Thesis for the Degree of Doctor of Philosophy

Towards clinically viable neuromuscular control of bone-anchored prosthetic arms with sensory feedback

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Front Cover: The figure on the front cover is composed by an illustration of the Artificial Limb Controller (ALC) connected to a prosthetic arm and to the e-OPRA Implant System. It also includes a picture of the first e-OPRA patient grasping a delicate item while blindfolded.
ALC illustration and front cover graphics by Jason Millenaar and Sara Manca.

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Dedicated to the memories of my mother Rosanna (1960-2016) and my friend Luca (1986-2016).

Abstract

Promising developments are currently ongoing worldwide in the field of neuroprosthetics and artificial limb control. It is now possible to chronically connect a robotic limb to bone, nerves, and muscles of a human being, and to use the signals sourced from these connections to enable movements of the artificial limb. It is also possible to surgically redirect a nerve, deprived from its original target muscle due to amputation, to a new target in order to restore the original motor functionality. Intelligent signal processing algorithms can now utilize the bioelectric signals gathered from remaining muscles on the stump to decode the motor intention of the amputee, providing an intuitive control interface. Unfortunately, clinical implementations still lag behind the advancements made in research, and the conventional solutions for amputees have remained largely unchanged for decades. More efforts are needed from researchers to close the gap between scientific developments and clinical practices.

This thesis ultimately focuses on the intuitive control of a prosthetic upper limb. In the first part of this doctoral project, an embedded system capable of prosthetic control via the processing of bioelectric signals and pattern recognition algorithms was developed. The design included a neurostimulator to provide direct neural feedback modulated by sensory information from artificial sensors. The system was designed towards clinical implementation and its functionality was proven by its use by amputee subjects in daily life. This system was then used during the second part of the doctoral project as a research platform to monitor prosthesis usage and training, machine learning based control algorithms, and neural stimulation paradigms for tactile sensory feedback. Within this work, a novel method for interfacing a multi-grip prosthetic hand to facilitate posture selection via pattern recognition was proposed. Moreover, the need for tactile sensory feedback was investigated in order to restore natural grasping behavior in amputees. Notably, the benefit for motor coordination of somatotopic tactile feedback achieved via direct neural stimulation was demonstrated. The findings and the technology developed during this project open to the clinical use of a new class of prosthetic arms that are directly connected to the neuromusculoskeletal system, intuitively controlled and capable of tactile sensory feedback.

Keywords: Electromyography (EMG), Osseointegration, Enhanced Osseointegrated Prostheses for the Rehabilitation of Amputees (e-OPRA), Prosthetic Controller, Sensory Feedback, Myoelectric Pattern Recognition, Closed-loop control

Preface

This thesis is a fulfillment for the degree of Doctor of Philosophy at Chalmers University of Technology within the context of the Author's industrial doctorate project.

The work resulting in this thesis was carried out between October 2014 and May 2019 between the Biomechatronics and Neurorehabilitation Laboratory within the Biomedical Signals and Systems Research Unit at the Department of Electrical Engineering of Chalmers, and Integrum AB, Mölndal.

Associate Professor Max Ortiz Catalan was the main supervisor. In addition, Professor Bo Håkansson and Associate Professor Sabine Reinfeldt were co-supervisors.

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Lastly, to all researchers and scientists who gave, and give everyday, their contribution to the field, with sincere apologizes to those who, erroneously, were left out from the citations' list.

List of Publications

This thesis is based on the work contained in the following appended papers:

Paper I
"Embedded System for Prosthetic Control Using Implanted Neuromuscular Interfaces Accessed Via an Osseointegrated Implant", Mastinu, E., Doguet, P., Botquin, Y., Håkansson, B., and Ortiz-Catalan, M.
Published on *IEEE Transactions in Biomedical Circuits and Systems*, vol. 11, no. 4, pp. 867-877, 2017.

Paper II
"An Alternative Myoelectric Pattern Recognition Approach for the Control of Hand Prostheses: A Case Study of Use in Daily Life by a Dysmelia Subject", Mastinu, E., Ahlberg, J., Lendaro, E., Hermansson, L., Håkansson, B., and Ortiz-Catalan, M.
Published on *IEEE Journal of Translational Engineering in Health and Medicine*, vol. 6, pp. 1-12, 2018.

Paper III
"Myoelectric signals and pattern recognition from implanted electrodes in two TMR subjects with an osseointegrated communication interface", Mastinu, E., Brånemark, R., Aszmann, O. and Ortiz-Catalan, M.
Published on *Proceedings of the 40th Annual International Conference of the IEEE Engineering in Medicine and Biology Society, July 18-21, 2018, Honolulu, U.S.A.*, pp. 5174–5177, 2018.

Paper IV
"Grip control and motor coordination with implanted and surface electrodes while grasping with an osseointegrated prosthetic hand", Mastinu, E., Clemente, F., Sassu, P., Aszmann, O., Brånemark, R., Håkansson, B., Controzzi, M., Cipriani, C., and Ortiz-Catalan, M.
Published on *Journal of NeuroEngineering and Rehabilitation*, vol. 16, no. 1, pp. 49, 2019.

Paper V
”Motor coordination in closed-loop control of osseo-neuromuscular upper limb prostheses”, Mastinu, E., Engels, L. F., Clemente, F., Dione, M., Sassu, P., Aszmann, O., Brånemark, R., Håkansson, B., Controzzi, M., Wessberg, J., Cipriani, C., and Ortiz-Catalan, M.
Included as draft manuscript, 2019.

Other related publications of the Author not included in this thesis:

- ”Real-time classification of non-weight bearing lower limb movements using EMG to facilitate phantom motor execution: engineering and case study application on phantom limb pain”, Lendaro, E., Mastinu, E., Håkansson, B., and Ortiz-Catalan, M., Published on *Journal of Frontiers in Neurology, section Neuroprosthetics*, vol. 8, pp. 1-12, 2017.
- ”Evaluation of Computer-Based Target Achievement Tests for Myoelectric Control”, Gusman, J., Mastinu, E., and Ortiz-Catalan, M., Published *IEEE Journal of Translational Engineering in Health and Medicine*, vol. 5, pp. 1-10, 2017.
- ”Stationary Wavelet Processing and Data Imputing in Myoelectric Pattern Recognition on a Low-Cost Embedded System”, Naber, A., Mastinu, E., and Ortiz-Catalan, M., Manuscript ready for submission to *IEEE Transactions on Neural Systems and Rehabilitation Engineering*, 2017.
- ”Analog Front-Ends comparison in the way of a portable, low-power and low-cost EMG controller based on Pattern Recognition”, Mastinu, E., Ortiz-Catalan, M., and Håkansson, B., *Proceedings of the 37th Annual International Conference of the IEEE Engineering in Medicine and Biology Society, August 25-29, 2015, Milano, Italy*, vol. 64, no. 4, pp. 2263–2269, 2015.
- ”Digital Controller for Artificial Limbs fed by Implanted Neuromuscular Interfaces via Osseointegration”, Mastinu, E., Ortiz-Catalan, M., and Håkansson, B., *Proceedings of the 38th Annual International Conference of the IEEE Engineering in Medicine and Biology Society, August 16-20, 2016, Orlando, U.S.A.*, 2016.
- ”Digital Controller for Artificial Limbs fed by Implanted Neuromuscular Interfaces via Osseointegration”, Mastinu, E., Håkansson, B., and Ortiz-Catalan, M., *Proceedings of the Trent International Prosthetic Symposium, September 28-30, 2016, Glasgow, Scotland*, 2016.
- ”Direct Neural Sensory Feedback and Control via Osseointegration”, Ortiz-Catalan, M., Mastinu, Brånemark, R., and Håkansson, B., *Proceedings of the 16th World Congress from the International Society for Prosthetics and Orthotics, May 8-11, 2017, Cape Town, South Africa*, 2017.
- ”Low-cost, open source bioelectric signal acquisition system”, Mastinu, E., Håkansson, B., and Ortiz-Catalan, M., *Proceedings of the 14th Annual International Conference on Wearable and Implantable Body Sensor Networks of the IEEE Engineering in Medicine and Biology Society, May 9-12, 2017, Eindhoven, Netherlands*, vol. 26, no. 4, pp. 261-263, 2017.

- ”Embedded Controller for Pattern Recognition and Neural Stimulation via Osseointegration”, Mastinu, E., Håkansson, B., and Ortiz-Catalan, M., *Proceedings of the* 2^{nd} *International Symposium on Innovations in Amputation Surgery and Prosthetic Technologies, May 10-12, 2018, Vienna, Austria*, 2018.

- ”Crosstalk Reduction in Epimysial EMG Recordings from Transhumeral Amputees with Principal Component Analysis”, Matran-Fernandez, A., Mastinu, E., Poli, R. Ortiz-Catalan, M., and Citi, L., Published on *Proceedings of the* 40^{th} *Annual International Conference of the IEEE Engineering in Medicine and Biology Society, July 18-21, 2018, Honolulu, U.S.A.*, pp. 5174–5177, 2018.

Abbreviations and Acronyms

ALC	Artificial Limb Controller
DC	Direct Control
DeTOP	Dexterous Transradial Osseointegrated Prosthesis
DoF	Degrees-of-Freedom
DSP	Digital Signal Processor
EMG	Electromyography
ENG	Electroneurography
e-OPRA	Enhanced Osseointegrated Prostheses for the Rehabilitation of Amputees
IMES	Implantable Myoelectric Sensor
MCU	Microcontroller Unit
MPR	Myoelectric Pattern Recognition
OHMG	Osseointegrated Human-Machine Gateway
OPRA	Osseointegrated Prostheses for the Rehabilitation of Amputees
FPGA	Field Programmable Gate Arrays
RPNI	Regenerative Peripheral Nerve Interface
TMR	Targeted Muscle Reinnervation
TSR	Targeted Sensory Reinnervation

Contents

I Introductory Chapters

II Included Papers

Part I

Introductory Chapters

Chapter 1

Introduction

The human hand consists of 27 bones, 28 muscles, 3 major nerves, multiple tendons, as well as arteries, veins and soft tissue. It is an incredibly complex system with a huge spectrum of functionality. Hands are essential not only to interact with different objects daily, but also necessary for social interactions, such communication and arts. The loss of a hand is a terrific traumatic experience, usually followed by significant psychological and rehabilitation challenges. The interaction between engineering and science has, for a long time, been pointed towards the restoration of the functionality of a lost limb, and this thesis aims to contribute to such goal.

1.1 Scope and Structure of the Thesis

This doctorate thesis is focused on the natural and intuitive control of an artificial limb to replace the lost functionality in cases of upper limb amputation. Electromyographic (EMG) (also defined as myoelectric) signals and their application for prosthetic control is an imperative background concept for this thesis.

Most of the efforts gathered for this doctoral project are logical consequential steps to a previous study where an osseointegrated human-machine interface was developed and implanted on a pilot subject [1]. This interface, shortly thereafter named e-OPRA, established a long-term interface to the bone, muscles, and nerves of a patient thanks to an osseointegrated percutaneous titanium implant, epimysial and cuff electrodes, and bidirectional feedthrough mechanisms. The osseointegration creates a stable mechanical attachment of the prosthesis, while the implanted electrodes provide long-term stable access to bioelectric signal sources and sites for peripheral nerves stimulation. The work carried within this doctoral project served dual purposes. Initially, the efforts came as an answer to a particular demand: the need of an advanced electronic control system compatible with the e-OPRA, capable of state-of-the-art processing algorithms and of direct neural stimulation. Therefore, the focus was set on the development and the validation of an embedded system to exploit the advantages of the e-OPRA for closed-loop prosthetic control, namely, to concurrently enable intuitive motor control and sensory feedback. Within the validation process, it was shown that this system can be used in conjunction with implanted electrodes (within the context of the e-OPRA) as well as with less invasive sensors (surface EMG electrodes). Once this package of hardware and software was made available for the e-OPRA recipients, the focus of the doctoral project moved to additional scientific investigations on prosthetic control of these particular subjects. In particular, the experiments performed suggested an inefficacy of visual-auditory-osseoperceptive incidental sensory feedback available to e-OPRA subjects to restore normal grasp behavior, and the consequent need for complementing this information with direct neural stimulation.

The thesis includes an introduction to the field, providing the reader with some of the background knowledge needed for the attached articles. Chap. 2 presents the current conventional clinical solutions for prosthetic applications, while Chap. 3 introduces the reader to some of the most advanced surgical techniques available today for amputees. Chap. 4 briefly points out the contraposition between the conventional control strategy for operating artificial upper limbs and the state-of-the-art strategy pushed forward by researchers, namely myoelectric pattern recognition (MPR), which is defined as capable of providing intuitive prosthetic control. Some MPR applications and examples are furtherly reported on Chap. 5. Chap. 6 outlines some of the main challenges and achievements in matter of neural interfaces, while Chap. 7 describes the concept of closed-loop prosthetic control. The latest advancements regarding the Artificial Limb Controller, the closed-loop prosthetic controller developed within the scope of this project, are included in the Chap. 8. Here, the latest hardware and software revision of the system is briefly presented.

In the second part of the thesis, five scientific articles developed within the time of this doctoral project are included. A brief description of their contributions can be found in Chap. 9.

Chapter 2

Conventional Clinical Solutions

Despite the amount of research spent over the last decades in the prosthetic field, the main solutions clinically available for patients remained basically unchanged in the last 40 years. In order to restore the functionality of a lost limb, two challenges need to be addressed: how to attach the prosthesis to the body, and how to functionally control the artificial limb. Suspended sockets are usually provided to patients to secure, by compression of the skin, the prosthetic extremity. The terminal devices can then be driven via either a system of cables (body-powered) or via bioelectric signal measured on the skin surface at the stump level (myoelectric), as shown from Fig. 2.1.

2.1 Suspended Sockets

The conventional method for attaching a prosthesis to the patient's stump is via a suspended socket. Sockets rely on mechanically compressing the tissues in the stump to secure the artificial limb. Therefore, skin contact and friction are essential elements for the attachment. The socket must be custom made according to the stump of each patient. There are several drawbacks related to the use of suspended sockets, of which the major ones are listed in the following:

- skin irritation or inflammation
- poor fit and mechanical reliability
- limited range of motion
- limitations in use due to environment temperature conditions
- sweating causing unpleasant smelling.

Depending on the patient and on his/her level of physical activity, these problems can escalate from an uncomfortable situation to a point where they can actually prevent the patient to wear the prosthesis. Today, suspended sockets are widely identified as one of the major source of issues for amputees all over the world.

2.2 Body-Powered Prostheses

The concept of an upper limb prosthesis driven by remaining parts of the body was pioneered in Germany at the beginning of the 19th century. Such device represents the first documented example of a so called ”body-powered” prosthesis. It relied on trunk movements transferred from a shoulder girdle to a terminal device through leather straps (Fig. 2.1, left). Since then, the biggest technologic improvement for body-powered prostheses came in 1948, when the first device using a Bowden cable was introduced. The body-powered prostheses available today are essentially optimizations of that design [2].

Regardless the simplicity of their design and the not-anthropomorphic appearance (most commonly a two-pronged hook), body-powered prostheses are still widely diffused in the amputees’ community [3]. This longevous success is due to their high value for money. They are lightweight, robust and require relatively simple maintenance; a skilled user can achieve an impressive range of functional motions, moreover, to some extent force discrimination and proprioperception is inherently possible by sensing the cable tension.

In 2016, the first edition of the Cybathlon was held in Switzerland (Fig. 2.2). This event was meant as an Olympic-inspired competition for people with disabilities exploiting assistive technologies. Interestingly, the upper limb prosthesis category was won by a body-powered user. Even though this event was mostly intended as a competition for robotic devices, the commitment to this event of the winning team was actually to proof the still superior efficacy of body-powered prostheses compared to state-of-the-art robotic devices.

2.3 Myoelectric Prostheses

The muscular efforts required to maneuver a body-powered prosthesis can often be fatiguing. Electrically-powered artificial limbs try to solve this by actuating motors through an electronic control system (Fig. 2.1, right). These devices, commonly defined as myoelectric prostheses, are based on the utilization of electrical activity measured at the stump from the remaining muscles (myoelectric signals). Thus, muscular contractions and the consequent myoelectric signals are triggered by the user to ultimately drive the prosthesis. Myoelectric prostheses were firstly proposed in the first half of the 20th century. Some early studies were carried out by De Luca *et*

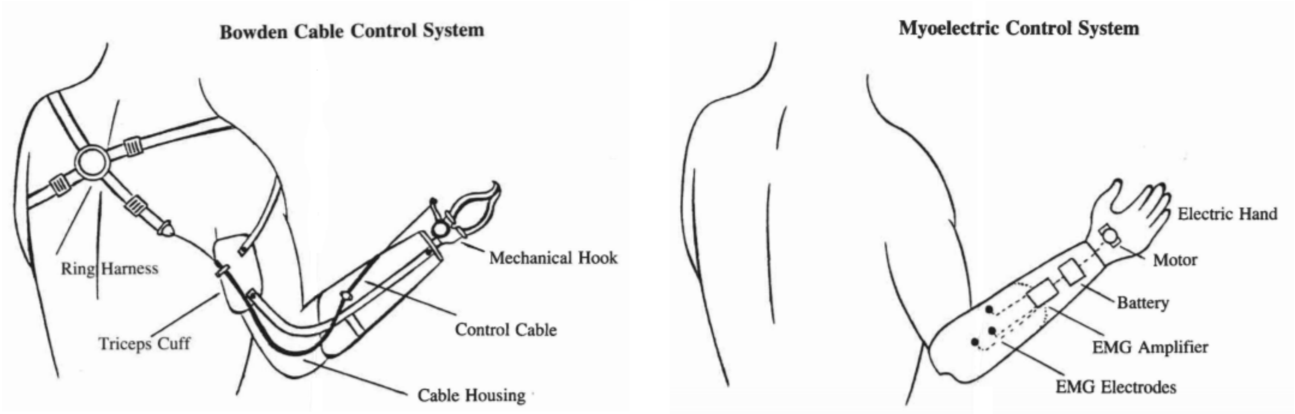

Figure 2.1: Representation of two typical solutions for below-elbow prosthesis [4]. Left) Body-powered Bowden cable prosthesis controlled by "gross" movements of the body. Right) Myoelectric prosthesis controlled by electomyographic (EMG) signal captured from residual muscles at the stump.

al. (starting from the 1970's) about the scientific definition of neuromuscular signals and the challenges behind their use for prosthetic control [5]. Indeed, due to critical technology limitations, myoelectric prostheses became a clinically valid solution only around the 1980's [2]. Since then, the technology has remained essentially the same.

Source electrodes are commonly non-invasive and placed over the skin surface of two groups of antagonist muscles. Proportional control is allowed by varying the intensity of the muscular activity. Besides some "incidental clues" like noise or vibrations from electric motors, sensory feedback is still not part of a standard myoelectric device prescription and therefore, visual feedback is constantly required to properly operate these devices. Most commonly, their aesthetics is superior of any body-powered prosthesis; the mechanics can be hidden under life-like hand silicone gloves available in different skin tonalities. The primary disadvantages of this type of prostheses are currently their cost and weight, but fragility and maintenance are also major concerns.

The biggest breakthrough of myoelectric terminal devices is represented by the advent of multi-functional robotic hands. Manufacturers started recently to equip their robotic terminal devices with microprocessors which allow for more complex functioning. Hand with multiple grips or postures are now an option on the market. Each pre-defined position can be reached by triggering some pre-defined pattern of EMG activity, e.g., a series of triple impulses on the "open hand" control signal. These gestures are meant to facilitate the user's manipulation of items through functioning fingers.

Figure 2.2: Medals ceremony of Cybathlon 2016 - ARM category (image from Cybathlon webpage). A transradial body-powered prosthesis user won, followed by a transradial myoelectric user operating one of the most advanced multi-functional hands, followed by a transhumeral e-OPRA user operating a standard myoelectric hand.

Chapter 3

Advanced Surgical Techniques

Considering the relative low efficacy of standard clinical solutions and their major limitations, alternative approaches have been suggested over the years from researchers, typically, involving a surgical procedure. The outcomes of a modern hand transplants surely identify it as one of the most promising and intriguing techniques. Alternatively, amputated nerves can be now redirected to new target muscles for both control and sensorial purposes. Osseointegration allows for direct skeletal anchorage of the prosthesis, its popularity is growing fast and it is often recognized as the future in the prosthetic field.

3.1 Targeted Muscle Reinnervation and Targeted Sensory Reinnervation

There are precise technology challenges regarding the recording of activity from the peripheral nervous system. Neural action potentials have characteristic amplitude of few micro volts and their direct use for prosthetic control imposes hard technological requirements. Due to amputation, some nerves are deprived of their original target muscle. In 1980, Hoffer and Loeb suggested a novel surgical technique to naturally amplify neural signals via reinnervating a cut nerve on a new target muscle, namely Targeted Muscle Reinnevation (TMR). After the reinnervation process settles, it is possible to use these new sites for prosthetic control via EMG acquisition from the surface of the skin. This idea, represented in Fig. 3.1, had its first clinical implementation in 2004 thanks to Kuiken *et al.*, where TMR allowed a bilateral shoulder articulation patient the control of a 3 Degrees-of-Freedom (DoF) prosthesis [6]. The TMR technique was more formally assessed by Kuiken *et al.* in 2009, where residual arm nerves where successfully transferred to alternative muscle sites in five patients and their ability in controlling a virtual prosthetic limb was measured, together with experimentation over multiple-DoF prostheses [7].

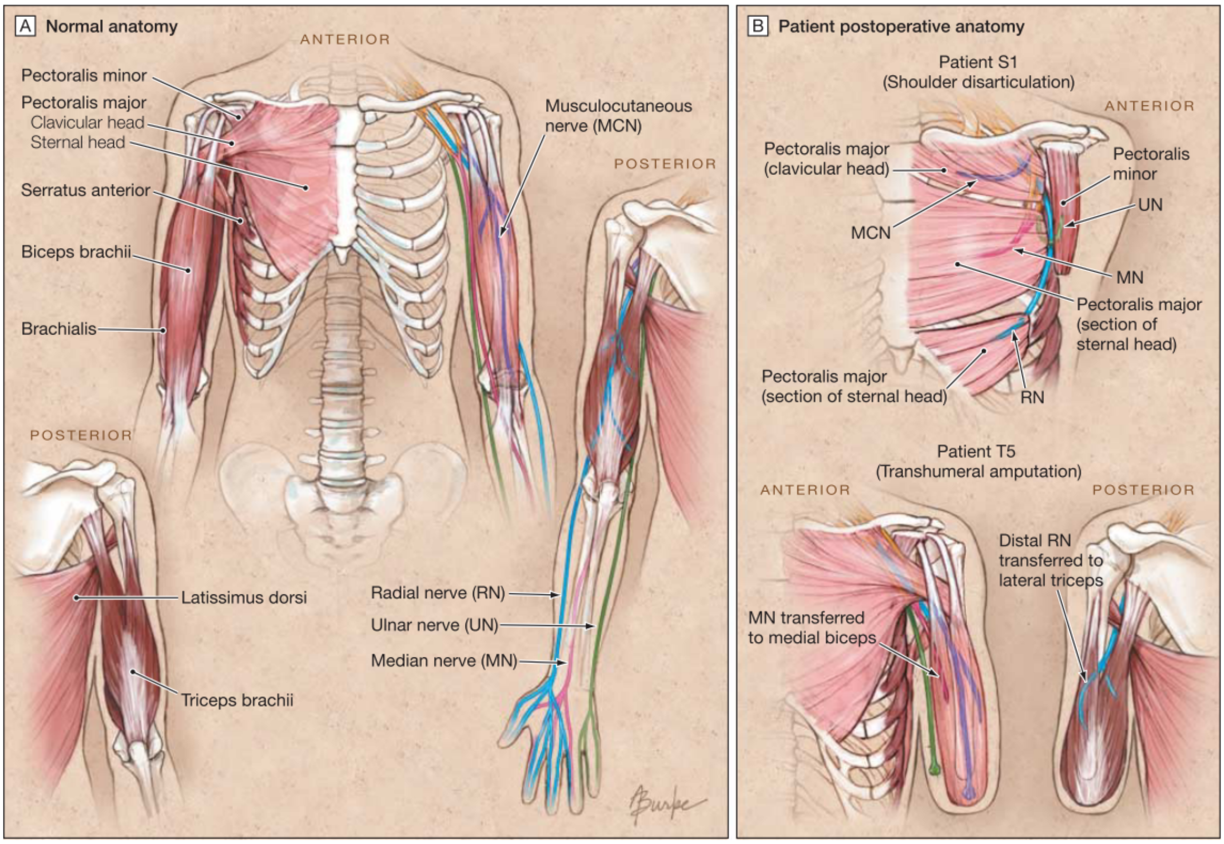

Figure 3.1: Representation of Targeted Muscle Reinnervation from Kuiken *et al.* [7].

An unexpected outcome of the first TMR patients was a sensory recovery on the preceptors of the skin overlaying the reinnervation sites. This was further investigated by extending the TMR to reinnervate sensory nerves to the main peripheral nerve trunk, developing a new surgical procedure defined as Targeted Sensory Reinnervation (TSR). The idea is to create a discrete spatial sensory hand map on a skin area relatively distant from the prosthesis. Early results on a single patient showed the effectiveness of the TSR to recover pressure sensation discrimination on amputees [8].

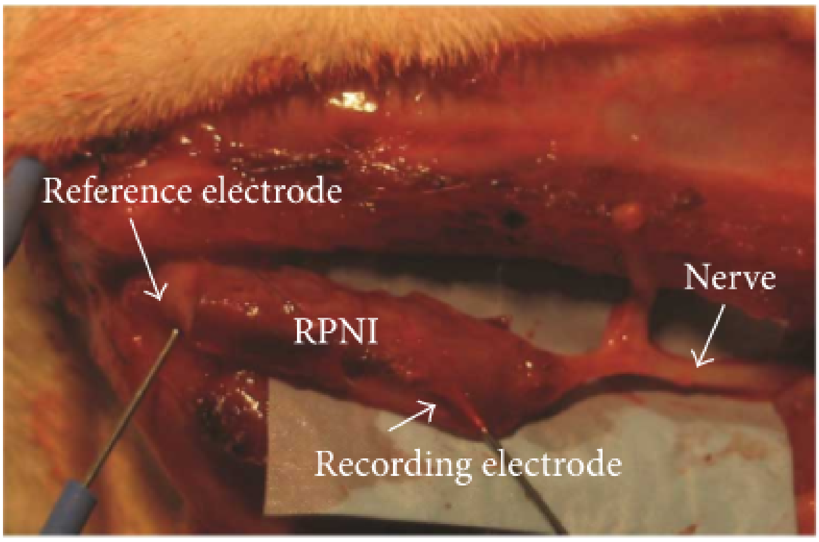

Figure 3.2: Representation of Regenerative Peripheral Nerve Interface (image from [10]). Small portions of muscles can be transplanted to serve as a target for nerves deprived of a functional target muscle after amputation.

3.2 Regenerative Peripheral Nerve Interface

An alternative to the TMR technique has been proposed, namely Regenerative Peripheral Nerve Interface (RPNI) [9,10]. Here, small portions of muscles can be transplanted to serve as a target for nerves deprived of a functional target muscle after amputation (Fig. 3.2). Multiple transplants can be executed on the same patient to create a matrix that can be further used for EMG acquisition and prosthetic control. Due to the small portion of muscle transplanted, this technique imposes the use of implanted electrodes (typically intramuscular) for EMG acquisition for a reliable control of the prosthesis [11]. The RPNI has been tested successfully on both animal models and humans as a treatment for post-amputation neuroma pain.

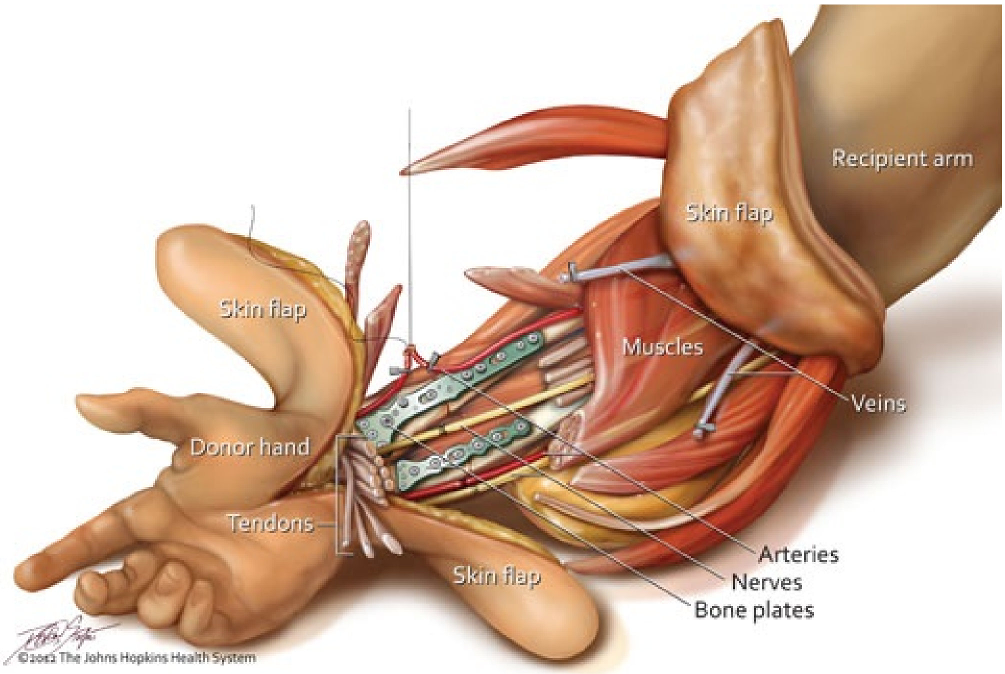

Figure 3.3: Representation of a hand transplantation (image from John Hopkins Medicine University, Comprehensive Transplant Center webpage).

3.3 Transplantation

Hand and upper limb transplantation represents certainly one of the most fascinating ways to restore the cosmesis and functionality of the lost peripheral limb. It is a complex surgical procedure which aims to transfer a hand (or a full forearm) from a donor to a recipient. The surgery can last from 8 to 12 hours and it involves bone fixation, reattachment of arteries, veins, tendons, nerves and skin (Fig. 3.3). It is followed by a heavy immunosuppression medication and a tedious rehabilitation procedure, which results can strongly vary from a patient to another. That is why patient selection is widely considered the most important aspect of the transplant technique, where a special emphasis on medical, behavioral, psychological, social factors, as adherence to immunologic and rehabilitative therapy is mandatory to achieve optimal outcomes [12].

Several failures are associated with the first reported attempts of this surgery, mostly due to primitive and insufficient immunosuppression medications and rehabilitation post-transplantation. This technique is not considered experimental anymore: its improvement in the quality of life is heavily recognized thanks to the modern outcomes in the matter of functionality and survival time (longest-lasting period of 16 years, [12]).

3.4 Osseointegration

Bone-anchored prostheses are a solution to the drawbacks related to coupling artificial limbs via suspended sockets (described in Section 2.1) which is the conventional way of attaching limb prostheses. Bone-anchored prostheses allow for direct transfer of external loads from the artificial limb to the skeleton, eliminating the need of a suspended socket. Direct skeletal attachment of the prosthesis is currently pursued thanks to the concept of osseointegration. Osseointegration was defined as ”close adherence of living bone tissue to an implant surface without intervening soft tissue, thus allowing for a structural functional connection between a load bearing implant and the bone tissue” [13]. A strong structural connection between living bone tissue and a foreign material is thus possible, provided the biocompatibility of that material. It was discovered in the early 1960’s by Dr. Per-Ingvar Brånemark in Gothenburg, Sweden, and now it is a world-wide consolidated clinical practice for dental implants. Its application for artificial limb attachment started in the 1990’s with titanium custom made implants that consequently led to the establishment of the Osseointegrated Prostheses for the Rehabilitation of Amputees (OPRA) (Integrum AB, Mölndal, Sweden). The OPRA (Fig. 3.4) Implant System is based on the implantation of a titanium externally-threaded cylindrical platform (fixture) into bone tissue in the stump. Another titanium unit (abutment) is then fixated (press-fit) into the fixture extending percutaneously from the residual limb and allowing for attachment of an external prosthesis. A third element (abutment screw) is then used to clamp and secure the abutment to the fixture. The OPRA Implant System was initially meant for lower limbs amputation, but it was shortly after applied to upper limb as well.

Other typologies of implants and anchoring technologies have been proposed around the world and are currently available, or under development, or under clinical validation. Some examples are:

- Integral Leg Prosthesis (ILP), Orthodynamics GMbH, Lübeck, Germany
- Osseointegrated Prosthetic Limb (OPL), Permedica s.p.a., Milan, Italy
- Intraosseous Transcutaneous Amputation Prosthesis, Stanmore Implants Worldwide (ITAP), Watford, United Kingdom
- Keep Walking Advanced, Tequir S.L., Valencia, Spain
- Percutaneous Osseointegrated Prosthesis (POP), DJO Global, Austin, U.S.A.
- COMPRESS, Zimmer Biomet, Warzaw, U.S.A.

A wide collection of scientific publications (mostly regarding the first Swedish system) validates the improvement of the quality of life of bone-anchored prosthesis

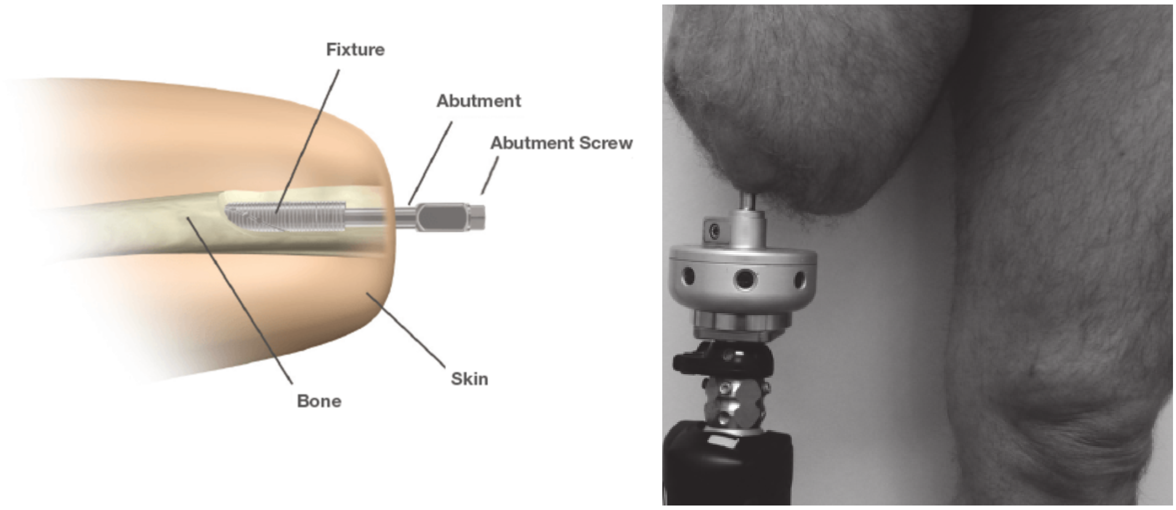

Figure 3.4: The Osseointegrated Prostheses for the Rehabilitation of Amputees (OPRA). Left) Schematic of the OPRA Implant System (image from Integrum AB, Mölndal, Sweden). The OPRA implies the implantation of a titanium platform (fixture) into bone tissue in the stump. Another titanium unit (abutment) is then fixated into the fixture and extends percutaneously, while a third element (abutment screw) is then used to clamp the abutment to the fixture. Right) Clinical photograph showing a patient with the osseointegrated implant attached to an external prosthesis [16].

users [14, 15]. Additional benefits of direct skeletal attachment of prosthetic limbs include:

- improved range of motion (for both upper and lower limbs)
- improved walking ability and reduced energy expenditure
- improved comfort during sitting position
- improved awareness via osseoperception.

Osseointegration, like any other surgical procedure, implies risks. Superficial infections can arise at the percutaneous interface, requiring an antibiotics treatment. Deeper infections are rare but, if not promptly treated, can led to the implant removal [16, 17].

The commercial interest in this technology is growing fast as well as the list of countries where the treatment is available. Moreover, the Food and Drug Administration federal agency of the U.S.A. recently approved the first bone-anchored implant (OPRA Implant System) and surgical procedure, and the U.S. Army has started a clinical trial, where lower limb amputees are treated with this system.

Chapter 4

Control Strategies for Myoelectric Prostheses

Despite the advances in prosthetic hardware that allow an increasing number of artificial joints to approach those of the lost limb (Modular Prosthetic Limb [18], DEKA arm [19], RIC arm [20]) a major issue remains unsolved, namely, how to achieve a reliable and natural control of the prosthetic limb. After decades of research and development on upper limb myoelectric prosthetics, current clinical applications for amputees still rely on a 30-years-old strategy for control, namely direct control (DC) [21].

4.1 Direct Control

Direct Control, also known as one-for-one or one-muscle-to-one-function, implies the utilization of rectified myoelectric signal from two groups of antagonist muscles (e.g., biceps and triceps for above elbow amputation, flexors and extensors for below elbow) to control the terminal prosthetic device (Fig. 4.1). For instance, hand open and close can then be driven via a set of two complementary movements (e.g., elbow flex and extend for above elbow amputation, wrist flex and extend for below elbow). Proportional control, defined as speed-controllable movements, is then achieved by modulating the intensity of the muscular electrical activity measured at the stump: a strong contraction would be translated in a fast prosthetic activation of that particular movement. For cases in which limited control sites are available, a configuration of one-muscle-to-two-functions is also possible, by matching different activation thresholds to different prosthetic movements (e.g., a weak and a strong elbow flexion for hand open and close). User's adaptation is usually required to get accustomed to the new set of muscular-contraction and expected-prosthesis-movement. The DC approach is pervasive mostly owing to its simplicity, relative good reliability, and ease to learn. Unfortunately, the functional outcome is commonly related to the specific

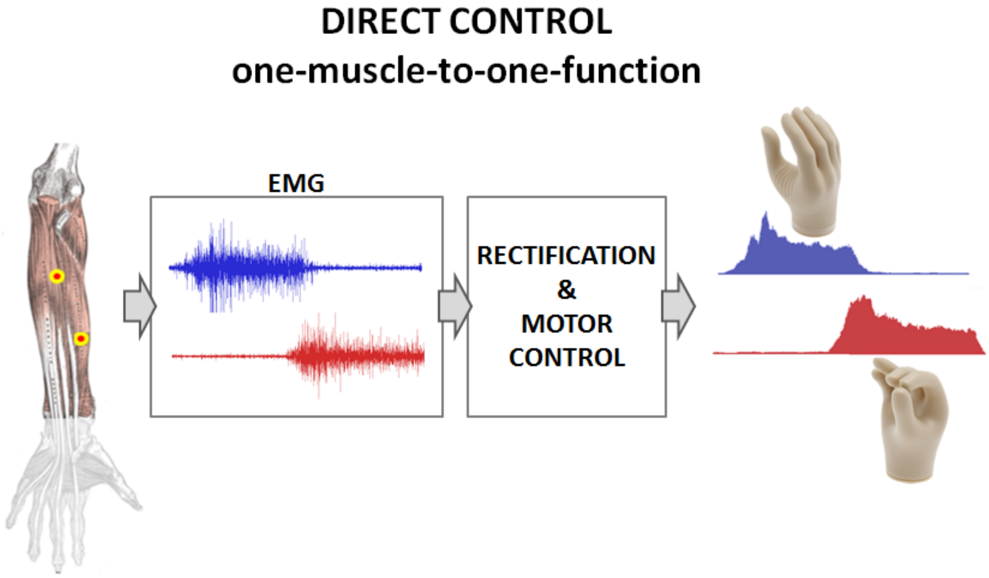

Figure 4.1: Representation of Direct Control strategy for myoelectric hand prostheses. It implies the utilization of rectified myoelectric signal from two groups of antagonist muscles (e.g., flexors and extensors for below elbow amputation) to control the terminal prosthetic device.

patient predisposition, thus often resulting in the rejection of the myoelectric prosthesis [22,23], or in the diminution of the robotic limb potential (independent fingers control, wrist rotation, elbow joint angulation) to a simple prosthetic claw. Different variations of the standard DC approach are available nowadays to provide more controllable DoF, but unfortunately, always with a cost of improved complexity and reduced intuitiveness of the control interface.

4.2 Myoelectric Pattern Recognition

Around the mid-1960's the field of neural prosthetics started to involve computer intelligence for improving the control experience for the user (and to reduce the training burden) [24]. The need for a more natural control interface met the growing potential of pattern recognition algorithms. Pattern recognition (namely also machine learning) is an umbrella term which covers a variety of algorithms, ranging from statistical to biologically inspired, which have in common the same task: identify patterns or regularities in data and consequently recognize them when a new sample of data is presented. These algorithms are usually defined as supervised, when the decision regarding new data is made in reference to analogous pre-labeled data used as a training set, or unsupervised, when no pre-labeled data is available. Moreover, we differentiate between classification and regression problems, when the decision of

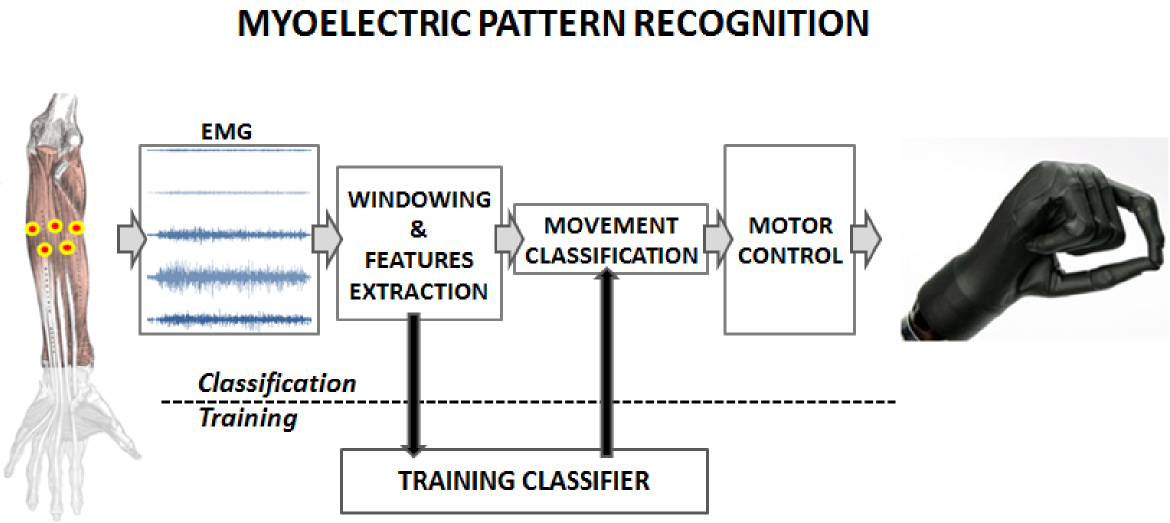

Figure 4.2: Representation of myoelectric pattern recognition strategy for a classification problem. The acquired EMG signals are windowed and a proper set of features is then extracted to reduce the dimensionality of the problem. Features sets from all target movements feed the classifier during its training (supervised learning), enabling it to recognize new analogous data and thus classify the motor intention of the user.

the algorithm has the form of a class (or a label), or the form of continuous values, respectively.

Natural control is defined in this context as the ability of providing control of the prosthesis in the same way as an intact physiological system would do. Thus, intuitive movements of the amputated arm, defined as the phantom arm, are properly translated to the artificial limb. Natural control is often sought via myoelectric pattern recognition (MPR), meaning machine learning applied to the prediction of the user's motor volition using EMG as input signal. Single-muscle targeting is not necessary for MPR, but instead, multiple channels are spread over the stump to gather as much useful information needed to characterize, and thus differentiate, each movement.

The first investigations of MPR started in the mid-1960's at the Rehabilitation Engineering Center of Philadelphia, and a complete report was published later by Wirta *et al.* [24] (Fig. 5.1). A multivariate statistical program was used to classify four movements via myoelectric signal previously recorded from six surface EMG sites from an able-bodied subject. Shortly after in 1973, Herberts *et al.*, reported MPR applied for the simultaneous control of a three DoF prosthesis [25]. The Discriminant Analysis in linear configuration (LDA) was deemed as the classification algorithm and currently, it is still one of the most renowned tools for MPR researchers. It was also in those same years (mid-1970's), that MPR researchers started to realize that targeting the muscles with surface EMG electrodes was not necessarily the optimal electrodes configuration. Instead, it was more convenient to find other configurations able to exploit the most of the information available on the stump (e.g., electrodes in between muscles [26]). MPR became slowly more and more popular among the prosthetic research field because of its appealing potential [27, 28]. Generally, all major promising algorithms developed over the years in the machine learning field were exploited by researchers for prosthetic MPR applications. Some examples are:

- Neural Networks,
- Support Vector Machine,
- Regression,
- K-Nearest Neighbor,
- Gaussian Mixture Model.

More recently, modern deep learning algorithms started to be used and evaluated for prosthetic control purposes [29, 30].

Even though MPR represents today the state-of-the-art for prosthetic control interface, its clinical implementation is still far from being a concrete reality for amputees. Up to date, there is only one commercially available MPR system, namely Complete Control from COAPT (Chicago, Illinois, U.S.A.), and although clinical investigations are ongoing, no results have been made publicly available in the scientific community. A still high rejection rate appears to be towards this technology, from both patients and clinicians. Potential reasons for the slow take off of MPR are due to well-known difficulties related to multiple channels surface EMG acquisition. Issues as motion artifacts, electromagnetic interference, frequent changes at the interface skin-electrode, socket manufacturing cost, contribute to make MPR still unpractical for wide dissemination.

Chapter 5

Upper Limb Myoelectric Pattern Recognition Systems

The first MPR embedded system for the control of a prosthetic arm was developed in the mid-1960's and it was composed by a simple weighted network of resistors (Fig. 5.1) [24]. For the first time, a MPR system was able to recognize different movements taking as input EMG activity recorded simultaneously from different channels. More precisely, it was fed by six EMG sites and capable of predicting four movements with reported accuracy around 90%. Shortly after, Herberts *et al.*, reported a similar pure-analogic MPR system applied for the simultaneous control of a three DoF prosthesis [25]. The battery-powered portable system was able to drive the robotic arm for hand prehension, wrist rotation and elbow flexion/extension and tested on an above-elbow amputee.

Opposed to portable systems, computer-based MPR systems started to appear in the literature around the 1980's [31]. Computer-based platforms were, and still remains, a very prolific source for literature studies, used as a test-bench for MPR algorithms and control performance [7,32,33], but also for "serious gaming", training and rehabilitation purposes [34,35], and for phantom limb pain reduction [36].

The advent of microprocessors and microcontroller units (MCU) was a crucial breakthrough towards any modern portable and wearable device, and this includes prosthetic controller as well. The first attempt of a MCU-based MPR system is dated 1977, included in a work published from Graupe *et al.* [26]. It relied on one of the first MCU, the 8080 from Intel (Santa Clara, California, U.S.A.), for real-time autoregressive analysis of EMG signal to classify motions and to properly actuate a robotic device. The reported classification accuracy was between 85% and 95%. The interest on MPR prosthetic control systems grew constantly and it developed in parallel with the computation capabilities of new emerging processing units. An interesting discussion was carried out by Xiao *et al.* about the advantages of having a GPU core for MPR prosthetic applications [37]. Approaches using Field-Programmable

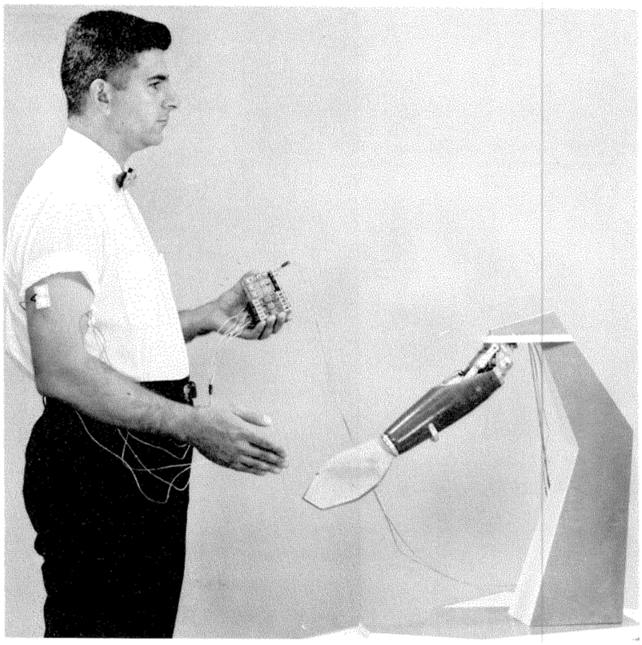

Figure 5.1: The first embedded system employing pattern recognition for the control of a prosthetic arm [24]. Developed in the mid-1960's, it was composed by a simple weighted network of resistors.

Gate Arrays (FPGA) have shown to be highly beneficial for accelerating the computation of pattern recognition algorithms [38]. FPGAs represent a valuable solution for prosthetic control which might appear more often in future embedded MPR systems, but currently no clinical implementation of such system has been reported. Digital signal processor (DSP), like the popular series TMS320 from Texas Instruments (Dallas, Texas, U.S.A.), have been selected for the development of portable MPR systems [39,40]. A portable speech recognition DSP-based system was also suggested by Lin *et al.*, as a solution for prosthetic control [41]. Other system designs involved more powerful but also more power demanding processors like the PXA270 from Intel or the CortexA8 from ARM (Cambridge, England, U.K.) [42, 43]. This approach obviously poses energy consumption challenges but still provides a remarkable processing capability for a wearable device. Processor cores from the Cortex-M family recently started to be a popular choice for MPR systems design given their efficient compromise between power consumption and computation capabilities [44]. This core was also chosen for the system presented in Paper I attached in this thesis. As previously mentioned, to date there is a single commercially available embedded MPR system from which limited information is available due to its commercial nature (Complete Control, COAPT, U.S.A.). Soon, one of the largest prosthetic components manufacturer should release on the market its MPR system (Myo Plus, Ottobock, Germany).

Chapter 6

Neural Interfaces for Myoelectric Prostheses

The functional challenges of any myoelectric prosthesis, MPR or not, are related to the sensors used to acquire the EMG signals. Clinical solutions typically include non-invasive electrodes, where conductive parts are located on the surface of the skin above the target muscles. The selectivity of this approach is limited due to tissues between the signal source (the muscle) and the sensing part (the electrode), crosstalk from neighboring muscles is a known aspect for surface EMG acquisition. An electrode misplacement or an electromagnetic field in proximity can potentially create artifacts able to involuntary drive the prosthesis. Moreover, environmental conditions (humidity and temperature) can cause impedance changes in the skin-electrode interface which can deteriorate the reliability of these systems and force to exhaustive recalibration.

Since all these aspects can greatly threat the overall functionality of non-invasive myoelectric devices, several invasive approaches have been investigated to potentially solve these problems. Invasive solutions basically rely on implanted electrodes for sensing the myoelectric signal. Several configurations for implanted neuromuscular electrodes are available today. Besides all the risks involved in the surgery and in foreign-body reactions, the major system-design challenge for invasive solutions has been historically how to functionally access the control signals sourced by implanted subcutaneous parts. Several solutions have been proposed.

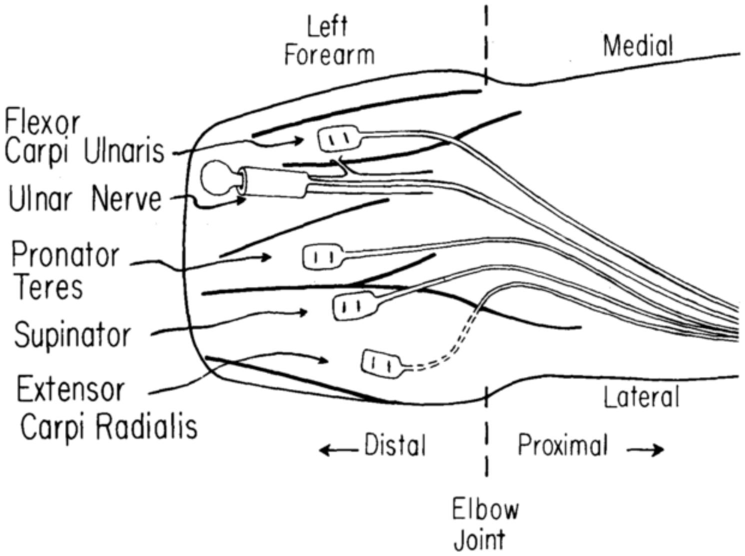

Figure 6.1: First attempt of a percutaneous neuromuscular interface for prosthetic control, 1980 [45]. A transradial amputee was implanted with four epimysial electrodes and a cuff electrode which leads converged on a percutaneous connector emerging from the skin of the upper arm.

6.1 Percutaneous Leads

Percutaneous leads have been explored and utilized in literature, and despite not being regarded as a long-term stable solution due to obvious problems at the interface between leads and skin, they played a crucial role in research for neural prosthetics. The first pioneering attempt of a percutaneous neuromuscular interface for prosthetic control is dated back to 1980, reported by Hoffer and Loeb [45] (Fig. 6.1). A transradial amputee was implanted with four epimysial electrodes on the muscles and a cuff electrode planted around one large fascicle of the ulnar nerve (proximal to the neuroma). Leadout cables converged onto a 12-pin socket percutaneous connector emerging from the skin of the upper arm. The difficulty to secure the cables at the interface and to prevent skin inflammation eventually led to an infection followed by the removal of the percutaneous connector.

To our knowledge, the longest reported time of implantation for percutaneous implants is over four years [46], but it is widely recognized that these solutions will eventually reach a functional failure. Currently, they do not represent a clinical viable solution for amputees but still they are an important source for basic (and not only) science research in the field of neural prostheses.

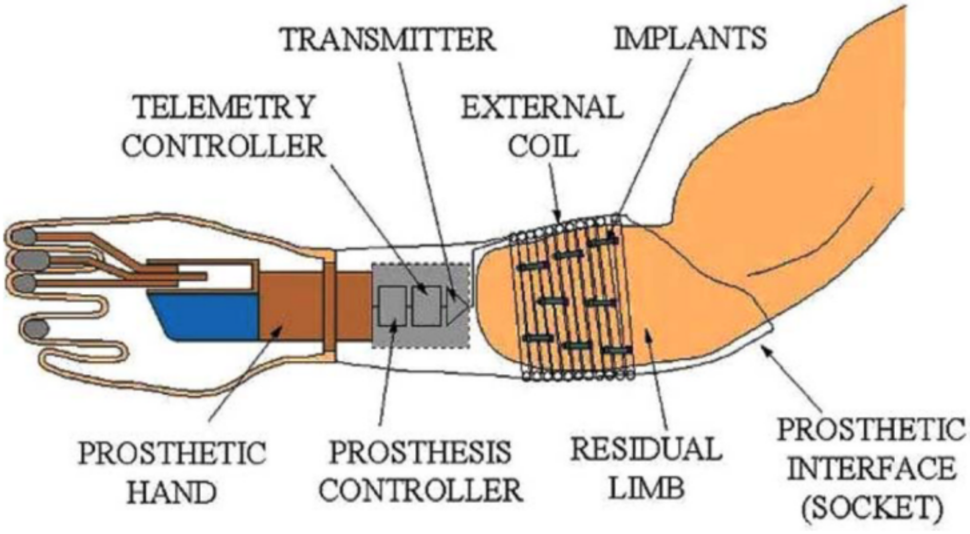

Figure 6.2: Representation of the IMES system [50]. The EMG sensors are implanted in the forearm and communicate wirelessly to the external coil laminated in the prosthetic socket.

6.2 Wireless Interfaces

Provided the limitations of percutaneous solutions, wireless neural interfaces have been suggested and developed over the years. Implanted telemetric systems can be used to bidirectionally transfer information between the body and the robotic control system. The first experimentation of a wireless system for prosthetic control was done by Herberts *et al.* in the 1968 [47]. Here, the six implanted electrode-capsules were wirelessly energized from a single external processing unit placed on the skin. EMG signals were successfully transferred via frequency modulation of the carrier wave. Two able-bodied subjects and two below-elbow amputees were recruited for experimentation; the implantation lasted from 3 up to 15 months, and some primitive foreign-body reactions were reported. Few years later, in 1974, Clippinger *et al.*, presented a wireless neural stimulation system aimed to integrate sensory feedback on a body-powered prosthetic system [48]. Here, oppositely to Herberts' system, all implanted electrodes converged to a centralized transmission unit connected wirelessly to the main external unit. The implant was removed several weeks after. The next clinical implementation of a wireless prosthetic system was not reported until 2014, when Pasquina *et al.* provided two transradial amputee subjects with the Implantable Myoelectric Sensor (IMES) technology [49]. The IMESs are small, cylindrical electrodes (16 mm long and 2.5 mm of diameter) capable of detecting and wirelessly transmitting EMG data [50] (Fig. 6.2). Thanks to these telemetric sensors the test subjects could functionally control a 3 DoF prosthetic arm.

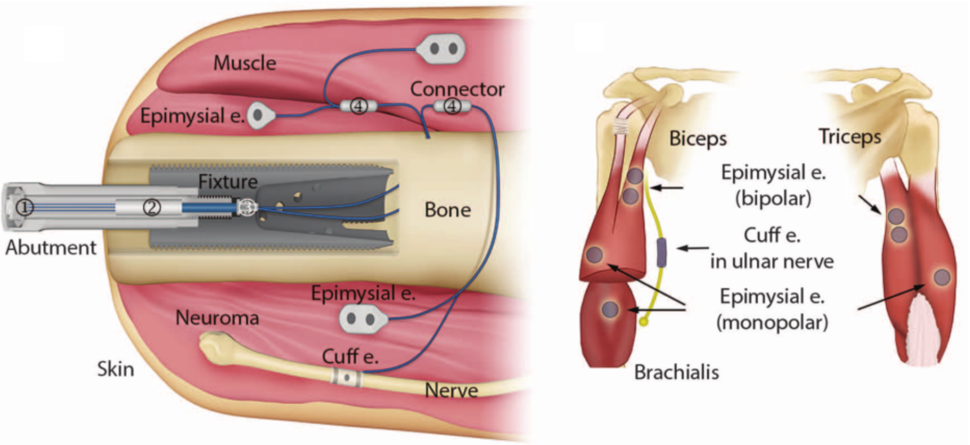

Figure 6.3: Enhanced Osseointegrated Prostheses for the Rehabilitation of Amputees (e-OPRA). Left) Representation of the modular system. Right) Placement of epimysial and cuff electrodes in the right upper arm of the first repicient transhumeral amputee [1].

6.3 Osseointegrated Human-Machine Gateway: the e-OPRA

The technology for the direct skeletal attachment of a limb prosthesis (started in 1990 [17]) provided the framework for an alternative method to gain access to the peripheral nervous system. In fact, osseointegration inherently predisposes of a percutaneous interface between the skin and the titanium abutment. In 2014, Ortiz-Catalan *et al.* demonstrated the possibility of a long-term bidirectional communication between the artificial limb and implanted neuromuscular interfaces by incorporating signal feedthrough mechanism into the osseointegrated implant [1]. Here, some of the parts constituting the OPRA Implant System (Integrum AB, Mölndal, Sweden) were modified to integrate feedthrough connectors to interface the implanted electrodes placed outside the bone in the soft tissue. The system included epimysial electrodes, in both monopolar and bipolar configuration, targeting biceps brachii and triceps brachii muscles, as well as a cuff electrode located around the ulnar nerve. This technology, named as enhanced-OPRA or e-OPRA (Fig. 6.3), was implanted on a transhumeral amputee subject and it is still currently functional after six years up to date. The advantages of implanted EMG sensors for prosthetic limb control were proven, as well as the functionality of the cuff electrode to deliver somatotopic sensations (i.e., perceived in the phantom hand) via direct neural stimulation.

Five more transhumeral amputees have recently been implanted as part of an ongoing clinical trial.

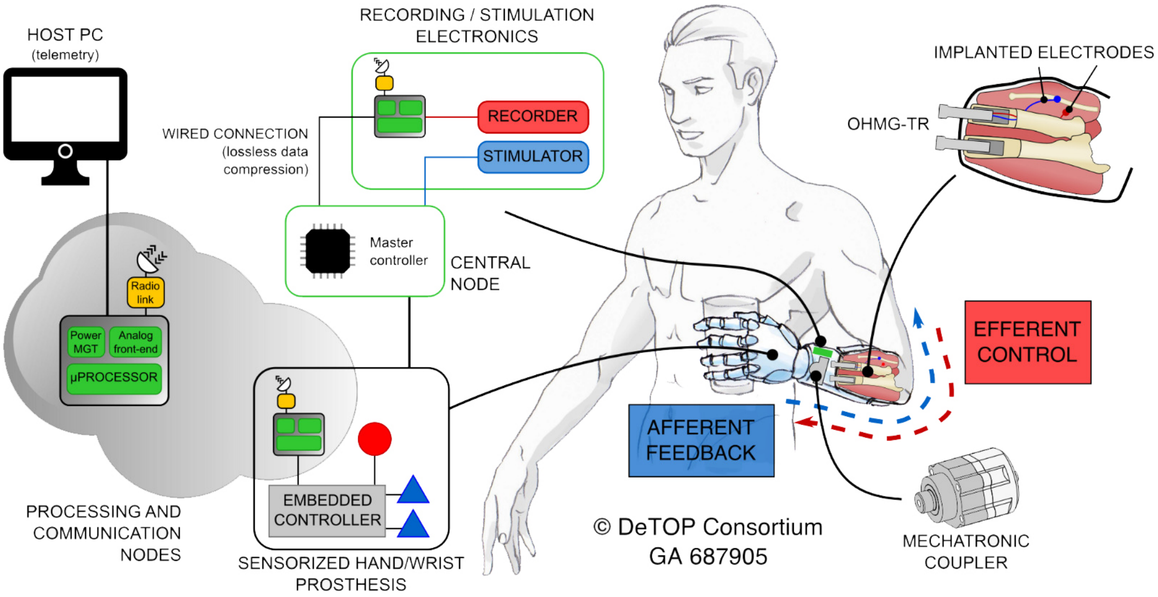

Figure 6.4: The DeTOP project aims to develop and clinically implement the neuromusculoskeletal e-OPRA Implant System on a transradial level of amputation (below elbow), as well as robotic sensing technologies for next-generation prostheses [53].

6.4 e-OPRA transradial: the DeTOP project

The DeTOP (Dexterous Transradial Osseointegrated Prosthesis) is an ongoing research project funded under the Horizon 2020 E.U. Framework Program for Research and Innovation. The DeTOP project aims to develop and clinically implement the neuromusculoskeletal e-OPRA Implant System on a transradial level of amputation (below elbow), as well as robotic sensing technologies for next-generation prostheses (Fig. 6.4). Therefore, the key objective of DeTOP consortium is to translate, exploit and appraise the already proven e-OPRA technology for transhumeral amputation to transradial amputation, opening this technology to a larger population of upper limb amputees. This required a redesign of the implanted parts for the two recipients bones of the forearm, the ulna and the radius, as well as the mechanical interface to them. Interestingly, within this context it was found that the axial rotation of these two implants is required to preserve natural forearm rotation, to distribute loads equally over the two implants (60% radius - 40% ulna), and to enable loading of the implants without unpleasant feelings for the patient [51]. The DeTOP consortium is also aiming to deliver a state-of-the-art robotic terminal device provided with sensorized fingertips for both normal and tangential force [52]. The first amputee was implanted in late 2018 and two more are planned within the project.

Chapter 7

Sensory Feedback and Closed-Loop Control

Even though active prosthesis can provide an acceptable restoration of functionality, sensory feedback is still missing and not purposely pursued in clinical practice. The lack of sensory feedback was pointed to be, by several surveys, one of the causes that prevents a wider acceptance of prosthetic devices over the amputees' community [54, 55]. Exteroception (sense of the surrounding environment) and proprioception (sense of the proper state, joint angles, etc) are mandatory requirements for any prosthetic device which wishes to be referred to as "able to provide a functional natural sensation". Tactile feedback is essential in the interaction with items, and researchers agree on the necessity of investigating viable methods to provide a closed-loop control of the prosthesis. In the last decades, several approaches have been proposed but none has been yet unanimously approved from clinicians to be suitable for daily operation. Sensory substitution is an approach that has been widely explored in research. It is based on the idea of providing sensory information to the body through a sensory channel that differs from the natural one, e.g., substitute touch with hearing, or via the same channel but in a different modality, e.g., substitute pressure with vibration. Vibrotactile and electrotactile are two examples of sensory substitution techniques investigated since decades [56].

Vibrotactile sensory substitution transfers information to the user by vibrating the skin at frequencies not higher than 500 Hz [58]. The information can be modulated acting on two main parameters, amplitude and frequency of the vibration. The discrimination capabilities of the user are strictly related to the location where the vibrating parts are applied. Mechanotactile stimulation operates force application on the skin. It is most often combined with a phantom hand map used as target for sensory feedback. It is a technique appealing because of its simplicity and effectiveness. Antfolk *et al.*, investigated further this idea developing a non-electric device (Fig. 7.1) and proving its efficacy with 12 amputee test subjects [57]. Electrotactile

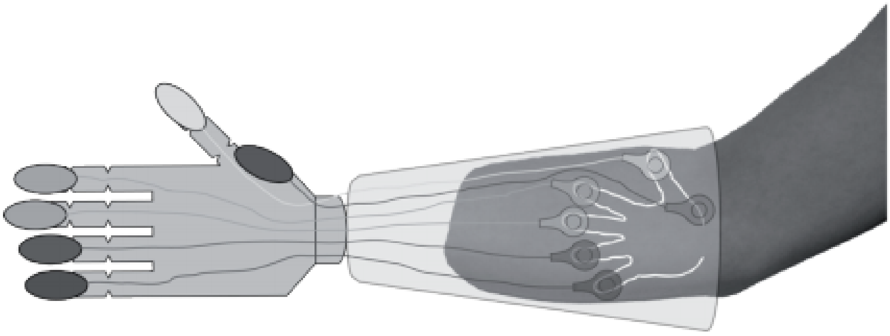

Figure 7.1: Non-electric device to provide mechanotactile feedback, developed by Antfolk *et al.* [57].

stimulation uses a local current to evoke sensations and convey information to the user [58,59]. Major parameters are current amplitude, shape, frequency and duration of the pulse waveform. Oppositely to vibrotactile, no mechanical parts are involved, therefore, electrotactile-capable devices are characterized by low power consumption and fast response. Further, a combination of vibro-electrotactile modes has been proposed [60].

Direct neural stimulation represents the most exciting approach for sensory feedback, since it can potentially restore somatic sensory deficiencies. For this reason it has gathered many attentions from researchers around the world. Revolutionary attempts to restore sensory feedback by electrical neural stimulation via implanted electrodes were reported already several decades ago [45, 61, 62]. In 2005, Dhillon and Horch showed that tactile as well as proprioceptive sensations could be elicited using intraneural electrodes [63]. In 2014, extraneural stimulation allowed Tan *et al.* to report long-term stable (over a year) perception defined as "natural" by two subjects [64]. Further progresses were shown in the use of neural stimulation to improve prosthetic control by allowing object compliance [65], texture [66], and position discrimination [67], as well as slippage detection [68] or to facilitate prosthesis embodiment and reduce phantom pain [69], and even to allow tasks execution with occluded auditory/visual feedback [70, 71]. Despite the promising and exciting results, a more systematic knowledge of the interactions between the peripheral and central nervous systems is imperative and still missing. The poor selectivity of current neural interfaces is one of the major limitations. Furthermore, the selectivity is inversely proportional to the functional duration of the implanted electrodes. For this reason, these type of experiments were typically carried out in controlled laboratory environments after which the invasive implants were removed from the experiment subjects. Recently, this trend started to change moving the focus to provide the closed-loop prosthetic control into amputees' daily environments, and ultimately to translate the aforementioned findings into more realistic use scenarios [1,72,73]. The e-OPRA Implant System (described in Section 6.3) together with the Artificial Limb Controller (described in Paper I and in Section 8.1) is currently the only technological setup capable of providing long-term stable, self-contained sensory prosthesis outside laboratories and into amputees' lives.

Figure 7.2: Neural stimulation for closed-loop prosthetic control: a changing trend from experiments confined within controlled environments (top) to amputees' daily environments and more realistic use scenarios (bottom). Top-Left) Experiments from Dhillon and Horch showed that tactile as well as proprioceptive sensations could be elicited using intraneural electrodes [63]. Top-Right) Experiment of object compliance recognition performed within the framework of the E.U. funded NEBIAS project, efforts that ultimately allowed a transradial amputee to walk outside the laboratory while equipped with tactile sensory feedback (Bottom-Left) [74]. Bottom-center) Transhumeral amputee equipped with tactile sensory feedback at home via the e-OPRA Implant System and the Artificial Limb Controller [72]. Bottom-Right) Home use of a neural-connected sensory prosthesis, from the work of Graczyk *et al.* [73].

Chapter 8

The Artificial Limb Controller

A first version of the Artificial Limb Controller (ALC) was developed to provide closed-loop intuitive prosthetic control to transhumeral e-OPRA patients. It was designed as a self-contained, wearable system electrically and mechanically compatible with the e-OPRA implant and with commercial prosthetic elbows and hands. The embedded neurostimulator allowed an e-OPRA patient to handle delicate items while blindfolded. Its design and verification is presented in the appended Paper I. Recently, the initial design was revisited to achieve:

- a size compatible also with transradial patients,
- increased number of acquisition channels,
- increased specifications of the neurostimulator.

The new hardware version was designed in an oval shape (60x40x24 mm, Fig. 8.1), it can provide up to 16 monopolar acquisition channels and, on top of these, other 8 can be generated as linear combination of the others. The new ALC has the same computational power of its predecessor: it allows for bioelectric signals acquisition, processing, decoding of motor volition, and prosthetic control. It can also be used as a current generator on all 16 channels, intended as a neurostimulator to elicit direct neural feedback. Direct myoelectric control was implemented as well as three robust pattern recognition algorithms: Linear Discriminant Analysis (enhanced via confidence-based rejection as from Scheme *et al.* [75]), Support Vector Machine, and Linear Regression [76]. These algorithms can provide simultaneous, proportional, multi-DoF prosthetic control. The ALC is provided with inertial sensors, UART, SPI, and CAN bus, two motor driver outputs and six analogic voltages outputs for controlling DC motors typically used in prosthetic components. In addition, a SD card is also included to log relevant information. As in the previous version, a Bluetooth dongle can be plugged in the system to achieve wireless communication with external devices. Bench tests showed lower power consumption compared to

Figure 8.1: Representation of the Artificial Limb Controller versions: ALC-transhumeral (left) and ALC-transradial (right). Such system provide a clinically viable solution for the control of upper limb prostheses, as well as a research platform for further investigations on prosthesis usage and training, machine learning techniques and neural stimulation paradigms.

the previous version, 35 mA versus 60 mA. Real-time functionalities were proven with time characterization of all embedded routines. Embedded pattern recognition algorithms showed average accuracy around 97% and 65% in offline and real-time tests, respectively. Its current dimensions allow for the fitting of transradial e-OPRA patients within the framework of the E.U. funded DeTOP project.

Chapter 9

Summary of the Thesis Contributions

In the second part of this thesis, five scientific articles developed within the time of this doctoral project are included. Four of them have been already published, and the fifth is currently under peer-review. A brief description of their contributions is presented in what follows.

- **Paper I** reports the development and the functional validation of the embedded system designed to exploit the advantages of the e-OPRA technology. The Artificial Limb Controller allowed for bioelectric signal acquisition, processing, and decoding of motor intent towards intuitive prosthetic control via pattern recognition. It included a neurostimulator to provide sensory feedback via neural stimulation, thus enabling closed-loop robotic limb control. The system was validated and its functionality was proven in a first pilot e-OPRA patient. This embedded controller allowed for out-of-the-lab applications of closed-loop prosthetic control.
  The author was responsible for the design of the system architecture, of the schematic and the layout of the electronic boards, as well as the development and verification of the low- and high-level software required to the functionality of the system. The author was responsible for acquiring and analyzing the data, and for writing the manuscript.

- **Paper II** presents the report of a short-term clinical application of the developed prosthetic controller (presented in Paper I) utilized in conjunction with non-invasive EMG electrodes and pattern recognition methods. The intuitive-control approach allowed for the discrimination of three fine grips and open/close hand in a multifunctional prosthetic hand. The system was used by a dysmelia subject for five consecutive days in out-of-the-lab context while information about prosthesis usage and real-time classification accuracy were collected. The functionality of the proposed approach was compared with the conventional myoelectric control approach. This work presents an alternative to the conven-

tional use of myoelectric signals in combination with multifunctional prosthetic hands. Moreover, it also represents a further validation of the Artificial Limb Controller.
The author supervised the design of the system architecture, as well as the development and verification of the low-level software. The author was responsible for analyzing the data and for writing the manuscript.

- **Paper III** reports the evolution of the TMR myoelectric signals from two e-OPRA subjects. EMG signals were recorded via implanted electrodes and monitored for up to 48 weeks after surgery. The signal evolution over time was analyzed with regard to amplitude (signal-to-noise ratio), independence (cross-correlation), and myoelectric pattern recognition (classification accuracy). TMR signals appeared at the first follow-up, one month post-surgery, suggesting that implanted electrodes allow for an earlier and more effective use of motor signals from TMR reconstructed sites compared to conventional skin surface electrodes. This study was accepted for publication in the EMBC conference and awarded as one of the finalists for the student paper competition.
  The author was responsible for acquiring and analyzing the data, and for writing the manuscript.

- **Paper IV** investigates control resolution and motor coordination of three e-OPRA subjects. Performance when utilizing implanted electrodes was compared with the standard-of-care technology for myoelectric prostheses, namely surface electrodes. Results showed that implanted electrodes provide superior grip force control resolution and reliability over the prosthetic terminal device compared to surface electrodes. However, despite being more functional and reliable, prosthetic control via implanted electrodes did not improve motor coordination and appeared to still depend highly on visual feedback. Our findings indicate that the visual, auditory, and osseoperceptive incidental sensory feedback available to these particular subjects was insufficient for restoring their natural grasp behavior, and suggest the idea that supplemental tactile sensory feedback is needed to learn and maintain the motor tasks internal model.
  The author coordinated the study between the international partners, and conducted the experiments. The author substantially contributed to the analysis and results interpretation, and to the writing of the manuscript.

- **Paper V** builds upon the findings of the precedent Paper IV and investigates the benefit of tactile sensory feedback via direct neural stimulation for motor control during grasping. The same e-OPRA subjects from Paper IV were enrolled in this study and asked to perform again the tests while provided with real-time tactile sensory feedback. Three different biomimetic extraneural stimulation modes for tactile sensory feedback were proposed in the study and compared to the conventional no-feedback control condition. The motor coordination was also assessed under uncertainty by suddenly changing the weight of the test object unbeknownst to the test subjects. In addition, besides the objective performance metrics, we aimed to assess the subjective experience of the feedback methods, in terms of sensation quality, intensity, naturalness, and pleasantness, by means of a questionnaire. Here, the potential of using extraneural stimulation for tactile feedback for restoring motor skills and mature grasp behavior in transhumeral e-OPRA recipients was confirmed. When the weight was certain, prosthetic control with tactile feedback produced more coordinated and faster performances, in a more feed-forward fashion than without feedback. Moreover, when the weight of the test object was unexpectedly changed, tactile feedback still allowed shorter load phases and higher grip force changes compared to no-feedback. As a result, the subjects responded to the weight uncertainty with a more cautious feedback-driven control approach, even though they showed also some promising feed-forward behavior as a potential indication of an early integration of the tactile feedback provided. In addition, the results seem to point to a winning feedback strategy among the ones proposed and compared here: the hybrid mode, which combines continuous modulation of the current amplitude of pulses delivered at a constant frequency with short bursts of pulses at higher frequency in correspondence with the discrete events of touch and release. Lastly, the scores given to naturalness of the perceived tactile feedback were low as expected, while the ones about pleasantness were surprisingly high. This study gives promising insights about the benefit of direct neural stimulation for tactile sensory feedback with e-OPRA subjects. The author coordinated the study between the international partners, and conducted the experiments. The author substantially contributed to the analysis and results interpretation, and to the writing of the manuscript.

Chapter 10

General Conclusions and Future Work

Some of the most exciting advancements in the field of upper limb prostheses from all around the world have been introduced within this thesis, with its main focus set on intuitive myoelectric prostheses. Promising developments are being made worldwide, with the popularity of the prosthetic field growing rapidly, perhaps encouraged by the science-fiction based appeal of robotics. Unfortunately, clinical implementations still lag behind the advancements of research in matter of robotic limbs, prosthetic control, and sensory feedback. More efforts are needed to close the gap.

Within this work, an embedded system capable of prosthetic control via the processing of bioelectric signals with pattern recognition algorithms was developed. The Artificial Limb Controller includes a neurostimulator to provide direct neural feedback based on sensory information. The system was ultimately designed to be reliably used in activities of daily life for real clinical implementations, as well as a research platform to monitor prosthesis usage and training, machine learning based control algorithms, and neural stimulation paradigms. It was shown that this system can be used not only with the implanted electrodes provided by the e-OPRA technology, but also with conventional surface electrodes. Such system is currently used daily by five e-OPRA recipients within the ongoing clinical investigation of the e-OPRA technology.

The hardware developed within the first part of this doctoral project allowed for some consequent scientific investigations in regard to the need for tactile sensory feedback to restore natural grasping behavior in amputees. In particular, it was confirmed the benefit for motor coordination of somatotopic tactile feedback achieved via direct neural stimulation. Electric pulses, modulated in amplitude according to the grip forces measured from the robotic hand, helped transhumeral e-OPRA subjects gain a better temporal relation between grip and load forces when interacting with an object. The perceived feedback was described as pleasant enough for clinical use, opening up the possibility for use in daily activities scenarios.

The findings and the technology developed during this project offer clinical use of a new class of prosthetic arms which are directly connected to the neuromusculoskeletal system, intuitively controlled and capable of tactile sensory feedback. This is possible thanks to the advantages of osseointegration and in the breakthrough represented by the e-OPRA technology. The combination of the e-OPRA technology and other advanced surgical procedures, such as TMR or RPNI, strengthened by the advancements of signal processing techniques, can very well improve the *status quo* for amputees with respect to functional control of their prosthetic limbs. Force sensors and tactile sensory feedback should be an essential requirement of any modern upper limb prosthesis, and it is now a concrete clinical possibility thanks to the long-term stable access to nerves via the e-OPRA. Still, further investigations are imperative. The ultimate focus is set on the intuitive control of a prosthetic limb. We aim for a control interface that is as natural as it can be, where the user is relieved from the burden of training and adaptation. Such interface shall guarantee a reliable, precise and responsive control over multiple degrees of freedom. This is the direction that should be taken building upon this doctorate project, in the exclusive interest of improving amputees' quality of life.

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