

Contents

Acknowledgements	v
Abstract (English/Français)	vii
List of figures	xiv
List of tables	xvi
1 Introduction	1
1.1 The somatosensory system	2
1.1.1 Anatomy and sensory processing	3
1.1.2 Heterogeneity of the primary sensory neurons	3
1.2 Clinical relevance for neuromodulation therapies	5
1.2.1 The chronic pain burden	5
1.2.2 Spinal cord injuries	7
1.3 Modalities for neural activity modulation	7
1.3.1 Electrical stimulation	8
1.3.2 Optical stimulation	9
1.4 Interfacing soft neural tissues	11
1.5 Outline of the thesis	13
2 Optical cuff for optogenetics in the peripheral nervous system	15
2.1 Background and state of the art	16
2.1.1 Light delivery strategies for optogenetics in the PNS	16
2.1.2 Optical stimulation using optic fibers	18
2.1.3 Mechanical and optical nerve properties	19
2.2 The optocuff, an optical interface with the PNS	21
2.2.1 Optocuff fabrication	21
2.2.2 Optocuff bio-integration	22
2.3 Epineural optogenetic stimulation	23
2.3.1 ChR2 expression in Thy1 ⁺ neurons	23
2.3.2 Orderly recruitment of motor units	23
2.3.3 Optocuff stimulation in awake, freely-behaving mice	24
2.4 Discussion	26

2.5	Conclusion	28
2.6	Contribution	28
3	A wireless optoelectronic system for optogenetic control of the peripheral nervous system	29
3.1	Optoelectronic wireless systems in optogenetics	30
3.1.1	μ -LED: an implantable light source	30
3.1.2	Wireless system technologies	32
3.1.3	An ultra-miniaturized wireless head-stage	33
3.2	A soft μ -LED-based peripheral interface	35
3.2.1	μ -LED array microfabrication	35
3.2.2	Integration of μ -LEDs on a flexible substrate	36
3.2.3	Characterisation of the μ -LED array	37
3.2.4	μ -LED array bio-integration	42
3.3	Remote optogenetic stimulation of peripheral pain pathways	44
3.3.1	Targeted expression of ChR2 in TRPV1 ⁺ neurons	45
3.3.2	Single-pulse optogenetic activation of nociceptors	46
3.3.3	Conditioned place aversion	47
3.3.4	Study of the neuroimmune interaction	49
3.4	Discussion	51
3.5	Conclusion	52
3.6	Contribution	53
4	A transversal spinal electrode array for rehabilitation of locomotion after spinal cord injury	55
4.1	Epidural electrical stimulations to restore locomotion after SCI	56
4.1.1	Specific recruitment of sensory proprioceptive neurons	56
4.1.2	Spinal implant neurotechnologies	57
4.2	A soft transversal epidural spinal implant, the belt array	58
4.2.1	Micro-cracked gold film topography	59
4.2.2	Soft neurotechnology for transversal spinal array	62
4.2.3	Belt array functionality	64
4.2.4	Belt array biocompatibility	67
4.3	Selective, multipolar stimulation of the spinal cord	68
4.3.1	Spatially-selective electrode distribution	68
4.3.2	Acute multipolar stimulation of the spinal cord	69
4.3.3	Multipolar stimulation combined with spatiotemporal neuromodulation	71
4.4	Discussion	73
4.5	Conclusion	75
4.6	Contribution	76

5	A soft optoelectronic implant for optogenetics in deep spinal structures	77
5.1	Background and state of the art	78
5.1.1	Fiber-based interfaces with the spinal cord	78
5.1.2	Optoelectronics interfacing with the spinal cord	79
5.2	A soft spinal optoelectronic implant	80
5.2.1	Spinal μ -LED array microfabrication	80
5.2.2	Spinal μ -LED array functionality	82
5.2.3	Optical and thermal modelling	85
5.2.4	Bio-integration of the spinal μ -LED array	87
5.3	Epidural optogenetic stimulation in the spinal cord	90
5.4	Discussion	94
5.5	Conclusion	95
5.6	Contribution	96
6	Discussion and perspectives	97
6.1	Selective neuromodulation	97
6.2	Towards softer and more robust neurotechnologies	98
6.3	The advent of optogenetics and novel modalities for parsing the nervous system	100
6.4	Translation to the clinic	101
A	Appendix	103
A.1	Optical cuff for optogenetics in the peripheral nervous system	103
A.1.1	Optocuff implantation	103
A.1.2	Thy1::ChR2 mouse breeding	104
A.1.3	Mechanical sensitivity assessment	104
A.1.4	Thermal sensitivity assessment	104
A.1.5	Dynamic weight bearing	104
A.1.6	Motor sciatic nerve assessment	104
A.1.7	DRG neuron culture and electrophysiology	105
A.1.8	Histology and immunohistochemistry	105
A.1.9	EMG electrode implantation and data acquisition	106
A.1.10	Optogenetic control <i>in vivo</i> and high-speed behavioural imaging	106
A.1.11	Stretchable optic fiber fabrication	106
A.2	A wireless optoelectronic system for optogenetic control of the peripheral nervous system	108
A.2.1	Meander-track geometry	108
A.2.2	μ -LED implant surgery	108
A.2.3	Histology and immunochemistry	109
A.2.4	Behavioural experiments	110
A.2.5	ChR2 expression in TRPV1 ⁺ neurons	111
A.2.6	Single pulse optogenetic stimulation <i>in vivo</i>	111
A.2.7	Conditioned place aversion	111
A.2.8	Flow cytometry	112

- A.3 A transversal spinal electrode array 113
 - A.3.1 Dorsal root trajectories 113
 - A.3.2 Scanning electron microscopy and micro-cracked gold morphology 113
 - A.3.3 Surface topography measurement and analysis 114
 - A.3.4 Electrochemical characterization of belt electrodes under elongation 115
 - A.3.5 Surgical procedures 115
 - A.3.6 Microcomputed tomography 116
 - A.3.7 Histology of the spinal cord 116
 - A.3.8 Acute EES of the spinal cord 117
 - A.3.9 Spinal cord injury model 117
 - A.3.10 Rehabilitation after spinal cord injury 118
 - A.3.11 Belt array substrate and superstrate material properties 120
- A.4 A soft optoelectronic implant for optogenetics in deep spinal structures 121
 - A.4.1 Comparison between the peripheral and spinal optoelectronic implants 121
 - A.4.2 Model of the light propagation in the spinal cord 121
 - A.4.3 Thermal model 122
 - A.4.4 Spinal μ -LED array implantation 122
 - A.4.5 Microcomputed tomography 123
 - A.4.6 Histology and immunochemistry 123
 - A.4.7 EMG electrode implantation and data acquisition 123

- Bibliography** **148**
- Glossary** **149**
- Curriculum Vitae** **151**