

# Design and validation of innovative integrated circuits and embedded systems for neurostimulation applications

Jonathan Castelli

### ► To cite this version:

Jonathan Castelli. Design and validation of innovative integrated circuits and embedded systems for neurostimulation applications. Electronics. Université de Bordeaux, 2017. English. NNT: 2017BORD0812. tel-01897367

## HAL Id: tel-01897367 https://theses.hal.science/tel-01897367

Submitted on 17 Oct 2018

**HAL** is a multi-disciplinary open access archive for the deposit and dissemination of scientific research documents, whether they are published or not. The documents may come from teaching and research institutions in France or abroad, or from public or private research centers. L'archive ouverte pluridisciplinaire **HAL**, est destinée au dépôt et à la diffusion de documents scientifiques de niveau recherche, publiés ou non, émanant des établissements d'enseignement et de recherche français ou étrangers, des laboratoires publics ou privés.





# **Thèse de Doctorat de** l'Université de Bordeaux

École doctorale des Sciences Physiques et de l'Ingénieur

Spécialité Électronique

Préparée au Laboratoire IMS

Par Jonathan Castelli

Design and validation of innovative integrated circuits and embedded systems for neurostimulation applications

> Sous la direction de Pr. Noëlle Lewis et de Pr. Sylvie Renaud Après l'avis de Pr. Serge Bernard et de Pr. Aymeric Histace Soutenue le 6 Décembre 2017

#### Devant le comité d'examen formé de:

Pr.	Serge Bernard	CNRS - LIRMM
Pr.	Aymeric Histace	ENSEA
Pr.	Ranu Jung	Florida International University
Dr.	Rémi Dubois	IHU LIRYC
Pr.	Noëlle Lewis	University of Bordeaux
Pr.	Sylvie Renaud	Bordeaux INP

Rapporteur Rapporteur Examinatrice Examinateur Directrice de Thèse Co-Directrice de Thèse

Thèse réalisée dans le laboratoire **IMS** au sein de l'équipe **Elibio**.

Université de Bordeaux Laboratoire IMS CNRS UMR-5218 351, cours de la Libération 33405 TALENCE Cedex

Stand at the base and look up at 3,000 feet of blankness. It just looks like there's no way you can climb it. That's what you seek as a climber. You want to find something that looks absurd and figure out how to do it. Tommy Caldwell

## Abstract

Bioelectronics is a cross-disciplinary field that studies interconnections and interactions between biological entities (cells, tissues, organs) and electronic systems, using the adequate transducer. For excitable cells or tissues (neurons, muscles, ...), the transducer takes the form of a simple electrode, as these tissues produce a spontaneous electrical activity or, in the opposite way, may be excited by an external electrical signal. This bi-directional communication gives rise to two experimental schemes: acquisition and stimulation. Acquisition consists in recording, processing and analyzing bio-signals whereas stimulation consists in applying the adequate electrical current to living tissues in order to trigger a reaction. This thesis focuses on the latter: two generations of stimulation systems have been developed, both being centered on an Application Specific Integrated Circuit, and adapted to different application contexts.

First, the scientific framework was given by the CENAVEX project, focusing on Functional Electrical Stimulation to rehabilitate the respiratory function, following a Spinal Cord Injury. Then, the design objectives were extended to cover new application needs: in situ electrical impedance monitoring and exploration of original stimulation waveforms. The first one could be a solution to follow the tissue reaction after electrode implantation, hence contributing to long-term biocompatibility of implants; the second one proposes to go further the conventional constant biphasic pulse and explore new waveforms that could be most efficient in terms of energy consumption, for a given physiological effect.

The work presented in this manuscript is a contribution to the design, fabrication and test of innovative stimulation devices. It leaded to the development of two integrated circuits and two stimulation devices permitting multichannel stimulation. Both electrical characterizations and biological validations, from in vitro feasibility to in vivo experiments, have been conducted and are described in this manuscript.

## Keywords:

Microelectronics, FPGA, Integrated circuits, Analog IC design, Functional Electrical Stimulation, Bioelectronics, Stimulation device, Closed-loop stimulation device, Open-loop stimulation device

## Résumé

La Bioélectronique est un domaine interdisciplinaire qui étudie les interconnexions et les interactions entre entités biologiques (cellules, tissus, organes) et systèmes électroniques, par l'intermédiaire du transducteur adéquat. Pour des cellules ou des tissus excitables (neurones, muscles, ...), le transducteur prend la forme d'une simple électrode, car ces tissus produisent une activité électrique spontanée ou, dans le sens inverse, peuvent être excités par un signal électrique externe. Cette communication bidirectionnelle donne lieu à deux schémas expérimentaux : l'acquisition et la stimulation. L'acquisition consiste à enregistrer, traiter et analyser les bio-signaux alors que la stimulation consiste à appliquer le courant électrique adéquat aux tissus vivants, pour déclencher une réaction. Cette thèse se concentre sur ce dernier point : deux générations de système de stimulation ont été développées, chacune basée sur un circuit intégré spécifique et adaptée à différents contextes applicatifs.

Tout d'abord, le cadre scientifique a été celui du projet CENAVEX, axé sur la stimulation électrique fonctionnelle pour réhabiliter la fonction respiratoire, suite à une lésion de la moelle épinière. Ensuite, les objectifs de conception ont été étendus pour couvrir de nouveaux besoins d'application : la surveillance de l'impédance électrique in situ et l'exploration des formes d'onde de stimulation originales. Le premier pourrait être une solution pour suivre la réaction tissulaire après l'implantation d'une électrode, contribuant ainsi à la biocompatibilité à long terme des implants ; le second propose d'aller au-delà de la conventionnelle impulsion biphasique carrée et d'explorer de nouvelles formes d'ondes qui pourraient être plus efficaces en termes de consommation d'énergie, pour un effet physiologique donné.

Le travail présenté dans ce manuscrit contribue à la conception, à la fabrication et au test de dispositifs de stimulation innovants. Cela a conduit au développement de deux circuits intégrés et de deux dispositifs de stimulation permettant une stimulation multicanal. Les caractérisations électriques et les validations biologiques, de la faisabilité in vitro aux expériences in vivo, ont été menées et sont décrites dans ce manuscrit.

## Mots-clés:

Micro-électronique, FPGA, Circuits Intégrés, Stimulation électrique fonctionelle, Bioélectronique, Système de stimulation, Boucle fermée, Boucle ouverte

# Contents

Li	st of	of Figures 1		15
Li	st of	Tables	3	17
1	Scie	entific o	context	23
	1.1	A brief	f history of electrical stimulation	23
	1.2	Excita	ble cells and tissues	24
		1.2.1	The nervous system, an input for electrical stimulation	24
		1.2.2	The neural cell	26
		1.2.3	External electric excitation	29
	1.3	Electri	cal stimulation in different research context	32
		1.3.1	Hyrene	32
		1.3.2	EDIFICe	34
		1.3.3	CENAVEX	34
	1.4	Synthe	esis of the issues addressed in that PhD thesis	35
		1.4.1	A wide range of applications and closed-loop need	35
		1.4.2	In situ electrical monitoring	36
		1.4.3	Exploration of efficient stimulation waveforms	36
	1.5	Conclu	sion: outline of the manuscript	36
2	Stat	te of th	ne art	39
	2.1	Introd	uction	39
	2.2	Neuros	stimulation	39
		2.2.1	Applications	39
		2.2.2	Characteristic electrical parameters	40
		2.2.3	System features for investigation of new stimulation paradigms	41
	2.3	Review	v of IC based stimulation devices	41
		2.3.1	Circuit architecture	44
		2.3.2	Supply voltage and technology	44
		2.3.3	Targeted application and consecutive output constraints	46
		2.3.4	Toward a multi-application stimulation system	46
	2.4	Advan	ced smart stimulation devices	47
		2.4.1	Stimulation waveform optimization	47
		2.4.2	In situ electrical monitoring	48
	2.5	Summa	ary	51

3	$\mathbf{M}\mathbf{u}$	tistim, a multi-application stimulation system with biphasic constant	
	cur	ent waveforms 5	53
	3.1	Introduction	53
	3.2	Overview of SHIVA's architecture 5	54
		3.2.1 A multiple application architecture	54
		3.2.2 On-chip analog/digital partition	55
		3.2.3 Summary of SHIVA's issues	56
		3.2.4 Description of Elementary Stimulation Channels	56
	3.3	Multistim, a multi-application stimulation system: from integrated circuit	
		to user interface	59
		3.3.1 Context and objectives	59
		3.3.2 Overview of the stimulation system	60
		3.3.3 Analog circuits	31
		3.3.4 SONIC	32
		3.3.5 Digital Controller	35
		3.3.6 Software	36
	3.4	Tests and in-vitro experiments	38
		3.4.1 In-vitro experiments	38
		3.4.2 Generation of complex stimulation waveforms	70
	3.5	Multistim limitations	72
	3.6	Conclusion	72
	<b>gen</b> 4.1	Introduction	<b>3</b> 73
		4.1.1 From Elementary Stimulation Channels to fully programmable Stim-	
		ulation IPs $\ldots$ $\ldots$ $7$	73
		4.1.2 Need for in situ electrical impedance monitoring	75
		4.1.3 Need for new waveforms for neurostimulation	75
	4.2	SPICY: A stimulation IC with electrode voltage measurement capability . 7	76
		4.2.1 Design specifications for bio-impedance measurement	76
		4.2.2 HV Operational Transconductance Amplifier	76
		4.2.3 Integrated Circuit architecture	78
		4.2.4 Fabricated chip	78
		4.2.5 Test, troubleshooting and perspectives	78
	4.3	A versatile digital stimulation controller with arbitrary waveform capability 8	34
		4.3.1 The stimulation program	-1
		F-O-	54
		4.3.2 The Stimulation Processor	84 36
	4.4	4.3.2 The Stimulation Processor	84 86 87
	4.4	4.3.2       The Stimulation Processor       8         System Integration       8         4.4.1       Digital Architecture       8	84 86 87 88
	4.4	4.3.2       The Stimulation Processor       8         System Integration       8         4.4.1       Digital Architecture       8         4.4.2       Compiler       8	84 86 87 88 89
	4.4	4.3.2       The Stimulation Processor       8         System Integration       8         4.4.1       Digital Architecture       8         4.4.2       Compiler       8         4.4.3       PCB Level       8	<ul> <li>84</li> <li>86</li> <li>87</li> <li>88</li> <li>89</li> <li>39</li> <li>39</li> <li>39</li> <li>30</li> </ul>
	<ul><li>4.4</li><li>4.5</li></ul>	4.3.2       The Stimulation Processor       8         System Integration       8         4.4.1       Digital Architecture       8         4.4.2       Compiler       8         4.4.3       PCB Level       8         Tests of the stimulation device       9         4.5.1       Static performance	<ul> <li>84</li> <li>86</li> <li>87</li> <li>88</li> <li>89</li> <li>89</li> <li>90</li> <li>90</li> <li>90</li> </ul>
	<ul><li>4.4</li><li>4.5</li></ul>	4.3.2       The Stimulation Processor       8         System Integration       8         4.4.1       Digital Architecture       8         4.4.2       Compiler       8         4.4.3       PCB Level       8         Tests of the stimulation device       9         4.5.1       Static performances - Linearity       9         4.5.2       Dumerria performances       9	<ul> <li>84</li> <li>86</li> <li>87</li> <li>88</li> <li>89</li> <li>39</li> <li>30</li> &lt;</ul>
	4.4 4.5	4.3.2 The Stimulation Processor8System Integration84.4.1 Digital Architecture84.4.2 Compiler84.4.3 PCB Level8Tests of the stimulation device84.5.1 Static performances - Linearity94.5.2 Dynamic performances9Improvements9	<ul> <li>84</li> <li>86</li> <li>87</li> <li>88</li> <li>89</li> <li>89</li> <li>90</li> <li>90</li> <li>90</li> <li>92</li> <li>92</li> <li>92</li> <li>92</li> <li>92</li> <li>92</li> </ul>

		4.6.2	System Level	94	
	4.7	Conclu	nsion	95	
5	Exp	erimer	ntal validation of the stimulation systems	97	
	5.1	In vive	experiments with Multistim	97	
		5.1.1	Open-loop stimulation	98	
		5.1.2	Closed-loop stimulation	98	
	5.2	Arbitra	ary stimulation waveforms with TWIST	100	
		5.2.1	Generation of a biphasic Gaussian stimulus	100	
		5.2.2	Other waveforms	104	
	5.3	Conclu	1sion	105	
6	Con	clusior	ı	109	
Δ	Mul	tistim	architecture details	113	
	A.1	Global	Architecture	113	
	A.2	Detaile	ed architecture	114	
		A.2.1	Kali configuration	114	
		A.2.2	Sequencer 8 channels	115	
		A.2.3	SPI Interface	115	
		A.2.4	state mgmt	115	
		A.2.5	stim parameters mgmt	116	
		A.2.6	stim_signal_mgmt	117	
В	SON	NIC an	d SPICY I/Os	121	
С	TW	IST de	eveloper guide	125	
Bi	Bibliography 1				

# List of Figures

1.1	History of Bioelectronics
1.2	Structure of the neuron
1.3	Neuron's membrane
1.4	The action potential
1.5	Stimulus strength-duration curve
1.6	Rectangular biphasic waveform
1.7	HYRENE project
1.8	CENAVEX project
0.1	
2.1	Applications of neural prostnesses
2.2	Stimulation waveform and stimulation circuit topologies
2.3	Gate-length vs. time
2.4	Waveform obtained using genetic algorithm
2.5	Two and four terminal impedance measurement techniques
3.1	Illustration of the multi-application approach
3.2	SHIVA's architecture
3.3	Elementary Stimulation Channel circuit
3.4	Multistim's architecture
3.5	Picture of Multistim
3.6	Stimulation parameters
3.7	Digital to Current converter
3.8	Picture of SONIC die and package
3.9	ESC test setup
3.10	ESC caracteristics
3.11	Multistim digital architecture
3.12	Timing management strategy on Multistim
3.13	Finite State Machines used in Multistim
3.14	Multistim Graphical User Interface
3.15	Experiments on micro-electrode array
3.16	Experiment on DBS electrode for rodents
3.17	Current-steering on Medtronic 3387 electrode
3.18	Burst envelope modulation on Multistim
4 1	Multisting up TWICT analitacunas
4.1	WILLISTIN VS. 1 WIDT ATCHITECUTES       (4         OTA architecture       77
4.2	OTA arcmeeture
4.3	OTA simulation setup
4.4	UIA simulated Bode diagram

4.5	SPICY architecture	80
4.6	SPICY micro-photography	80
4.7	SPICY test environment	81
4.8	SPICY's ESC test environment	81
4.9	Functional and non-functional ESCs	82
4.10	OTA test setup	82
4.11	OTA AC behavior	83
4.12	Non-working OTA with large amplitude input	83
4.13	Stimulation Processor architecture	86
4.14	Program counter manager Finite State Machine	87
4.15	TWIST PCB system-level architecture	88
4.16	TWIST digital architecture	89
4.18	Digital to Current Converter architecture	91
4.19	Test setup of TWIST	91
4.20	TWIST static performances	93
4.21	Anodic/Cathodic mismatch	94
5.1	CENAVEX open-loop setup	98
5.2	CENAVEX open-loop results	99
5.3	CENAVEX closed-loop setup	99
5.4	CENAVEX closed-loop experimental results: two representative stimulation	
	cycles	100
5.5	CENAVEX closed-loop experimental results: breath-volume vs. stimulation	
-	envelope	101
5.6	TWIST toolchain	102
5.7	Experimental setup for the test of arbitrary stimulus generation	102
5.8	Gaussian biphasic stimulus	103
5.9	Medtronic Capsure©VDD-2 5038	103
5.10	Generation of decreasing exponential stimulus using TWIST	104
5.11	Generation of a multi-sine stimulus using TWIST	105
5.12	Multi-sine spectrum	106
A 1	Stimulation parameters addresses	117
A 2	Built-in memory architecture	119
11.4		110
B.1	Inputs/outputs of SONIC and SPICY Chips on a QFP100 package	122
B.2	SONIC bonding	123
B.3	SPICY bonding	124

# List of Tables

2.1	Stimulation parameters and applications	41
2.2	Review of recently published stimulation circuits and systems	42
2.3	Existing sine wave based impedance monitoring ICs	51
2.4	Existing rectangular pulse-based impedance monitoring ICs	52
3.1	Resources used by Multistim controller on a Xilinx Spartan 6 FPGA	65
4.1	OPCODE parameters	85
4.2	Stimulation instruction structure	85
4.3	Scale information	85
4.4	Goto instruction structure	85
4.5	Trigger instruction structure	86
4.6	Resources used by TWIST on a Xilinx Artix 7 FPGA	88
4.7	Comparison with similar research in the literature	92
4.8	Timing characterization of stimulation channels of TWIST	92

# Acknowledgments

This chapter is going to be in French and a little bit in English.

Tout d'abord, je souhaite remercier Claude Pellet et Yann Deval pour m'avoir accueilli dans le laboratoire IMS pour la réalisation de mes travaux de thèse.

Mes premières pensées vont à Noëlle Lewis et Sylvie Renaud, qui ont encadré et coencadré ma thèse. Noëlle, merci pour ta patience et ton soutien tout au long de ces trois ans, pour ton organisation rigoureuse qui ont su mettre de l'ordre dans mon "chaos productif", et m'aider à le structurer pour le rendre intelligible. Sylvie, merci de m'avoir fait découvrir la bioélectronique pendant mes études à l'ENSEIRB, mais surtout de m'avoir proposé cette thèse.

Je tiens à remercier chaleureusement Serge Bernard et Aymeric Histace, rapporteurs de cette thèse, pour leur lecture, commentaires et discussions sur mes travaux. Merci également aux membres du jury, Ranu Jung, Rémi Dubois et James J. Abbas pour votre intérêt pour mes travaux de recherche et les riches discussions qui ont suivi ma présentation.

Yannick, le "numéricien" que je suis te dois beaucoup, ça a été toujours sympa de discuter de toutes ces architectures et systèmes, mais aussi de tout ces sujets divers et variés. Je me souviendrai des ateliers "gaufres plates du nord" pendant longtemps.

Gilles, en plus de ta grande aide pour les différents projets, je souhaite te remercier pour ton humour toujours bien placé, souvent au bon moment.

Merci aux anciens également. Florian pour avoir assuré la transition entre ta thèse et la mienne, j'ai beaucoup appris à tes cotés, et je suis heureux d'avoir pu mettre ma pierre à l'édifice que tu as commencé. Merci également pour ta bonne humeur, et ton ouverture d'esprit. C'est super maintenant de te revoir sur les blocs et falaises du monde, mais je t'en conjure, ne goute plus aux cordes d'escalade. Merci François pour ton réalisme, ta clairvoyance et tes conseils avisés. Je suis admiratif de ta connaissance experte des puissances de deux pour l'analogicien que tu es.

Un immense merci à Amélie, Antoine et Luigi. J'ai bien du mal à exprimer en quelques lignes à quel point votre entourage m'a été bénéfique, au niveau travail mais surtout au niveau personnel. J'ai hâte de vous revoir.

J'ai également une pensée pour les membres de l'équipe AS2N, notamment Jean pour ton soutien technique vis-à-vis des logiciels de design, et Sylvain pour tes conseils avisés.

Merci à Valérie pour ta gymnastique de haut-niveau entre les différentes missions, devises et moyens de transport pour les nombreuses missions que j'ai eu la chance d'effectuer.

Merci Simone pour ton accueil et ton soutien lors de la fin de la thèse.

Merci aux stagiaires, Olivier, Corentin et Jiabo, qui ont participé de près ou de loin aux réalisations de cette thèse.

Un très grand merci à mes parents, à ma famille, pour avoir cru en moi tout au long de mes études et pour m'avoir soutenu dans les moments difficiles. Désolé Axelle, mais j'ai eu mon doctorat en premier! Ranu and Jimmy, and all the ANS Team in Miami, thanks a lot! It was a pleasure to work with you in Miami, I learnt many things related to biomedical engineering thanks to you. Good luck Ricardo for the end of your PhD, I'm sure you'll do great!

Merci également à tout mes amis de l'escalade, aussi partenaires d'entrainement et compagnons de voyage, ainsi qu'à mes coachs, Patrick et Maxime puis Jean-Marc. Je pense que l'escalade m'a apporté de l'équilibre entre vie personnelle et professionnelle ces dernières années, et m'a appris beaucoup de choses sur moi même.

# Introduction

Electronic devices have been revolutionizing medicine, since the early 20th century. They have first been used for diagnostic of heart disease with the development of the electrocardiograph, which helped defining the field of cardiology. Now, electronic systems are being widely used for a wide range of applications in medicine from imaging applications to computer-aided surgery. On a more academic point of view, the study of biology has been transformed by electronics progress: in the late 1940s, the molecular basis of nerve and muscle function was studied using high-impedance amplifiers, which permitted to do quantitative biology and practical clinical neuroscience. Within all the application of electronics to medicine, we are going to focus on bioelectronics.

Bioelectronics is a cross-disciplinary field that studies interconnections and interactions between biological entities (cells, tissues, organs) and electronic systems. It includes a wide range of topics, from fundamental studies to the development of implantable devices to improve people lives after injury or to cure the effect of a disease. With the aging population, bioelectronics devices are being more and more implanted and applied to a wider range of applications. Cardiac implanted pacemakers or defibrillators are now very common for patients with heart disease and/or arrhythmias. Deep Brain Stimulation (DBS) allows reducing the effects of Parkinson's disease, cochlear implants restores hearing to deaf patients. New kind of prosthetic devices are being developed, such as 'mind' controlled arm with neuro-feedback, which aim is not only restoring the lost functionality, but also the feeling. All those applications' target is to help patients to overcome a disability or a disease.

For most of those devices, biological signals are acquired, amplified, computed and then an electrical signal is send to the targeted organ(s) in order to initiate a reaction. This work will focus on the latter: electrical stimulation. This wide area of research will be studied at different aspects in this manuscript: from the integrated circuit design to the system integration and its application to different research projects. This document is organized as follow.

The first chapter presents a brief history of electrophysiology, provides some basics in neuro-biology to help understanding the presented work and details the different research projects on which it is based. At this step, we expose the general approach of this PhD work and detail the addressed issues: the design of IC-based multi-application stimulation systems, highly configurable, with open- and closed-loop capabilities, and an evolution of the specifications to enable the measurement of implanted electrode impedance and the exploration new stimulation waveforms. A state of the art on electrical stimulation, bioimpedance measurement and optimization of the stimulation waveform are presented is the second chapter. The specifications of the further presented systems are derived from this synthesis. The third and fourth chapter are dedicated to the design, testing and electrical characterization of two different stimulation devices that have been built during this work. Finally, the fifth chapter presents experimental results illustrating the capabilities of both stimulation devices, including closed-loop in-vivo experiments for the first system and generation of arbitrary stimulation waveforms for the second one.

# Chapter 1 Scientific context

Electrical stimulation is a widely-used technique to induce physiological reactions in excitable cells and tissues, for a wide range of therapeutic applications. However, electrical stimulation is still a subject of cross-disciplinary research: from electrophysiology to circuit design, involving biologists, physicists, engineers, etc. This research leads to improvements of implants and electrodes design. In electrical engineering, neuro-stimulation applications are challenging in terms of reliability, safety, integration and optimization. Dealing with all these aspects requires a general understanding of both electronics and electrophysiology. The purpose of this chapter is to give the reader some notions in biology of excitable cells which are the target of neuro-stimulation devices, and then the scientific context of this PhD will be introduced

## 1.1 A brief history of electrical stimulation

The discovery of bioelectricity has been made about two thousand years ago. A general timeline of the evolution of stimulation devices is presented in figure 1.1(a). The first modern foundation of experimental electrophysiology was performed around 1660 by the Dutch biologist Jan Swammerdam. One of these experiments is illustrated in the figure 1.1(b). This setup is based on a nerve-muscle preparation, on which an 'irritation' of the nerve can be performed, inducing a mechanical reaction of the muscle. The irritation was performed with a silver wire that could cause electrical stimulation [1].

First enhancements of the stimulation were made at the end of the 19th century. The first demonstration of a stimulation basic circuit was performed after the invention of Leyden jar, the first electrical storage device. The best example is the experiment performed by Galvani and Aldini [2] as illustrated by figure 1.1(c), on 'animal electricity'. This experiment illustrated the electrical nature of the neural impulse and allowed a first investigation correlating stimulation strength and mechanical response. It was also the first demonstration of functional electrical stimulation on a limb. Similar experiments were performed by Volta in 1800 [3]. In a letter dated of 1800, A. Volta signed a major contribution on both electrophysiology and electrical engineering, with the design of the first electrochemical battery; Volta described effects of this electricity on body, and wrote the first description of 'crackling and boiling' sensations. Half a century later, advances have been performed, giving a better understanding of neural mechanisms. The electrical current is associated to the neural activity by Matteucci (1842) [4], using first electrical measurements by galvanometers. This discovery allowed a direct quantification of the neural cell response to the

stimulation. Next advance came from Helmholtz (1850) [5], who measured the celerity of the electrical signal propagation on the nerve and performed the first quantitative study of an electrical stimulation on excitable cells. It can be noticed that these two major advances were performed in an historical context of the first formulation of modern electro-magnetic theory by Maxwell in 1863 [6]. The 20st century is the time of the fundamental advances for stimulation. The evolution of both physics and biology allowed scientists to conduct quantitative experiments. One illustration is the first application of the electro-chemistry laws to electrophysiology: in the beginning of the 1900s, the Nernst law is applied to the neural cell by Bernstein (1902) [7]. In the 1950's, a succession of discoveries led to a better understanding of the electrical stimulation and the possibility of integration for stimulation circuits. Bio-realistic neural models are developed by Curtis and Cole (1940) [8] and then by Hodgkin and Huxley (1952) [9]. Almost at the same time, a revolution is starting in the electrical engineering field, with the discovery of the transistor by J. Bardeen, W. Schokley and W. Brattain and the invention of planar fabrication processes by J. Kilby.

All these contributions made possible the use of electrical stimulation for therapeutic applications. The first implanted electrical prosthesis was developed in the late 1950s, using discrete semiconductors. The first attempt of auditory recovery by stimulation of the auditory nerve was performed by Djourno and Eyries (1957) [10]. Shortly after, the first cardiac pacemaker was developed and successfully implanted by Elmgvist et al. (1963) [11] (figure 1.1(d)).

Recent advances in neuroscience led to the understanding of different physio-pathological mechanisms and successful clinical trials, and resulted in new implantable stimulators. Today, in the USA alone, defibrillators are implanted at a rate of 160000 per year, to restore proper activity to diseased hearts.

## 1.2 Excitable cells and tissues

An excitable cell is a cell able to be electrically excited resulting in the generation of action potentials. Neurons and muscle fibers (skeletal, cardiac, and smooth) are examples of excitable cells. Muscle fibers can be excited to produce an electrical activity inducing contraction and neuronal cells initiate and propagate electrical activity along the nervous system.

#### 1.2.1 The nervous system, an input for electrical stimulation

When speaking about electrical signals in the body, our first thought goes to brain and nerves. The nervous system is indeed a huge (and efficient...) electrical system that drives our body. The nervous system can be split into two different parts: the Central Nervous System (CNS) and the Peripheral Nervous Sytem (PNS). The CNS is composed by the brain, the cerebellum and the spinal cord. It is the place where our thoughts happen, our feeling, our ideas and memory (Kolb and Wishaw, 2008 [12]). The PNS is the link between the CNS and the others parts of our body. It can also be divided into two parts: the somatic nervous system which is associated with the voluntary control of the body and sensory feedback, and the autonomic nervous system which drives functions not linked to our will: digestion, perspiration, etc. The elementary part of our nervous system is called a neuron. Let us now focus on this very important kind of excitable cell, which is the main



Figure 1.1: (a) Important dates for bioelectronics and electrical engineering, (b) Nervemuscle preparation from Swammerdam (1758), (c): Illustration of the laboratory of L. Galvani with limbs and electrical generators from Galvani and Aldini (1792), (d): Image of the first implanted cardiac pacemaker in 1958 (photography from Siemens), (e):Picture of recent implant for DeepBrain Stimulation fimage from Medtronic)



Figure 1.2: Anatomical structure of the neuron (adapted from [13])

excitable cell of our body.

#### 1.2.2 The neural cell

#### Neuron anatomy

Different kind of neural cells exist in the nervous system. Despite their differences in functionality, they share a common structure, represented figure 1.2, which can be subdivided in three morphologically defined regions: the cell body, the dendrites and the axon. The cell body, termed soma, is the central part of the neuron. It is in charge of the main activity of the neuron. Ionic exchanges described in the next section are taking place there. The second part of the neuron is composed of dendrites, about 7000 for one neuron. They play the role of input interface to the neuron, and are in charge of conducting the electrochemical stimulations received from other neural cells to the soma. The third part of the neuron is called the axon. It plays the role of output interface of the neural cell. This part of the cell can be very long, sometimes more than 1 meter [13]. It consists in an elongated fiber that extends from the soma to the terminal endings and transmits the neural signal to downstream neurons through synapses to post-synaptic dendrites. Some axons are insulated by a myelin sheath. This dielectric material ensures a better transmission of the information from the soma to the extremities of the neurons, called dendrites.

#### Neuron physiology

In electronics, the information is carried by electrons, but in biology, it is a matter of ions. There are responsible for carrying electrical charge. The main ions in charge of the neuron functionality are Sodium (Na+) and the Potassium (K+), they are present inside and outside the cells. When a neuron is inactive, the cytoplasm inside the cell has a negative electrical charge, and the fluids outside the cell are positive. This is called the resting potential. It is created by transport proteins called 'sodium-potassium pump' which are



Figure 1.3: Neuron membrane with Sodium-Potassium pump, Sodium channel and Potassium channel

located along the cell membrane as presented figure 1.3. This protein moves large numbers of Sodium ions outside the cell, creating a positive charge, and moves Potassium ions into the cell's cytoplasm. As the number of Sodium ions moved outside the cell is greater than the number of Potassium ions moved inside, the cell is more positive outside than inside. Alongside the pumps, we can find sodium and potassium channels which can open and close in response to signals like electrical changes.

When a stimulus reaches a resting neuron, the neuron propagates the signal as an impulse called an action potential. Its transmission is made by K+ and Na+ crossing back and forth the neuron's membrane, through channels across the cell membrane. This causes electrical changes, through time regarding the membrane voltage, which are described hereafter:

- 1. The stimulus causes sodium channels to open, hence allowing Na+ ions that were outside the membrane to rush into the cell. This cause the cell's potential to become more positive
- 2. If there is strong enough signals on the membrane [14], and reaches an amplitude called threshold, it triggers an action potential. More sodium channels are opening, hence more Na+ ions enters the cell. This causes the cell to become more positively charged than the extracellular medium. It is called the depolarization.
- 3. Once the cell membrane is depolarized, Na+ channels close and K+ channels opens. The same way Sodium ions entered the cell, Potassium ions are exiting the cell through their channels by diffusion. The membrane voltage is therefore decreasing: this is the repolarization.
- 4. The next step is called hyperpolarization. It is due to the fact that the membrane voltage is decreasing slightly more than the resting potential because of the joint action of Potassium channels and Sodium-Potassium pumps.



Figure 1.4: The action potential

5. During the last step, the neuron enters a refractory period. All the ionic channels are closed, and Sodium-Potassium pumps redistribute ions in order to return to the original resting potential.

If plotted, the evolution of the membrane potential is shaped like a voltage peak. It is called action potential, by opposition to resting potential. Figure 1.4 presents a schematic plot of an action potential.

#### Neural signal propagation

Once an action potential is generated on the neuron surface, it propagates by conduction towards the end of the axon. In order to "jump" from one neuron to another, the action potential has to cross a synaptic gap, using synapses. Synapses can be either electrical or chemical, the last one being the most common for vertebrates. The depolarization of the pre-synaptic cell activates the release of molecules called neurotransmitter into the postsynaptic cleft. Those molecules are detected by receptors located on the post-synaptic cell. The result is the opening of ionic channels on the post-synaptic cell. If enough neurotransmitters are transmitted, not necessary by a unique neuron, it results in an action potential in the post-synaptic cell.

We now understand the underlying concepts about the way neurons are working together to generate action potential and to communicate with each other. There are three different kinds of neurons: sensory neurons, motor neurons and interneurons. All three have different functions, but they work as described above. Motor neurons are in charge of carrying signals from the brain and spinal cord to the muscles, and are a great input for electrical stimulation to trigger muscle contraction. Sensory neurons are responsible for converting external stimuli from the environment into electrical impulses. For example, they can respond to tactile stimuli and activate motor neurons or provide a feedback to the brain. Sensory neurons are a great input for electrical stimulation in order to provide a sensory feedback from prosthetic limbs as an example.

Let us now focus on how we can electrically induce a neural response and interface with neural systems.

#### **1.2.3** External electric excitation

A current carrying electrode is used to excite a nerve. The location of the electrode may be located on different places depending on the targeted nerves and application. It can be on the skin (transcutaneous stimulation), as a needle inserted through the skin, as a catheter electrode, as a part of an active implant or as a microelectrode inserted into an axon or an exposed nerve. In order to induce an action potential, we have seen previously that action potential is the result of a strong enough stimulus from pre-synaptic cells, meaning a given number of ions needs to be moved. For a single cell, the charge was calculated to be of the order of  $0.5 \,\mathrm{pC}$  [14]. The polarized cell is positively charged at the external cell surface. Therefore, a short negative polarity pulse from an external electrode would decrease the membrane potential and thus be excitatory. This phenomenon has been demonstrated experimentally. We can note that a positive pulse may trigger a reaction, but the threshold is much higher.

The electrical stimulus is therefore build using a negative polarity current, called a cathodic pulse. The most used current waveform is rectangular monophasic or biphasic. Electrophysiologists have been studying the impact of the cathodic pulse duration on the minimum current threshold, and they showed that as the pulse duration increases, the current threshold decreases asymptotically to a baseline current called rheobase. An example of this behavior is presented in figure 1.5. The chronaxie is defined as the pulse duration with the double rheobase current.

We can cite as an example two of the most known model for the current-duration relationships for rectangular pulses. Weiss [15] used a hyperbolic model presented equation 1.1, and Lapicque [16] used an exponential one, equation 1.2.

$$I = I_0 * (1 + \frac{\tau}{t})$$
 (1.1)

$$I = \frac{I_0}{e^{-\frac{\tau}{t}}} \tag{1.2}$$

Where I is the minimum current for stimulation with a pulse width t,  $\tau$  is a time constant characteristic for the nerve tissue and electrode geometry, and I0 is the rheobase current.  $\tau$  for motor nerves is approximately 0.3 ms and for myocard 3 ms. Figure 1.5 shows a calculated current-duration graph with linear scales based on the hyperbolic model. We used I0=1.3mA, and  $\tau = 0.3$  ms. The needed charge to reach the threshold is constant for short pulse durations and increase with longer pulses. The energy necessary to reach the threshold goes through a minimum near the chronaxie [14]. Those are the results for a monophasic cathodic pulse. However, as mentioned in [17], the electrical stimulus has to be charge balanced in order to provide safe stimulation, and not result in electro-chemical reactions on the electrode surface. The consequence is a numerical condition on the current stimulus that can be expressed as:



Figure 1.5: Cathodic current level versus pulse duration, according to the hyperbolic rheobase model



Figure 1.6: Typical biphasic current stimulation waveform with active and/or passive charge balancing

$$\langle Q \rangle = \int_0^{T_{stim}} i_{stim}(t) dt = 0 \tag{1.3}$$

With Qstim the amount of charge injected in the tissue over a stimulation period Tstim with a istim stimulation waveform. There is no clear defined limit on the maximal timing under which charge balancing should be performed. However, [18] observed that unbalanced external stimulation over the minute range leads to strong lesions of the tissue surrounding the electrode. This is why a biphasic stimulation waveform should be used for safe stimulation, as presented figure 1.6.

It consists in a cathodic pulse, which is used to trigger a cell reaction, and an anodic pulse for active charge compensation. In order not to hyper-polarize neurons targeted by stimulation [17] or depolarize untargeted cells in lateral zones, the anodic current Ianod is generally lower than the cathodic current. Anodic time duration Tanod is then chosen to have a global null charge over a stimulation period. Under the assumption that current are constants, the anodic duration for charge balancing is calculated from: :

$$T_{anod} = T_{cath} * \frac{I_{cathod}}{I_{anod}} \tag{1.4}$$

Another method for charge balancing is called passive charge compensation. Electrode is discharged through a resistor. It may be used along active charge compensation or instead. It is the most efficient to ensure safety of the stimulation. However, a huge drawback of this technique is that the resulting current peak value is not controlled and might hyperpolarize target neurons [17] or depolarize untargeted cells.

Generally, a dead time is inserted between cathodic and anodic pulses. [17] explains that it prevents from hyperpolarizing the cells that were triggered by the anodic phase and guaranties the effectiveness of the stimulation. This inter-pulse interval is most of the time smaller than the cathodic pulse width.

## **1.3** Electrical stimulation in different research context

The PhD work presented in this manuscript has been realized within the Electronics Interfacing Biology (Elibio) team, from the Bioelectronics group of IMS laboratory. The team in involved in numerous projects, collaborating with clinicians, biologists, analog and digital circuit designers, neuromorphic systems designers, etc. Those projects share a common ground in the fact that they all involve the communication between electronic systems and biological tissues. This communication can be either unidirectional or bidirectional. For both case, two kinds of interactions can be distinguished: bio-signal acquisition and processing, and electrical stimulation. In research projects including acquisition and stimulation, everyone in the team is involved, contributing with a specific expertise, among acquisition, real time processing and electrical stimulation of tissues (in-vivo or ex-vivo).

Most of the projects of the team target the long-term development of implanted devices for rehabilitation, which would help patients suffering from a disability resulting from an accident or a disease. For such implants, size, power consumption, safety and reliability are very important parameters. All projects, although differing in terms of application, rely on similar functionalities, and Elibio's policy regarding systems innovations and development is to build multi-applications devices. As a consequence, designed devices need to be tunable and versatile, which is also an advantage to explore new experimental paradigms.

The next sections present the different projects in which Elibio team has been working on during this PhD thesis. These projects gave me the opportunity to conduct experimental validations for the developed stimulation devices (HYRENE) or to think about new specifications of smart implanted stimulators (EDIFICE). I was directly involved in the CENAVEX project, to develop and carry out a stimulation device within rat in vivo experiments.

#### 1.3.1 Hyrene

The Hyrene project, funded by the French national research agency (ANR) is a perfect example of a closed-loop bioelectronics project. The ambitious goal of this project is to build a neuroprosthetic "bridge" to restore the connection between two parts of a spinal cord. This system involved a micro-electrode array for acquisition purpose (upstream of the lesion), an artificial neural network to compute those inputs, and a micro-electrode array located in the lower section of the spinal cord to inject stimulation. The chosen model is ex-vivo rat spinal cord. When stimulated, it generates a spontaneous activity corresponding to locomotor functions. Central Pattern Generators (CPG) are activated in the brainstem, and this activity is propagated along the spinal cord. The aim of this project was to allow the propagation of this signal regardless of full lesion on the spine, during in-vitro experiments.

This project is the result of collaboration with a team from CLINATEC (Grenoble, France) in charge of the experiments on rodents, the team AS2N from IMS (Bordeaux), in charge of the integration of artificial neural networks, and ESIEE, from Noisy-le-Grand who built the custom micro-electrode arrays.



Figure 1.7: Illustration of the HYRENE project, adapted from [19]. (a) the injured spinal cord is prepared for generation of commands ordered by stimulation in the brainstem; motor-like activity is observed on lumbar ventral roots; the setup consists in microelectrodes array for rec recording and stimulating spinal neurons; the bridge between the two arrays is performed by neuromorphic circuits. (b) Photography of one MEA fork placed in the ex vivo spinal cord; four glass micro-pipette electrodes are placed for lumbar activity recording.

#### 1.3.2 Edifice: EmbeddeD Impedance spectroscopy for characterizing the FIbrosis induced by Cardiac implants – EDIFICe

Pacemakers and implantable defibrillators play a crucial role in the treatment of heart rhythm disorders. As the range of applications widens and the population is aging, the number of patients with cardiac devices continues to increase. In France, 250 000 patients are equipped with pacemakers or implantable defibrillators. These patients require regular monitoring of their prosthesis. Implanted devices induce an immediate and sustained inflammatory response that has an impact on the electrode impedance and the efficiency of the electrical stimulation. Given that fibrosis is a major obstacle to long-term efficiency of modern pacing or resynchronising cardiac implants, EDIFICE project aims at developing methods and instruments to characterise the fibrous capsule surrounding implanted leads. EDIFICE will address 3 objectives:

- Better understand the mechanism of fibrogenesis and sustained fibrosis induced by an implant,
- Assess the capability of in situ impedance spectroscopy for the real-time and noninvasive monitoring of the implant-induced fibrosis,
- Produce a prototype of electronic system that altogether implements impedance spectroscopy measurement and an innovative fibrosis monitoring algorithm.

Besides the Elibio team, this project involves the LYRIC laboratory (L'Institut de RYthmologie et modélisation Cardiaque) from Bordeaux, the IJL laboratory from Université de Lorraine and the ASTRE team from ETIS laboratory (University of Cergy Pontoise).

This project is the latest one being studied within the Elibio team, it represents the context of the current PhD work of Amélie Degache. Part of the work presented in this manuscript will hopefully be useful to this study.

## 1.3.3 The CENAVEX project: Computation-Enabled Adaptive Ventilatory Control System

This project has been closely linked to this work, and provided the experimental context to validate one of the stimulation device presented in this manuscript. This very interesting project is the result of a collaboration with the Adaptive Neural System team from Florida International University (Miami, FL, USA). It has been funded by the National Institutes of Health (NIH) and the ANR.

Most people with Spinal Cord Injury (SCI) that require ventilation management are initially supported with positive pressure-mechanical ventilation, which is associated with significant discomfort and can lead to respiratory diseases and prevent optimal recovery. Alternatively, ventilation can be achieved by diaphragmatic pacing by electrical phrenic nerve stimulation. More recently, intramuscular stimulation of multiple respiratory muscles has been proposed as a viable less surgically invasive approach. The open-loop stimulation strategy currently utilized for pacing has major limitations including the need for manual stimulation parameter tuning, and inability to alter stimulation parameters on muscle fatigue or changing metabolic demand.

The CENAVEX project proposes the design, development and prototype realization of a novel closed-loop control system as illustrated in Figure 1.8. It will specifically address the challenge of simultaneously adapting the rhythm and pattern of oscillatory drive to achieve



Figure 1.8: Illustration of the closed-loop strategy for ventilatory control prosthesis: the physiological need is sensed by monitoring the air flow and CO2 concentration, a specific controller computes those information to control the stimulation of muscles involved in the ventilatory function

effective and efficient control of the respiratory function using neuromorphic hardware. A neuromorphic controller will receive inputs from measurements on ventilatory systems and will drive a stimulator which targets three muscular groups: the external intra-costal muscles, the diaphragm and the abdominal muscles.

After describing the context, the last part of this chapter proposes a summary of the issues considered in this thesis and announces the organization of the manuscript.

## 1.4 Synthesis of the issues addressed in that PhD thesis

#### 1.4.1 A wide range of applications and closed-loop need

As explained previously, stimulation devices can address a wide range of diseases and disabilities, from Parkinson's disease to cardiac arrhythmia. Depending on the application, different electrodes and sets of stimulation parameters are being used. Electrodes area can vary a lot from a few square micrometers to a few square centimeters, which has a direct impact on their impedance. Stimulation parameters such as current amplitude, frequency and even the waveform itself can differ a lot. As an example, current amplitude for neuro-stimulation is two decades lower than for muscle stimulation (milliamp range). This means that stimulation devices are either specific to a target application or are very tunable with wide output current or voltage spans. Moreover, the actual organ response to the stimulation parameters in real time. As examples, we can cite the pacemaker stimulation frequency that must increase when the patient is exercising and decrease when the patient is at rest or the mandatory adaptation of respiratory rhythm to fulfill the metabolic needs of the patient [20]. Closed-loop adaptive control of electrical stimulation may therefore be necessary to achieve the best treatment to each patient through.
### 1.4.2 In situ electrical monitoring

Long term efficacy of implantable devices is also a very important feature to be investigated. After the implantation of an electrode or any device, an immediate and sustained inflammatory response occurs, mainly manifested by fibrosis or gliosis in the brain. This inflammatory response persists until the material is encapsulated in a dense layer of fibrotic connective tissue which shields the implant from the immune system and isolates it from the surrounding tissues 21. Fibrous encapsulation compromises implanted device efficacy and can lead to device failure [22]. This encapsulation has two main consequences: a medical issue and an electrical one. The medical issue results from the fibrotic attachment of the leads that can make their extraction dangerous for the patient when needed; this is the case for cardiac pacemakers when leads are damaged. The modification of the electrodetissue interface may result in an increased impedance as fibrotic tissues are less conductive [23] and may imply an increased stimulation threshold. From engineering prospective, this consequence is a major issue: a greater power is therefore needed to produce the desired therapeutic effect, hence shortening the lifespan of the stimulator battery [24]. As fibrotic encapsulation is due to a remodeling of the tissue surrounding the electrode, it must be reflected in electrical impedance of the electrode-tissue interface [25]. That is why we postulate that fibrosis or gliosis evolution through time can be monitored using in situ embedded impedance measurements.

### 1.4.3 Exploration of efficient stimulation waveforms

Beyond the widespread use of the biphasic current pulse, the exploration of new waveforms that are more efficient from an energetic or therapeutic point of view, remains a subject of study [26, 27]. This exploration is also relevant in the context of the measurement of electrode impedance. A few stimulation systems assess this problem, and a very few have been used within in vivo experimental setup [28]. Given the stimulation waveform optimization issue and the in situ embedded impedance measurement need, a specific stimulator with arbitrary waveform generation capabilities might be a part of the solution.

### 1.5 Conclusion: outline of the manuscript

Based on the previous analysis, this thesis has focused at first on the design and implementation of multi-application stimulation systems, compatible with closed-loop paradigm, and then on new architectures allowing the exploration of original stimulation waveforms, including the impedance monitoring feature. The chapter 2 of this manuscript will focus on the state of the art of stimulation systems, their analog and digital architectures as well as their controllability for different applications. It will also include an overview of research works on stimulation waveform exploration and bio-impedance measurement. The chapter 3 will present a multi-application stimulation system, from the integrated circuit design to user interface, named Multistim. This fully configurable IC-centered stimulator has been designed to investigate muscle stimulation paradigms. It provides 8 current stimulation channels with high-voltage compliance and real-time operation capabilities; it can be used in a standalone mode, or within a closed-loop setup. The chapter 4 will detail a novel stimulation architecture which permits the exploration of new stimulation waveforms as well as electrode impedance characterization. This second system, named Twist, provides 8 Stimulation Channel IP that can provide user-defined waveforms for open and closed-loop experimental setup. Finally, experimental results are presented in the chapter 5, including in vitro and in vivo experimentation for both stimulation systems.

## Chapter 2

## State of the art

### 2.1 Introduction

After introducing the context and the objectives of this PhD dissertation (chapter 1), this chapter aims to draw up the state of the art of stimulation circuits and systems. Before coming to a technical study, an overview of the scope of neurostimulation applications is proposed (2.2). Then we will review IC-based stimulation devices that have been classified according to classical criteria (2.3). Finally, an overview of new research pathways is given, demanding new capabilities to advanced stimulators (2.4).

### 2.2 Neurostimulation

### 2.2.1 Applications

Electrical stimulation is a widely-used technique for various therapeutic applications or as an experimental tool for neuroscience applications. An electrical charge is injected through electrodes to target excitable cells or organs, in the form of pulsed signals, with appropriate duration and amplitude. Many applications of electrical stimulation have been reported in the literature, for the treatment of neural disorders or dysfunction of the central and peripheral nervous system. Nag and Thakor published a recent review of the trends in that field [29]. Figure 2.1 is directly extracted from this publication; it shows the variety of neural prostheses applications, with their associated purposes and target organs.

As depicted in Figure 2.1, electrical stimulation therapies are applicable to the central, peripheral and autonomic nervous systems and the target organs can be the brain, the spinal cord, nerves, muscles, retina and cochlea. Hence, applications may be classified in sensory-motor prostheses (restoration of movement or touch and proprioception), nerve prostheses (restauration of autonomic regulation functions), visual, auditory and vestibular prostheses (restauration of vision, hearing or physical balance). Heart artificial pacing is a classic example of functional stimulation. Selective stimulation of the cochlea [30, 31] can restore hearing. The artificial restoration of sight has been shown possible using electrical stimulation of the retina [32–34] or the visual cortex [35]. The treatment of Parkinson's disease effects [36] and epilepsy [37] by electrically stimulating the deep brain has also been demonstrated. Microstimulation of nerves can restore sensory and motor perception [38–40], and large current delivery to muscles can enable movement [41]. In addition, the



Figure 2.1: Comprehensive summary of applications of neural prostheses, from [29]

spinal cord can be electrically stimulated to reproduce central pattern signals for motor movements [40, 42].

### 2.2.2 Characteristic electrical parameters

Electrical stimulation can be either monophasic or biphasic. The first one is generally used when long-term safety of the stimulation is not a major concern. However, biphasic rectangular stimulation pulses are beneficial for charge-balanced safe stimulation (ref Safe stimulation protocols). In general, cathodic (negative polarity) monophasic stimulation pulses are preferred over anodic pulses (positive polarity). Cathodic pulses evoke single or compound action potentials by depolarizing cell or nerve membranes [29, 43]. Biphasic constant current stimulation pulses are preferred over constant voltage pulses, as they allow to control the injected charge which is an advantage for accurate charge balancing. Biphasic stimulus can be either cathodic first or anodic first, but cathodic-first pulses trigger neural activities at a lower charge delivery threshold [43] hence are more commonly used in the literature. The parameters describing the stimulation waveform (current/voltage mode, pulse magnitude, pulse duration, inter-pulse duration, etc.) depend on a number of factors, such as the properties of the excited tissues, the types of electrodes used or electrode placement [44]. Depending on the application, those parameters can differ a lot. Table 2.1. is a second extract from Nag and Thakor paper [29]; it illustrates the various modes, organs and electrical parameters that have been reported for sensory perception or functional restoration.

**Table 2.1:** Typical electrical stimulation parameters adopted for clinical/scientific applications, from (N Thakor). Magnitude and duration depend on electrode location, size of target organ and distance between them. IDP: Inter-pulse duration, NHP: non-human primate, -: Not available

Parameters	[44]	[45]	[46]	[47]	[41]	[40]
Areas	Brain	Brain	Nerve	Nerve	Muscle	Spinal Cord
	(M1, S1)	(S1)	(femoral)	(median)		
Mode	Current	Current	Current	Voltage	Current	Voltage
M 1.	50 to	30 to	0.04 to	1 to	2 to	$0 \in V$
Magintude	200 µA	$50\mu\mathrm{A}$	$5\mathrm{mA}$	$5\mathrm{V}$	$8\mathrm{mA}$	2.3 V
Duration	200 115		10 to	$1.026  \mathrm{mg}$	200 115	40 ms
Duration	200 µs	-	$500\mu{ m s}$	1.020 1115	200 µs	40 1115
IPD	$100\mu s$	-	-	-	-	-
Subject	NHP	NHP	Human	NHP	NHP	Human
Year	2007	2008	2010	2013	2012	2014

### 2.2.3 System features for investigation of new stimulation paradigms

Electrical stimulation systems can be classified as closed-loop and open-loop. The closedloop approach uses inputs associated with the targeted pathology in order to control the stimulation, whereas open-loop control does not depend on feedback from the target or an associated organ of interest. The closed-loop approach is gaining more importance, compared to the open-loop, due to its increased safety, robustness and efficacy. According to [20], research in respiratory neuroprosthetic devices should focus on systems that adapt stimulation patterns to metabolic needs of the patient. The closed-loop methods have the ability to alter stimulation charge delivery, timing or spatial attributes [48]. Closed-loop adaptive control of electrical stimulation may therefore be necessary to achieve complete restoration of a targeted function. Modulation of the stimulus pulse train parameters can allow fine muscular control by being able to elicit a desired muscle activation profile [49, 50]. In order to investigate and assess the efficacy and safety of new stimulation protocols, the stimulation system should be highly configurable and achieve real-time operation to facilitate closed-loop experiments [51]. More specifically, the stimulator needs to be multichannel, in order to be able to be efficient in applied research for functional rehabilitation [51]. A few multi-channel systems allow pulse-width modulation of the stimulus parameters [52, 53] or burst parameters modulation [54], and a very few allow envelope modulation and timing modulation [55]. To assess complex stimulation schemes, stimulation devices have to be tunable and programmable, controlled by computers or embedded digital electronics [55-58].

### 2.3 Review of IC based stimulation devices

To synthesize the strategies and trends of integrated circuits (IC) for neuro-stimulation, we performed a literature review running from 1999 to 2016 [59]–[112], and extracted the circuits' main features as shown in Table 2.3.

**Table 2.2:** Review of recently published stimulation circuits and systems in the literature. 'N.I': not indicated, 'N.A.': not applicable, 'DBS':Deep Brain Stimulation, 'FES' for Functional Electrical Stimulation, active charge balancing as primary charge balancing technique, 'P': passive charge balancing as the only charge balancing technique, \* Circuits with a higher  $V_{max}$  than  $V_{supply}$  using internal DC/DC converters.

source	I/V	# of channel(s)	technology	$\max(V_{supply}, V_{max})^*(V)$	$I_{max}$	discharge	application	Die Size $(mm^2)$
Abdelhalim 2011[59]	Ι	N.I.	0.13 CMOS	3	1.2mA	А	N.I.	N.I.
Arabi 1999[60]	Ι	4	1.2  CMOS	N.I.	6.3mA	А	Neuromuscular	16
Arfin 2009[61]	Ι	4	$0.5 \ \mathrm{CMOS}$	5	1mA	А	N.I.	N.I.
Arfin 2012[62]	Ι	1	0.35  CMOS	N.I.	N.I.	N.I.	N.I.	N.I.
Azin 2011[63]	Ι	4	0.35  CMOS	5	$94.5 \mu A$	A/P	N.I.	N.I.
Bihr 2013[64]	Ι	N.I.	$0.18 \ \mathrm{HV} \ \mathrm{CMOS}$	15	15mA	А	N.I.	N.I.
Blum 2007[65]	V	16	0.35  CMOS	3.8	N.I.	N.I.	N.I.	N.I.
Chang 2004[66]	Ι	1	0.35  CMOS	3.3	2.8mA	А	nerve	N.I.
Chang 2006[67]	Ι	1	$0.35 \ \mathrm{HV} \ \mathrm{CMOS}$	13.5	11.3mA	А	spinal cord	N.I.
Chen 2010[68]	Ι	254	$0.18 \ \mathrm{HV} \ \mathrm{CMOS}$	$\pm 12$	$5\mu A$	A/P	retinal	27
Chen 2014[69]	Ι	8	$0.18 \ \mathrm{CMOS}$	10 *	$30 \mu A$	А	epileptic seizure	13.47
Chun 2013[70]	Ι	N.I.	65n  CMOS	3	$8\mu A$	A/P	N.I.	N.I.
Chun 2010[71]	Ι	N.I.	$0.35 \ \mathrm{HV} \ \mathrm{CMOS}$	20	1mA	А	N.I.	0.04
Constandinou 2008[72]	Ι	3	0.35  CMOS	10	$735 \mu A$	A/P	vestibular	1.71
			(10V  process)					
Coulombe 2007[73]	Ι	16	$0.18 \ \mathrm{CMOS}$	3.3	N.I.	А	visual cortex	8.96
DeMarco 2003[28]	Ι	9	1.2  CMOS	$\pm 7$	$400 \mu A$	А	retinal	4.84
Dommel 2009[74]	Ι	2	$0.35 \ \mathrm{HV} \ \mathrm{CMOS}$	20	1,24mA	A/P	retinal	N.I.
Dongen 2013[75]	V	2	$0.18 \ \mathrm{HV} \ \mathrm{CMOS}$	10 *	N.I.	А	N.I.	N.I.
Eftekhar 2007[ <b>76</b> ]	Ι	8	0.35  CMOS	3.3	5mA	А	FES	3
Fang 2007[77]	V	1	$0.18 \ \mathrm{CMOS}$	3.3	N.I.	А	N.I.	N.I.
Georgiou 2005[ <b>7</b> 8]	Ι	16	$0.8 \ \mathrm{CMOS}$	4.2	$700 \mu A$	А	$\operatorname{cochlear}$	21
Gong 2006[79]	Ι	16	$0.18 \ \mathrm{CMOS}$	1.8	$80\mu A$	А	retinal	N.I.
Gong 2013[80]	Ι	16	$0.18 \ \mathrm{CMOS}$	1.8	$120 \mu A$	А	FES	2.1
Gudnason 1999[81]	Ι	4	2  CMOS	10	2mA	А	FES	12
Hitzelberger 2001[82]	Ι	12	$0.7 \ \mathrm{CMOS}$	3.3	2mA	А	FES	42

Hu 2008[83]	Ι	1	$0.5 \ \mathrm{CMOS}$	$\pm 1.5$	$35\mu A$	А	N.I.	0.2
Dai Jiang 2011[84]	Ι	1	$0.6 \ \mathrm{HV} \ \mathrm{CMOS}$	18	1.02mA	А	vestibular	8.19
Jiang 2012[85]	Ι	1	$0.6 \ \mathrm{HV} \ \mathrm{CMOS}$	12	1mA	A/P	vestibular	21.42
Kelly 2011[86]	V	1	1.5  CMOS	$\pm 1.75$	N.I.	А	N.I.	N.I.
Langlois 2010[87]	Ι	5	$0.6 \ \text{SOI CMOS}$	30	16mA	Р	nerve	N.I.
Lee 2013[88]	Ι	4	$0.5 \ \mathrm{CMOS}$	4.6	2.48mA	А	DBS	2.25
Lee 2008[89]	Ι	8	0.18  CMOS	N.I.	$135 \mu A$	N.I.	DBS	2.25
Lin 2013[90]	Ι	1	$0.35 \ \mathrm{HV} \ \mathrm{CMOS}$	10 *	$40\mu A$	A/P	Epileptic seizure	0.7
Liu 2000[91]	Ι	20	1.2  CMOS	9	$600 \mu A$	А	retinal	N.I.
Liu 2006[92]	Ι	1	0.35  CMOS	5	1mA	А	N.I.	N.I.
Liu 2011 <mark>[93</mark> ]	Ι	2	$0.6 \ \text{SOI CMOS}$	12	N.I.	Р	FES	4
Liu 2012[94]	Ι	4	0.6  SOI CMOS	18	8mA	Р	FES	27.3
Nadeau 2006[95]	Ι	1	0.8 HV CMOS	$\pm 10$	2mA	А	Neuromuscular	10.96
Ngamkham 2015[96]	Ι	1	$0.18 \ \mathrm{HV} \ \mathrm{CMOS}$	$\pm 18$	1.05mA	A/P	cochlear	0.042
Noorsal 2012[97]	Ι	4	$0.35 \ \mathrm{HV} \ \mathrm{CMOS}$	20	1mA	A/P	epiretinal	0.2
Ortmanns 2007[98]	Ι	116	0.35  HV CMOS	35	$500 \mu A$	А	epiretinal	22
Shahrokhi 2010[99]	$\mathbf{V}$	128	0.35  CMOS	3.3	N.I.	N.I.	cortical	8.5
Shen 2010[100]	Ι	1	0.35  CMOS	3.3	$165 \mu A$	А	DBS	N.I.
Shulyzki 2010[101]	Ι	1	0.35  CMOS	3.3	$250 \mu A$	А	cortical	0.02
Sit 2007[102]	Ι	1	$0.7 \ \mathrm{HV} \ \mathrm{CMOS}$	15(-9,+6)	1mA	А	N.I.	1.44
Sivarprakasam 2005[103]	Ι	8	1.5  CMOS	$\pm 6.5$	$600 \mu A$	A/P	retinal	4.84
Soulier 2008[104]	Ι	1	$0.35 \ \mathrm{HV} \ \mathrm{CMOS}$	N.I.	N.I.	A/P	FES	N.I.
Suaning 2001[105]	Ι	50	2  CMOS	N.I.	2mA	А	retinal	31.28
Tan 2011[106]	Ι	1	0.35  CMOS	3	10mA	А	FES	N.I.
Techer 2004[107]	Ι	2	0.8 HV CMOS	N.I.	5mA	Р	FES	15.3
Tokuda 2009[108]	Ι	1	0.35  CMOS	5	1.05mA	А	retinal	0.04
Troyk 2012[109]	Ι	16	0.8 BiCMOS	5	$63.5 \mu A$	А	N.I.	N.I.
Valente 2010[110]	Ι	1	$0.35 \ \mathrm{HV} \ \mathrm{CMOS}$	12	N.I.	N.I.	DBS	N.I.
Valente 2012[111]	Ι	3	$0.35 \ \mathrm{HV} \ \mathrm{CMOS}$	12	N.I.	А	DBS	0.71
Williams 2013[112]	Ι	8	$0.18 \ \mathrm{HV} \ \mathrm{CMOS}$	11.5	$504 \mu A$	А	FES	5.4

### 2.3.1 Circuit architecture

As explained in the previous paragraph, some design choices reach a quasi-unanimous consensus. The first concerns current-mode stimulation, better adapted to control the injected charge in a tissue (91 of the considered circuits). Next, all propositions implement biphasic waveform generation, which is a mandatory feature for safety reasons [111]. A typical biphasic current stimulation waveform is composed of two constant current pulses as described in Figure 2.2(a) first a cathodic, negative, current (Ic) pulse is delivered, lasting Tc to induce firing or inhibition of targeted cells; adequate Ic and Tc values are chosen by electro-physiologists or clinicians and depend on the electrode and the tissue properties. Then an anodic, positive, current (Ia) pulse lasting Ta is provided, in order to avoid electrochemical reactions due to accumulation of injected charges that can damage tissue. Such a strategy is called active charge balancing. Another alternative for charge balancing is a passive discharge of the electrode after the cathodic phase, by discharging the capacitance of the electrode (see 'discharge' column in Table 2.3. Biphasic current stimulus and charge balancing is closely related to the topology of the front-end current generation.

The generic front-end circuit for current-mode stimulation consists in a current source connected to an electrode using a combination of switches. As a unique current source can only provide a mono-polar current, different architectures combining switches and sources have been developed to deliver positive or negative current. Three topologies, presented in Figure 2.2(a), are basically used in stimulation circuits:

- One source, passive balancing: this topology is based on one current source and two switches and can only deliver cathodic current pulses compensated by passive balancing.
- One source, active balancing: active balancing can be achieved by using more switches. The current polarity is changed using switches organized in a H-bridge structure, using an asymmetrical supply. Passive charge balancing can also be performed by breaking the symmetry of the switching command pattern or by adding a fifth switch in parallel with the stimulation load. Nevertheless, this structure cannot be used with multi-channel electrodes that have a common current return path; in such a configuration, asynchronous stimulation of different channels can cause short-circuits between electrodes and tissue damage by involuntary charge injection.
- Two sources, active balancing: this circuit includes two current sources, each associated with one switch, and the electrode is referenced to the ground potential. As a consequence, any multi-electrode configuration can be addressed. However, this structure requires a symmetrical supply. Passive balancing can be achieved by adding one switch connecting the electrode to the ground.

Systems listed in Table 2.3 are mostly based on active balancing (topologies ii) and iii)). Few are based on passive balancing only (8 It should also be noted that topologies ii) and iii) can be modified for special electrode combinations [74] or specific optimization, as in [92] or in [70].

### 2.3.2 Supply voltage and technology

As indicated in Table 2.3., voltage compliance higher than 4V represents 62 of the considered systems; this is a direct consequence of the high value of the electrode impedance.



Figure 2.2: (a). Typical biphasic current stimulation waveform with active balancing. The cathodic current Ic is negative and applied during a time Tc required to trigger excitable cells, and the injected charge is then balanced using a positive anodic pulse of duration Ta. Both pulses are generated with current sources activated by  $\Phi c$  and  $\Phi a$  switching commands. (b) Circuits used for biphasic stimulation front-end. The electrode is represented by Zstim., istim is the variating stimulation current. Ic and Ia are current sources generating the cathodic or anodic currents, respectively; switches are controlled by signals  $\Phi c$  and  $\Phi a$  as described in (a), except for topology i) where charge balancing is achieved by applying a closing control signal  $\Phi$ short to create a short circuit. For topologies i) and iii), the ground signal is the lowest potential of the supply source, for topology ii) the ground signal is the middle point of the symmetrical supply Vdd/Vss.



Figure 2.3: Evolution of process gate-length used for stimulation ICs. Red dots correspond to the process minimal gate length; solid line: linear interpolation of the gate length versus time; dots line: Moore's law. Dashed line: linear interpolation starting from the highest stimulator gate length in 1999.

Except for circuits with embedded DC/DC converters, high compliance is achieved by increasing the supply voltage. While the majority of systems are CMOS-based, many (58 use High-Voltage (HV) or Silicon-on-Substrate (SOI) processes, or mature processes capable of reaching supplies of over 5V (over  $0.7 \,\mu$ m). The evolution over time of process gate-length for Table 2.3. circuits is plotted in Figure 2.3. Gate lengths have relatively high values compared to the last available technologies for IC fabrication. The interpolated evolution of gate lengths for these stimulation ICs does not follow Moore's law but decreases much more slowly. We can also observe a relative stagnation on  $0.35 \,\mu$ m and  $0.18 \,\mu$ m processes after 2006, as these two technologies have reliable HV processes.

### 2.3.3 Targeted application and consecutive output constraints

The fourth column in Table 2.3 indicates the targeted application and shows the extent of the neuro-stimulation spectrum. We note that output current per channel ranges from a few  $\mu$ A to several 10 mA (4 decades). However, the required supply voltage is bounded in a range from a few Volts to a few tens of Volts (less than 1 decade), since the impedance of electrodes generally decreases while the current level increases.

### 2.3.4 Toward a multi-application stimulation system

In the review previously analyzed, the design of stimulation devices is usually 'applicationspecific': a stimulator is associated with one application with a corresponding set of specifications and constraints, depending on the electrodes and targeted tissue. In a mature research context close to clinical validation, optimizing the stimulator's features such as its size and power consumption is essential. However, such a specific approach restricts the possibilities of exploring new techniques and protocols. In the ELIBIO team, the strategy was rather to develop generic stimulators that could be used for a large panel of therapeutic applications and allow exploration of new paradigms. This 'multi-application' strategy was already adopted during the PhD thesis of Florian Kölbl [113] and gave rise to a modular multi-application stimulation ASIC based on Elementary Stimulation Channels (ESCs), that will be described in chapter 3.

### 2.4 Advanced smart stimulation devices

#### 2.4.1 Stimulation waveform optimization

The last two decades focused on optimization and miniaturization of electronics and minimization of associated power consumption. Energy considerations play an important role in the design of stimulation systems, especially for battery-powered implanted devices. As stated by Jezernik and Morari [26], in implantable neural prosthetic systems, much of energy is needed for the generation of stimulation pulses. Ondo and Vuong [24] shown that battery life of an implant is linked to stimulation waveform parameters, especially pulse-width and amplitude of the stimulus. Early research on energy efficiency of the stimulation waveform started in 1976, with the work of Klafter [114]. Their study shown that the selection of a proper pulse shape between a limited set of 4 different waveforms (including the classic biphasic pulse) can lower the threshold stimulating energy. This early stage of waveform optimization was conducted using dog subjects, in-vivo, with a modified pacemaker. Since [114], extensive research has been carried out using nerve models and computer simulation. Jezernik and Morari [26] performed the comparison between squared biphasic and exponentially rising biphasic waveforms. They had shown that the latter would provide better results with a lower energy. Sahin [115] tested alternative waveforms to determine if pulse shape has an effect on the strength-duration relation. They tested 7 different waveforms, on an electrode model combined to a cross mammalian nerve model, and deduced that the most 'efficient pulse shapes' are Gaussian shaped waveform as well as linear and exponential decrease. Foutz [116] studied new stimulation waveforms specifically for Deep Brain Stimulation and found that a 1 ms centered-triangular pulse can decrease energy consumption by 64 when compared with the standard 100 µs rectangular pulse, with the same therapeutic effects. Their study involved the comparison of a wide range of charge-balanced biphasic waveforms with rectangular, exponential, triangular, Gaussian and sinusoidal stimulus pulse shapes. Those studies have been carried out using simulation, as most stimulation circuits are designed and optimized for squared biphasic pulses. One circuit that permits experimental waveform optimization has been developed by [28]. A very promising and innovating work has been carried out by Wongsampigoon [117]. Their work involved the use of a genetic algorithm in order to find the less energy consuming stimulation waveform, using a computer model. Then, they compared the therapeutic effects of the classic biphasic squared stimulus with the stimulus found with the genetic-algorithm computation. Their results shown that the latter is more efficient, and that the stimulation waveform (presented figure 2.4) converged to a Gaussian-like shape.

More recently, Grill [118] published a study that reviews the use of computational models to understand the effects of stimulation waveform on the energy efficiency of neural excitation and to design novel stimulation waveforms to increase the efficiency of neural stimulation. This review defines clearly the different optimization objectives and involved



Figure 2.4: Adapted from [117], Energy-Optimal stimulation waveforms resulting from a genetic-algorithm for a pulse-width of 1ms and 2ms

metrics. Two important considerations when selecting or designing stimulation parameters are selectivity and efficiency. Selectivity is the ability to activate the targeted neural elements without activating the non-target neural elements. The degree of selectivity determines the magnitude of the therapeutic effect (efficacy) as well as the type and magnitude of side effects. Efficiency is achieving the required response (with clinical efficacy) with the minimum 'amount' of stimulation. The 'amount' of stimulation can be measured with respect to a number quantities including stimulation current or voltage amplitude, stimulation charge, stimulation power, and stimulation energy. Both selectivity and efficiency are dependent on the choice of the stimulation waveform. This review concludes firstly that no single waveform shape was simultaneously energy, charge, and power-optimal, and thus the performance requirement of specific applications of neurostimulation need to be defined for the design process. Secondly, most analyses focused exclusively on efficiency, not on stimulation selectivity. Finally, energy optimal waveform shapes yielded comparatively small gains in efficiency, which may explain that clinical devices continue to use rectangular stimulation pulses. However, this computational study highlights the importance of using an appropriately complex model to analyze the effects of waveform on neural excitation, as prior simplified models yielded suboptimal results, and optimal stimulation waveform parameters were dependent on the electrode geometry and electrical properties of the tissue. This last point marks the limitations of a simulation-based study and calls for real experiments. Thus, we decided to include the arbitrary waveform feature to the second stimulation system developed in this thesis work (chapter 4).

### 2.4.2 In situ electrical monitoring

#### Long term bio-compatibility

A major weakness of any implantable device is located at the implant-tissue interface; implanted devices induce an immediate and sustained inflammatory response mainly manifested by fibrosis [119] (or gliosis for brain stimulation). It is characterised by the infiltration of inflammatory cells to the area of the implant. As the foreign material cannot be phagocytosed and removed, the inflammatory response persists until the material becomes encapsulated in a dense layer of fibrotic connective tissue, which shields it from the immune system and isolates it from the surrounding tissues [21]. Fibrous encapsulation often compromises the efficiency of the device and can lead to device failure [22]. Fibrosis has two kinds of consequences. The first one is a medical consequence, fibrotic tissue attachment to the electrode leads can make their extraction very dangerous for the patient - leads may have to be removed if damaged, obstructing veins or if being the source of chronic or acute infections. As an example, fibrotic attachments that develop between chronically implanted pacemaker leads and the venous, valvular and cardiac structures are the major obstacles to safe and consistent lead extraction. Also, recent devices feature a higher number of electrodes for stimulation and recording/sensing which increase the issues mentioned before. The second consequence is electrical: fibrosis of the tissue-electrode interface is cited as an important problem, which increases the stimulation threshold [25] and adversely affecting any sensing/feedback function. Despite the revolution of steroidelution leads, fibrosis remains a sensitive issue [120]. Those two major issues underline the need for a method to monitor fibrosis growth at the tissue/electrode interface, which can be done through bioimpedance measurements. Bioimpedance measurements reflect dielectrics properties of body tissues at different scales.

#### **Bioimpedance monitoring**

**Impedance measurement schemes** Measurement of impedance can be performed using different techniques. In all of them the sample under test is excited using a signal small enough to maintain linear electrical behaviour. Common techniques [121] are based on excitation schemes including the Wheatstone bridge, ratiometric reading and current/voltage technique. We focused on the last one as we intend to add a feature to a stimulation circuit, that already delivers a controlled current.

Multi-point current/voltage impedance measurement techniques Multi-point measurement techniques are often used to measure the impedance of a material, biological of not. Figure 2 illustrates the mainly used techniques: two-terminal and four-terminal. In the two-terminal technique, the same two electrodes are used to drive currents into the medium and to measure the potential difference (figure 2.5, left). A source of measurement error comes with this method as the electrodes and leads impedances are taken into account. This can have a significant effect when measuring low impedances or when doing low-frequency measurements, with electrode polarization effects at the electrode/electrolyte interface. The result is a capacitive effect that can dominate the signal at low frequencies. It is possible to correct those issues by post-processing the measurement, if the electrode impedance is known. This method has been used in vivo by many reference in the literature [122–125] as weel as in vitro [17, 125]. In the four-terminal measurement technique, two electrodes are used to drive current into the tissue and two different ones are used to measure the voltage across the tissue (figure 2.5, right). Theoretically, this method eliminates series and interface impedances errors, as long as the input amplifier impedance is high enough [126]. We can cite as an example [23, 122] who used this technique. A three-point technique is also available, less used, and sensitive to a surface impedance in the vicinity of the voltage monitoring electrode.

**Types of stimuli for Electrical Impedance Spectroscopy** Depending on the targeted application, impedance measurement can be done at one frequency or over a given



Figure 2.5: Illustration of two impedance measurement techniques: on the left twoterminal measurement, on the right four-terminal measurement

frequency range. The latter is called Electrical Impedance Spectroscopy (EIS), and is the main method used to study long-term biocompatibility. To realize EIS, several stimuli can be used: rectangular waves, sine signals with varying frequency (chirp signal) or signals which combine different sine signals at different fixed frequencies (multisine). We have to keep in mind our context of electrical stimulation: the chosen approach has to be compatible with the therapeutic signal (often rectangular), either it uses this signal itself or the additive impedance measurement stimulus does not disturb this therapeutic signal. Rectangular waves stimulation signals can be used to extract electrode and tissue impedance spectrum, but it requires a post-processing step in order to exctract the impedance spectrum, using different algorithms as [127-129].

Sine waves with varying frequencies (chirp signal) are easier to analyze and maybe the most conventional way to measure the impedance spectrum. It provides the most precise measurement as it cover a wide frequency span. It can be done easily using either analog or digital circuits [130–132], with a frequency span generally comprised between 1Hz and 1MHz.

Multisine signals present the advantage of enabling impedance measurement at different frequencies with the same signal. It is a good compromise regarding computational resources compared to rectangular waveform and chirp signal. Still, it is not compatible with functional electrical stimulation. This use of such signals can be found in [133, 134].

For the last two cases, due to the electrical stimulation context, solutions must be found in order that the impedance stimulus signal does not trigger any biological reaction.

Tables 2.3 and 2.4 give and overview of integrated circuits applied to bioimpedance monitoring.

Those studies provide us information about the relevant frequency span as well as some post-processing methods that could be associated with rectangular pulse measurement.

Paper	Technology — Power-supply	Number of Channel	Biological target — Objective	Frequency Span	Signal Amplitude
Ausin 2013 [130]	LVCMOS 0.35 µm — 0-3V	scalable	Skin — Health monitoring	1Hz to 1MHz	N/A
Liu 2010 [131]	СМОЅ 0.5 µm — 0-3.3V	5	Cellular membrane — Biotoxin detection	1Hz to 10kHz	100pA to 100nA
Triantis 2011 [132]	CMOS 0.6 µm — ±2.5V	4	Lungs — Neonate lung function monitoring	10kHz to 1MHz	300 μA peak-peak and 500 μA peak-peak

Table 2.3: Existing sine wave based impedance monitoring ICs

### 2.5 Summary

This chapter presented the various applications of neuro-stimulation and reviewed the ICbased stimulation circuits. From a specific application to another, stimulation current, voltage compliance, number of channels, etc. can differ a lot. In the context of this PhD work, in order to explore different stimulation schemes corresponding to different research projects described in chapter 1, we decided to build a multi-application stimulation device that can be used in different setups and applications. This idea was at the basis of the two systems presented in chapters 3 and 4. Using more energy efficient stimulus would allow stimulation devices to last longer and reduce the need for battery replacement surgery. Exploration of the energy efficiency of the stimulus waveform has been done mainly using computer simulation approach, hence we propose in the chapter 4 a system that permits to verify experimentally those theories. Impedance measurement at the electrode-tissue interface is a promising method to monitor the alteration of the tissue surrounding an implant and then contribute to long-term biocompatibility in vivo study. Therefore we propose also in the chapter 4 to include a dedicated impedance measurement unit in a stimulation IC.

Uranga 2007 [129]	Lo 2014 [128]	Czaja 2012 [127]	Paper	
ASIC CMOS HV 0.7 µm	Implantable Neural Stimulation IC + off the shelf microcontroller	8 bits microcontroller	Circuit	
3 (Bladder) or 8 (Hand grasp)	4	1	Number of Channels	(
Bladder and Hand grasp,Urinary urge incontinence and lead failure diagnosis	Platinum electrode in vitro — Evaluation of proximity between electrodes and targeted tissue for neurostimulation	Unknown — Smart sensors for wireless health monitoring	Biological or model target — Objective	(
Monophasic20mA 600µspulse width (16V or 28V compliance)	Biphasic10 µA and 100 µA 1ms pulse-width Interpulseduration: 1ms	Monophasic 5V Various timings	Pulse Parameters	(
Bisection Algorithm to find the resistive component	Measurement of the electrode response to fit Randle cell model	Extraction of three parameters by Randle cell model fitting	Post- processing method	

## Chapter 3

# Multistim, a multi-application stimulation system with biphasic constant current waveforms

### 3.1 Introduction

The design of stimulation devices is usually 'application-specific': a stimulator is associated with one application, with a corresponding set of specifications and constraints, depending among others on the electrodes and targeted tissue. In a mature research context close to clinical validation, optimizing the stimulator's features such as its size and power consumption is essential. However, such a specific approach restricts the possibilities of exploring new techniques and protocols. For our research purposes, we chose to design a stimulation platform, Multistim, which architecture has been thought in a multi-application objective and it is based on an ASIC previously designed and carried out by F. Kölbl during his PhD project [113]. This ASIC, named SHIVA, was the first stimulation IC developed in the team ELIBIO. SHIVA is a mixed analog-digital IC that implements front-end stimulation circuits and their digital controlling circuits. SHIVA's modular architecture is based on Elementary Stimulation Channels (ESCs) that can be combined in various stimulation topologies, from a scheme of micro-electrode arrays with a high channel density and low-level currents, to one with few channels and high-level currents. This proof-of-concept ASIC integrates 8 ESCs and their controlling digital circuits, using a HV (High Voltage) 0.35 µm CMOS process. SHIVA has a voltage compliance of  $\pm 18$  V with a maximal current per ESC of 1 mA and a minimal output impedance of  $40 \,\mathrm{M}\Omega$ . In addition to the on-chip controlling circuits, a digital architecture has been implemented on an external FPGA to allow the combination of several ESCs on an ASIC, and the combination of several ASICs on the system, to target a higher number of electrodes. Thanks to this modular design, we successfully demonstrated the possibility of multiple user-defined configurations in different in vitro experimental schemes [135].

This chapter presents the work that has been carried out in order to build a complete and reliable stimulation system, from integrated circuit design to user interface. The digital part of SHIVA chip presented some issues, that might be related to a layout issue or a manufacturing defect: the control of the chip through its digital serial interface was erratic and could not allow the control of the stimulation signal amplitude. After an overview of the development of SHIVA and the resulting knowledge and experience we learn from it,



Figure 3.1: Illustration of the multi-application approach. A controlled bidirectional current source is used for the Elementary Stimulation Channel (ESC), to stimulate the smallest electrode with a biphasic waveform. An electrode is represented by  $Z_{stim}$ ,  $i_{stim}$  is the stimulation current. Ic and Ia are current sources; switches are controlled by  $\Phi c$  and  $\Phi a$ . Several ESCs can be associated to provide multi-channel stimulation, stimulation of larger electrode or even complex stimulation schemes such as current steering with multi-polar electrodes;  $\alpha$  represents the current steering ratio [110]

the design of a new functional multi-application stimulation device named Multistim will be presented, as well as electrical characterization results. Finally, in-vitro experiments using this stimulation system will be detailed.

### 3.2 Overview of SHIVA's architecture

### 3.2.1 A multiple application architecture

SHIVA stands for Stimulation circuit with High-Voltage compliance for Various Applications. It consists in a mixed signal integrated circuit built using AMS HVCMOS  $0.35 \,\mu\text{m}$ process. It provides eight stimulation channels, with a  $\pm 20$ V power supply. Stimulation channels termed Elementary Stimulation Channels (ESC), can be combined with others in order to allow different stimulation paradigms as detailed figure 3.1, from standalone stimulation channels to current-steering applications.

In the *Standalone channels* mode, ESCs are used independently; as the stimulation channels can be asynchronous, each block is driven independently. In the Ganged channels mode, for larger electrode geometries, ESCs are combined and outputs are summed up on the electrode. The number of ganged channels can vary with respect to the total current requirement. In the Current steering channels mode, combination of ganged channels can also be combined to provide complex architecture able of current steering over multi-polar electrodes, as made by [110].



Figure 3.2: Low power analog and digital circuits generating the current inputs and switching commands for the 8 ESCs. The figure identifies the 4 parts of the architecture: in green the Analog Control, in blue the Digital Control, in orange the Configuration and in purple the 8 ESCs (HV compliant part).

### 3.2.2 On-chip analog/digital partition

The architecture of SHIVA is presented hereafter in figure 3.2. We can distinguish 4 different parts in the design: Analog control, Digital control, Configuration, and ESCs.

The Analog Control part provides the 8 ad hoc current sources for the ESCs. A first circuit ('Current Sources') outputs 8 fixed currents. A second circuit ('Analog Path Selector) consists in an 8 inputs-8 outputs current adder matrix, based on a combination of current mirrors. When used with weighted current references, this block is equivalent to a Digital to Analog Converter (DAC). A third circuit ('Current Divider') receives the 8 outputs of the Analog Path Selector and enables the division of each generated current by a fixed ratio (1, 3/4, 1/2, 1/4) to perform complex configurations such as current steering. The Digital Control part processes the 8 commutation orders. A register ('Sign Register') stores 8 commutation states (one of anodic, cathodic or none). A second block ('Digital Path Selector') is composed of 8 pairs of 8-to-1 multiplexers (one for each channel, one for either anodic or cathodic commands). It enables fast commutation synchronization of ESCs for channel combination. In order to perform more complex stimulation schemes, an additional block ('Cath2An') allows a change of polarity of the stimuli: cathodic first or anodic first. This feature can be required for current steering applications. Finally, a configuration block comprises a serial interface and a set of 16 8-bit registers to store the digital parameters. These registers can be written through a 3-wire serial interface by 12-bit configuration words (4 bits for address and 8 bits for data). The 'Sign memory' buffer copies the content of the first address of the 'Addressable Registers', at the rising edge of an external load control ('Load\_D'), which ensures an accurate stimulation timing control.

### 3.2.3 Summary of SHIVA's issues

The smart design of SHIVA permits to test separately the digital and the analog part, as well as the ESCs. During my Master project, I contributed to the test of the fabricated SHIVA chips. Together with Florian Kölbl, we designed a complete FPGA-based test system allowing testing each part of the integrated circuit. Results of the tests firstly revealed a manufacturing defect and secondly inspired me an improvement in the architecture:

- The on-chip Serial Interface was not functional; hence the Analog and Digital Path Selectors could not be properly tested. In-depth study of the digital Serial Interface shown that this issue was linked to the behavior of the implemented flip-flops from AMS HVCMOS 0.35 µm design kit. However, ESCs were fully functional.
- Functional analysis of the system architecture showed that the power consumption of the Analog Control part could be optimized (figure 3.2, in green): instead of generating a current and divide it after the Path Selector, it is better to generate directly the required current for a given ESC.

In conclusion, we decided to re-use the ESCs in the next generation of stimulation ASIC and to integrate separately the analog low-voltage compliant part, including current sources, and digital control of the channels.

### 3.2.4 Description of Elementary Stimulation Channels

The Elementary Stimulation Channel (ESC) has a current-mode analog input and digital inputs to control the cathodic and anodic commutations. These input signals are low voltage (LV) while the electrode output voltage can reach levels higher than the standard CMOS supply voltage. Therefore, we used High-Voltage (HV) processes. Such HV processes are adapted from standard CMOS technologies, as shown in [136] and require only two additional fabrication masks. The HV 0.35 µm AMS process includes 50 V compatible transistors, as explained in [137]; basic circuits using these technologies are developed in [136] and [110]. Figure 3.2 shows the schematic of a full ESC. We can divide it into three sub-circuits that are described below.



Figure 3.3: Schematic of the ESC circuit. This channel is composed of (from right to left): the electrode driver delivering the stimulation current to the electrode, a LV to HV interface block and a pure logic block combining the control anodic and cathodic signals. *SWan* and *SWcath* are internal signals,  $I_{bias1}$ ,  $I_{bias2}$ ,  $I_{bias3}$ ,  $I_{bias4}$  are internal biasing currents. *Ic* and *Ia* are current sources; switches are controlled by  $\Phi$ c and  $\Phi$ a.

#### Electrode driver

This circuit is connected to the electrode through an external DC blocking capacitor. It delivers the current stimulus with the highest voltage compliance; it is therefore supplied with high voltage  $VDD/VSS = \pm 20$  V. The Electrode Driver is composed of two current sources based on cascode current mirrors. The mirror formed by transistors M1 to M4 is used for the anodic current and the mirror M5 to M8 for the cathodic current. These two sources use LV transistors which have a higher gain factor and lower Early effect than HV transistors; this optimizes the mirror accuracy and output impedance. Both anodic and cathodic current sources are designed with a current gain of 5. Since the drain-source voltage of LV transistors cannot exceed 3.3 V, the current source voltage is controlled with MH3 and MH4, HV transistors acting as anodic and cathodic switches. These HV transistors with thin gate oxide have approximately the same threshold voltage as LV transistors. The gate-source voltage of these transistors cannot exceed 3.3 V, which limits the voltage of the current sources, M3-M4 and M7-M8, to less than 3.3 V. In order to reach the HV input potential of this bi-directional current source, two interface blocks were designed: the Current HV Interface generates the anodic and cathodic currents with potentials shifted from LV to HV, and the Logic Level Shifter acts in the same way for the digital signals controlling the switches.

#### Current HV interface

This circuit inputs are a LV generated current, the LV anodic and cathodic logic commands and generates the currents with HV compliance for the Electrode driver. It is supplied by VDDA = 3.3V. In the event of an anodic stimulation, a current mirror (Mi1 to Mi4) with a gain of 1 is triggered by the anodic command  $\Phi a$ . This cascode current mirror exhibits good precision in current copy and relies only on LV transistors. The anodic current is provided to M1-M2 through the HV transistor MH1. This transistor has a maximal drainsource voltage bigger than the HV supply (20V) and ensures the voltage compliance. It also limits the power consumption when the anodic stimulation is off; it has a thin gate oxide and is directly controlled by the  $\Phi a$  command. In the event of a cathodic stimulation, a first LV cascode current mirror (Mi1-Mi2 and Mi5-Mi6) with a gain of 1 is triggered by the cathodic command  $\Phi_{\rm C}$ ; the current is then flipped with a second LV current mirror formed by Mi7 to Mi10. The cathodic current is provided to M4-M5 through the HV transistor MH2 ensuring the voltage compliance. In order to prevent pointless power consumption, the transistor MS1 is directly controlled by  $\Phi c$ , which disables the branch formed by Mi5 to Mi8. A biasing current (Ibias $1=0.8\,\mu\text{A}$ ) is added through MS1 and subtracted through MS2 to prevent LV transistor Mi10 from any drain voltage drift over its compliance.

#### Logic Level Shifter

The Logic Level Shifter circuit takes as inputs LV logic commands (0-3.3V) of cathodic or anodic stimulation and generates the signals controlling the switches MH3 and MH4 of the electrode driver, respectively SWan and SWcath. The transistor MH3 requires voltage levels from VDD (VDD = 20V) to VDD - 3.3V. The transistor MH4 requires voltage levels from VSS (VSS = -20V) to VSS + 3.3V. This circuit is powered by both LV (VDDA) and HV (VSS and VDD) supplies. The two sub-circuits for anodic and cathodic circuits are symmetrical, thus only the anodic level shifter will be described further. The anodic Logic

Level Shifter relies on a voltage mirror [136, 138] formed by LV transistors Md1 and Md6 to Md9. Md1 is used as a static current generator providing Ibias1 with a corresponding W/L = n. The n-ratio is applied to two pairs of n-sized transistors, Md6-Md7 and Md8-Md9. These two pairs are controlled through the two HV switches Md4 and Md5, controlled by the  $\Phi$ a anodic command and its complement. The current Ibias1 passes through Md6-Md7 or Md8-Md9, which are connected to the HV supply VDD. It generates a potential difference of 3.3 V across the concerned pair attached on the high voltage level VDD. An additional inverter I3 ensures the buffering of SWan, the shifted logic signal.

### 3.3 Multistim, a multi-application stimulation system: from integrated circuit to user interface

### 3.3.1 Context and objectives

The stimulation system, Multistim, is based on SONIC IC and specifically adapted to the needs of the CENAVEX project. As explained in Chapter 1, this project makes use of Functional Electrical Stimulation (FES) to restore motor functions following Spinal Cord Injury (SCI). In high cervical SCI, motor function of ventilatory muscles can be drastically reduced, or cease entirely. Solutions to this problem are either to use mechanical ventilation [139] or FES to activate the paralyzed muscles [140]. The development of Multistim was guided by the following specifications:

- Closed-loop compatibility: According to [20], research in respiratory neuroprosthetic devices should focus on systems that adapt stimulation patterns to metabolic needs of the patient. Closed-loop adaptive control of electrical stimulation will therefore be necessary to achieve complete restoration of ventilatory function.
- Real-time operation: The achievement of real-time operation is a pre-requisite for closed-loop experiments and Multistim had to be compatible with the real-time acquisition and processing system developed by the ELIBIO team: Multimed [141].
- Multi-channel stimulation: The stimulator needs to be multi-channel, to drive not only diaphragm pacing, but also intercostal muscles and abdominals, in order to restore the most natural and efficient breathing movement.
- Biphasic current pulse modulation: Modulation of the stimulus pulse train allows fine muscular control by being able to elicit a desired muscle activation profile [49, 55]. A few multi-channel systems allow pulse-width modulation of the stimulus parameters [52, 53] or burst parameters modulation [54], and a very few allow envelope modulation and timing modulation [55].
- High level of configurability and user interface: In order to investigate and assess the efficacy and safety of new stimulation protocols, the stimulation system should be highly configurable, preferably using a user-friendly interface for biologists and physiologists. To assess complex stimulation schemes, stimulators have to be tunable and programmable, controlled by computers or embedded digital electronics [55–58]. Also, a user-centered interface is important, as the stimulation functionalities tend to be more complex and diverse [55].
- Safety: Charge balancing of each stimulus and emergency shutdown of the stimulation are necessary in order to safely use Multistim for in vivo stimulation.



Figure 3.4: Overview of the stimulator architecture, presenting the main parts involved in control and generation of the stimulus



Figure 3.5: The stimulator: on the left: output connectors for electrodes, center: the ASIC, on the right: FPGA circuits, top-right: micro-usb connector for computer interfacing

### 3.3.2 Overview of the stimulation system

The core elements of the system are a the SONIC full-custom integrated circuit, built with 8 ESC from SHIVA's design, and an FPGA-based digital design (depicted in figures 3.4 and 3.5). The analog part of the system generates the current pulses according to the stimulation manager within the FPGA. Eight independently controllable stimulation channels are available. For each of the 8 channels, the system allows single-spike stimulation, continuous stimulation, burst-mode stimulation and continuous burst mode stimulation (infinite burst-shaped stimulation) (figure 2.6). All parameters describing these 3 modes can be tuned in real time. Timing parameters have a resolution of 20 µs and amplitude parameters are set as multiple of 4 µA. The stimulator has an output voltage swing of  $\pm 18.8$  V with up to 1 mAcurrent amplitude. Channels can be programmed and triggered using either a user-friendly interface, or a digital input on the electronic board. The stimulator interfaces with a computer using an USB port.

For safety concerns and to guarantee charge balancing [17], amplitude and timing parameters related to cathodic phase and anodic phase can be updated only between two biphasic pulses (during 'Interpulse Timing' and 'Interburst Timing' (figure 3.6)) or when the stimulation is off.



**Figure 3.6:** (a) Burst mode parameters – On this example, each burst is composed of three elementary stimuli (b) Stimulus Parameters. PW: Pulse Width, An : anodic, Cath: cathodic

#### 3.3.3 Analog circuits

The analog part of the system is responsible for translating the FPGA commands into stimulation currents, as shown in figure 3.7(a). It is composed of an 8-bit DAC, 8 voltage-to-current converters and the ASIC SONIC.

The ASIC SONIC (StimulatiON Integrated Circuit) was designed using the Cadence  $\bigcirc$  CAD suite and fabricated with AMS HVCMOS 0.35 µm (High-Voltage CMOS) process. It corresponds to the validated part of the previous SHIVA IC (see paragraph 3.2.3). SONIC provides biphasic current stimuli that respect charge balancing, on 8 independent ESC. Each ESC takes a current as an input, with two digital commutation orders that can be either anodic (for positive current stimulation) or cathodic (for negative current stimulation) and transforms a low-voltage compliant stimulus into a high-voltage compliant one (figure 3.7(b)). This multi-channel architecture can adapt to a wide variety of electrodes and loads with  $\pm 18.8$  V compliance.

Each input current to the ASIC is generated by a Digital to Analog Converter (DAC) and a Voltage to Current Converter (V2C), that are driven by the digital controller implemented on the FPGA. The DAC and V2C were designed with commercial components. The 8-channel DAC (LTC1665) has been chosen with the following specifications: 8 channels, and a SPI communication port to lower the amount of IOs needed on the FPGA board. The DAC presents an integral non-linearity of  $\pm 0.2$  LSB and a differential non-linearity of  $\pm 0.1$  LSB. The V2C generates the 8 currents needed on the low voltage SONIC inputs; its architecture, based on an active cascode configuration (3.7(a), generates the absolute value of the current stimulus injected in SONIC.



Figure 3.7: (a) Analog part of the design and schematic of the Voltage to Current converter. The DAC outputs 8 voltages, V(0) to V(7), which are converted to stimulation currents, and then made high-voltage compliant through SONIC. Commutations of the stimulation channels are controlled using two 8-bit buses, *Cathodic orders* and *Anodic orders*. (b) Schematic view of an Elementary Stimulation Channel (ESC) on SONIC.

### 3.3.4 SONIC

#### SONIC chip

SONIC was designed using the Cadence  $\bigcirc$  CAD suite and fabricated with AMS 0.35 µm HVCMOS (High-Voltage CMOS) process. The chip presents a surface area of  $3.9 \text{ mm}^2$  (figure 3.8(a)). It consists in eight stimulation channels with the same structure as the Elementary Stimulation Channels from SHIVA, presented on figure 3.3. 20 chips have been fabricated, and 3 have been packaged (QFP100) (figure 3.8(b)).

#### SONIC electrical characterization

All stimulation channels from those 3 packaged chips have been characterized and tested using a Keithley 6487 pico-ammeter and voltage source. The test setup is presented on figure 3.9.

The output voltage ranges from -18.8 V to 18.8 V for a HV supply of 20 V. ESC static current consumption is kept below  $10\,\mu\text{A}$ , which could be further optimized. The equivalent output resistance is in the  $10\,\text{M}\Omega$  range (15.1 M $\Omega$  for anodic branch and  $15\,\text{M}\Omega$  for cathodic branch). These two characteristics confirm that the ESC is compatible with electrodes having an impedance in the M $\Omega$  range. ESCs have been tested up to 1 mA. A maximum dispersion of 1.7% on the current output can be observed for the cathodic branch, and a 2.0% error on the ESC current gain between the anodic and cathodic branches; this gain difference is stable between the channels of a given chip and between the different measured chips. This difference, although small, cannot be neglected for charge balancing; it is corrected in the software generating the numerical values for the anodic and cathodic currents and timings.



Figure 3.8: (a) SONIC die micro-photography: the 8 ESCs can be distinguished in the core, the 12 HV pads in the bottom pad row: 8 for the ESCs outputs and 4 for the  $\pm 20$  V and  $\pm 16.7$  V supply pads, the 8 left LV pads correspond to the Anodic Control inputs and the 8 right ones to the Cathodic Control inputs; in the top pad row are located the 8 Current inputs, the LV supply pads (+3.3 V ; gnd) and a last control pad that returns a logic signal at '1' when one ESC at least is active; (b) Packaged SONIC – QFP100



**Figure 3.9:** Test setup– Left: An ESC among 8 in SONIC; Right: Keithley 6487 picoammeter



**Figure 3.10:** Measurements on 24 ESC (3 different chips). (a) Static transfer characteristics and (b) Static output characteristics.



**Figure 3.11:** Digital circuits implemented on the FPGA. The stimulator can be controlled either using a computer (USB interface) or a digital device (Direct input). The FTDI circuit converts USB frames into UART protocol. Direct input allows direct control of the stimulator using another digital device bypassing the microprocessor, which enhances real-time capabilities.

Table 3.1: Resources used by Multistim controller on a Xilinx Spartan 6 FPGA

	used	% of the FPGA
IO utilization	62	18%
Number of Slice Registers	6960	5%
Number of Slice LUTs	9824	15%
Number of Block RAM used	18	13%

### 3.3.5 Digital Controller

The system controller (figure 3.11) is implemented on a Xilinx Spartan 6 FPGA, clocked at 100 MHz. It consists of an 8-bit softcore microprocessor and a stimulation controller. The microprocessor performs the control of the stimulation parameters flow towards the stimulation controller through a USB interface. It has been developed by the ELIBIO team to be integrated within most of their FPGA-based projects. It can access the flash memory associated with the FPGA, allowing its reconfiguration without using a specific programmer (JTAG). This feature is particularly interesting when an update of the system need to be done remotely, or with a reduced amount of equipment. The design, synthesized using Xilinx ISE suite 14.7, uses a limited amount of resources on the *Spartan 6* FPGA, detailed in table

reftbl:ressFPGA. The maximum operating frequency for this design is 165.839 MHz.

Our design strategy for Multistim controller was to optimize area, in order to prepare for an integrated version of the stimulation controller using digital synthesis.

Therefore, the stimulation channels are sharing a common architecture for stimulus control. A sequencer manages resource allocation through time for each stimulation chan-



Figure 3.12: Timing management strategy on Multistim

nel, with a time slot of  $2.5 \,\mu\text{s}$  per channel, resulting in a minimal time step of  $20 \,\mu\text{s}$  for the whole system. The sequencer outputs a flag to announce a new channel, and the channel number being computed (figure 3.12).

Stimulation parameters for all the channels are stored in a local memory managed by the Signal Management module. This gives an input for the Stimulation State Controller, which computes the timings and transitions for each channel during its time slot. It is achieved using 2 Finite State Machines (FSMs): the Master FSM (figure 3.13(a)) updates stimulation parameters, according to the stimulation state of the channel defined by the Stimulus FSM (figure 3.13(b)).

Each commutation and amplitude order is then achieved by sending digitals commands to the ASIC SONIC and to the serial DAC.

In order to guarantee real time control of stimulation within a closed-loop stimulation paradigm, the microprocessor can be bypassed and each channel can be controlled using the *external trigger bus* and the *closed-loop input* of the system. Those two ports make low-level digital configuration of the hardware possible. They can be connected to a digital device such as another processor or a Spiking Neural Network. This guarantees the best timing when stimulation is not being controlled by a computer USB/serial interface, as the stimulation parameters can be updated directly from a digital controller who accesses the system memory.

### 3.3.6 Software

A multi-platform Graphical User Interface (GUI) presented on figure 3.14 has been developed in Python language with an Application Programming Interface (API). The host computer controls the stimulator using a proprietary protocol, through a USB to Serial interface at 115.200 bps. The GUI gives access to all stimulation parameters presented in figure 3.6 and to the polarity of each stimulation channel: cathodic first or anodic first. The user can also save and recall stimulation configurations for each channel. In order to have more complex stimulation schemes, 4 groups of synchronized channels can be defined. Gain difference 3.3.4 between cathodic and anodic channels can be minimized within the software code. Finally, the user can choose to enable the closed-loop feature of the stimulator in order to give control of the stimulator to another peripheral if needed. The API is designed to permit complex control figures for the stimulator, like frequency or amplitude modulation.



**Figure 3.13:** Finite State Machines used to control stimulation on Multistim. (a) *Master* FSM in charge of triggering actions to a specific channel according to the *Stimulus FSM* (b)

Channel 0	Channel 1	Channel 3	Channel	ch.	a contra	Channel E	Channel 6	01
Chennel 0	Channel 1	Channel 2	Channel J	Che	nnel 4	Channel 5	Channel o	0
Delay		0 🗘 us			P	olarity		
Cathodic curre	ent	0,000 🔹 mA				Cathodic F	first	
Cathodic Pulse Width		20	\$	us			Anodic Fin	st
Interphase Width		0	\$	us F			File Management	
Anodic Current		0,000	٥	mA		[	Save Config	uration
Anodic Pulse 1	Midth	20	٥	us		1	Open Config	uration
Frequency Pulse		0,1	٥	Hz			loss i oso Ma	
Blanking Widt	h	20	4 10	us			Crose coop Management	
Amount of pul	lses per burst	1	\$	pulses/burst			0 micro sec	
Amount of Bu	rsts	1	\$	burst(s)				
Burst Frequen	cy	0,1	\$	Hz				
Interburst Tim	sing	20	(A) (T)	us				
send par	ameters	start	t stim					
	Channel 0	Channel 1	Channel 2 C	hannel 3	Channel 4	Channel 5	Channel 6	Channel
Start Group	L 🕅							
Start Group								
Start Group								
Start Group								
			Reset	System				
			Close Loop	Mode Ena	ibled			
		_	Close Loop	Mode Disi	bled		_	
		Se	end Amplitudes	(Close L	oop Only)			
		S	end TcathMax	(Close Lo	op Only)			

Figure 3.14: Multistim Graphical User Interface

### 3.4 Tests and in-vitro experiments

We present hereafter first experimental validations of Multistim, either on a resistive load or on a series of stimulation electrodes in a a phosphate-buffered saline solution (PBS). In vivo experiments related to the CENAVEX project are presented further in chapter 5. The current section demonstrates that Multistim can adapt to a variety of electrodes, with different current requirements. It also proves Multistim's ability to deliver biphasic current pulses with automated amplitude modulation.

### 3.4.1 In-vitro experiments

In collaboration with biologists and physicists, we were able to use our stimulation system in a variety of experimental protocols that can take advantage of an ESC-based stimulation system. Results from the biology point-of-view are not discussed, but are referenced when available. The context and scientific objectives of each project have also been summarized in chapter 1. For each experiment, we present the voltage measured on the stimulation electrode in response to a given stimulation current.

In a first experiment, the system was configured to deliver a multi-channel stimulation current to a penetrating electrode-array for ex vivo rodent spinal cord stimulation, used for the Hyrene project detailed in the first chapter of this manuscript [19]. In this 4x8 multishank array, the electrodes have a 30 µm diameter, with inter-electrode spacing of 100 µm, and hence a contact area of  $7 \times 10^{-4}$  mm<sup>2</sup> (figure 3.15, left). The electrodes are surrounded by a common ground surface used as current return path. Figure 3.15 shows the output current and voltage of one channel. The cathodic current level ranges from 50 µA to 250 µA;



Figure 3.15: Electrode voltage measurements with stimulation performed with one ESC among 8, on a penetrating micro-electrode-array, for different current levels. The left pictogram represents the microelectrode array geometry and electrical connection to one of the 8 ESCs

the cathodic pulse duration is 60 µs and the inter-pulse delay 20 µs. The charge balancing constraint imposes an anodic amplitude five time smaller than the cathodic amplitude. For this test, the electrode-array was placed in a phosphate-buffered saline solution (PBS). The different current levels were successfully generated by the ASIC, with negligible rising times; the measured voltage follows the expected shape that can be fitted by a RC-like model.

In a second experiment, three ESCs were ganged to deliver stimulation to a custom macro-electrode that was used for rodent DBS [142]: a needle-like two-wire electrode of twisted tungsten (figure 3.16, left). The wire section, with a 200 µm diameter, is used as the stimulation pole. The current return path is managed by a long wrap (2 mm) of the second wire. For bilateral DBS stimulation, two electrodes are mounted, in parallel, on a custom-made Printed Circuit Board. The total contact area is thus  $6 \times 10^{-2}$  mm<sup>2</sup>. In this experiment, the cathodic and anodic current levels are both set at 2.4 mA, and obtained by ganging three ESCs. Each ESC delivers a 0.8 µA symmetrical biphasic pulse, with a cathodic timing of 500 µs and an inter-pulse delay of 100 µs. The ganged configuration and ESCs parameters values are defined using the Multistim GUI. Figure 3.16 shows the stimulation pulse and the voltage response across the electrode, immersed in PBS.

In a third experiment, the system was configured to enable a more complex combination adapted to current steering. A commercial quadri-polar macro-electrode typically used for human deep brain stimulation (Medtronic 3387 lead) was connected to our system. In this case, three ESCs were programmed. Each of the four cylindrical electrodes has a diameter of 1.27 mm and a length of 1.5 mm, corresponding to a contact area of  $6 \text{ mm}^2$  (see figure



Figure 3.16: Measurements performed in the *Ganged-mode* configuration, on a macroelectrode used for DBS rodent experiments. The left pictogram represents a schematic view of the electrode and the three ESCs combined; metallic parts are colored in pink. Tungsten part is built from tungsten Wire .008 Bare, .0110 Coated, Phymep, France.

3.17, left). Contact #2 receives the original stimulation pattern consisting in a 240 µA symmetric biphasic stimulus. Contact #1 (end of the needle) receives a stimulus with the quarter of the amplitude, contact #4 receives the inverted stimulation pattern and contact #3 is used as a current return pole directly connected to the ground potential. The combination of the ESCs and channel inversion were performed using the Multistim GUI. Figure 3.17 presents the electrode voltage measurement and the stimulation currents.

### 3.4.2 Generation of complex stimulation waveforms

This last test was performed for the needs of CENAVEX project, in which the protocols involves complex shaping of the stimulation signal with on-line stimulation parameters modification. In vivo closed-loop experiments of CENAVEX project will be discussed in the last chapter of this manuscript, chapter 5; in this section we test the ability of Multistim to deliver biphasic current pulses with on line amplitude control, through the USB port. To obtain the measurements presented on figure 3.18, the stimulator was connected to a resistive load of  $10 \,\mathrm{k}\Omega$  which voltage is used as a feedback control to close the loop. More specifically, we used the envelope detector from an adaptive Pattern-Generator/Pattern Shaper (PG/PS) controller developed originally to adapt stimulation parameters to metabolic needs [143] in CENAVEX; for the test we connected it to the resistive load voltage instead of connecting it to the breath volume sensor. Multistim was configured to deliver gaussian-shaped bursts, that allow smooth recruitment of muscle fibers. As shown on figure 2.18, this test was successful and Multistim delivered a Gaussian-



Figure 3.17: Measurements performed in the Current-steering-mode configuration, on a quadri-polar macro-electrode; in blue, current quantities over pad #2 of a Medtronic 3387; red plots relate to pad #1, blue plots related to pad #2, violet plots relate to pad #4; voltages are measured with pad #3 as a reference for current return. On the left: schematic view of the electrode setup.


**Figure 3.18:** a) The stimulation envelope follows the adaptive controlling signal over extended periods of time. (b) The gaussian stimulation pattern is composed of bursts with cathodic/anodic pulses, interpulse and frequency respectively set to 200 µs, 40 µs and 75 Hz.

shaped train of bursts with smooth increased amplitude, to reach a target value.

# 3.5 Multistim limitations

Multistim is an operational system, yet it can be improved on several aspects described hereafter. System integration can be optimized: the stimulator specifications have changed since the initial design, and additional PCB boards were necessary in order to allow those evolutions. The result is a stack of 4 boards that could be integrated in one. Some peripherals that can facilitate the experiments have been added to the system: two ADC PCB board for direct connection to sensors, and a SD card slot for data storage. Those peripherals are not yet supported by the firmware on the FPGA. The GUI can be improved for easier control of the stimulation device and its various configurations, including closed-loop management. It could also include a log, in order to generate an automatic report describing the stimulation setup and the stimulation parameters updates during the experiment.,

# 3.6 Conclusion

We have presented Multistim, a versatile stimulation platform with open and closed-loop capabilities, and the ability to perform real-time stimulation parameters management. This IC-based stimulator provides current stimulation with a high output voltage swing and is adapted to the investigation of complex stimulation schemes with up to eight independent channels. It was successfully validated in preliminary FES experiments (results in chapter 5). Multistim is the first multi-application, user-oriented and fully validated stimulation platform of the team ELIBIO, which can be productively used for future experiments.

# Chapter 4

# TWIST, a multi-application stimulation system with arbitrary waveform generation

# 4.1 Introduction

The previous chapter was dedicated to Multistim, a fully configurable stimulation system, based on an 8-channel ASIC (SHIVA) with high-voltage compliance and real-time operation capabilities, equipped with a graphical user interface. The design of Multistim as a multi-application device has been successful on many aspects. It has been validated on various in-vitro experiments (chapter 3) and extensively used for in-vivo experiments of rat ventilator muscles stimulation (chapters 3 and 5). In the next sections, we however draw structural limitations and new application needs that guided the design of a second stimulation system, named TWIST.

# 4.1.1 From Elementary Stimulation Channels to fully programmable Stimulation IPs

Figure 4.1 presents the system architecture of Multistim as detailed chapter 3, compared with the system architecture of TWIST. The main difference between those systems is the digital control of the stimulation. A shared architecture is used in Multistim, while a parallel one is used in TWIST.

Multistim featured 8 Elementary Stimulation Channels (ESCs) which shared a common controller, and a unique 8-channel serial Digital to Analog Converter (DAC). With such an architecture, Multistim was indeed optimized for applications using 8 channels. If a fewer number of channels is needed, the timing performances cannot be better as each channel is processed after the other, regardless if it is used or not. Moreover, this architecture is not totally flexible, being optimized for 8 channels, and scaling the number of channels implies modifying the Register Transfer Level (RTL) description of the controller (chapter 3.3.5). If the number of channels driven by Multistim was to be increased for a new application, the minimum *Timestep* of the digital controller would be increased, as more channels would have to be processed. In other terms, Multistim initiated an IP-based architecture, for a multi-application context, but the IP level was located at the analog front-end stage and based on the ESCs, implemented on SONIC chip. This concept could not be extended to





**Figure 4.1:** (a) Multistim architecture, (b) TWIST architecture. In blue, digital circuits implemented on a FPGA, in green off-the-shelf components for digital to current conversion (DAC: Digital to Analog Converter, V2C: Voltage to Current converter), in orange Elementary Stimulation Channels (ESCs). Two kind of peripherals can be used to control each stimulation device: either a computer through a USB interface or a digital circuit that can be plugged to parallel or serial ports available on the system.

the digital design in Multistim because of PCB-level limitations (serial multichannel DAC) that has been built before the design of the stimulation controller.

Re-using the ESC blocks implemented on an HV ASIC, for the next stimulation device I decided to extend the concept of 'Stimulation IP' to the digital controller part, to really allow design reuse and fast implementation of the controller. Figure 4.1 highlights the architectural differences between Multistim and TWIST: the Stimulation IPs in TWIST are no longer limited to the ESCs alone, but are extended to the digital controller, now called 'Stimulation Processor', for reasons that will be detailed in the following. The result is a mixed-signal Stimulation IP that allow design reuse, fast development of multichannel devices and versatility of the stimulation.

The whole system architecture will be detailed in paragraphs 4.3 and 4.4.

Besides this objective of an extended versatility of the stimulation device, based on a mixed analog-digital stimulation IP, two main areas of research were taken into account to add new features to the final system.

#### 4.1.2 Need for in situ electrical impedance monitoring

It has been shown [119] that implantation of a stimulation device induces an immediate and sustained inflammatory response, mainly manifested by fibrosis (in muscles) or gliosis (in the brain). At the level of implanted electrodes, this response tends to increase the loading impedance of the stimulator [23] which results in a higher stimulation threshold and then in a shorter lifetime for the embedded battery. In the context of recent miniaturized lead-less pacemakers [144], the limitation of electrical power consumption is crucial. From another prospective, some medical complications require the removal of the implanted electrodes and fibrotic attachments are an obstacle to safe extraction [145].

Hence, we propose to contribute to long-term efficiency of implanted stimulation devices by characterizing the evolution through time of electrode-tissue impedance. Furthermore, a systematic characterization of implant-induced reaction would allow testing new biocompatibility solutions for electrodes, as well as providing information to practitioners in order to fine-tune stimulation parameters.

This objective requires firstly to include in the stimulator the adequate circuits to monitor the electrode voltage, corresponding to a given stimulation current: a new ASIC has been designed that will be described in paragraph 4.2. Secondly, for an exploration of impedance spectral behavior, the proper pre- or post-processing computation algorithm should be studied.

#### 4.1.3 Need for new waveforms for neurostimulation

A second trend that was taken into account is the exploration of new stimulation waveforms. As developed in the chapter 2, recent works suggest that the traditional rectangular waveform might not be the most efficient in terms of energy consumption, for a given physiological effect. However, despite numerous simulations performed on tissues and neurons models and exploring the effect and efficiency of the stimulation waveform [27, 146], few in-vivo or in-vitro experiments have been conducted.

We then propose to take benefit from the new architectural objective (paragraph 4.1.1) to include this feature of arbitrary waveform generation in the second stimulation system.

Moreover, the exploration of the stimulus shape has an interest for the impedance spectroscopy characterization evoked previously, the question being which stimulus waveform can provide the best spectrum for impedance identification.

# 4.2 SPICY: A stimulation IC with electrode voltage measurement capability

# 4.2.1 Design specifications for bio-impedance measurement

As described in chapter 2, bioimpedance measurements can be performed using multi-point techniques. We propose to add in-situ voltage monitoring to the chip implementing the ESCs, passing from SONIC (StimulatiON Integrated Circuit) to SPICY (Stimulation and Impedance measurement Circuit). Although the four-terminal measurement technique is the most directly informative on tissue properties, it might be incompatible with existing stimulation leads, often consisting in bipolar electrodes. In order to be compatible with different experimental setups, we decided to propose a circuit topology that enables two-, three- or four-terminal impedance measurement.

Before dealing with circuit and system design, one should keep in mind several constraints. Firstly, the electrode voltage can reach a high level, from -18 V to +18 V when delivering the stimulation current. Secondly, as mentioned in chapter 2, bio-impedance measurement could be interesting from 0 Hz to 1 MHz. According to the Nyquist criteria, our voltage measurement device should be able to acquire signal with a frequency greater than 2 MHz. Finally, high input impedance will be needed in order not to change the stimulation current. Considering these constraints, we decided to use an Operational Transconductance Amplifier (OTA) to monitor the electrode voltage and provide a proportional low-voltage compliant current. Afterwards, this output current can be digitized and processed by a low-voltage ADC. We decided not to implement an ADC directly on the chip, but rather to use off-the-shelf components, to avoid the clock noise that would interfere with the stimulation channels.

# 4.2.2 HV Operational Transconductance Amplifier

#### OTA design

An Operational Transconductance Amplifier (OTA) is an amplifier that converts a differential voltage input into a current with a transconductance gain Gm. It features a high input impedance that prevents the amplifier from influencing measured signals. As explained previously, the specificity of this OTA is that it must generate a LV-compliant current, proportional to the HV-compliant differential input voltage.

Figure 4.2 presents the architecture of the designed OTA. We decided to use a topology inspired by a degenerated sources differential long tail pair, as it provides a better linearity to OTA, compared to other architectures. Given the poor transconductance factor of HV-compliant transistors [136], we implemented a mixed architecture using HV-transistors only when needed, for the long-tail pair (M14-M15) and to protect the different voltage parts (M5, M12, and M13). For this prototype, we decided to keep off-chip the biasing current source Ibias and the gain resistor R, as it allows to tune the gain easily and reduce the silicon area if high resistance values are needed.



Figure 4.2: Architecture of the integrated OTA. M5 - M12 - M13 - M14 and M15 are HV compliant transistors. The others are LV compliant classic transistors from AMS  $0.35 \,\mu\text{mLVCMOS}$  design kit



Figure 4.3: Simulation setup for the designed OTA

#### OTA simulated performances

We performed electrical simulations of the OTAs before layout, using Cadence Suite, in order to verify their functionality and performances. Post-layout simulation could not be achieved, in the absence of the adequate software license in our lab. The schematic used for simulation is presented in figure 4.3. We used a biasing current source Ibias =  $10 \,\mu\text{A}$  and a gain resistor  $R = 5 \,M\Omega$  for these simulations.

AC simulations have been performed and Bode diagram results are presented in figure 4.4. The simulated OTA presents an input impedance in the tens of M $\Omega$  range, with a capacitive component of 62 fF, its bandpass at -3dB is 43MHz. Transient simulation shown an input dynamic range of 38 V peak to peak.

# 4.2.3 Integrated Circuit architecture

SpICy stands for Stimulation and Impedance Circuit. SPICY is composed of eight independent ESCs (Elementary Stimulation Channels, copy of the blocks integrated in SONIC IC) and three Operational Transconductance Amplifiers. Three OTAs have been placed on SPICY, in order to permit multi-point impedance measurement, as depicted in figure 4.5.

# 4.2.4 Fabricated chip

As for the SONIC chip, SPICY chip requires five different voltages for power supply:  $\pm 20$  V,  $\pm 16.7$  V and 3.3 V. In order to optimize stimulation platforms developed for the team, we made SPICY footprint compatible with SONIC's one, that makes them interchangeable for different stimulation projects. SPICY has been designed using the Cadence Suite and the design kit AMS HVCMOS AMS 0.35 µm. It presents a surface of 4.78 mm<sup>2</sup>. A microphotography of the fabricated chip picture is shown in figure 4.6.

# 4.2.5 Test, troubleshooting and perspectives

We performed tests of SPICY chip using a dedicated PCB Board presented figure 4.7. It is composed of a FPGA board (Digilent CMOD A7, hosting a Xilinx Spartan 6 FPGA),



Figure 4.4: Bode diagram of the simulated OTA

a Digital to current Converter (DAC followed by V2C) to provide current inputs to the ESCs, power supplies, and current sources for OTA biasing.

All the ESCs have been tested and characterized using the setup already used for SONIC characterization (figure 3.9), composed of a Keithley 6487 pico-ammeter and voltage source. We tested each ESC using the same setup as for SONIC's ESCs, as detailed figure 4.8. For each chip, there are 7 functional ESCs among the 8 and they present the same transfer and output characteristics as the ESCs integrated on SONIC chip: this is summarized in figure 4.9(a). For each chip, the ESC connected to the 2-terminal measurement setup is not functional. When a load is connected to its output, the current sources are not stable. This can be seen on the output characteristics depicted in figure 4.9(b). Hence, SPICY chips could be used as a 7-ESCs chip.

OTAs have been tested using the setup presented in figure 4.10. It appears that OTAs are not functional. The biasing current and the gain resistor have no effect on the output signal. With its inputs grounded, the output current is not equal to the expected static current.

Figure 4.11 is presented here for documentation purpose only. We injected a 3 V peakto-peak input voltage, with a frequency varying from 1Hz to 10MHz. When the input signal is larger than 3.8V peak-to-peak, the output signal appears distorted. This is illustrated in figure 4.12, with a voltage input of 15V peak-to-peak.

None of the three OTAs of the three chips tested are exploitable. Unfortunately, we could not perform any post-layout and full chip simulations before foundry, but they could help us to further investigate the problem and find a solution. It is not advisable to use SPICY as a stimulation circuit, despite the fact that most of the ESCs are functional, as the OTAs are heating-up the chip, which could damage it during a long experiment. In depth analysis of the layout files should be performed in order to understand why we experienced the issues presented above. Sadly, I did not have time to focus on that during



**Figure 4.5:** SPICY chip architecture. From left to right: ESC with two terminal measurement capability, ESC with four-terminal measurement capability, ESC with three-terminal measurement capability, 5 ESCs with no impedance measurement capability. All the ESCs implemented on the chip share a common ground for stimulation current return



**Figure 4.6:** Micro-photography of SPICY chip; with 8 ESCs and three OTAs, the die area of4.78 mm<sup>2</sup>. The full description of input/output pins and bonding to QFP100 package is given in Appendix B.



Figure 4.7: Setup used to test SPICY ESCs and OTAs. A small FPGA is used to control and generates commutation orders, a QFP100 socket is used to connect SPICY chips to the system, inputs and outputs of each OTA are accessible and 3 tunable current sources provide biasing current to each OTA. A 'resistor scale' is used to create a precise tuning of bandwidth and gain of the OTA.



Figure 4.8: Test-setup for SPICY's ESCs. To the left: one ESC among 8 of SPICY chip, to the right: a Keithley 6487 picoammeter with its controlled voltage source. Input applied current varies from 0A to  $200 \,\mu\text{A}$ 



**Figure 4.9:** (a) Output characteristic of a functional ESC. Anodic and cathodic currents are respectively plotted in blue and red (b) output characteristic of one ESC connected to the 2-terminal impedance measurement setup



Figure 4.10: OTA Test setup, with a gain resistance R of  $5 M\Omega$ , a bias current Ibias of  $10 \,\mu\text{A}$  and a load resistance of  $100 \,k\Omega$ .



Figure 4.11: Example of AC transconductance behavior of one four-terminal measurement OTA



**Figure 4.12:** 4-terminal measurement OTA output current, when a 15V peak-to-peak, 15kHz sinusoidal voltage input

my time in the laboratory.

In order to lower the costs, and reduce the risks in case a circuit was not functional, we decided to fabricate two ICs in the same run: SONIC, a first prototype with only ESCs, and SPICY, a second prototype that included the voltage measurement circuitry to the ESCs. Fortunately, SONIC chip was fully functional, with robust characteristics, as presented in Chapter 3. In the following paragraphs, we present the new digital architecture developed to control the analog integrated ESCs.

# 4.3 A versatile digital stimulation controller with arbitrary waveform capability

To explore new stimulus waveforms impact on in-vivo stimulation experiments, we had to design a new kind of stimulation controller. The way we used Multistim consisted in programming about 10 pre-defined parameters for a squared biphasic waveform. For arbitrary waveform, one needs more flexibility, hence a different way to define the waveform and a different digital architecture for the controller. My idea was that the user should be able to choose the waveform he wants to use and send it to the stimulation device, hence program the stimulator. A waveform can be described as a set of timing/amplitude coordinates. For stimulation devices, this is not enough, we need to add information such as whether the user want to do single-spike stimulation, continuous stimulation, burstmode stimulation, continuous burst-mode stimulation (infinite burst-shaped stimulation) or even use an external trigger. I developed the concept of programming the stimulation device with a given waveform and ended up with the idea that given the fact that we should add some specific information to the timing/amplitude coordinates in order to build a Stimulation Program, with its corresponding Stimulation Processor. This stimulation program would consist in a set of instructions, built by the user, in order to describe the wanted stimulation waveform. We had to comply to commercially available DAC, and to PCB design constraints in order to choose the minimal time step for our stimulus. The shorter the timing definition of the stimulus, the faster the DAC needs to be, implying also a more sensitive PCB design regarding signal routing. Considering those points, in accordance with the team engineer, we chose to give the system a minimal time step of 1 µs. Amplitude is to be encoded on 8-bits, with 1 mA maximum amplitude, a higher level of current being achievable by ganging two or more ESCs.

Let us focus on the encoding of the information that describes the stimulus, before going deeper in the digital architecture.

# 4.3.1 The stimulation program

As described before, the stimulation program consists in a set of instructions describing each stimulation pulse using three parameters: step duration, sign of the stimulus (cathodic or anodic), and amplitude. Additional instructions are added to use inputs such as triggers or to perform branch structures. The instruction set is composed of fixed-size 32-bit instructions, the four upper bits of which representing the operation code itself: 'OPCODE' (table 4.1). This operation code specifies the operation to be performed with a given instruction and the meaning of the following bits. Its 4-bit width allows up to sixteen different instructions.

OPCODE	Operation
"0000"	Stimulation instruction
"0001"	Goto instruction
"0010"	Trigger instruction
from "0011" to "1111"	Not used

 Table 4.1: OPCODE parameters

So far, only three instructions type have been implemented, leaving free space to new functions as the requirements for the stimulation device may evolve with the team projects.

#### Stimulation instruction

We designed the stimulation instruction as presented table 4.2. It is composed of 5 parameters. The 'Stim Opcode' header identifies the instruction as a stimulation instruction, the sign bit indicates if the phase is cathodic (sign = '1') or anodic (sign = '0'). The 'Pulse Width' section represents the amount of time step (according to the 'Scale') that determine the length of the pulse being generated and the amplitude

 Table 4.2:
 Stimulation instruction structure

4 bits	3  bits	1  bit	16  bits	8  bits
Stim Opcode	Scale	Sign	Pulse Width	Amplitude

The stimulation instruction features an additional 'Scale' section which permits to make the minimal time step longer, based on predefined values as presented table 4.3. This allows to save instruction memory if a long pulse is required for a given stimulation pattern.

#### Table 4.3: Scale information

Scale	Time Step
"000"	$1\mu s$ (default)
"001"	$500\mu s$
"010"	$1\mathrm{ms}$
"011"	$10\mathrm{ms}$

#### Goto instruction

The Goto instruction's structure is as follow:

 Table 4.4:
 Goto instruction structure

4 bits	20 bits	8 bits
Go To Opcode	Not used	Go to address

This instruction changes the next instruction to be executed by the stimulation processor to the one detailed in the "Go to address" section of the instruction.



Figure 4.13: Stimulation Processor architecture

**Trigger** instruction

 Table 4.5:
 Trigger instruction structure

4 bits	28 bits
Trigger Opcode	Not used

The trigger instruction puts the stimulation channel controller in an idle state, waiting for an external trigger to be enabled and then carries on with the next instructions of the program. This description of the stimulation program is then uploaded into the Stimulation Processor which is detailed in the next section.

# 4.3.2 The Stimulation Processor

This section will detail the design of the Stimulation Processor. Our aim was to enable the user to choose the current stimulation waveform, for optimizing its efficacy or performing impedance spectroscopy. The waveform program memory on the stimulation device is limited to 256 instructions at first, and can be extended if needed. The minimal chosen time step is 1 µs. The idea behind the Stimulation Processor is to create a single IP that can be duplicated easily to allow the fast development of massive multichannel controller. Also, combined with the Elementary Stimulation Channel (its analog counterpart), it becomes possible to design new generations of stimulation devices very quickly. Its architecture should be simple, flexible and easily improved with new functionalities and 'OPCODES'. The custom Stimulation Processor is built with a Von Neumann-like architecture (figure 4.13), executing the program describing the user-defined stimulation waveform as presented in the previous section.



Figure 4.14: Finite State Machine of the *Program Counter Manager*. Process units are enabled during the *idle state* (in blue)

Figure 4.13 presents the Stimulation Processor IP architecture. It can be interfaced with any digital system featuring an 8-bit address/data access (CPU IN and CPU OUT on the figure). The stimulation controller can be duplicated within a design as many times as needed, to match the number of channels needed for a given application. They can be synchronized between each other with appropriate control, so complex stimulation schemes can be achieved, such as current steering, merged channels, etc. A Program *Counter Manager* module has been implemented in order to cadence the system, and is built in order to extract each instruction. It reads the instruction in the program memory and outputs it on a shared *Instruction bus*, between peripherals in charge of executing a given instruction. To improve the system flexibility, a specific process unit is given to each kind of instruction. This specificity allows quick adding of functions. As an example, stimulation instructions are executed by the module Stimulation Process Unit. Each process unit is connected to the Program Counter Manager through its instruction bus and an 'instruction ready' flag from the Program Counter Manager that indicates when the instruction is ready. Once execution of the instruction is done, the concerned process unit outputs a fetch signal to the *Program Counter Manager*. The precise behavior of the program counter is presented on figure 4.14, through its finite state machine.

The *Stimulation Processor* circuit is ready for ASIC synthesis in its current version. Only a clock gating option should be added at the clock input in order to reduce energy consumption when channel is turned off.

# 4.4 System Integration

The full stimulation system, termed TWIST (arbiTrary Waveform STimulation system), is composed of a SONIC integrated circuit (8 ESCs), a Xilinx Artix 7 FPGA, power-supplies



Figure 4.15: System-level architecture on TWIST PCB. In blue, digital circuits implemented on a FPGA, in green off-the-shelf components for digital to current conversion (DAC: Digital to Analog Converter, V2C: Voltage to Current converter), in orange Elementary Stimulation Channels (ESCs). Two kind of peripherals can be used to control each stimulation device: either a computer through a USB interface or a digital circuit that can be plugged to parallel or serial ports available on the system. An FTDI circuit converts USB data into UART protocol for the 8-bit RISC.

and discrete components to provide low-voltage stimulation current needed for SONIC, as presented figure 4.15. In order to facilitate the development of the system, we decided to use a commercially available FPGA board (Neso, Numato Labs Company) to host the digital part of the architecture. For the ESCs, we chose to interface SONIC through a QFP100 socket in order to be able to quickly change the chip in case of a failure. On the FPGA, in order to facilitate the communication from external peripherals (computer, digital circuits, etc.) to *Stimulation Processors*, we implemented an 8-bits softcore RISC processor. This RISC processor has been developed by Yannick Bornat, and is used is most of the FPGA-based projects of the team.

# 4.4.1 Digital Architecture

The digital architecture implemented in TWIST FPGA is as described in figure 4.16.

Synthesis of the digital part of the design has been made using Xilinx Vivado Suite 2016.2. Table 4.6 presents the resources used by eight stimulation controllers, with a softcore 8-bit RISC processor to manage computer communications on a Xilinx Artix 7 FPGA. The maximum clock frequency of our design is 160.7 MHz, which is above our working frequency of 100MHz.

Table 4.6:         Resources used	by 8 digital stimul	lation controller,	and a custom s	softcore 8-bit
microprocessor on a Xilinx	Artix 7 FPGA			

	Used	% Utilization
Slice LUT	1258	1.98
Flip Flop	1250	0.99
Block RAM	17	12.59
Bonded IOB	108	51.43



**Figure 4.16:** Digital architecture implemented on TWIST FPGA: a FTDI circuit converts USB frames to UART which is then used by an 8-bit softcore microprocessor. The purpose of this micro-processor is to manage communications between digital inputs (from computer or other peripheral) and Stimulation Processor. 8 Stimulation Processors are implemented on the FPGA in order to manage the 8 ESCs of SONIC chip

# 4.4.2 Compiler

The stimulation program can be generated by a computer and then sent to the stimulator. We developed a compiler in Matlab in order to convert a user-defined waveform into a stimulation program that can be sent to the Stimulation Program Memory of a given Stimulation Channel Controller. First, the waveform should be described in a microsecond time base in order to be processed by the compiler: at first, amplitudes are discretized as multiples of  $4\,\mu\text{A}$  (1mA maximum amplitude, encoded on 8 bits). Then, the duration of each phase is computed, i.e. when two consecutive values are equals, the compiler builds up a larger step by summing up their duration. Once this is done, sign of the stimulus is encoded in order to have the cathodic/anodic information, and the amplitude information is made positive only. Stimulus information is then concatenated in a binary base. A scale vector is also created according to table 0.5. User can choose to use a trigger during the stimulation program, as well as create a jump instruction.

# 4.4.3 PCB Level

The first version of TWIST is presented below. Needed power supplies for the ESCs, the peripherals and the FPGA board are built on the PCB. Most of the board organization is schematized in figure 16 and a picture of the system is presented figure 4.17.

For faster development time, we chose to make the V2Cs from commercial components and bought also the DACs, hence, they are not yet embedded on integrated circuits. We chose single channel 8-bit DAC with a high bandwidth in order to have the smallest conver-



#### Figure 4.17: P

hotography of TWIST]Photography of TWIST. Power supplies and DAC are located on the left part of the board. To the right, the FPGA board and in the middle the QFP100 socket

sion time, to generate a signal from digital Stimulation Processor to the integrated circuit. We chose a AD5424 from Analog Device, with 1Msamples/s. The schematic combining the DAC and V2C is shown in figure 4.18.

# 4.5 Tests of the stimulation device

# 4.5.1 Static performances - Linearity

Our stimulation device can be considered as a current-mode DAC as it provides an analog current with a given digital input from the controller. Linearity of DACs is usually characterized by two parameters: Integral Non Linearity (INL) and Differential Non Linearity (DNL). Both have been computed from measurement done using a pico-ammeter Keithley 6487, while the system was loaded by a resistor of  $R=10 k\Omega$  as depicted in figure 4.19. In order to compare our work to the arbitrary stimulation circuit built by [28], we computed INL with respect to equation 4.1, and DNL is measured as the ration of the actual step size to the nominal step size (equation 4.2).

$$INL(n) = \frac{(I(n+1) - n * LSB)}{LSB}$$
 with  $LSB = \frac{I_{max} - I_0}{2^N}$  and  $N = 8$  (4.1)

$$DNL(n) = \frac{(I(n+1) - I(n))}{LSB} - 1$$
(4.2)

We measured the output current for both anodic and cathodic phases, using the setup described figure 4.19. Results are presented in figure 4.20(a) and 4.20(b). Our system



**Figure 4.18:** Digital to Current Converter architecture (DAC followed by Voltage to Current Converter) implemented on TWIST with off-the-shelf components



Figure 4.19: Test setup of TWIST. A Matlab interface is used to program a Ramp waveform, from -1mA to 0mA, and then from 0mA to 1mA in order to characterize both cathodic and anodic phase. Output current measurements are done using a Keithley 6487 picoammeter, on a  $10 \,\mathrm{k}\Omega$  load.

	This work	[28]
INL (LSB) – worst	4.4	3.11
DNL (LSB) - worst	0.8	2.15
Anodic/Cathodic mismatch (LSB) – worst	11.3	14.56
Maximum output current	$1\mathrm{mA}$	$0.4\mathrm{mA}$
Bits used to encode amplitude	8	8

Table 4.7: Comparison with similar research in the literature

 Table 4.8: Timing characterization of stimulation channels of TWIST

	Rising-time (0 to full scale)	Falling-time (Full scale to 0)
Anodic phase	1.6 µs	0.68 µs
Cathodic phase	1.59 µs	0.59 µs

presents a worst DNL of 0.8 LSB and a worst INL of 4.4 LSB, as presented on figures 4.20(c) to 4.20(f).

Figure 4.21 presents the mismatch between anodic and cathodic phase for each channel in terms of LSB. We can observe that the maximum mismatch is 11.3 LSB for channel 3 of the characterized chip. This would justify the use of a digital block in order to modify anodic amplitude codes in order to minimize the mismatch, hence have a better charge balancing.

Table 4.7 presents a comparison with [28]. The authors carried out similar work: they designed an arbitrary waveform stimulus circuit for visual prostheses.

Our performances on INL are of the same order, and on DNL are better. Regarding mismatch between anodic and cathodic channels are better in our application. This last parameter is the most important as it influences charge balancing and thus is strongly related to the safety of the stimulation.

# 4.5.2 Dynamic performances

We performed timing characterization of the Stimulation Channels IP, in anodic or cathodic stimulation mode. Results are summed-up in table 4.8.

Despite our  $1 \,\mu\text{s}$  precision in the digital controller, our system will be limited to a maximum frequency of  $625 \,\text{kHz}$  according to table 4.8.

# 4.6 Improvements

Improvements can be made on the mixed-signal Stimulation Channel IP and on the system (hardware) in order to make it more versatile and performant.



**Figure 4.20:** (a) Anodic output current vs. input code,(b) Cathodic output current vs. input code, (c) INL vs. input code for anodic phase, (d) INL vs. input code for cathodic phase, (e) DNL vs. input code for anodic phase, (f) DNL vs. input code for cathodic phase



Figure 4.21: Anodic/Cathodic mismatch

# 4.6.1 Stimulation Processor Improvements

# Loop Management

It would allow very complex stimulation waveforms with a reduced program memory size. Its development is pretty straightforward from the *GoTo process unit*. Nonetheless, it brings more complexity on the stimulation waveform compiler. In my opinion, it is the most important feature to add to the Stimulation Processor.

# Direct control of the stimulator

This process unit would bypass the *Program Counter Manager* and most of the Stimulation Processor by taking as inputs amplitude and commutation orders from an external controller. This module would be useful for testing and characterizing subsequent modules or to allow a direct closed-loop control of the circuits.

# Automated charge balancing for arbitrary waveforms

This process-unit would be enabled by a specific instruction. It would monitor amplitudes orders and sign of the stimulation in order to automatically annihilate the residual charge that may result from a misuse of the stimulator, trigger maybe an emergency stop and then improve its safety.

# 4.6.2 System Level

# Toward a close-loop stimulation device

We added a few digital Inputs/Outputs to the TWIST PCB, connected to the FPGA, in order to use extensions boards from industry or custom made. This would permit to use different digital interface and bypass the need for a computer to use the stimulation device. Moreover, sensors could be used in order to propose a full close-loop system for various applications.

#### Toward a robust compiler and user interface

So far, TWIST is definitely not user friendly as Multistim can be. A basic command-line program coded in Matlab language is now being used, and there is a huge need for a Graphical User Interface that would allow users with no programming experience to use TWIST. It is also a challenge as there is a high number of parameters for the different channels being used, which can include loops and triggers. Moreover, even if Matlab language has been used for prototyping, it would be interesting to use an open source language like Python for further development of the control software and user interface.

#### Cathodic/Anodic mismatch compensation

We mentioned that the mismatch between cathodic and anodic channel is of 11.3 LSB for the worst channel. In the next version of TWIST, designers should try to bring this figure to less than 1 LSB using a kind of 'digital trimming' on one of the phase for each channel, to balance the anodic/cathodic stimulation.

# 4.7 Conclusion

This chapter presented a new and versatile architecture for a stimulation system, TWIST, capable of generating user-defined waveforms to experiment their effects on living tissues or exploit wide band frequencies signals for tissue impedance characterization. The Operational Transconductance Amplifier implemented on a new stimulation ASIC could not be used due to layout issues that have not been fully explained up to now. Fortunately, the system was designed to host either the new chip or the previous one, SONIC, that included ESCs alone. Software engineering is still required to provide a fully operational platform with a proper user interface, as it is the case for the previous system Multistim. For the next version, a totally integrated system could be studied, including the Stimulation Processor and the Digital to Current converters, in order to have fewer peripherals on the PCB and work towards a complete implantable system.

The next chapter presents in-vivo and in-vitro experimental results using Multistim and in-vitro stimulation results using TWIST.

# Chapter 5

# Experimental validation of the stimulation systems

The two previous chapters were dedicated to the design and electrical characterization of two different stimulation systems: Multistim and TWIST. Both devices use a common analog front-end (the ESCs, integrated on SONIC IC) to provide a high-voltage compliant current stimulus, and can be used within an open-loop or a closed-loop setup. Their main difference resides in the digital controller architecture and the resulting system configuration: Multistim presents a shared controller for all ESCs whereas TWIST consists in a parallel architecture with fully programmable mixed-signal Stimulation Channels IPs. In terms of functionality, Multistim comes with an optimized architecture to provide rectangular-biphasic stimulation and TWIST's architecture can provide any kind of arbitrary stimulation pattern, with respect to the specifications presented in chapter 4.

Multistim has reached a high level of development, from the stimulation IC to the full system integration, with a dedicated control software and user interface. On the other side, TWIST is in its early stage of development and further improvements need to be done as presented in chapter 4. This chapter is thus organized in two parts. First, we will detail some in-vivo experiments that have been carried out using Multistim in the framework fo CENAVEX project and second, we will prove the ability of TWIST to generate arbitrary waveforms, using the first version of its Matlab-based software.

# 5.1 In vivo experiments with Multistim

Multistim has been used for experiments in the context of the CENAVEX project, described in the first chapter of this manuscript. Those experiments involved bilateral stimulation of the diaphragm muscle which is the main muscle used for breathing. The work presented hereafter has been carried out in collaboration with Adaptive Neural Systems Team, from FIU – USA, in their lab, under the supervision of Pr. Ranu Jung. It consists in two main steps:

- Open-loop experiments to validate the fact that Multistim could provide bilateral stimulation in a rodent's diaphragm.
- Closed-loop experiments, in order to propose a proof of concept of a closed-loop stimulation device that would permit the rehabilitation of the breathing function after Spinal Cord Injury (SCI).



**Figure 5.1:** Experimental setup diagram for open loop stimulation. The developed Python GUI is used to control Multistim. Two stimulation channels are used in order to provide bilateral diaphragm stimulation. A pneumotachometer is used to measure the flow which is integrated afterwards in order to obtain the lung volume variation, a capnograph is used to measure EtCO2 and the ECG is recorded as well.

Experiments presented hereafter have been conducted in a preliminary study on noninjured rodent. Experiments on injured rats are currently in progress.

#### 5.1.1 Open-loop stimulation

Multistim was tested during diaphragm pacing open-loop experiments on an uninjured rat model; in this model, electrical stimulation enhances the breath amplitude. The goal of this experiment was to confirm that our device delivers stimulation pulses that are suitable for effective activation of motoneurons in an in-vivo preparation. Two synchronized stimulation channels were used to provide bilateral stimulation of the diaphragm muscles, as described in figure 5.1. Ventilatory related parameters (such as air flow and end tidal CO2 (EtCO2)) and electrocardiogram (ECG) were recorded. The stimulation signal could not be directly measured but we can clearly see the stimulation artefact on the recorded ECG signal trace. In this test, the stimulator was set in burst mode with constant amplitude. Experiments show, as expected, an increase of the natural lung volume when stimulation is on (figure 5.2).

This experiment was the first one ever done in-vivo using Multistim and its dedicated Graphical User Interface. It illustrated its ease of configurability, and allowed us to prepare closed-loop experiments, presented in the next section.

# 5.1.2 Closed-loop stimulation

For closed-loop stimulation experiments, we replaced our open-loop GUI by a custom closed-loop controller that can take into account breath volume and EtCO2. This experiment was a proof of concept for an adaptive closed-loop stimulation device for breathing applications. The goal of this closed-loop experiment was to maintain a desired lung volume throughout the trial. Multistim output was modulated by a Pattern Shaper (PS) controller implemented in the LabVIEW environment by Ricardo Siu. It is based on a biomechanical model developed by [143]. Experimental setup is presented figure 5.3.

Multistim stimulation is in burst mode, with an adaptive envelope amplitude modulation provided by the PS controller. It results in a Gaussian-shaped train of bursts with smooth increased amplitude, as already shown in chapter 3, figure 3.18. Burst period and



Figure 5.2: Representative stimulation cycles of the breath volume variation. At breathing cycle #60, the stimulation is turned on (stimulation artefact visible on red track). Natural lung volume is increasing from 1.6 mL when stimulation is off, towards 2 mL when stimulation is on. Cathodic/anodic pulses amplitude, duration, interphase and frequency are respectively set to 1 mA, 400 µs, 40 µs and 75 Hz. Stimulation burst is delivered each 200 ms.



Figure 5.3: Experimental setup diagram for closed-loop stimulation



**Figure 5.4:** Two representative stimulation cycles with stimulation artifact (red) measured on the ECG channel, and measured volume (black), acquired using the pneumotachometer. The controller communicates with Multistim to modulate amplitude for each pulse and thus contract the diaphragm to elicit the desired volume.

duration were obtained from baseline trial before turning the stimulation on. While biphasic pulses amplitude were modulated by the PS, timing parameters used were the same as the ones used for open-loop trials: 400  $\mu$ s for both cathodic and anodic pulse duration, 40  $\mu$ s for interphase duration and 75Hz for pulse frequency. Figure 5.4 presents two representative cycles of the breathing volume, with the stimulation artifact, and figure 5.5 breath volume and stimulation envelope through time.

This experiment was a success as we managed to provide adaptive stimulation within a closed-loop setup using Multistim, which was controlled by metabolic inputs processed by a specific controller. Improvements on this setup could be done on the custom-controller which computes the stimulation parameters: in order to make the system more reactive, we could implement it on Multistim's FPGA in order to have a system more simple and compact.

# 5.2 Arbitrary stimulation waveforms with TWIST

Most of the literature on new waveforms for electrical stimulation come from a computational approach. In order to test the flexibility of our system, we decided to generate two waveforms that are detailed in [27, 146], which are supposedly the 'most efficient', plus a multi-sine waveform that could be used to characterize tissue impedance for example. This part is going to detail how to generate a waveform using the toolchain developed using Matlab.

# 5.2.1 Generation of a biphasic Gaussian stimulus

We chose to generate a biphasic Gaussian stimulus as it this waveform is often cited as the most efficient in the literature [27, 117, 146]. The waveform presented in this section has been directly inspired by [117], it was presented as monophasic in this study but we add a second opposite phase, in order to make it biphasic and charge-balanced.

Figure 5.6 presents a schematic view of the 'design flow' of a stimulation waveform, from the user's idea to the Stimulation Program up-loaded in TWIST. As detailed in the previous chapter, TWIST's Stimulation Processors have a time base of 1  $\mu$ s, and an amplitude precision of 4  $\mu$ A. Hence, after waveform design, the data is discretized in multiples of 1  $\mu$ s and 4  $\mu$ A and a sign vector is created. In order to save space in the



**Figure 5.5:** (a) and (b): Breath volume through breathing cycles, target volume is represented in dot line and measured volume in solid line. (c) and (d): Stimulation envelope through breathing cycles. Stimulation amplitude first increases gradually to cause entrainment. Initial synchrony (red line) is achieved within 8 cycles, after which, Multstim's envelope amplitude is decreased by the controller to lower stimulation and match targeted volume. By cycle 85, a stable stimulation waveform resulting in minimal error has been found. (Courtesy of R. Siu, ANS Lab, FIU)



Figure 5.6: Toolchain developed using Matlab. The waveform is created by the user, and then converted into binary data, compressed in order to minimize the needed amount of instruction and sent to chosen Stimulation Channels on TWIST



Figure 5.7: Experimental setup for the test of arbitrary stimulus generation

Stimulation Program Memory, compression of the waveform is performed to remove two (or more) consecutive instructions with the same sign and amplitude, and replace them by a single one with a longer timing corresponding to the sum of each instruction duration.

In this first example, we decided to build a signal with respect to equation 5.1, with maximum amplitude of 1mA.

$$i(t) = a * e^{-(tb)^2/(2c^2)} \text{ with } \begin{cases} a = -1 + 10^{-3}; b = 50; c = 15 \text{ if } t \in [0; 99] \mu s\\ a = 1 + 10^{-3}; b = 50; c = 15 \text{ if } t \in [100; 254] \mu s \end{cases}$$
(5.1)

Signal has been created using the toolchain presented figure 5.6, and then sent to TWIST through the USB connection.

First, we used a resistive load on one Stimulation Channel in order to acquire the current, as depicted in figure 5.7. The result of this acquisition is presented in figure 5.8(a). Then we replaced the  $10 \,\mathrm{k\Omega}$  resistor by a bipolar pacemaker electrode Medtronic Capsure©VDD-2 5038 (see picture of figure 5.9), immersed in PBS; this second acquisition is presented in figure 5.8(b). The resulting electrode voltage presents a smooth waveform that reproduces of the current stimulus; we do not observe voltage discontinuities as in the case rectangular biphasic stimulus (see for example paragraph 3.4 of chapter 3).



**Figure 5.8:** (a) Measured biphasic Gaussian stimulation waveform; the current level reported here was calculated from the output voltage on the  $10 \text{ k}\Omega$  resistor, (b) Electrode voltage measurement



**Figure 5.9:** Bipolar electrode Medtronic Capsure©VDD-2 5038 used in our test-setup, we connected the stimulation channel output to (a) and used (b) as a return electrode



Figure 5.10: Decreasing exponential current stimulus: the current level reported here was calculated from the output voltage on the  $10 \text{ k}\Omega$  resistor

#### 5.2.2 Other waveforms

We ran some tests on other kind of waveforms; here are two more examples of a user defined waveform.

#### Decreasing exponential cathodic phase and charge balancing

This waveform is composed of two different phases as described in equation number 5.2. The first one is a decreasing amplitude cathodic phase with an exponential shape, followed by a rectangular anodic phase for charge balancing.

$$\begin{cases} i(t) = 10^{-3} * e^{-0.04 * t} \text{ if } t \in [0; 140] \mu \text{s} \\ i(t) = 0.2 * 10^{-3} \text{ if } t \in [142; 272] \mu \text{s} \\ i(t) = 0 \text{ otherwise} \end{cases}$$
(5.2)

This waveform has been inspired by [27]. Again, the current waveform was created using the toolchain presented figure 5.6, and then sent to TWIST through the USB connection; for the test, the set-up already described in figure 7 was used. The measurement results are shown in figure 5.10.

This biphasic waveform is composed of the exponential decreasing cathodic phase and the rectangular anodic phase. The last one was calculated to balance the integral of the cathodic phase, with an arbitrary constant current.

#### Multi-sine stimulus

Finally, we decided to reproduce a multi-sine signal inspired by [122]. This kind of signal can allow impedance measurement and characterization of biological tissues at different frequencies with one signal. In our case, it consists in a signal combining 2 different sines at 2 frequencies: 50kHz and 10kHz. We created our signal according to equation 5.3. The real output current of the programmed stimulation channel, measured on the 10 k $\Omega$  resistor, is presented in figure 5.11, and the spectrum of this signal is available in figure 5.12.



Figure 5.11: TWIST stimulation multi-sine signal (zoom on one period): the current level reported here was calculated from the output voltage on the  $10 \text{ k}\Omega$  resistor

$$i(t) = [sin(2\pi * 5 * 10^{4} * t) + sin(2\pi * 10 * 10^{4} * t)] * 0.3$$
(5.3)

The spectrum presents 2 rays respectively at 10kHz and 50kHz as expected. The frequencies composing or signal were chosen arbitrarily, nonetheless, we demonstrated that we can generate multi-sine signals at given frequencies.

This experiment shows that we can use TWIST as a multi-sine stimulus generator, hence for impedance spectroscopy experiments, in the context of the EDIFICE project.

As explained in the chapter 4, our maximum stimulation signal frequency is 625kHz. This limitation comes from the discrete components used for the Digital to Current Converter and from the commutation time of the ESCs. The digital architecture on the FPGA is not the limiting factor for the system maximal operating frequency.

# 5.3 Conclusion

Multistim has been successfully used during in-vivo applications, both in open and closedloop experimental setups. It is today the most mature stimulation device of ELIBIO team, with a robust design and a fully functional user interface. Multistim has been duplicated and implemented in the Adaptive Neural Systems Team of Pr. Ranu Jung, in FIU at Miami; I contributed to the proper installation of the system for CENAVEX project. Projects involving Multistim in ex-vivo electrical stimulation of myocardium and neurons culture are currently being studied.



Figure 5.12: Spectrum computed from the stimulus current measurement presented figure 5.11

TWIST can be used for in vivo and in vitro application: we demonstrated its ability to generate various kinds of waveforms. It will make possible to implement new projects to study the impact of given stimulation waveforms and discuss the simulation results found in the literature. A Graphical User Interface is being developed today by Gilles N'Kaoua, in order to make it easily usable by non-expert experimenters. I hope it will also be useful on the Electrode Spectroscopy Impedance measurements carried within the EDIFICE project.
# Chapter 6

# Conclusion

This thesis summarizes three years of research and development on integrated circuits and systems dedicated to neuro-stimulation. This work proposed two devices which allow exploring new stimulation paradigms and new stimulation waveforms.

## Chapter 1

The first chapter introduced the scientific context of this work. After a brief history of electrical stimulation, some basics notions regarding the neurons were detailed to highlight how an external electrical stimulation can elicit an action potential. The different research projects that were in progress in ELIBIO team during my PhD were also presented in that chapter. We concluded then by developing the issues addressed in that PhD thesis: the design of multi-application stimulation systems, highly configurable, with open- and closed-loop capabilities, and an evolution of the specifications towards in situ electrical monitoring and exploration new stimulation waveforms.

## Chapter 2

This chapter began with an overview of the variety of neuro-stimulation therapeutic applications and then focused on the state of the art of stimulation systems, especially those based on a specific IC core. This review allowed highlighting the large range of electrical parameters specifications when addressing multiple applications, as well as the similarities in the design of those stimulation devices. This analysis was at the basis of the modular ASIC architecture using the Elementary Stimulation Channels (ESCs). We also learned in this chapter that exploration of the stimulus waveform energy efficiency is an approach that could help reduce stimulation implants energy consumption, although most of the literature studies were done using a computer simulation approach. Bioimpedance measurement at the level of implanted electrode was finally investigated throughout the literature, as it could provide a diagnosis of implants long-term compatibility. An overview of impedance measurement techniques using integrated circuits was presented.

# Chapter 3

This chapter presented the work that has been carried out in order to build a reliable multiapplication stimulation system, from integrated circuit design to user interface: Multistim. This fully configurable IC-centered stimulator has been designed to investigate muscle stimulation paradigms. It provides 8 current stimulation channels with high-voltage compliance and real-time operation capabilities. It consists in a mixed-signal system, built around a full-custom integrated circuit, SONIC, and controlled by a multichannel FPGA-based digital controller. Several in vitro experiments were described at the end of this chapter, that prove the ability of Multistim to adapt to very different experiments, from mono-channel to multi-channel ones, with different way of combining the ESCs.

# Chapter 4

The chapter 4 detailed a novel stimulation architecture dedicated to the exploration of new stimulation waveforms as well as electrode impedance characterization. This second system, named Twist, provides 8 Stimulation Channel IPs that can provide user-defined waveforms for open and closed-loop experimental setup. An attempt to build an integrated high-voltage Operational Transconductance Amplifier for electrode voltage measurement has been presented. Despite good simulation results, the tests of this amplifier were not conclusive. However, the new system was designed to be compatible the previous ASIC, SONIC, that included ESCs alone. Using the developed Stimulation Channel IP, from analog current generation front-end to specific Stimulation Processor, will reduce the design cycle and optimization of further multi-channel stimulation systems of ELIBIO team and open the way to a totally integrated system.

# Chapter 5

The last chapter of this manuscript presents in-vivo results of Multistim and the generation of arbitrary waveforms using TWIST on resistive loads as well as on a pacemaker cardiac electrode. Multistim has been successfully used during in-vivo applications, both in open and closed-loop setup, in the context of CENAVEX project, for the rehabilitation of the breathing function. The ability to generate any kind of waveforms using TWIST has been finally demonstrated, with examples chosen from computational studies from the literature.

# Perspectives

The investigations, developments and systems built during this PhD thesis open different perspectives for future research in the team. Multistim platform has proven to be robust and usable in all the projects involving electrical stimulation. A project associating this system and electrical stimulation of neuronal cultures in a Micro Electrode Array is being studied. On another aspect of stimulation, TWIST will provide a versatile environment to study the impact of the stimulation waveform on excitable cells and compare real experiments to simulation. The question of miniaturization of the system should be examined in a final objective of implantable device. It would need digital synthesis of the Stimulation Processor as well as integrating the digital to current converters. This would be a major step in order to study the different stimulation waveform in-vivo, the actual system being too big to be used in-vivo unless the subject is anesthetized. Wireless configuration of the stimulator would be also an interesting new feature in that context. Further investigation need to be done to understand why the designed OTA did not work. The simulations being conclusive, I think the layout should be checked conscientiously and re-done on a dedicated chip. The result could provide another brick to study the electrode/tissue impedance. To conclude on that context of bioimpedance characterization, TWIST will enable the generation of multi-sine and novel measurement signals in order to carry out comprehensive impedance spectroscopy.

# Appendix A

# Multistim architecture details

This document presents the implementation of the stimulation system within the Multistim design. It allows the control of 8 stimulation channels using DACs (from PCB boards) and four SHIVAs circuits. The digital architecture has been developed using ISE 14.7.

### A.1 Global Architecture

A top-level file named "multistim" which contains the system itself "multistim\_inside" composes the architecture. The top level file acts like a shell, allowing the matching in between the PCB names and the digital design names. I/O of the system (multistim\_inside):

- clk : (in, 1 bit) system clock, should be @ 100MHz
- rst\_hard : (in , 1 bit) system reset, from hardware (the system can also be restarted through UART)
- start\_stim\_close\_loop : (in, 1 byte) hard trigger for stimulation. One bit for each channel
- rx : (in, 1 bit) serial port
- tx : (out, 1 bit) serial port
- LED : (out, 1 byte) bus used to control the LEDs on the PCB
- kali\_sclk : (out, 1 bit) clk of the SPI bus in between switches on Kali and the FPGA. This SPI connection allows the configuration of the switches in order to provide stimulation This switches are configured at startup and their state should not be modified at any time
- kali\_mosi : (out, 1 bit) same as above
- kali\_ss\_n: (out, 1 byte) same as above, chip select of the different components
- dac\_sclk : (out, 1 bit) sclk of the SPI allowing the configuration of the DACs, for stimulation
- dac\_mosi : (out, 1 bit) same as above
- dac\_cs\_n : (out, 1 bit) chip select of the DACs, same as above
- anodic\_DC : (out, 1 byte) orders for anodic stimulation to SHIVAs ICs. Each bit corresponds to one stimulation channel
- cathodic\_DC: (out, 1 byte) same as above, but for cathodic stimulation
- n\_rst\_shiva: (out, 1 bit) SHIVAs 'reset. Active on low level.
- n\_clr\_dac : (out, 1 bit) cf. DAC datasheet

Within the top-level file (i.e. Multistim), some outputs such as DCx and GFx (x = 1, 2, 3, 4) are set to low-level or high level. Those should not be modified by any means, in order to keep SHIVAs ICs within the right configuration.

As eight different channels need to be driven, and in order to lower the resources used by the stimulator on the FPGA, each stimulation channel is computed at a time. The time allowed by the system to one channel is called "Time slot". A time-slot length is 20 micro-seconds, and is presented in figure 3.12.

As the minimum time-step is a Time-Slot (TS), stimulation parameters will be expressed as a finite amount of time-slots.

Within all the stimulation parameters, only Tdelay and Tinterpulse can be zeroed. The minimum timing for the others parameters equals to 1 TS, i.e. 20 µs.

In order to have a 20 µs timing (minimum) for any of the temporal parameters described (fig. 1), one can set the given parameter to the hexadecimal value X"00000000". In order to get a 40 µs timing, the user got to enter the value X"00000001", and so on.

In order to bypass the Delay phase or the Interphase, one should use the value X"FFFFFFF" for those parameters.

## A.2 Detailed architecture

#### A.2.1 Kali configuration

This bloc configures the Kali board peripherals in order to prepare it for stimulation. It is composed of a finite state machine, a RAM, and a SPI driver. The RAM (8\*8 bits) can be accessed from the CPU in order to change the configuration parameters (feature is there, but should not be used in order to guarantee a correct behavior of the system). I/O of config\_kali:

- clk : (in, 1 bit, in) system clock
- reset : (in, 1 bit) system reset
- start\_config : (in, 1 bit) signal from the CPU, triggers the beginning of Kali configuration
- enable\_1 : (in, 1 bit) write enable signal of the RAM
- data in 1 : (in, 1 byte) input data port of the RAM
- addr\_1 : (in, 3 bits) address port of the RAM
- config\_done : (out, 1 bit) flag, high level when Kali is configured
- mosi : (out, 1 bit) SPI data bus, to the switches on Kali
- sclk : (out, 1 bit) serial clock of SPI bus
- ss\_n : (out, 1 byte) chip select of the components for configuration
- data\_out\_1 : (out, 1 byte) output data port of the RAM

The FSM reads the RAM data, and transfers it to the SPI driver (SPI\_master\_switch) which sends the data through the SPI bus to the switches, at a rate of 1MHz (slck frequency). First line of the RAM corresponds to data for the first switch; second line is for the second switch, and so on.

#### A.2.2 Sequencer 8 channels

This bloc is used to cadence the whole system, in order to provide the channel computed by the FSM.

- I/O of sequencer 8 channels:
- clk : (in, 1 bit) system clock, 100MHz
- rst : (in, 1 bit) system reset
- start\_sequencer : (in, 1 bit) trigger from the CPU, on high-level, starts the sequencer
- stop\_sequencer : (in, 1 bit) trigger from the CPU, on high-level, stops the sequencer. Mostly used for debugging
- channel\_number: (out, 4 bits) channel number, that will be processed by the stimulator. Range is from 0 to 8. The 8th channel is not hardware related, it is used for special operations and synchronization in between stimulation channels
- new\_channel : (out, 1 bit) flag to announce that a new channel can be processed

#### A.2.3 SPI Interface

SPI interface in between the FPGA and the DAC used to generate the voltage thus converted into stimulation current. This interface operates at an SCLK frequency of 20MHz (provided by an internal DCM), an in mode 0. I/O of spi\_interface:

- rst : (in, 1 bit) system reset
- clk : (in, 1 bit) system clock
- amplitude (1 byte) : amplitude of the stimulation
- channel (3 bits) : channel addressed
- transition: cathodic\_stim, anodic\_stim, no\_stimdata\_tx : (in, 12 bits) data to be sent to the DAC
- addr: (in, 2 bits) address of the peripheral, stuck to "00" for the system as it got only one DAC
- trigger : (in, 1 bit) starts the data transmission when transitioning form low to high level
- sclk : (out, 1 bit) SPI clock, 20MHz
- mosi: (out, 1 bit) SPI data
- cs\_n: (out, 2 bit) chip select of the spi\_interface. Not used and not connected. The chip select for the DAC is driven externally in another module (stim\_signal\_mgmt) due to the DAC specifications

#### A.2.4 state mgmt

This module takes as an input all the stimulation parameters of the current channel (given by the sequencer) and determines whether a transition should happen or not (i.e. cathodic or anodic or no stimulation). When stimulation is requested on a given channel (asynchronous event) by the user or any external device, the stimulation is effectively started on this channel during the 8th channel time-slot (provided by the sequencer). This allows synchronization in between all the stimulation channels.

I/O of state\_mgmt:

• clk : (in, 1 bit) system clock, 100MHz

- rst : (in, 1 bit) system reset
- parameters\_rdy : (in, 1 bit) Input flag, indicates that all the stimulation parameters at the input are valid
- channel\_number : (in, 4 bits) channel number being processed, from sequencer
- new\_channel : (in, 1 bit) flag to announce that a new channel can be processed, from sequencer
- amplitude\_cath : (in, 1 byte) cathodic phase amplitude
- amplitude\_an : (in, 1 byte) anodic phase amplitude
- start\_stim\_in\_v : (in, 1 byte) trigger for each channel. LSB is for channel 0, MSB is for channel 7
- TS\_delay : (in 8 bytes) amount of time-slots which determines the length of the delay. No delay when TS\_delay = X"FFFFFFF". Please refer to XX for more information
- TS\_cath : (in 8 bytes) amount of time-slots which determines the duration of the cathodic pulse
- TS\_an : (in 8 bytes) amount of time-slots which determines the duration of the anodic pulse
- TS\_interphase : (in 8 bytes) amount of time-slots which determines the duration between cathodic and anodic pulse. Follows the same rule as TS\_delay
- TS\_blanking : (in 8 bytes) amount of time-slots which determines the duration in between two pulses in a row
- TS\_interburst : (in 8 bytes) amount of time-slots which determines the length of the anodic pulse
- amount\_of\_pulse : (in 8 bytes) amount of pulses in a row, to form a burst
- amount\_of\_burst : (in 8 bytes) amount of bursts in a row
- busy: (in, 1 bit) flag from downstream modules to be removed in the next version, not used anymore within state\_mgmt
- trigger\_send\_data : (1 bit, out) triggers downstream module stim\_signal\_mgmt
- order: (out, stimulation\_order) data needed for stimulation. stimulation\_order is a record, its data structure is detailed below:
  - amplitude (1 byte) : amplitude of the stimulation
  - channel (3 bits) : channel addressed
  - transition: cathodic\_stim, anodic\_stim, no\_stim

#### A.2.5 stim\_parameters\_mgmt

This module extracts stimulation parameters from a built-in RAM double access, in accordance with the current\_channel from the sequencer and output them to the state\_mgmt module. Once all of those parameters are ready, the flag parameters\_rdy is set to highlevel. I/Os are not fully detailed for this module as they are common with state\_mgmt.

The built-in RAM can be accessed from the outside of the module in order to specify the parameters (for example using a CPU). The stimulation parameters are 32 bits length words, but as 8 bits CPUs are commonly used within the team, the memory look like a 8\*320 bits memory from the input port of the module, and is used as a 32\*80 bits memory inside the module. Figure A.1 presents the memory mapping used to store the stimulation parameters and figureA.2 presents the architecture of the built-in RAM.

I/O of stim\_parameters\_mgmt:

- rst : (in, 1 bit) system reset
- clk : (in, 1 bit) system clock
- channel\_number : (in, 4 bits) channel number being processed, from sequencer
- new\_channel : (in, 1 bit) flag to announce that a new channel can be processed, from sequencer
- ram\_enable : (in, 1 bit) input port of the ram. Enable
- ram\_data\_in : (in, 1 byte) data input of the RAM
- ram\_data\_out : (out, 1 byte) data output of the RAM
- ram\_addr : (in, 10 bits) address input of the RAM. The 2 LSB determine which RAM is addressed, the 8 MSB define the actual address
- (...) Stimulation parameters
- parameters\_rdy : (out, 1 bit) Input flag, indicates that all the stimulation parameters at the input are valid

@ (HEX)	@ alias name	Data (32 bits)	Signal name
X"00"	addr_amplitude_cath	Amplitude Cathodic phase	amplitude_cath
X"08"	addr_amplitude_an	Amplitude Anodic phase	amplitude_an
X"10"	addr_TS_delay	Amount of TS delay	TS_delay
X"18"	addr_TS_cath	Amount of TS Cath	TS_cath
X"20	addr_TS_interphase	Amount of TS interphase	TS_interphase
X"28"	addr_TS_an	Amount of TS Anodic phase	TS_an
X"30"	addr_TS_blanking	Amount of TS Blanking	TS_blanking
X"38"	addr_TS_interburst	Amount of TS Interburst	TS_interburst
X"40"	addr_amount_of_pulse	Amount of pulses within a burst	amount_of_pulse
X"48"	addr_TS_amount_of_burst	Amount of burst in a row	amount_of_burst

Figure A.1: Stimulation parameters addresses

#### A.2.6 stim signal mgmt

This block prepares the stimulation orders to be sent to the DAC and to SHIVAs circuits. Therefor it provides the direct control signals for SHIVAs circuits, specific signals for the DAC.

I/O of stim\_signal\_mgmt:

- rst : (in, 1 bit) system reset
- clk : (in, 1 bit) system clock
- trigger : (in, 1 bit) trigger for the module to start operate the stimulation parameters
- stim\_order : (in, stimulation\_order) stimulation\_order, from state\_mgmt
- spi\_busy : (in, 1 bit) flag from spi\_interface, SPI still active when high
- stim\_polarity : (in, 1 byte) allows polarity inversion on a given channel (cathodic pulse becomes positive and the anodic one become negative), MSB -> Channel 7, LSB -> Channel 0
- data\_tx\_spi : (out, 12 bits) data to be sent to the DAC through spi\_interface
- trigger\_spi : (out, 1 bit) triggers the spi\_interface module

- busy : (out, 1 bit) flag, on high-level as long as the module and dependences are in operation
- anodic\_DC : (out, 1 byte) Anodic direct control orders for SHIVA
- cathodic\_DC : (out, 1 byte) Cathodic direct control orders for SHIVA
- cs\_dac : (out, 1 bit) Chip-select for the DAC
- n\_rst\_shiva : (out, 1 bit) SHIVA's reset signal, active on low
- n\_clr\_dac : (out, 1 bit) reset-like signal for the DAC. For further information please refer to the datasheet

8 bits I/Os side





# Appendix B SONIC and SPICY I/Os

Broche n° Fonction 9 Anod 7 10 Anod 6 11 Anod 5 12 Anod 4 13 Anod 3 14 Anod 2 15 Anod 1 16 Anod 0 31 VSS 32 Stim Ch 0 33 Stim Ch 1 34 VDDL 35 Stim Ch 2 36 Stim Ch 3 37 VSSH 38 Stim Ch 4 39 Stim Ch 5 40 VDD 41 Stim Ch 6 42 Stim Ch 7 59 Cathod 0 60 Cathod 1 61 Cathod 2 62 Cathod 3 63 Cathod 4 64 Cathod 5 65 Cathod 6 66 Cathod 7 89 VSSA 90 Events 91 VDDA	SONIC	
<ul> <li>9 Anod 7</li> <li>10 Anod 6</li> <li>11 Anod 5</li> <li>12 Anod 4</li> <li>13 Anod 3</li> <li>14 Anod 2</li> <li>15 Anod 1</li> <li>16 Anod 0</li> <li>31 VSS</li> <li>32 Stim Ch 0</li> <li>33 Stim Ch 1</li> <li>34 VDL</li> <li>35 Stim Ch 2</li> <li>36 Stim Ch 3</li> <li>37 VSSH</li> <li>38 Stim Ch 4</li> <li>39 Stim Ch 5</li> <li>40 VDD</li> <li>41 Stim Ch 6</li> <li>42 Stim Ch 7</li> <li>59 Cathod 0</li> <li>60 Cathod 1</li> <li>61 Cathod 2</li> <li>62 Cathod 3</li> <li>63 Cathod 4</li> <li>64 Cathod 5</li> <li>65 Cathod 6</li> <li>66 Cathod 7</li> <li>89 VSSA</li> <li>90 Events</li> <li>91 VDDA</li> </ul>	Broche n°	Fonction
10 Anod 6 11 Anod 5 12 Anod 4 13 Anod 3 14 Anod 2 15 Anod 1 16 Anod 0 31 VSS 32 Stim Ch 0 33 Stim Ch 1 34 VDL 35 Stim Ch 2 36 Stim Ch 3 37 VSSH 38 Stim Ch 4 39 Stim Ch 5 40 VDD 41 Stim Ch 6 42 Stim Ch 7 59 Cathod 0 60 Cathod 1 61 Cathod 2 62 Cathod 3 63 Cathod 4 64 Cathod 5 65 Cathod 6 66 Cathod 7 89 VSSA 90 Events 91 VDDA	9	Anod 7
11 Anod 5 12 Anod 4 13 Anod 3 14 Anod 2 15 Anod 1 16 Anod 0 31 VSS 32 Stim Ch 0 33 Stim Ch 1 34 VDDL 35 Stim Ch 2 36 Stim Ch 3 37 VSSH 38 Stim Ch 4 39 Stim Ch 5 40 VDD 41 Stim Ch 6 42 Stim Ch 7 59 Cathod 0 60 Cathod 1 61 Cathod 2 62 Cathod 3 63 Cathod 4 64 Cathod 5 65 Cathod 6 66 Cathod 7 89 VSSA 90 Events 91 VDDA	10	Anod 6
12 Anod 4 13 Anod 3 14 Anod 2 15 Anod 1 16 Anod 0 31 VSS 32 Stim Ch 0 33 Stim Ch 1 34 VDDL 35 Stim Ch 2 36 Stim Ch 3 37 VSSH 38 Stim Ch 4 39 Stim Ch 5 40 VDD 41 Stim Ch 6 42 Stim Ch 7 59 Cathod 0 60 Cathod 1 61 Cathod 2 62 Cathod 3 63 Cathod 4 64 Cathod 5 65 Cathod 6 66 Cathod 7 89 VSSA 90 Events 91 VDDA	11	Anod 5
13 Anod 3 14 Anod 2 15 Anod 1 16 Anod 0 31 VSS 32 Stim Ch 0 33 Stim Ch 1 34 VDDL 35 Stim Ch 2 36 Stim Ch 2 36 Stim Ch 3 37 VSSH 38 Stim Ch 4 39 Stim Ch 5 40 VDD 41 Stim Ch 6 42 Stim Ch 7 59 Cathod 0 60 Cathod 1 61 Cathod 2 62 Cathod 3 63 Cathod 4 64 Cathod 5 65 Cathod 6 66 Cathod 7 89 VSSA 90 Events 91 VDDA	12	Anod 4
14 Anod 2 15 Anod 1 16 Anod 0 31 VSS 32 Stim Ch 0 33 Stim Ch 1 34 VDDL 35 Stim Ch 2 36 Stim Ch 2 36 Stim Ch 3 37 VSSH 38 Stim Ch 4 39 Stim Ch 5 40 VDD 41 Stim Ch 6 42 Stim Ch 7 59 Cathod 0 60 Cathod 1 61 Cathod 2 62 Cathod 3 63 Cathod 4 64 Cathod 5 65 Cathod 6 66 Cathod 7 89 VSSA 90 Events 91 VDDA	13	Anod 3
15 Anod 1 16 Anod 0 31 VSS 32 Stim Ch 0 33 Stim Ch 1 34 VDDL 35 Stim Ch 2 36 Stim Ch 2 36 Stim Ch 3 37 VSSH 38 Stim Ch 4 39 Stim Ch 4 39 Stim Ch 5 40 VDD 41 Stim Ch 6 41 Stim Ch 7 59 Cathod 0 60 Cathod 1 61 Cathod 2 62 Cathod 3 63 Cathod 4 64 Cathod 5 65 Cathod 6 66 Cathod 7 89 VSSA 90 Events 91 VDDA	14	Anod 2
16 Anod 0         31 VSS         32 Stim Ch 0         33 Stim Ch 1         34 VDDL         35 Stim Ch 2         36 Stim Ch 3         37 VSSH         38 Stim Ch 4         39 Stim Ch 5         40 VDD         41 Stim Ch 6         42 Stim Ch 7         59 Cathod 0         60 Cathod 1         61 Cathod 2         62 Cathod 3         63 Cathod 4         64 Cathod 5         65 Cathod 6         66 Cathod 7         89 VSSA         90 Events         91 VDDA	15	Anod 1
31 VSS 32 Stim Ch 0 33 Stim Ch 1 34 VDDL 35 Stim Ch 2 36 Stim Ch 3 37 VSSH 38 Stim Ch 4 39 Stim Ch 4 39 Stim Ch 5 40 VDD 41 Stim Ch 6 42 Stim Ch 7 59 Cathod 0 60 Cathod 1 61 Cathod 2 62 Cathod 3 63 Cathod 4 64 Cathod 5 65 Cathod 6 66 Cathod 7 89 VSSA 90 Events 91 VDDA	16	Anod 0
31 VSS 32 Stim Ch 0 33 Stim Ch 1 34 VDDL 35 Stim Ch 2 36 Stim Ch 3 37 VSSH 38 Stim Ch 4 39 Stim Ch 4 39 Stim Ch 5 40 VDD 41 Stim Ch 6 42 Stim Ch 7 59 Cathod 0 60 Cathod 1 61 Cathod 2 62 Cathod 3 63 Cathod 4 64 Cathod 5 65 Cathod 6 66 Cathod 7 89 VSSA 90 Events 91 VDDA		
32 Stim Ch 0 33 Stim Ch 1 34 VDDL 35 Stim Ch 2 36 Stim Ch 3 37 VSSH 38 Stim Ch 4 39 Stim Ch 5 40 VDD 41 Stim Ch 6 42 Stim Ch 7 59 Cathod 0 60 Cathod 1 61 Cathod 2 62 Cathod 3 63 Cathod 4 64 Cathod 5 65 Cathod 6 66 Cathod 7 89 VSSA 90 Events 91 VDDA	31	VSS
33 Stim Ch 1 34 VDDL 35 Stim Ch 2 36 Stim Ch 3 37 VSSH 38 Stim Ch 4 39 Stim Ch 5 40 VDD 41 Stim Ch 6 42 Stim Ch 7 59 Cathod 0 60 Cathod 1 61 Cathod 2 62 Cathod 3 63 Cathod 4 64 Cathod 5 65 Cathod 6 66 Cathod 7 89 VSSA 90 Events 91 VDDA	32	Stim Ch 0
34 VDDL 35 Stim Ch 2 36 Stim Ch 3 37 VSSH 38 Stim Ch 4 39 Stim Ch 5 40 VDD 41 Stim Ch 6 42 Stim Ch 7 59 Cathod 0 60 Cathod 1 61 Cathod 2 62 Cathod 3 63 Cathod 4 64 Cathod 5 65 Cathod 6 66 Cathod 7 89 VSSA 90 Events 91 VDDA	33	Stim Ch 1
35 Stim Ch 2 36 Stim Ch 3 37 VSSH 38 Stim Ch 4 39 Stim Ch 5 40 VDD 41 Stim Ch 6 42 Stim Ch 7 59 Cathod 0 60 Cathod 1 61 Cathod 2 62 Cathod 3 63 Cathod 4 64 Cathod 5 65 Cathod 6 66 Cathod 7 89 VSSA 90 Events 91 VDDA	34	VDDL
36 Stim Ch 3 37 VSSH 38 Stim Ch 4 39 Stim Ch 5 40 VDD 41 Stim Ch 6 42 Stim Ch 7 59 Cathod 0 60 Cathod 1 61 Cathod 2 62 Cathod 3 63 Cathod 4 64 Cathod 5 65 Cathod 6 66 Cathod 7 89 VSSA 90 Events 91 VDDA	35	Stim Ch 2
37 VSSH 38 Stim Ch 4 39 Stim Ch 5 40 VDD 41 Stim Ch 6 42 Stim Ch 7 59 Cathod 0 60 Cathod 1 61 Cathod 2 62 Cathod 3 63 Cathod 4 64 Cathod 5 65 Cathod 6 66 Cathod 7 89 VSSA 90 Events 91 VDDA	36	Stim Ch 3
38 Stim Ch 4 39 Stim Ch 5 40 VDD 41 Stim Ch 6 42 Stim Ch 7 59 Cathod 0 60 Cathod 1 61 Cathod 2 62 Cathod 3 63 Cathod 4 64 Cathod 5 65 Cathod 6 66 Cathod 7 89 VSSA 90 Events 91 VDDA	37	VSSH
39 Stim Ch 5 40 VDD 41 Stim Ch 6 42 Stim Ch 7 59 Cathod 0 60 Cathod 1 61 Cathod 2 62 Cathod 3 63 Cathod 4 64 Cathod 5 65 Cathod 6 66 Cathod 7 89 VSSA 90 Events 91 VDDA	38	Stim Ch 4
40 VDD 41 Stim Ch 6 42 Stim Ch 7 59 Cathod 0 60 Cathod 1 61 Cathod 2 62 Cathod 3 63 Cathod 4 64 Cathod 5 65 Cathod 6 66 Cathod 7 89 VSSA 90 Events 91 VDDA	39	Stim Ch 5
41 Stim Ch 6 42 Stim Ch 7 59 Cathod 0 60 Cathod 1 61 Cathod 2 62 Cathod 3 63 Cathod 4 64 Cathod 5 65 Cathod 6 66 Cathod 7 89 VSSA 90 Events 91 VDDA	40	VDD
42 Stim Ch 7 59 Cathod 0 60 Cathod 1 61 Cathod 2 62 Cathod 3 63 Cathod 4 64 Cathod 5 65 Cathod 6 66 Cathod 7 89 VSSA 90 Events 91 VDDA	41	Stim Ch 6
59 Cathod 0 60 Cathod 1 61 Cathod 2 62 Cathod 3 63 Cathod 4 64 Cathod 5 65 Cathod 6 66 Cathod 7 89 VSSA 90 Events 91 VDDA	42	Stim Ch 7
59 Cathod 0 60 Cathod 1 61 Cathod 2 62 Cathod 3 63 Cathod 4 64 Cathod 5 65 Cathod 6 66 Cathod 7 89 VSSA 90 Events 91 VDDA		
60 Cathod 1 61 Cathod 2 62 Cathod 3 63 Cathod 4 64 Cathod 5 65 Cathod 6 66 Cathod 7 89 VSSA 90 Events 91 VDDA	59	Cathod 0
61 Cathod 2 62 Cathod 3 63 Cathod 4 64 Cathod 5 65 Cathod 6 66 Cathod 7 89 VSSA 90 Events 91 VDDA	60	Cathod 1
62 Cathod 3 63 Cathod 4 64 Cathod 5 65 Cathod 6 66 Cathod 7 89 VSSA 90 Events 91 VDDA	61	Cathod 2
63 Cathod 4 64 Cathod 5 65 Cathod 6 66 Cathod 7 89 VSSA 90 Events 91 VDDA	62	Cathod 3
64 Cathod 5 65 Cathod 6 66 Cathod 7 89 VSSA 90 Events 91 VDDA	63	Cathod 4
65 Cathod 6 66 Cathod 7 89 VSSA 90 Events 91 VDDA	64	Cathod 5
66 Cathod 7 89 VSSA 90 Events 91 VDDA	65	Cathod 6
89 VSSA 90 Events 91 VDDA	66	Cathod /
90 Events 91 VDDA	00	
91 VDDA	89	VSSA
91 VDDA	90	Events
07 Current Input 7	91	Current Input 7
92 Current Input 7	92	Current Input 7
95 Current Input 6	93	Current Input 6
94 Current Input 5	94	Current Input 5
95 Current Input 4	95	Current Input 2
97 Current Input 3	90	Current Input 3
97 Current Input 2	97	Current Input 2
99 Current Input 0	90	Current Input 0

SPICY	
Broche n° Fonction	Broche n° Fonction
9 Anod 7	84 I_pol_OTA_1
10 Anod 6	85 R_OTA_1_a
11 Anod 5	86 R_OTA_0_b
12 Anod 4	87 I_pol_OTA_0
13 Anod 3	88 R_OTA_0_a
14 Anod 2	
15 Anod 1	89 VSSA
16 Anod 0	90 Events
	91 VDDA
31 VSS	92 Current Input 7
32 Stim Ch 0	93 Current Input 6
33 Stim Ch 1	94 Current Input 5
34 VDDL	95 Current Input 4
35 Stim Ch 2	96 Current Input 3
36 Stim Ch 3	97 Current Input 2
37 VSSH	98 Current Input 1
38 Stim Ch 4	99 Current Input 0
39 Stim Ch 5	
40 VDD	
41 Stim Ch 6	
42 Stim Ch 7	
44 Vrefi	
45 VIEI2	
59 Cathod 0	
60 Cathod 1	
61 Cathod 2	
62 Cathod 3	
63 Cathod 4	
64 Cathod 5	
65 Cathod 6	
66 Cathod 7	
77 Current_ouput_OTA_0	
78 Current_ouput_OTA_1	
79 Current_ouput_OTA_2	
80 R_OTA_2_b	FPGA - Numérique
81 I_pol_OTA_2	Alim
82 R_OTA_2_a	Analogique
83 R_OTA_1_b	SPICY - Analogique

Figure B.1: Inputs/outputs of SONIC and SPICY Chips on a QFP100 package  $% \mathcal{A}$ 



Figure B.2: SONIC bonding



Figure B.3: SPICY bonding

# Appendix C TWIST developer guide

#### Hardware, how to control TWIST

To control the stimulator, one needs to send instruction to the stimulation program memory. It consists in 256 32-bits wide instructions.

Each instruction starts a 4-bit OPCODE which indicates the type if instruction. It can be either:

- Stimulation instruction
- Jump (GoTo instruction)
- Wait for trigger instruction

OPCODE	Operation
"0000" (OPCODE_STIM)	Stimulation instruction
"0001"	Goto instruction
"0010"	Trigger instruction
From "0011" to "1111"	Not used

The table above details codes for each of the instructions.

Each instruction then differs from its structure depending on its function:

Stimulation instruction structure:

4 bits	3 bits	1 bit	16 bits	8 bits
Stim Opcode	Scale	Sign	Pulse Width	Amplitude

The stimulation instruction features an additional "Scale" section which permits to make the minimal time step longer on predefined values as presented in the next table:

Scale	Time Step
"000"	1 us (default)
"001"	500 us
"010"	1 ms
"011"	10 ms

Table 1: Scale values and their corresponding time-step

This allows to save instruction memory if a long pulse is required for a given stimulation pattern. It should not occur for most projects, but "he can do more can do less"...

The sign bit indicates if the phase is cathodic (sign = '1') or anodic (sign = '0').

The Pulse Width section represent the amount of time step (according to the Scale) that determine the length of the pulse being generated.

Go to instruction structure:

4 bits	20 bits	8 bits
Go To Opcode	Not Used	Go to address

This instruction changes the next instruction to be executed by the stimulation processor to the one detailed in the "Go to address' section of the instruction. The Program Counter jumps from the current address to the next one when this instruction is being read.

Trigger instruction structure:

4 bits	28 bits
Trigger Opcode	Not Used

Algorithm to generate stimulation program:



### Example:

Time (ms)	Amplitude (µA)
0	5
0.01	-50
0.02	-200
0.03	-200
0.04	400



Time (µs) Amplitude (µA) Sign

0	1	0
10	12	1
20	50	1
30	50	1
40	100	0



Time (µs)	Amplitude (µA)	Sign	Duration (µs)
		-	

0	1	0	10
10	12	1	10
20	50	1	10
30	<u>5</u> 0	1	10
40	100	0	10

Duration (μs) Amplitude (μA) Sign

10	1	0
10	12	1
20	50	_1 ]
10	100	0
	-	



Duration (µs/16bits)	Amplitude (µA/8bits)	Sign
000000000001010	0000001	0
000000000001010	00001100	1
000000000010100	00110010	1
000000000001010	00110100	0
	1	1

Duration (µs/16bits)	Amplitude (µA/8bits)	Sign
000000000001010	0000001	0
000000000001010	00001100	1
000000000010100	00110010	1
000000000001010	00110100	0



_	Opcode	Scale	Sign	Duration (µs/16bits)	Amplitude (µA/8bits)
	0000	000	0	000000000001010	0000001
	0000	000	1	000000000001010	00001100
	0000	000	1	000000000010100	00110010
	0000	000	0	000000000001010	00110100

Stim prgm:



Stim program with trigger and GoTo instruction:

#### TWIST embedded software

The 8-bits softcore RISC included in TWIST is used to control each Stimulation Processor.

There are all connected to the CPU data bus.

The CPU is in charge of 5 tasks:

- Managing UART
- Sending Program Counter start command to a given channel
- Sending Start command to a given channel
- Sending Trigger command (if needed) to a given channel
- Sending Stimulation Parameters to a channel

Each channel is given addresses on the CPU bus. The 256\*32 bits stimulation memory program can be addressed through a set of four addresses: ADD\_SHIVA\_BANK\_[channel\_number]\_[X] with X being the number of the bank. Each of those addresses allow to send data to the right register through DATA\_bank\_[channel\_number].

Let us take a given instruction instr = HH HL LH LL (big-endianess representation)

#### Corresponding X to byte order:

X=0	X=1	X=2	X=3
НН	HL	LH	LL

A general purpose bus STIM\_IO\_[channel\_number] for each stimulation channel controller is connected to the CPU .

The STIM\_IO register is 8-bit wide and contains the following information:

Bits 7 to 2	Bit 1	Bit 0 (LSB)
Not used	Start PC (active on "1")	Stim Trigger ("active on "1")

The following table presents the stimulation registers addresses from the CPU to the different stimulation controllers.

Channel #		Register	Address	Comment
	0	ADD_SHIVA_BANK_00	0x0C0	НН
		ADD_SHIVA_BANK_01	0x0C1	HL
		ADD_SHIVA_BANK_02	0x0C2	LH
		ADD_SHIVA_BANK_03	0x0C3	LL
		STIM_IO_0	0x0E0	Stim general los
		DAT_BANK_0	0x0E8	Data register for stim prgm
	1	ADD_SHIVA_BANK_10	0x0C4	НН

	ADD_SHIVA_BANK_11	0x0C5	HL
	ADD_SHIVA_BANK_12	0x0C6	LH
	ADD_SHIVA_BANK_13	0x0C7	LL
	STIM_IO_1	0x0E1	Stim general los
	DAT_BANK_1	0x0E9	Data register for stim prgm
2	ADD_SHIVA_BANK_20	0x0C8	НН
	ADD_SHIVA_BANK_21	0x0C9	HL
	ADD_SHIVA_BANK_22	0x0CA	LH
	ADD_SHIVA_BANK_23	0x0CB	LL
	STIM_IO_2	0x0E2	Stim general los
	DAT_BANK_2	0x0EA	Data register for stim prgm
3	ADD_SHIVA_BANK_30	0x0CC	НН
	ADD_SHIVA_BANK_31	0x0CD	HL
	ADD_SHIVA_BANK_32	0x0CE	LH
	ADD_SHIVA_BANK_33	0x0CF	LL
	STIM_IO_3	0x0E3	Stim general los
	DAT_BANK_3	0x0EB	Data register for stim prgm
4	ADD_SHIVA_BANK_40	0x0D0	нн
	ADD_SHIVA_BANK_41	0x0D1	HL
	ADD_SHIVA_BANK_42	0x0D2	LH
	ADD_SHIVA_BANK_43	0x0D3	LL
	STIM_IO_4	0x0E4	Stim general los
	DAT_BANK_4	0x0EC	Data register for stim prgm
5	ADD_SHIVA_BANK_50	0x0D4	НН
	ADD_SHIVA_BANK_51	0x0D5	HL
	ADD_SHIVA_BANK_52	0x0D6	LH
	ADD_SHIVA_BANK_53	0x0D7	LL
	STIM_IO_5	0x0E5	Stim general los
	DAT_BANK_5	0x0ED	Data register for stim prgm
6	ADD_SHIVA_BANK_60	0x0D8	нн
	ADD_SHIVA_BANK_61	0x0D9	HL
	ADD_SHIVA_BANK_62	0x0DA	LH
	ADD_SHIVA_BANK_63	0x0DB	LL
	STIM_IO_6	0x0E6	Stim general los
	DAT_BANK_6	0x0EE	Data register for stim prgm
7	ADD_SHIVA_BANK_70	0x0DC	НН
	ADD_SHIVA_BANK_71	0x0DD	HL
	ADD_SHIVA_BANK_72	0x0DE	LH
	ADD_SHIVA_BANK_73	0x0DF	LL
	STIM_IO_7	0x0E7	Stim general los
	DAT_BANK_7	0x0EF	Data register for stim prgm

The next table presents registers' addresses corresponding to UART interface on the CPU.

Register	address
UART_STATUS	0x00F
UART_RXR	0x00A
UART_TXR	0x00A

#### **Communication with TWIST**

This part details the communication protocol in between TWIST and the control computer.

TWIST should be plugged using a USB wire, and accessed through a virtual COM PORT on the computer. One can determine which COMPORT number is given to TWIST by the computer by checking computer's parameters.

The serial communication should respect the following:

- Speed: 115200 bauds
- No parity
- 1 Stop bit
- 8 data bits

Once the stimulation program is ready, according to the first part of this guide, you can send it in binary format, starting with the command "a[channel\_number]", "channel\_number" being the targeted channel on the system, from 0 to 7. If you want to send the same stimulation program to all the channels, replace "channel\_number" with "a". The corresponding command would then be "aa".

If your stimulation program is shorter than 256 row, you have to zero pad it in order to reach 256 rows.

In order to start the program counter of a given channel, send "p[channel\_number]". To start all of them, send "pa".

Finally, to send a trigger to a channel, send "t[channel\_number]", or "ta" to send a trigger to all of them.

# Author's publications

## International conferences

Castelli, J., Kölbl, F., Siu, R., N'Kaoua, G., Bornat, Y., Mangalore, A., Hillen, B., Abbas, J.J., Renaud, S., Jung, R. and Lewis, N., 2017, July. An IC-based controllable stimulator for respiratory muscle stimulation investigations. In Engineering in Medicine and Biology Society (EMBC), 2017 39th Annual International Conference of the IEEE (pp. 1970-1973). IEEE. European finalist to the Best Student Paper Competition

Jonathan Castelli, Sylvie Renaud, Yannick Bornat, Florian Kolbl, Ricardo Siu, Gilles N'Kaoua, Ashwin Mangalore, Brian Hillen, James Abbas, Noëlle Lewis and Ranu Jung. An IC-Based Controllable Stimulator For In Vivo Experiments, CRCNS Conference, October 2016, Paris

## Journal

F. Kölbl, J. Castelli, G. N'Kaoua, A. Mangalore, Y. Bornat, S. Renaud and N. Lewis, Design and validation of an IC-based multi-channel multi-application neurostimulator, 2017, submitted to IEEE Transactions on Biomedical Circuits and Systems.

# National Conferences

J. Castelli, S. Renaud and N. Lewis, Circuit de stimulation et de surveillance de l'interface tissu/implant, 2016, In GdR Soc-Sip

# Bibliography

- [1] Matthew Cobb. Timeline: exorcizing the animal spirits: Jan swammerdam on nerve function. *Nature Reviews Neuroscience*, 3(5), 2002.
- [2] Luigi Galvani and Giovanni Aldini. De Viribus Electricitatis In Motu Musculari Comentarius Cum Joannis Aldini Dissertatione Et Notis; Accesserunt Epistolae ad animalis electricitatis theoriam pertinentes. Apud Societatem Typographicam, 1792.
- [3] Alexander Volta. On the electricity excited by the mere contact of conducting substances of different kinds. in a letter from mr. alexander volta, frs professor of natural philosophy in the university of pavia, to the rt. hon. sir joseph banks, bart. kbprs. *Philosophical transactions of the Royal Society of London*, pages 403–431, 1800.
- [4] C Matteucci. Sur le courant électrique de la grenouille: second mémoire sur l'électricité animale faisant suite à celui sur la torpille. Ann Chim Phys, 6:301, 1842.
- [5] Hermann Helmholtz. Note sur la vitesse de propagation de l'agent nerveux dans les nerfs rachidiens. CR Acad Sci (Paris), 30:204–206, 1850.
- [6] J Clerk Maxwell. A dynamical theory of the electromagnetic field. Proceedings of the Royal Society of London, 13:531–536, 1863.
- [7] Julius Bernstein. Untersuchungen zur thermodynamik der bioelektrischen ströme. Archiv für die gesamte Physiologie des Menschen und der Tiere, 92(10-12):521-562, 1902.
- [8] Howard J Curtis and Kenneth S Cole. Membrane action potentials from the squid giant axon. Journal of Cellular Physiology, 15(2):147–157, 1940.
- [9] Alan L Hodgkin and Andrew F Huxley. A quantitative description of membrane current and its application to conduction and excitation in nerve. The Journal of physiology, 117(4):500-544, 1952.
- [10] A Djourno and C Eyries. Auditory prosthesis by means of a distant electrical stimulation of the sensory nerve with the use of an indwelt coiling. La Presse Médicale, 65(63):1417–1417, 1957.
- [11] Rune Elmgvist, Johan Landegren, Sven Olov Pettersson, Åke Senning, and Göran William-Olsson. Artificial pacemaker for treatment of adams-stokes syndrome and slow heart rate. *American Heart Journal*, 65(6):731–748, 1963.
- [12] B Kolb and IQ Whishaw. Cerveau et comportement [brain and behaviour] de boeck université, 2008.

- [13] Eric R Kandel, James H Schwartz, Thomas M Jessell, Steven A Siegelbaum, A James Hudspeth, et al. *Principles of neural science*, volume 4. McGraw-hill New York, 2000.
- [14] Orjan G Martinsen and Sverre Grimnes. Bioimpedance and bioelectricity basics. Academic press, 2011.
- [15] Georges Weiss. Sur la possibilite de rendre comparables entre eux les appareils servant a l'excitation electrique. Archives Italiennes de Biologie, 35(1):413–445, 1990.
- [16] L Lapique. Recherches quantitatives sur l'excitation electrique des nerfs traitee comme une polarization. J Physiol Pathol Gen, 9:620–635, 1907.
- [17] Daniel R Merrill, Marom Bikson, and John GR Jefferys. Electrical stimulation of excitable tissue: design of efficacious and safe protocols. *Journal of neuroscience methods*, 141(2):171–198, 2005.
- [18] Wassilios Meissner, Christian E Gross, Daniel Harnack, Bernard Bioulac, and Abdelhamid Benazzouz. Deep brain stimulation for parkinson's disease: Potential risk of tissue damage associated with external stimulation. *Annals of neurology*, 55(3): 449–450, 2004.
- [19] Sébastien Joucla, Matthieu Ambroise, Timothée Levi, Thierry Lafon, Philippe Chauvet, Sylvain Saïghi, Yannick Bornat, Noëlle Lewis, Sylvie Renaud, and Blaise Yvert. Generation of locomotor-like activity in the isolated rat spinal cord using intraspinal electrical microstimulation driven by a digital neuromorphic cpg. Frontiers in neuroscience, 10, 2016.
- [20] Graham Creasey, John Elefteriades, Anthony DiMarco, Pasi Talonen, et al. Electrical stimulation to restore respiration. *Journal of rehabilitation research and development*, 33(2):123, 1996.
- [21] Barbara Rolfe, Jane Mooney, Bing Zhang, Sani Jahnke, Sarah-Jane Le, Yu-Qian Chau, Qiping Huang, Hao Wang, Gordon Campbell, and Julie Campbell. The fibrotic response to implanted biomaterials: implications for tissue engineering. In Regenerative Medicine and Tissue Engineering-Cells and Biomaterials. InTech, 2011.
- [22] James M Anderson, Analiz Rodriguez, and David T Chang. Foreign body reaction to biomaterials. In *Seminars in immunology*, volume 20, pages 86–100. Elsevier, 2008.
- [23] Warren M Grill and J Thomas Mortimer. Electrical properties of implant encapsulation tissue. Annals of biomedical engineering, 22(1):23–33, 1994.
- [24] William G. Ondo, Catherine Meilak, and Kevin D. Vuong. Predictors of battery life for the Activa?? Soletra 7426 Neurostimulator. *Parkinsonism and Related Disorders*, 13(4):240–242, 2007. ISSN 13538020. doi: 10.1016/j.parkreldis.2006.11.002.
- [25] Harry G Mond, John R Helland, Kenneth Stokes, Gene A Bornzin, and RICK McVENES. The electrode-tissue interface: The revolutionary role of steroid-elution. *Pacing and Clinical Electrophysiology*, 37(9):1232–1249, 2014.

- [26] Sašo Jezernik and Manfred Morari. Energy-optimal electrical excitation of nerve fibers. *IEEE Transactions on Biomedical Engineering*, 52(4):740–743, 2005. ISSN 00189294. doi: 10.1109/TBME.2005.844050.
- [27] Thomas J Foutz and Cameron C McIntyre. Evaluation of novel stimulus waveforms for deep brain stimulation. *Journal of neural engineering*, 7(6):066008, 2010.
- [28] S C DeMarco, W Liu, P R Singh, G Lazzi, M S Humayun, and J D Weiland. An Arbitrary Waveform Stimulus Circuit for Visual Prostheses USing a Low-Area Multibias DAC. *IEEE Journal of Solid-State Circuits*, 38(10):12, 2003.
- [29] Sudip Nag and Nitish V Thakor. Implantable neurotechnologies: electrical stimulation and applications. *Medical & biological engineering & computing*, 54(1):63–76, 2016.
- [30] Henryk Skarzynski, Artur Lorens, Anna Piotrowska, and Ilona Anderson. Partial deafness cochlear implantation provides benefit to a new population of individuals with hearing loss. *Acta oto-laryngologica*, 126(9):934–940, 2006.
- [31] Ziyan Zhu, Qing Tang, Fan-Gang Zeng, Tian Guan, and Datian Ye. Cochlear-implant spatial selectivity with monopolar, bipolar and tripolar stimulation. *Hearing research*, 283(1):45–58, 2012.
- [32] Mark S Humayun. Intraocular retinal prosthesis. Transactions of the American Ophthalmological Society, 99:271, 2001.
- [33] Joseph F Rizzo, John Wyatt, John Loewenstein, Shawn Kelly, and Doug Shire. Perceptual efficacy of electrical stimulation of human retina with a microelectrode array during short-term surgical trials. *Investigative ophthalmology & visual science*, 44 (12):5362–5369, 2003.
- [34] James Weiland and Mark Humayun. Retinal prosthesis. In Neural Engineering, pages 635–655. Springer, 2013.
- [35] Edward J Tehovnik, Warren M Slocum, Stelios M Smirnakis, and Andreas S Tolias. Microstimulation of visual cortex to restore vision. *Progress in brain research*, 175: 347–375, 2009.
- [36] Marjan Jahanshahi. Effects of deep brain stimulation of the subthalamic nucleus on inhibitory and executive control over prepotent responses in parkinson's disease. *Frontiers in systems neuroscience*, 7, 2013.
- [37] Heng Guo, Hua Zhang, Yongqin Kuang, Chao Wang, Xiaorong Jing, Jianwen Gu, and Guodong Gao. Electrical stimulation of the substantia nigra pars reticulata (snr) suppresses chemically induced neocortical seizures in rats. *Journal of Molecular Neuroscience*, 53(4):546–552, 2014.
- [38] Aritra Kundu, Kristian Rauhe Harreby, Ken Yoshida, Tim Boretius, Thomas Stieglitz, and Winnie Jensen. Stimulation selectivity of the "thin-film longitudinal intrafascicular electrode"(tflife) and the "transverse intrafascicular multi-channel electrode"(time) in the large nerve animal model. *IEEE transactions on neural systems* and rehabilitation engineering, 22(2):400–410, 2014.

- [39] Stanisa Raspopovic, Marco Capogrosso, Francesco Maria Petrini, Marco Bonizzato, Jacopo Rigosa, Giovanni Di Pino, Jacopo Carpaneto, Marco Controzzi, Tim Boretius, Eduardo Fernandez, et al. Restoring natural sensory feedback in real-time bidirectional hand prostheses. *Science translational medicine*, 6(222):222ra19–222ra19, 2014.
- [40] Claudia A Angeli, V Reggie Edgerton, Yury P Gerasimenko, and Susan J Harkema. Altering spinal cord excitability enables voluntary movements after chronic complete paralysis in humans. *Brain*, 137(5):1394–1409, 2014.
- [41] Christian Ethier, Emily R Oby, MJ Bauman, and Lee E Miller. Restoration of grasp following paralysis through brain-controlled stimulation of muscles. *Nature*, 485(7398):368–371, 2012.
- [42] Romulo Fuentes, Per Petersson, William B Siesser, Marc G Caron, and Miguel AL Nicolelis. Spinal cord stimulation restores locomotion in animal models of parkinson's disease. *Science*, 323(5921):1578–1582, 2009.
- [43] John E Hall. *Guyton and Hall Textbook of Medical Physiology E-Book*. Elsevier Health Sciences, 2015.
- [44] NA Fitzsimmons, W Drake, TL Hanson, MA Lebedev, and MAL Nicolelis. Primate reaching cued by multichannel spatiotemporal cortical microstimulation. *Journal of Neuroscience*, 27(21):5593–5602, 2007.
- [45] Brian M London, Luke R Jordan, Christopher R Jackson, and Lee E Miller. Electrical stimulation of the proprioceptive cortex (area 3a) used to instruct a behaving monkey. *IEEE Transactions on Neural Systems and Rehabilitation Engineering*, 16(1):32–36, 2008.
- [46] Matthew A Schiefer, Katharine H Polasek, RJ Triolo, GCJ Pinault, and DJ Tyler. Selective stimulation of the human femoral nerve with a flat interface nerve electrode. *Journal of neural engineering*, 7(2):026006, 2010.
- [47] Noah M Ledbetter, Christian Ethier, Emily R Oby, Scott D Hiatt, Andrew M Wilder, Jason H Ko, Sonya P Agnew, Lee E Miller, and Gregory A Clark. Intrafascicular stimulation of monkey arm nerves evokes coordinated grasp and sensory responses. *Journal of neurophysiology*, 109(2):580–590, 2013.
- [48] D. Guggenmos and R. Nudo. *Clinical systems neuroscience*. Springer, 2014.
- [49] Cheryl L Lynch and Milos R Popovic. Functional electrical stimulation. IEEE control systems, 28(2):40–50, 2008.
- [50] Han-Chang Wu, Shuenn-Tsung Young, and Te-Son Kuo. A versatile multichannel direct-synthesized electrical stimulator for fes applications. In *Instrumentation* and *Measurement Technology Conference*, 2000. IMTC 2000. Proceedings of the 17th IEEE, volume 1, pages 180–185. IEEE, 2000.

- [51] Jonathan Castelli, Florian Kölbl, Ricardo Siu, Gilles N'Kaoua, Yannick Bornat, Ashwin Mangalore, Brian Hillen, James J Abbas, Sylvie Renaud, Ranu Jung, et al. An ic-based controllable stimulator for respiratory muscle stimulation investigations. In Engineering in Medicine and Biology Society (EMBC), 2017 39th Annual International Conference of the IEEE, pages 1970–1973. IEEE, 2017.
- [52] Wen-Yaw Chung, Chiung-Cheng Chuang, Yu-Liang Liao, and Cheng-Wen Chang. A new microstimulator with pulse width modulation. *Journal of Medical and Biological Engineering*, 24:125–132, 2004.
- [53] Shou-Jung Chang, Wen-Yaw Chung, and Chiung-Cheng Chuang. System design of implantable micro-stimulator for medical treatments. In *Circuits and Systems, 2006.* APCCAS 2006. IEEE Asia Pacific Conference on, pages 478–481. IEEE, 2006.
- [54] Sungjin Oh, Jae-Hyun Ahn, Jongyoon Shin, Hyoungho Ko, Yong-Sook Goo, and Dong-Il Dan Cho. Pulse count modulation based biphasic current stimulator for retinal prosthesis and in vitro experiment using rd1 mouse. In *Engineering in Medicine* and Biology Society (EMBC), 2014 36th Annual International Conference of the IEEE, pages 1711–1714. IEEE, 2014.
- [55] Han-Chang Wu, Shueun-Tsong Young, and Te-Son Kuo. A versatile multichannel direct-synthesized electrical stimulator for fes applications. *IEEE Transactions on Instrumentation and Measurement*, 51(1):2–9, 2002.
- [56] Erik A Cheever, Dirk R Thompson, Brian L Cmolik, William P Santamore, and David T George. A versatile microprocessor-based multichannel stimulator for skeletal muscle cardiac assist. *IEEE transactions on biomedical engineering*, 45(1):56–67, 1998.
- [57] Brian Smith, P Hunter Peckham, Michael W Keith, and Dennis D Roscoe. An externally powered, multichannel, implantable stimulator for versatile control of paralyzed muscle. *IEEE Transactions on Biomedical Engineering*, (7):499–508, 1987.
- [58] Milan Ilic, Dragan Vasiljevic, and Dejan B Popovic. A programmable electronic stimulator for fes systems. *IEEE Transactions on rehabilitation engineering*, 2(4): 234–239, 1994.
- [59] Karim Abdelhalim and Roman Genov. CMOS DAC-sharing stimulator for neural recording and stimulation arrays. In 2011 IEEE Int. Symp. Circuits Syst., pages 1712–1715. IEEE, May 2011.
- [60] Karim Arabi and Mohamad A Sawan. Electronic design of a multichannel programmable implant for neuromuscular electrical stimulation. *IEEE Transactions on Rehabilitation Engineering*, 7(2):204–214, 1999.
- [61] Scott K Arfin, Michael A Long, Michael S Fee, and Rahul Sarpeshkar. Wireless neural stimulation in freely behaving small animals. *Journal of neurophysiology*, 102 (1):598–605, 2009.

- [62] Scott K Arfin and Rahul Sarpeshkar. An energy-efficient, adiabatic electrode stimulator with inductive energy recycling and feedback current regulation. *IEEE transactions on biomedical circuits and systems*, 6(1):1–14, 2012.
- [63] Meysam Azin, David J. Guggenmos, Scott Barbay, Randolph J. Nudo, and Pedram Mohseni. A Battery-Powered Activity-Dependent Intracortical Microstimulation IC for Brain-Machine-Brain Interface. *IEEE J. Solid-State Circuits*, 46(4):731–745, April 2011.
- [64] Ulrich Bihr, Thomas Ungru, Hongcheng Xu, Jens Anders, Joachim Becker, and Maurits Ortmanns. A bidirectional neural interface with a hv stimulator and a lv neural amplifier. In *Circuits and Systems (ISCAS)*, 2013 IEEE International Symposium on, pages 401–404. IEEE, 2013.
- [65] R A Blum, J D Ross, E A Brown, and S P DeWeerth. An Integrated System for simultaneous, Multichannel Neuronal Stimulation and Recording. *IEEE Transactions* on circuits and systems - I: Regular papers, 54(12):11, 2007.
- [66] C W Chang, W Y Chung, C C Chuang, R L Wei, and J X Dai. A novel system design for implantable stimulator application, 2004.
- [67] S J Chang, W Y Chung, and C C Chuang. System Design of Implantable Microstimulator for Medical Treatments. *IEEE Asia Pacific Conference on Circuits and Systems*, page 4, 2006.
- [68] K Chen, Z Yang, L Hoang, J Weiland, M Humayun, and W Liu. An Integrated 256-Channel Epiretinal Prosthesis. *IEEE Journal of Solid-State Circuits*, 45(9):11, 2010.
- [69] Wei-Ming Chen, Herming Chiueh, Tsan-Jieh Chen, Chia-Lun Ho, Chi Jeng, Ming-Dou Ker, Chun-Yu Lin, Ya-Chun Huang, Chia-Wei Chou, Tsun-Yuan Fan, et al. A fully integrated 8-channel closed-loop neural-prosthetic cmos soc for real-time epileptic seizure control. *IEEE journal of solid-state circuits*, 49(1):232–247, 2014.
- [70] A H Chun, O Kavehei, N Tran, and S Skafidas. A Flexible Biphasic Pulse Generating and Accurate Charge Balancing Stimulator with a 1 microW Neural Recording Amplifier. *Circuits and Systems (ISCAS), 2013 IEEE International Symposium on*, page 4, 2013.
- [71] H Chun, T Lehmann, and Y Yang. Implantable Stimulator For Bipolar Stimulation Without Charge Balancing Circuits. In *IEEE Biomedical Circuits and Systems Conference*, page 4, 2010.
- [72] T G Constandinou, J Georgiou, and C Toumazou. A Partial-Current-Steering Biphasic Stimulation Driver for Vestibular Prostheses. *IEEE Transactions on Biomedical Circuits and Systems*, page 8, 2008.
- [73] J Coulombe, M A Sawan, and J-F. Gervais. A Highly Flexible System for Microstimulation of the Visual Cortex: Design and Implementation. *IEEE Transactions on Biomedical Circuits and Systems*, 1(4):12, 2007.

- [74] N B Dommel, Y T Wong, T Lehmann, C W Dodds, N H Lovell, and G J Suaning. A CMOS retinal neurostimulator capable of focussed, simultaneous stimulation. *Jour*nal of Neural Engineering, 6(1):10, 2009.
- [75] M N von Dongen and W A Serdijn. A Switched-Mode Multichannel Neural Stimlulator with a Minimum Number of External Components. *Circuits and Systems* (ISCAS), 2013 IEEE International Symposium on, page 4, 2013.
- [76] A Eftekhar, T G Constandinou, I F Triantis, C Toumazou, and E M Drakakis. Towards a reconfigurable sense-and-stimulate neural interface generating biphasic interleaved stimulus. *Proceedings of the 3rd International IEEE EMBS Conference* on Neural Engineering, page 4, 2007.
- [77] W Fang, J Wills, J Granacki, J LaCoss, A Arakelian, and J Weiland. Novel Charge-Metering Stimulus Amplifier for Biomimetic Implantable Prosthesis. *IEEE Interna*tional Symposium on Circuits and Systems, page 4, 2007.
- [78] J Georgiou and C Toumazou. A 126-μW Cochlear Chip for a Totally Implantable System. *IEEE Journal of Solid-State Circuits*, 40(2):14, 2005.
- [79] C S A Gong, M T Shiue, C H Su, and Y Chang. An Efficient Micro-Stimulator Array Using Unitary-Size DAC With Adiabatic Baseband Scheme. *IEEE International Conference on Electronics Circuits and Systems*, page 4, 2006.
- [80] Cihun-Siyong Alex Gong, Kai-Wen Yao, and Muh-Tian Shiue. A cmos multichannel electrical stimulation prototype system. *International Journal of Circuit Theory and Applications*, 41(3):238–258, 2013.
- [81] G Gudnason, E Bruun, and M Haugland. An implantable mixed Analog/Digital Neural Stimulator Circuit. Proceedings of the 1999 IEEE International Symposium on Circuits and Systems, page 4, 1999.
- [82] C Hitzelberger, Y Manoli, R Hakenes, and S Gross. A Microcontroller Embedded ASIC for an Implantable Electro-Neural Stimulator. Proceedings of the 27th European Solid-State Circuits Conference, page 4, 2001.
- [83] J Hu and C Gordon. A General Adaptive Charge-Balancing Stimulator. 51st Midwest Symposium on Circuits and Systems, page 4, 2008.
- [84] Dai Jiang, Andreas Demosthenous, Timothy Perkins, Xiao Liu, and Nick Donaldson. A stimulator asic featuring versatile management for vestibular prostheses. *IEEE transactions on biomedical circuits and systems*, 5(2):147–159, 2011.
- [85] D Jiang, A Demosthenous, T A Perkins, X Liu, and N Donaldson. An Implantable 3-D Vestibular Stimulator with Neural Recording. ESSCIRC (ESSCIRC), 2012 Proceedings of the, 1(1):4, 2012.
- [86] S K Kelly and J L Wyatt. A Power-Efficient Neural Tissue Stimulator With Energy Recovery. IEEE Transactions on Biomedical Circuits and Systems, 5(1):10, 2011.

- [87] P J Langlois, A Demosthenous, I Pachnis, and N Donaldson. High-Power Integrated Stimulator Output Stages With Floating Discharge Over a Wide Voltage Range for Nerve Stimulation. *IEEE Transactions on Biomedical Circuits and Systems*, 4(1):10, 2010.
- [88] H-M. Lee, H Park, and M Ghovanloo. A Power-Efficient WIreless System With Adaptive Supply Control for Deep Brain Stimulation. *IEEE Journal of Solid-State Circuits*, 48(9):14, 2013.
- [89] J Lee, H G Rhew, D Kipke, and M Flynn. A 64 Channel Programmable Closed-loop Deep Brain Stimulator with 8 Channel Neural Amplifier and Logarithmic ADC. 2008 Symposium on VLSI Circuits Digest of Technical Papers, page 2, 2008.
- [90] Chun-Yu Lin, Wei-Ling Chen, and Ming-Dou Ker. Implantable stimulator for epileptic seizure suppression with loading impedance adaptability. *IEEE transactions on biomedical circuits and systems*, 7(2):196–203, 2013.
- [91] W Liu, K Vichienchom, M Clements, S C DeMarco, C Hughes, E McGucken, M S Humayun, E de Juan, S D Weilan, and R Greenberg. A Neuro-Stimulus Chip with Telemetry Unit for Retinal Prosthetic Device. *IEEE Journal of Solid-State Circuits*, 35(10):11, 2000.
- [92] X Liu, A Demosthenous, and N Donaldson. A Stimulator Output Stage with Capacitor Reduction and Failure-Checking Techniques. *IEEE ISCAS*, page 4, 2006.
- [93] X Liu, A Demosthenous, and N Donaldson. An integrated Stimulator With DC-Isolation and Fine Current Control for Implanted Nerve Tripoles. *IEEE Journal of Solid-State Circuits*, 46(7):14, 2011.
- [94] X Liu, A Demosthenous, A Vanhoestenberghe, D Jiang, and N Donaldson. Active Books: The Design of an Implantable Stimulator That Minimizes Cable Count Using Integrated Circuits Very Close to Electrodes. *IEEE Transactions on Biomedical Circuits and Systems*, 6(3):12, 2012.
- [95] P Nadeau and M Sawan. A flexible high voltage biphasic current-controlled stimulator. *IEEE*, page 4, 2006.
- [96] W Ngamkham, M N Van Dongen, W A Serdijn, C J Bes, J J Briaire, and J H M Frijns. for cochlear implants suitable for a large number of channels. pages 1–13.
- [97] E Noorsal, K Sooksood, H Xu, R Hornig, J Becker, and M Ortmanns. A Neural Stimulator Frontend With High-Voltage Compliance and Programmable Pulse Shape for Epiretinal Implants. *IEEE Journal of Solid-State Circuits*, 47(1):13, 2012.
- [98] M Ortmanns, A Rocke, M Gehrke, and H-J. Tiedkte. A 232-Channel Epiretinal Stimulator ASIC. *IEEE Journal of Solid-State Circuits*, 42(12):14, 2007.
- [99] F Shahrokhi, K Abdelhalim, D Serletis, P L Carlen, and R Genov. The 128-Channel Fully Differential Digital Integrated Neural Recording and Stimulation Interface. *IEEE Transactions on Biomedical Circuits and Systems*, 4(3):13, 2010.

- [100] D L Shen and Y J Chu. A Linearized Current Stimulator for Deep Brain Stimulation, 2010.
- [101] Ruslana Shulyzki, Karim Abdelhalim, and Roman Genov. Cmos current-copying neural stimulator with ota-sharing. In *Circuits and Systems (ISCAS), Proceedings* of 2010 IEEE International Symposium on, pages 1232–1235. IEEE, 2010.
- [102] Ji-Jon Sit and Rahul Sarpeshkar. A low-power blocking-capacitor-free chargebalanced electrode-stimulator chip with less than 6 na dc error for 1-ma full-scale stimulation. *IEEE Transactions on Biomedical Circuits and Systems*, 1(3):172–183, 2007.
- [103] M Sivarprakasam, W Liu, M Humayun, and J D Weiland. A Variable Range Bi-phasic Current Stimulus Driver Circuitry for an Implantable Retinal Prosthetic Device. *IEEE Journal of Solid-State Circuits*, 40(3):9, 2005.
- [104] F Soulier, J B Lerat, L Gouyet, S Bernard, and G Cathebras. A Neural Stimulator Output Stage for Dodecapolar Electrodes. *IEEE Computer Society Annua Symposion* on VLSI, page 4, 2008.
- [105] G J Suaning and N H Lovell. CMOS Neurostimulation ASIC with 100 CHannels, Scaleable Output, and Bidirectional Radio-Frequency Telemetry. *IEEE Transactions* on Biomedical Engineering, 48(2):13, 2001.
- [106] J Y J Tan, X Liu, K H Wee, S C Yen, Y P Xu, and T C Tan. A Monolithic Programmable Nerve/ Muscle Stimulator, 2011.
- [107] S D Techer, S Bernard, Y Bertrand, G Cathébras, and D Guiraud. New Implantable Stimulator for the FES of Paralyzed Muscles. Solid-State Circuits Conference, 2004. ESSCIRC 2004. Proceeding of the 30th European, page 4, 2004.
- [108] T Tokuda, K Hiyama, S Sawamura, K Sasagawa, Y Terasawa, K Nishida, Y Kitaguchi, T Fujikado, Y Tano, and J Ohta. CMOS-Based Multichip Networked Flexible Retinal Stimulator Designed for Image-Based Retinal Prosthesis. *IEEE Transactions on Electron Devices*, 56(11):9, 2009.
- [109] P R Troyk, V K Meshahwar, R B Stein, S Suh, and D Everaert. An Implantable Neural Stimulator for Intraspinal MicroStimulation. 34th Annual International Conference of the IEEE EMBS, 1(1):4, 2012.
- [110] V Valente, A Demosthenous, and R Bayford. Design of a Current-Steering Implantable Stimulator with Electric Field Shifting for Deep Brain Stimulation. *IEEE*, page 4, 2010.
- [111] V Valente, A Demosthenous, and R Bayford. A Tripolar Current-Steerin Stimulator ASIC for Field Shaping in Deep Brain Stimulation. *IEEE Transactions on Biomedical Circuits and Systems*, 6(3):11, 2012.
- [112] I Williams and T G Constandinou. An Energy-Efficient, Dynamic VOltage Scaling Neural Stimulator for a Proprioceptive Prosthesis. *IEEE Transactions on Biomedical Circuits and Systems*, 7(2):10, 2013.
- [113] Florian Kolbl. Design of elecrical adaptive stimulators for different pathological contexts, a global approach. PhD thesis, University of Bordeaux, 2014.
- [114] R. D. Klafter and L. Hrebien. An in vivo study of cardiac pacemaker optimization by pulse shape modification. *IEEE Transactions on Biomedical Engineering*, 23(3):233– 9, 1976. ISSN 0018-9294. URL http://www.ncbi.nlm.nih.gov/pubmed/1262034.
- Tie. Non-rectangular waveforms for neural [115] Mesut Sahin and Yanmei stimulation with practical electrodes. Journal of neural engineering, 4 (3):227-33,2007.ISSN 1741-2560. doi: 10.1088/1741-2560/4/3/008.URL http://www.pubmedcentral.nih.gov/articlerender.fcgi?artid= 3759998{&}tool=pmcentrez{&}rendertype=abstract.
- [116] Thomas J Foutz and Cameron C McIntyre. Evaluation of novel stimulus waveforms for deep brain stimulation. Journal of Neural Engineering, 7(6):066008, 2010. ISSN 1741-2560. doi: 10.1088/1741-2560/ 7/6/066008. URL http://stacks.iop.org/1741-2552/7/i=6/a=066008?key= crossref.95bccb7b5d8fda3742b961c8d9996b7d.
- [117] Amorn Wongsarnpigoon and Warren M Grill. Energy-efficient waveform shapes for neural stimulation revealed with a genetic algorithm. *Journal of neural engineering*, 7(4):046009, 2010.
- [118] Warren M Grill. Model-based analysis and design of waveforms for efficient neural stimulation. Progress in brain research, 222:147–162, 2015.
- [119] Georg Wick, Cecilia Grundtman, Christina Mayerl, Thomas-Florian Wimpissinger, Johann Feichtinger, Bettina Zelger, Roswitha Sgonc, and Dolores Wolfram. The immunology of fibrosis. Annual review of immunology, 31:107–135, 2013.
- [120] Petr Dvorak, Miroslav Novak, Pavel Kamaryt, Bronislava Slana, Jolana Lipoldova, and Pavel Dvorak. Histological findings around electrodes in pacemaker and implantable cardioverter-defibrillator patients: comparison of steroid-eluting and nonsteroid-eluting electrodes. *Europace*, 14(1):117–123, 2011.
- [121] Brian Goldstein, Dongsoo Kim, Jian Xu, T Kyle Vanderlick, and Eugenio Culurciello. Cmos low current measurement system for biomedical applications. *IEEE transactions on biomedical circuits and systems*, 6(2):111–119, 2012.
- [122] B Sanchez, A Guasch, P Bogonez, C Galvez, V Puig, C Prat, CE Semino, A Bayes-Genis, and R Bragos. Towards on line monitoring the evolution of the myocardium infarction scar with an implantable electrical impedance spectrum monitoring system. In Engineering in Medicine and Biology Society (EMBC), 2012 Annual International Conference of the IEEE, pages 3223–3226. IEEE, 2012.
- [123] Justin C Williams, Joseph A Hippensteel, John Dilgen, William Shain, and Daryl R Kipke. Complex impedance spectroscopy for monitoring tissue responses to inserted neural implants. *Journal of neural engineering*, 4(4):410, 2007.

- [124] GC McConnell, RJ Butera, and RV Bellamkonda. Bioimpedance modeling to monitor astrocytic response to chronically implanted electrodes. *Journal of neural engineer*ing, 6(5):055005, 2009.
- [125] André Mercanzini, Philippe Colin, Jean-Charles Bensadoun, Arnaud Bertsch, and Philippe Renaud. In vivo electrical impedance spectroscopy of tissue reaction to microelectrode arrays. *IEEE Transactions on biomedical engineering*, 56(7):1909– 1918, 2009.
- [126] T Dowrick, C Blochet, and D Holder. In vivo bioimpedance measurement of healthy and ischaemic rat brain: implications for stroke imaging using electrical impedance tomography. *Physiological measurement*, 36(6):1273, 2015.
- [127] Zbigniew Czaja. A microcontroller system for measurement of three independent components in impedance sensors using a single square pulse. Sensors and Actuators A: Physical, 173(1):284-292, jan 2012. ISSN 09244247. doi: 10. 1016/j.sna.2011.10.018. URL http://linkinghub.elsevier.com/retrieve/pii/ S0924424711006091.
- [128] Yi-Kai Lo, Chih-Wei Chang, and Wentai Liu. Bio-impedance characterization technique with implantable neural stimulator using biphasic current stimulus. 2014 36th Annual International Conference of the IEEE Engineering in Medicine and Biology Society, pages 474-477, aug 2014. doi: 10.1109/EMBC.2014.6943631. URL http://ieeexplore.ieee.org/lpdocs/epic03/wrapper.htm?arnumber=6943631.
- [129] Arantxa Uranga, Jordi Sacristán, Teresa Osés, and Núria Barniol. Electrode Tissue Impedance Measurement CMOS ASIC for Functional Electrical Stimulation Neuroprostheses. 56(5):2043–2050, 2007.
- [130] J L Ausín, J Ramos, and G Torelli. Live Demonstration : A Wireless Multichannel Bio- impedance Spectrometer for Patient Monitoring. (April):2013, 2013.
- [131] Xiaowen Liu, Daniel Rairigh, and Andrew Mason. A fully integrated multichannel impedance extraction circuit for biosensor arrays. *Proceedings of 2010 IEEE International Symposium on Circuits and Systems*, pages 3140–3143, may 2010. doi: 10.1109/ISCAS.2010.5537965. URL http://ieeexplore.ieee.org/lpdocs/ epic03/wrapper.htm?arnumber=5537965.
- [132] Iasonas F. Triantis, Andreas Demosthenous, Mohamad Rahal, Hongwei Hong, and Richard Bayford. A multi-frequency bioimpedance measurement ASIC for electrical impedance tomography. 2011 Proceedings of the ESSCIRC (ESSCIRC), pages 331– 334, sep 2011. doi: 10.1109/ESSCIRC.2011.6044974. URL http://ieeexplore. ieee.org/lpdocs/epic03/wrapper.htm?arnumber=6044974.
- [133] Tomas Garcia-Sanchez, Antoine Azan, Isabelle Leray, Javier Rosell-Ferrer, Ramon Bragos, and Lluis M Mir. Interpulse multifrequency electrical impedance measurements during electroporation of adherent differentiated myotubes. *Bioelectrochemistry*, 105:123–135, 2015.

- [134] Gerard Amorós-Figueras, Esther Jorge, Tomás García-Sánchez, Ramón Bragós, Javier Rosell-Ferrer, and Juan Cinca. Recognition of fibrotic infarct density by the pattern of local systolic-diastolic myocardial electrical impedance. *Frontiers in physiology*, 7, 2016.
- [135] J. Castelli et al. F. Kolbl. Design and validation of an ic-based multi-channel multiapplication neurostimulator. *TBCAS*, 0(0):0, 2018.
- [136] Hussein Ballan and Michel Declercq. High voltage devices and circuits in standard CMOS technologies. Springer Science & Business Media, 2013.
- [137] Martin Knaipp, Jong Mun Park, and Verena Vescoli. Evolution of a cmos based lateral high voltage technology concept. *Microelectronics journal*, 37(3):243–248, 2006.
- [138] Richard M Forsyth. Technology and design of integrated circuits for up to 50 v applications. In *Industrial Technology*, 2003 IEEE International Conference on, volume 1, pages 7–13. IEEE, 2003.
- [139] John J Como, Erica RH Sutton, Maureen McCunn, Richard P Dutton, Steven B Johnson, Bizhan Aarabi, and Thomas M Scalea. Characterizing the need for mechanical ventilation following cervical spinal cord injury with neurologic deficit. *Journal* of Trauma and Acute Care Surgery, 59(4):912–916, 2005.
- [140] Chester H Ho, Ronald J Triolo, Anastasia L Elias, Kevin L Kilgore, Anthony F DiMarco, Kath Bogie, Albert H Vette, Musa L Audu, Rudi Kobetic, Sarah R Chang, et al. Functional electrical stimulation and spinal cord injury. *Physical medicine and rehabilitation clinics of North America*, 25(3):631–654, 2014.
- [141] AM Zbrzeski, Ricardo Siu, Yannick Bornat, BK Hillen, Ranu Jung, and Sylvie Renaud. A versatile fast-development platform applied to closed-loop diaphragmatic pacing. In *Neural Engineering (NER), 2015 7th International IEEE/EMBS Conference on*, pages 791–794. IEEE, 2015.
- [142] Florian Kölbl, Gilles N'Kaoua, Frédéric Naudet, Florent Berthier, Emilie Faggiani, Sylvie Renaud, Abdelhamid Benazzouz, and Noëlle Lewis. An embedded deep brain stimulator for biphasic chronic experiments in freely moving rodents. *IEEE transactions on biomedical circuits and systems*, 10(1):72–84, 2016.
- [143] Ranu Siu Ricardo Abbas, J. James Jung. Parametrization of a closed-loop adaptive controller for respiratory pacing in a rodent model. 2016 Neuroscience Meeting Planner, 2016.
- [144] Martin Deterre. Toward an energy harvester for leadless pacemakers. PhD thesis, Univ. Paris-Sud, 2013.
- [145] Robert C Rennert, Kristine Rustad, Kemal Levi, Mark Harwood, Michael Sorkin, Victor W Wong, Amin Al-Ahmad, Paul Zei, Henry Hsia, Ramin E Beygui, et al. A histological and mechanical analysis of the cardiac lead-tissue interface: implications for lead extraction. Acta biomaterialia, 10(5):2200–2208, 2014.

[146] Mesut Sahin and Yanmei Tie. Non-rectangular waveforms for neural stimulation with practical electrodes. *Journal of neural engineering*, 4(3):227, 2007.