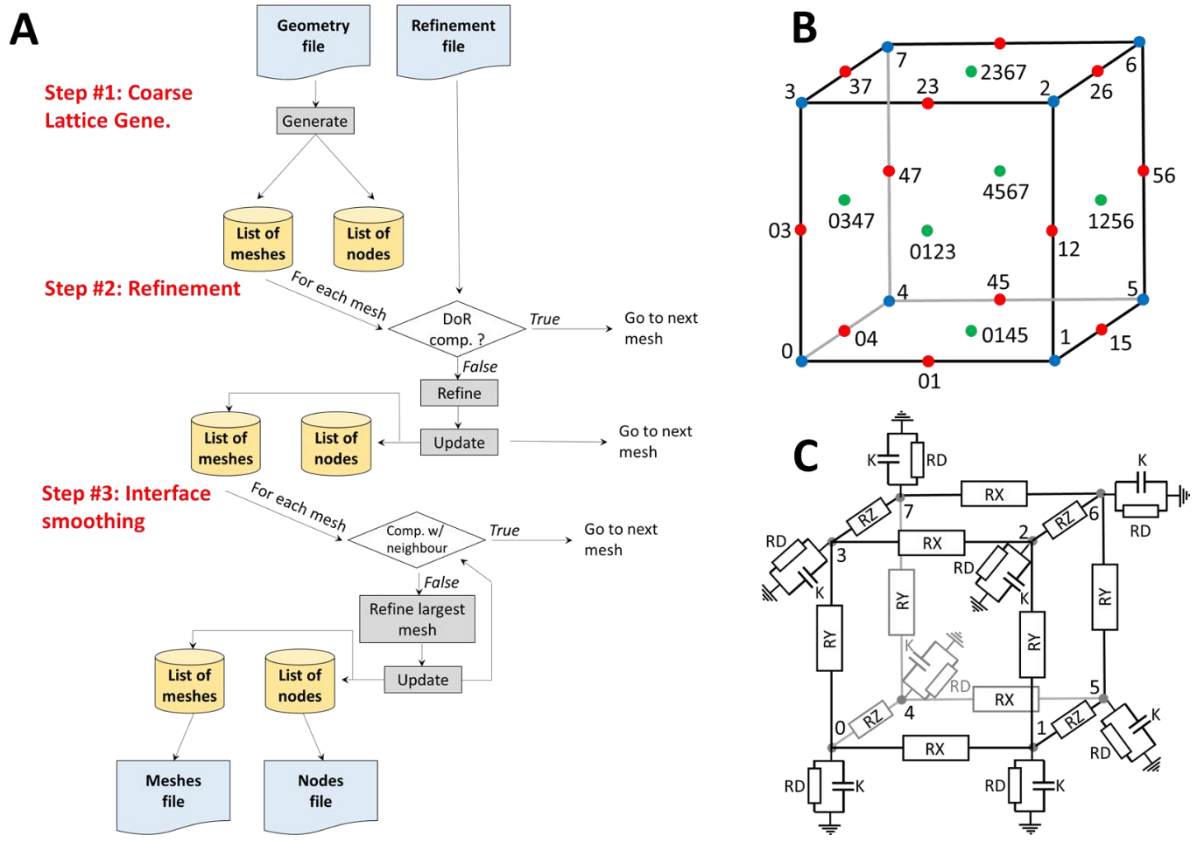

FIGURE 23 – (A) MESHING ALGORITHM USED IN BB-SPICE 3D. (B) THE 26 POTENTIAL CONNECTIONS OF THE ELEMENTARY MESH. THE BLUE NODES (CORNERS) ARE ALWAYS IMPLEMENTED AND CONNECTED. A RED NODE (CENTER OF AN EDGE) EXISTS ONLY IF AT LEAST ONE OF THE FOUR NEIGHBORS THAT SHARE THE SAME EDGE IS DIVIDED. A GREEN NODE (CENTER OF A FACE) EXISTS ONLY IF THE NEIGHBOR THAT SHARES THE SAME FACE IS DIVIDED. (C) THE COMPLETE MODEL OF THE ELEMENTARY MESH FOR THE CASE OF A UNIFORM LATTICE (ONLY THE RED NODES ARE CONNECTED).

VALIDATION

The validation of BB-SPICE 3D is done with 2-D and 3-D cases for which analytical solutions exist. First, the focus is put on the 2-D model. We consider the reaction chamber as a square. A reaction synthesizes a constant flux of molecules on the left border. The concentration at the right border is fixed to 0 and no-flux boundary conditions are applied at the top and bottom border. Four different lattices have been generated for this test, with a number of nodes ranging from 1,600 to 25,600. The error between the simulation results provided by BB-SPICE 3D and the analytical solution is below 5% for the coarsest lattice and below 1% for the finest one. The variable-size lattice is a good tradeoff with a maximal of 2.5 % and a number of nodes of about 2,800 (FIGURE 24A and FIGURE 24B).

Second, another 2-D use case is analyzed. We still consider a square reaction area but this time, the reaction takes place at the center of the cube. A zero-concentration condition is applied for all nodes of the lattice that are not inside the circle inscribed in this square. Under this condition, the system has a symmetry of revolution. Thus, we observe the concentration as a function of the distance to the center. Eleven lattices have been generated, with a number of meshes ranging from 400 to 36,500. All of them give acceptable results. The mean error, excluding the central node (for which the expected value is infinite because of the punctual source), is less than 10 % for coarsest lattice and down to 2% for the finest. Simulation time as a function of the number of nodes (FIGURE 24D) as well as the computation time versus accuracy diagram (FIGURE 24E) is given for all the lattices.

Third, these two use cases are transposed in 3-D. Results are quite similar that in 2-D. Transient simulation results for the first case are given in FIGURE 24C and compared with numerical simulation on MATLAB. Results are obtained with an intermediate lattice. The maximal error is 4 %. Steady-state simulation of the second case is given in FIGURE 24F.

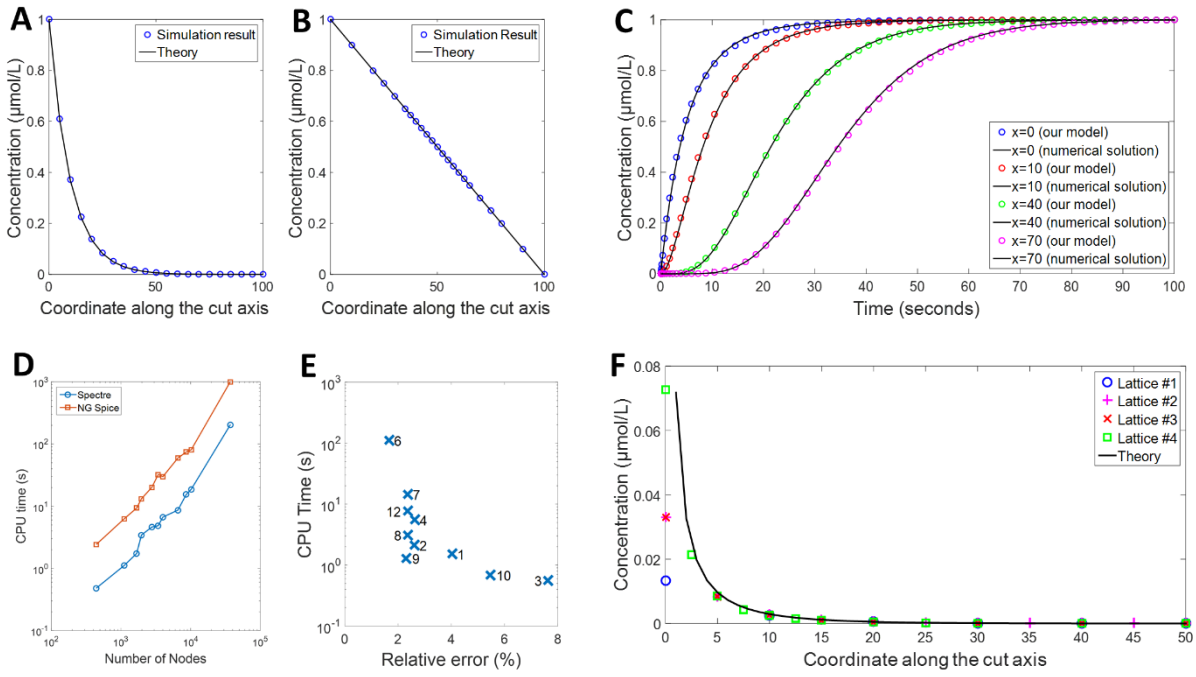

FIGURE 24 – VALIDATION OF BB-SPICE 3D. (A) CORRESPONDS TO THE 2D SQUARE WITH A CONSTANT PRODUCTION ON THE LEFT, A CONCENTRATION FIXED AT 0 ON THE RIGHT AND NO-FLUX BOUNDARY CONDITION ON THE TOP AND BOTTOM. (B) IS THE SAME CASE EXCEPT THAT MOLECULES ARE NEVER DEGRADED. (C) IS THE TRANSIENT SIMULATION OF THE SAME USE CASE. (D) GIVES THE COMPUTATION TIME AS A FUNCTION OF THE NUMBER OF NODES FOR 11 DIFFERENT LATTICES IN THE CASE OF A 2D SQUARE WITH A CONSTANT SOURCE AT THE CENTER. (E) IS A PLOT GIVING THE REPARTITION OF THESE 11 LATTICES IN TERMS OF COMPUTATION TIME AND PERFORMANCES (RELATIVE ERROR IN COMPARISON TO THE ANALYTICAL SOLUTION). (F) IS THE SIMULATION OF THE 3D CASE FOR A CUBE WITH A CONSTANT SOURCE AT THE CENTER.

OUTCOMES

This work was mostly conducted by Elise Rosati during her Ph.D. project. The results of this research were published in a review and served as a pillar for two other journals for which the emphasis is on application to modeling biosensors (see SECTION 3). The work has also been presented at the IEEE MIXDES 2015 conferences.

E. ROSATI, M. MADEC, J-B. KAMMERER, L. HÉBRARD, C. LALLEMENT, J. HAIECH, *EFFICIENT MODELING AND SIMULATION OF SPACE-DEPENDENT BIOLOGICAL SYSTEMS*, IN JOURNAL OF COMPUTATIONAL BIOLOGY, MAI 2018, DOI:10.1089/CMB.2018.0012.

This project gives also a continuity to the development of the electrothermal simulator. It brings this tool up to a multiphysics simulator of systems integrating electronics, biology, thermal and maybe, in the near future mechanics and microfluidics. It is a part of a more ambitious project described in the next part of the document (prospective research). The tool is operational but some improvement is still possible. First, the tool has to be more user-friendly in order to be shared with the community. Second, alternative discretization scheme needs to be tested. The implementation of finite elements instead of finite differences is, for instance, under consideration.

3. MODELING OF BIOSENSORS

The manipulation of biological models with SPICE is an asset that is not limited to the field of systems biology. It is also of great interest for the virtual prototyping of biosensors on the one hand and for synthetic biology on the other hand. In this subsection, the focus is put on biosensors. Most of the time, biosensors are composed of a biological transducer, an electrical transducer, and biasing and processing electronic circuits. The biological transducer aims at generating a detectable biophysical signal (pH change, fluorescent proteins, etc.) that depends on the concentration of the molecule of interest. The electrical transducer transforms this biophysical signal into an electronic one. The biasing and processing electronic circuit analyses this electrical signal to retrieve the information of interest. The ability to describe biological models with an HDL enables the extension of virtual prototyping approaches to biosensors. Two examples are described in the following.

3.1. VIRTUAL PROTOTYPING OF A BIOSENSOR WITH VHDL-AMS

DESCRIPTION OF THE USE CASE

The first use case is a lab-on-chip (LOC) designed for the detection of micropollutant in drinking water. The schematic of this LOC is given in FIGURE 25A. It is composed of five subsystems:

1. A microfluidic circuit that stores and transports different reagents;
2. The biochemical transducer which is based on a competitive enzyme-linked immunosorbent assay (ELISA) [Engvall and Perlmann, 1971]. The signal of interest is the concentration of micropollutant. The detectable signal is a change of pH due to the production of H^+ ions at a rate that depends on the signal of interest;
3. An electrochemical transducer, namely an ion-sensitive field effect transistor (ISFET), *i.e.* a transistor which characteristics depends on the pH [Bergveld, 1970];
4. A conditioning and processing electronic circuit that biases the ISFETs and generates an output voltage linear with the pH;
5. A sequencer that drives microfluidics and electronic readout circuit in accordance with the LOC measurement protocol.

VHDL-AMS MODEL

The model of such LOC wraps three domains: the microfluidic, the biochemistry and the electronics (FIGURE 25B). For microfluidic, COMSOL Multiphysics simulations were performed in order to dimension the circuit and to derive simple first-order macro-models suitable for a VHDL-AMS

implementation. For biochemistry, the model of the ELISA assay was first studied with Virtual Cell. The model of the reaction was exported in SBML and then translated in VHDL-AMS with the tool described in SUBSECTION 2.2. For electronics, a simple model of a long-channel ISFET [Janicki *et al.*, 2004] was implemented. Two ISFET models were coupled with standard models of electronic devices to obtain a VHDL-AMS description of the complete biasing and readout circuit. ISFETs are biased with a constant drain current and drain-source voltage and the variation of the source voltage between both ISFETs is amplified to give the output voltage. A detailed description of each block is given in [Guiton *et al.*, 2014].

Putting all the models together led to a complete virtual prototype of the system (FIGURE 26).

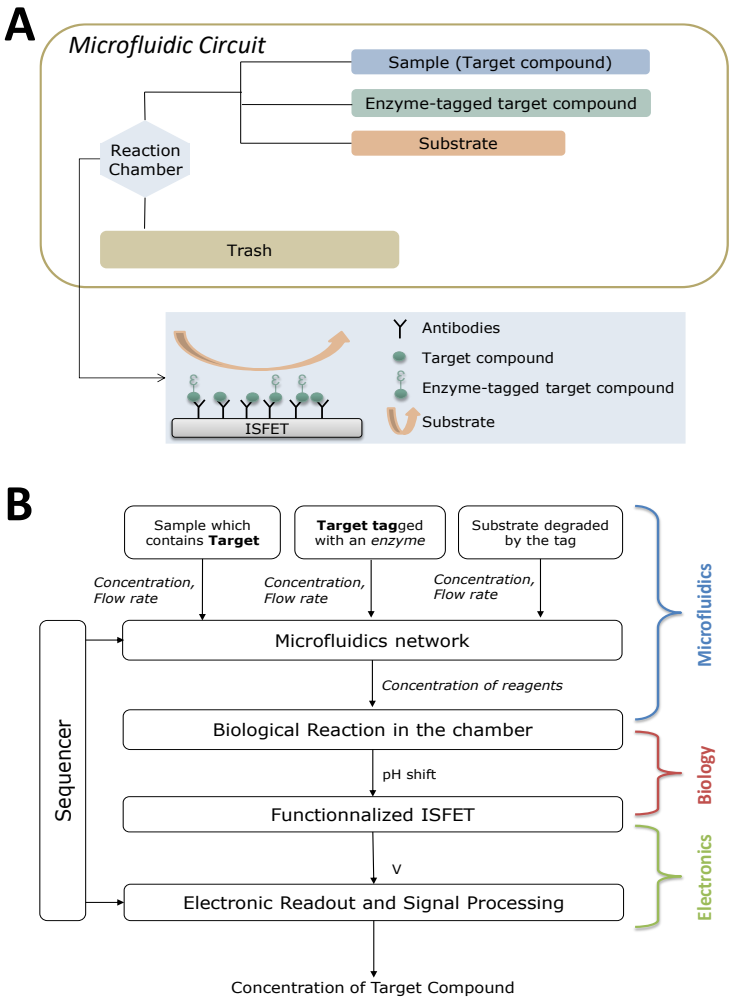

FIGURE 25 – (A) DESCRIPTION OF THE LAB-ON-CHIP. (B) ASSOCIATED MODEL.

SIMULATION RESULTS

The model was simulated with Dolphin SMASH. As expected, the output response depends on the concentration of the targeted molecule. The higher the concentration, the faster the pH evolution (FIGURE 26). The model was used to analyze the impact of the different parameters (volume of the reaction chamber, the concentration of reactants, biasing of the ISFET, etc.) on the system response. Moreover, Monte-Carlo simulations were performed in order to estimate the robustness of the system. It turns out that the system is quite sensitive to the variation of these parameters.

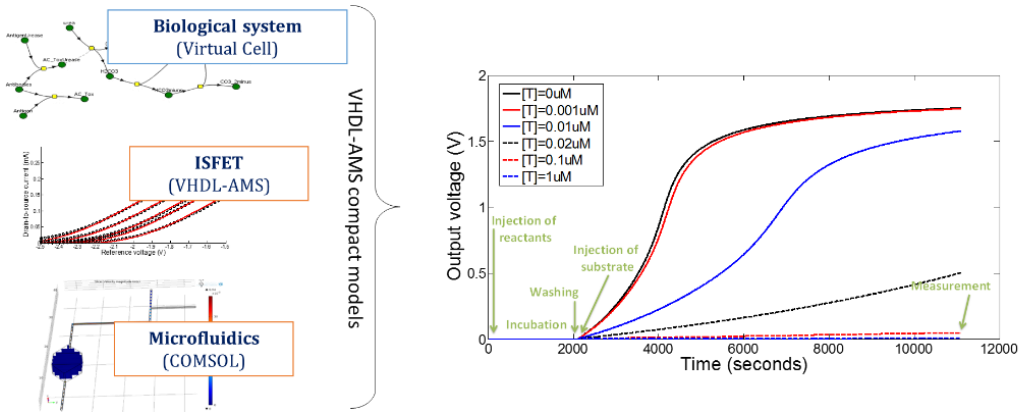

FIGURE 26 – COMPLETE VHDL-AMS MODEL OF THE LAB-ON-CHIP AND SIMULATION RESULT ON THE COMPLETE SYSTEM.

OUTCOMES

This work was very important for us as it bridged our activities on design-oriented modeling of heterogeneous systems and our activities in the field of biological system modeling. The work on the detection of micropollutants was carried out in the context of Stéphanie Guiton's Ph.D. project. This project was granted by Bürkert SAS in a CIFRE partnership. For health reasons, the project had to be stopped prematurely but the preliminary results were encouraging enough to convince the company about the interest of the virtual prototyping approach. The results were presented at two international IEEE conferences as well as in the International Journal of Microelectronics and Computer Sciences (extension of 2014 IEEE MIXDES paper).

> S. GUITON, A. REZGUI, M. MADEC, C. LALLEMENT, F. RUFI, J. HAIECH, *SYSTEM-LEVEL MODELING OF A LAB-ON-CHIP FOR MICROPOLLUTANTS DETECTION*, INTERNATIONAL JOURNAL OF MICROELECTRONICS AND COMPUTER SCIENCE, PAGES 116-125, VOLUME 5, N° 3, 2014, DOI:10.1109/MIXDES.2014.6872196

3.2. VIRTUAL PROTOTYPING OF A BIOSENSOR WITH BB-SPICE

DIMENSIONLESS SYSTEM

In this example, we demonstrate the interest of BB-SPICE for the study on an ISFET-based penicillin biosensor, a fictitious example used as a proof of concept. The sensor architecture is inspired from an actual device published 34 years ago [Caras and Janata, 1985]. The device, represented in FIGURE 27A, is composed of two ISFETs in contact with a solution confined in measurement chambers by a semi-permeable gel. One of the measurement chambers contains penicillinase, an enzyme that catalyzes the hydrolysis of penicillin, releasing H^+ ions. Unlike H^+ ion and penicillin, penicillinase molecules are too big to cross the semi-permeable gel. ISFETs measure the pH in both measurement chambers and a readout circuit converts the signal into an exploitable voltage.

The model of the complete system is described in FIGURE 27B. The biological part of the model is composed of 16 chemical species (only 6 chemical species are involved in the system but 5 of them are instantiated three times to distinguish the concentration in the main chamber and in each measurement chamber), one enzymatic reaction, 10 diffusion mechanisms through the gel membrane and 3 binding reactions for the phosphate buffer. The model is described in BB-SPICE and converted into a SPICE subcircuit. For the electrochemical transducer, Martinoina's SPICE model is used [Martinoia and Massobrio, 2000]. The readout circuit is described in [Liu *et al.*, 1998].

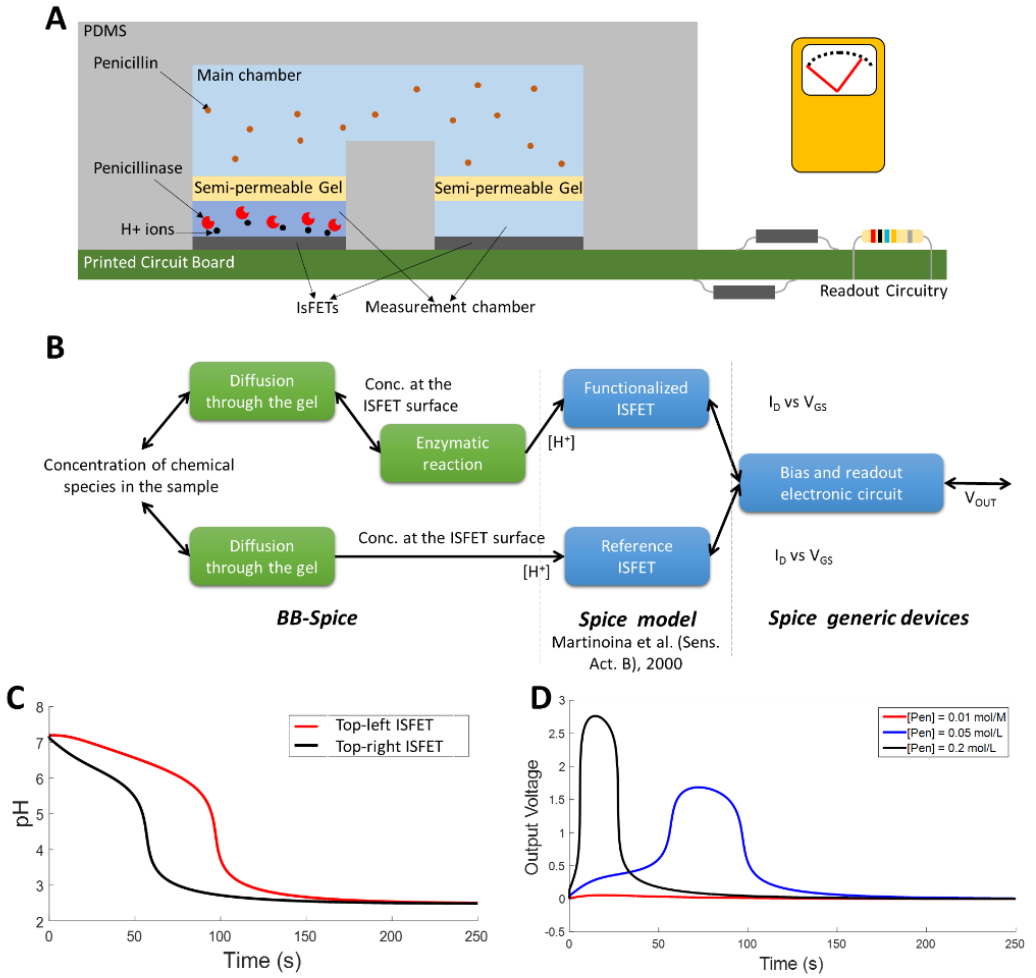

FIGURE 27 – (A) DESCRIPTION OF THE ISFET-BASED PENICILLIN SENSOR. (B) BLOCK-DIAGRAM OF THE COMPLETE MODEL. (C) SIMULATION OF THE BIOCHEMICAL MODEL FOR AN INITIAL CONCENTRATION OF PENICILLIN OF 0.05 MOL/L. THE BLACK CURVE CORRESPONDS TO THE TOP-LEFT ISFET WHERE THE REACTION OCCURS AND THE RED ONE TO THE TOP-RIGHT ISFET REACHED BY H^+ IONS AFTER DIFFUSION THROUGH THE MAIN CHAMBER AND BOTH SEMI-PERMEABLE GELS. (D) IS A SIMULATION RESULT OF THE COMPLETE MODEL FOR DIFFERENT INITIAL PENICILLIN CONCENTRATIONS.

Simulation results are given in FIGURE 27C and FIGURE 27D. With an intermediate concentration of penicillinase, the simulated response exhibit three phases. First, several penicillin molecules reach the measurement chamber with penicillinase due to diffusion. H^+ ions are produced but the phosphate buffer plays its role and the pH does not change. Second, a large amount of H^+ ions are accumulated in the measurement chamber. The buffer gets saturated and the pH decreases quickly. Third, H^+ ions diffuse back in the main chamber, then in the second measurement chamber. In the meantime, all the penicillin is consumed and H^+ production is turned off. At the equilibrium, pH on both ISFET are the same and the output voltage decrease to 0. If the initial concentration of penicillin is high, the first phase is too short to be observed. Conversely, if the initial concentration of penicillin is low, the buffer is never saturated and the pH does not change.

SPACE- AND TIME-DEPENDENT SYSTEM

Up to now, space was not been taken into account. That is to say that the model is based on the assumption that the concentration of each chemical species is uniform inside each chamber, which is obviously not so realistic. We now consider a variation on the ISFET-based penicillin sensor. The

principle is the same, except that the semi-permeable gel is removed and penicillinase is deposited somewhere on a wall of the reaction cavity. The detection is performed by two ISFETs: the measurement ISFET which is close to the deposit and thus will sense the pH change early and reference ISFET which is far away (FIGURE 28A). With this configuration, taking the gradients of concentration into account in the model is unavoidable.

Several geometries of the device were tested, both in 2-D and in 3-D (FIGURE 28A to FIGURE 28C). The block diagram of the sensor model is given in FIGURE 28D. This model is valid for both 2-D and 3-D analysis and whatever the configuration. The model is composed of 4 sub-circuits. Sub-circuits for the ISFET and for the biasing/processing electronic circuit are the same as for the dimensionless problem. The model for of the reaction is reduced to a single enzymatic reaction ruled by a Michaelis-Menten rate equation. Finally, the model for the molecular diffusion inside the cavity is obtained with BB-SPICE. As two species are likely to diffuse (H^+ ions and penicillin) two lattices have to be defined, one for each molecule. Both lattices are composed of at about 1,500 cubes and are refined close to the penicillinase deposits where the gradients of concentration are significant. For both lattices, positions of nodes r_1 to r_k match with the positions of the penicillinase deposit. A model of the biochemical reaction connects each node r_i of one module with the corresponding node r_i of the other. By the same way, the positions of nodes s_1 and s_2 match with the position of both ISFET. The H^+ terminal on each ISFET is respectively connected to nodes s_1 and s_2 of the H^+ diffusion module.

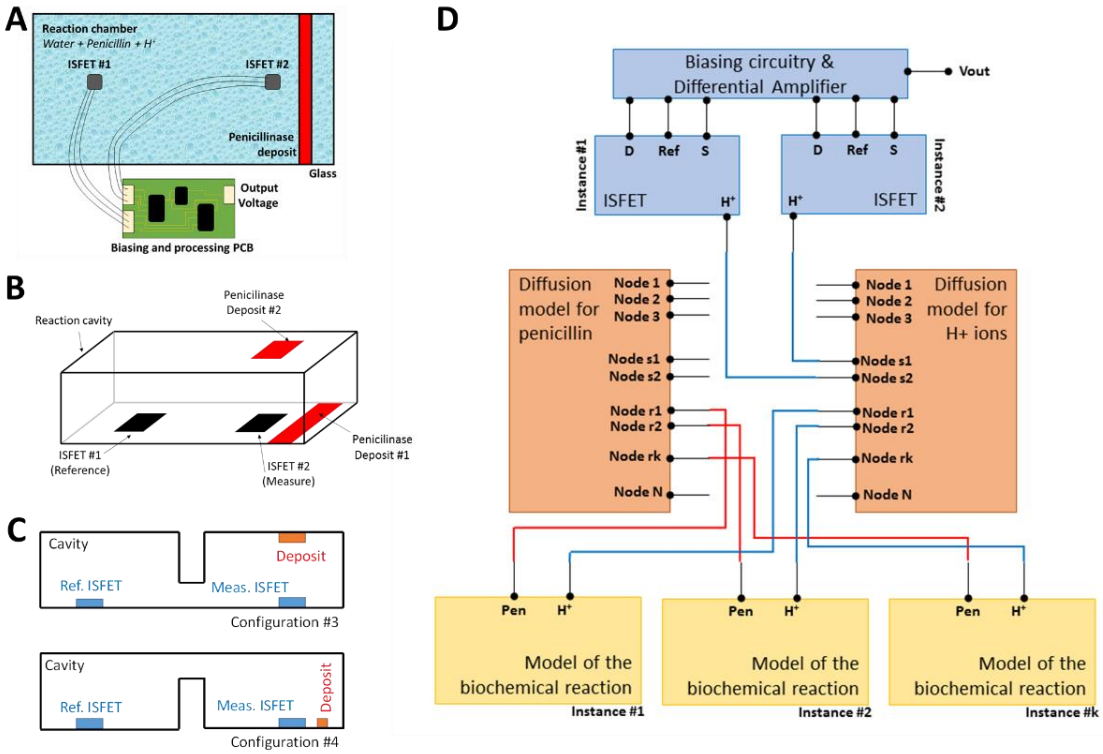

FIGURE 28 – SECOND VERSION OF THE ISFET-BASED PENICILLIN SENSOR. (A) STRUCTURE OF THE SENSOR FOR THE ANALYSIS IN 2-D. ISFET AND PENICILLINASE DEPOSIT ARE ON THE SAME PLANE. SEVERAL RELATIVE POSITIONS OF ISFETS AND SEVERAL POSITIONS AND SHAPES OF THE PENICILLINASE DEPOSIT HAVE BEEN TESTED. (B) 3D-VIEW OF THE SENSOR WITH TWO POSSIBLE PENICILLINASE DEPOSIT POSITION (CONFIGURATIONS #1 AND #2). (C) AN ENHANCED VERSION OF THE SENSOR WITH A NON-PARALLELEPIPEDIC CAVITY (CONFIGURATIONS #3 AND #4). (D) BLOCK DIAGRAM OF THE SENSOR MODEL WHICH IS VALID IN 2-D AND IN 3-D AND WHATEVER THE CONFIGURATION.

More details on models, especially for the biochemical reaction, are given in [Madec *et al.*, 2018]. Biochemical parameters, including the diffusion constant of molecules in water, are gathered from the literature. Some simulation results are given in FIGURE 29: concentration map at the steady state, simulated response of the complete system. Analysis of simulation also showed that the configuration leading to the higher sensitivity is the configuration #3, with the deposit on the ceiling of the cavity just above the measurement ISFET and a wall reducing the diffusion towards the second ISFET.

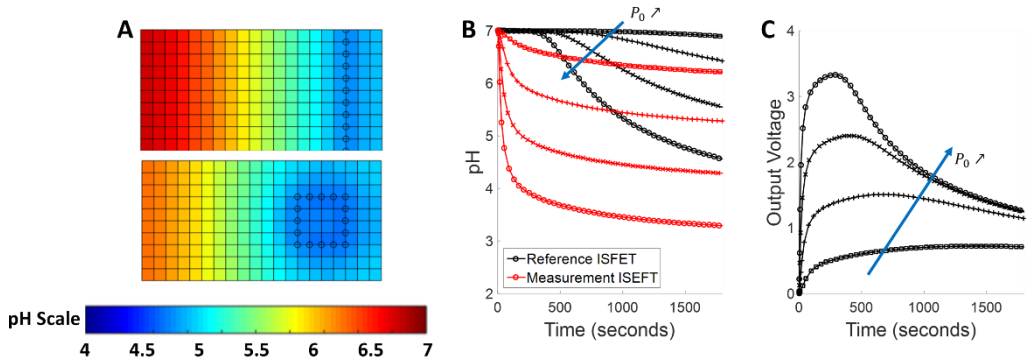

FIGURE 29 – SIMULATION RESULTS ON THE ISFET-BASED PENICILLIN SENSOR. (A) IS THE STEADY-STATE CONCENTRATION MAP OH H^+ IONS CONSIDERING CONSTANT H^+ SOURCES AT THE POSITIONS MARKED BY A CIRCLE OBTAINED (SIMULATIONS PERFORMED WITH THE 2D MODEL). (B) TRANSIENT EVOLUTION OF THE PH ABOVE EACH ISFET AS A FUNCTION OF THE INITIAL CONCENTRATION OF PENICILLIN. (C) THE OUTPUT VOLTAGE OF THE SYSTEM AS A FUNCTION OF THE INITIAL CONCENTRATION OF PENICILLIN.

OUTCOMES

Investigations presented in this part are the topic of two publication in IEEE journal: a paper invited for a special session on compact modeling in IEEE TED and paper in the special issue of IEEE T-CAS with a selection of the best papers of NEWCAS 2018. Works were also been presented at 4 international IEEE conferences (MIXDES and NEWCAS).

> M. MADEC, A. BONAMENT, E. ROSATI, J. HAIECH, L. HÉBRARD, C. LALLEMENT, *ENVIRONNEMENT FOR MODELING AND SIMULATION OF BIOSYSTEMS, BIOSENSORS AND LAB-ON-CHIPS*, IEEE TRANSACTIONS ON ELECTRON DEVICES, VOLUME 66, DECEMBER 2018, DOI:10.1109/TED.2108.28811320

> M. MADEC, L. HÉBRARD, J-B. KAMMERER, A. BONAMENT, E. ROSATI, C. LALLEMENT, *MULTIPHYSICS SIMULATION OF BIOSENSORS INVOLVING 3D BIOLOGICAL REACTION-DIFFUSION PHENOMENA IN A STANDARD CIRCUIT EDA ENVIRONMENT*, IEEE TRANSACTIONS ON CIRCUITS AND SYSTEMS. PART I, REGULAR PAPERS, VOLUME 99, JANUARY 2019. DOI: 10.1109/TCSI.2018.2885223

We are convinced that the proposed approach is relevant and of great interest to accelerate the design of biosensors and lab-on-chips. The next step is to include the term of convection in order to enable the modeling of continuous-flow lab-on-chips. The continuity of this activity is discussed in CHAPTER 3.

4. DESIGN AUTOMATION IN SYNTHETIC BIOLOGY

The ability to express biological models with HDL and SPICE also paves the way for the adaptation of Electronic Design Automation (EDA) workflow for synthetic biology.

4.1. SYNTHETIC BIOLOGY

Synthetic biology is a relatively recent field of investigation commonly defined as the application of engineering principles to biology. Basically, the aim of synthetic biology is to create and integrate into host cells artificial genes that do not exist in nature to provide them with a new biological function. The idea is not new since it has already been suggested in 1912 by Stéphane Leduc [Leduc, 1912]. Nevertheless, it took about 90 years to see the first concrete realizations [Elowitz and Leibler, 2000; Gardner, Cantor and Collins, 2000]. This emergence can be explained both by the progress made in biotechnologies (cloning, high throughput sequencing, micromanipulation, microfluidic ...) and by the creation of a dedicated research team made of researchers from biotechnology, chemistry, engineering science, mathematics and computer science. The application range of synthetic biology is very large, including therapeutics, the creation of innovative biomaterials, biosensors [Khalil and Collins, 2010; Kitney and Freemont, 2012; Peccoud and Isalan, 2012].

Today's innovation in synthetic biology is a multi-way crossroad. Efforts have been made in order to improve biotechnologies used for experimental aspects. In parallel, computational tools to facilitate the design process of these systems have been developed. Such tools are commonly called Biology Design Automation (BDA) or Genetic Design Automation (GDA), echoing Electronic Design Automation. Several GDA tools have already been developed around the concept of reusable genetic parts [Knight, 2003]. For instance, with GenoCAD [Czar, Cai and Peccoud, 2009], BioJADE [Goler, 2004] or TinkerCell [Chandran, Bergmann and Sauro, 2009], users can virtually assemble DNA parts picked up in a library and simulate the resulting construct. Even more interesting is the end-to-end workflow realized by Nielsen *et al*. It is composed of a suite of tools that starts from high-level specifications given in a specific language and that lead to DNA assembly that meets the requirements [Nielsen *et al.*, 2016].

In such a context, our idea was to evaluate the possibility to extend and/or adapt EDA tools in order to them applicable in biology.

4.2. DESIGN AUTOMATION AT BOOLEAN LEVEL OF ABSTRACTION

THE BOOLEAN ABSTRACTION OF GENE REGULATORY NETWORK

A Gene Regulatory Network (GRN) is a set of genes encoding for particular molecules and which expression is regulated by other molecules of the network. The biological toggle switch, which reaction diagram is represented in FIGURE 16, is an example of a GRN composed of 3 molecules (R1, R2 and GFP) and 3 regulations: one gene inhibited by R1 controls the production of R2, one gene inhibited by R2 controls the production of R1 and another gene inhibited by R1 controls the production of GFP.

Such a network can be analyzed in different ways. At the higher level of abstraction, so-called Boolean level, one considers that a gene can only be in two states: active or inactive. If at least one of the genes that encode for a given molecule is active, the molecule is in the *high* state. Otherwise, it is in the *low* state. Thus, a set of regulations can be interpreted as a Boolean function composed of elementary operators (AND, OR, NOT, NAND, NOR, etc). To illustrate the purpose, examples of genetic AND, OR and NOR gates are given in FIGURE 30.

THE TOOL

In electronics, the synthesis of Boolean or digital circuits from a high-level specification (*e.g.* truth table, conditional statement, process) can be automated with a digital synthesizer. These algorithms find the optimal circuit that matches the specification by minimizing a cost function that depends on

the complexity of elementary gates to implement, their performances but not on the underlying technology. Therefore, digital synthesizers can be directly reused in the context of GRNs. That is the idea of the GeNeDA environment (Gene Network Design Automation).

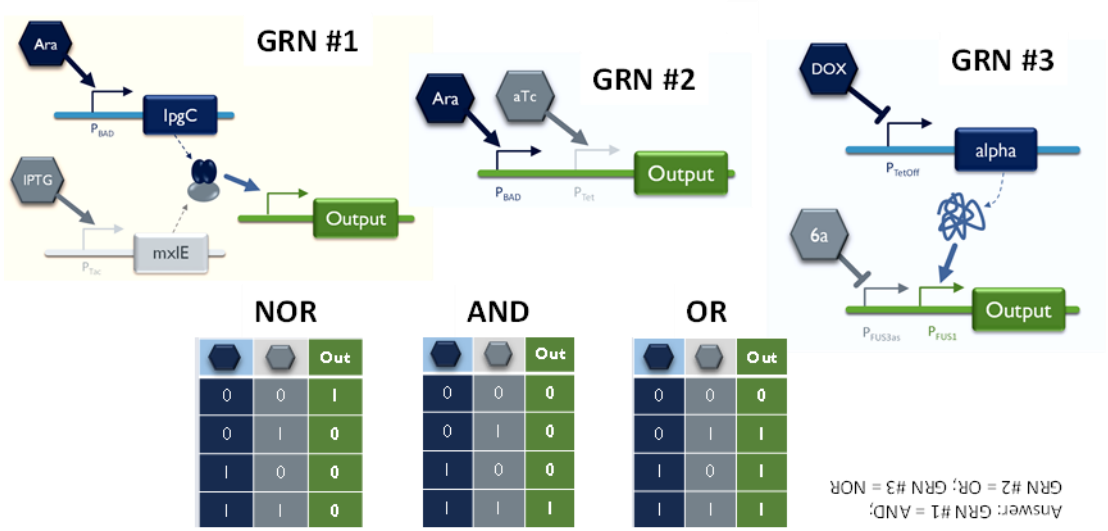

FIGURE 30 – BREAK TIME. ASSOCIATE EACH GRN TO ITS CORRESPONDING TRUTH TABLE.

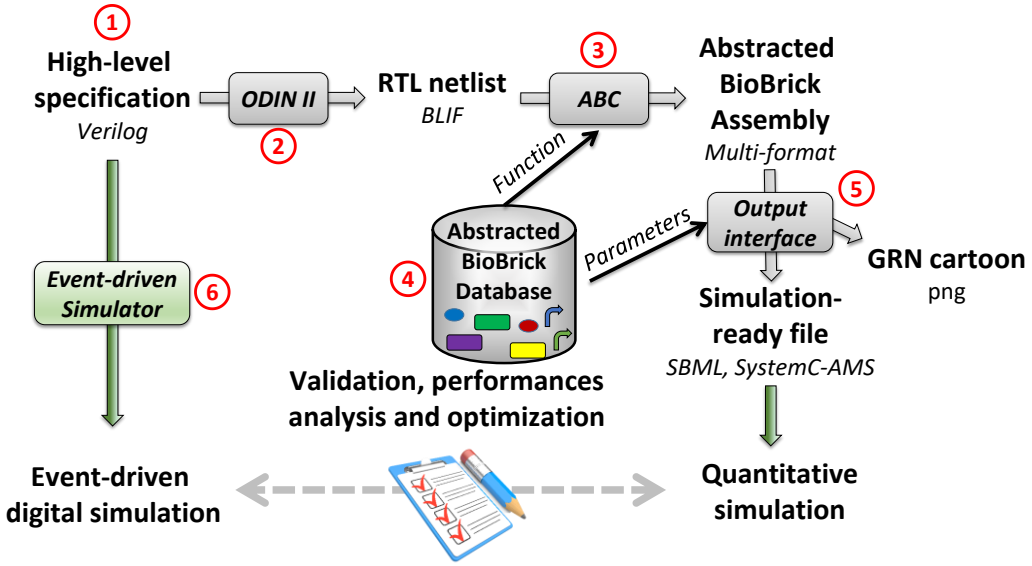

FIGURE 31 – OVERVIEW OF GENEDA FRAMEWORK.

GeNeDA is composed of six parts (FIGURE 31). The main function of each part is described in the following. More details are given in [Madec *et al.*, 2016].

1. The input interface used to specify the targeted Boolean function. The input could be a Verilog file or a Berkeley Logic Interchange Format (BLIF) netlist or simply a truth table;
2. ODIN II, an open-source digital synthesizer that interprets the input file and converts it into an RTL-Netlist, *i.e.* a list of elementary operators and registers [Jamieson *et al.*, 2010];
3. ABC, a circuit compiler, that picks up parts from a database of Boolean function achievable with a given technology and assemble them to meet the function of the RTL-Netlist. Most of the time, the solution is not unique and ABC evaluates a cost function to find the best solution;

4. The Genetic Part Library (GPL) which is the database described above. A Boolean function, a cost and the delay introduced in the circuit are attached to each part. In the current version of GeNeDA, five default GPLs have been implemented: GPL0 contains only the basic regulation scheme whereas GPL4 contains 15 regulation schemes with up to 4 regulations per gene. The cost of a part reflects the difficulty to construct an actual system. In default GPLs, costs have been affected to parts according to an empirical law that matches the following assumptions: i) the difficulty to realize get promoter increases exponentially with the number of regulations on it and ii) inhibition is more common than activation;
5. The output interface that writes the output of ABC in an exploitable file. Three files are generated: a description of the GRN in SBML, a SystemC-AMS model ready to simulate and a text file that can be given to PigeonCAD to draw the GRN [Bhatia and Densmore, 2013];
6. An event-driven simulator used to simulate the input specification and check its consistency.

RESULTS

We realized a benchmark of 8 circuits commonly met in digital electronics and 5 different GPLs. FIGURE 32 shows the result obtained for a 4-input AND gate with four different GPLs. All the synthesis results are given in the Supporting Information of [Madec *et al.*, 2016]. The main conclusions of this study on combinatorial circuits that deserve to be highlighted are the following:

- As expected, the complex (and thus expensive) parts added into library GPL3 and GPL4 are used sparingly in the designs;
- For the very simple Boolean function, the use of complex parts on the same promoter does not bring remarkable improvement with respect to the cost or the circuit delay;
- For more complex functions, GPLs with complex regulation schemes enable to cost delay reductions. For instance, a 25% cost and delay reduction can be reached for an 8-bit comparator between GPL0 and GPL4.

OUTCOMES

GeNeDA was, for us, a first experience in extending open-source EDA tools to the biological context. Investigations were made by two Ph.D. students: Yves Gendrault for the framework and the preliminary version and Elise Rosati for the development of realistic GPLs and the benchmark. This work was realized in partnership with Pr. François Pêcheux (Computer Science Laboratory Paris 6) and Pr. Jacques Haiech (Therapeutic Innovation Laboratory, Strasbourg).

Results on combinatorial circuits are encouraging and are published in the Journal of Computational Biology. They were also presented at two IEEE conferences. We also opened the question of the design of sequential systems and the scaling up to realize more complex digital functions. These points are discussed in CHAPTER 3 (Prospective Research).

> M. MADEC, F. PÊCHEUX, Y. GENDRAULT, E. ROSATI, C. LALLEMENT, J. HAIECH, *GENEDA: AN OPEN-SOURCE WORKFLOW FOR DESIGN AUTOMATION OF GENE REGULATORY NETWORKS INSPIRED FROM MICROELECTRONICS*, IN JOURNAL OF COMPUTATIONAL BIOLOGY, VOLUME 13, N° 6, JUNE 2016, DOI:10.1089/CMB.2015.0229

4.3. DESIGN AUTOMATION AT LOWER LEVELS OF ABSTRACTION

LIMITS OF THE BOOLEAN LEVEL OF ABSTRACTION

Boolean abstraction is a very rough approximation of how GRNs work. By opposition to digital electronics, the transition between states in the transfer function can be very smooth and the

threshold may change drastically from one gate to another. The propagation of this distortions may lead *in fine* to a behavior of the global system that is very different from what Boolean abstraction analysis predicts. Moreover, Boolean abstraction does not cover all the behavior encountered in synthetic biology. Basu's band-pass (cells in which a fluorescent protein is only expressed for the intermediate concentration of the input molecule) is a counter-example. Thus, it is often necessary to supplement the high-level design by a design at a lower level of abstraction.

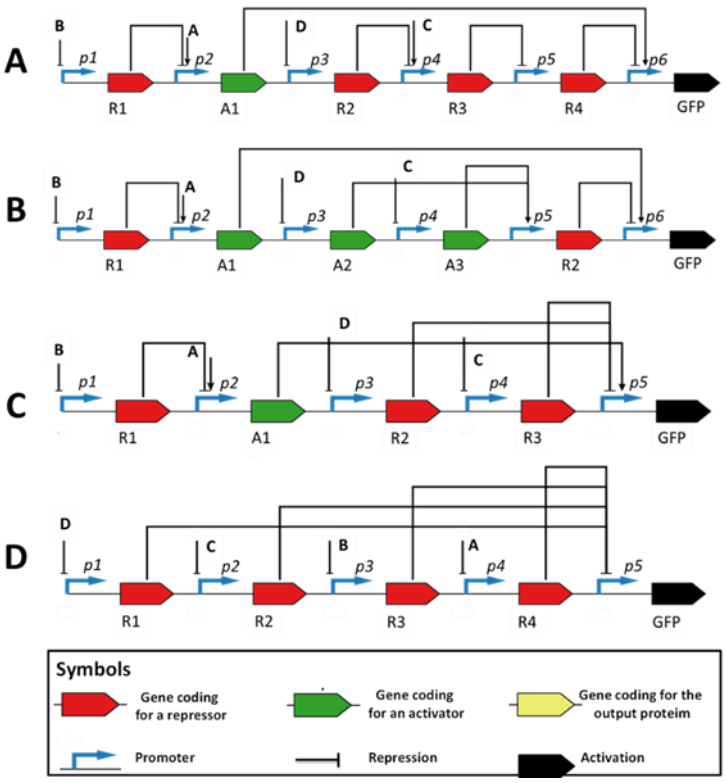

FIGURE 32 – SYNTHESIS RESULT FOR A 4-INPUT AND GATE OBTAINED WITH 4 DIFFERENT GPL. (A) GRN OBTAINED WITH THE BASIC GPL CONTAINS THE ONLY GENE WITH ONE POSITIVE AND ONE NEGATIVE REGULATION. 6 PROMOTERS ARE REQUIRED AND THE CRITICAL PATH (D-R2-R3-R4-GFP) IS 4. (B) GRN OBTAINED WITH THE SECOND GPL IN WHICH DOUBLE POSITIVE AND NEGATIVE REGULATION IS ALLOWED. THE CIRCUIT STILL HAS 6 PROMOTERS BUT THE CRITICAL PATH IS REDUCED TO 3 (D-A2-R2-GFP). (C) GRN OBTAINED WITH THE THIRD GPL IN WHICH TRIPLE REGULATION ARE ALLOWED. THE NUMBER OF THE PROMOTER IS REDUCED TO 5 AND THE CRITICAL PATH IS STILL 3 (B-R1-A1-GFP). (D) GRN OBTAINED WITH THE FOURTH GPL. THE NUMBER OF PROMOTERS IS THE SAME BUT THE CRITICAL PATH IS REDUCED TO 2 (D-R1-GFP).

FUZZY LOGIC

A way to improve the modeling of the behavior of the promoter/regulator interactions is to use multivalued logic. Multivalued logic introduces new intermediate states between the active and inactive states of a variable. It becomes therefore possible to distinguish different "NOT" behavior depending on the strength of the repressor and/or the steepness of the transition between active and inactive states.

We demonstrated in [Gendrault, Madec, Lemaire, *et al.*, 2014] the interest of fuzzy logic for the design of GRNs specified by a non-Boolean behavior (*e.g.* band-pass) and/or by a targeted dose-response curve rather than a simple Boolean function. Basically, we built a library composed of 6 variants of inverter and 36 variants of each 2-input gates. Up to now, an exhaustive research is performed over all the possible combinations. For each, the algorithm computes the dose-response curve for each

combination and ranks them as a function of the difference between targeted and obtained responses. More sophisticated optimization algorithms, including stochastic optimization algorithms, are still under consideration.

Genetic Programming for the Design of GRN

Design automation of GRNs at the analog level of abstraction is an issue very close to the analog synthesis in microelectronics. This topic has been widely investigated since the beginning of the 1980s and is still an open question. Among other methods, genetic programming gave outstanding results in some specific cases [Koza, 2003]. We tried to apply such an approach to GRNs design automation. Encouraging preliminary results was obtained on Basu's system. Starting from a blank page, the algorithm retrieves the architecture of the GRN as well as some properties on models parameters that have to be met in order to obtain the band-pass response.

Outcomes

This work was an opportunity to become familiar with new concepts such as fuzzy logic or deterministic and stochastic optimization algorithms. Results of these investigations have so far been published in international conferences (IEEE BioCAS and EvoStar). Up to now, they are however not advanced enough to be worth for a journal publication. Nevertheless, with this first experience, we have a better knowledge of the assets and the limitation of design automation algorithms and are therefore more comfortable to consider their application in other contexts.

5. Summary

In this chapter, we gave an overview of our projects on the adaptation of existing tools from the domain of electronics and engineering sciences to biology. GeNeDA and BB-SPICE are two mature tools that might be applied directly in synthetic biology or biosensors design projects. We also made the proof of concept for BB-SPICE 3D but the tool still deserves some improvements of the user interface and some optimization of the model of the elementary mesh. This could be the topic of a Master 2 internship project.

According to me, these investigations do not require any additional major academic effort (*e.g.* Ph.D. project). Armed with these tools and know-how, we are well set to go toward applications in collaboration with biologists. In 2015, I submitted an ANR project in collaboration with the Computer Science Laboratory (Paris 6), The Biotechnology and Cell Signaling laboratory (Strasbourg) and the Center for Developmental Biology (Toulouse) on the development of new cancer therapies by a better understanding and a control intracellular calcium signaling. Modeling, simulation and design automation were at the heart of this project. Unfortunately, this project was selected for the second round but not granted. Nevertheless, we have a couple of other ideas in mind within the same scope and for which we will look for project financing. They are described in the next part of the document.

PART TWO -
PROSPECTIVE RESEARCH

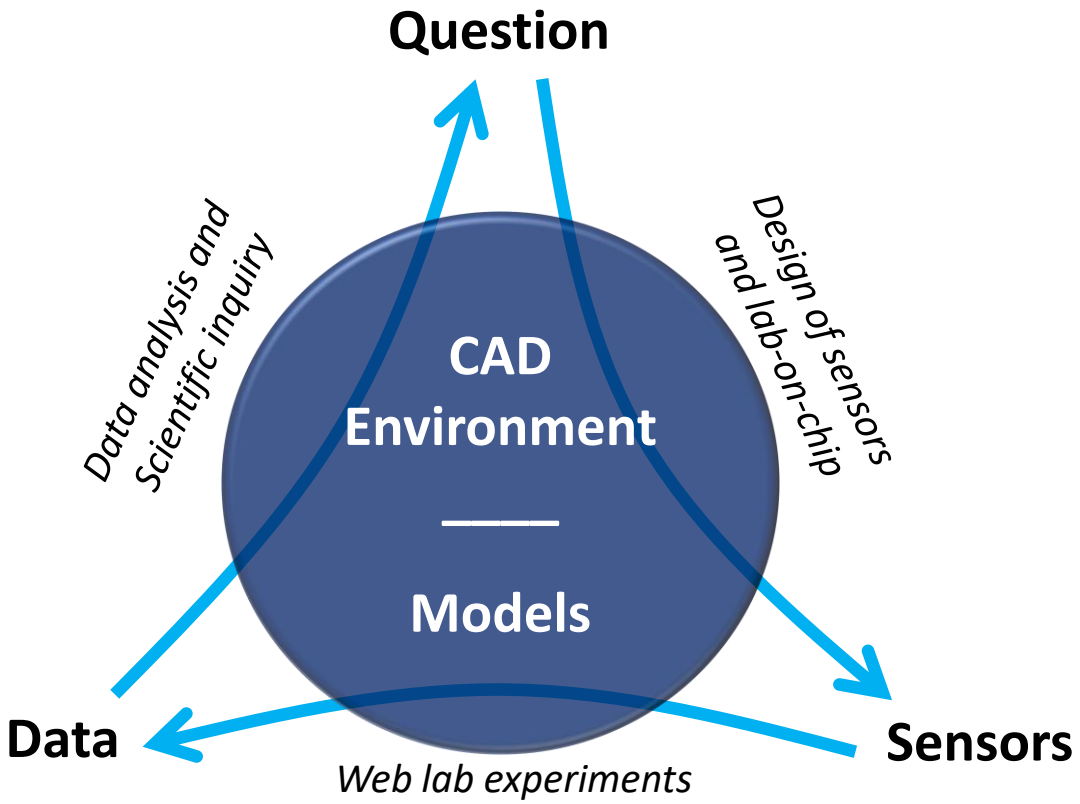

FIGURE 33 – RESEARCH CYCLE COMPOSED OF THREE STAGES: THE DATA ANALYSIS AND SCIENTIFIC INQUIRY THAT LEAD TO A SCIENTIFIC QUESTION, THE DESIGN OF SENSORS AND LAB-ON-CHIPS THAT LEAD TO MEASUREMENT DEVICES AND THE WET LAB EXPERIMENTS THAT PROVIDE NEW DATA. THIS CYCLE CAN BE EFFICIENTLY SUPPORTED BY MODELING AND A DEDICATED CAD TOOLS ENVIRONMENT.

My mid-term goal is to drive or to participate in projects aiming at providing the biologists with innovative software and hardware tools that would enable a better understanding of life. For that purpose, the dual skills acquired in electronics and systems' engineering on the one hand and biology and biotechnologies on the other hand, are two major assets. Outlooks described in this part settle in with the research cycle described in FIGURE 33. It is composed of three stages: i) the inquiry phase which consists of the analysis of existing data in order to drive new scientific questions; ii) the design phase including the setting of the experimental plan and the development of associated measurement devices and iii) the experimental phase during which wet-lab experiments that generate new data are performed. The three cornerstones of such a cycle are the scientific questions, the sensors and the experimental data.

To strengthen this cycle, we aim at creating a dedicated computer-aided design environment which will cover the three stages of the cycle. This environment would encompass tools that already exist (CHAPTER 2) and tools that have to be developed. The environment is completed by a database of models for the building blocks of the different interacting domain (electronics, biology, microfluidics, thermal physics …) and at different levels of abstraction. During the inquiry phase, simulation on existing models, behavioral prediction and *in silico* hypothesis validation will be enabled by the CAD environment. During the design phase, the CAD environment will provide the designer with efficient virtual prototypes of measurement devices, just as an electronic design automation tool does in the context of purely electronic systems. Finally, during the experimental phase, models and CAD tools will facilitate the exploitation of experimental data.

More details on these outlooks are given in the two next chapters. In CHAPTER 3, the focus is put on the CAD environment. First, we will describe some tools that still need to be developed in order to increase the scope of our environment in the domain of synthetic biology, system biology and/or biosensors design. Then, some potential applications of the environment on actual cases are given. They correspond to the inquiry phase and the experimental phase of the diagram described in FIGURE 33. CHAPTER 4 deals with the design phase. It describes several projects focusing on the realization of innovative measurement devices for biological and biochemical applications. Three main kinds of sensors will be considered: µNMR-based sensor, impedance spectroscopy and whole-cell sensors.

CHAPTER 3 – CAD TOOLS

1. SYNTHETIC BIOLOGY

1.1. POSTTRANSCRIPTIONAL REGULATION CIRCUITS

DEFINITION

Up to recently, synthetic biology efforts for the engineering of artificial regulatory circuits have focused mainly on protein-DNA interaction. Circuits achieved logical operations [Anderson, Voigt and Arkin, 2007], oscillator [Elowitz and Leibler, 2000] or toggle switch [Gardner, Cantor and Collins, 2000]. In such systems, the expression of genes is controlled by the presence of other proteins. More details are given in CHAPTER 2 SECTION 4. As these regulations increase or reduce the transcription rate of DNA into mRNA, they are called transcriptional regulation.

However, there are other ways to regulate proteins synthesis. For instance, translation of the mRNA into proteins can be controlled. In this case, the transcription of DNA into mRNA occurs without regulation. This kind of regulation is called post-transcriptional regulation. Different mechanisms exist to perform such regulation [Isaacs, Dwyer and Collins, 2006]. Riboswitches are probably the most common ones. They consist of an mRNA sequence, namely the upstream regulating sequence, put before the coding sequence. Riboswitches can be in two configurations: the off state in which mRNA is in a hairpin-shaped configuration (thus, the ribosome binding site is not accessible) and the on state in which mRNA strand is unfolded (thus, the coding sequence can be translated). Small molecules serve as a trigger to switch from one state to the other [Hermann and Patel, 2000].

Another approach consists in using small RNA stands (typ. 21-30 nucleotides) which sequences are complementary of the target mRNA. Thus, they bind on the target mRNA which becomes inoperative or is sometimes degraded. There are two kinds of small RNAs that operate roughly in the same way: the small interfering RNAs (siRNAs) and the micro RNAs (miRNAs) [Zamore and Haley, 2005]. These molecules are naturally synthesized by living organisms. They have been identified for different species and listed in databases such as miRBase [Griffiths-Jones *et al.*, 2007].

APPLICATIONS

siRNA or miRNA can be combined with artificial gene regulatory network (GRN) to realize a Boolean function. In 2007, *Rinaudo et al.* demonstrated a complex 5-input Boolean function realized in human kidney cells by combining artificial genes, natural siRNA and small molecules that establish inhibitory links with the siRNA [Rinaudo *et al.*, 2007]. With a very similar approach, *Xie et al.* realized a cell classifier. An artificial GRN realizes a Boolean function depending on six endogenous miRNAs. The output, a fluorescent protein, is active if the combination of miRNAs inside the cell matches a predetermined pattern which is typical of the HeLa cervical cancer cell line [Xie *et al.*, 2011]. More recently, *Miki et al.* developed artificial miRNA switches for the detection and the purification of the cell population [Miki *et al.*, 2015].

Compared to transcriptional regulation, post-transcriptional regulation exhibits several assets:

- They exhibit a reduced response time. Indeed, the switching time from one state to the other is only limited by the miRNA/mRNA binding time and the activation/inactivation time of the mRNA

translation process. Unlike for circuits based on transcriptional regulation, the transcription process is always active [Miyamoto *et al.*, 2013];

- They are much easier to interface with natural regulation networks. Adding a posttranscriptional regulation consists in inserting a non-coding RNA sequence before or after the coding sequence of a natural gene [Kobayashi *et al.*, 2004];
- siRNAs/miRNAs are much more numerous than the transcription factors used in standard GRNs. Moreover, they are more specific. It is thus more convenient to find a set of orthogonal miRNAs in order to reduce the risk of cross-talk between regulations [Rinaudo *et al.*, 2007].

Objective

The posttranscriptional regulatory circuits described in the last subsection were designed by hand. Although *in sillico* automated design of posttranscriptional regulatory circuits seems quite feasible, to our knowledge, there is no tool performing this operation. Thus, we aim at developing a design automation tool for posttranscriptional regulatory circuits. This work will be highly inspired by the tool we already developed for transcriptional GRNs (Chapter 2 Section 4.2). Our strategy is described in the following.

First and foremost, we need to identify the set of Boolean functions that can be achieved by miRNA-based regulatory networks. In the first instance, we take inspiration from the circuits described in [Rinaudo *et al.*, 2007] and [Xie *et al.*, 2011]. An example is depicted in Figure 34. Then, two strategies will be considered. We can reuse GeNeDA framework [Madec *et al.*, 2016] and define a library of functions identified hereabove. However, we may face two major issues. First, the establishment of an exhaustive list of accessible functions to put on the library will be very difficult: the number of possible combinations is much higher than for conventional GRNs. Second, GeNeDA is programmed to provide a unique solution for a given Boolean equation. For that purpose, a cost function is associated with each part of the library in order to sort equivalent part assemblies and suggest only the less expensive. In the case of GRNs, the cost of a part is directly related to the number of genes and transcription factor it requires. Here, fixing the cost for each operator seems much more dubious.

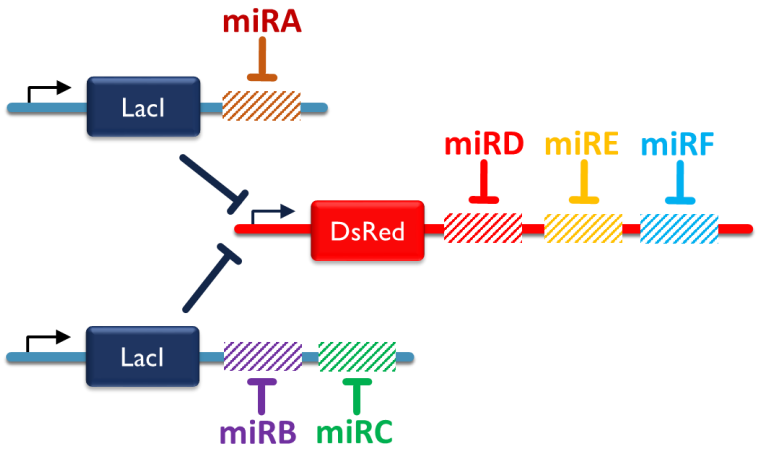

Figure 34 – miRNA-based regulatory network performing the Boolean function *DrRed* = *miRA* ∧ (*miRB* ∨ *miRC*) ∧ NOT(*miRD* ∨ *miRE* ∨ *miRF*). On the top gene, On the top left gene, LacI is produced if miRA is not present. On the bottom left gene, LacI is produced when miRB and miRC are absent. Finally, on the right gene, DsRed is produced if neither miRD, nor miRE nor miRF are present and if upstream LacI synthesis is inhibited. Inspired by [Xie *et al.*, 2011].

Consequently, the development of a tool dedicated to this application seems more appropriate. The algorithm will combine formal methods used for the synthesis of combinatorial circuits (*e.g.* Shannon decomposition, Quinn-McCluskey algorithm, etc) as well as stochastic optimization algorithms to provide multiple variants for each given targeted Boolean function, which is of great interest from a biological perspective. Finally, it can also be relevant to add links with existing miRNA databases, such as [Griffiths-Jones *et al.*, 2007] in order to provide constructions with actual gene and miRNA instead of an abstracted one.

The design of the software is a short-term project that can be proposed as a Master thesis or integrated into a larger academic Ph.D. work. Experimental validations of the networks suggested by the tool would also be very exciting. However, this is a much more ambitious project which can only be considered in collaboration with a partner able to conduct wet lab experiments.

1.2. Design of Sequential GRNs

Definition

Most of the Boolean GRNs that have been demonstrated over the last two decades performed combinatorial function, *i.e.* function for which the state of the output depends only on the input combination [Nikolayeva *et al.*, 2007; Zhou, Arugula and Halamek, 2009; Tamsir, Tabor and Voigt, 2011; Ausländer *et al.*, 2012; Miyamoto *et al.*, 2013]. However, sophisticated digital functions that can be found in electronic systems (such as automata, calculators or processors) require the realization of sequential function*, i.e.* a function for which the output depends both on the input combination and on the current state of the system. They are represented as a closed-loop system (Figure 35A) with feedback composed of Boolean variable encoding the state of the system. Among systems that exhibit sequential behavior, the toggle switch is very famous for being the first synthetic GRN in 2000, together with the repressilator [Gardner, Cantor and Collins, 2000]. This system is depicted in Figure 35B. It is composed of two constructs, each of them being composed of a negatively regulated promoter and a gene that codes for a molecule that plays the role of a repressor for the other promoter. The system has two stable steady states: one with the first gene being expressed while the second is inhibited and a second state with the opposite configuration. The switch from one state to the other is triggered by the release of the negative feedback by an external stimulus (input).

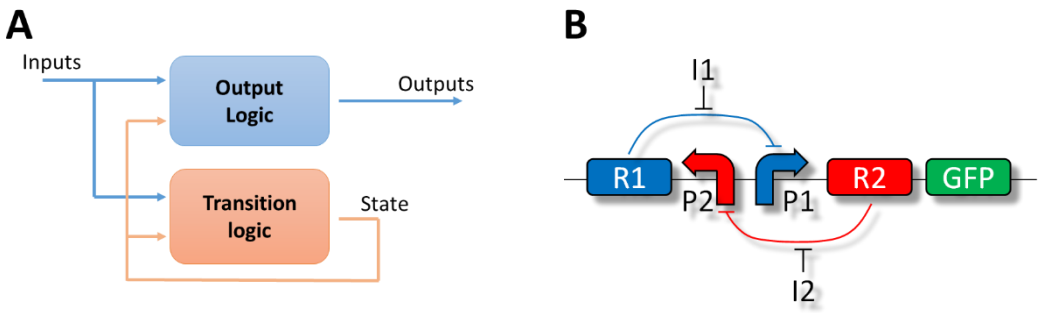

Figure 35 – Sequential gene regulatory networks. (A) A generic representation of sequential digital systems. The "Output logic" computes the output of the system as a function of the inputs and internal signals that codes for the current state of the system. The "Transition logic" computes the next state of the system as a function of the current one and the inputs. (B) is the cartoon of the toggle switch designed by Gardner *et al.* in 2000. Promoters P1 and P2 are respectively repressed by protein R1 and R2. I1 and I2 are two inputs capable of inhibition release. GFP (green fluorescent protein) is a reporter. Inspired by [Gardner, Cantor and Collins, 2000]

The design of sequential GRNs is still an active research topic. Sequential bio-circuits have been demonstrated using transcriptional or posttranscriptional regulations [Benenson, 2012] or protein-protein interactions (DNA origami) [Padirac, Fujii and Rondelez, 2012]. More recently, in a review, Lin *et al*. formalized a biological control unit, the first step toward a synthetic bio-computer [Lin, Kuo and Li, 2018].

Asynchronous Sequential Functions and Limitations

Basically, a sequential system is described by a flow graph composed of states and transitions between states. Regardless of the way the system is implemented, a sequential system is ruled by two kinds of Boolean equations: the equation of the output logic that gives the output as a function of the input and the current state and the equation of the transition logic that gives the next state as a function of the current one and the input. Several algorithms exist to derive these Boolean equations from the flow graph, the most common one being the Huffman's method [Micheli, 1994]. GeNeDA can be then used on these equations to obtain the appropriate GRN. We already performed this approach on several examples and simulated the dynamics of the resulting GRN [Goerlich *et al.*, 2018].

However, this study also highlights the limitations of this approach. One is inherent to the method itself and is a well-known issue of asynchronous sequential systems called critical races. It occurs when multiple bits encoding for the state change simultaneously during a transition. If one bit switches before the other (which is always the case on an actual circuit), the system goes through an unexpected intermediate state. Another one is more specific to sequential GRNs. Sequential circuits are very sensitive to the steepness of the transitions, which is smoother in genetic circuits than in electronic ones. Smooth and noisy transitions also cause malfunctions in GRNs. This has been demonstrated in simulation for with a single internal variable (no risk of critical races). It is much more marked for a multiple-variable system without any risk of critical race. [Goerlich *et al.*, 2018]

In microelectronics, two alternatives have been investigated to overpass such limitations. The first one, and also the most common one, consists in synchronizing the transitions. It is discussed in the next subsection. The second one relies on recent theories in the design methodologies of robust asynchronous controllers and processors in electronics [Cortadella *et al.*, 2002]. For a given function, the asynchronous approach often requires a lower number of gates compared to the synchronous one. Thus asynchronous approach deserves to be investigated in the biological context.

Design of Synchronous Biological Systems

Synchronous sequential circuits exhibit the same closed-loop architectures as asynchronous ones FIGURE 35A, except that the feedback of internal variables to the input of the system is synchronized by an external signal, *i.e.* the clock. The synchronization device is called a flip-flop or a register. Thus, the realization of a biological register is a prerequisite for the construction of synchronous sequential GRNs. This is a tricky challenge which has not been deeply addressed in the literature. In 2012, Hoteit *et al.* [Hoteit, Kharma and Varin, 2012] suggested a GRN which is a direct transposition of the master-slave architecture used in electronics [Paul Horowitz and Hill, 1989]. The GRN is large (7 promoters and involves 10 regulating proteins). They suggest using light as a clock signal and light-induced promoters. The system has only be validated in simulation. Recently, another approach has been proposed by Lin *et al*. [Lin, Kuo and Li, 2018]. The complexity is comparable to Hoteit's construct but in this work, the clock signal is realized by posttranscriptional regulation.

The realization of automata, even with a very small number of states, requires several registers. Integrating such an amount of artificial gene in a single cell seems unrealistic, even considering the evolution of synthetic biology technologies in the near future. Moreover, each register should be realized with an orthogonal set of promoters and transcription factors in order to avoid crosstalk. Thus, alternatives have to be explored. On the one hand, we suggested a more compact architecture of register in [Rosati *et al.*, 2015]. Basic simulations have been made in order to validate the concept but a deeper investigation has to be made to improve the stability of the construct. On the other hand, a common strategy to realize large GRNs is to split the circuit into independent sub-circuits, integrate each sub-circuit in a single cell and connect cells using a natural or an artificial cell-to-cell communication mechanism, such as quorum sensing [Waters and Bassler, 2005]. Such a technique reduces the quantity of artificial gene that has to be inserted in a single cell, reduces the risk of crosstalk and allow the reuse the same promoter and/or transcription factors on the different part of the system. This approach has already been demonstrated experimentally. FIGURE 36 depicts two examples: a 2-input XOR gate [Tamsir, Tabor and Voigt, 2011] or a 2-to-1 multiplexer [Regot *et al.*, 2011].

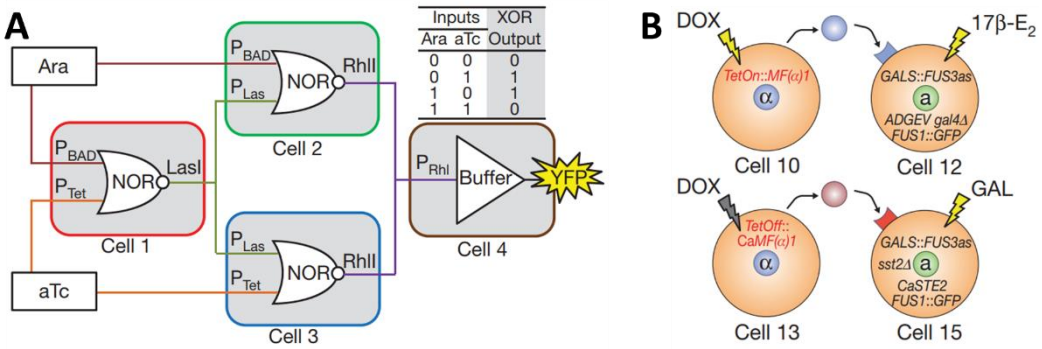

FIGURE 36 – TWO EXAMPLES OF MULTI-CELL GRNS. (A) IS AN XOR GATE FROM [TAMSIR, TABOR AND VOIGT, 2011]. IT IS COMPOSED OF 4 DIFFERENT CELLS. THE EQUATION OF EACH CELL IS RESPECTIVELY *LASI* = NOT(*ARA* V *ATC*) FOR CELL 1, $RHLI_2$ = NOT(*ARA* V *LASI*) FOR CELL 2, $RHLI_3$ = NOT(*ATC* V *LASI*) FOR CELL 3 AND *YFP* = $RHLI_2$ + $RHLI_3$ FOR CELL 4. COMBINING EQUATIONS TOGETHER LEADS TO *YFP* = *ARA* XOR *ATC*. (B) IS A 2-TO-1 MULTIPLEXER FROM [REGOT *ET AL.*, 2011]. IT IS ALSO COMPOSED OF 4 DIFFERENT CELLS. CELL 10 AND 13 RESPONDS TO DOXYCYCLINE (DOX) AND PRODUCES RESPECTIVELY THE BLUE MOLECULE (PHEROMONE FROM *S. CEREVISAE*) WHEN DOX IS PRESENT AND THE RED MOLECULE (PHEROMONE FROM *C. ALBICANS*) WHEN DOX IS ABSENT. CELL 12 SYNTHESIZES GPF WHEN BOTH THE BLUE MOLECULE AND OESTRADIOL (17B-E_2) ARE PRESENT. CELL 15 SYNTHESIZE GFP WHEN BOTH THE RED MOLECULE AND GALACTOSE (GAL) ARE PRESENT. FINALLY, THE EQUATION OF THE COMPLETE SYSTEM IS *GFP* = (*BLUE* ∧ $17BE_2$) V (*RED* ∧ *GAL*) = (*DOX* ∧ $17BE_2$) V (NOT(DOX) ∧ *GAL*), THE EQUATION OF A MULTIPLEXER WITH DOX AS THE SELECTION INPUT.

1.3. TOWARDS BIOLOGICAL PROGRAMMABLE LOGIC DEVICES

In digital electronics, a programmable logic device (PLD) is a digital circuit which architecture can be configured in order to achieve a wide range of complex digital functions. Electronic PLDs are composed of a large set (from 1,000 to 1,000,000) of logic blocks that can be connected to each other. Each block can achieve any Boolean function of 4 inputs and include a register that can be connected at the output of the block. PLDs have been a major breakthrough for digital electronics in the early 1980s, giving users the ability to perform very complex logic functions with a single generic circuit.

Considering the available technologies for the realization of Boolean functions in synthetic biology, the transposition of the concept of PLD to biology seems realistic. The requirements for a BioPLD are the following:

- A unique architecture that can realize a large set of combinatorial Boolean functions. This can be achieved for instance by posttranscriptional regulation (see SECTION 1.1. and FIGURE 34);
- A mechanism for cell configuration (*i.e.* fixing the Boolean function achieved by the cell). For this part, the DNA strand displacement technique seems to be a good candidate. It provides irreversible configuration but uses molecules that are not likely to interact with the miRNA or other transcription factors [Qian and Winfree, 2011]. Integrases would also be another interesting option [Benenson, 2013];
- A mechanism for controlled cell-to-cell communication. Such a mechanism has already been demonstrated (see FIGURE 36). Moreover, Billerbeck *et al*. recently demonstrated the possibility of high-order scalable and tunable cell-to-cell communication topologies realized with peptide/G-protein-coupled receptors [Billerbeck *et al.*, 2018];
- A register inside each BioPLD. This point has already been discussed in SECTION 1.3;
- The ability for the consortium of cells to share the clock signal. Coupling oscillators in a multi-cellular network have already been demonstrated [Fernández-Niño *et al.*, 2017]. Nevertheless, it is often based on *quorum sensing* mechanisms, which is also used for cell-to-cell communication. On the other hand, an optical clock signal used with light-induced promoters [Shimizu-Sato *et al.*, 2002] can also be used to distribute synchronously the clock to all the cells.

2. FROM SYNTHETIC BIOLOGY TO SYSTEM BIOLOGY

2.1. SYSTEM BIOLOGY

The modeling, simulation and computer-aided design tools described in CHAPTER 2 have primarily been developed for applications in synthetic biology. However, they may also be applied in the field of system biology. Synthetic biology is the engineering of new artificial biological constructs that do not exist in nature and that produce a response that meets a specification given *a priori*. System biology aims at understanding and establishing theoretical models of complex biological systems from experimental data. In other words, it consists in figuring out what could be the biological constructs that natively exist inside a cell and that produces an observed response. Thus, from a computational perspective, both sciences share the same tools (FIGURE 37).

Applications of our computational tools developed for synthetic biology in the field of system biology also deserves to be investigated. This was one of the objectives of the 6-month sabbatical for research (CRCT) I made at the Center for Biological Signaling Studies (BIOSS, Freiburg, Germany). Within this context, I started an investigation on the mechanism of pathogens (e.g *Pseudomonas aeruginosa)* invasion in mammalian host cells. The project is described in SUBSECTION 2.2. Moreover, the immersion in the laboratory also allowed me to identify other issues for which modeling and simulation can be very helpful. Some of them are listed in SUBSECTION 2.3.

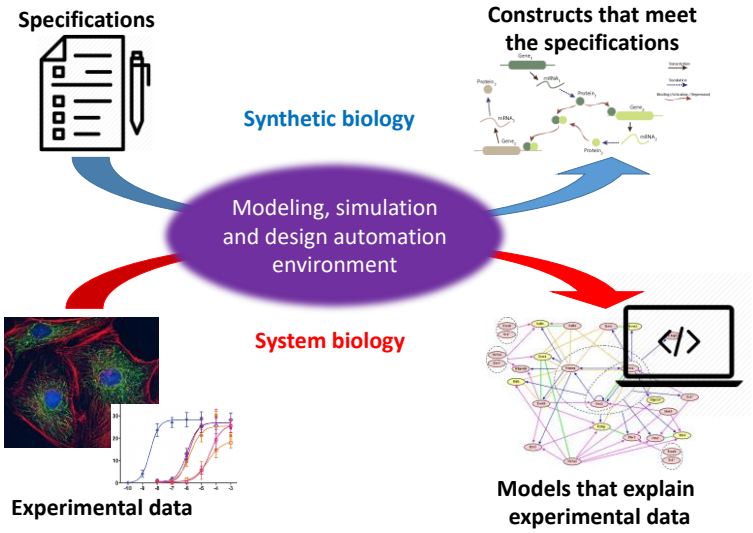

FIGURE 37 – THE COMMON FRAMEWORK OF THE SYSTEM AND SYNTHETIC BIOLOGY

2.2. *P. AERUGINOSA* INVASION MECHANISMS

CONTEXT

Pseudomonas aeruginosa (PA) is a multi-resistant pathogen able to infect a wide range of hosts such as insects, plants, animals, and humans. Although not very virulent in healthy individuals, they can cause severe infections for people who suffer from immunodeficiency diseases (cancers, AIDS, serious burn victims, etc.). According to statistics published by the French National Institute of Health and Medical Research (INSERM) in 2015, PA is responsible of 8,4% of the nosocomial infections, which ranks it third behind *Escherichia coli* (26%) and *Staphylococcus aureus* [Lucet, no date]. Moreover, PA is the main cause of mortality in cystic fibrosis [Mulcahy *et al.*, 2008].

PA are seldom alone in a biological environment. Most of the time, they join together in the extracellular matrix to form biofilms. This biofilm protects the bacteria and gives them the ability to strongly adhere to another cell (host cells). Thus, removing such bacteria out of infected patients is a big challenge. Most of the time the biofilm coexist with host cells for a long time without infection. However, sometimes, PA become virulent and start to invade host cells, leading to severe symptoms such as respiratory deficiencies. Given this context, the goal of our project is to combine experiment and modeling in order to better understand the environmental factors that trigger the invasion process.

NEW MODELS FOR QUORUM SENSING, BIOFILM FORMATION, ADHERENCE AND INVASION

Invasion of PA has been investigated for years. It is a very complex mechanism that depends on several factors. Some of them depend on the bacteria environment, some are controlled by the bacteria themselves. Quorum sensing (QS) is one of the first mechanism that comes into play. QS is a cell-to-cell communication process allowing bacteria to sense their density in a medium. QS has first been reported in 1970 by Nealson *et al.* on a bioluminescent marine bacteria, *V. fisheri* [Nealson, Platt and Hastings, 1970]. Two QSs systems have been identified in PA: the *Las* system and the *Rhl* systems. They seem to operate in parallel (QS still occurs when one of the two systems is knocked down) but are interdependent [Latifi *et al.*, 1996]. QS regulates several mechanisms, including the one that is involved in invasion [Lazdunski, Ventre and Sturgis, 2004].

A large number of genes, molecules, and regulatory mechanisms are involved in QS but most of them are not yet fully understood. Thus, most of existing QS models are primarily phenomenological models. J. Perez-Velazquez *et al.* made a review of the most common modeling approaches used over the last 10 years [Pérez-Velázquez, Gölgeli and García-Contreras, 2016]. *P. aeruginosa* QS mechanisms can be described in 0-D by a regulatory network [Dockery and Keener, 2001]. It is depicted in FIGURE 38 and can be simulated with BB-SPICE (SEE CHAPTER 2 SECTION 2). Moreover, QS is often linked to biofilm formation. In this case, vertical growth [Chopp *et al.*, 2002] and/or lateral growth [Ward *et al.*, 2004] of the biofilm, as well as molecules and cells displacement inside the biofilm, are taken into account. Thus, the model is composed of 1-D or 2-D partial differential equations (PDE), which keeps them compatible with the extended version of BB-SPICE.

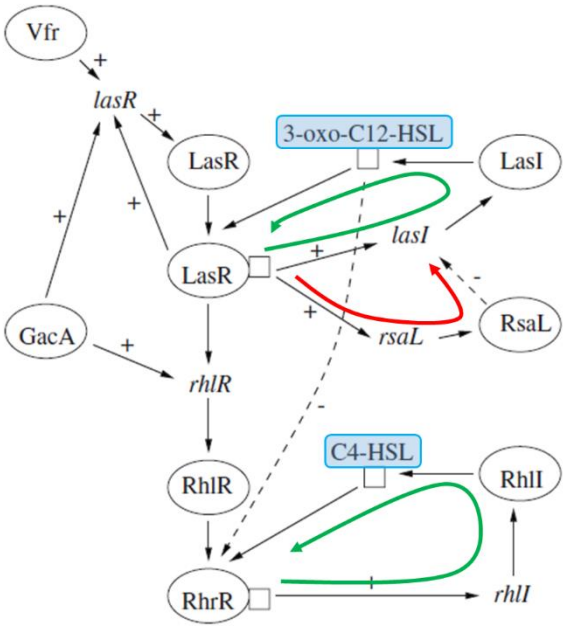

FIGURE 38 – REGULATORY NETWORK OF THE QUORUM SENSING IN *PSEUDOMONAS AERUGINOSA*, FROM [DOCKERY AND KEENER, 2001]. IN BLUE, THE TWO HOMOSERINE LACTONES THAT ARE INVOLVED IN BOTH QS SYSTEMS (3-OXO-C12-HSL IN THE LAS SYSTEM AND C4-HSL IN THE RHL SYSTEM). IN GREEN, THE TWO POSITIVE FEEDBACK LOOPS ASSOCIATED WITH EACH SYSTEM THAT LEADS TO A HIGH CONCENTRATION OF HSL WHEN THE NUMBER OF BACTERIA IS HIGH. IN RED, NEGATIVE CONTROL OF THE CONCENTRATION OF HSL ASSOCIATED WITH THE LAS SYSTEM.

The models described hereabove have been developed for open systems. However, it has been demonstrated that the behavior of QS and biofilm formation highly depends on the substrate [Janakiraman *et al.*, 2009]. To our knowledge, models coupling QS, biofilm formation, adhesion and invasion of host cells do not exist yet. Relying on published data and experiments realized in partnership with the BIOSS, we aim at investigating in this way. In particular, we will enrich existing models with new mechanisms involving molecules that play a key role in the invasion process, such as lectins [Eierhoff *et al.*, 2014].

MODELS TO IMPROVE EXPLOITATION OF EXPERIMENTAL RESULTS

The study of invasion requires a high throughput way to measure invasion efficiency. For that purpose, the BIOSS developed an automated method based on optical detection. The set-up is described in FIGURE 39. The assay is made in two 96-wells plates in parallel. For both plates, host cells are first exposed to bacteria during the incubation time. Second, plate B is washed in order to remove extra

bacteria and culture medium. Third, host cells are lysed and bacteria that invaded the cell are released. At this stage, the invasion ratio can be obtained by comparing the number of bacteria in plate A and B. These numbers are evaluated by measuring the optical density after allowing the bacteria to grow enough to be detected.

One experiment provides the transient evolution of the optical density (OD) measured for each well. Data processing consists in retrieving the initial population from the growth curve. The most common way to do that is to compute the time required to reach a given OD value, also called time to detection (TTD). It has been demonstrated that a linear relationship exists between this time and the decimal logarithm of the initial number of bacteria [Mytilinaios *et al.*, 2012], thus, the invasion ratio is the difference between the TTD measured for a given experimental condition on the plate A and on the plate B. To reduce the impact of noise, the same method can be applied for different OD in order to have several estimations of the invasion ratio.

We compared the results provided by this method with the one obtained with a manual assay. Both experiments exhibit the same trend, *i.e.* a decrease of the invasion ratio with the density of bacteria, but the calculated ratio differs. This needs to be more deeply investigated. For that purpose, we first have to find an appropriate growth model that fits with experimental conditions. The TTD processing algorithm relies on Baranyi's growth models [Baranyi and Roberts, 1994], which is simple enough to be manipulated analytically. However, our design environment enables the manipulation of more complex models, even if they do not have closed-form solutions. Thus, more sophisticated models, such as the Gompertz's model [Lo, 2007], can be explored. Then, this growth model will be used to explore and check the robustness of new processing algorithms.

As the first step inside this project, we already developed another algorithm that exploits the exponential phase of the growth curve. Up to now, these new methods give results comparable to those obtained with the multiple TTD method.

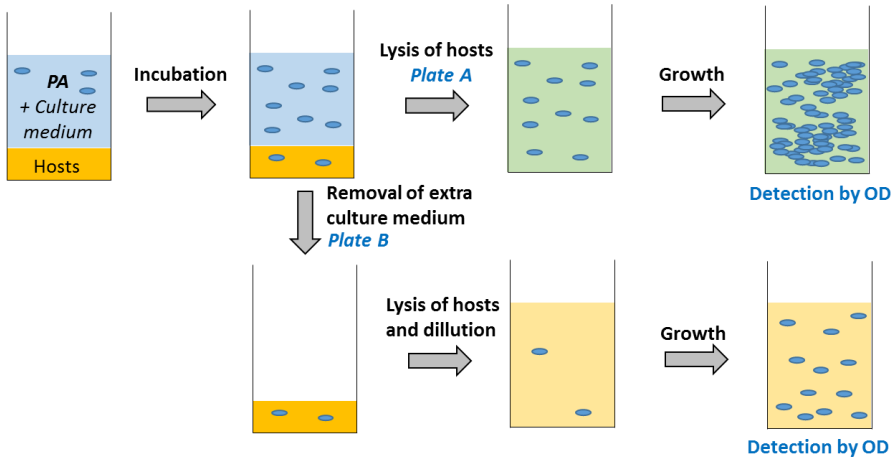

FIGURE 39 – DESCRIPTION OF THE AUTOMATED INVASION MEASUREMENT SET-UP.

2.3. OTHER OUTLOOKS

My stay at the BIOSS was also an opportunity to identify and to start investigations on other topics for which our know-how would be of great interest. The main research topic of Winfried Romer's team is the interaction between pathogens and host cells, and more specifically on adhesion, cytoskeleton

remodeling and cellular uptake. They mostly work on the experimental part and have facilities to carry a wide range of assay to study the factors that have an impact on this phenomenon. Our know-how on modeling and simulation could offer an alternative and complementary way to tackle these problematics.

In the meantime, we are also trying to establish partnerships with the laboratory of Biotechnology and Cell Signaling (BCS) of the University of Strasbourg and the Institute of Genetics and Molecular and Cell Biology (IGBMC) in Strasbourg. This BCS is composed of 7 research teams aim at decoding cell signaling pathways and at developing new strategies for therapeutics. The IGBMC involves 52 research teams conducting research on various topics, ranging from structural analysis of proteins to human genetics, stem cells, biophysics, and epigenetics. As for the BIOSS, our experience and our modeling and simulation tools can complete their know-how to tackle very ambitions open biological questions. Moreover, their building is located on the same campus as ICube, which should undoubtedly facilitate discussions and collaboration.

3. CAD TOOLS FOR THE DESIGN OF BIOSENSORS AND LAB-ON-CHIP

3.1. OBJECTIVE

Biosensors are analytical devices that combine one or several physicochemical detection methods in order to measure biological signals. These devices are composed of three main parts: (i) a biological front-end that is used to transform a targeted biological signal into a measurable signal, (ii) a transducer that converts this signal into an electrical signal and (iii) an electronic back-end that computes this raw electrical signal to give an exploitable measurement. The signals of interest are various: molecular or cell concentration, molecular or cell localization, neuron activity, cell size or shape, physicochemical properties such as pH, etc. Most of the time, biosensors are combined with a microfluidic circuit that controls the delivery of reactants and mixes them in reaction chambers with controlled properties, leading to autonomous measurement devices called lab-on-chip (LOC). In addition to biology, electronics, and microfluidics, other domains of physics can be involved in such devices: optics, thermal physics, etc.

The democratization of biosensors and lab-on-chips has been possible thanks to the improvement and the standardization of manufacturing technologies on the one hand and the development of computer-aided design tools able to handle such multi-physic devices on the other hand. We already demonstrated the ability to model and simulate lab-on-chip with the EDA tools. Now, we would like to go further by developing a complete CAD environment for the design of biosensors and lab-on-chip similar to the one that exists for integrated circuits in microelectronics. In our opinion, such a tool would be a stepping stone for scaling-up systems in this domain.

3.2. STATE OF THE ART

The dream for such a tool is not new and many approaches have already been explored. The four main pillars of such a tool would be the same as in the EDA environment. That is to say:

- A human-readable and computer-friendly language that can be used for the description of the system at different levels of abstraction whatever the domain;
- A simulation environment which encompasses the different domains (electronic, biology, microfluidic and other physics);

- A database of plug-and-play models of the most common parts of a lab-on-chip (biochemical reaction, microfluidics circuits, transducers);
- Algorithms for the optimization and/or the automated generation of every part of the system.

Hardware Description Languages for Lab-on-chips

The question of the formalization and the standardization of the description of biological protocols have been addressed since the beginning of this century. BioStream is a pioneer in this domain [Thies *et al.*, 2008]. The software offers the designer a way to describe a protocol as a sequence of fluid manipulation. BioStream also includes a simulator for *in silico* validation of the protocol.

More recently, BioCoder, an extension of BioStream has been released [Ananthanarayanan and Thies, 2010]. A BioCoder description starts with a list of fluids, solids, and containers used in the protocol. Then, the user describes step-by-step the protocol using dedicated configurable functions such as *inoculate()*, *centrifuge()*, *store()*, *mix(),* etc. The BioCoder description is then compiled in order to check its consistency, to provide a textual description of the protocol in a standard and unambiguous way, to list the required material and/or to give a representation of the protocol as a block diagram.

Within the same approach, AquaCore can also be mentioned [Amin *et al.*, 2007]. AquaCore' philosophy is inspired by the assembly language for microprocessors. It assumes the existence of a virtual generic lab-on-chip that can perform a set of elementary fluidic operations such as mixing, transporting fluids, storing, heating, etc. A protocol is described as a sequence of elementary instruction. This approach is interesting but it relies on the existence of such a generic lab-on-chip, which, up-to-now, only exists *in silico*. Moreover, as it is the case for assembler in microelectronics, the language is attached to specific hardware. Thus, it is not suitable for the description of custom devices.

The Microfluidic Hardware Description Language (MHDL) introduced by McDaniel in 2013 uses a different approach [McDaniel, Curtis and Brisk, 2013]. With MHDL, the focus is put on the chip architecture rather than on the assay protocol. Thus, MHDL and BioCoder are very complementary and their coupling offers a high-level specification environment going from the assay to the physical layout of the associated lab-on-chip [McDaniel, Grover and Brisk, 2017]. With the same order of idea, Densmore *et al*. developed recently MINT (MIcrofluidic NetlisT format), which is another hardware description language dedicated to microfluidic circuits [Sanka *et al.*, 2016]. MINT language is very close to VHDL-AMS (probably due to the electrical engineering background of their developers), except that primitives are microfluidics blocks (terminal, channel, mixer, valve, etc) instead of electronic ones. The CAD framework is completed with Fluigi, another software that handles MINT description [Huang and Densmore, 2014]. This environment mostly targets the design of microfluidics chips for assays in synthetic biology.

Modeling and Simulation Environment

The modeling and simulation of LOCs have to be considered at two different levels. At the level of a single device, model composed of PDEs (Navier-Stokes) is used. Such models are simulated with numerical methods such as the finite element method. Commercial solutions exist to establish and simulate such models. COMSOL [Comsol, 2019], Fluent [Ansys, 2019] or Coventor [Coventor, 2019] are the most commonly used. Open-sources alternatives, such as FreeFEM++ or Feel++ also exist [Hecht, 2012; Prud'homme *et al.*, 2012]. Such an approach provides simulation results very close to the actual behavior of the microfluidic devices. Thus, it is suitable for the design and the optimization of a single device [Jeon and Shin, 2009; Hashim, Diyana and Adam, 2012; Das, Biswas and Das, 2014; Lei, Hill and

Glynne-Jones, 2014]. In return, they would lead to prohibitive computation times at the level of complete systems.

At the level of a complete system, LOCs can be modeled as an assembly of an elementary device connected by microfluidics wires. The modeling and simulation of microfluidic chips with HDL used in microelectronics has already been demonstrated [Voigt, Schrag and Wachutka, 1998]. They are based on the analogy that exists between electrical Kirchhoff's law and microfluidic in static laminar flows. Within the same scope Habib *et al.* model a complete microfluidic device performing a polymerase chain reaction (PCR) with an open-source HDL, *i.e.* SystemC-AMS [Habib and Pecheux, 2010]. In 2007, Wang *et al*. present an environment for the simulation of LoC based on a plug-and-play assembly of microfluidics circuit behavioral models [Wang, Lin and Mukherjee, 2006]. The library of parts included basic fluidic functions (channels, straight passive mixers, intersections, etc) but also more sophisticated functions such as electrophoresis. Models of parts consist of input-output relationships between flows and pressures. Moreover, concentration profiles in the perpendicular direction to the flow might also be required in the case of mixers and intersections. Models have been implemented in Verilog-A and validated, at the level of the system, with experimental data in some two use cases: micro-mixing and electrophoresis separation. In a later paper, they also integrated some basic biochemical models within this environment [Wang *et al.*, 2007].

Design Kits

In microelectronics, design kits are databases of devices and part of circuits. They contain mathematical models as well as blueprints for their manufacturing. Most of the time, they are provided by foundries and bridges the gap between on-computer design and on-silicon realization.

Regarding LOCs, a design kit would be composed of biological parts, microfluidic part, transducers, and electronic parts. For microfluidic and electronics devices, such a library already exists. For transducers, the design kit does not exist but can be partially created by gathering existing models that have been published in the literature. Some examples are listed in TABLE 1. Making a design kit for biochemistry would be trickier because, most of the time, the involved reaction depends on the assay. Nevertheless, a list of common biological mechanisms can still be drawn. Among others, this would include enzyme-linked immunosorbent assay (ELISA) tests, PCR, bacterial growth, enzymatic reaction, antigen-antibody binding, etc.

Design Automation Algorithms

Generally speaking, design automation (DA) algorithms take as an input a description of the system and produces the blueprint for its manufacturing. Regarding microfluidics, two main categories of circuits have to be distinguished: digital microfluidics and continuous microfluidics. On the one hand, digital microfluidic chips are composed of a glass plate and an array of electrodes and manipulate droplets containing reactants. They can be moved by electrical fields created by the electrodes and/or mixed to induce reactions and analyzed. Most of the time, the architecture of such a device is fixed and the design automation of the process consists in computing the most appropriate pulse sequence to realize the assay given as a specification [Grissom and Brisk, 2012; Ting-Wei Chiang, Chia-Hung Liu and Juinn-Dar Huang, 2013].

On the other hand, in continuous microfluidics, displacements and mixing of reactants are made by continuous flow driven channels, valves and pumps. The layout of a given circuit is adapted to the assay to realize. Thus, DA for continuous microfluidics is much more challenging than for digital one.

The rare example of a workflow that can be found in the literature relies on the following strategy. The system is decomposed in flow layers, *i.e.* the microfluidics channels and a control layer, *i.e.* fluid control devices such as valves, pumps, flowmeters, etc. For the second layer, Amin *et al* developed Micado in 2009 [Amin, Thies and Amarasinghe, 2009]. This software infers the valves to be implemented in a microfluidic circuit in order to meet a requirement given as ISA and provide an AutoCAD schematics of the multilayer soft lithography mask required to manufacture the chip. The problematic for the first layer is very similar to the one of the placement and routing on electronic devices on a printed circuit board. *Simulated annealing* seems to be the most common algorithm used to automate such task [McDaniel, Parker and Brisk, 2014].

TABLE 1 – EXISTING MODELS FOR THE MOST COMMON TRANSDUCERS USED IN LAB-ON-CHIPS

Transducer	Type of model	Related publication
Ion-sensitive field-effect Transistor	Compact (SPICE)	[Kaisti, Zhang and Levon, 2017]
FET-based transistors	Compact (SPICE)	[Fernandes *et al.*, 2012]
Surface acoustic wave (SAW)	Numerical (COMSOL)	[Ten *et al.*, 2016]
Surface acoustic wave (SAW)	Transmission line	[Gaso Rocha *et al.*, 2013]
Electrical models of cells (impedencemetry)	Complex Impedence	[Xu *et al.*, 2016]
Integrated optoelectronic devices (photodiode, silicon photomultiplier, single-photon avalanche, laser diode)	Compact (SPICE)	[Zappa *et al.*, 2009] [Marano *et al.*, 2013] [Ravezzi *et al.*, 2000] [Plantier, Bes and Bosch, 2005]
Microcantilever	Numerical (FEM)	[Goericke and King, 2008]
Microcantilever	Compact model (SPICE)	[Chowdhury, Ahmadi and Miller, 2005]

3.3. OUR IDEA

The state-of-the-art highlights that the DA of LOC is not yet mature. Despite some attempts, there is no software that established itself as a standard, except for the multiphysics simulation at the level of a single device. In this context, our goal is to provide a single modeling and simulation environment enabling the mixing of the different domain of the physics different levels of abstraction. We already demonstrated such an approach for space-dependent bio-chemical systems (CHAPTER 2 SUBSECTION 2.5) or earlier in the team on the electrothermal simulation of integrated circuits [Krencker *et al.*, 2014]. Our idea will be to extend the existing tool to a new domain, *i.e.* the microfluidics. By this way, four domains will be supported by the tool: electronics, biology, microfluidics, and thermal physics. The current version of the simulator is able to simulate together multiphysics 2-D/3-D models solved by the finite difference method and 0-D models. We identified several features to implement in the future versions of this tool.

Practically, we identified several tasks for this project:

- We have to develop the design kit of 0-D models for biosensors and LOCs. For electronics and biology, such models already exist. For transducers, some models have already been established and we have a good experience in compact modeling of multiphysics sensors. The 0-D modeling of microfluidics looks trickier. Results of existing works, *e.g.* [Voigt, Schrag and Wachutka, 1998] could be reinvested but some challenges still need to be overcome: finer modeling of complex structures,

integration of inhomogeneity of fluid and on the concentration profile of molecules in solution, the effect of the temperature, etc;

- Regarding the 2-D/3-D models, we already have a model of thermal diffusion (Fourier's law) as well as a model of diffusion for molecules in a solution (Fick's law). To be complete, the equations of fluid dynamics in microfluidic channels should also be implemented. Numerical resolution of Navier-Stokes equations looks more difficult than the resolution of convection-diffusion equations. Thus this task seems too hazardous and could be useless if we consider only systems in a continuous flow, *i.e.* systems for which the local pressures and fluid velocity vector does not change during the simulation. Thus, this is not a priority;
- The interface between 0-D models and 2-D/3-D models needs to be improved. Up to now, the connection of 0-D model nodes on the lattice used for the 2-D/3-D model (CHAPTER 2 SUBSECTION 3.2) is performed manually in a very naive and intuitive way. Such an interface has to be better formalized and automated;
- Up to now, the discretization scheme used to solve the PDEs is the finite difference method applied to cubes. Alternative methods have to be studied. For instance, it has been already demonstrated that finite element method can also be implemented as electronic equivalents circuits [Jia Tzer Hsu and Vu-Quoc, 1996]. The interest of such a method has to be evaluated and put in the contract with the increase of computation time it induces;

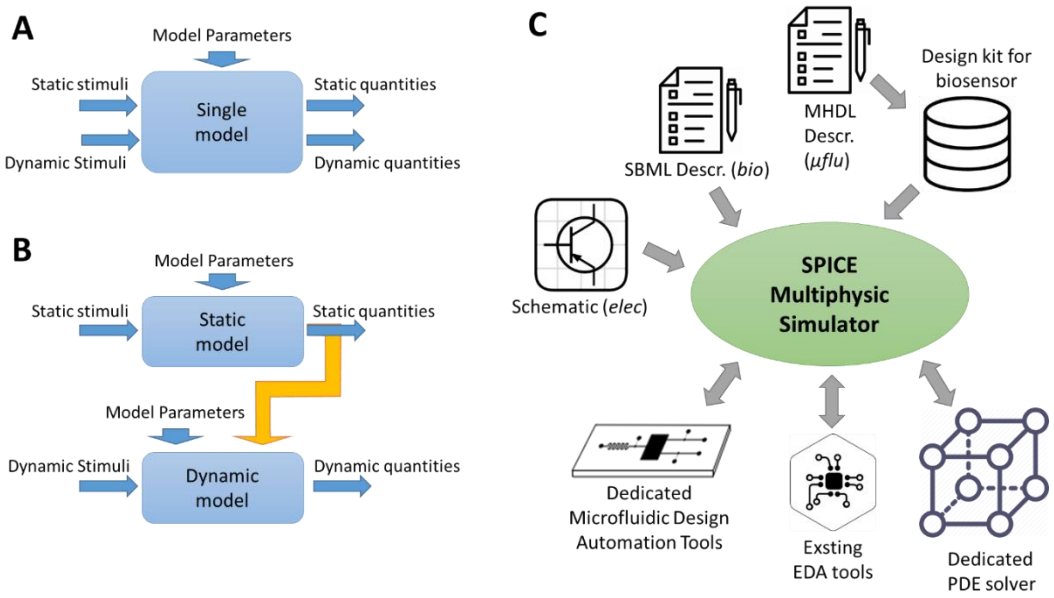

FIGURE 40 – (A) AND (B) ILLUSTRATES THE MAIN DIFFERENCES BETWEEN THE DIRECT METHOD AND RELAXATION METHOD TO SOLVE MULTI-DOMAIN PDE. IN THE DIRECT METHOD (A), ALL EQUATION ARE SOLVED TOGETHER AND IN DYNAMIC. IN THE RELAXATION METHOD (B), STATIC MODELS ARE COMPUTED FIRST AND SIMULATION RESULTS ARE INTEGRATED INTO THE DYNAMIC MODEL AS PARAMETERS. (C) IS A REPRESENTATION OF THE COMPLETE ENVIRONMENT WITH THE SPICE MULTIPHYSICS SIMULATOR AT THE HEART, TRANSLATORS FOR ELECTRICAL SCHEMATICS, BIOLOGICAL DESCRIPTIONS (*E.G.* SBML), MICROFLUIDIC CIRCUITS DESCRIPTIONS (*E.G.* MHDL), A DESIGN KIT FOR BIOSENSORS AND LAB-ON-CHIPS AND INTERFACES WITH DEDICATED PDE SOLVERS, WITH EXISTING EDA TOOLS AND WITH DEDICATED MICROFLUIDIC DESIGN AUTOMATION TOOLS.

- The direct coupling between 2-D/3-D models and 0-D models and/or between different physics is not always required. Replacing this direct method by a relaxation method (FIGURE 40A) whenever possible and appropriate would reduce dramatically the computation time. The simulation of static quantities can be performed with SPICE, but it is probably not the most efficient way to solve such

equations. Open source alternatives exist, such as Free++ [Hecht, 2012] or Feel++ [Prud'homme *et al.*, 2012]. In the first version of the tool, one of these simulators would be used to perform the simulation of static quantities. Results of this simulation will then be used as an input parameter for the SPICE simulation. Then, using open-source SPICE simulator and finite element solvers, we could consider a direct coupling between both simulators, with NgSPICE in charge of OD models and Feel++ or FreeFEM in charge of the 2D/3D models. Such a coupling is by no means obvious and would require important development time, but could be worthy.

This simulator can eventually be at the heart of a complete virtual prototyping environment (FIGURE 40B). It would be completed by existing design assistance or automation tools based on the one described above. Moreover, even if the design constraints are not exactly the same in microfluidics and microelectronics [McDaniel, Grover and Brisk, 2017], having SPICE as unique simulator paves the way to the extension of EDA tools. For instance, place-and-route algorithms used in both domain are very closed [McDaniel, Parker and Brisk, 2014].

4. SUMMARY

Several prospectives on the development of the use of CAD tools dedicated to biological applications was described. Regarding applications in synthetic biology, our background in the design of digital circuits and our experience in synthetic biology give us the required knowledge to identify problematics and to offer solutions. In particular, an issue which is well-known in synthetic biology is the standardization at all level: standardization of the building blocks (biological devices), standardization of the interconnections, standardization of the description, the modeling and the simulation tools, standardization of the interface between the dry and the wet lab, etc. I am convinced that efforts of standardization made by the electronics since 1970 have been one of the main assets that gave momentum to this technology. I cannot state that the model of electronics can be directly transferred to synthetic biology but we observed trends moving in that direction since the last decade. My double background gives us the credibility to advance our ideas in this domain. The projects I described could be realized during a Master thesis and/or can be integrated into an academic Ph.D. project. However, it would be much more motivating to integrate them into a more complete and ambitious project going from the formalization of the problem to the realization of experimental proofs of concept. For that purpose, a collaboration with research teams in the field of experimental synthetic biology and cell signaling is required.

Applications in system biology will put us in a direct collaboration with biologists on very specific problematics. Again, my double background highly facilitates such partnership. Such works could also highlight the limitations of our tools and, more generally speaking, the system-level modeling in biology. In return, this approach would provide the biology community with new perspectives. The simulation helps in the formalization and the validation of hypotheses, in the prediction of the system's behavior and in the implementation of new experimental plans. My 6-month sabbatical at the BIOSS convinced me of the richness of such work. Moreover, being in direct contact with experimental aspects of biology allows me to identify critical biological signals to monitor in an experimental process. Here again, this part is not to be considered as a project itself, but as a part of a bigger project addressing a biological question.

Finally, the development of the CAD tools for the design of biosensors and LOCs is probably the project with the higher applicative potential. Here, we are convinced that the scale-up of such technology will be sooner or later limited by the absence of formalized and standardized tool. The know-how required for this work matches perfectly with our background, and more generally the experience acquired by our research team over the last 20 years. Nowadays, this project is still one the exploratory phase and results are expected at intermediate-term. An academic Ph.D. student is already working on the integration of microfluidics in the existing simulator. In addition, another Ph.D. student with a mathematics and computer science background would also be necessary to release the complete CAD environment described in FIGURE 40.

CHAPTER 4 – MULTIPHYSICS SENSORS

1. MINIATURIZED NMR

1.1. STATE-OF-THE-ART

THE PRINCIPLE OF NUCLEAR MAGNETIC RESONANCE SPECTROSCOPY

Nuclear Magnetic Resonance (NMR) spectroscopy is a common technique used for the analysis of the composition of the matter since decades. The principle of NMR is the following. A sample under analysis is submitted to a large constant magnetic field B_0. Magnetic nuclear spins of atoms align themselves within the direction of this field. Then, a weak transverse oscillating magnetic field is applied. The so-called RF pulse disturbs the spin alignment. After the pulse, spins turn back in their initial alignment in a precession trajectory. The electromagnetic wave emitted by the spin during this process is measured by a detection coil. The oscillation frequency of this electromagnetic wave corresponds to the Larmor's frequency of the nucleus. However, in molecules, spin-to-spin interactions occur between neighbour atoms, which slightly shift the precession frequency. Thus, the spectrum of the measured signal reveals several peaks around the Larmor frequency. Their distribution and height form a unique signature which enables molecular identification and quantification.

NMR has multiple applications in chemistry and structural biology [Jacobsen, 2007]. However, the application range of standard NMR systems is limited by its lack of mobility (size of the device, high power supply, necessity cryogenic coolant for the superconductor magnet). *In vivo* biochemical signaling, tissue analysis, *in situ* sample analysis or on-line quality control on industrial production lines are, for instance, excluded. Moreover, the cost of the instrument and the associated consumable is also prohibitive. To expend the application range of NMR, miniaturization of the magnet and the associated electronics has been considered since the last two decades [Zalesskiy *et al.*, 2014].

NMR MINIATURIZATION: SENSITIVITY AND RESOLUTION

The two main challenges of NMR miniaturization are the reduction of the magnet size and the integration of the probe. Both tend to reduce the sensitivity and the resolution. The sensitivity is defined as the density of nuclei in the sample required to obtain a signal that emerges from background noise. Besides, the resolution quantifies the ability of the system to distinguish between two consecutive peaks in the spectrum (and, thus, the ability to distinguish several species in the solution). Basically, during the NMR readout, the time-domain NMR signal is given by:

$$s(t) = s_0 \cdot e^{\frac{t}{T_2^*}} \cdot e^{i \cdot \omega_0 \cdot t} \qquad \text{Eq. 7}$$

where T_2^* the relaxation time, ω_0 is the Larmor frequency and s_0 the amplitude of the signal received by the coil. This signal depends itself on the Larmor frequency of the molecule ω_0, the magnetization of the spin M_0 (proportional to the B_0 field), the unitary field B_u of the coil (*i.e.* the field produced by a 1A current flowing in the coil), the sample volume V_s and the nutation angle:

$$s_0 = \omega_0 \cdot M_0 \cdot B_u \cdot V_s \cdot sin(\theta) \qquad \text{Eq. 8}$$

Most of the time, the NMR signal analysis is performed in the frequency domain. The sensitivity is related to the signal-to-noise (SNR) ratio, which can be approximated as the following expression [Grisi, 2017]:

$$\mathrm{SNR_f} = \frac{\mathrm{s_0}}{n_{sd}} \cdot \sqrt{\frac{T_2^*}{2}} \qquad \text{Eq. 9}$$

where n_{sd} is the noise spectral density of the readout circuitry. The metric commonly used to quantify sensitivity is the limit of detection (LOD) defined in term of number of spins as following [Grisi, 2017]

$$LOD = 3 \cdot \frac{N_{spins}}{SNR_f} \qquad \text{Eq. 10}$$

where N_{spins} is the number of spins to be detected in the experiment. On the other hand, the resolution is often given in ppm of the Larmor frequency and mostly depends on the homogeneity of the B_0 field and the quality of the quantization electronics. A resolution of 1 ppm at 42.5 MHz (Larmor frequency of ^{1}H at 1 Tesla) means that a frequency shift of at least 42.5 Hz is required in order to distinguish between two peaks in the spectrum.

State-of-the-art

Reduction of magnet size can be achieved by replacing helium-cooled superconductor magnets by small rare-earth permanent magnets. The price to pay is a decrease of the amplitude of the magnetic field and thus, according to equation Eq. 8, a reduction of the sensitivity. Moreover, if B_0 becomes less homogeneous inside the sample volume, the Larmor frequency is slightly different for each molecule depending on their location. The consequence is a widening of peaks in the spectrum and, in turn, a decrease of the resolution. Nevertheless, tiny magnets assemblies, based on Halbach structures [Halbach, 1980], have already exhibited acceptable performances (1T magnetic field with a 0.1 ppm homogeneity inside a volume which corresponds to standard 5-mm NRM tubes) [Zalesskiy *et al.*, 2014].

Besides, the coil size fixes both V_s and B_u. The ideal case is when the coil draws a measurement area that perfectly matches with the sample volume. The first integrated NMR micro-probe composed of a planar coil deposited on a gallium arsenide substrate has been demonstrated in 1994 [Peck *et al.*, 1994]. Since then, other devices have been designed. Most of them integrated the micro-coil and the emission and reception circuitry within the same chip. The integration of micro-coil also enabled to design new kinds of device, such as capillaries [Norcross *et al.*, 2010] in which samples flow and around which coils are wrapped or lab-on-chips [Trumbull *et al.*, 2000]. Integrated micro-coils are very small and can thus be easily duplicated within the same ship in order to obtain microprobes arrays used for NMR imagery or for multi-nuclei measurement [Keil and Wald, 2013].

Coupling small permanent magnets and microprobes lead to integrated spectrometers exhibiting resolutions down to 0.1 ppm. For example, McDowell *et al.* developed a sub-kilogram 1T spectrometer with a spectral resolution of 0.24 ppm in a single shot [McDowell and Fukushima, 2008] (Figure 41A). In 2011, Sun *et al.* developed a 100 g NMR-based sensor including a 0.56 T magnet capable of measuring very low concentrations of avidin in water (1 molecule among 6,108 water molecules) [Sun *et al.*, 2011] (Figure 41B). Roughly at the same time, Anders *et al.* from EPFL (Switzerland) designed also a CMOS chip in a 0.35µm technology with an array of eight planar micro-coils featuring underneath eight co-integrated amplifying channels based on a low-noise amplifier [Anders *et al.*, 2009] (Figure 41C to Figure 41E). Their spectral resolution was about 1 ppm. An analysis of existing of mass-limited NPR microprobes is given in [Badilita *et al.*, 2012]. The state-of-the-art has been completed with more recent publications in [Grisi, 2017]. It turns out that the limit of detection for 1 µL sample is between 10 and 1000 $\mathrm{nmol}/\sqrt{\mathrm{Hz}}$ and the resolution is between 0.01 and 1 ppm.

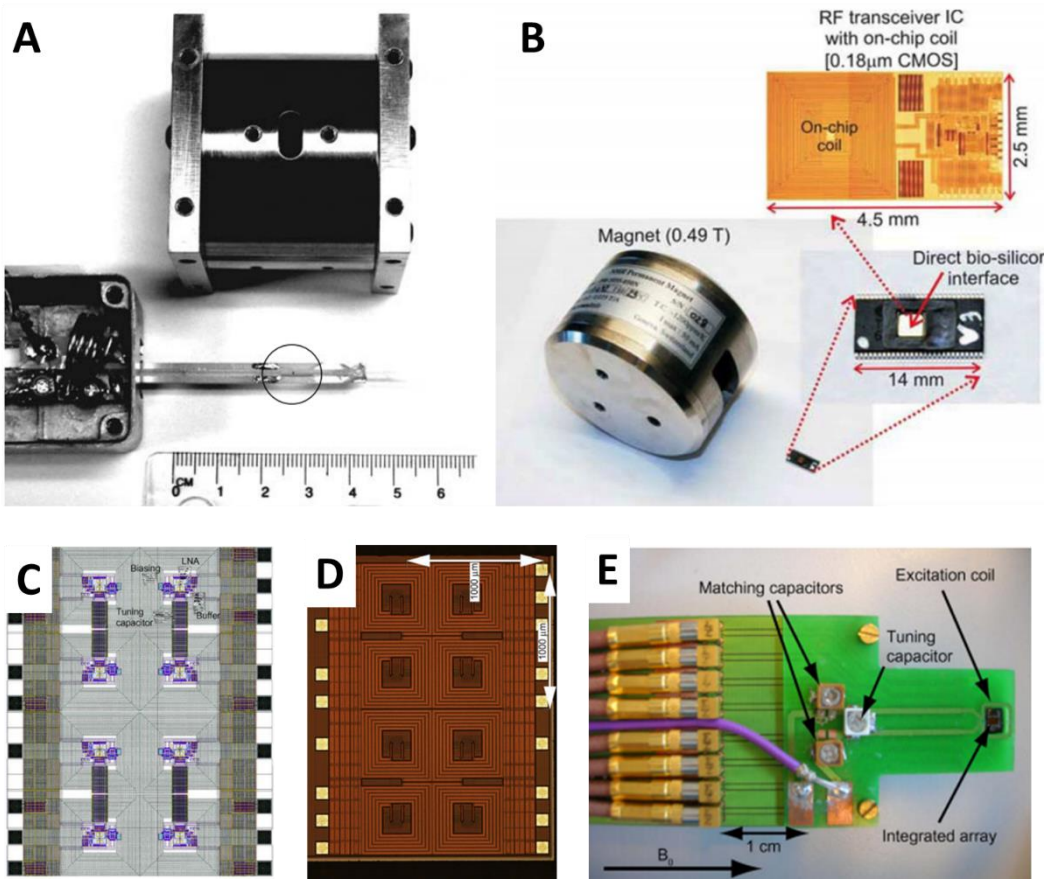

FIGURE 41 – EXAMPLES OF REALIZATION OF µNMR SYSTEMS. (A) IS A PHOTOGRAPH OF THE MAGNET AND THE MICROPROBE (IN THE BLACK CIRCLE) USED BY [MCDOWELL AND FUKUSHIMA, 2008] FOR THEIR SUB-KILOGRAM 1T SPECTROMETER. (B) IS A PHOTOGRAPH OF THE MAGNET AND THE INTEGRATED CIRCUIT USED BY [SUN *ET AL.*, 2011] FOR THE DEVELOPMENT OF A 100-G SPECTROMETER. (C) IS THE LAYOUT OF THE INTEGRATED CIRCUIT REALIZED BY [ANDERS *ET AL.*, 2009]. THE 8 ANALOG FRONT-END CHAINS FOR EACH CHANNEL CAN BE EASILY IDENTIFIED. (D) IS THE MICROGRAPH OF THE SAME DEVICE ON WHICH THE 8 COILS ARE VISIBLE. FINALLY, (E) IS A PHOTO OF THE INTEGRATED CIRCUIT MOUNTED ON AN 8-CHANNEL PRINTED CIRCUIT BOARD.

The resolution achieved by miniaturized NMR system integrating permanent magnet is not high enough to enable standard NMR spectroscopy on an unknown sample. However, quantifying known molecules with a relatively high concentration in a sample seems achievable. Thus, µNMR have to be considered as a potential candidate for the design of biochemical sensors. Our team has started investigations on the design of such sensors since a couple of years. We are coordinating the IvMRS project (ANR-16-CE19-0002) [Agence Nationale de la Recherche, 2016]. This project aims at designing the first chronically implantable smart µNMR probe able to monitor over several months the cerebral metabolites for normal aging and for Alzheimer's disease animal models. Coupling the encouraging preliminary results we get, our know-how on the design of application-specific integrated circuits (ASIC), our experience on applications at the interface with biochemistry and the modeling and simulation environment described in CHAPTER 2 paves the way for the development of integrated biochemical measuring instruments based on this technology. Two examples, which correspond to projects submitted for grant applications, are described in the following.

1.2. Detection of Pollutant in Drinking Water

Goal

This project consists in realizing an integrated system for the monitoring of several pollutants in drinking water. The main goal is to increase the number and the frequency of water quality controls and to reduce the time to decisions, two major challenges for public health. The focus is put on chemical pollution, *i.e.* detection of microbial or bacterial contamination is not considered. The key features for such a measurement device are:

- the autonomy, both from an electrical and a chemical perspective (reactants, buffers, etc);
- the reliability and the sensitivity (no false negative, avoidance to false positives ...);
- the ability to cover a large spectrum of pollutants;
- the price which has to be reasonable to consider a large-scale deployment.

State-of-the-art and Strategy

Several technologies have already been investigated to detect chemical pollution in water. They were mostly based on optical techniques [Wang and Yu, 2013; Dai *et al.*, 2014; De Góes, Muller and Fabris, 2017] or on electrochemical detection [Zhang *et al.*, 2017; Bettazzi *et al.*, 2018; Noori *et al.*, 2018]. Most of them led to prototypes that had been validated in the laboratory but failed to get a foothold on the market of water quality for large scale deployment. In this project, the potential of micro-NMR is investigated.

As discussed at the end of Subsection 751.1, the resolution of miniaturized NMR systems is too weak for spectroscopy application. Moreover, the expected concentration of pollutants in water are hopefully very low. Thus, a µNMR-based sensor that can detect multiple pollutants directly in a water sample is a utopia. To tackle this challenge, we devised a new sensor architecture, which block diagram is depicted in Figure 42.

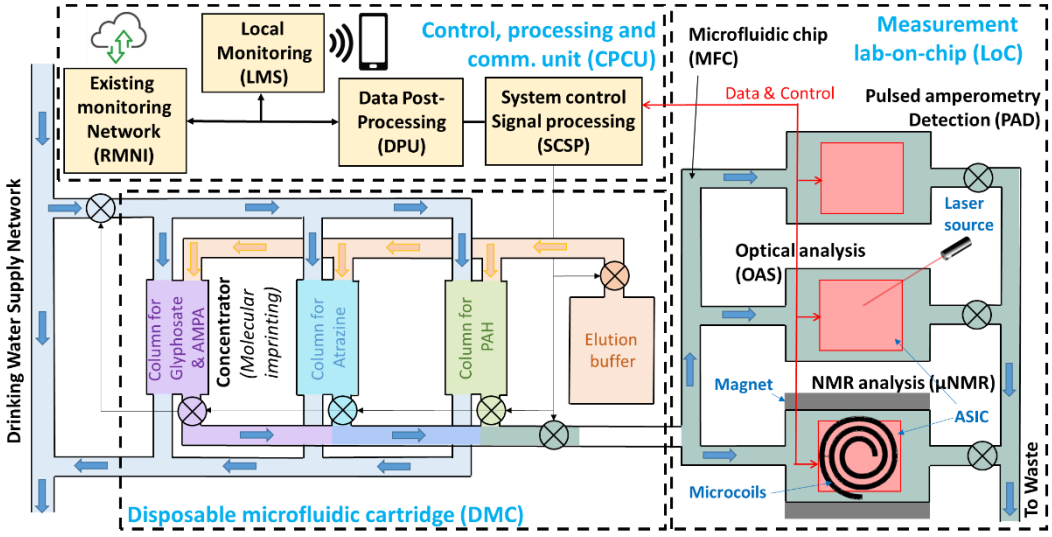

Figure 42 – Block diagram of the targeted system.

The system is composed of three main parts: a disposable microfluidic cartridge (DMC), a measurement lab-on-chip (LoC) and the control, processing, and communication unit (CPCU). The DMC is a microfluidic circuit composed of concentrators through which a fixed amount of drinking water flows. These concentrators are realized with molecular imprinting polymer (MIP) technique [Osma and

Stoytcheva, 2014]. The efficiency of such technology for the detection of pollutant in drinking water, *e.g.* glyphosate [Zhao *et al.*, 2011] and atrazine [Piletsky *et al.*, 1995] has already been demonstrated. Commercial solutions for such technology already exist [Claude *et al.*, 2017]. It also includes a tank for the elution buffer required to release trapped molecules as well as solutions used for positive and negative controls. With current technologies, we estimate that a MIP column may be reused about 100 times. Thus, with 1 measurement per day, the DMC in the final device will have to be changed every 3 months.

Basically, the LoC is composed of four parts: a miniaturized on-chip NMR detection system (µNMR), an optical analysis system (OAS) based on the principle of time-resolved fluorescence spectroscopy [Léonard *et al.*, 2014], a pulsed amperometry detection (PAD) [Sato *et al.*, 2001; Weltin, Kieninger and Urban, 2016] and a microfluidic chip (MFC) that routes samples from the output of the DMC to the three detection systems. The OAS can be used to detect native fluorescent pollutant, such as polycyclic aromatic hydrocarbons. The PAD is efficient for redox-active substance. The µNMR is composed of an integrated circuit for the RF pulse generation, detection and processing and a small permanent magnet that generates a 1T homogeneous magnetic field. Besides, the OAS is composed of a time-resolved laser-induced fluorescence system that measures the optical properties of the sample. It includes a picosecond laser diode pulse generator, a single photon avalanche diode with a time-correlated photon counting system and a set-up of optical devices (*e.g.* filters, etc). The PAD is composed of thin-film noble metal electrodes that are deposited directly on a glass substrate. The electrode material and the pulse sequence should be adapted to the targeted molecule and the elution buffer.

Finally, the CPCU is composed of discrete electronic circuits. Four mains parts can be identified. First, the system control and signal processing (SCSP) unit is the system controller. It triggers the measurement process every day, drives the microfluidic pumps and valves, generates the NMR control sequences, processes and digitalizes the data received by the µNMR circuit, controls the OAS and transfers raw data to the rest of the CPCU. Second, the Data Processing Unit (DPU) oversees the data processing, generating quantitative data and alerts. Those signals are transmitted to a local monitoring system (LMS) and a remote monitoring network interface (RMNI). The LMS logs the data that can be monitored by a local user through a wireless interface (NFC, Bluetooth …). For the RMNI, we will plug our monitoring system to an existing monitoring network developed by Bürkert SAS, a partner of this project. The integration of urban long-range communication protocols (LoRa, SigFox) will also be investigated.

PROJECT SUBMISSION

The project was submitted for a 3-years INTERREG funding. It has been selected at the first round in September 2018. This means that it will be granted after the redaction of the final application form and the official approbation of the Interreg Commission. The consortium is composed of 6 academic partners and 2 companies:

- The University of Strasbourg, and more specifically the ICube laboratory and the Laboratory of Biotechnologies and Cell Signaling (UMR 7242);
- The Institute for Microsystems Techniques of the Hochschule Furthwangen (HFU), Germany;
- The Laboratory of Sensors of the Institut for Microtechnics (IMTEK) of the Albert-Lüdwigs-Universität, Freiburg, Germany;
- The Chemistry Department of the Technische Universität of Kaiserslautern (TUK), Germany;
- The Life Science Department of the Fachhochschule Northwest Schweitz (FHNW), Switzerland;

- The Bürkert Flow Control company in Triembach-au-Val, France;
- The Metrolab SAS company, Plan-les-Ouates, Switzerland.

The Gantt diagram of the project is given in FIGURE 43. The overall tentative budget is 1,275 k€ with 500 k€ coming from the European Regional Development Fund (ERDF), 250 k€ coming from French and German regions (Grand-Est, Bade-Würtemberg, and Rheinland-Pfatz), 155 k€ coming from the Swiss Confederation, 56 k€ frow Swiss regions (Basel-Stadt, Basel-Landschaft, Aargau and Jura) and 314 k€ corresponding to self-funding. The project is expected to start in September 2019.

Actions and tasks	Trimesters												Leader
	T1	T2	T3	T4	T5	T6	T7	T8	T9	T10	T11	T12	
WP1 : Disposable molecule concentrator													**Unistra**
T1.1 : Development of the concentrator.													Unistra
T1.2 : Integration of the MIP column into a DCM													Unistra
T1.3 : Validation and characterization													Unistra
WP2 : Development of the micro-NMR measurement unit													**Unistra**
T2.1 : Preliminary results using Metrolab chip													Metrolab / FHNW
T2.2 : Design and realization of the NMR circuit													Unistra / FHNW
T2.3 : Electrical characterization													Unistra
T2.4 : Validation on standard solutions													Unistra
WP3 : Development of the optical analysis system													**Unistra**
T3.1 : Preliminary results on existing sensor													Unistra
T3.2 : Design and realization of the dedicated circuit													Unistra
T3.3 : Electrical characterization													Unistra
T3.4 : Validation on standard solutions													Unistra
WP4 : Development of the PAD system													**IMTEK**
T4.1 : Choice of electrode material and pulsing scheme													IMTEK
T4.2. : Realization of the device													IMTEK
T4.3 : Optimization of the PAD protocol													IMTEK
T4.4 : Validation on standard solutions													IMTEK
WP5 : Lab-on-chip													**HFU**
T5.1 : System behavioural modeling and specifications													Unistra / All
T5.2 : Microfluidic sample transportation													HFU / IMTEK
T5.3 : Integration of the NMR measurement unit													HFU / Unistra
T5.4 : Integration of the optical measurement unit													HFU / Unistra
T5.5 : Integration of the PAD measurement unit													HFU / IMTEK
T5.6 : Validation													HFU/IMTEK/Unistra
WP6 : Data analysis and fusion													**FHNW**
T6.1 : Data analysis													FHNW / Unistra
T6.2 : Offline development of processing algorithm													FHNW
T6.3 : On-the-fly implementation of the algorithms													FHNW / Unistra
WP7 : System deployment													**Unistra**
T7.1 : Integration to the Bürkert platform													Unistra / Bürkert
T7.2 : In-field testing													Bürkert
WP8 : Project coordination													**Unistra**
T8.1 : System-level specification and model													All
T8.2 : Development of an internal wiki													Unistra
T8.3 : Strategy for project continuation													All
T8.4 : Consortium meetings													All
WP9 : Dissemination													**Unistra**
T9.1 : External website development													Unistra
T9.2 : Patent filling (if required)													All
T9.3 : Scientific communication													All
T9.4 : Workshops													All + Extrenal

FIGURE 43 – GANTT DIAGRAM OF THE WATER POLLUTION SENSOR PROJECT

1.3. *IN OPERANDO* MONITORING OF CATALYTIC REACTIONS

Within the same scope, we also would like to investigate the application of µNMR for the monitoring of chemical reactions and the acquisition of reaction kinetic information based on the non-intrusive/non-invasive determination of the composition of reaction media with light-weighed equipment.

GOAL

Monitoring chemical reaction is a critical issue in the chemical industry. On the understanding of reaction kinetics depends one's rationalization of chemical transformations. On the quality of the acquired data and on the time resolution achieved in acquiring the fastest chemical events, depends the reliability of the mechanistic conclusion. From the latter depends on the subsequent optimization of catalysts, be they organic, inorganic or organometallic. This project materializes a response to this challenge by proposing to bring NMR spectroscopy to the reaction medium where the key information is produced. We aim at developing a miniaturized medium field (1T to 2T) NMR dip device capable of

acquiring *in solutio* NMR spectra in chemical reactions vessels or reactors loaded with diamagnetic reagents.

Existing Methods

If the acquisition of data *in situ* and *in operando* is now amenable by other optical or ionization-based spectroscopic methods, the more challenging NMR spectroscopy has stalled on this field to methods that are in fact highly intrusive and hardly transposable to hazardous large scale chemical production plants and extreme conditions. These techniques are essentially based on set-ups where a large or laptop-type NMR device imposes experimental constraints on the measure. In most common set-ups, a small volume of the solution is continuously picked up from the reactor and transferred in a flowcell at the center of the NMR magnet. NMR spectra are acquired at different time steps and the relative height of the spectral lines are compared to monitor the reaction. Such a system has been demonstrated by Khajeh *et al.* in 2010 in order to measure the kinetics of protein reactions in a 7 T standard NRM spectrometer [Khajeh, Bernstein and Morris, 2010]. With this set-up, a spectral resolution of 0.003 ppm and a temporal resolution of 0.1 samples per second (SPS) has been achieved. The Achilles heel of this method is the continuous flow of samples from the reactor to the magnet. If it is too fast, a fraction of excited nuclei has already left the flowcell before the start of acquisition, which decreases the quality of the measurement. If it is too slow, the reaction goes on within the flowcell but under uncontrolled conditions (temperature, pressure). Thus kinetic parameters might be irrelevant. Moreover, such a system has an unavoidable latency between the effective start of the reaction and the arrival of the first sample in the flowcell. As a consequence, early measurements, which are often the most relevant in chemical kinetics monitoring, are missing.

To avoid flowcell, an alternative consists in building micro-reactors directly inside the magnet. In 2016, Brächer *et al.* validated this approach on the monitoring of the esterification of methanol [Brächer *et al.*, 2016]. They designed a 34 µL micro-reactor controlled in pressure and temperature and put it in a 9.7 T spectrometer. A spectral resolution of 0.002 ppm and a temporal resolution of 0.5SPS have been achieved in this way. However, this set-up remains hard to implement and requires expensive, non-transportable material. Moreover, such microreactors are not suitable for all applications.

Miniaturizing the NMR system implies a loss of sensitivity and spectral resolution (see SECTION 1.1). However, according to Dalitz, a 0.1 ppm spectral resolution can be sufficient for monitoring of chemical reaction [Dalitz *et al.*, 2012]. Thus, benchtop NMR are good candidates to reduce costs and set-up complexity. In 2016, Elipe *et al.* developed an experimental set-up with such material for the monitoring of slow chemical reactions (1 measurement every 15 minutes but the actual maximal acquisition rate is not given in the paper) [Silva Elipe and Milburn, 2016]. In 2005, Wensink *et al.* demonstrated a lab-on-chip for reaction monitoring [Wensink *et al.*, 2005] composed of a microfluidic chip that plays the same role as the flowcell and an external 1.4T magnet. They reached a temporal resolution of 0.1 SPS. Although more compact, this implementation does not overcome drawbacks related to the use of a flowcell.

Project Description

The state of the art shows that there is no *in situ* reaction monitoring system with 0.1 SPS temporal resolution. Nevertheless, miniaturized permanent magnet and micro-probes make such breakthrough possible. The cornerstone is the figure of merit (FoM) of the spectrometer which can be defined as the product of its spectral and temporal resolution. Different solutions can be investigated in order to

increase this FoM. One of them consists of parallelizing the measurements. For that purpose, we aim at designing of millimetric NMR integrated micro-sensors composed of a microprobe, a 1T permanent magnet, and an analog front-end integrated circuit. Several of such sensors can be dipped directly into the reactor (FIGURE 44). Dipping the NMR probe directly into the reactor reduces the risk of alteration of chemical information in comparison with pick and analyze methods. Measurements are gathered by an external acquisition and control circuit (ACC). Micro-probes, as well as the ACC circuit, will be designed in a generic way in order to enable different operating modes, such as for instance:

- a parallel acquisition mode in which the ACC circuit accumulates the spectra from different sensors in order to increase the sensitivity without degrading the temporal resolution;
- a sequential acquisition mode in which sensors operate during shifted time windows and accumulate several spectra in order to increase the sensitivity on one sensor. Gathered data are then post-processed (deconvoluted) in order to obtain the kinetic parameters;
- a multi-nuclei mode in which different sensors, each designed to be sensitive to a given nucleus, operate in parallel. The lack in spectral resolution is compensated by cross-correlations between spectra from different nuclei;
- a spatial mode in which focus is put on spatial resolution instead of a temporal one. Acquisitions made on different points of the reactor are compared in order to estimate the homogeneity of the solution.

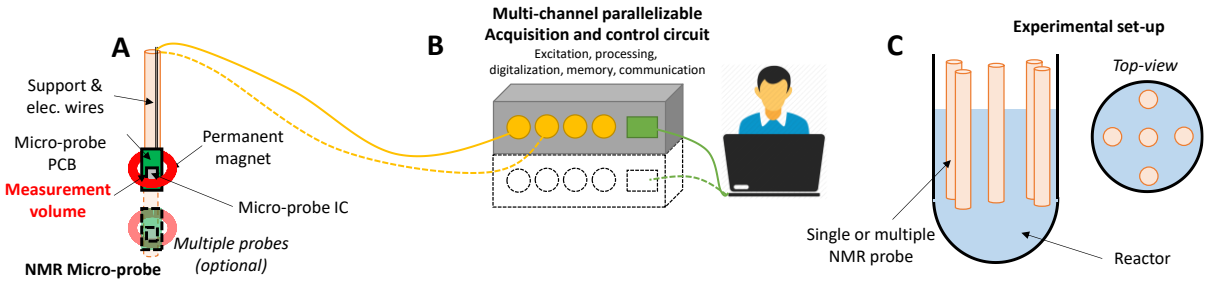

FIGURE 44 - (A) DESCRIPTION OF THE MICROPROBE. IT IS COMPOSED OF A ROD THAT CARRIES A PRINTED CIRCUIT BOARD (PCB) THAT HOSTS THE MICROPROBE INTEGRATED CIRCUIT (POWER AMPLIFIER, MICRO-COIL, SWITCH, LOW-NOISE AMPLIFIER, ETC) AND A PERMANENT MAGNET. THE MEASUREMENT AREA IS A SMALL VOLUME ABOVE THE MICRO-COIL. THE FIRST VERSION OF THE MICROPROBE IS COMPOSED OF ONLY ONE PROBE. A VERSION WITH MULTIPLE PROBES ON THE SAME ROD IS ALSO ENVISAGED LATER ON. (B) IS THE ACQUISITION AND CONTROL CIRCUIT. FIRST, A SINGLE-CHANNEL VERSION WILL BE DESIGNED. THEN, MULTI-CHANNEL VERSIONS ARE ENVISAGED. THESE SYSTEMS WILL BE STACKED AND CONTROLLED IN PARALLEL FROM A LAPTOP SOFTWARE IN ORDER TO ADAPT TO THE NUMBER OF IMPLEMENTED MICRO-PROBES. (C) IS THE EXPERIMENTAL SET-UP COMPOSED OF 5 RODS IN THE SAME REACTOR.

The project is very challenging and several breakthroughs have to be made in order to achieve a functional prototype. The first one is the integration of the magnet. State-of-the-art Halbach magnets reached a uniformity of 0.1 ppm in the volume of an RMN tube (*i.e.* 5mm) [Zalesskiy *et al.*, 2014]. In our case, the measurement area is smaller. Thus, even higher uniformity can be achieved. We also contacted a world-leading company of custom magnet design, Arnold Magnetics (Switzerland). Our preliminary discussions reassured us on the feasibility of such a device. Moreover, if required, the implementation of miniaturized and flexible shim coils [Li *et al.*, 2013] to compensate non-uniformity can be investigated.

The second challenge is related to the probe itself and the signal quality which is crucial if we want to optimize the FoM of a microprobe. Our idea is to integrate the analog front-end (low-noise amplifier) with the coil on a single chip. By this way, the noise will be reduced and the FoM increased. Moreover,

if required, the integration of an analog-to-digital converter within the probe ASIC can also be investigated.

The temperature is also an important issue. High temperature (>70°C) may cause demagnetization of neodymium magnets. As a consequence, this will limit the temperature range of the reaction. Moreover, weaker temperature changes of the magnet, due for instance to the reaction process, can also induce an alteration of the value and the homogeneity of the magnetic field and thus disturb the measurement. A thermal sensor can be integrated within the probe to control this effect.

From a chemical perspective, efficient monitoring of the kinetics of a reaction requires the reaction rate not to be limited by diffusion. The geometry of the probe is critical to ensure that the reaction near the measurement and in the rest of the reactor are the same. Moreover, another issue for the dip-in device will be its solvent-tight insulation. The most sensitive components have to be protected from the corrosive chemical medium (solvents & reagents). Several options will be considered such as the inclusion within a PTFE polymer lining and the confinement of the measurement channel in a fused quartz-based capillary.

The design process will be consolidated with virtual prototyping. For such a multidisciplinary project, we are convinced that it is a critical task to ensure success and an efficient collaboration.

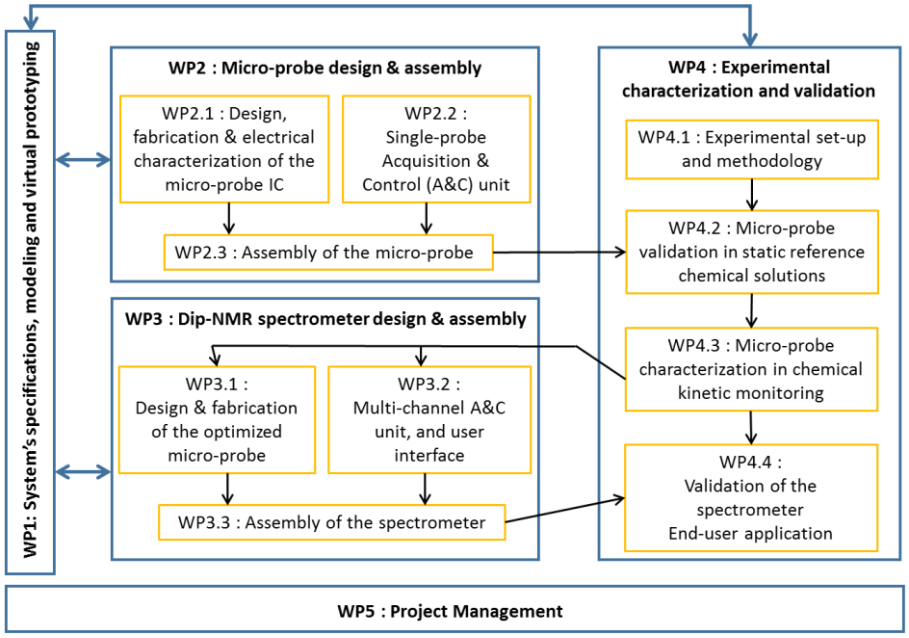

FIGURE 45 – DIP-NMR PROJECT ORGANIZATION AND WORK PACKAGES

PROJECT SUBMISSION

I applied for an ANR grant funding for this project. The project is planned over 48 months with a tentative budget of 508 k€. It was first submitted in 2018. It passed the first round and was on the waiting list after the second round. It was resubmitted in 2019 and successfully passed the first round. The full proposal is now under examination. The consortium is composed of 3 academic partners and 1 company:

- The University of Strasbourg, and more specifically the ICube laboratory and the Institute of Chemistry (UMR 7177);
- The Life Science Department of the Fachhochschule Northwest Schweitz (FHNW), Switzerland;

- The RS2D company in Mundolsheim, France.

The project is split into five work packages (FIGURE 45): the system's specification, modeling and virtual prototyping (WP1), the design of a single microprobe and its assembly (WP2), the integration of the complete Dip-NMR spectrometer (WP3), the experimental characterization and validation (WP4) and the project coordination (WP5). The Gantt diagram of the project is also given in FIGURE 46.

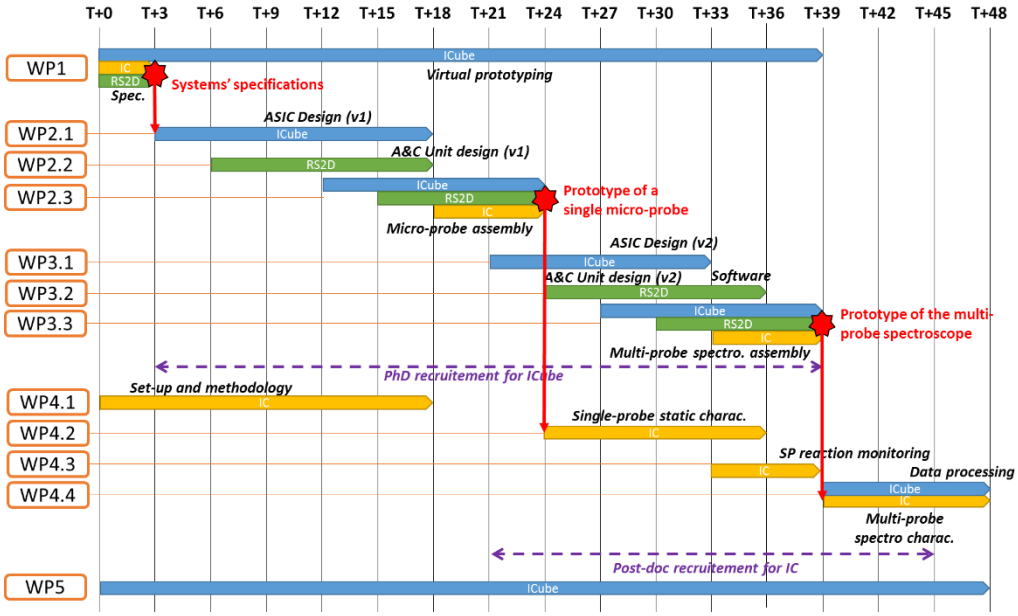

FIGURE 46 – GANTT DIAGRAM FOR THE DIP-NMR PROJECT

1.4. MID-TERM PROJECTS

The projects described hereabove should give us at mid-term a good experience on the techniques associated with µNMR. Therefore, lots of exciting applications based on NMR can be envisaged. NMR can be stand-alone or coupled with alternative detection technique (fluorescence microscopy, atomic magnetic force microscopy, etc) in order to increase the measurement quality and the range of measurable biological signals. Here are some examples.

PORTABLE BIOSENSORS

Portable NMR relaxometers and spectrometers are commonly used for biomolecule sensing. In relaxometry, the signal of interest is not the Larmor frequency but the relaxation time (T_2^* in EQ. 7). For instance, Sun *et al.* demonstrated an avidin sensor using biotin-coated nanoparticules [Sun *et al.*, 2011]. Without avidin, nanoparticles are dispersed in the solution. With avidin, they tend to form clusters which divide by 2 the relaxation time of the system. The limit of detection of such a system is very low (5 nmol/L in 4 µL). The same system was also used for the detection of specific cells (bladder cancer cells in this case) [Sun *et al.*, 2011]. Again, nanoparticles coated with monoclonal antibodies are used. The relaxation time of the system depends on the state of the antibodies (free or bound to a cancer cell). Author claims a sensisitity of 18 cells per µL has been reached.

In 2017, Grisi *et al*. demonstrated a device performing NMR spectroscopy on sub-nanoliter volumes (0.1 to 0.5 nL). For that purpose, he designed a dedicated microchip embedding the micro-coil and the analog front-end. Samples, *i.e.* ovum isolated in an agarose gel, are analyzed under an external 7T magnetic field. The sensitivity and the resolution of the device are high enough to observe variations

of NMR spectrum over time, what suggests changes in the intrinsic properties of the ova [Grisi *et al.*, 2017].

MICRO-SCALE MRI

NMR is a powerful technique for the non-invasive 3D imaging of tissues. Magnetic Resonance Imaging (MRI) is commonly used for clinical diagnosis in hospital. In standard NMR systems, the sample under analysis is put in a uniform magnetic field. In MRI systems, gradients of magnetic field are generated in the three dimensions of the space. Gradients change locally the Larmor frequency and the phase of the relaxation signal in a unique way which encoding for the location of the signal. A 3D map of spin concentration can then be reconstructed by exciting spins with different sequences of PF pulses and scanning the precession signal over different frequencies.

Micro-scale MRI acquisitions on single cells have been achieved with standard MRI scanners and micro-coils for years. In 2004, Ciobanu imaged *Spyrogira alga* with such set-up and reached a spatial resolution of 3.7 µm [Ciobanu and Pennington, 2004]. More recently, Weiger *et al*. reached a 3 µm resolution under an 18.8-T static field [Weiger *et al.*, 2008]. The spatial resolution of micro-scale MRI is limited by two main effects: the necessity to generate large magnetic field gradient over a tiny volume and the sensitivity which is proportional to the sample volume (and thus decreases when spatial resolution increases). The spatial resolution obtained with state-of-the-art µMRI systems is small enough to envisage single-cell imaging. It should also be mentioned that the acquisition time required to obtain acceptable images quality on actual tissues is, up to now, rather prohibitive (hours to days) [Moore and Tycko, 2015]. Despite these limitations, potential applications of µMRI techniques for cell tracking are numerous: visualization of immune cell homing, inflammation, cell physiology, gene expression or image-guided immune cell delivery techniques [Ahrens and Bulte, 2013].

VELOCIMETRY

Velocimetry aims at measuring the velocity of fluids. Among others, velocimeter can be achieved by NMR or MRI, using the time-of-flight principle. A fraction of ^{1}H atoms transported by the flow is excited at a given time and position in the channel. Then, µMRI is used to image their dispersion over time Sahebjavaher showed in 2010 one of the first portable velocimeter composed of a small 0.6T permanent magnet and microfabricated cooper coils that achieve a gradient of 1.7T/m [Sahebjavaher, Walus and Stoeber, 2010]. With this set-up, a 40-µm resolution was reached. This value is about 10 times weaker than the one obtained with a 7T magnet. Nevertheless, such a resolution is sufficient to detect flows at velocity up to 50 mm/s.

2. IMPEDANCE SPECTROSCOPY

2.1. STATE-OF-THE-ART

THE PRINCIPLE OF IMPEDANCE SPECTROSCOPY

The measurement of electrical properties of biological samples is a common technique used for the detection of biochemical compounds in a medium, the identification of cells in suspension or the characterization of bones, tissues, blood, etc. Generally speaking, biological tissues are composed of molecules that can either conduct electrical current (*e.g.* ions, polarized molecules) or either play the role of a dielectric (*e.g.* lipids). Let us consider the example of a cell. The cytoplasm and the extracellular medium are primarily composed of water and ions. They can be modeled by a resistor. Conversely, the

membrane is composed of an isolating lipid bilayer which can be modeled by a capacitor. Its value can be estimated at 1µF/cm² [Schwan, 1983]. In practice, the heterogeneous assembly of molecules in living matter forms a complex network of resistors and capacitors. Impedance spectroscopy (EIS) measures the network equivalent impedance Z as a function of the frequency f:

$$Z(f) = R(f) + j \cdot X(f) \qquad \text{Eq. 11}$$

In Eq. 11, $R(f)$ is the equivalent resistance and $X(f)$ is the equivalent reactance of the network. Most of the time, the network of resistors and capacitors is too complex to be deciphered by a single impedance spectrum measurement. However, monitoring the variation of impedance during an experiment provides a wide range of biological signals.

Macroscopic-scale Applications

EIS can be applied at the macroscopic scale. Most of the applications go around the analysis of cells behavior. The pioneer of this domain is Hugo Fricke, about one century ago. He used a hand-balanced Wheatstone bridge to measure the impedance of breast tissues and correlated the results with the presence of tumors [Fricke and Morse, 1926]. Since then, EIS has been widely used for the analysis of tissues and their behavior in the response of an external stimulus. The most common applications are the detection of cancer cells [Estrela da Silva, Marques de Sá and Jossinet, 2000], hematocrit tests on blood samples [Egot-Lemaire *et al.*, 2009], the measurement of glucose rate [Treo *et al.*, 2002] or the evaluation of the rate of fatty mass (*e.g.* diagnostic scale) [Kotler *et al.*, 1996]. Still at the macroscopic scale, EIS is also used for cell counting. The more cell in solution under analysis, the highest capacitance. Application of this property for the monitoring of the population growth [Asami, Gheorghiu and Yonezawa, 1999] or, conversely, for (natural or induced) apoptosis monitoring [Arndt *et al.*, 2004] has already been demonstrated.

Single-cell EIS

EIS at the macroscopic scale is limited to the analysis of cell populations. Measuring the properties of a single cell is much more challenging. Performing single-cell EIS (SCEIS) requires the ability to isolate cells and/or to design electrodes with a size comparable to the size of cells. Moreover, the reduction of sizes and volumes also decreases the amplitude of electrical signals and, thus, increases the sensitivity to noise. This imposes new challenges in measurement electronics.

The design of miniaturized electrodes has been enabled by new micro-technologies processes such as micro-etching and/or thin film deposition of microstructures. The concept of multi-electrode was introduced about 50 years ago by Thomas *et al.* They designed a 30 pixels electrode array. Pixels were arranged in two rows with a 50-µm pitch between two consecutive electrodes and a 100-µm pitch between the rows [Thomas *et al.*, 1972]. The pitch size was fixed to ensure that it can be filled by, at the most, one single cell. Nowadays, matrices of 256x256 composed of cellular-scale electrodes (25.5µm x 25.5 µm) are achievable (Figure 47A and Figure 47B) [Tsai *et al.*, 2017]. An alternative electrode geometry, introduced by Ehret in 1997 is the interdigitated comb (Figure 47G) [Ehret *et al.*, 1997].

Regarding the ability to isolate single cells, several approaches exist. The most straightforward consists in placing manually a single cell between two electrodes which gap matches the size of the cell [Ghenim *et al.*, 2010]. In this case, the design of the electrode is straightforward but the placement requires manual manipulation and microscopy for the verification. An alternative consists in spreading a small

number of cells onto an interdigitated electrode. Again, the clearance between each comb finger has to match with the cell size. This method simplifies the cell manipulation without putting severe constraints on the electrode design. In counterpart, measurements are not truly performed on a single cell but on several single-cell in parallel. If cells behave similarly, the absolute impedance value is shifted down without spectrum distortion. Thus, differential or dynamic measurements remain possible [Mamouni and Yang, 2011]. Finally, microfluidic is the ultimate solution for SCEIS. In this case, cells are isolated inside droplets which properties are measured by integrated electrodes within the microfluidic chip. Such a method is called microfluidic impedance spectrometry flow cytometry (FIGURE 47D) [Sun and Morgan, 2010]. The technique was first demonstrated by Gawad in 2001 (FIGURE 47E) [Gawad, Schild and Renaud, 2001]. Since then, it has been used for the realization of a label-free cell sorter (FIGURE 47C) [Cheung, Gawad and Renaud, 2005] in 2005 or an automated red blood invasion assay (FIGURE 47F) in 2013 [Du *et al.*, 2013].

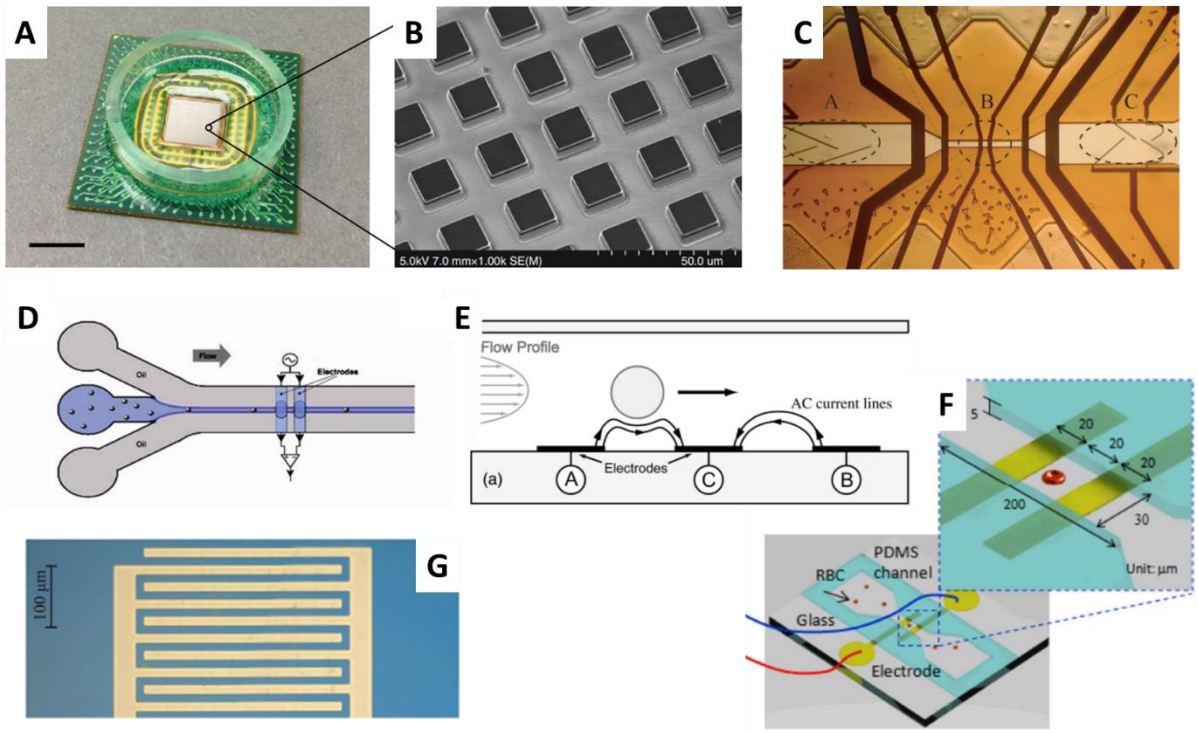

FIGURE 47 - (A) PICTURE AND (B) SCANNING ELECTRON MICROGRAPH OF THE PACKAGED 256X256 CMOS MATRIX DESIGNED BY [TSAI *ET AL.*, 2017]. (C) CLOSED-VIEW OF THE MICROFLUIDIC DEVICE DEVELOPED BY [CHEUNG, GAWAD AND RENAUD, 2005]. THE LEFT PART OF THE CIRCUIT IS THE INPUT CHANNEL WITH ELECTRODES FOR CELL FOCUSING. CELL SIZE IS MEASURED BY ELECTRODES IN THE CENTRAL PART. THE RIGHT PART SORTS CELLS ON THE TOP OR ON THE BOTTOM OUTLET AS A FUNCTION OF THEIR SIZE. (D) EXAMPLE OF A MICROFLUIDIC CIRCUIT COMBINING CELL ISOLATION AND EIS. THE CELL BUFFER SOLUTION IS SQUEEZED BETWEEN TWO OIL FLOWS IN ORDER TO FORM A CHANNEL WITH A WIDTH THAT CORRESPONDS TO CELL SIZE. CELLS ARE TRANSPORTED BY THE FLOW TO THE ELECTRODES [SUN AND MORGAN, 2010]. (E) ANOTHER EXAMPLE OF EIS FLOW CYTOMETRY COMPOSED OF 3 ELECTRODES. WHEN A CELL CROSSING IS MEASURED AS A PERTURBATION OF CURRENT LINES, AND THUS A DIFFERENCE OF IMPEDANCE BETWEEN A AND B ON THE ONE HAND AND B AND C ON THE OTHER [GAWAD, SCHILD AND RENAUD, 2001]. (F) DEVICE FOR THE ANALYSIS OF RED BLOOD CELL INVASION BY PLASMODIUM FALCIPARUM [DU *ET AL.*, 2013]. RED BLOOD CELLS ARE TRAPPED BETWEEN ELECTRODES. (G) EXAMPLE OF AN INTERDIGITATED COMB ELECTRODE

For the majority of SCEIS microsystems met in the literature, impedance measurements are performed with an external impedance-meter. Such a device can be very expensive (1 to 50 k€, depending on accuracy and bandwidth). Thus, low cost and/or systems that require multi-points measurements

require the realization of custom accurate impedance measurement circuits. Moreover, custom measurement circuits are also required to open the way for new functionalities, such as sophisticated excitation strategies and/or on-line signal processing and/or electrical control of the experimental conditions. For instance, at the level of a molecule, pulsed voltages can be applied before the measurement in order to induce oxidation or hydrolysis reactions. This technique is applied for pulsed amperometry detection (PAD) that can be used for the detection of small molecules such as glucose [Fanguy and Henry, 2002] or glyphosate [Sato *et al.*, 2001]. At the level of a cell, the application of voltage pulses may induce electroporation, *i.e.* increase of cell membrane permeability allowing chemical compounds to penetrate inside the cell. [Ghosh, Keese and Giaever, 1993].

The application range of microscopic EIS encompasses drugs efficiency [Anh-Nguyen *et al.*, 2016], healing on epithelial tissues [Lundien *et al.*, 2002], cell adhesion process [Giaever and Keese, 1986; Kowolenko *et al.*, 1990; Mitra, Keese and Giaever, 1991], cell growth [Lin, Kyriakides and Chen, 2009], cell migration [Nguyen *et al.*, 2013], biofilm formation [Piasecki *et al.*, 2013; van Duuren *et al.*, 2017], cell invasion mechanisms [Ribaut *et al.*, 2009; Du *et al.*, 2013], etc.

MODELING AND VIRTUAL PROTOTYPING

The design of EIS-based sensor is quite challenging. It encompasses the realization and the optimization of an efficient microfluidic chip for cell isolation, the choice of electrode material and geometry, the integration of electrodes within the microfluidic circuit, the design of an electronic circuit for excitation, impedance measurement and signal processing as well as the control of environmental conditions. Virtual prototyping can be very profitable in this context. The overall model of an EIS-based sensor is given in FIGURE 48. It is composed of a model of biochemical reaction translated into an electric equivalent circuit by BB-SPICE (see CHAPTER 2 SUBSECTION 2.4), the bio-electrical model of the sample and the electrical model of the measurement and excitation circuit. Electrical models of cells are known for a long time. They are mostly composed of an assembly of resistors and capacitors which value may vary with respect to biochemical quantities. A first SPICE model of a single cell was established in 1991 by Grattarola *et al*. [Grattarola *et al.*, 1991]. Since then, other investigations have been carried out in order to enrich the model by dependences with the biological context or sensor geometry [Sun and Morgan, 2010; Ibrahim *et al.*, 2011].

A coupling with microfluidics is also required in order to model SCEIS-based fully integrated lab-on-chip. The use of co-simulation of 2D/3D microfluidics and electrostatics models in order to optimize the device has already been demonstrated [Ibrahim *et al.*, 2011; Ngo *et al.*, 2014]. Such coupling is also intended for the next version of our virtual prototyping environment described in CHAPTER 3 SECTION 3. Moreover, the need for a direct coupling in a single environment of biology and electronic is enhanced if the electrical behavior has also an impact on biological one, *e.g.* electroporation. Existing bioelectrical models for this phenomenon deserve to be considered [Warindi *et al.*, 2013].

2.2. PROJECTS

During my 6-month sabbatical at the Centre for Biological Signaling Studies (BIOSS) in Freiburg, I identified several open questions that might be addressed by EIS. In particular, Winfried Romer's team is interested in deciphering the behavior of several pathogens, *e.g. Pseudomonas aeruginosa*, on host cells. The context of this study is described with more details in CHAPTER 3 SUBSECTION 2.2. Up to now, experimental data have been obtained by indirect optical measurement. Considering the state-of-the-art, and more specifically research that has been made on similar topic [Ribaut *et al.*, 2009; Du *et al.*,

2013; Piasecki *et al.*, 2013; van Duuren *et al.*, 2017], we are convinced that EIS could be a good alternative to indirect optical measurement. EIS can be highly integrated, which makes it compatible with high throughput measurement. Moreover, EIS would enable dynamic measurement of the invasion process, providing data that are not accessible with the current method.

Another project, still at the BIOSS, concerns the design of a biochip for the study of the fate of individual cells within an epithelium. The current version of the biochip is composed of a surface for the cell culture, a microfluidic circuit that drives drugs to the cells and micro-pores for the connection between cells and drugs. By this way, the basolateral microenvironment of a confined number of neighboring cells within the epithelial layer can be controlled [Thuenauer *et al.*, 2018]. Up to now, the device is suitable for fluorescence microscopy (the device is transparent) and atomic force microscopy (the cell at the surface are accessible). It would be of great interest to add EIS as an additional modality to increase the application range of such biochip.

EIS can also be combined with imaging in order to identify and quantify bacteria in a solution. This is the main idea of a project started at the BIOSS and which context cannot be described because of confidentiality issues. Beside the EIS part, the complete project also includes system-level design and embedded signal processing, which also falls in the scope of our team's activities.

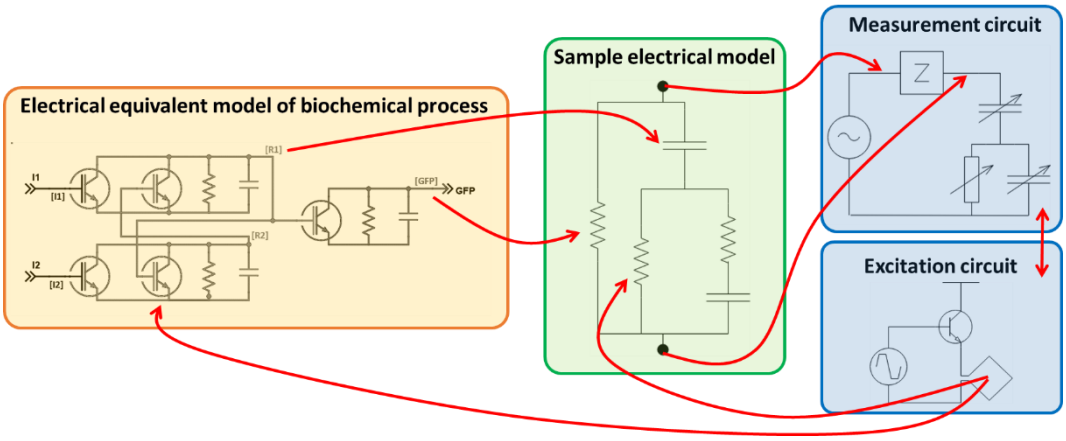

FIGURE 48 – GENERIC ARCHITECTURE OF SYSTEM-LEVEL MODEL FOR AN EIS-BASED SENSOR. THE MODEL IS COMPOSED OF THE ELECTRICAL EQUIVALENT MODEL OF THE BIOLOGICAL PROCESS (*IN YELLOW*), THE ELECTRICAL EQUIVALENT MODEL OF THE SAMPLE UNDER ANALYSIS (*IN GREEN*) AND THE MODELS FOR THE ELECTRICAL CIRCUITS (MEASUREMENT AND EXCITATION, *IN BLUE*). RED ARROWS MARK THE INTERACTION BETWEEN MODELS: BIOLOGICAL SIGNALS COMPUTED BY THE YELLOW MODEL ALTER THE VALUE OF THE DEVICE IN THE GREEN MODEL. THE IMPEDANCE COMPUTED BY THE GREEN MODEL CHANGES THE VOLTAGES COMPUTED BY THE BLUE MODEL. EXCITATION AND MEASUREMENT CIRCUITS CAN BE COUPLED AND THE ELECTRICAL EXCITATION CAN MODIFY PARAMETERS OF THE SAMPLE MODEL AND/OR DIRECTLY PARAMETERS IN THE BIOCHEMICAL MODEL.

The projects described hereabove are, by nature, transdisciplinary. Beside the biological aspects, for which the know-how of the BIOSS is unavoidable, expertise in the design of electrodes and dedicated microfluidic chips is also required. Starting from scratch on this topic and acquiring the equipment for the manufacturing of the device would be a waste of time and money. We are rather considering a collaboration with two neighboring laboratories that are worldwide recognized for their expertise in this domain: the Institut Jean Lamour in Nancy [Ibrahim *et al.*, 2011; Ngo *et al.*, 2014] with which discussions on this topic are already initiated and the Institut für Mikrosystemtechnik in Freiburg [Nguyen *et al.*, 2013; Weltin *et al.*, 2014; Anh-Nguyen *et al.*, 2016] which is a partner of the INTERREG project described in SECTION 1.2. Our contribution will be on the design of efficient driving and

processing circuit, based on a system-level design approach and relying on the virtual prototyping environment described in CHAPTER 3 SECTION 3.

3. WHOLE-CELL SENSOR

Synthetic biology and synthetic biology recently met each other to give rise to a new generation of biosensors. In this case, the reprogrammed cell plays the role of a "biological transducer" turning a biological signal under interest into another measurable biological signal.

3.1. THE FIRST GENERATION OF WHOLE-CELL SENSOR

Using living organisms as biological transducers is a strategy that has been exploited for years (FIGURE 49). In the beginning, organisms served as guinea pigs and the information of interest is their ability to survive in a given environment. For instance, mussels' behavior has been used as an early indicator of coastal water pollution. Nowadays, most of the existing applications fall within the scope of the environment. Moreover, due to ethical questions, single microorganisms tend to be preferred than living animals and/or plants. In a review in 2014, Hernandez *et al*. recorded more than 150 applications over the last 30 years, using more than 100 different cell strains and detecting a large range of molecules including small molecules (glucose, ethanol, carbohydrates, etc), amino acids, peptides, proteins, pathogens or herbicides (*e.g.* atrazine), poisons (arsenic, mercury, cadmium, heavy metals, etc) [Hernandez and Osma, 2014]. The detection is performed by diverse technique, mostly optically and electrically.

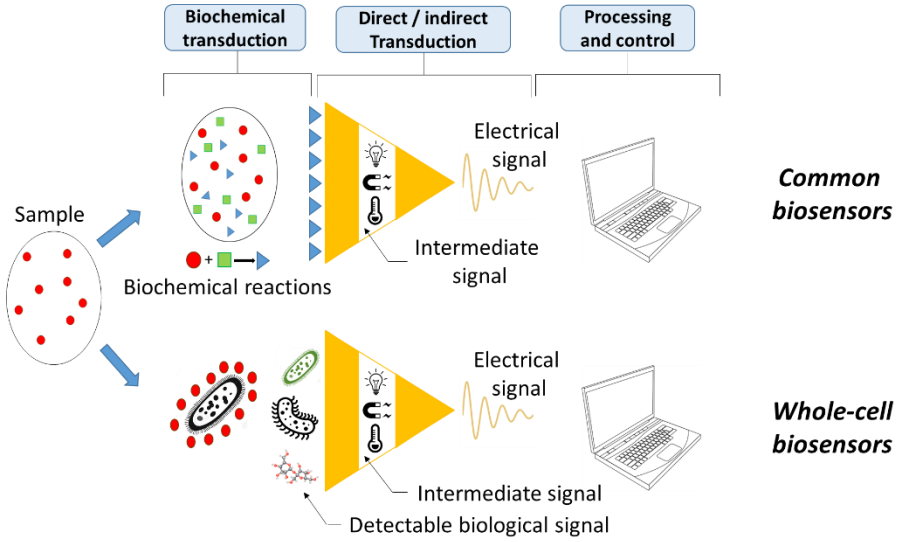

FIGURE 49 – COMPARISON BETWEEN COMMON BIOSENSORS AND WHOLE-CELL BIOSENSOR. IN COMMON BIOSENSORS, A BIOCHEMICAL REACTION IS INDUCED IN ORDER TO PRODUCE A DETECTABLE MOLECULE THAT IS, IN TURN, TRANSDUCED INTO AN ELECTRICAL SIGNAL. FOR A WHOLE-CELL BIOSENSOR, THE BIOCHEMICAL TRANSDUCTION IS PERFORMED BY A CELL WHICH PROPERTIES CHANGE IN THE PRESENCE OF THE MOLECULE OF INTEREST.

3.2. BIOSENSING MEETS SYNTHETIC BIOLOGY

Up to recently, whole-cell biosensors have been microorganisms that naturally emitted a detectable signal, such as bioluminescence [Lee *et al.*, 1992] or microorganisms in which natural genes emitting a detectable signal have been transfected from another organism. The recent emergence of synthetic

biology opened new perspectives (FIGURE 50), such as the detection of new molecules or of combinations of multiple molecules [Ausländer *et al.*, 2012] or the integration of basic signal processing function (amplification, filtering, Boolean function) inside the biological transducer [Bonnet *et al.*, 2013; Daniel *et al.*, 2013]. An early demonstration of such coupling was made in 2006 by an iGEM team of the Edinburgh University. They built an artificial construct based on two existing genes, namely *asrR* and *lacZ*, to change *Escherichia coli* bacteria into arsenic detectors. Reprogrammed *E. coli* alter the surrounding pH in the presence of arsenic [Aleksic *et al.*, 2007]. In the set-up described in the paper, pH is measured by an external device but the integration of a pH sensor (*e.g.* ISFET) within the *E. coli* can also be considered. A similar approach has then been applied for the detection of other heavy metals [Bereza-Malcolm, Mann and Franks, 2015]. In 2013, Wang *et al*. demonstrated a whole-cell biosensor sensitive to multiple inputs thanks to an artificial GRN based on metal-sensitive promoters. *E. coli* involving this construct were able to detect in parallel three heavy metals (namely arsenic, mercury and copper) and to perform Boolean operations [Wang, Barahona and Buck, 2013].

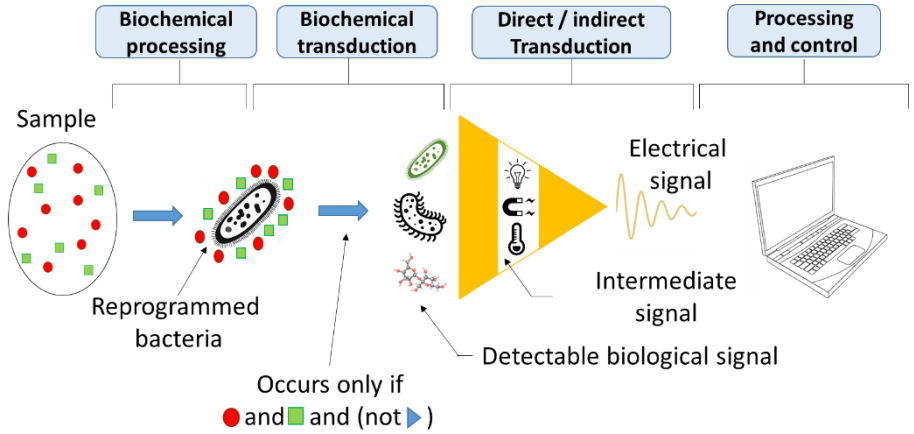

FIGURE 50 – DESCRIPTION OF A WHOLE-CELL BIOSENSOR BASED ON SYNTHETIC BIOLOGY. THE DETECTABLE BIOLOGICAL SIGNAL IS GENERATED ONLY IF A GIVEN CONDITION IS MET. REPROGRAMED BACTERIA ARE IN CHARGE OF SENSING AND PROCESSING THE MOLECULES OF INTEREST.

Applications also arise in the domain of innovative therapies for sensitive diseases, such as infectious diseases and cancer [Slomovic, Pardee and Collins, 2015; Saltepe *et al.*, 2018]. Here are some examples of recent achievements in this domain:

- In 2012, Xie *et al.* designed a HeLa cancel cell classifier (FIGURE 51A). A gene regulatory network using RNA silencing molecules (see CHAPTER 3 SUBSECTION 1.1) has been designed in order to detect a given combination of six µRNA which characterize cancer cells [Xie *et al.*, 2011]. On the published paper, the cancerous cell that had the good combination generated a red fluorescent signal detected optically but this fluorescent signal can eventually be replaced by a molecule that trigs apoptosis.
- In 2015, Danino et *al.* reprogrammed *E. coli* bacteria for the diagnosis of liver cancers (FIGURE 51B). Bacteria are ingested by the mouse and colonize only liver cancer cell. Once they are in a sufficient quantity, a biochemical reaction is triggered and bioluminescence proteins are synthesized. Then, the proteins are evacuated into mice urines that are analyzed optically. The presence of the bioluminescence signal is proof of a cancer cell.
- Engineered bacteriophages expressing a reporter gene upon infection are also a promising approach for the identification of contamination in food or beverages by pathogenic bacteria and

their toxins [Smartt and Ripp, 2011].

- In 2017, Rogers et *al.* designed a pipeline of 4 synthetic biosensors used for the detection of metabolites such as acrylate, glucarate, erythromycin or naringenin [Rogers *et al.*, 2015].

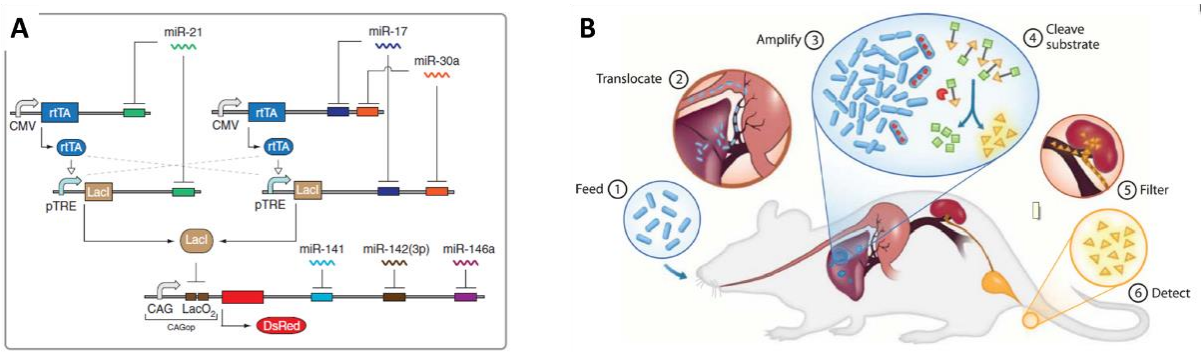

FIGURE 51 – TWO EXAMPLES OF WHOLE-CELL BIOSENSORS USING SYNTHETIC BIOLOGY. (A) IS AN ARTIFICIAL CONSTRUCT USED FOR HELA CELL CLASSIFICATION. DSRED IS PRODUCED IF A GIVEN COMBINATION OF THE 6 INPUT µRNA IS MET [XIE *ET AL.*, 2011]. (B) CORRESPONDS TO DANINO'S CONCEPT. THE MOUSE IS FED WITH MODIFIED BACTERIA. IF MICE HAVE CANCEROUS CELLS, BACTERIA PRODUCE A GIVEN MOLECULE THAT CAN BE DETECTED IN THEIR URINES. [DANINO *ET AL.*, 2015]

3.3. TOWARDS CELL-FREE SYNTHETIC BIOLOGY

While promising, whole-cell biosensors have several limitations. First, by definition, such devices are composed of living matter. Thus, mechanisms have to be implemented for their survival and the control of the growth of their population. Second, to be detected such way, a chemical compound has to cross the cellular membrane, which is not natively the case for most of the molecules. Thus, genes coding for extra endocytose mechanisms have to be added to the cell, in addition to gene achieving the sensing and the processing. Finally, whole-cell biosensors are not good candidates for sensitive application such as toxicology or pollution monitoring because sensing cells might get killed by what they are trying to measure.

Cell-free synthetic biology can be a good way to avoid such limitations. Cell-free synthetic systems use the cellular machinery to produce protein from DNA without the need of a living cell [Perez, Stark and Jewett, 2016; Lu, 2017]. Thus, it is possible to develop a biological transducer devoted to the detection without taking care about survival and replication. To operate, the artificial GRN has to be put in the presence of some required molecules (enzymes of transcription and translation DNA polymerase, ribosome, dNTP, tRNAs, amino acids …). This can be done in different environments: test tube, Petri dish, 96-well plate, microfluidic circuit, giant vesicle or deposit on different surfaces (silicon, a sheet of paper, metal …)

Cell-free synthetic biology is an emerging technique which has not yet been largely exploited in the field of biosensors. Nevertheless, results obtained with pioneer are very promising. For instance, Pardee's Zika virus detector deserves to be highlighted [Pardee *et al.*, 2016]. The cell-free device is deposited on a paper which color changes in the case of contamination. Sensors are manufactured at low cost and are stable at 20°C for one year. The diagnostic assay is fully automated by a microcontroller and takes 3 hours. Two years before, Pardee already demonstrated a paper-based low-cost test for Ebola virus [Pardee *et al.*, 2014].

4. SUMMARY

Several projects were described in this chapter. The common denominator of these projects is to provide the life science domain with innovative measurement devices. We focus on technologies that are cheap and/or efficient and/or miniaturized in order to target *in situ* measurement devices.

Projects about µNMR sensors are about to start. Indeed, our research team started investigations on this topic three years ago and produced last year the first prototype of NMR micro-probe. Moreover, two funding applications have been submitted on this topic: a 3-year INTERREG project and a 4-year ANR project. The first has been selected and will start in September 2019. The grant request covers the salary of a Ph.D. student for 3 years as well as the equipment, subcontracting and consumable required for the realization of the project. The second passed the first round of selection. Last year, it was put on the waiting list. We are hoping for better luck this year. This project would allow us to recruit a second Ph.D. student on this topic.

Projects about EIS are rather mid-term projects. If applications are clearly identified, we do not have yet, within our team, the know-how and the equipment required for the realization of electrodes. Thus, we are rather considering cooperation with other research teams specialized in this field, such as the Institut Jean Lamour in Nancy or the Institut for Microsystem Techniques in Freiburg. At short term, a collaboration with Julien Claudel from Nancy is going to be established in order to show the feasibility of EIS for PA invasion. Depending on the results, all the solutions enabling the realization of the project will be explored. The most likely is to start with a co-tutored academic thesis topic to clear the field, then to submit the project to a French-German call for projects (*e.g.* ANR/DFG or some other organizations promoting bilateral project).

Finally, the design of biosensors based on whole-cell or cell-free synthetic biology is a long-term project. For whole-cell sensors, the main challenge is the integration of living matter into the sensor and the long-term survival of the cells. For cell-free synthetic biology, the integration seems more straightforward but we have first to identify partners with experience with these emerging techniques.

Working on applications of such devices would be for me a unique opportunity to join two facets of my research activities: sensors and synthetic biology.

PART THREE -
TEACHING, TUTORING AND ADMINISTRATIVE TASKS

Beside my research activities, I am also well invested in my teaching at Télécom Physique Strasbourg (TPS), an engineering school at the University of Strasbourg. Since my appointment in 2008, I have given lectures and animated tutorials and practicals in digital and analog electronics and have created several new courses to keep the curriculum up to date. I took the responsibility of electronics specialization in 2014. Moreover, I also created new teaching on topics related to my research activities at the interface between electronics and biology in the new Health-IT diploma at TPS but also in the Biotechnologies School of Strasbourg (ESBS) and in the recent Cell Physics Master. More details on my teaching activities are given in SECTION 2 of this chapter.

During the last 10 years, I co-supervised 5 Ph. D. students and 11 Master students on projects related to my research activities. Additionally, I regularly the supervisor of student projects (about 2 per years) and of short-time internship taken by students from TPS and ESBS. I co-authored 11 communications in international conferences with at least one student in the author list. I was also the tutor of 3 iGEM (an international inter-university contest on synthetic biology) teams composed of students from TPS and the ESBS. A more exhaustive summary of my tutoring activities is given in SECTION 3.

Finally, I have also been given research and pedagogic administrative tasks. I am concerned by the management of my research team where I am currently thematic leader and participate in diverse commissions and councils. I submitted about 20 grant applications and I regularly review papers for international conferences and journals. More details on these aspects are given in SECTION 4.

CHAPTER 5 – EXTENDED RESUME

1. EDUCATION AND EXPERIENCE

EDUCATION

- 1998: Scientific *Baccalaureat* with honors.
- 2000: Certificate of the preparatory courses for "grandes Ecoles" at the *Lycee Fustel de Coulanges*, Strasbourg.
- 2003: Engineering degree at the *Ecole Nationale Supérieure de Physique de Strasbourg* (ENSPS, now renamed Telecom Physic Strasbourg).
- 2003: Master 2 degree in Instrumentation and Microelectronics at *the Université Louis Pasteur* (now renamed Master in Micro- and Nanoelectronics of the University of Strasbourg).
- 2006: Ph.D. degree in Engineering Sciences at the *Université Louis Pasteur*, Strasbourg.

EXPERIENCE

- Mar. – Aug. 2003: **Internship at *Optronis GmbH*, Kehl, Germany**.
  During this internship, I worked on the design of a highly sensitive CCD camera. I designed the driving electronics for the CCD sensor and implemented several digital noise reduction techniques on a field-programmable gate array (FPGA). I also participate in the characterization of the camera.
- Oct. 2003 – Nov. 2006: **Ph.D. thesis at the *Institut d'Electronique du Solide et des Systèmes*** (InESS, which is now a department of the ICube laboratory) in CIFRE convention with the company ***Micro Module SAS*** (Brest, France) company.
  The goal of my Ph.D. project was to study feasibility and interest in using optical processing to implement reconstruction algorithms for tomographic images. For that purpose, I established system-level models and realized set-up for two common mathematical operators used in images reconstruction: the Fourier transform and the Radon transform. For the first, experimental validations revealed strong limitations in terms of image quality. In addition, the model showed that the speed-up provided by the optoelectronic implementation was not relevant enough in comparison with a digital implementation. For the second, a complete prototype running at low speed was established and validated. We showed, with the system-level model, that with appropriate devices (*e.g.* high-speed high-dynamic spatial light modulator), optoelectronic architecture would overtake standard implementation in term of computation time by at least one order of magnitude. However, the price of the equipment and the quality of images remained two major bottlenecks.
  Ph.D. supervisor: Dr. Yannick HERVE, Univ. of Strasbourg
  Ph.D. co-supervisors: Dr. Wilfried UHRING and Dr. Jean-Baptiste FASQUEL, Univ. of Strasbourg.
- Sept. 2006 – Aug. 2008: **Teaching assistant (ATER) at the *Institut of Technology (IUT) of Haguenau* and at the ENSPS.**
  I was in charge of tutorial and practical in analog electronics, digital electronics and C language. I also supervised several student projects in the domain of electronics and informatics. During this period, I was attached to the InESS laboratory for my research activities.
- Since Sept. 2008: **Associate professor (Maître de conferences) at the ENSPS.**
  A detailed description of my teaching activities is given in PART ONE of this document. I am still with the *Heterogeneous Systems and Microsystem* team at ICube for the research.

- Sept. 2018 – Feb. 2019: **Research and thematic reconversion sabbatical (CRCT) at the *Albert-Ludwigs University of Freiburg*.**
  I was hosted at the BIOSS (Center for Biological Signaling Studies) in Prof. Winfried Romer's team. The goal of this CRCT was to challenge the biocomputational tools I have developed with real case studies. The preliminary outcomes of this experience, as well as prospective projects, are described in CHAPTER 4 of this manuscript.
- Since Jan. 2019: **Invited researcher at the *Albert-Ludwigs University of Freiburg*.**
  I got this position to carry on the project initiated during the CRCT.

HONORS AND DISTINCTION

I received the **Prix Espoirs of the University of Strasbourg** for my researches on the extension of electronic design automation environment to the biology. This award came with a 10,000 € grant to be used for the development of the activity. This money covered travel costs and registration fees for two international conferences as well as for the salary of two Master internships.

2. EDUCATIONAL ACTIVITIES

2.1. TEACHING

LIST OF COURSES

An exhaustive list of my teaching is given in TABLE 2. Courses marked with an asterisk correspond to the one I have set up. I am giving, on average, about 200 hours of 'face-to-face' teaching (which exclude project supervision and educational responsibilities).

PEDAGOGICAL INNOVATION

I took the responsibility for the first-year course on digital electronics in 2012. I deeply modified it in 2015 to make it more attractive and more interactive through the Moodle platform. Now it can be likened to a Massive Open Online Course (MOOC). In addition to standard material (a 120-page handout, PowerPoint presentations of the lectures, tutorials and practicals), students can find on the platform additional videos recalling prerequisites, detailing the main methods on examples and giving an overview of advanced circuits or methods. They can also self-evaluate by optional online quizzes, each corresponding to one tutorial. I am now considering to go further and transform this course into an actual MOOC taking profits of facilities of the Institut Mines Télécom. The course is accessible at https://moodle3.unistra.fr/course/view.php?id=1609 (anonymous access, password: padawan)

NEW COURSES IN BIOLOGY

Since 2013, I have also participated in the "Current Topics in Synthetic Biology" course given to third-year students and Master students at the Biotechnologies School of Strasbourg (ESBS). My teaching is divided into two parts. First, I give an 8-hour tutorial on the modeling of biological systems. This tutorial basically covers the theoretical notions described in CHAPTER 2 SECTION 1. Then, students have a 20-hour project during which they analyze a publication, build a model, simulate it with different approaches and, finally, analyze the simulation results to go beyond the publication content. Each student is associated with a 3-year student of TPS in the Health-IT diploma (corresponding to the *Project in Synthetic Biology* described in TABLE 2). Mixing students from both schools is very rewarding. Students discover challenges of transdisciplinary projects and of communication between engineers with very different backgrounds.

I am also involved in the Cell Physics Master since its creation in 2015. This Master is composed of lectures on basics of physics, biology, chemistry and mathematics and of eight 2-day practicals. I'm animating two of them: the "numerical simulation" workshop, which was quite similar to the tutorial given at the ESBS, and the "electronics" workshop. The last one follows a double objective: giving the students the basics in electronics (Kirchhoff's law, operational amplifier, digital gates) and highlighting analogies that can be found between electronic circuits and several behaviors encountered in biology (feedback and feedforward loops, gene regulatory networks, etc.)

TABLE 2 – EXHAUSTIVE LIST OF MY TEACHINGS

Year / option	Title of the teaching + content	Hours	Period
1A TPS	Basics in digital electronics See the description in PEDAGOGICAL INNOVATION subsection	50 h	2011-…
	Sensors applied to automotive* Overview of sensors for different physical quantities (accelerometer, optical tachymeter, thermal regulation), common biasing and processing circuits.	20 h	2010-2014
2A TPS	Basics on microcontrollers Microprocessor/microcontroller architecture, assembly language, input/output, interruptions. App.: realization of an MP3 player with Arduino.	20 h	2013-2018
	Technologies of digital devices* Analog-to-digital and digital-to-analog converters, memories, FPGA.	15 h	2009-…
	Design of digital integrated circuits* Design flow of integrated circuits, digital synthesis, technologies of standard cells, practical with Cadence.	10 h	2009-…
	VHDL and FPGA programming* Advanced VHDL, simulation, FPGA programming. Application: implementation of filtering operators in FPGA.	15 h	2012-…
	Design of printed circuit board* PCB design flow, technologies of passive devices, standard packages, PCB design rules, good practices, practical on Altium Designer.	15 h	2013-
	Introduction to biology* Basics in biochemistry, biotechnologies, metabolism, genetics and cell biology. Application: MATLAB modeling of a biological system.	30 h	2011-2017
3A TPS Electronic and Embedded Systems	Compact modeling and device characterization* Golden rules for compact modeling, Verilog-A for device-level modeling, fitting functions, model validation a characterization, practical with IC-CAP.	12 h	2009-2017
	Introduction to digital communications* (A)Synchronous data transmission, binary codes, error detection and correction, introduction to cryptography. Application of FPGA.	12 h	2015-…
3A TPS Health IT	Project in synthetic biology* See the description in NEW COURSES IN BIOLOGY subsection	40 h	2013-…
	Realization of a DNA chip Practical organized at the CIME in Grenoble. Glass surface functionalization, DNA extraction, fluorescent labeling, PCR, electrophoresis, data analysis.	15 h	2013-…
3A ESBS	Modeling and simulation in systems biology* See the description in NEW COURSES IN BIOLOGY subsection	8 h	2013-…
M2 Cell Physics	Workshop on numerical simulations* See the description in NEW COURSES IN BIOLOGY subsection	16 h	2015-…
	Workshop on electronics* See the description in NEW COURSES IN BIOLOGY subsection	16h	2015-…

2.2. ACADEMIC RESPONSIBILITIES

ELECTRONIC AND EMBEDDED SYSTEM SPECIALTY

I have been in charge of the electronic specialty at Télécom Physique Strasbourg since 2014. This responsibility includes the update of the list of courses for the specialty, the establishment of the timetable for the elective courses, the follow-up of the students in this specialty, the organization of a

jury for the evaluation of final year projects, the communication about the specialty, the recruitment of academic and/or industrial lecturers, the prospective for industrial projects, the coupling with the *Master of Micro and Nanoelectronics* and the animation of the educational team.

In 2017, the name of the specialty changed from *Micro and Nanoelectronics* to *Electronics and Embedded System* in order to put the emphasis on the digital aspects and to distinguish the TPS specialty and the Master 2 one. Moreover, in 2018, I was also in charge of a complete revision of the organization of electronics teaching at TPS. The new organization is given in FIGURE 52.

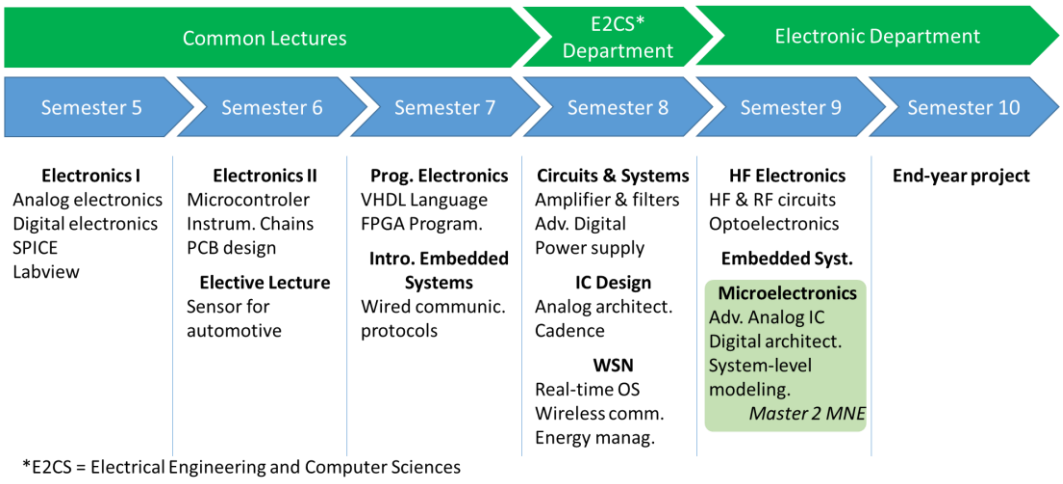

FIGURE 52 - NEW ORGANIZATION OF THE TEACHING OF ELECTRONICS AT TÉLÉCOM PHYSIQUE STRASBOURG

HEALTH-IT DIPLOMA

In 2011, TPS opened a new Health-IT diploma to train engineers at the interface between engineering sciences and healthcare. This curriculum covers two aspects of healthcare: medical engineering (imaging, surgical robotics, etc.) and biotechnologies (lab-on-chip, biosensors, innovative therapeutics, etc.). I participated with my colleague Pr. Christophe Lallement (co-leader of this new diploma) to the elaboration of courses list for the innovative therapeutics specialization. I also participated in the organization of the candidate selection committee in Paris between 2011 and 2015.

STUDENT TEACHING EVALUATION

Since 2012, I have been in charge of the student teaching evaluation process at TPS. This task consists in updating of the evaluation forms, setting up the website for the evaluation campaign, communicating toward students, gathering and analyzing the result and reporting toward TPS's Improvement Council. Last year, a new evaluation process has been established for the dual training cursus. This new process is still under experiment this year but will probably be extended to all the cursus in 2020.

2.3. EDUCATIONAL COMMUNICATION

I regularly share my teaching experiences during the Pedagogical Days of the National Coordination for Training in Microelectronics (JPCNFM):

- 2012: new teachings on synthetic biology and feedback on the experience of common projects between students from TPS and the ESBS.
- 2014: new teachings around lab-on-chip in the Health-IT curriculum.
- 2016: training courses on the design of analog integrated circuits.

- 2018: mock-up shared for the practical in electronics and in automatics (OPA-based continuous-time compensator).

Extended versions of 2012, 2014 and 2018 communications were also published in the *Journal of the teaching on sciences and technologies for information and systems* (J3EA, a French journal with an educational scope).

2.4. SCIENCE POPULARIZATION

I also participated in science popularization events. A complete list is given in TABLE 3. In 2018, for the *Fête de la Science*, we realized an escape game on the genetics with a former Ph.D. student, Dr. Elise Rosati. Participants had 60 minutes to identify among 20 test tubes the one that contains an antidote that would save the world from a dreadful virus. For that, players had to search a lab to find clues and to solve puzzles related to live science (computation of the molar mass of glucose, matching of genetic sequences, translating a DNA sequence into an amino acids sequence, computing the truth table of a gene regulatory network) in order to obtain the color and the number of the tube. Scientific concepts behind puzzles were explained on posters hang on in the room. The game was a big success and was well publicized, *e.g.* a half-page article in a local newspaper. This experience was for me very rewarding and strengthened my interest in the development of serious game for teaching and scientific popularization.

TABLE 3 – PARTICIPATION IN SCIENCE POPULARIZATION EVENTS

Date	Event	Theme
2004	Fête de la science	High-speed imaging
2005	Fête de la science	Optoelectronic and optical signal processing
2010	Conference	Microelectronics and synthetic biology
2012	Mediation in high school	Optical experiments: limits of the visible
2014	Fête de la science	Experiments with microfluidics and lab-on-chip
2015	Fête de la science	See the invisible
2018	Fête de la science	Escape Game

2.5. INVOLVEMENT IN COMMITTEES

TABLE 4 summarizes my involvement in research- and/or teaching-related councils and commissions.

TABLE 4 – INVOLVEMENT IN COUNCILS, COMMISSION AND JURY

Authority	Dates
InESS Laboratory Council	2005 – 2012
Improvement Council – Télécom Physique Strasbourg	2009 – 2013
School Council – Télécom Physique Strasbourg	2013 – 2017
Health-IT candidate selection committee - Télécom Physique Strasbourg	2011 – 2015
Selection committee for the recruitment of an associate professor – Unistra	2011
Expert Commission of the Academic Section 61-63 - Unistra	2013 - …
Qualification-based admission jury - Télécom Physique Strasbourg	2013 - …
Selection committee for the recruitment of an associate professor – Unistra	2013
Library Commission – Télécom Physique Strasbourg	2016 - …
ICube Electronic department Council	2018 - …

3. TUTORING

3.1. PH.D. THESIS

During the last 10 years, I co-supervised of 5 Ph.D. students on different projects. I took profit of two Ph.D. grants of the doctoral school to initiate the research activity on the extension of EDA tools for biological engineering. For the second Ph.D., we recruited a student with a background in biotechnology instead of in microelectronics. This experience was very rewarding. Thus we renewed the experience with a Pharm.D degree and an engineering degree in chemistry. Titles and co-supervision are summarized in TABLE 5. Short summaries of the Ph.D. project of students I co-supervised are given in the following.

TABLE 5 – CO-SUPERVISION OF PH.D. STUDENTS

Student	Title	Defense	Co-supervision
Nicolas CHEVILLON	Study and compact modeling of ultimate FinFET transistor. Link: http://www.theses.fr/2012STRAD016/document	2012	C. Lallement (Dir. 50%) F. Prégaldiny (40%) **M. Madec (10%)**
Yves GENDRAULT	Structuring the design flow for synthetic biology Link: http://www.theses.fr/2013STRAD022/document	2013	C. Lallement (Dir. 50%) **M. Madec (50%)**
Stéphanie GUITON	Modeling and design of a lab-on-chip for the detection of micropollutants in water.	-	C. Lallement (Dir. 50%) **M. Madec (30%)** A. Rezgui (20%)
Elise ROSATI	Computer-aided design tools for biological engineering. Link: https://www.theses.fr/2018STRAD008/document	2018	C. Lallement (Dir. 50%) **M. Madec (50%)**
Alexi BONAMENT	Virtual prototyping environment for the design of biosensors	Exp. 2020	C. Lallement (Dir. 50%) **M. Madec (30%)** A. Rezgui (20%)

NICOLAS CHEVILLON

Nicolas Chevillon was in charge of the development of design-oriented compact models for FinFET transistor valid at the nanoscale dimension. He developed a Verilog-A model that takes into account the short channel effects, the channel length modulation, the mobility degradation, the quantum mechanics effects and the transcapacitances. The model has been validated by comparison with 3D simulations and was used to establish a design kit composed of gate-level models of the most common logic gates realized with FinFET. Besides, he also developed a model for multigate SOI MOSFET with lightly doped channels and temperature dependence. I co-supervised Nicolas on the development of the design kit (see CHAPTER 1 SUBSECTION 1.1).

- Background of the student: Master Degree in Microelectronics from the Unistra.
- Type of project: European Project FP7 COMON (COmpact MOdeling Network)
- Publications: 1 international journal, 2 international conferences, 1 national conference.

YVES GENDRAULT

Yves Gendrault was the first Ph.D. student on the topic of synthetic biology and more specifically on the adaptation of EDA tools to this emerging field. He worked on the formalization of the biological models (see CHAPTER 2 SUBSECTION 2.1). We co-tutored an iGEM team aiming at the development of a VHDL-AMS model generator for the biological system (see CHAPTER 2 SUBSECTION 2.2). He also developed

the first version of GeNeDA (see CHAPTER 2 SUBSECTION 4.2). Yves's Ph.D. got an award from the Foundation of the University of Strasbourg in 2014.

- Background of the student: Master Degree in Microelectronics from the Unistra.
- Type of project: Academic grant from the doctoral school.
- Publications: 3 international journals, 9 international conferences, 2 national conferences.

STÉPHANIE GUITON

Stéphanie Guiton's Ph.D. topic was about the development of a lab-on-chip for the detection of pollutants in drinking water (see CHAPTER 2 SUBSECTION 3.1). She was in charge of the design and the experimental validation of the lab-on-chip, the electrical characterization of the ISFET used for the pH measurement and the study of the biochemical reaction that induces a pH change depending on the concentration of the molecule of interest. Besides, she had to develop a system-level model of the lab-on-chip which includes models for the electronics, the microfluidics and the biology. I co-supervised Stéphanie more specifically on this part. Unfortunately, due to health issues, she was not able to finish her Ph.D. project.

- Background of the student: Engineer Degree from the National School for Water and Environmental Engineering (ENGEES, Strasbourg).
- Type of project: CIFRE partnership with the company Bürkert SAS.
- Publications: 1 international journal, 1 international conference, 1 national conference.

ELISE ROSATI

Elise Rosati was the second Ph.D. student working on the development of CAD tools for biological engineering. Her Ph.D. project was divided into two part. First, she worked on design automation for gene regulatory networks (see CHAPTER 2 SECTION 4). She participated in the development of GeNeDA and explored the potential of nature-inspired algorithms for the design at a lower level of abstraction. Second, she developed BB-SPICE 3D (see CHAPTER 2 SUBSECTION 2.5), a simulator based on SPICE used for the simulation of reaction-diffusion problems.

- Background of the student: Master and Engineer Degree in Biotechnologies from the ESBS.
- Type of project: Academic grant from the doctoral school.
- Publications: 4 international journals, 13 international conferences, 1 national conference.

ALEXI BONAMENT

Alexi Bonament is doing his Ph.D. on the development of a virtual prototyping environment for biosensors and lab-on-chip that takes electronics, microfluidics and biology into account. For the electronics, he is in charge of the development of a database gathering design-oriented models of the most common tranducers. For the microfluidics and the biology, he is extending BB-SPICE 3D in order to add the convention into the simulator. Moreover, he is also working on the coupling of high-level models of microfluidics channels (flow, pressure and hydraulic resistor) and low-level ones (convection-diffusion-reaction equation) (see CHAPTER 3 SUBSECTION 3.3). Finally, he is also designing an experimental set-up to validate microfluidic models.

- Background of the student: Pharm.D degree of the University of Claude Bernard (Lyon) and Engineer Degree in Chemistry of the Chemistry and Physics Engineering School (CPE Lyon).
- Type of project: Academic grant from the doctoral school.
- Publications: 2 international journals, 2 international conferences.

3.2. MASTER 2 STUDENTS

During the last 10 years, I also supervised 11 Master students. The list is given in TABLE 6. Eight of them came from the Master of Microelectronics of the University of Strasbourg, two from the Master Cell Physics of the University of Strasbourg and one from the Master of Electrical Engineering of the University of Guilan, Iran. Six of these Master projects led to a communication in international conferences.

TABLE 6 – SUPERVISION OF MASTER 2 STUDENTS

Student	Title	Year	Communication
Yves GENDRAULT	Modeling of biological gene regulatory network in VHDL-AMS at the Boolean and analog level of abstraction.	2010	IEEE MIXDES
Loïc BAUER	Adaptation of a logic synthesizer for the design of gene regulatory network and modeling in SystemC-AMS	2013	IEEE BIOCAS
Martin LEMAIRE	Modeling, simulation and design automation of gene regulatory networks with fuzzy logic.	2014	IEEE BIOCAS
Laurent OSBERGER	Compact modeling of vertical Hall-effect device and assessment of spinning-current technique.	2014	IEEE NEWCAS
Nicolas TOUSSAINT	Implementation of genetic algorithms for the design and the optimization of gene regulatory networks	2015	Evo Star
Olufemi BOLAJI	Development of BB-SPICE: modeling and simulation of biological systems with SPICE	2016	IEEE NEWCAS
Nicolas GAYTE	Study of intracellular calcium signaling and implementation of evolutionary algorithms	2017	
Kadim BABOU	Modeling and simulation of vertical Hall-effect device with COMSOL and extraction of compact models.	2017	
Adel ABDELAK	Modeling and simulation of vertical Hall-effect device with COMSOL and extraction of compact models.	2017	
Mohammadreza DOLATPOOR	Design and simulation of a power amplifier for micro-NMR applications.	2018	
Thomas GARELLO	Design-oriented modeling of a micro-NMR system: driving and processing electronics, magnetic coupling, chemistry	2019	

3.3. OTHER PROJECTS AND INTERNSHIP TUTORING

STUDENT PROJECTS

Since 2008, I supervise in average two student projects per year in all of the curriculum proposed at TPS. Such projects (about 300 student-hour for a first-year project and 600 s-h for a second-year project) can be either related to my research activity or submitted by companies. Here are some examples:

- Realization of a coins counting system for CashDev, Vagney, France (2018)
- Development of a smart patches for a connected catheter for ICube (2018)
- Development of an acquisition system for a ferromagnetic nanoparticle detector for Eurorad, Eckbolsheim, France (2015 and 2016)
- Realization of a translator between SBML and other languages for ICube (2015)
- Development of a smart eco-driving human-vehicle interface for Viveris, Oberhausbergen, France (2011)

Besides, I participated in the supervision of Licence 3 and Master 1 student projects of the Master of engineering at the University of Strasbourg. In addition, I co-supervised with Pr. François Pêcheux (LIP6, Sorbonne University) a student project of the Master of Computer Science of the University of Paris 6 on the deployment of biological simulators on graphics processing units (GPUs) in 2018.

SHORT-TIME INTERNSHIPS

Since 2008, I also supervised about 30 students for short-time internships (less than 2 months). Most of them are first-year students at TPS. Some others came from the ESBS or the Magister of Physics. The topics of the internships correspond to either specific needs related to a research project, or a subject related to my teaching activities. Here are some examples:

- Realization of a contactless payment system for the student lounge at TPS (2016 and 2018)
- Development of a website for an online version of GeNeDA, see CHAPTER 2 SUBSECTION 4.2 (2015)
- Realization of electronic boards for the first-year practicals (2012, 2015 and 2017)
- Development of exercises and project for the Arduino course (2014)
- Development of a library of VHDL models (2011).

IGEM PROJECT

iGEM (International Genetic Engineering Machine) is an international inter-university contest organized by the Massachusetts Institute of Technology (MIT) and reserved for undergraduate students. Participating teams choose a topic related to synthetic biology and develop it between February and October. I co-tutored three iGEM different teams:

In 2008, the team was composed of 7 students from the ESBS. They worked on a cell division counter realized with GRNs. I gave the team some tricks on the modeling and simulation of the GRN with VHDL [iGEM ESBS, 2008]. In 2010, a mixed team composed of students from TPS and ESBS worked on the realization of a light-controlled protein degradation system, both on the experimental and computational aspects [iGEM ESBS, 2010]. In 2011, I was responsible for a team made up of students from TPS only who competed in the software track of the competition. Their objective was the realization of a VHDL-AMS model generator for GRN [iGEM ENSPS, 2011]. Each time, the team were awarded by a bronze medal for honorable work.

3.4. PUBLICATION AND COMMUNICATIONS

In addition to the publication already mentioned, *i.e.* the education-related publications (SUBSECTION 2.3) and the publication related to a Master 2 project (SUBSECTION 3.2), several short-time internships or student projects have also been published in national or international conferences:

- In 2009, results of the first iGEM project (K. Karstens, S. Dittman, M. Gersbacher, R. Sorg, M. Wild, M. Müller and P. Bourgine) were the heart of a presentation given for the conference IEEE TAISA-NEWCAS 2009 in Toulouse, France, on the analogies between electronics and biology [Madec *et al.*, 2009].
- In 2012, results of the last iGEM project (M. Andraud and V. Wlotzko) were presented at IEEE EMBC 2012, San Diego, California [Gendrault *et al.*, 2012].
- In 2015, the project in synthetic biology realized by 2 TPS students (M. Renou and T. Wallois) and 2 ESBS students (Z. Blank and L. Talide) on the modeling of intercellular signaling was presented at the *student workshop* of the advances in System and Synthetic Biology Spring School, Strasbourg, France [Talide *et al.*, 2015].

- In 2018, the results of a TPS short-time internship (V. Pasteur) on the modeling of the porosity of double-emulsions were presented at the MicroFlu 2018 conference, Strasbourg, France [Dumas *et al.*, 2018].
- In 2018, the results of a short-time internship of two students from the Magister of Physics (A. Bisquet and R. Goerlich) on the realization of sequential GRN were presented at the *student workshop* of the advances in System and Synthetic Biology Spring School, Evry, France [Goerlich *et al.*, 2018].
- In 2018, the results of several successive short-time internships were presented at the Pedagogical Days of the National Coordination for Training in Microelectronics (JPCNFM). The first poster described the realization of a contactless payment system for the student lounge at TPS (M. Mounissens, R. Enjalbert, E. Michelet, R. Bounoua) [Mounisens *et al.*, 2018]. The second was one about the realization of a set of willingly faulty electronic boards to train students to the debugging of digital circuits (M. Labonne, K. Wanaverberque, P. Bernou, M. L'Huillier) [Rosati, Madec, Rezgui, *et al.*, 2018].

4. Responsibilities Related to the Research Activities

4.1. Involvement in my Research Team

After my appointment in the team in 2008, I was first assigned as a go-between for two research thematics, namely the *compact modeling of advanced CMOS devices* (Pr. Christophe Lallement) and the *design of integrated sensors* (Pr. Luc Hébrard). In 2010, Pr. Christophe Lallement and Pr. Jacques Haiech from the Laboratory of Innovative Therapeutics (University of Strasbourg) initiated a new research activity on the possible interfaces between electronics and biotechnologies. I took an active part in the take-off of this activity, which became in 2014 a transdisciplinary research orientation of our research team entitled *System Engineering for Medical and Biological Applications* (SEMBA). I was the leader of SEMBA between 2014 and 2018. Since 2018, I have been promoted leader for one of the two thematics of our team, namely the *technologies of computer-aided design.* I also participated in the redaction of the research activities summary and the prospective for the previous HCERES evaluation in 2017.

TABLE 7 – LIST OF GRANT APPLICATIONS MANAGED AS A COORDINATOR OR PRINCIPAL INVESTIGATOR FOR ICUBE

Organism	Date	Project	Result
Unistra (BQR)	2010	Characterization of Hall-effect sensors	35 k€
ANR (JCJC)	2013	Design tool for synthetic biology	Not granted
ANR (JCJC)	2014	Design tool for synthetic biology	Not granted
Unistra (API ICube)	2015	Genetic programming for GRN design automation	6.5 k€
Aviesan	2015	Connected hospital room	Not granted
ANR (JCJC)	2015	Design tool for synthetic biology	Not granted
ANR (PRC)	2016	Calcium Signaling Computer-Aided Design Environment	Second round
Unistra (Prix espoir)	2016	Extension of microelectronic CAD tools for biology	10 k€
ITMO (HTE)	2016	Study of cell-cell communication in glioblastomas genesis	Not granted
HFSP	2016	Study of cell-cell communication in glioblastomas genesis	Not granted
CNRS	2017	microNMR spectroscopy for chemical reaction monitoring	Not granted
Unistra (USIAS)	2017	Calcium Signaling Computer-Aided Design Environment	Not granted
ANR (PRC)	2017	Calcium Signaling Computer-Aided Design Environment	Not granted
Unistra (API ICube)	2017	Modeling of germinal center	7 k€
ANR (PRCE)	2018	microNMR spectroscopy for chemical reaction monitoring	Waiting list

Unistra (Idex)	2018	Design of a power amplifier for microNMR applications	4 k€
ANR (PRCE)	2019	microNMR spectroscopy for chemical reaction monitoring	Under evaluation
Interreg OS	2019	Sensors for the monitoring of drinking water quality	1 M€
EU (Eurostars)	2019	A miniaturized detector for pesticides in drinking water	Under evaluation

TABLE 8 – LIST OF GRANTED PROJECTS IN WHICH I HAVE BEEN INVOLVED

Organism	Date	Project	Leader / HSM PI
ANR (JCJC)	2005	New technologies for magnetic sensors	L. Hébrard
European (FP7)	2008	Compact modeling Network	B. Iniguez / C. Lallement
Interreg OS	2012	Network for synthetic biology	C. Kedinger / C. Lallement
CIFRE	2013	Lab-on-chip for the detection of micropollutant	C. Lallement
Unistra (API ICube)	2015	Modeling of germinal center	A. Jeandin

4.2. PROJECT FOUNDING AND MANAGEMENT

Since 2010, I have been submitting 19 grant applications toward different organisms as a coordinator or as a principal investigator for ICube. They are summarized in TABLE 7. Moreover, I have been involved in 5 granted projects (TABLE 8). The two more recent projects (ANR project submitted in 2019 and the INTERREG project) are respectively described in CHAPTER 4 SUBSECTIONS 1.2 and 1.3.

TABLE 9 – AWARDS AND JOURNAL COVERS

Date	Event	Award	Paper
2010	IEEE MIXDES Wroclaw, Poland	Poland Section IEEE ED Chapter Special Award	Design methodology for synthetic biosystems
2012	IEEE NEWCAS Montréal, Canada	Best Paper Awards	Compact Modeling of Vertical Hall-effect Device: Electrical Behaviour
2014		Cover IEEE Trans. on Biomedical Engineering	Modeling Biology With HDL Languages: A First Step Toward a Genetic Design Automation Tool Inspired From Microelectronics
2016	CDN-Live Munchen, Germany	Academic Track Best Paper Award	Application of Electronic Design Automation in Biological Context

4.3. TUTORIALS, KEYNOTE INVITATION, AWARDS

I received the best paper awards at three international conferences and one of my paper made the cover of an IEEE transaction on Medical Engineering issue (TABLE 9). I have also been invited to give keynotes for 4 events (TABLE 10) and tutorials during 7 conferences and/or thematic schools (TABLE 11)

TABLE 10 – LIST OF TUTORIALS

Date	Event	Topic
2015	IEEE MIXDES Lodz, Poland	Challenges in Design-oriented Modeling in Biology joined keynote with C. Lallement
2015	MOS-AK Graz, Austria	Modeling of biological systems with SPICE
2016	SRC Workshop Newcastle, UK	Synergy between Biology DA – Electronic DA Introducing keynote and panelist
2017	JNRDM Strasbourg, France	Biosystems: a new challenge for microelectronics

TABLE 11 – LIST OF KEYNOTES

Date	Event	Topic
2015	aSSB Thematic School Strasbourg, France	Use of fuzzy logic for the modeling of GRN
2016	aSSB Thematic School Evry, France	Use of fuzzy logic for the modeling of GRN
2016	Training Courses on Compact Modeling Tarragona, Spain	Application of EDA tools in the biological context
2017	aSSB Thematic School Lyon, France	Use of fuzzy logic for the modeling of GRN
2017	European Summer School on the Physics of Living Matter Strasbourg, France	Modeling and simulation of biological systems
2018	aSSB Thematic School Evry, France	Use of fuzzy logic for the modeling of GRN
2018	IEEE NEWCAS Montréal, Canada	Virtual prototyping of biosensors

4.4. EVENT ORGANIZATION

In 2015, I was a member of the Organization Committee of the Advances in Systems and Synthetic Biology (aSSB) thematic school organized at Télécom Physique Strasbourg. The 5-days event attendance was about 80 including graduate and undergraduate students from all European countries as well as 20 researchers with a background in biology, mathematics, physics or computer sciences.

In 2016, I organized a joint thematic day between two GDRs (Soc² and BioSynSys) on the potential interactions between microelectronics and synthetic biology. There were about 20 attendees. The agenda of the day included a presentation of the two GDRs (Pr. Luc Hébrard and Dr. Gilles Truan), a didactic introduction to synthetic biology (Pr. Matthieu Jules), three keynotes (Pr. Franck Molina, Dr. Yannick Rondelez and myself) and a round table.

In 2017, I was Technical Program Chair (TPC) for the IEEE NEWCAS conference organized in Strasbourg from 25th to 28th of June 2017. About 150 researchers from all over the world attended at the conference. As a TPC, I was in charge of the preparation of the call for papers, the recruitment of Track Chairs and Reviewer Committee Members, the follow-up of the review process, the selection of papers and the scheduling of the conference. Following the conference, I was also been co-editor of the Special Issue on Analog Integrated Circuits and Signal Processing gathering a selection of the best papers of the conference.

4.5. REVIEW AND PROJECT EVALUATION

I am regularly reviewing papers for international conferences and journals. A list over the four last years is given in TABLE 12.

I also participate in the selection committee for the recruitment of two colleagues (associate professor at TPS) in 2011 and 2013. Moreover, in 2018, I was asked to review an ANR project in microelectronics as well as a grant application from the Engineering and Physical Sciences Research Council (EPSRC, UK) in the domain of synthetic biology.

4.6. INVOLVEMENT IN COMMITTEES

TABLE 4 summarizes my involvement in research- and/or teaching-related councils and commission.

TABLE 12 – JOURNALS AND CONFERENCE REVIEW OVER THE LAST FOUR YEARS

Name	Conf / Journal	Number of reviews				
		Total	2015	2016	2017	2018
ACS Synthetic Biology	Journal	1		1		
Biochiomica and Biophysica Acta	Journal	1	1			
Biochemistry and Biophysics Report	Journal	1		1		
Biomateriala Acta	Journal	1				1
Electronics Letter	Journal	1		1		
Sensors and Actuators A	Journal	1		1		
Analog Integrated Circuits and Signal Proc.	Journal	3				3
Transaction on Electronic Devices	Journal	3	1		1	1
IEEE NEWCAS	Conference	27	4	3	17	3
IEEE BioCAS	Conference	3		1	2	
International Conference on Microelectronics	Conference	4	4			

CONCLUSION

As a conclusion, I could say that I consider myself lucky. Lucky with my Ph.D. which allowed me to discover the power of design-oriented modeling of complex systems, lucky to have been recruited as a young padawan in my research team, lucky for the trust my colleagues put in me, lucky to have meet enthusiast and engaging persons that opened my mind on new domains and issues (*e.g.* biology) and lucky to have been able to rely on very good Ph.D. (5) and Master 2 students (11).

The research activities I described in the first part of the manuscript gave me a strong combination of skill in system-level and design-oriented modeling for multiphysics systems and in biology. With this double culture, I can more easily discuss with researchers from the domain of life science and understand their issues. This point is the cornerstone of for the prospective research described in the second part of the manuscript.

Up to now, I mostly worked on the software/modeling aspects. Of course, I would like to pursue this activity and develop, in an intermediate term, a complete virtual prototyping environment for biological applications such as synthetic biology, biosensors and/or lab-on-chip. However, according to me, it is necessary to go toward the realization of actual devices and systems.

About CAD tools for biosystem, most of the academic investigations have already been done and proof of concept has been made on the virtual use case. Now is the time to apply these tools in actual cases. Thus, I can imagine pursuing this activity in the context of applicative projects (typically ANR, European projects) rather than in the context of academic ones.

Conversely, the design of biosensor based on µNMR, impedance spectroscopy and/or whole-cell devices, is quite new for us (with the exception of µNMR which has been investigated in our team for 3 years). Preliminary research and feasibility studies have to be performed before envisaging a grant application. An academic Ph.D. project co-supervised by a biologist and/or colleague from another laboratory that has more accustomed to these techniques would be perfect for such a preliminary investigation.

Still on the applicative side, we are establishing (or would like to establish) collaborations with several academic partners inlife science. Three of them are our neighbor on Illkirch's campus: the Faculty of Pharmacy, the Laboratory of Biotechnology and Cell Signaling and the Institute of Genetics and Molecular and Cellular Biology. Moreover, I just spent 6 months at the Center for Biological Signaling Study in Freiburg in Pr. Winfried Römer's team. This sabbatical period in immersion in a biological lab gave me the opportunity to start several promising collaborative projects and lead to 3-year Invited Professor position.

_____

Having an accurate long-term vision of my research activity is not so easy: the evolution of a researcher's career also depends on opportunities he gets and, to be quite honest, is also driven by success in funding applications. Therefore, I cannot say which of the perspectives presented in the second part will succeed and which will stay as a draft on the paper. However, I can say that I would be very proud to contribute in developing software tools that could have an impact on heterogeneous systems applied to biology as significant as SPICE, Verilog or Cadence had on the development of microelectronics over the last decades.

Finally, in parallel with my research activity, I will pursue my commitment to the educational side. The short-term goal is to take over the evolution of electronic teaching for the next three years. I also would like to further develop project-based learning, being convinced that know-how is more essential than knowledge. Moreover, following the rewarding experiences I got with the ESBS and the Cell Physics Master, I would be pleased to get involved in other curriculum and teach to students with different cultures and backgrounds. Finally, I would like to federate students around major projects. iGEM was, for instance, a very rewarding experience. Innovation contests, such as Hackathons, or Serious Game contests would also be very exciting.

May the force be with me!

REFERENCES

Agence Nationale de la Recherche (2016) *Projet IvMRS (Sonde implantable miniature pour Spectroscopie de Résonance Magnétique in-vivo...) | ANR - Agence Nationale de la Recherche*. Available at: http://www.agence-nationale-recherche.fr/Projet-ANR-16-CE19-0002 (Accessed: 31 January 2019).

Ahrens, E. T. and Bulte, J. W. M. (2013) 'Tracking immune cells in vivo using magnetic resonance imaging', *Nature Reviews Immunology*. Nature Publishing Group, 13(10), pp. 755–763. doi: 10.1038/nri3531.

Akinwande, D. *et al.* (2008) 'Analytical ballistic theory of carbon nanotube transistors: Experimental validation, device physics, parameter extraction, and performance projection', *Journal of Applied Physics*. American Institute of Physics, 104(12), p. 124514. doi: 10.1063/1.3050345.

Aleksic, J. *et al.* (2007) 'Development of a novel biosensor for the detection of arsenic in drinking water', *IET Synthetic Biology*, 1(1), pp. 87–90. doi: 10.1049/iet-stb:20060002.

Ali Javey, † *et al.* (2005) 'High Performance n-Type Carbon Nanotube Field-Effect Transistors with Chemically Doped Contacts'. American Chemical Society. doi: 10.1021/NL047931J.

Amar, P. and Paulevé, L. (2015) 'HSIM: A Hybrid Stochastic Simulation System for Systems Biology', *Electronic Notes in Theoretical Computer Science*. Elsevier, 313, pp. 3–21. doi: 10.1016/J.ENTCS.2015.04.016.

Amin, A. M. *et al.* (2007) 'Aquacore', in *Proceedings of the 34th annual international symposium on Computer architecture - ISCA '07*. New York, New York, USA: ACM Press, p. 254. doi: 10.1145/1250662.1250694.

Amin, N., Thies, W. and Amarasinghe, S. (2009) 'Computer-aided design for microfluidic chips based on multilayer soft lithography', in *2009 IEEE International Conference on Computer Design*. IEEE, pp. 2–9. doi: 10.1109/ICCD.2009.5413185.

Ananthanarayanan, V. and Thies, W. (2010) 'BioCoder: A programming language for standardizing and automating biology protocols', *Journal of Biological Engineering*. BioMed Central, 4(1), p. 13. doi: 10.1186/1754-1611-4-13.

Anders, J. *et al.* (2009) 'A single-chip array of NMR receivers', *Journal of Magnetic Resonance*. Academic Press, 201(2), pp. 239–249. doi: 10.1016/J.JMR.2009.09.019.

Anderson, J. C., Voigt, C. A. and Arkin, A. P. (2007) 'Environmental signal integration by a modular AND gate.', *Molecular systems biology*. European Molecular Biology Organization, 3, p. 133. doi: 10.1038/msb4100173.

Anh-Nguyen, T. *et al.* (2016) 'An impedance biosensor for monitoring cancer cell attachment, spreading and drug-induced apoptosis', *Sensors and Actuators A: Physical*. Elsevier, 241, pp. 231–237. doi: 10.1016/J.SNA.2016.02.035.

Ansys (2019) *Logiciel de simulation CFD | simulation des fluides ANSYS*. Available at: https://www.ansys.com/fr-fr/products/fluids (Accessed: 10 May 2019).

Arifin, D. Y., Lee, L. Y. and Wang, C.-W. (2006) 'Mathematical modeling and simulation of drug release from microspheres: Implications to drug delivery systems', *Advanced Drug Delivery Reviews*. Elsevier, 58(12–13), pp. 1274–1325. doi: 10.1016/J.ADDR.2006.09.007.

Arndt, S. *et al.* (2004) 'Bioelectrical impedance assay to monitor changes in cell shape during apoptosis.', *Biosensors & Bioelectronics*, 19(6), pp. 583–94. Available at: http://www.ncbi.nlm.nih.gov/pubmed/14683642 (Accessed: 26 February 2019).

Asami, K., Gheorghiu, E. and Yonezawa, T. (1999) 'Real-Time Monitoring of Yeast Cell Division by Dielectric Spectroscopy', *Biophysical Journal*. Cell Press, 76(6), pp. 3345–3348. doi: 10.1016/S0006-3495(99)77487-4.

Ausländer, S. *et al.* (2012) 'Programmable single-cell mammalian biocomputers', *Nature*, 487(7405). doi: 10.1038/nature11149.

Badilita, V. *et al.* (2012) 'Microscale nuclear magnetic resonance: a tool for soft matter research', *Soft Matter*.

The Royal Society of Chemistry, 8(41), p. 10583. doi: 10.1039/c2sm26065d.

Baranyi, J. and Roberts, T. A. (1994) 'A dynamic approach to predicting bacterial growth in food', *International Journal of Food Microbiology*. Elsevier, 23(3–4), pp. 277–294. doi: 10.1016/0168-1605(94)90157-0.

Basu, S. *et al.* (2005) 'A synthetic multicellular system for programmed pattern formation.', *Nature*, 434(7037), pp. 1130–4. doi: 10.1038/nature03461.

Benenson, Y. (2012) 'Biomolecular computing systems: principles, progress and potential', *Nature Reviews Genetics*, 13(7), pp. 455–468. doi: 10.1038/nrg3197.

Benenson, Y. (2013) 'Recombinatorial Logic', *Science (New York, N.Y.)*, 340(6132), pp. 554–5.

Bereza-Malcolm, L. T., Mann, G. and Franks, A. E. (2015) 'Environmental Sensing of Heavy Metals Through Whole Cell Microbial Biosensors: A Synthetic Biology Approach', *ACS Synthetic Biology*. American Chemical Society, 4(5), pp. 535–546. doi: 10.1021/sb500286r.

Bergveld, P. (1970) 'Development of an Ion-Sensitive Solid-State Device for Neurophysiological Measurements', *IEEE Transactions on Biomedical Engineering*, BME-17(1), pp. 70–71. doi: 10.1109/TBME.1970.4502688.

Bettazzi, F. *et al.* (2018) 'Glyphosate Determination by Coupling an Immuno-Magnetic Assay with Electrochemical Sensors', *Sensors*. Multidisciplinary Digital Publishing Institute, 18(9), p. 2965. doi: 10.3390/s18092965.

Bhatia, S. and Densmore, D. (2013) 'Pigeon: a design visualizer for synthetic biology', *ACS synthetic biology*. ACS Publications, 2(6), pp. 348–350.

Billerbeck, S. *et al.* (2018) 'A scalable peptide-GPCR language for engineering multicellular communication', *Nature Communications*. Nature Publishing Group, 9(1), p. 5057. doi: 10.1038/s41467-018-07610-2.

Bonnet, J. *et al.* (2013) 'Amplifying genetic logic gates.', *Science (New York, N.Y.)*. American Association for the Advancement of Science, 340(6132), pp. 599–603. doi: 10.1126/science.1232758.

Borghans, J. M., Dupont, G. and Goldbeter, A. (1997) 'Complex intracellular calcium oscillations. A theoretical exploration of possible mechanisms.', *Biophysical chemistry*, 66(1), pp. 25–41. Available at: http://www.ncbi.nlm.nih.gov/pubmed/17029867 (Accessed: 20 October 2016).

Bornstein, B. J. *et al.* (2008) 'LibSBML: an API library for SBML.', *Bioinformatics (Oxford, England)*. Oxford University Press, 24(6), pp. 880–1. doi: 10.1093/bioinformatics/btn051.

Brächer, A. *et al.* (2016) 'Application of a new micro-reactor 1H NMR probe head for quantitative analysis of fast esterification reactions', *Chemical Engineering Journal*. Elsevier, 306, pp. 413–421. doi: 10.1016/J.CEJ.2016.07.045.

Brinkman, W. F., Dynes, R. C. and Rowell, J. M. (1970) 'Tunneling Conductance of Asymmetrical Barriers', *Journal of Applied Physics*. American Institute of Physics, 41(5), pp. 1915–1921. doi: 10.1063/1.1659141.

Byrne, D. M. and Keating, B. A. (1989) 'A laser diode model based on temperature-dependent rate equations', *IEEE Photonics Technology Letters*, 1(11), pp. 356–359. doi: 10.1109/68.43375.

Calzone, L., Fagès, F. and Soliman, S. (2006) 'BIOCHAM: an environment for modeling biological systems and formalizing experimental knowledge', *Bioinformatics*, 22(14), pp. 1805–1807. doi: 10.1093/bioinformatics/btl172.

Caras, S. D. and Janata, J. (1985) 'pH-based enzyme potentiometric sensors. Part 3. Penicillin-sensitive field effect transistor.', *Analytical Chemistry*, 57(9). doi: 10.1021/ac00286a029.

Chandran, D., Bergmann, F. T. and Sauro, H. M. (2009) 'TinkerCell: modular CAD tool for synthetic biology.', *Journal of biological engineering*, 3(1), p. 19. doi: 10.1186/1754-1611-3-19.

Cheung, K., Gawad, S. and Renaud, P. (2005) 'Impedance spectroscopy flow cytometry: On-chip label-free cell differentiation', *Cytometry Part A*, 65A(2), pp. 124–132. doi: 10.1002/cyto.a.20141.

Chevillon, N. *et al.* (2012) 'Generalization of the concept of equivalent thickness and capacitance to multigate MOSFETs modeling', *IEEE Transactions on Electron Devices*, 59(1), pp. 60–71. Available at: http://ieeexplore.ieee.org/xpls/abs_all.jsp?arnumber=6062403 (Accessed: 13 June 2014).

Chevillon, N., Madec, M. and Lallement, C. (2012) 'Gate-level modeling for CMOS circuit simulation with ultimate FinFETs', in *Proceedings of the 2012 IEEE/ACM International Symposium on Nanoscale Architectures, NANOARCH 2012*.

Chopp, D. L. *et al.* (2002) 'A mathematical model of quorum sensing in a growing bacterial biofilm', *Journal of Industrial Microbiology and Biotechnology*. Nature Publishing Group, 29(6), pp. 339–346. doi: 10.1038/sj.jim.7000316.

Chowdhury, S., Ahmadi, M. and Miller, W. C. (2005) 'A closed-form model for the pull-in voltage of electrostatically actuated cantilever beams', *Journal of Micromechanics and Microengineering*. IOP Publishing, 15(4), pp. 756–763. doi: 10.1088/0960-1317/15/4/012.

Ciobanu, L. and Pennington, C. H. (2004) '3D micron-scale MRI of single biological cells', *Solid State Nuclear Magnetic Resonance*. Academic Press, 25(1–3), pp. 138–141. doi: 10.1016/J.SSNMR.2003.03.008.

Claude, B. *et al.* (2017) 'Preliminary recovery study of a commercial molecularly imprinted polymer for the extraction of glyphosate and AMPA in different environmental waters using MS', *Environmental Science and Pollution Research*, 24(13), pp. 12293–12300. doi: 10.1007/s11356-017-8844-5.

Comsol (2019) *COMSOL Multiphysics® Modeling Software*. Available at: https://www.comsol.com/ (Accessed: 10 May 2019).

Cortadella, J. *et al.* (2002) *Logic Synthesis of Asynchronous Controllers and Interfaces*. Springer Berlin Heidelberg. Available at: https://books.google.fr/books?id=0sLqCAAAQBAJ&pg=PA13&lpg=PA13&dq=design+asynchronous+controllers&source=bl&ots=YDcJLU03U1&sig=rjHqKh2znhO5unYb8cIdajOtpJk&hl=fr&sa=X&ved=2ahUKEwiPr76nzO3fAhVJhxoKHTYODv0Q6AEwBHoECAYQAQ#v=onepage&q=design asynchronous controllers&f=false (Accessed: 14 January 2019).

Coventor (2019) *home | Coventor*. Available at: https://www.coventor.com/ (Accessed: 10 May 2019).

Czar, M. J., Cai, Y. and Peccoud, J. (2009) 'Writing DNA with GenoCAD', *Nucleic acids research*, 37(2), pp. W40–W47.

Dai, H. *et al.* (2014) 'Determination of trace glyphosate in water with a prism coupling optical waveguide configuration', *Sensors and Actuators A: Physical*. Elsevier, 218, pp. 88–93. doi: 10.1016/J.SNA.2014.07.022.

Dalitz, F. *et al.* (2012) 'Process and reaction monitoring by low-field NMR spectroscopy', *Progress in Nuclear Magnetic Resonance Spectroscopy*, 60, pp. 52–70. doi: 10.1016/j.pnmrs.2011.11.003.

Daniel, R. *et al.* (2013) 'Synthetic analog computation in living cells.', *Nature*. Nature Publishing Group, a division of Macmillan Publishers Limited. All Rights Reserved., 497(7451), pp. 619–23. doi: 10.1038/nature12148.

Danino, T. *et al.* (2015) 'Programmable probiotics for detection of cancer in urine.', *Science translational medicine*. NIH Public Access, 7(289), p. 289ra84. doi: 10.1126/scitranslmed.aaa3519.

Das, D., Biswas, K. and Das, S. (2014) 'A microfluidic device for continuous manipulation of biological cells using dielectrophoresis', *Medical Engineering & Physics*. Elsevier, 36(6), pp. 726–731. doi: 10.1016/J.MEDENGPHY.2013.12.010.

Deb, K. and Agrawal, R. W. (1995) 'Simulated binary crossover for continuous search space', *Complex Systems*, 9, pp. 115–148.

Deng, J. and Wong, H.-S. P. (2007) 'A Compact SPICE Model for Carbon-Nanotube Field-Effect Transistors Including Nonidealities and Its Application—Part I: Model of the Intrinsic Channel Region', *IEEE Transactions on Electron Devices*, 54(12), pp. 3186–3194. doi: 10.1109/TED.2007.909030.

Desgreys, P. *et al.* (2002) 'Opto-electro-thermal model of a VCSEL array using VHDL-AMS', in *Proceedings of the 2002 IEEE International Workshop on Behavioral Modeling and Simulation, 2002. BMAS 2002.* IEEE, pp. 123–126. doi: 10.1109/BMAS.2002.1291070.

Dockery, J. D. and Keener, J. P. (2001) 'A Mathematical Model for Quorum Sensing in Pseudomonas aeruginosa', *Bulletin of Mathematical Biology*. No longer published by Elsevier, 63(1), pp. 95–116. doi: 10.1006/BULM.2000.0205.

Donahue, M. J. (1999) *OOMMF user's guide, version 1.0*. Gaithersburg, MD. doi: 10.6028/NIST.IR.6376.

Dormand, J. R. (2017) *Numerical methods for differential equations : a computational approach*. Available at: https://www.crcpress.com/Numerical-Methods-for-Differential-Equations-A-Computational-Approach/Dormand/p/book/9781315896007 (Accessed: 12 April 2019).

Du, E. *et al.* (2013) 'Electric impedance microflow cytometry for characterization of cell disease states', *Lab on a Chip*, 13(19), p. 3903. doi: 10.1039/c3lc50540e.

Dubowik, J. *et al.* (2003) 'Interlayer exchange coupling across Cu/Ti/Cu spacer layer', *physica status solidi (a)*. John Wiley & Sons, Ltd, 196(1), pp. 86–89. doi: 10.1002/pssa.200306359.

Dumas, N. *et al.* (2018) 'Simulating Diffusion Transport Between Droplets In A Microfluidics Chip', in *Microflu*.

van Duuren, J. B. J. H. *et al.* (2017) 'Use of Single-Frequency Impedance Spectroscopy to Characterize the Growth Dynamics of Biofilm Formation in Pseudomonas aeruginosa', *Scientific Reports*. Nature Publishing Group, 7(1), p. 5223. doi: 10.1038/s41598-017-05273-5.

Efron, U. (1995) *Spatial light modulator technology : materials, devices, and applications*. Marcel Dekker. Available at: https://www.crcpress.com/Spatial-Light-Modulator-Technology-Materials-Devices-and-Applications/Efron/p/book/9780824791087 (Accessed: 8 April 2019).

Egot-Lemaire, S. *et al.* (2009) 'Dielectric spectroscopy of normal and malignant human lung cells at ultra-high frequencies', *Physics in Medicine and Biology*, 54(8), pp. 2341–2357. doi: 10.1088/0031-9155/54/8/006.

Ehret, R. *et al.* (1997) 'Monitoring of cellular behavior by impedance measurements on interdigitated electrode structures', *Biosensors and Bioelectronics*. Elsevier, 12(1), pp. 29–41. doi: 10.1016/0956-5663(96)89087-7.

Eierhoff, T. *et al.* (2014) 'A lipid zipper triggers bacterial invasion.', *Proceedings of the National Academy of Sciences of the United States of America*. National Academy of Sciences, 111(35), pp. 12895–900. doi: 10.1073/pnas.1402637111.

Elowitz, M. B. and Leibler, S. (2000) 'A synthetic oscillatory network of transcriptional regulators', *Nature*. Nature Publishing Group, 403(6767), pp. 335–338.

Engvall, E. and Perlmann, P. (1971) 'Enzyme-linked immunosorbent assay (ELISA) quantitative assay of immunoglobulin G', *Immunochemistry*, 8(9), pp. 871–874. doi: 10.1016/0019-2791(71)90454-X.

Ermentrout, G. B. and Edelstein-Keshet, L. (1993) 'Cellular Automata Approaches to Biological Modeling', *Journal of Theoretical Biology*, 160(1), pp. 97–133. doi: 10.1006/jtbi.1993.1007.

Escher, C., Geelhaar, T. and Bohm, E. (1988) 'Measurement of the rotational viscosity of ferroelectric liquid crystals based on a simple dynamical model', *Liquid Crystals*. Taylor & Francis Group , 3(4), pp. 469–484. doi: 10.1080/02678298808086395.

Essid, S. *et al.* (2005) 'Electro-optical switching properties for measuring the parameters of a ferroelectric liquid crystal', *Liquid Crystals*. Taylor & Francis Group , 32(3), pp. 307–314. doi: 10.1080/02678290500033596.

Estrela da Silva, J., Marques de Sá, J. P. and Jossinet, J. (2000) 'Classification of breast tissue by electrical impedance spectroscopy', *Medical & Biological Engineering & Computing*. Springer-Verlag, 38(1), pp. 26–30. doi: 10.1007/BF02344684.

Fanguy, J. C. and Henry, C. S. (2002) 'Pulsed amperometric detection of carbohydrates on an electrophoretic microchip', *The Analyst*. The Royal Society of Chemistry, 127(8), pp. 1021–1023. doi: 10.1039/b205980k.

Fernandes, P. G. *et al.* (2012) 'SPICE macromodel of silicon-on-insulator-field-effect-transistor-based biological sensors', *Sensors and Actuators B: Chemical*. Elsevier, 161(1), pp. 163–170. doi: 10.1016/J.SNB.2011.10.002.

Fernández-Niño, M. *et al.* (2017) 'A synthetic multi-cellular network of coupled self-sustained oscillators', *PLOS ONE*. Edited by M. Isalan, 12(6), p. e0180155. doi: 10.1371/journal.pone.0180155.

Fricke, H. and Morse, S. (1926) 'The Electric Capacity of Tumors of the Breast', *The Journal of Cancer Research*. American Association for Cancer Research Journals, 10(3), pp. 340–376. doi: 10.1158/jcr.1926.340.

Gardner, T. S., Cantor, C. R. and Collins, J. J. (2000) 'Construction of a genetic toggle switch in Escherichia coli',

Letters of Nature, 403(6767), pp. 339–342.

Gaso Rocha, M. I. *et al.* (2013) 'Love Wave Biosensors: A Review', in *State of the Art in Biosensors - General Aspects*. InTech. doi: 10.5772/53077.

Gawad, S., Schild, L. and Renaud, P. (2001) 'Micromachined impedance spectroscopy flow cytometer for cell analysis and particle sizing', *Lab on a Chip*. The Royal Society of Chemistry, 1(1), p. 76. doi: 10.1039/b103933b.

Gendrault, Y. *et al.* (2012) 'Using digital electronic design flow to create a Genetic Design Automation tool.', in *Conference proceedings : ... Annual International Conference of the IEEE Engineering in Medicine and Biology Society. IEEE Engineering in Medicine and Biology Society. Conference*, pp. 5530–3. doi: 10.1109/EMBC.2012.6347247.

Gendrault, Y., Madec, M., Lemaire, M., *et al.* (2014) 'Automated design of artificial biological functions based on fuzzy logic', in *IEEE 2014 Biomedical Circuits and Systems Conference, BioCAS 2014 - Proceedings*. doi: 10.1109/BioCAS.2014.6981651.

Gendrault, Y., Madec, M., Lallement, C., *et al.* (2014) 'Modeling biology with HDL languages: A first step toward a genetic design automation tool inspired from microelectronics', *IEEE Transactions on Biomedical Engineering*, 61(4). doi: 10.1109/TBME.2014.2298559.

Gendrault, Y. *et al.* (2017) 'A microelectronic approach to identifying and modeling biological noise', in *2017 15th IEEE International New Circuits and Systems Conference (NEWCAS)*. IEEE, pp. 181–184. doi: 10.1109/NEWCAS.2017.8010135.

Ghenim, L. *et al.* (2010) 'Monitoring impedance changes associated with motility and mitosis of a single cell', *Lab on a Chip*, 10(19), p. 2546. doi: 10.1039/c004115g.

Ghosh, P. M., Keese, C. R. and Giaever, I. (1993) 'Monitoring electropermeabilization in the plasma membrane of adherent mammalian cells', *Biophysical Journal*, 64(5), pp. 1602–1609. doi: 10.1016/S0006-3495(93)81531-5.

Giaever, I. and Keese, C. R. (1986) 'Use of Electric Fields to Monitor the Dynamical Aspect of Cell Behavior in Tissue Culture', *IEEE Transactions on Biomedical Engineering*, BME-33(2), pp. 242–247. doi: 10.1109/TBME.1986.325896.

Gillespie, D. T. (2007) 'Stochastic Simulation of Chemical Kinetics', *Annual Review of Physical Chemistry*. Annual Reviews, 58(1), pp. 35–55. doi: 10.1146/annurev.physchem.58.032806.104637.

Goericke, F. T. and King, W. P. (2008) 'Modeling Piezoresistive Microcantilever Sensor Response to Surface Stress for Biochemical Sensors', *IEEE Sensors Journal*, 8(8), pp. 1404–1410. doi: 10.1109/JSEN.2008.920706.

Goerlich, R. *et al.* (2018) 'Modelling of biological asynchronous sequential systems', in *Proc. of the Every Spring School on advances in Systems and Synthetic Biology*. Evry: EDP Science, pp. 39–50.

De Góes, R. E., Muller, M. and Fabris, J. L. (2017) 'Spectroscopic Detection of Glyphosate in Water Assisted by Laser-Ablated Silver Nanoparticles.', *Sensors (Basel, Switzerland)*. Multidisciplinary Digital Publishing Institute (MDPI), 17(5). doi: 10.3390/s17050954.

Goler, J. A. (2004) *BioJADE: a design and simulation tool for synthetic biological systems*. PhD dissertation, Massachusetts Institute of Technology.

Grattarola, M. *et al.* (1991) 'Computer simulations of the responses of passive and active integrated microbiosensors to cell activity', *Sensors and Actuators B: Chemical*. Elsevier, 4(3–4), pp. 261–265. doi: 10.1016/0925-4005(91)80120-9.

Griffiths-Jones, S. *et al.* (2007) 'miRBase: tools for microRNA genomics', *Nucleic Acids Research*. Oxford University Press, 36(Database), pp. D154–D158. doi: 10.1093/nar/gkm952.

Grisi, M. (2017) *Broadband single-chip transceivers for compact NMR probes*. Ecole Polytechnique Fédérale de Lausanne.

Grisi, M. *et al.* (2017) 'NMR spectroscopy of single sub-nL ova with inductive ultra-compact single-chip probes', *Scientific Reports*. Nature Publishing Group, 7(1), p. 44670. doi: 10.1038/srep44670.

Grissom, D. and Brisk, P. (2012) 'Path scheduling on digital microfluidic biochips', in *Proceedings of the 49th*

Annual Design Automation Conference on - DAC '12. New York, New York, USA: ACM Press, p. 26. doi: 10.1145/2228360.2228367.

Guiton, S. *et al.* (2014) 'System-level modeling of a Lab-On-Chip for micropollutants detection', *International Journal of Microelectronics and Computer Science*, 5(3), pp. 116–125.

Habib, A. and Pecheux, F. (2010) 'Modeling and simulation of a manycore PCR-CE lab-on-chip for DNA sequencing using SystemC/SystemC-AMS', in *2010 IEEE International Behavioral Modeling and Simulation Workshop*. IEEE, pp. 63–68. doi: 10.1109/BMAS.2010.6156600.

Haiech, J. *et al.* (2014) 'A general framework improving teaching ligand binding to a macromolecule', *Biochimica et Biophysica Acta - Molecular Cell Research*, 1843(10). doi: 10.1016/j.bbamcr.2014.03.013.

Halbach, K. (1980) 'Design of permanent multipole magnets with oriented rare earth cobalt material', *Nuclear Instruments and Methods*. North-Holland, 169(1), pp. 1–10. doi: 10.1016/0029-554X(80)90094-4.

Hashim, U., Diyana, P. N. A. and Adam, T. (2012) 'Numerical simulation of Microfluidic devices', in *2012 10th IEEE International Conference on Semiconductor Electronics (ICSE)*. IEEE, pp. 26–29. doi: 10.1109/SMElec.2012.6417083.

Hecht, F. (2012) 'New development in freefem++', *Journal of Numerical Mathematics*. De Gruyter, 20(3–4), pp. 251–266. doi: 10.1515/jnum-2012-0013.

Hehn, M. *et al.* (2008) '360° domain wall generation in the soft layer of magnetic tunnel junctions', *Applied Physics Letters*. American Institute of Physics, 92(7), p. 072501. doi: 10.1063/1.2838455.

Hermann, T. and Patel, D. J. (2000) 'Adaptive recognition by nucleic acid aptamers.', *Science (New York, N.Y.)*, 287(5454), pp. 820–5. Available at: http://www.ncbi.nlm.nih.gov/pubmed/10657289 (Accessed: 4 January 2019).

Hernandez, C. A. and Osma, J. F. (2014) 'Whole-cell biosensor', in Osma Cruz, J. F. and Stoytcheva, M. (eds) *Biosensors : recent advances and mathematical challenges*. OmniaScience, p. 51.

Hoops, S. *et al.* (2006) 'COPASI—a complex pathway simulator', *Bioinformatics*. Oxford Univ Press, 22(24), pp. 3067–3074.

Hoteit, I., Kharma, N. and Varin, L. (2012) 'Computational simulation of a gene regulatory network implementing an extendable synchronous single-input delay flip-flop', *BioSystems*. Elsevier Ireland Ltd, pp. 1–15. doi: 10.1016/j.biosystems.2012.01.004.

Huang, H. and Densmore, D. (2014) 'Fluigi: Microfluidic Device Synthesis for Synthetic Biology', *ACM Journal on Emerging Technologies in Computing Systems*. ACM, 11(3), pp. 1–19. doi: 10.1145/2660773.

Huard, S. (1997) *Polarization of light*. John Wiley. Available at: https://www.wiley.com/en-us/Polarization+of+Light-p-9780471965367 (Accessed: 8 April 2019).

Hucka, M. (2003) 'The systems biology markup language (SBML): a medium for representation and exchange of biochemical network models', *Bioinformatics*, 19(4), pp. 524–531. doi: 10.1093/bioinformatics/btg015.

Hucka, M. *et al.* (2018) 'The Systems Biology Markup Language (SBML): Language Specification for Level 3 Version 2 Core', *Journal of Integrative Bioinformatics*, 15(1). doi: 10.1515/jib-2017-0081.

Ibrahim, M. *et al.* (2011) 'Physical and Electrical Modeling of Interdigitated Electrode Arrays for Bioimpedance Spectroscopy', in. Springer, Berlin, Heidelberg, pp. 169–189. doi: 10.1007/978-3-642-17943-3_9.

iGEM ENSPS (2011) *Team:ENSPS-Strasbourg - 2011.igem.org*. Available at: http://2011.igem.org/Team:ENSPS-Strasbourg (Accessed: 10 May 2019).

iGEM ESBS (2008) *Team:ESBS-Strasbourg - 2008.igem.org*. Available at: https://2008.igem.org/Team:ESBS-Strasbourg (Accessed: 10 May 2019).

iGEM ESBS (2010) *Team:ESBS-Strasbourg - 2010.igem.org*. Available at: http://2010.igem.org/Team:ESBS-Strasbourg (Accessed: 10 May 2019).

Isaacs, F. J., Dwyer, D. J. and Collins, J. J. (2006) 'RNA synthetic biology', *Nature Biotechnology*, 24(5), pp. 545–

554. doi: 10.1038/nbt1208.

Jacobsen, N. E. (2007) *NMR spectroscopy explained : simplified theory, applications and examples for organic chemistry and structural biology*. Wiley-Interscience.

Jamieson, P. *et al.* (2010) 'Odin II-an open-source verilog HDL synthesis tool for CAD research', in *Field-Programmable Custom Computing Machines (FCCM), 2010 18th IEEE Annual International Symposium on*, pp. 149–156.

Janakiraman, V. *et al.* (2009) 'Modeling Growth and Quorum Sensing in Biofilms Grown in Microfluidic Chambers', *Annals of Biomedical Engineering*, 37(6), pp. 1206–1216. doi: 10.1007/s10439-009-9671-8.

Janicki, M. *et al.* (2004) 'Ion sensitive field effect transistor modelling for multidomain simulation purposes', *Microelectronics Journal*. Elsevier, 35(10), pp. 831–840. doi: 10.1016/J.MEJO.2004.06.015.

Jeon, W. and Shin, C. B. (2009) 'Design and simulation of passive mixing in microfluidic systems with geometric variations', *Chemical Engineering Journal*. Elsevier, 152(2–3), pp. 575–582. doi: 10.1016/J.CEJ.2009.05.035.

Jia Tzer Hsu and Vu-Quoc, L. (1996) 'A rational formulation of thermal circuit models for electrothermal simulation. I. Finite element method [power electronic systems]', *IEEE Transactions on Circuits and Systems I: Fundamental Theory and Applications*, 43(9), pp. 721–732. doi: 10.1109/81.536742.

Kaisti, M., Zhang, Q. and Levon, K. (2017) 'Compact model and design considerations of an ion-sensitive floating gate FET', *Sensors and Actuators B: Chemical*. Elsevier, 241, pp. 321–326. doi: 10.1016/J.SNB.2016.10.051.

Kammerer, J.-B. *et al.* (2004) 'A Two-Axis Magnetometer Using a Single Magnetic Tunnel Junction', *IEEE Sensors Journal*, 4(3), pp. 313–321. doi: 10.1109/JSEN.2004.824232.

Kammerer, J.-B., Madec, M. and Hébrard, L. (2010) 'Compact modeling of a magnetic tunnel junction-Part I: Dynamic magnetization model', *IEEE Transactions on Electron Devices*, 57(6). doi: 10.1109/TED.2010.2047070.

Keil, B. and Wald, L. L. (2013) 'Massively parallel MRI detector arrays', *Journal of Magnetic Resonance*, 229, pp. 75–89. doi: 10.1016/j.jmr.2013.02.001.

Keysight Technologies (2019) *IC-CAP Device Modeling Software -- Measurement Control and Parameter Extraction | Keysight (formerly Agilent's Electronic Measurement)*. Available at: https://www.keysight.com/en/pc-1297149/ic-cap-device-modeling-software-measurement-control-and-parameter-extraction?cc=FR&lc=fre (Accessed: 10 May 2019).

Khajeh, M., Bernstein, M. A. and Morris, G. A. (2010) 'A simple flowcell for reaction monitoring by NMR', *Magnetic Resonance in Chemistry*, 48(7), pp. 516–522. doi: 10.1002/mrc.2610.

Khalil, A. S. and Collins, J. J. (2010) 'Synthetic Biology : Applications Come of Age', *Nature Reviews Genetics*. Nature Publishing Group, 11(5), pp. 367–379. doi: 10.1038/nrg2775.Synthetic.

Kitney, R. and Freemont, P. (2012) 'Synthetic biology – the state of play', *FEBS Letters*. Federation of European Biochemical Societies, 586(15), pp. 2029–2036. doi: 10.1016/j.febslet.2012.06.002.

Knight, T. (2003) 'Idempotent vector design for standard assembly of biobricks', in *MIT Synthetic Biology Working Group Technical Report*.

Kobayashi, H. *et al.* (2004) 'Programmable cells: interfacing natural and engineered gene networks.', *Proceedings of the National Academy of Sciences of the United States of America*. National Academy of Sciences, 101(22), pp. 8414–9. doi: 10.1073/pnas.0402940101.

Konkoli, Z. (2011) 'Safe uses of Hill's model: an exact comparison with the Adair-Klotz model.', *Theoretical biology & medical modelling*. BioMed Central Ltd, 8(1), p. 10. doi: 10.1186/1742-4682-8-10.

Kools, J. C. S. *et al.* (1999) 'Effect of finite magnetic film thickness on Néel coupling in spin valves', *Journal of Applied Physics*. American Institute of Physics, 85(8), pp. 4466–4468. doi: 10.1063/1.370376.

Kotler, D. P. *et al.* (1996) 'Prediction of body cell mass, fat-free mass, and total body water with bioelectrical impedance analysis: effects of race, sex, and disease', *The American Journal of Clinical Nutrition*, 64(3), pp. 489S-497S. doi: 10.1093/ajcn/64.3.489S.

Kowolenko, M. *et al.* (1990) 'Measurement of macrophage adherence and spreading with weak electric fields.', *Journal of immunological methods*, 127(1), pp. 71–7.

Koza, J. R. (2003) *Genetic Programming IV: Routine Human-Competitive Machine Intelligence*. Norwell, MA, USA: Kluwer Academic Publishers.

Krencker, J.-C. *et al.* (2014) 'Electro-thermal high-level modeling of integrated circuits', *Microelectronics Journal*. Elsevier, 45(5), pp. 491–499. doi: 10.1016/J.MEJO.2014.02.001.

Latifi, A. *et al.* (1996) 'A hierarchical quorum-sensing cascade in Pseudomonas aeruginosa links the transcriptional activators LasR and RhIR (VsmR) to expression of the stationary-phase sigma factor RpoS.', *Molecular microbiology*, 21(6), pp. 1137–46. Available at: http://www.ncbi.nlm.nih.gov/pubmed/8898383 (Accessed: 18 January 2019).

Lazdunski, A. M., Ventre, I. and Sturgis, J. N. (2004) 'Regulatory circuits and communication in Gram-negative bacteria', *Nature Reviews Microbiology*. Nature Publishing Group, 2(7), pp. 581–592. doi: 10.1038/nrmicro924.

Leduc, S. (1912) *La biologie synthétique*. A. Poinat. Available at: https://books.google.fr/books/about/La_biologie_synthétique.html?id=CdMrAQAAMAAJ&redir_esc=y (Accessed: 16 April 2019).

Lee, S. *et al.* (1992) 'A novel microbial sensor using luminous bacteria', *Biosensors and Bioelectronics*. Elsevier, 7(4), pp. 273–277. doi: 10.1016/0956-5663(92)87005-A.

Lei, J., Hill, M. and Glynne-Jones, P. (2014) 'Numerical simulation of 3D boundary-driven acoustic streaming in microfluidic devices', *Lab Chip*. The Royal Society of Chemistry, 14(3), pp. 532–541. doi: 10.1039/C3LC50985K.

Léonard, J. *et al.* (2014) 'High-throughput time-correlated single photon counting.', *Lab on a chip*, 14(22), pp. 4338–43. doi: 10.1039/c4lc00780h.

Li, X. *et al.* (2013) 'Simple procedure for the fabrication of flexible NMR shim coils', *Comptes Rendus Chimie*. Elsevier Masson, 16(11), pp. 967–971. doi: 10.1016/J.CRCI.2013.05.008.

Lin, C.-L., Kuo, T.-Y. and Li, W.-X. (2018) 'Synthesis of control unit for future biocomputer', *Journal of Biological Engineering*. BioMed Central, 12(1), p. 14. doi: 10.1186/s13036-018-0109-4.

Lin, S.-P., Kyriakides, T. R. and Chen, J.-J. J. (2009) 'On-line observation of cell growth in a three-dimensional matrix on surface-modified microelectrode arrays', *Biomaterials*, 30(17), pp. 3110–3117. doi: 10.1016/j.biomaterials.2009.03.017.

Liu, J. *et al.* (1998) 'H+ISFET-based biosensor for determination of penicillin G.', *Biosensors & bioelectronics*, 13(9), pp. 1023–8. Available at: http://www.ncbi.nlm.nih.gov/pubmed/9839390 (Accessed: 18 November 2016).

Lo, C. F. (2007) 'Stochastic Gompertz model of tumour cell growth', *Journal of Theoretical Biology*. Academic Press, 248(2), pp. 317–321. doi: 10.1016/J.JTBI.2007.04.024.

Loew, L. M. and Schaff, J. C. (2001) 'The Virtual Cell: a software environment for computational cell biology', *Trends in Biotechnology*, 19(10), pp. 401–406. doi: 10.1016/S0167-7799(01)01740-1.

Lopez, C. *et al.* (2013) 'Programming biological models in Python using PySB', *Molecular systems biology2*, 9. doi: 10.1038/msb.2013.1.

Lu, Y. (2017) 'Cell-free synthetic biology: Engineering in an open world', *Synthetic and Systems Biotechnology*. Elsevier, 2(1), pp. 23–27. doi: 10.1016/J.SYNBIO.2017.02.003.

Lucet, J.-C. (no date) *Infections nosocomiales | Inserm - La science pour la santé*. Available at: https://www.inserm.fr/information-en-sante/dossiers-information/infections-nosocomiales (Accessed: 18 January 2019).

Lundien, M. C. *et al.* (2002) 'Induction of MCP-1 expression in airway epithelial cells: role of CCR2 receptor in airway epithelial injury.', *Journal of clinical immunology*, 22(3), pp. 144–52. Available at: http://www.ncbi.nlm.nih.gov/pubmed/12078856 (Accessed: 26 February 2019).

Madec, M. *et al.* (2007) 'Compatibility of temporal multiplexed spatial light modulator with optical image processing', *Optics Communications*, 275(1), pp. 27–37. doi: 10.1016/j.optcom.2007.02.062.

Madec, M. *et al.* (2008) 'Optoelectronic implementation of helical cone-beam computed tomography algorithms', *Optical Engineering*, 47(5), p. 058201. doi: 10.1117/1.2931691.

Madec, M. *et al.* (2009) 'Synthetic biology and microelectronics : a similar design flow', in *2009 Joint 7th International IEEE Northeast Workshop on Circuits and Systems and TAISA Conference*.

Madec, M. *et al.* (2011) 'An accurate compact model for CMOS cross-shaped Hall effect sensors', *Sensors and Actuators A: Physical*. Elsevier, 171(2), pp. 69–78. doi: 10.1016/J.SNA.2011.05.027.

Madec, Morgan *et al.* (2011) 'An accurate compact model for CMOS cross-shaped Hall effect sensors', *Sensors and Actuators A: Physical*. Elsevier B.V., 171(2), pp. 69–78. doi: 10.1016/j.sna.2011.05.027.

Madec, M., Kammerer, J.-B., *et al.* (2012) 'An improved compact model for CMOS cross-shaped Hall-effect sensor including offset and temperature effects', *Analog Integrated Circuits and Signal Processing*, 73(3), pp. 719–730. doi: 10.1007/s10470-012-9872-1.

Madec, M., Schell, J.-B., *et al.* (2012) 'Compact modeling of vertical hall-effect devices: Electrical behavior', in *10th IEEE International NEWCAS Conference*. Ieee, pp. 183–195. doi: 10.1007/s10470-013-0112-0.

Madec, M. *et al.* (2016) 'GeNeDA: An Open-Source Workflow for Design Automation of Gene Regulatory Networks Inspired from Microelectronics', *Journal of Computational Biology*, 23(10). doi: 10.1089/cmb.2015.0229.

Madec, M. *et al.* (2018) 'Environment for modeling and simulation of biosystems, biosensors and lab-on-chips', *IEEE Transactions on Electron Devices*, 99.

Madec, M. *et al.* (2019) 'Multiphysics Simulation of Biosensors Involving 3D Biological Reaction-Diffusion Phenomena in a Standard Circuit EDA Environment', *IEEE Transactions on Circuits and Systems I: Regular Papers*, pp. 1–10. doi: 10.1109/TCSI.2018.2885223.

Madec, M., Kammerer, J.-B. and Hébrard, L. (2010) 'Compact Modeling of a Magnetic Tunnel Junction—Part II: Tunneling Current Model', *IEEE Transactions on Electron Devices*, 57(6), pp. 1416–1424. doi: 10.1109/TED.2010.2047071.

Madec, M. and Kammerer, J. (2011) 'Analysis of the efficiency of spinning-current techniques thru compact modeling', *Proc. of IEEE Sensor Conference*, 7163. Available at: http://ieeexplore.ieee.org/xpls/abs_all.jsp?arnumber=6127318 (Accessed: 13 June 2014).

Madec, M., Lallement, C. and Haiech, J. (2017) 'Modeling and simulation of biological systems using SPICE language', *PloS one*, 12(8). doi: 10.1371/journal.pone.0182385.

Madec, M., Osberger, L. and Hébrard, L. (2013) 'Assessment of the spinning-current efficiency in cancelling the 1/f noise of Vertical Hall Devices through accurate FEM modeling', *Proc. of IEEE Sensor Conference*, pp. 3–6. Available at: http://ieeexplore.ieee.org/xpls/abs_all.jsp?arnumber=6688323 (Accessed: 13 June 2014).

Mamouni, J. and Yang, L. (2011) 'Interdigitated microelectrode-based microchip for electrical impedance spectroscopic study of oral cancer cells', *Biomedical Microdevices*, 13(6), pp. 1075–1088. doi: 10.1007/s10544-011-9577-8.

Marano, D. *et al.* (2013) 'Improved SPICE electrical model of silicon photomultipliers', *Nuclear Instruments and Methods in Physics Research Section A: Accelerators, Spectrometers, Detectors and Associated Equipment*. North-Holland, 726, pp. 1–7. doi: 10.1016/J.NIMA.2013.05.127.

Marti, K. (2015) *Stochastic Optimization Methods*. Berlin, Heidelberg: Springer Berlin Heidelberg. doi: 10.1007/978-3-662-46214-0.

Martinoia, S. and Massobrio, G. (2000) 'A behavioral macromodel of the ISFET in SPICE', *Sensors and Actuators B: Chemical*, 62(3), pp. 182–189. doi: 10.1016/S0925-4005(99)00377-9.

Maximus, B. *et al.* (1991) 'Ion transport in SSFLCD's', *Ferroelectrics*. Taylor & Francis Group , 121(1), pp. 103–112. doi: 10.1080/00150199108217614.

McDaniel, J., Curtis, C. and Brisk, P. (2013) 'Automatic synthesis of microfluidic large scale integration chips from a domain-specific language', in *2013 IEEE Biomedical Circuits and Systems Conference (BioCAS)*. IEEE, pp. 101–104. doi: 10.1109/BioCAS.2013.6679649.

McDaniel, J., Grover, W. H. and Brisk, P. (2017) 'The case for semi-automated design of microfluidic very large scale integration (mVLSI) chips', in *Design, Automation & Test in Europe Conference & Exhibition (DATE), 2017*. IEEE, pp. 1793–1798. doi: 10.23919/DATE.2017.7927283.

McDaniel, J., Parker, B. and Brisk, P. (2014) 'Simulated annealing-based placement for microfluidic large scale integration (mLSI) chips', in *2014 22nd International Conference on Very Large Scale Integration (VLSI-SoC)*. IEEE, pp. 1–6. doi: 10.1109/VLSI-SoC.2014.7004170.

McDowell, A. and Fukushima, E. (2008) 'Ultracompact NMR: 1H Spectroscopy in a Subkilogram Magnet', *Applied Magnetic Resonance*. Springer-Verlag, 35(1), pp. 185–195. doi: 10.1007/s00723-008-0151-3.

Michaelis, V. L. and Maud Menten, M. L. (1913) 'Die Kinetik der Invertinwirkung', *Biochemistry*, 29, pp. 332–369.

Micheli, G. De (1994) *Synthesis and optimization of digital circuits*. McGraw-Hill Higher Education.

Miki, K. *et al.* (2015) 'Efficient Detection and Purification of Cell Populations Using Synthetic MicroRNA Switches', *Cell Stem Cell*, 16(6), pp. 699–711. doi: 10.1016/j.stem.2015.04.005.

Mitra, P., Keese, C. R. and Giaever, I. (1991) 'Electric measurements can be used to monitor the attachment and spreading of cells in tissue culture.', *BioTechniques*, 11(4), pp. 504–10. Available at: http://www.ncbi.nlm.nih.gov/pubmed/1793585 (Accessed: 26 February 2019).

Miyamoto, T. *et al.* (2013) 'Synthesizing biomolecule-based Boolean logic gates.', *ACS synthetic biology*. American Chemical Society, 2(2), pp. 72–82. doi: 10.1021/sb3001112.

Moore, E. and Tycko, R. (2015) 'Micron-scale magnetic resonance imaging of both liquids and solids.', *Journal of magnetic resonance (San Diego, Calif. : 1997)*. NIH Public Access, 260, pp. 1–9. doi: 10.1016/j.jmr.2015.09.001.

Mounisens, M. *et al.* (2018) 'Projet étudiant : réalisation d'un système de payement sans contact pour le foyer des étudiants', in *Journées Pédagogiques du CNFM*.

Mulcahy, H. *et al.* (2008) 'Pseudomonas aeruginosa RsmA Plays an Important Role during Murine Infection by Influencing Colonization, Virulence, Persistence, and Pulmonary Inflammation', *Infection and Immunity*, 76(2), pp. 632–638. doi: 10.1128/IAI.01132-07.

Mytilinaios, I. *et al.* (2012) 'Growth curve prediction from optical density data', *International Journal of Food Microbiology*, 154(3), pp. 169–176. doi: 10.1016/j.ijfoodmicro.2011.12.035.

Nealson, K. H., Platt, T. and Hastings, J. W. (1970) 'Cellular control of the synthesis and activity of the bacterial luminescent system.', *Journal of bacteriology*, 104(1), pp. 313–22. Available at: http://www.ncbi.nlm.nih.gov/pubmed/5473898 (Accessed: 18 January 2019).

Nenzi, P. and Vogt, H. (2011) 'Ngspice Users Manual Version 23'. Available at: https://pkgs.fedoraproject.org/repo/extras/ngspice/ngspice23-manual.pdf/eb0d68eb463a41a0571757a00a5b9f9d/ngspice23-manual.pdf (Accessed: 11 October 2016).

Ngo, T.-T. *et al.* (2014) 'A Planar Interdigital Sensor for Bio-impedance Measurement: Theoretical analysis, Optimization and Simulation', *Journal of Nano and Electronic Physics*, 6(1). Available at: https://hal.univ-lorraine.fr/hal-01397314 (Accessed: 26 February 2019).

Nguyen, T. A. *et al.* (2013) 'Microfluidic Chip with Integrated Electrical Cell-Impedance Sensing for Monitoring Single Cancer Cell Migration in Three-Dimensional Matrixes', *Analytical Chemistry*, 85(22), pp. 11068–11076. doi: 10.1021/ac402761s.

Nielsen, A. A. K. *et al.* (2016) 'Genetic circuit design automation', *Science*. American Association for the Advancement of Science, 352(6281), p. aac7341. doi: 10.1126/science.aac7341.

Nikolayeva, O. *et al.* (2007) 'Design of a biological half adder', *IET Synthetic Biology*, 1(1), pp. 53–58. doi: 10.1049/iet-stb:20070013.

Noori, J. *et al.* (2018) 'Detection of Glyphosate in Drinking Water: A Fast and Direct Detection Method without Sample Pretreatment', *Sensors*. Multidisciplinary Digital Publishing Institute, 18(9), p. 2961. doi: 10.3390/s18092961.

Norcross, J. A. *et al.* (2010) 'Multiplexed NMR: An Automated CapNMR Dual-Sample Probe', *Analytical Chemistry*,

82(17), pp. 7227–7236. doi: 10.1021/ac101003f.

Le Novère, N. *et al.* (2006) 'BioModels Database: a free, centralized database of curated, published, quantitative kinetic models of biochemical and cellular systems', *Nucleic acids research*, 34(1), pp. 689–691.

Osma, J. F. and Stoytcheva, M. (eds) (2014) *Biosensors: Recent advances and mathematical challenges*. OmniaScience. doi: 10.3926/oms.98.

Padirac, A., Fujii, T. and Rondelez, Y. (2012) 'Bottom-up construction of in vitro switchable memories.', *Proceedings of the National Academy of Sciences of the United States of America*. National Academy of Sciences, 109(47), pp. E3212-20. doi: 10.1073/pnas.1212069109.

Pardee, K. *et al.* (2014) 'Paper-based synthetic gene networks.', *Cell*. Howard Hughes Medical Institute, 159(4), pp. 940–54. doi: 10.1016/j.cell.2014.10.004.

Pardee, K. *et al.* (2016) 'Rapid, Low-Cost Detection of Zika Virus Using Programmable Biomolecular Components.', *Cell*. Elsevier, 165(5), pp. 1255–1266. doi: 10.1016/j.cell.2016.04.059.

Pascal, J., Hebrard, L., *et al.* (2008) '3D Hall probe integrated in 0.35 µm CMOS technology for magnetic field pulses measurements', in *2008 Joint 6th International IEEE Northeast Workshop on Circuits and Systems and TAISA Conference*. IEEE, pp. 97–100. doi: 10.1109/NEWCAS.2008.4606330.

Pascal, J., Hébrard, L., *et al.* (2008) 'First Vertical Hall Device in standard 0.35 µm CMOS technology', *Sensors and Actuators A: Physical*. Elsevier, 147(1), pp. 41–46. doi: 10.1016/J.SNA.2008.03.011.

Paul Horowitz and Hill, W. (1989) *The Art of Electronics*. Cambridge University Press.

Pauwels, H. *et al.* (1989) 'One dimensional stationary states with constant electrical induction in ferroelectric liquid crystals', *Liquid Crystals*. Taylor & Francis Group , 4(5), pp. 497–504. doi: 10.1080/02678298908033184.

Peccoud, J. and Isalan, M. (2012) 'The PLOS ONE synthetic biology collection: six years and counting.', *PloS one*, 7(8), p. e43231. doi: 10.1371/journal.pone.0043231.

Pecheux, F., Madec, M. and Lallement, C. (2010) 'Is SystemC-AMS an appropriate "promoter" for the modeling and simulation of bio-compatible systems?', in *Proceedings of 2010 IEEE International Symposium on Circuits and Systems*. IEEE, pp. 1791–1794. doi: 10.1109/ISCAS.2010.5537669.

Peck, T. L. *et al.* (1994) 'NMR microspectroscopy using 100 µm planar RF coils fabricated on gallium arsenide substrates', *IEEE Transactions on Biomedical Engineering*, 41(7), pp. 706–709. doi: 10.1109/10.301740.

Pérez-Velázquez, J., Gölgeli, M. and García-Contreras, R. (2016) 'Mathematical Modelling of Bacterial Quorum Sensing: A Review', *Bulletin of Mathematical Biology*, 78(8), pp. 1585–1639. doi: 10.1007/s11538-016-0160-6.

Perez, J. G., Stark, J. C. and Jewett, M. C. (2016) 'Cell-Free Synthetic Biology: Engineering Beyond the Cell.', *Cold Spring Harbor perspectives in biology*. Cold Spring Harbor Laboratory Press, 8(12). doi: 10.1101/cshperspect.a023853.

Piasecki, T. *et al.* (2013) 'Evaluation of Pseudomonas aeruginosa biofilm formation using Quartz Tuning Forks as impedance sensors', *Sensors and Actuators B: Chemical*. Elsevier, 189, pp. 60–65. doi: 10.1016/J.SNB.2012.12.087.

Piletsky, S. A. *et al.* (1995) 'Atrazine sensing by molecularly imprinted membranes', *Biosensors and Bioelectronics*. Elsevier, 10(9–10), pp. 959–964. doi: 10.1016/0956-5663(95)99233-B.

Plantier, G., Bes, C. and Bosch, T. (2005) 'Behavioral model of a self-mixing laser diode sensor', *IEEE Journal of Quantum Electronics*, 41(9), pp. 1157–1167. doi: 10.1109/JQE.2005.853364.

Popović, R. S. (2004) *Hall effect devices*. Institute of Physics Pub. Available at: https://www.crcpress.com/Hall-Effect-Devices/Popovic/p/book/9780750308557 (Accessed: 6 April 2019).

Prud'homme, C. *et al.* (2012) 'Feel++ : A computational framework for Galerkin Methods and Advanced Numerical Methods', *ESAIM: Proceedings*. Edited by F. Coquel et al. EDP Sciences, 38, pp. 429–455. doi: 10.1051/proc/201238024.

Qian, L. and Winfree, E. (2011) 'Scaling up digital circuit computation with DNA strand displacement cascades.',

Science (New York, N.Y.). American Association for the Advancement of Science, 332(6034), pp. 1196–201. doi: 10.1126/science.1200520.

Ravezzi, L. *et al.* (2000) 'A versatile photodiode SPICE model for optical microsystem simulation', *Microelectronics Journal*, 31(4), pp. 277–282. doi: 10.1016/S0026-2692(99)00145-7.

Regot, S. *et al.* (2011) 'Distributed biological computation with multicellular engineered networks', *Nature*. Nature Publishing Group, 469(7329), pp. 207–211. doi: 10.1038/nature09679.

Rezgui, A. *et al.* (2015) 'Integration of SBML models for the description of biological system in a lab-on-chip', in *2015 22nd International Conference Mixed Design of Integrated Circuits & Systems (MIXDES)*. IEEE, pp. 165–170. doi: 10.1109/MIXDES.2015.7208504.

Ribaut, C. *et al.* (2009) 'Electrochemical impedance spectroscopy to study physiological changes affecting the red blood cell after invasion by malaria parasites', *Biosensors and Bioelectronics*, 24(8), pp. 2721–2725. doi: 10.1016/j.bios.2008.12.018.

Rinaudo, K. *et al.* (2007) 'A universal RNAi-based logic evaluator that operates in mammalian cells.', *Nature biotechnology*. Nature Publishing Group, 25(7), pp. 795–801. doi: 10.1038/nbt1307.

Ritzenthaler, R. *et al.* (2011) 'Analytical modelling of Multiple-gate MOSFETs', in *Proceedings of the 8th Spanish Conference on Electron Devices, CDE'2011*. IEEE, pp. 1–4. doi: 10.1109/SCED.2011.5744159.

Rogers, J. K. *et al.* (2015) 'Synthetic biosensors for precise gene control and real-time monitoring of metabolites.', *Nucleic acids research*. Oxford University Press, 43(15), pp. 7648–60. doi: 10.1093/nar/gkv616.

Rosati, E. *et al.* (2015) 'Design and simulation of a compact genetic flip-flop', in *Proc. of the Strasbourg Spring School on advances in Systems and Synthetic Biology*, pp. 115–124.

Rosati, E., Madec, M., Rezgui, A., *et al.* (2018) 'Développement d'outils pour la formation au dépannage de circuits électroniques,' in *ournées Pédagogiques du CNFM*.

Rosati, E., Madec, M., Kammerer, J.-B., *et al.* (2018) 'Efficient modeling and simulation of space-dependent biological systems', *Journal of computational biology2*, under pres.

Saberkari, A. *et al.* (2018) 'Design of Broadband CNFET LNA Based on Extracted I-V Closed-Form Equation', *IEEE Transactions on Nanotechnology*. doi: 10.1109/TNANO.2018.2822599.

Sahebjavaher, R. S., Walus, K. and Stoeber, B. (2010) 'Permanent magnet desktop magnetic resonance imaging system with microfabricated multiturn gradient coils for microflow imaging in capillary tubes', *Review of Scientific Instruments*, 81(2), p. 023706. doi: 10.1063/1.3280171.

Sallese, J.-M. *et al.* (2005) 'A design oriented charge-based current model for symmetric DG MOSFET and its correlation with the EKV formalism', *Solid-State Electronics*. Pergamon, 49(3), pp. 485–489. doi: 10.1016/J.SSE.2004.11.013.

Saltepe, B. *et al.* (2018) 'Cellular Biosensors with Engineered Genetic Circuits', *ACS Sensors*, 3(1), pp. 13–26. doi: 10.1021/acssensors.7b00728.

Sanka, R. *et al.* (2016) 'MINT - Microfluidic Netlist', in *International Workshop on Bio-Design Automation*. Newcastle, United Kingdom.

Sato, K. *et al.* (2001) 'Integrated pulsed amperometric detection of glufosinate, bialaphos and glyphosate at gold electrodes in anion-exchange chromatography', *Journal of Chromatography A*. Elsevier, 919(2), pp. 313–320. doi: 10.1016/S0021-9673(01)00843-3.

Schmidt, H. and Jirstrand, M. (2006) 'Systems Biology Toolbox for MATLAB: a computational platform for research in systems biology', *Bioinformatics*. Oxford University Press, 22(4), pp. 514–515. doi: 10.1093/bioinformatics/bti799.

Schwan, H. P. (1983) 'Electrical properties of blood and its constitutents: Alternating current spectroscopy', *Blut*. Springer Berlin Heidelberg, 46(4), pp. 185–197. doi: 10.1007/BF00320638.

Shimizu-Sato, S. *et al.* (2002) 'A light-switchable gene promoter system', *Nature Biotechnology*. Nature Publishing Group, 20(10), pp. 1041–1044. doi: 10.1038/nbt734.

Silva Elipe, M. V. and Milburn, R. R. (2016) 'Monitoring chemical reactions by low-field benchtop NMR at 45 MHz: pros and cons', *Magnetic Resonance in Chemistry*, 54(6), pp. 437–443. doi: 10.1002/mrc.4189.

Slomovic, S., Pardee, K. and Collins, J. J. (2015) 'Synthetic biology devices for in vitro and in vivo diagnostics.', *Proceedings of the National Academy of Sciences of the United States of America*. National Academy of Sciences, 112(47), pp. 14429–35. doi: 10.1073/pnas.1508521112.

Slonczewski, J. C. (1989) 'Conductance and exchange coupling of two ferromagnets separated by a tunneling barrier', *Physical Review B*. American Physical Society, 39(10), pp. 6995–7002. doi: 10.1103/PhysRevB.39.6995.

Smartt, A. E. and Ripp, S. (2011) 'Bacteriophage reporter technology for sensing and detecting microbial targets', *Analytical and Bioanalytical Chemistry*. Springer-Verlag, 400(4), pp. 991–1007. doi: 10.1007/s00216-010-4561-3.

Somogyi, R. and Stucki, J. (1991) 'The Journal of biological chemistry.', *Journal of Biological Chemistry*. American Society for Biochemistry and Molecular Biology, 266, pp. 11068–11077. Available at: http://www.jbc.org/content/266/17/11068.short (Accessed: 28 October 2017).

Spruce, G. and Pringle, R. D. (1988) 'Measurement of spontaneous polarization in ferroelectric smectic liquid crystals', *Liquid Crystals*. Taylor & Francis Group , 3(4), pp. 507–518. doi: 10.1080/02678298808086397.

Stamatakis, M. and Mantzaris, N. (2009) 'Comparison of Deterministic and Stochastic Models of the lac Operon Genetic Network', *Biophysical Journal*. Cell Press, 96(3), pp. 887–906. doi: 10.1016/J.BPJ.2008.10.028.

Sun, N. *et al.* (2011) 'Palm NMR and 1-Chip NMR', *IEEE Journal of Solid-State Circuits*, 46(1), pp. 342–352. doi: 10.1109/JSSC.2010.2074630.

Sun, T. and Morgan, H. (2010) 'Single-cell microfluidic impedance cytometry: a review', *Microfluidics and Nanofluidics*. Springer-Verlag, 8(4), pp. 423–443. doi: 10.1007/s10404-010-0580-9.

Sze, S. M. and Ng, K. K. (2007) *Physics of semiconductor devices*. Wiley-Interscience.

Talide, L. *et al.* (2015) 'Modeling of intercellular transport for emerging applications in synthetic biology', in *Advances in Systems and Synthetic Biology*, pp. 149–156.

Tamsir, A., Tabor, J. J. and Voigt, C. A. (2011) 'Robust multicellular computing using genetically encoded NOR gates and chemical "wires"', *Nature*. Nature Publishing Group, 469(7329), pp. 212–215. doi: 10.1038/nature09565.

Tehrani, S. *et al.* (2003) 'Magnetoresistive random access memory using magnetic tunnel junctions', *Proceedings of the IEEE*, 91(5), pp. 703–714. doi: 10.1109/JPROC.2003.811804.

Ten, S. T. *et al.* (2016) 'Numerical simulation on development of a SAW based biosensor', in, p. 020089. doi: 10.1063/1.4948907.

Thies, W. *et al.* (2008) 'Abstraction layers for scalable microfluidic biocomputing', *Natural Computing*. Springer Netherlands, 7(2), pp. 255–275. doi: 10.1007/s11047-006-9032-6.

Thomas, C. A. *et al.* (1972) 'A miniature microelectrode array to monitor the bioelectric activity of cultured cells', *Experimental Cell Research*. Academic Press, 74(1), pp. 61–66. doi: 10.1016/0014-4827(72)90481-8.

Thuenauer, R. *et al.* (2018) 'A microfluidic biochip for locally confined stimulation of cells within an epithelial monolayer', *RSC Advances*. The Royal Society of Chemistry, 8(14), pp. 7839–7846. doi: 10.1039/C7RA11943G.

Ting-Wei Chiang, Chia-Hung Liu and Juinn-Dar Huang (2013) 'Graph-based optimal reactant minimization for sample preparation on digital microfluidic biochips', in *2013 International Symposium onVLSI Design, Automation, and Test (VLSI-DAT)*. IEEE, pp. 1–4. doi: 10.1109/VLDI-DAT.2013.6533817.

Du Trémolet de Lacheisserie, E., Gignoux, D. and Schlenker, M. (Michel) (2005) *Magnetism*. Springer.

Treo, E. F. *et al.* (2002) 'Hematocrit measurement by dielectric spectroscopy', in *Proceedings of the Second Joint 24th Annual Conference and the Annual Fall Meeting of the Biomedical Engineering Society] [Engineering in Medicine and Biology*. IEEE, pp. 1750–1751. doi: 10.1109/IEMBS.2002.1106634.

Trumbull, J. D. *et al.* (2000) 'Integrating microfabricated fluidic systems and NMR spectroscopy', *IEEE Transactions on Biomedical Engineering*, 47(1), pp. 3–7. doi: 10.1109/10.817611.

Tsai, D. *et al.* (2017) 'A very large-scale microelectrode array for cellular-resolution electrophysiology', *Nature Communications*, 8(1), p. 1802. doi: 10.1038/s41467-017-02009-x.

Vachoux, A., Grimm, C. and Einwich, K. (2003) 'Analog and mixed signal modelling with SystemC-AMS', in *Circuits and Systems, 2003. ISCAS'03. Proceedings of the 2003 International Symposium on*, pp. III--914.

Versnel, W. (1981) 'Analysis of symmetrical Hall plates with finite contacts', *Journal of Applied Physics*. American Institute of Physics, 52(7), pp. 4659–4666. doi: 10.1063/1.329347.

Voigt, P., Schrag, G. and Wachutka, G. (1998) 'Microfluidic system modeling using VHDL-AMS and circuit simulation', *Microelectronics Journal*. Elsevier, 29(11), pp. 791–797. doi: 10.1016/S0026-2692(97)00093-1.

Wang, B., Barahona, M. and Buck, M. (2013) 'A modular cell-based biosensor using engineered genetic logic circuits to detect and integrate multiple environmental signals', *Biosensors and Bioelectronics*. Elsevier, 40(1), pp. 368–376. doi: 10.1016/J.BIOS.2012.08.011.

Wang, C. and Yu, C. (2013) 'Detection of chemical pollutants in water using gold nanoparticles as sensors: a review', *Reviews in Analytical Chemistry*. De Gruyter, 32(1), pp. 1–14. doi: 10.1515/revac-2012-0023.

Wang, Y. *et al.* (2007) 'System-level modeling and simulation of biochemical assays in lab-on-a-chip devices', *Microfluidics and Nanofluidics*. Springer-Verlag, 3(3), pp. 307–322. doi: 10.1007/s10404-006-0123-6.

Wang, Y., Lin, Q. and Mukherjee, T. (2006) 'Composable Behavioral Models and Schematic-Based Simulation of Electrokinetic Lab-on-a-Chip Systems', *IEEE Transactions on Computer-Aided Design of Integrated Circuits and Systems*, 25(2), pp. 258–273. doi: 10.1109/TCAD.2005.855942.

Ward, J. P. *et al.* (2004) 'Cell-signalling repression in bacterial quorum sensing.', *Mathematical medicine and biology : a journal of the IMA*, 21(3), pp. 169–204. Available at: http://www.ncbi.nlm.nih.gov/pubmed/15471245 (Accessed: 18 January 2019).

Warindi *et al.* (2013) 'Modeling and simulation of electroporation system with measured bioimpedance: Determining parameters', in *2013 3rd International Conference on Instrumentation, Communications, Information Technology and Biomedical Engineering (ICICI-BME)*. IEEE, pp. 367–372. doi: 10.1109/ICICI-BME.2013.6698526.

Waters, C. M. and Bassler, B. L. (2005) 'Quorum Sensing: Cell-to-Cell Communication in Bacteria', *Annual Review of Cell and Developmental Biology*. Annual Reviews, 21(1), pp. 319–346. doi: 10.1146/annurev.cellbio.21.012704.131001.

Weiger, M. *et al.* (2008) 'NMR microscopy with isotropic resolution of 3.0 µm using dedicated hardware and optimized methods', *Concepts in Magnetic Resonance Part B: Magnetic Resonance Engineering*. John Wiley & Sons, Ltd, 33B(2), pp. 84–93. doi: 10.1002/cmr.b.20112.

Weltin, A. *et al.* (2014) 'Cell culture monitoring for drug screening and cancer research: a transparent, microfluidic, multi-sensor microsystem.', *Lab on a chip*, 14(1), pp. 138–46. doi: 10.1039/c3lc50759a.

Weltin, A., Kieninger, J. and Urban, G. A. (2016) 'Microfabricated, amperometric, enzyme-based biosensors for in vivo applications', *Analytical and Bioanalytical Chemistry*. Springer Berlin Heidelberg, 408(17), pp. 4503–4521. doi: 10.1007/s00216-016-9420-4.

Wensink, H. *et al.* (2005) 'Measuring reaction kinetics in a lab-on-a-chip by microcoil NMR', *Lab on a Chip*, 5(3), p. 280. doi: 10.1039/b414832k.

Xie, Z. *et al.* (2011) 'Multi-input RNAi-based logic circuit for identification of specific cancer cells.', *Science (New York, N.Y.)*, 333(6047), pp. 1307–11. doi: 10.1126/science.1205527.

Xu, Y. *et al.* (2016) 'A review of impedance measurements of whole cells', *Biosensors and Bioelectronics*. Elsevier, 77, pp. 824–836. doi: 10.1016/J.BIOS.2015.10.027.

Yokoyama, H. and Brorson, S. D. (1989) 'Rate equation analysis of microcavity lasers', *Journal of Applied Physics*. American Institute of Physics, 66(10), pp. 4801–4805. doi: 10.1063/1.343793.

Yu, B. *et al.* (2008) 'A Unified Analytic Drain–Current Model for Multiple-Gate MOSFETs', *IEEE Transactions on Electron Devices*, 55(8), pp. 2157–2163. doi: 10.1109/TED.2008.926228.

Zalesskiy, S. S. *et al.* (2014) 'Miniaturization of NMR Systems: Desktop Spectrometers, Microcoil Spectroscopy, and "NMR on a Chip" for Chemistry, Biochemistry, and Industry', *Chemical Reviews*. American Chemical Society, 114(11), pp. 5641–5694. doi: 10.1021/cr400063g.

Zamore, P. D. and Haley, B. (2005) 'Ribo-gnome: The Big World of Small RNAs', *Science*, 309(5740), pp. 1519–1524. doi: 10.1126/science.1111444.

Zappa, F. *et al.* (2009) 'SPICE modeling of single photon avalanche diodes', *Sensors and Actuators A: Physical*. Elsevier, 153(2), pp. 197–204. doi: 10.1016/J.SNA.2009.05.007.

Zhang, C. *et al.* (2017) 'A highly selective electrochemical sensor based on molecularly imprinted polypyrrole-modified gold electrode for the determination of glyphosate in cucumber and tap water', *Analytical and Bioanalytical Chemistry*, 409(30), pp. 7133–7144. doi: 10.1007/s00216-017-0671-5.

Zhao, P. *et al.* (2011) 'Determination of glyphosate in foodstuff by one novel chemiluminescence-molecular imprinting sensor', *Spectrochimica Acta Part A: Molecular and Biomolecular Spectroscopy*. Elsevier, 78(5), pp. 1482–1486. doi: 10.1016/J.SAA.2011.01.037.

Zhou, J., Arugula, M. and Halamek, J. (2009) 'Enzyme-based NAND and NOR logic gates with modular design', *The Journal of Physical Chemistry B*, 113(49), pp. 16065–16070. Available at: http://pubs.acs.org/doi/abs/10.1021/jp9079052 (Accessed: 1 December 2015).

EXHAUSTIVE LIST OF PUBLICATIONS

INTERNATIONAL JOURNALS WITH REVIEW COMMITTEE (23)

[IJ01] **M. Madec, W. Uhring, J-B. Fasquel , P. Joffre , Y. Hervé**
Compatibility of temporal multiplexed spatial light modulator with optical image processing, Optics Communications, Elsevier (IF : 1.588, SNIP : 0.924, SJR : 0.633), pages 27--37, Volume 275, 2007, doi:10.1016/j.optcom.2007.02.062

[IJ02] **M. Madec, J-B. Fasquel , W. Uhring, P. Joffre , Y. Hervé**
Optical implementation of the filtered backprojection algorithm, Optical Engineering, Society of Photo-optical Instrumentation Engineers (SPIE) (IF : 1.082, SNIP : 0.812, SJR : 0.406), pages 108202_1--16, Volume 46, 2007, doi:10.1117/1.2786450

[IJ03] **M. Madec, W. Uhring, Y. Hervé**
Analogue-driven bistable ferroelectric liquid crystals, Analog Integrated Circuits and Signal Processing, Springer Verlag (IF : 0.623, SNIP : 0.579, SJR : 0.233), pages 187--196, Volume 57, 2008, doi:10.1007/s10470-008-9171-z

[IJ04] **M. Madec, J-B. Fasquel , W. Uhring, P. Joffre , Y. Hervé**
Optoelectronic implementation of helical cone-beam computed tomography algorithms, Optical Engineering, Society of Photo-optical Instrumentation Engineers (SPIE) (IF : 1.082, SNIP : 0.812, SJR : 0.406), pages 058201_1--15, Volume 47, 2008, doi:10.1117/1.2931691

[IJ05] **M. Madec, W. Uhring, É. Hueber , J-B. Fasquel , J. Bartringer, Y. Hervé**
Methods for improvement of spatial light modulator image rendering, Optical Engineering, Society of Photo-optical Instrumentation Engineers (SPIE) (IF : 1.082, SNIP : 0.812, SJR : 0.406), pages 034002_1--13, Volume 48, 2009, doi:10.1117/1.3099644

[IJ06] **J-B. Kammerer, M. Madec, L. Hébrard**
Compact modeling of a magnetic tunnel junction - Part I: Dynamic magnetization model, IEEE Transactions on Electron Devices, Institute of Electrical and Electronics Engineers (IEEE) (IF : 2.605, SNIP : 1.735, SJR : 1.022), pages 1408--1415, Volume 57, 2010

[IJ07] **M. Madec, Y. Gendrault, C. Lallement, J. Haiech**
Design methodology and modeling for synthetic biosystems, International Journal of Microelectronics and Computer Science, Department of Microelectronics and Computer Science (DMCS) of Technical University of Lodz (Poland), pages 147--155., Volume 1, 2010

[IJ08] **M. Madec, J-B. Kammerer, L. Hébrard**
Compact modeling of a magnetic tunnel junction - Part II: Tunneling current model, IEEE Transactions on Electron Devices, Institute of Electrical and Electronics Engineers (IEEE) (IF : 2.605, SNIP : 1.735, SJR : 1.022), pages 1416--1424, Volume 57, 2010

[IJ09] **Y. Gendrault, M. Madec, C. Lallement, F. Pêcheux , J. Haiech**
Synthetic biology methodology and model refinement based on microelectronic modeling tools and languages, Biotechnology Journal, Wiley-VCH Verlag (IF : 3.649, SNIP : 0.969, SJR : 1.29), pages 796--806., Volume 6, juin 2011, doi:10.1002/biot.201100083

[IJ10] **M. Madec, J-B. Kammerer, L. Hébrard, C. Lallement**
An accurate compact model for CMOS cross-shaped Hall effect sensors, Sensors and Actuators A: Physical, Elsevier (IF : 2.499, SNIP : 1.655, SJR : 0.803), pages 69--78, Volume 171, 2011, doi:10.1016/j.sna.2011.05.027

[IJ11] **N. Chevillon, J-M. Sallese, C. Lallement, F. Prégaldiny, M. Madec, J. Sedlmeir, J. Aghassi**
Generalization of the concept of equivalent thickness and capacitance to multigate MOSFETs modeling, IEEE Transactions On Electron Devices, Institute of Electrical and Electronics Engineers (IEEE) (IF : 2.605, SNIP : 1.735, SJR : 1.022), pages 60--71, Volume 59, n° 1, janvier 2012, doi:10.1109/TED.2011.2171347

[IJ12] **M. Madec, J-B. Kammerer, L. Hébrard, C. Lallement**
An improved compact model for CMOS cross-shaped Hall-effect sensor including offset and temperature effects, Analog Integrated Circuits And Signal Processing, Springer Verlag (IF : 0.623, SNIP : 0.579, SJR : 0.233), pages 719--730, Volume 73, 2012, doi:10.1007/s10470-012-9872-1

[IJ13] **M. Madec, J-B. Schell, J-B. Kammerer, C. Lallement, L. Hébrard**
Compact modeling of vertical Hall-effect devices: electrical behavior, Analog Integrated Circuits And Signal Processing, Springer Verlag (IF : 0.623, SNIP : 0.579, SJR : 0.233), pages 183-195, Volume 77, novembre 2013, doi:10.1007/s10470-013-0112-0

[IJ14] **Y. Gendrault, M. Madec, C. Lallement, J. Haiech**
Modeling Biology With HDL Languages: A First Step Toward a Genetic Design Automation Tool Inspired From Microelectronics, IEEE Transactions on Biomedical Engineering, Institute of Electrical and Electronics Engineers (IEEE) (IF : 3.577, SNIP : 1.995, SJR : 1.214), pages 1231-1240, Volume 61, n° 4, janvier 2014, doi:10.1109/TBME.2014.2298559. **Couverture de la revue**.

[IJ15] **S. Guiton, A. Rezgui, M. Madec, C. Lallement, F. Rufi , J. Haiech**
System-level modeling of a Lab-On-Chip for micropollutants detection, International journal of microelectronics and computer science, Department of Microelectronics and Computer Science (DMCS) of Technical University of Lodz (Poland), pages 116-125, Volume 5, n° 3, 2014, doi:10.1109/MIXDES.2014.6872196

[IJ16] **J. Haiech, Y. Gendrault, M-C. Kilhoffer , R. Ranjeva , M. Madec, C. Lallement**
A general framework improving teaching ligand binding to a macromolecule, Bba - Molecular Cell Research, Elsevier (IF : 4.521, SNIP : 1.248, SJR : 2.727), pages 2348-2355, Volume 843, octobre 2014, doi:10.1016/j.bbamcr.2014.03.013

[IJ17] **M. Madec, J-B. Schell, J-B. Kammerer, C. Lallement, L. Hébrard**
An improved compact model of the electrical behavior of the 5-contact Vertical Hall device, Analog Integrated Circuits And Signal Processing, Springer Verlag (IF : 0.623, SNIP : 0.579, SJR : 0.233), pages 677-691, Volume 81, n° 3, décembre 2014, doi:10.1007/s10470-014-0438-2

[IJ18] **M. Madec, F. Pêcheux , Y. Gendrault, E. Rosati, C. Lallement, J. Haiech**
GeNeDA: an open-source workflow for design automation of gene regulatory networks inspired from microelectronics, Journal of Computational Biology, Mary Ann Liebert (IF : 1.032, SNIP : 0.725, SJR : 1.216), page 10.1089/cmb.2015.0229, Volume 13, n° 6, juin 2016, doi:10.1089/cmb.2015.0229

[IJ19] **M. Madec, C. Lallement, J. Haiech**
Modeling and simulation of biological systems using SPICE language, PLOS ONE, Public Library of Science (IF : 2.806, SNIP : 1.092, SJR : 1.201), 2017, doi:https://doi.org/10.1371/journal.pone.0182385

[IJ20] **E. Rosati, M. Madec, J-B. Kammerer, L. Hébrard, C. Lallement, J. Haiech**
Efficient modeling and simulation of space-dependent biological systems, Journal of Computational Biology, Mary Ann Liebert (IF : 1.032, SNIP : 0.725, SJR : 1.216), page 10.1089/cmb.2018.0012, mai 2018, doi:10.1089/cmb.2018.0012

[IJ21] **A. Saberkari , O. Khorgami , J. Bagheri , M. Madec, S. Hosseini-Golgoo , E. Alarcón-Cot**
Design of Broadband CNFET LNA Based on Extracted I–V Closed-Form Equation, IEEE Transactions on Nanotechnologies, IEEE Nanotechnology Council, page 10.1109/TNANO.2018.2822599, Volume 17, n° 4, juillet 2018, doi:10.1109/TNANO.2018.2822599

[IJ22] **M. Madec, L. Hébrard, J-B. Kammerer, A. Bonament, E. Rosati, C. Lallement**
*Multiphysics simulation of biosensors involving 3D biological reaction-diffusion phenomena in a standard circuit EDA environment***,** IEEE Transactions on Circuits and Systems. Part I, Regular Papers, Volume 99, janvier 2019. doi: 10.1109/TCSI.2018.2885223

[IJ23] **M. Madec, A. Bonament, E. Rosati, Y. Takakura, J. Haiech, L. Hébrard, C. Lallement**
Environnement for modeling and simulation of biosystems, biosensors and lab-on-chips, IEEE Transactions on Electron Devices, Volume 66, décembre 2018, doi:10.1109/TED.2108.28811320

BOOK CHAPTER (1)

M. Madec

[B1] *Biomolecular interactions***,** Engineering of micro/nano bio systems: fundmentals and applications, Alain Bosseboeuf (Eds.), Chapitre. 2.1, Springer, 2018. ISBN: 978-981-13-6549-2

INTERNATIONAL CONFERENCES WITH PROCEEDINGS AND REVIEW COMMITTEE (38)

M. Madec, W. Uhring, J-B. Fasquel , P. Joffre , Y. Hervé

[ICP01] *FLC-SLM dynamic improvement with temporal multiplexing: Application to optical image processing*, Photonics Europe 2006, Strasbourg, France, pages 390--399, edited by C. Righini (Eds.), SPIE, Proceedings of the Society of Photo-optical Instrumentation Engineers, Volume 6183, avril 2006. ISBN 9780819462398, doi:10.1117/12.662952

M. Madec, Y. Hervé, W. Uhring, O. Rolland

[ICP02] *VHDL-AMS models of FLC for spatial light modulator virtual prototyping*, Photonics Europe 2006, Strasbourg, France, pages 400--412, edited by C. Righini (Eds.), SPIE, Proceedings of the Society of Photo-optical Instrumentation Engineers, Volume 6183, avril 2006. ISBN 9780819462398,

M. Madec, W. Uhring, Y. Hervé

[ICP03] *VHDL-AMS model of ferroelectric liquid crystals*, Forum on specification & Design Languages (FDL'06), Darmstadt, Germany, pages 31--39, septembre 2006

M. Madec, J-B. Kammerer, F. Prégaldiny, L. Hébrard, C. Lallement

[ICP04] *Compact modeling of magnetic tunnel junction*, Joint 6th International IEEE Northeast Workshop on Circuits and Systems and TAISA Conference (NEWCAS-TAISA'08), Montréal, Canada, pages 229--232, IEEE, juin 2008. doi:10.1109/NEWCAS.2008.4606363

N. Chevillon, M. Tang, F. Prégaldiny, C. Lallement, M. Madec

[ICP06] FinFET compact modeling and parameter extraction, 16th IEEE International Conference Mixed Design of Integrated Circuits and Systems (MIXDES'2009), Lodz, Poland, pages 55--60, IEEE, juin 2009. Papier invité.

M. Madec, C. Lallement, K. Karstens , S. Dittman , M. Gersbacher , R. Sorg , M. Wild , M. Müller , P. Bourgine , M. Donzeau ,J. Haiech

[ICP07] *Synthetic biology and microelectronics: A similar design flow*, Joint 7th International IEEE Northeast Workshop on Circuits and Systems and TAISA Conference (NEWCAS-TAISA'09), Toulouse, France, IEEE, juin 2009. doi:10.1109/NEWCAS.2009.5290444

F. Pêcheux, M. Madec, C. Lallement

[ICP08] *Is SystemC-AMS an appropriate "promoter" for the modeling and simulation of bio-compatible systems?,* IEEE International Symposium on Circuits and Systems (ISCAS 2010), Paris, France, pages 1791--1794, IEEE, mai 2010. doi:10.1109/ISCAS.2010.5537669

M. Madec, J-B. Kammerer, L. Hébrard

[ICP09] *An improved compact model of cross-shaped horizontal CMOS-integrated Hall-effect sensor*, 8th IEEE International Northeast Workshop on Circuits and Systems Conference (NEWCAS 2010), Montreal, Canada, pages 397--400, IEEE, juin 2010.

M. Madec, C. Lallement, Y. Gendrault, J. Haiech

[ICP10] *Design methodology for synthetic biosystems*, 17th IEEE International Conference Mixed Design of Integrated Circuits and Systems (MIXDES'2010), Wrocaw, Poland, pages 621--626, IEEE, juin 2010. **Poland Section IEEE ED Chapter Special Award**

Y. Gendrault, M. Madec, C. Lallement, J. Haiech

[ICP11] *Multi-abstraction modeling in synthetic biology*, 3rd IEEE International Symposium on Applied Sciences in Biomedical and Communication Technologies (ISABEL 2010), Rome, Italy, IEEE, novembre 2016 doi:10.1109/ISABEL.2010.

[ICP14] **M. Madec, J-B. Kammerer, L. Hébrard, C. Lallement**
Analysis of the efficiency of spinning-current techniques thru compact modeling, 10th IEEE International Conference on Sensors (Sensors 2011), Limerick, Ireland, pages 542--545, IEEE, octobre 2011.doi:10.1109/ICSENS.2011.6127318

[ICP15] **N. Chevillon , M. Madec, C. Lallement**
Gate-level modeling for CMOS circuit simulation with ultimate FinFETs, 2012 IEEE/ACM International Symposium on Nanoscale Architectures (NANOARCH), Amsterdam, Netherlands, pages 22--29, IEEE, juillet 2012.http://ieeexplore.ieee.org/xpl/articleDetails.jsp?arnumber=6464139

[ICP16] **M. Madec, J-B. Schell, J-B. Kammerer, C. Lallement, L. Hébrard**
Compact modeling of vertical Hall-effect devices: Electrical behavior, 10th IEEE International NEWCAS Conference (NEWCAS 2012), Montreal, Canada, pages 213--216, IEEE, juin 2012. http://ieeexplore.ieee.org/xpl/articleDetails.jsp?arnumber=6328994, doi:10.1109/NEWCAS.2012.6328994. **Best paper award**.

[ICP17] **M. Madec, Y. Gendrault, C. Lallement, J. Haiech**
A game-of-life like simulator for design-oriented modeling of biobricks in synthetic biology, 34th Annual International Conference of the IEEE Engineering in Medicine and Biology Society (EMBC 2012), San Diego, United States, pages 5462--5465, IEEE, août 2012. http://ieeexplore.ieee.org/xpl/articleDetails.jsp?arnumber=6347230, doi:10.1109/EMBC.2012.6347230

[ICP18] **Y. Gendrault, M. Madec, V. Wlotzko, M. Andraud , C. Lallement, J. Haiech**
Using digital electronic design flow to create a genetic design automation tool, 34th Annual International Conference of the IEEE Engineering in Medicine and Biology Society (EMBC 2012), San Diego, United States, pages 5530--5533, IEEE, août 2012. http://ieeexplore.ieee.org/xpl/articleDetails.jsp?arnumber=6347247, doi:10.1109/EMBC.2012.6347247

[ICP19] **M. Madec, J-B. Schell, J-B. Kammerer, C. Lallement, L. Hébrard**
An Improved Compact Model of the Electrical Behaviour of the 5-Contact Vertical Hall-effect Device, 11th IEEE International New Circuits and Systems Conference (NEWCAS), Paris, France, juin 2013, doi:10.1109/NEWCAS.2013.6573659

[ICP20] **M. Madec, F. Pêcheux , Y. Gendrault, L. Bauer , J. Haiech, C. Lallement**
EDA inspired Open-source Framework for Synthetic Biology, IEEE Biomedical Circuits and Systems Confrence (BIOCAS 2013), Rotterdam, Netherlands, pages 374-377, octobre 2013, doi:10.1109/BioCAS.2013.6679717

[ICP21] **Y. Gendrault, M. Madec, V. Wlotzko, C. Lallement, J. Haiech**
Fuzzy Logic, an Intermediate Description Level for Design and Simulation in Synthetic Biology, IEEE Biomedical Circuits and Systems Confrence (BIOCAS 2013), Rotterdam, Netherlands, pages 370-373, octobre 2013, doi:10.1109/BioCAS.2013.6679716

[ICP22] **M. Madec, L. Osberger, L. Hébrard**
Assessment of the spinning-current efficiency in cancelling the 1/f noise of Vertical Hall Devices through accurate FEM modeling, IEEE Sensor 2013, Baltimore, United States, IEEE, novembre 2013.http://ieeexplore.ieee.org/xpl/articleDetails.jsp?arnumber=6688323

[ICP23] **Y. Gendrault, M. Madec, C. Lallement, J. Haiech**
Genetic networks modeling inspired from electronic design automation, Advances in Systems and Synthetic Biology, Evry, France, pages 73-78, Amar P, Képès F, Norris V (Eds.), EDP Sciences, ISBN: 978-2-7598-1201-1, mars 2014

[ICP24] **M. Madec, F. Pêcheux , F. Jezequel , Y. Gendrault, C. Lallement, J. Haiech**
Opportunities and challenges for the virtual prototyping of synthetic biological functions, IEEE International Symposium on Circuits and Systems (ISCAS), Melbourne, Australia, pages 2013-2016, juin 2014, doi:10.1109/ISCAS.2014.6865559

[ICP25] **S. Guiton, A. Rezgui, M. Madec, C. Lallement, F. Rufi , J. Haiech**
Modeling and simulation of a Lab-On-Chip for micropollutants detection, 21st International Conference & Mixed Design of Integrated Circuits and Systems" (MIXDES 2014), Lublin, Poland, pages 256-261, juin 2014, doi:10.1109/MIXDES.2014.6872196

[ICP26] **M. Madec, L. Osberger, J-B. Schell, J-B. Kammerer, C. Lallement, L. Hébrard**
Compact Modeling of Offset Sources in Vertical Hall-Effect Devices, New Circuits and Systems Conference (NEWCAS), 2014 IEEE 12th International, Trois-Rivieres, QC, Canada, France, juin 2014, doi:10.1109/NEWCAS.2014.6934031

[ICP27] **Y. Gendrault, M. Madec, M. Lemaire, C. Lallement, J. Haiech**
Automated design of artificial biological functions based on fuzzy logic, IEEE Biomedical Circuits an Systems Conference (BIOCAS 2014), Lausanne, Switzerland, pages 85-88, octobre 2014, doi:10.1109/BioCAS.2014.6981651

[ICP28] **E. Rosati, M. Madec, F. Pêcheux , Y. Gendrault, C. Lallement, J. Haiech**
Design and simulation of a compact genetic flip-flop, Advances in Systems and Synthetic Biology, Strasbourg, France, pages 115-124, mars 2015

[ICP29] **L. Talide , Z. Blanck , M. Renou , T. Wallois , E. Rosati, M. Madec, A. Rezgui, C. Lallement, J. Haiech**
Modeling of intercellular transport for emerging applications in synthetic biology, Advances in Systems and Synthetic Biology, Strasbourg, France, pages 149-156, mars 2015

[ICP30] **M. Madec, A. Rezgui, Y. Gendrault, C. Lallement, J. Haiech**
Tutorial: Design of artificial gene regulatory networks with logic approach, Advances in Systems and Synthetic Biology, Strasbourg, France, pages 169-178, Genopole (Eds.), mars 2015

[ICP32] **A. Rezgui, M. Madec, J. Haiech, C. Lallement**
Integration of SBML Models for the Description of Biological Systems in a Lab-On-Chip, 22nd IEEE International Conference Mixed Design of Integrated Circuits & Systems (MIXDES 2015), Torun, Poland, IEEE, juin 2015, doi:10.1109/MIXDES.2015.7208504

[ICP33] **E. Rosati, M. Madec, J-B. Kammerer, A. Rezgui, C. Lallement, J. Haiech**
Verilog-A Compact Space-dependent Model for Biology, 22nd IEEE International Conference Mixed Design of Integrated Circuits & Systems (MIXDES 2015), Torun, Poland, pages 171-176, juin 2015, doi:10.1109/MIXDES.2015.7208505

[ICP38] **L. Osberger, V. Frick, M. Madec, L. Hébrard**
High resolution, low offset Vertical Hall device in Low-Voltage CMOS technology, IEEE 13th International New Circuits and Systems Conference (NEWCAS 2015), Grenoble, France, juin 2015, doi: 10.1109/NEWCAS.2015.7182008

[ICP39] **E. Rosati, M. Madec, J-B. Kammerer, A. Rezgui, C. Lallement, J. Haiech**
Verilog-A Compact Space-dependent Model for Biology, Advances in Systems and Synthetic Biology, Evry, France, pages 103-117, Genopole (Eds.), EDP science, ISBN : 978-2-7598-1971-3, Volume 15, mars 2016

[ICP40] **E. Rosati, M. Madec, A. Rezgui, Q. Colman, N. Toussaint, C. Lallement, P. Collet**
Application of Evolutionary Algorithms in Synthetic Biology, EuroGP - EvoStar 2016, Porto, Portugal, ed. Springer/verlag, ISBN: 978331931203, Volume 9597, mars 2016,

[ICP43] **M. Madec, O. Bolaji, C. Lallement, J. Haiech**
Virtual prototyping for biosystems: A spicy challenge, IEEE 15th International New Circuits and Systems Conference (NEWCAS 2017), Strasbourg, France, juin 2017, doi: 10.1109/NEWCAS.2017.8010150

[ICP44] **Y. Gendrault, M. Madec, C. Lallement, J. Haiech**
A microelectronic approach to identifying and modeling biological noise, IEEE 15th International New Circuits and Systems Conference (NEWCAS 2017), Strasbourg, France, juin 2017, doi: 10.1109/NEWCAS.2017.8010135

[ICP45] **N. Dumas, E. Rosati, M. Madec, V. Pasteur, D. Funfschilling**
Simulating Diffusion Transport Between Droplets In A Microfluidics Chip, Microflu 2018, Strasbourg, France, février 2018.

[ICP46] **R. Goerlich , A. Biquet , E. Rosati, M. Madec, C. Lallement**
Modelling of biological asynchronous sequential systems, Advances in Systems and Synthetic Biology, pages 103-117, Genopole (Eds.), EDP science, ISBN : 978-2-7598-2266-9, Volume 17, mars 2018

[ICP47] **M. Madec, A. Bonament, E. Rosati, L. Hébrard, C. Lallement**
Virtual prototyping of biosensors involving reaction-diffusion phenomena, IEEE 16th International New Circuits and Systems Conference (NEWCAS 2018), Montréal, Quebec, Canada, juin 2018, doi: en cours

[ICP48] **D-V. Nguyen, L. Werling, C. Po, N. Dumas, M. Madec, W. Uhring, L. Hébrard, L. Fakri-Bouchet , J. Pascal , Y. Wadghiri**
On the influence of strong magnetic field on MOS transistors, IEEE ICECS 2018, Bordeaux, France, pages 637-640, juin 2018, doi:10.1109/ICECS.2018.8617922

INTERNATIONAL CONFERENCES WITH REVIEW COMMITTEE W/O PROCEEDINGS (8)

[IC05] **M. Madec, É. Hueber , W. Uhring, J-B. Fasquel , Y. Hervé**
Procedures for SLM image quality improvement, European Optical Society Annual Meeting 2008, Paris, France, septembre 2008

[IC12] **Y. Gendrault, M. Madec, C. Lallement, J. Haiech**
A design kit for synthetic biology, International Conference on Synthetic Biology, Evry, France, décembre 2010

[IC34] **M. Madec, F. Pêcheux , Y. Gendrault, E. Rosati, C. Lallement, J. Haiech**
Reuse of microelectronics software for gene regulatory networks design automation, BioSynSys 2015, Paris, France, septembre 2015

[IC35] **E. Rosati, M. Madec, Q. Colman, N. Toussaint, A. Rezgui, C. Lallement, J. Haiech, P. Collet**
A Nature-Inspired Evolutionnary Algorithm for the Design and Optimization of Gene Regulatory Networks, BioSynSys 2015, Paris, France, septembre 2015

[IC36] **A. Rezgui, M. Madec, C. Lallement, J. Haiech**
SBML to VHDL-AMS models for Describing Biological Systems in a Lab-On-Chip, BioSynSys 2015, Paris, France, septembre 2015

[IC37] **E. Rosati, M. Madec, J-B. Kammerer, A. Rezgui, C. Lallement, J. Haiech**
A Verilog-A Mesher Based on Eletronics to Model Space-Dependent Biological Systems, BioSynSys 2015, Paris, France, septembre 2015

[IC41] **M. Madec, A. Rezgui, Y. Gendrault, E. Rosati, F. Pêcheux , C. Lallement, J. Haiech**
Application of Electrical Design Automation in Biological Context, CDN Live 2016, Munich, Germany, mai 2016. **Academic Track Best Paper Award**

[IC42] **O. Bolaji, M. Madec, E. Rosati, C. Lallement**
Evaluation of Open Source Electrical Simulator in a Biological Context, 2nd international conference of the GDR BioSynSys, Bordeaux, France, juin 2016

INTERNATIONAL CONFERENCES – INVITED PAPERS (2)

[IIC13] **Y. Gendrault, M. Madec, C. Lallement, F. Pêcheux , J. Haiech**
Computer-aided design in synthetic biology: A system designer approach, 4th International Symposium on Applied Sciences in Biomedical and Communication Technologies (ISABEL 2011), Barcelona, Spain, octobre 2011. papier invité, doi:10.1145/2093698.2093869

[IIC31] **C. Lallement, M. Madec**
Challenges in Design-oriented Modeling in Biology, 22nd IEEE International Conference Mixed Design of Integrated Circuits & Systems (MIXDES 2015), Torun, Poland, pages 17-22, juin 2015, doi:10.1109/MIXDES.2015.7208471. Keynote invite.

FRENCH JOURNALS (4)

[FJ01] **A. Rezgui, M. Madec, N. Dumas, S. Guiton, C. Lallement, L. Hébrard, J. Haiech, F. Rufi**
Nouvelles unités d'enseignement autour de l'étude et de la conception de laboratoires sur puces, journal sur l'enseignement des sciences et technologies de l'information et des systemes, EDP Sciences, page 2012, Volume 14, septembre 2015, doi:10.1051/j3ea/2015024

[FJ02] **M. Madec, Y. Gendrault, C. Lallement, J. Haiech**
Introduction à la biologie synthétique et au développement d'outils de conception dédiés, journal sur l'enseignement des sciences et technologies de l'information et des systemes, EDP Sciences, page 2015, Volume 14, septembre 2015, doi:10.1051/j3ea/2015027

[FJ03] **M. Madec, J. Haiech, E. Rosati, A. Rezgui, Y. Gendrault, C. Lallement**
Application à la biologie synthétique des méthodes et outils de CAO de la microélectronique, MEDECINE/SCIENCES : M/S, EDP Sciences (IF : 0.417, SNIP : 0.204, SJR : 0.203), Volume 32, n° 2, 2017

[FJ04] **H. Omran, M. Madec, V. Schuh , B. Bayle**
Carte électronique générique à base de compensateurs avance-retard pour les travaux pratiques d'automatique continue, journal sur l'enseignement des sciences et technologies de l'information et des systemes, EDP Sciences, Under Press.

FRENCH CONFERENCES (16)

[FC01] **M. Madec, W. Uhring, J-B. Fasquel , K. Bouamama , P. Joffre , Y. Hervé**
Amélioration de la dynamique des modulateurs spatiaux de lumière rapides à cristaux liquides par multiplexage temporel. Application à la corrélation optique, 5ème Colloque Francophone du Club Contrôles et Mesures Optiques pour l'Industrie (CMOI 2004), Saint-Etienne, France, pages 312--318, novembre 2004

[FC02] **K. Bouamama , J-B. Fasquel , P. Joffre , M. Madec, W. Uhring, Y. Hervé**
Modulateurs spatiaux de lumière et filtrage optique rapide de données médicales, 5ème Colloque Francophone du Club Contrôles et Mesures Optiques pour l'Industrie (CMOI 2004), Saint-Etienne, France, pages 570--576, novembre 2004

[FC03] **M. Madec**
Les modulateurs spatiaux de lumière. État de l'art et application à la corrélation optique, VIIIèmes Journées Nationales du Réseau Doctoral de Microélectronique (JNRDM'2005), Paris, France, mai 2005.

[FC04] **J-B. Fasquel , M. Madec, W. Uhring, K. Bouamama , P. Joffre , Y. Hervé**
Filtrage optique de données médicales, Colloque international OPTRO 2005, Paris, France, mai 2005

[FC05] **M. Madec, Y. Hervé**
La microélectronique et le traitement optique de l'information, IXèmes Journées Nationales du Réseau Doctoral de Microélectronique (JNRDM'2006), Rennes, France, mai 2006

[FC06] **M. Madec, W. Uhring, Y. Hervé**
Analogue-driven bistable ferroelectric liquid crystals, 7ème Colloque sur le Traitement Analogique de l'Information, du Signal et ses Applications (TAISA'2006), Strasbourg, France, octobre 2006

[FC07] **M. Madec, J-B. Fasquel , W. Uhring, Y. Hervé**
La microélectronique et le traitement optique de l'information, 9èmes Journées Pédagogiques du CNFM (JPCNFM 2006), Saint-Malo, France, novembre 2006. Papier invité

[FC08] **M. Madec, J-B. Fasquel , W. Uhring, P. Joffre , Y. Hervé**
*Processeurs optoélectroniques dédiés aux algorithmes de reconstruction d'images en tomographie***,** 8ème Colloque Francophone du Club Contrôles et Mesures Optiques pour l'Industrie (CMOI 2007), Arcachon, France, novembre 2007

[FC09] **M. Madec, W. Uhring, Y. Hervé**
Commande analogique des cristaux liquides ferroelectriques, 9e colloque francophone du club Contrôle et Mesures Optiques pour l'Industrie (CMOI 2008), Nantes, France, novembre 2008

[FC10] **N. Chevillon , M. Tang , F. Prégaldiny, M. Madec, C. Lallement**
Modèle compact de FinFET et extraction de paramètres, Journées-atelier des Groupement de Recherche SiP SoC et Nanoélectronique, Bordeaux, France, décembre 2009

[FC11] **M. Madec, Y. Gendrault, C. Lallement, J. Haiech**
Introduction à la biologie synthétique et au développement d'outils de conception associés, 12èmes Journées Pédagogiques du CNFM (JPCNFM 2012), Saint-Malo, France, pages 123--128, novembre 2012. http://ccmo.univ-rennes1.fr/JP-CNFM/JP-2012/JP-CNFM-12-sommaire.htm

[FC12] **L. Osberger, V. Frick, M. Madec, L. Hébrard**
Etude de la technique du courant tournant pour la réduction du bruit en 1/f des capteurs à effet Hall verticaux par simulation FEM, JNRDM14, Lille, France, mai 2014

[FC13] **A. Rezgui, M. Madec, N. Dumas, S. Guiton, C. Lallement, L. Hébrard, J. Haiech, F. Rufi**
Environnement de modélisation et de simulation pour la conception des laboratoires sur puces, Treizième Journées Pédagogiques du CNFM JPCNFM'2014, Saint-Malo, France, pages P21 - 4 pages, novembre 2014

[FC14] **A. Rezgui, M. Madec, N. Dumas, W. Uhring, C. Lallement, J. Haiech, F. Rufi**
Détection de polluants dans l'eau par des laboratoires sur puce, Journée, Electronique et Environnement, Journées électronique et environnement, France, Club EEA (Eds.), octobre 2015

[FC15] **L. Hébrard, F. Schwartz, M. Madec**
Conception de circuits intégrés analogiques : des architectures simples aux architectures à faible tension d'alimentation, 14ème Journées Pédagogiques du CNFM, JPCNFM'16, Montpellier, France, page P25, 4pages, novembre 2016

[FC16] **E. Rosati, M. Madec, J.-B. Kammerer, L. Hébrard, C. Lallement, J. Haiech**
Modélisation compacte en Verilog-A des problèmes biologiques dépendant de l'espace, Journée nationales du réseau des doctorants en microélectronique (JNRDM 2017), Strasbourg, France, novembre 2017. Keynote.

[FC17] **M. Mounisens , E. Michelet , R. Enjalbert , R. Bounoua, L. Cuvillon, M. Madec**
Projet étudiant : réalisation d'un système de payement sans contact pour le foyer des étudiants, 15 èmes journées pédagogiques du CNFM, Saint-Malo, France, page P16, Volume ISBN 2-9522395-7-6, novembre 2018

[FC18] **D-V. Nguyen, N. Dumas, M. Madec, W. Uhring, L. Hébrard**
Conception d'un circuit intégré pour l'analyse micro-RMN dans un laboratoire sur puce, 15 èmes journées pédagogiques du CNFM, Saint-Malo, France, page P18, Volume ISBN 2-9522395-7-6, novembre 2018

[FC19] **H. Omran, M. Madec, V. Schuh , B. Bayle**
Carte électronique générique à base de compensateurs avance-retard pour les travaux pratiques d'automatique continue, 15 èmes journées pédagogiques du CNFM, Saint-Malo, France, page P11, Volume ISBN 2-9522395-7-6, novembre 2018

[FC20] **E. Rosati, M. Madec, A. Rezgui, A. Bonament, M. Frey , P. Bernou , K. Wanaverbecq , M. Labonne , L. Hébrard**
*Développement d'outils pour la formation au dépannage de circuits électroniques***,** 15 èmes journées pédagogiques du CNFM, Saint-Malo, France, page P21, Volume ISBN 2-9522395-7-6, novembre 2018

PATENTS (1)

[P1] **M. Madec, J-B. Fasquel , W. Uhring**
Processeur opto-électronique de reconstruction de données tomographiques. Dépôt de brevet français (déposant : Micromodule, U. Strasbourg, CNRS, IRCAD), n° FR0608361, le 22 septembre 2006, publication n° FR2906375, le 28 mars 2008, délivrance n° FR2906375, le 29 mai 2009.

TABLE OF CO-AUTHORS

Author	Affiliation	Number of common publications							
		Total	IJ	ICP	IC	IIC	JF	CF	P
C. Lallement	ICube – SMH team	61	15	29	7	2	3	5	
J. Haiech	LIT, Strasbourg, FR	42	9	19	6	1	3	4	
L. Hébrard	ICube – SMH team	25	9	10			1	5	
Y. Gendrault	ICube – SMH team (Ph.D.)	24	5	12	3	1	2	1	
E. Rosati	ICube – SMH team (Ph.D.)	19	4	7	5		1	2	
J.-B. Kammerer	ICube – SMH team	18	8	8	1			1	
W. Uhring	ICube – SMH team	18	4	4	1			8	1
A. Rezgui	ICube – SMH team	17	1	7	4		2	3	
Y. Hervé	ICube – SMH team	16	4	3	1			8	
J.-B. Fasquel	IRCAD	11	3	1	1			5	1
F. Pêcheux	LIP6, Paris, FR	9	2	4	2	1			
P. Joffre	Micromodule SAS, FR	8	3	1				4	
N. Dumas	ICube – SMH team	6		2			1	3	
J.-B. Schell	ICube – SMH team	5	2	3					
F. Rufi	Bürkert Fluid Control, FR	5	1	1			1	2	
A. Bonament	ICube – SMH team (Ph.D.)	4	2	1				1	
F. Prégaldiny	ICube – SMH team	4	1	2				1	
S. Guiton	ICube – SMH team (Ph.D.)	4	1	1			1	1	
L. Osberger	Master 2 student	4		3				1	
N. Chevillon	ICube – SMH team (Ph.D.)	3	1	1				1	
K. Bouamama	LSP, Strasbourg, FR	3						3	
E. Hueber	MIPS, Mulhouse, FR	2	1		1				
V. Wlotzko	TPS student	2		2					
M. Tang	ICube – SMH team (Ph.D.)	2		1				1	
P. Collet	ICube – CSTB team	2		1	1				
N. Toussaint	Master 1 student	2		1	1				
C. Colman	TPS student	2		1	1				
O. Bolaji	Master 2 student	2		1	1				
P. Collet	ICube – CSTB team	2		1	1				
N. Toussaint	Master 1 student	2		1	1				
C. Colman	TPS student	2		1	1				
O. Bolaji	Master 2 student	2		1	1				
V. Frick	ICube – SMH team	2		1				1	
D.-V. N'Guyen	ICube – SMH team (Ph.D.)	2		1				1	
H. Omran	ICube – AVR team	2					1	1	
B. Bayle	ICube – AVR team	2					1	1	
V. Schuh	TP (Ass. Prof.)	2					1	1	
J.-M. Sallese	EPFL, Lausanne, SW	1	1						
J. Sedlmeir	Intel, Neubiberg, GE	1	1						
J. Aghassi	Intel, Neubiberg, GE	1	1						
M.-C. Kilhoffer	LIT, Strasbourg, FR	1	1						

R. Ranjeva	LIT, Strasbourg, FR	1	1			
A. Saberkari	MRL, Guilan, IR	1	1			
O. Khorgami	MRL, Guilan, IR	1	1			
J. Bagheri	MRL, Guilan, IR	1	1			
S. Hosseini-Golgoo	MRL, Guilan, IR	1	1			
E. Alarcon-Cot	TUC, Barcelona, SP	1	1			
Y. Takakura	ICube – TRIO team	1	1			
J. Bartringer	ICube (Proj. Engin.)	1	1			
O. Roland	SystemVIP, Strasbourg, FR	1		1		
M. Donzeau	BCS, Strasbourg, France	1		1		
F. Jezequel	LIP6, Paris, FR	1		1		
D. Funfschilling	ICube – MecaFlu team	1		1		
L. Werling	ICube – SMH team (Ph.D.)	1		1		
C. Po	ICube – Imagines	1		1		
L. Fakri-Bouchet	ISA, Lyon, FR	1		1		
J. Pascal	FHNW, Muttenz, SW	1		1		
Y. Wadghiri	LMC, New-York, US	1		1		
K. Karstens	ESBS student	1		1		
S. Dittman	ESBS student	1		1		
M. Gersbacher	ESBS student	1		1		
R. Sorg	ESBS student	1		1		
M. Wild	ESBS student	1		1		
M. Müller	ESBS student	1		1		
P. Bourguine	ESBS student	1		1		
M. Andraud	TPS student	1		1		
L. Bauer	TPS / Master 2 student	1		1		
M. Lemaire	TPS / Master 2 student	1		1		
L. Talide	ESBS student	1		1		
Z. Blanck	ESBS student	1		1		
M. Renou	TPS student	1		1		
T. Wallois	TPS student	1		1		
V. Pasteur	TPS student	1		1		
R. Goerlich	Master 1 student	1		1		
A. Biquet	Master 1 student	1		1		
F. Schwartz	ICube – SMH team	1				1
L. Cuvillon	ICube – AVR team	1				1
M. Frey	TPS (Tech. Ass.)	1				1
M. Mounisens	TPS student	1				1
E. Michelet	TPS student	1				1
R. Enjalbert	TPS student	1				1
R. Bounoua	TPS student	1				1
P. Bernou	TPS student	1				1
K. Wanaverbecq	TPS student	1				1
M. Labonne	TPS student	1				1