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Prediction of Motor Volition in the Lower Limbs

Towards a Treatment for Phantom Limb Pain

Master’s thesis in Biomedical Engineering

Eva Lendaro

Department of Signals and Systems
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Abstract

Immediately after an amputation, patients commonly experience the vivid sensation that the amputated limb is still present. However, quite often the awareness of a phantom limb is also accompanied by persistent pain. The mechanisms underlying this condition, known as phantom limb pain (PLP), are not completely understood and many different treatment strategies have been proposed with limited efficacy. PLP has been found repeatedly correlated to changes taking place in the sensorimotor cortex after the loss of the limb. A newly introduced rehabilitation treatment, which attempts to reverse these changes by training the patient to move the phantom limb, has shown promising results. The system promotes motor execution via Augmented Reality (AR), Virtual Reality (VR) and gaming, which are controlled by phantom motions decoded using myoelectric pattern recognition (MPR). This technology has been tested on upper limb amputees suffering from chronic PLP with positive outcomes. Lower limb amputations are more frequent than upper limbs, and therefore it is important to validate the technology in such population. The goal of this master's thesis was to translate the aforementioned technology to treat lower limb amputees.

This work started by investigating the feasibility of MPR to decode motor volition of lower limbs in healthy and amputee subjects. In order to overcome the difficulties of recording Myoelectric Signals (MES), different methodologies for placing the electrodes were compared in terms of their performance in classifying non-weight bearing movements. The results of the study were applied to the MPR/VR treatment and used to treat one patient with trans-femoral amputation suffering from chronic PLP. The patient, amputated 35 years earlier and suffering from constant and intense PLP, was treated at the "Centre for the Advanced Reconstruction of Extremities (C.A.R.E.)" at Sahlgrenska University Hospital, approximately twice a week for a total of 25 sessions.

A preferred electrode configuration was identified and adopted for the MPR/VR therapy. Furthermore, the new recording technique makes also the electrode placement easier, which is essential in the perspective of a technology use by clinicians and patients. The subject, who could not find relief with any previous therapy, experienced a significant decrease in pain at the end of the treatment.

This work identifies a preferred methodology for acquiring MES to be used to treat PLP and suggest the effectiveness of the MPR/VR therapy. The positive results, despite being limited to a single patient, justify further investigation in a wider study.

Key words: phantom limb pain, virtual reality, myoelectric control, electromyography, pattern recognition, neurorehabilitation

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Many people contributed directly or indirectly to my formation as an engineer and if today I am here writing these words in conclusion of my thesis, it is thanks to each one of them. In the limited space of this acknowledgment note I will express my deepest gratitude:

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Finally, a collective thought to all the people not mentioned above but that have played a role in my academic life nonetheless: Thanks to all my friends and inspiring professors that have made these years fly.

List of Publications

This master thesis is partly based on the work contained in the following publications referred by Roman numerals in the text.

I. **E. Lendaro**, M. Ortiz-Catalan, **Classification of Non-Weight Bearing Lower Limb Movements: Towards a Potential Treatment for Phantom Limb Pain Based on Myoelectric Pattern Recognition**., Proceedings of the 38th Annual International Conference of the IEEE Engineering in Medicine and Biology Society. Orlando, Aug 16-20, 2016 (To appear)

II. **E. Lendaro**, E. Mastinu, M. Ortiz-Catalan, **Real-Time Classification of Non-Weight Bearing Lower Limb Movements: A Viable Alternative to Differential Recording for Rehabilitation Use**., (In manuscript)

Contents

Abbreviations

AR	Augmented Reality
CNS	Central Nervous System
EMG	Electromyography
IZ	Innervation Zone
MES	Myoelectric Signals
MPR	Myoelectric Pattern Recognition
MPQ	McGill Pain Questionnaire
PNS	Peripheral Nervous system
PLP	Phantom Limb Pain
PLS	Phantom Pain Sensation
PRI	Pain Rating Index
SP	Stump Pain
SF-MPQ	Short Form McGill Questionnaire
TBC	Targeted Bipolar Configuration
TMC	Targeted Monopolar Configuration
UMC	Untargeted Monopolar Configuration
VR	Virtual Reality
WDP	Weighted Pain Distribution

1

"It is often said, humorously but with a grain of truth, that there are two kinds of pain: mine, which is always real, and yours, which is nothing but a lot of complaining."
Fernando Cervero

1.1 Introduction

A child is moving his first stumbling steps on his own when he trips and falls. He bursts into tears. The mother promptly sits on his side and asks where he feels the pain. She kisses his knee and the weeping vanishes. This situation resembles the way each of us learned the meaning of the world "pain".

The perception of pain is intrinsic and the first tissue injury is painful without needing any previous experience or clarification on what pain really is. Yet, the definition of pain, along with the explanation of the underlying mechanisms, has always been a vexing issue. The contemporary definition of pain proposed by International Association on the Study of Pain (IASP) represents the culmination of centuries of theories postulated by philosophers and scientists. Pain is "an unpleasant sensory and emotional experience associated with actual or potential tissue damage, or described in terms of such damage": to notice how the definition avoids linking the pain to an external noxious stimulus. Normally, the pain should serve as a defence system: the reflexive retraction from a harmful situation increases the possibilities to survive, while the limited use of an injured body part allows us to heal. This kind of pain disappears when the dangerous stimulus is removed or the body has healed. Sometimes however, pain arises in absence of an obvious cause; it persists even after the removal of the danger or beyond healing. In this is the cases the pain loses its protective purpose and it interferes with daily life.

An example of pain generally considered chronic is Phantom Limb Pain (PLP). Following an amputation, it is common to experience the awareness of the missing body part, known as phantom sensation (PS). In the majority of the cases, the phantom assumes a painful connotation: the pain is felt in the absent body part and it is often described as excruciating. Approximately 70% of the individuals that undergo amputation suffer from PLP [1]. This acquires particular significance when considering that in 2005 the number of people with limb loss in the USA alone was estimated to be about 1.6 million. Moreover, the same study projected the number of amputees to increase to 3.6 million by 2050 [2]. It is known that brain reorganization (so called plasticity) takes places after amputation. Correlation between PLP and cortical reorganization [3], and more recently, reduction in cortical communication [4], have been found using fMRI. A novel treatment proposed by Ortiz Catalan at Chalmers University of Technology aims to revert such changes and it has shown promising results in intractable PLP sufferers by [5]. In the proposed approach, a virtual limb responds directly to phantom motions (decoded using myoelectric pattern recognition), while the illusion of a restored limb is enhanced via augmented reality (AR). Furthermore, phantom motions are facilitated and encouraged via gaming and virtual rehabilitation (VR), and since the therapy is computerized, progression and improvements are automatically tracked, thus providing timely feedback to clinicians. This approach has been tested on a patient with upper limb amputation, and it has confirmed its effectiveness in a preliminary clinical study on 14 upper limb patients [6]. Dr. Ortiz Catalan hypothesized that the success of the therapy is due to restauration of the original cortical maps, and inter-hemispheric communication, by reclaiming the use of motor cortical areas related to the phantom limb. The system, which was developed at Chalmers University of Technology, the Centre of Orthopaedic

Osseointegration at Sahlgrenska University Hospital, and Integrum AB, is currently available only for the upper limb amputations. This leaves out lower limb amputees, which are estimated to be the majority, with a ratio of upper to lower limb amputation of 1:35 [2] and are more likely to suffer from PLP (40% of upper limb amputees suffer from PLP against 80% of the lower limb) [1], to have access to a potentially effective solution.

1.2 Aim

This master's thesis work aims to translate the technology to the lower limb and to investigate the efficacy in treating the PLP. In order to achieve this goal, it was necessary to determine the best way to acquire myoelectric signals from the lower limb. For this reason, it was studied thoroughly how to place the electrodes and the work resulted in two publications. Once the method to acquire signals was set, it was used in the clinical investigation on a patient with transfemoral amputation and chronic PLP. Chapter 2 is dedicated to the phantom limb pain: a general background about the clinical aspects, the neural mechanisms and the current treatments is provided in order to give the idea about why projects like the one presented in this Master's Thesis are relevant. Chapter 3 is intended as clarification and reference on basic notions of electromyography, myoelectric pattern recognition and electrode configuration. Chapter 4 presents the software used to conduct the studies presented in this work, introduces the system for PLP treatment and briefly explains the questionnaires for pain and progress tracking. Chapter 5 is the heart of this Master's Thesis work: it contains the report of the clinical investigation on a patient using the PLP treatment presented in Chapter 4. Finally, Chapter 6 contains a short summary of the publications, which are included in the appendix of this Thesis work.

2

The topics in this chapter should give a general idea about why projects such as this one are needed, and what is done today to help people who suffer from phantom limb pain.

Limb loss has profound and devastating effects on the quality of life and daily functionality, yet it is hard to obtain precise figures on the global epidemiology of limb loss. According to estimates for the United States, in 2005 there were 1.6 million persons living with limb deficiency and the number is expected to double by 2050 [2]. Similar attempts to quantify the extent of the amputee population in Sweden have projected the number of new amputations to be somewhere between 1000 and 1100 every year. In both countries, and generally in all the developed countries, the majority of the amputations is connected to the consequences of diabetes and cardiovascular diseases. In contrast, the most common cause of amputation in countries torn by war such as Cambodia, Iraq, and Afghanistan are landmine explosions [7]. Other reasons of limb loss in war-torn and developing countries may include environmental or industrial accidents, juridical amputations (as a form of corporal punishment), terrorist attacks and the absence of public health that fails to prevent diabetes, infection and gangrene.
Regardless of the cause, amputation is a tragic event that hinders the ability of a person to perform daily life activities “in the manner considered normal for a human being”, therefore falling into the definition of disability. Although the use of prosthetics may considerably restore the functionality of the missing limb, other aspects such as chronic pain may pose as a challenge to the quality of independent living.
Immediately after an amputation, patients commonly experience the vivid sensation that the amputated limb is still present. Such a phenomenon is known as phantom limb and it is reported by 95-100% [8] of people who loose and arm or a leg. The most remarkable feature of a phantom limb is its reality to the amputee. It is not rare that the awareness of a phantom limb is accompanied by somatic feeling such as warmth, cold, joint position or pain [9]. Collectively, any non-painful sensation in the missing body part is defined as phantom limb sensation (PS), whereas painful sensations in the absent limb are referred as phantom limb pain (PLP) [10]. The pain localized in the remaining part of the limb is called stump pain (SP). Phantoms are not exclusively associated with the amputation of limbs: they can be related to any body part. For example, it is common that phantoms are reported in response to surgical removal of teeth, tongue, breast, genital organs and bladder. Interestingly, amputation is not necessary for the insurgence of a phantom: after avulsion of the brachial plexus, patients report a painful ‘third arm’ even though the real arm is still intact. In a similar way, a complete break of the spinal cord might lead to a phantom body perceived below the level of the break [11]. Even denervation is not essential: subjects who receive an anaesthetic block of the sensory and motor nerves of the arm or leg report a vivid phantom with a position that is usually unrelated to the position of the real limb when the eyes are closed. However, the phantom fuses with the real limb once the subject looks at it [12]. The present thesis work focuses exclusively on phantom limb phenomena (pain and sensations) deriving from the amputation of a limb, and in particular, the lower limb.

2.1 History of PLP

The term ‘phantom limb’ was originally introduced in 1872 by Silas Weir Mitchell (1829-1914), an American physician and surgeon [13]. Nevertheless, phantom limb phenomena were known long before Mitchell. The first medical description is attributed to Ambroise Paré (1510-1590) when in

1551 he reported that, "For the patients, long after the amputation is made, say that they still feel pain in the amputated part"[13]. A century later the French philosopher René Descartes (1596-1650) described phantom sensations in amputated limbs in various writings [14]. He was the first to attempt at a theoretical explanation, yet limiting himself to use the observations as a proof that sensory information can be deceptive and ultimately as a demonstration of his dualistic philosophy of mind. Only later was it understood that these phenomena could be used to gain insight into sensory functions. William Porterfield (ca.1696-1771), a Scottish physician who had a leg amputated, was the first medical doctor to describe and interpret the feelings of missing leg from the first person's point of view [15]. Moreover, he used the phantom limb experiences to support a general theory of perception based on the philosophical knowledge of his time, which can be traced back to Descartes. Years later, Charles Bell (1774-1842), a British surgeon well known for having developed the concept of specificity within the sensory pathways, used the phantom limb phenomena to back his theory of specific nerve energies[14]. To conclude, it is worth to notice that many other reports of phantom limbs can be found in the literature antecedent Mitchell. However, thanks his descriptive literature, Mitchell was acknowledged not only for coining the term but also for drawing the attention of both medical community and, for the first time, lay public.

2.2 Clinical aspects of PLP

As aforementioned, virtually all of the amputees experience a phantom limb that appears almost immediately after the loss of a limb. Sometimes the phantom is perceived as painful and this condition, known as PLP, is suffered by approximately 70% of the subjects [1], [16]. In adults the occurrence of PLP is independent of age, gender, side, level of the amputation or cause [1], [16]–[18]. A study on a large number of subjects has shown that PLP is present in 40% of the upper limb and 80% of the lower limb amputees [1], and is less frequent in young children (48.5%) and subject with congenital limb loss (4%). Most of the studies have found no significant relationship between the presence of PLP and the cause of amputation. PLP has usually an early onset [13],[14], but cases have been reported where the PLP manifests itself decades after the limb was removed [21]. PLP is most commonly experienced in intermittent episodes of various length and frequency that differs from subject to subject [18]–[20]. The pain seems most intense and most commonly located in the distal part of the phantom and it is usually described with a wide range of different qualities such as sticking, shooting, burning, stabbing, cramping and throbbing [16],[22]. Some retrospective studies have evidenced pain before amputation as a risk factor [18], [19]; other studies have shown that the PLP may have similar qualities and localization of the pain experienced before the loss of the limb as if 'repressed memories' emerged in the phantom [23], [24]. SP and PLP are correlated and many authors have reported higher proportions of subjects with PLP when SP was present[16], [20], [22]. Moreover, in some of the amputees with phantom phenomena the distal part of the limb is perceived as undergoing a gradual retraction towards the stump and in some instances the phantom limb disappears inside the remaining part of the limb [25]. This phenomenon is known as "telescoping" and it is illustrated in Figure 1. Phantom phenomena are modulated by a number of factors that can be classified as internal (depending on the subject, e.g. genetic predisposition to anxiety, chronic pain etc.) or external (depending on the environment, e.g. weather change, use of prosthesis, etc.) [10]. In summary, PLP is classified as neuropathic chronic pain since in the majority of the cases the pain intensity persists over long periods of time [26].

Figure 1: Phantom limbs can be perceived as gradually retracting inside the stump. The phenomenon is known as 'telescoping'.

2.3 Theory

All we know about PLP comes from experimental and clinical studies and the true underlying cause is still poorly understood. While in the past PLP was believed to be a psychological illness connected to the difficulty of coping with the loss of the limb, today the consensus has shifted to theories that see PLP correlated to plastic changes at various level of the nervous system. The scientific community unanimously supports these changes, divided into peripheral and central mechanisms, even though none of the theories can explain alone the phenomenon. Yet, although the psychogenic origin of PLP has been dismissed, factors such as depression, anxiety and stress are acknowledged to aggravate the PLP. All the proposed mechanisms to explain phantom limb pain are shown in Table 1 and described in the rest of this section.

2.3.1 Peripheral mechanisms

Peripheral changes are the rearrangements occurring in the peripheral nervous system (PNS) after amputation or nerve injury. Among these, stump pain and neuromas are recognized as the principal mechanisms that contributes to PLP. Following nerve injury or cut, the fibres are likely to undergo unregulated regeneration and the axons in the distal part sprout abnormally forming a tangled mass called “neuroma”. Neuromas present an increased density of sodium channels which translates into hyper-excitability of those neurons: this eventually causes increased activity in the stump [27]. Stump neuromas are believed to be accountable for both stump and phantom pain. In fact, phantom pain is significantly more frequent in those subjects who suffer from persistent stump pain [28] and its resolution often leads to a reduction of the PLP [20]. For example, in one study, 11 subjects with established stump and phantom pain had their peripheral nerves treated with neuromuscular blocking

Table 1: Proposed mechanisms to explain phantom limb pain.

Peripheral mechanisms		Stump pain Neuroma hyperactivity
Central mechanisms	***spinal level***	Central sensitization Functional reorganization
	brain level	Cortical reorganization and sensory-motor conflict
Psychogenic mechanisms		Catastrophizing and other psychological factors

agents. All subjects reported a decrease in the rating of both phantom and stump pain [29]. On the other hand, peripheral mechanisms solely cannot explain phantom pain phenomena in all their complexity. To demonstrate, PLP can appear immediately after amputation before a possible neuroma could generate. Moreover, subjects with congenital limb absence have been reported to suffer from PLP [30] and other studies found that local anaesthesia of the stump does not eliminate PLP in all the amputees [31]. In short, it is clear that neuromas need not to be involved for PLP to be present and the cause of painful sensations must be investigated more centrally.

2.3.2 Central mechanisms

As the name suggests, central changes involve structures of the central nervous system. Moreover, they can be distinguished into spinal or cerebral changes according to where the reorganization takes place.

2.3.2.1 Changes at the spinal cord level

Clinical observations suggest that spinal factors play an important role for PLP [32], even though direct proof of these effects on human amputees is limited. One of the consequences of peripheral nerve amputation commonly found in amputee is known as central sensitization[29]. The process, caused by an increased activity of the peripheral nociceptors, consists in permanent changes in the way the neurons in the dorsal horn of the spinal cord respond to stimuli [33]. Manifestations of central sensitization are allodynia (pain evoked by stimuli that would normally not be painful) and mechanical hyperalgesia (actual painful stimuli are perceived as more painful than they should) [34]. Another mechanism relevant to PLP consists in the functional reorganization of the spinal cord accompanied by an expansion of the receptive fields [35]. It has been proposed that the spinal reorganization contributes to PLP [36], however the extent to which is not known [10].

2.3.2.2 Changes at the brain level

The organization of the cerebral cortex is often described in terms of cortical maps. In essence, a cortical map is the correspondence between some events external to the brain, for instance a sensory input from the foot, and a specific cortical site where neurons are part of a network with common properties.
The cortical maps of the motor cortex, responsible for planning and executing movements, and the sensory cortex, responsible for the sense of touch, are depicted in Figure 2: these maps are known as

cortical homunculi and they illustrate how the human body is represented within the brain. From Figure 2 it is obvious that the cortical representation of different body parts does not reflect the real physical size. The extent of the cortex dedicated to any part of the body is in fact proportional to the amount of innervation of that area.
Studies on animals and humans have shown that amputation, and the loss of sensory input, leads to an extensive reorganization in both sensory and motor cortex [35], [37], [38]. In other words, areas of the brain, which once represented the amputated limb, are invaded and taken over by surrounding regions of both primary motor and sensory cortex. Interestingly, a direct relationship between the degree of cortical reorganization and the intensity of PLP has been observed [39], even though it is currently not clear why this kind of plasticity, renamed as "maladaptive plasticity", should cause pain rather than merely abnormal perception. One theory proposes that the pain may arise from activity of the motor cortex which sends commands to the missing limb without being inhibited by the sensory cortex, in turn responsible of verifying that the required movement has actually happened [40]. In addition, a discrepancy between senses such as proprioception and vision is created. A compelling evidence of this can be found in a study where pain-free healthy volunteers were exposed to sensory-motor conflict. Fascinatingly, the majority of the participants reported anomalous symptoms of pain despite no nociceptive stimulus was applied [41].

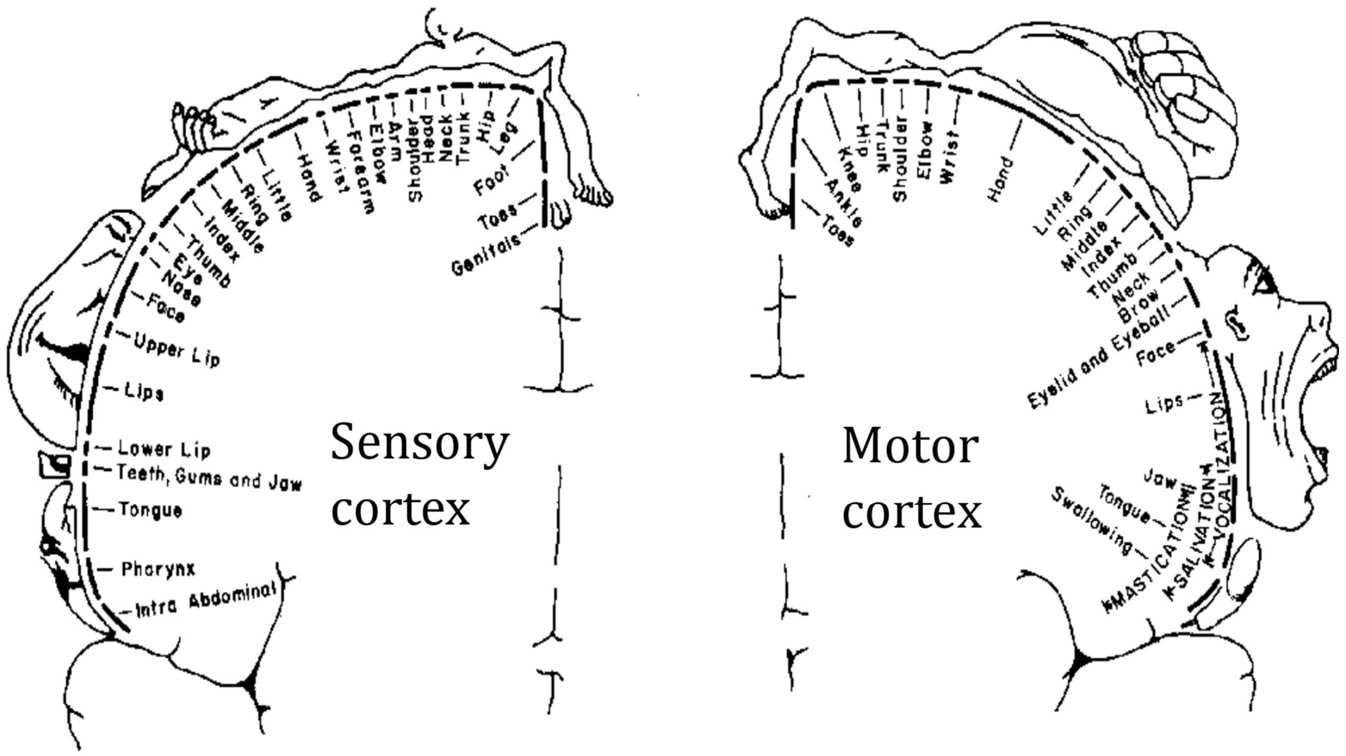

Figure 2: Penfield's maps of the brain representing the cortical organization of sensory cortex (left) and motor cortex (right). This image is a derivative work of [88]

In contrast to the evidence supporting maladaptive plasticity as the cause of PLP, a recent study argue for an alternative hypothesis by suggesting that the plasticity may be induced by a combination of sensory deprivation and pain experience [42]. According to the study, PLP is caused either by nociceptive inputs from the periphery, or by signals from pain-related regions of the brain. The experience of PLP is then responsible of driving plasticity by preserving cortical representation of the phantom limb while distorting the connectivity among different areas of the primary sensorimotor cortices.

2.3.3 Psychogenic mechanisms

Despite the fact that recent literature does not support the psychogenic origin of PLP, emotional states such as anxiety, depression and stress are suspected to accentuate PLP [43]. Furthermore, a link between the coping style of a subject who undergoes amputation and PLP has been revealed. In particular, the presence of passive coping strategies and catastrophizing traits (tendency to exaggerate the experience of pain and feel more helpless about it) before the amputation and may play a role in the development and maintenance of PLP[44].
In general, it is important to realize the challenge posed by the identification of factors associated to PLP: most of these aspects could as well be caused by, instead of contributing to PLP. Once established, these factors can take part in the maintenance of the PLP, despite not being the original cause.

2.4 Treatments

A big variety of treatments for chronic pain after amputation have been devised, and commonly they can be classified as medical, non-medical and surgical [10]. Medical treatments involve the use of medication such as analgesics, antidepressants, anaesthetics, opioids, etc. [45],[46]. Surgical treatments are invasive and imply either further deafferentiation or neurostimulation [46] and, due to the invasiveness and the associated risk, they are normally employed only when other therapies have failed. Finally, non-medical treatments cover a broader spectrum of methodologies where (Transcutaneous Electrical Nerve Stimulation) TENS, physical therapy (i.e. massage, manipulation and passive movements), psychological treatment (i.e. counselling, acupuncture, bio-feedback and hypnosis) are few examples [47].
Despite the big number of treatments available, PLP still presents itself as a condition difficult to solve. Several studies have observed that most of the treatments are ineffective and fail to take into account the mechanisms underlying the real cause of PLP[43].
As mentioned earlier, findings from brain imaging suggest that the cortical reorganization has a role in PLP. At the same time, studies on monkeys have observed that extensive behaviourally relevant stimulation of a body area results in an enlargement of the cortical map representation of the stimulated part [48]. Given these results, the hypothesis that intensive use of myoelectric prosthesis can contrast the maladaptive changes is logically sound. Moreover, a study has revealed that the use of myoelectric prosthesis is positively correlated to both less PLP and less cortical reorganization[49]. Another behaviourally oriented approach showed that sensory discrimination training (stimulation applied on the stump) has significant results in reverting the cortical reorganization [50]. In general, the major advantages of behavioural methods are the absence of complication and side effects and the fact that the treatment is easy to repeat and therefore induce plasticity.

2.4.1 Mirror therapy

The mirror therapy was introduced by Ramachandran in 1992 as a technique for treating PLP and hemiparesis due to stroke [51]. A mirror is placed vertically and the subject is instructed to place the phantom on one side while keeping the intact limb on the other side. Doing so, the patient is able to see the reflection of the intact limb superimposed where he/she perceives the phantom limb. Figure 3 consists of a sketch of the mirror box: the device that was built by Ramachandran for the use in upper limb amputees.
The methodology, born from the need to explore the effect of visual input on phantom sensation, has in many cases enabled movements in patients who claimed to have paralyzed phantoms. Moreover, the therapy attempts to decrease the pain by reconciling the discrepancy between vision and proprioception. Interestingly, many clinical studies have confirmed the beneficial effects for patients

suffering from PLP [52]–[54]. Additionally, a study using fMRI confirmed a partial reversal of cortical reorganization with consequent reduction of pain thanks to mirror feedback therapy [55].
Another component enabled by the therapy than might intervene in the modulation of pain is the mirror neuron system [56]. Mirror neurons are present in the inferior frontal cortex and superior parietal lobe. These neurons, unlike normal neurons, not only do they fire when performing an action, but also when the observer watches a second individual performing a movement. However, the observer does not perceive to be touched when he/she sees someone else being touched because the receptors of the skin send a ‘null signal’ to the brain informing that no touch has happened. As a result, the ‘null signal’ inhibits the output of the mirror neurons that leads to conscious perception and allow the observer to see the world from the perspective of the other individual. In the case of an amputee however, there is no ‘null signal’ that can be sent to the brain resulting in the illusion of touch. Furthermore, the activation of mirror neurons is thought to block the perception of pain in the phantom limb [57].

2.4.1.1 Limitations of the mirror therapy

Although this method has proved to be successful and promising under certain aspects, there are also some limitations that must be taken into account. First of all, mirror therapy is not suitable for bilateral amputees, since one intact limb is required in order to provide the mirror visual feedback. Second, the patients have no direct volitional control over their phantom limb: they need to move the contralateral limb, and the visual feedback received consequently enables the kinaestatic sensation in the phantom. This means that the actual effort to produce phantom motion is disregarded and only motions where the two limbs move symmetrically are possible. For the lower limb, this is a drawback since symmetric movements are not natural. Third, the mirror therapy is monotonous and may result boring over time. This leads to the risk of the patient dismissing the therapy because scarcely engaged. Finally, the therapy has not shown to be effective in reducing pain in all the subject: a controlled trial reported an improvement in the movements that the phantom could execute but did not alleviate PLP [58].

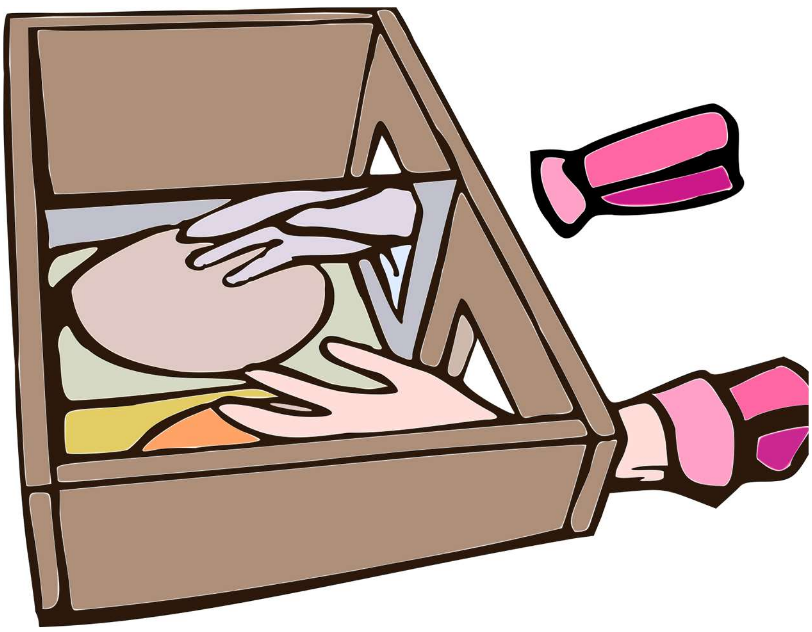

Figure 3: The mirror box, as Ramachandran conceived this therapeutic device.

2.4.2 Virtual Reality, Augmented Reality and Gaming

Virtual Reality (VR) is a computer technology that simulates the user's physical presence within an artificial environment, and can be displayed on computer monitor or with a head mounted display. Through the use of standard input devices such as a keyboard and mouse, or more sophisticated devices such as such an instrumented glove or motion tracking technology, VR makes possible to recreate the sensory experience (i.e. sight, hearing) of the virtual environment. By contrast, Augmented Reality (AR) does not replace the real world with a virtual one, but rather 'enhances' the physical world. AR represents the real world surrounding the observer, but the environment is altered or elements are added by computer generated sounds, video or graphics. Thanks to these characteristics and the increasing availability for cheaper prices of computers, video capture devices, motion tracking technologies and software, VR and AR lend themselves particularly well to a big variety of applications ranging from videogames to education, from architecture to rehabilitation. Within the particular interest of rehabilitation from PLP, the spread of VR and AR has led to the introduction of more sophisticated variations of the mirror therapy: Table 2 presents a summary of the publications where these systems are presented.

Many examples of VR or AR mirror therapy rely on the presence of a sound limb: motion data is captured with different techniques from the intact limb and it is then used to move a contralateral virtual limb [59][60][61]. Compared to a simple mirror, however, VR and AR add several advantages that make their use preferable. First of all, it is possible to shape the virtual limb in a way that matches perfectly how the phantom limb is perceived - sometimes the phantom limb is felt as deformed- so to improve the illusory effect. Secondly, VR and AR allow the interaction with virtual objects and the implementation of more engaging exercises in order to motivate the daily practice [62]. The main drawbacks, however, are the necessity of the contralateral limb, which is a limitation for bilateral amputees, and the disregard of the actual effort to move the phantom limb.

A further step has been taken by implementations that capture the motion data directly from the stump (instead of the opposite limb) with the effect of engaging the correct side of the brain. In a first attempt made by Cole *et al*. [63], motion data is captured from electro-magnetic sensors attached to either the remaining part of the arm or the leg. An obvious disadvantage of the system is the impossibility to control movement of the distal part of the limb (i.e. the fingers), which need to be pre-animated. In order to overcome this obstacle, Anderson et al. [64] introduce a system that uses surface myoelectric signals from muscles of the stump to control the virtual limb. The control strategy is analogous to the direct control of myoelectric prosthesis. Essentially, the user has to learn combinations of contractions and co-contractions and each combination corresponds to a different movement that the virtual limb can perform (unnatural control). Although this method increases considerably the number of degrees of freedom possible to control, these are still limited and strictly dependant on the level of the amputation: the higher the amputation, the fewer muscles are present and the fewer combination are possible. In 2014, Ortiz Catalan et al. [5] published a treatment for PLP that makes use of natural patterns of myoelectric signal as they are generated during the volitional activation of the motor cortex. In short, the user is required to actively perform phantom limb movements, which in turn produce synergistic activation of the available stump muscles. The patterns of muscular activation are acquired by the system which performs myoelectric pattern recognition (MPR) and enables the intuitive control of a virtual limb. The advantage of MPR over the traditional myoelectric control is clear: using MPR the subject perform phantom movements in the same way they would move the limb if it was still present. Furthermore, the system includes VR, AR and a game included in order to engage the patient in executing these movements.

Table 2: List of the publications where Mirror Therapy and (Virtual Reality) VR/ (Augmented Reality) AR systems for the treatment are presented. VF= Visual Feedback, Inst. G.= Instrumented Glove, MT=Mirror Therapy, EMG= use of surface electromyography to control the VR/AR environments, MPR=use of Myoelectric Pattern Recognition to control VR/AR environments, ips. =ipsilateral limb, contr.=contralateral limb.

First Author	First Author	VF	Inst. G.	MT	EMG	MPR	Limb used for control ips./contr.	Display device	VR/AR
2003	O'Neill		x				contr.	screen	AR
2006	Desmond		x				contr.	screen	AR
2006	Murray		x				contr.	HMD	VR
2009	Cole			x			ips.	screen	VR
2010	Sato		x	x			contr.	screen	VR
2011	Kamping		x					HDM	VR
2012	Penelle			x			contr.	3D screen	AR
2012	Anderson				x		ips.	screen	AR
2013	Trojan	x					contr.	HMD	AR
2013	Heckman			x			contr.	screen	AR
2014	Ortiz-Catalan					x	ips.	screen	VR/AR
2014	Carrino			x			contr.	HMD	AR
2014	Diers		x				contr.	HMD	VR

3

In this chapter basic notions about surface electromyography and myoelectric pattern recognition are given as they are intended as reference later in this Thesis. A short description of the problems encountered when recording myoelectric signals from the stump of lower limb amputees follows, along with the proposed solutions.

3.1 Surface Electromyography

S urface electromyography (sEMG) records the electrical activity of a muscle from the skin above the muscle and the surface electrodes can be placed either in monopolar or bipolar configuration. The monopolar configuration (Figure 4) uses a pair of electrodes: one electrode is placed over the muscle while the other electrode acts as reference, and is placed far away on an electrically neutral tissue. The differential signal between the two electrodes (the difference between the potential recorded by the two electrodes) is amplified and recorded.

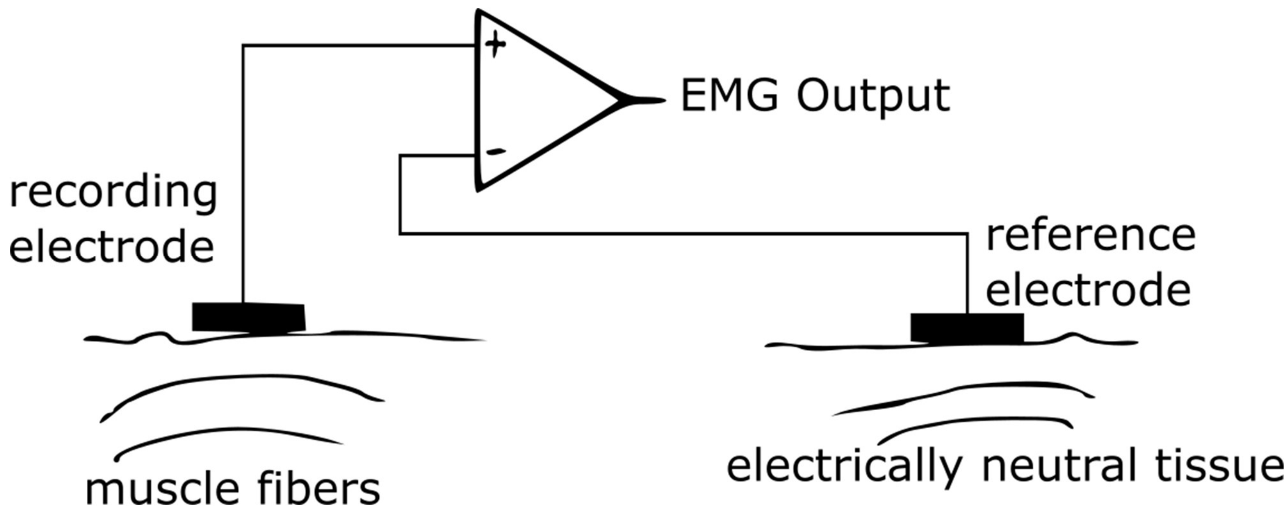

Figure 4: Monopolar configuration[89]

In the bipolar configuration (Figure 5: Bipolar configuration), two electrodes are placed over the muscle in proximity to each other while a third one is used as reference and, again as in the monopolar configuration, it is placed over an electrically neutral tissue. The signal between the two electrodes placed over the muscle is amplified differentially with respect to the reference electrode. The advantage of the bipolar configuration is the elimination of the common noise of the two electrodes and for this reason, the bipolar configuration is the most common method.

3.1.1 Electrode placement

The quality of a myoelectric signal (MES) is heavily influenced by factors depending on the experimental conditions. In particular, it is known that different electrode locations over the same muscle can yield signals with considerably different features. It is therefore important to be aware of few notions regarding the correct placement of the electrodes.

1. **Location of the electrodes over the muscle:** surface MES are affected by the placement of the electrodes with respect to the innervation zones (IZs). When recording differentially over an IZ, any small displacement of the sensors with respect to the IZ will give not stable or

reproducible signals [65]. It is therefore advisable to place the two surface electrodes between the IZ and the tendon. This is easily done in muscles having fibres running parallel to each other where the innervation zones are generally distributed in a narrow band around muscle belly [66]. More challenging could be the electrode placement on muscles with complex structure, such as pennate muscles, where the innervation zones are scattered over the muscle [66].

2. **Thickness of the subcutaneous tissue layers:** MES are particularly influenced by the depth of the subcutaneous tissue over which the surface electrodes are placed. In particular, sEMG signals are attenuated in the subcutaneous tissue and its thickness, which greatly varies among subjects, partly explains the variance among individuals in sEMG amplitude [67].
3. **Inter-electrode distance:** In a bipolar configuration, two electrodes are placed in proximity; the distance between them is called inter-electrode distance (IED) and has to be chosen wisely. In fact, as the IED increases, the magnitude of the target signal and the magnitude of the crosstalk signals (signals coming from muscles other than the targeted one) also increase [68]. The ideal IED represents a trade-off between maximizing the target signal and minimizing the crosstalk signals.
4. **Inclination of the detection system relative to muscle fibre orientation:** Optimal surface MES are recorded with surface electrodes orientated parallel to the muscle fibres and therefore parallel to the direction of the action potential propagation [69]. Particular attention must be paid to pennate muscles as determining the direction of the fibres might be more problematic. Using a monopolar configuration, the problem of the electrode alignment with the fibres is bypassed.

A widely referenced report from the Surface EMG for Non-invasive Assessment of Muscles (SENIAM) initiative contains a set of guidelines covering exhaustively the subject [70]. The use of such guidelines is highly recommended in the common practice of sEMG.

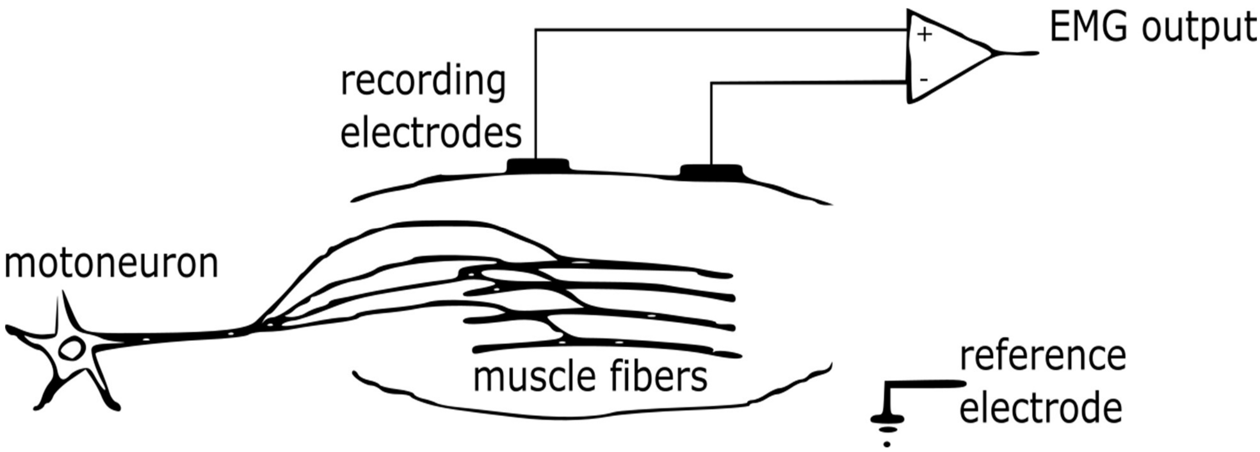

Figure 5: Bipolar configuration[89]

3.2 Myoelectric Control

Autonomic and voluntary movements of the body are possible thanks to the action of muscles which are in turn controlled by the brain. In brief, the CNS sends neural commands down efferent nerve fibres to the PNS where each moto neuron forms neuromuscular junctions with a group of skeletal muscles fibres (motor unit). A simplified schema of basic motor nervous system function is shown in Figure 6. There is a 1:1 relationship between a moto neuron and the fibres of its motor unit: a signal that reaches the motor neuron will necessarily generate a signal in the muscle fibres and therefore a contraction. Different intensities of contraction are produced by variating the number of motor units

recruited and the frequency of neural commands sent to motor neurons. For these reasons, MES are considered faithful information about the motor intention. Furthermore, they can be detected easily and noninvasively using electrodes placed over the skin.
These signals can be exploited to control intuitively prostheses or rehabilitation devices; in fact they have been employed for controlling upper limb prostheses since 1948 [71].
Myoelectric control systems can be divided into two groups: non-pattern recognition- and pattern recognition-based [72].
Non-pattern recognition systems are generally based on threshold or proportional algorithms and finite state machines. In these systems the output is a limited number of pre-defined commands based on a sequence of input signal.
In the second group, the MES are acquired and then amplified, filtered and digitized. The obtained signals are treated and reduced to features that are then fed into a classifier. The output of the classifier is then used to control an artificial device [72].

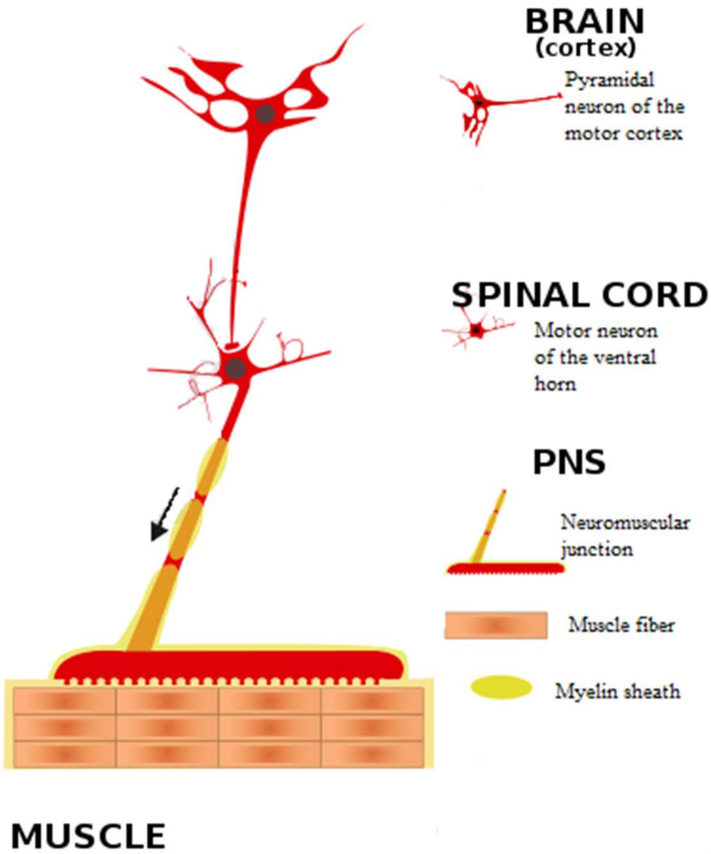

Figure 6: Simplified schema of basic motor nervous system function. Signals from the motor cortex are sent to the spinal cord and then out to motor neurons via the efferent division of the PNS. This image is a derivative work of [90]

3.2.1 Myoelectric Pattern Recognition (MPR)

A typical myoelectric pattern recognition (MPR) control system usually consists of the following components (Figure 7):

- **Data segmentation:** MES signals, due to their randomness, cannot be used directly as input of the classifier, but they must be reduced to a more suitable form.
- **Feature extraction:** The segmented data is then mapped into smaller dimension vectors by computing a set of pre-determined features. The feature vectors are used as input of the classifier.
- **Classification:** A pattern recognition algorithm recognizes signal patterns, and classifies them into pre-defined categories.
- **Controller:** Uses the output of the classifier to generate commands to control an artificial device. Post-processing techniques, such as majority voting, can be applied after classification to dampen the effect of misclassifications and smoothen out the output.

However, in some cases the four different components above described may be omitted or merged together.

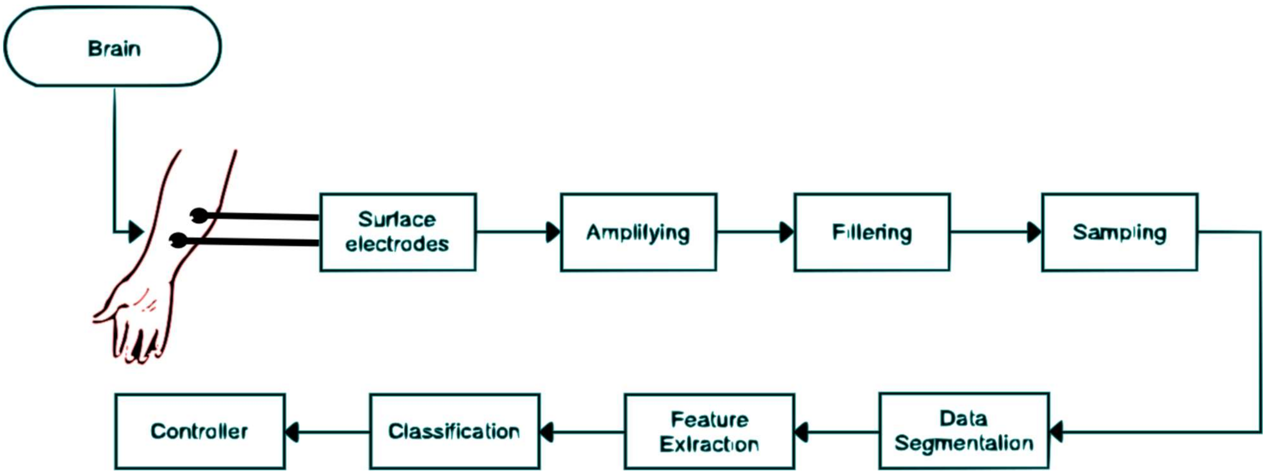

Figure 7: Flowchart of a typical myoelectric pattern recognition system

3.2.2 MPR in the lower limb

Despite the fact that amputations of the lower limb are more frequent, research on MPR has mainly focused on the upper extremities. While the recent introduction of powered knees controlled by microprocessors has improved the mobility of individuals with transfemoral amputation, it has also highlighted the necessity of an intuitive way to switch between different walking modes (i.e. level walking, sitting, standing, stair ascent, etc.). MPR in the lower limb, as a strategy to include neural information in prosthetic control, has been explored in several recent studies which have taken two distinct paths: Prediction of movements in weight bearing and non-weight bearing conditions.

In weight bearing conditions, almost the totality of the research has rotated around the discrimination of the intended walking stage [73], [74] and to trigger mode transition [75][76][77][78][79]. One major challenge for MPR-based control in lower limb is undoubtedly reliability: in fact, any misclassification or disturbance in the EMG signal could lead to loss of balance and endanger the user.

However, one mode that seems to be particularly well suited for this kind of control strategy is when the subject is in sitting position (non-weight bearing condition). MPR under this circumstances has been studied and accomplished offline [80] and in real-time [81]. Hargrove et al. [81] demonstrated

the discrimination of eight leg movements (knee flexion/ extension, ankle plantarflexion/dorsiflexion, femoral rotation, and tibia rotation) in both able-bodied and amputee subjects recording surface MES signals from nine residual thigh muscles. A summary of the studies that treat MPR in the lower limb can be found in Table 3. The table enlist the publications, along with the list of muscles targeted for the acquisition of the MES. Only applications that make use of exclusively MES as a control source, which are also suitable for transfemoral amputees are considered.
At the time of writing, the author has no knowledge of any MPR application for the lower limb used for rehabilitation purposes. Particularly interesting would be to enable the prediction of motor volition to treat PLP in lower limb amputees, in an analogous way to what was done by Ortiz-Catalan et al. [5]. The study illustrates the use of MPR for physiologically appropriate control of a virtual arm while providing visual feedback via augmented and virtual reality and the focus of this Master's thesis work is to translate the mentioned technology to accommodate the needs of trans-femoral amputees.

Table 3: List of the publications treating Myoelectric Pattern Recognition (MPR) for applications. Only applications that make use of exclusively myoelectric signals as a control source, which are also suitable for transfemoral amputees are considered.

Year	First Author	Muscles	Walking Modes	Non-weight Bearing	Control	Subjects		MPR	
						healthy	*amputee*	Offline	Real Time
2009	Huang	GMA,GME, Sart,RF,VL,VM,ST,G,BF	x		-	8	2	x	
2011	Ha	hamstring and quadriceps		1 DoF	prosthesis		3		x
2013	Hargrove	ST,BF,TFL,RF,VL,VM,Sart, AM, G		4 DoF	VR / prosthesis	6	6		x
2015	Taimoor	ST,BF,TFL,RF,VL,VM,Sart, G		4 DoF		7	-	x	

Legend

Sart= sartorius	AM=adductus magnus	TFL=tensof fasciae latae
VM=vastus medialis	G=gracilis	BF=biceps femoris
ST=semitendineus	RF=rectus femoris	VL=vastus lateralis
GMA=gluteous maximus	GME=gluteous medius	

3.2.2.1 Muscles of the lower limb

In order to place surface electrodes in an appropriate way, and overcome the possible difficulties of translating the technology presented in [5] to the lower limb, it is important to familiarize with the anatomy of the muscular structure of the lower limb.
The lower extremity can be divided in different regions: hip, thigh, leg and foot. The term leg is colloquially used to indicate the whole lower extremity; however, the leg is just the portion comprised between the knee and the ankle.

This project is interested in exploring the possibility of MPR in transfemoral amputees and this limit the focus to the superficial muscles of the thigh, which are illustrated in Figure 8, where it is also indicated whether the muscles are pennate or have fibres running parallel.

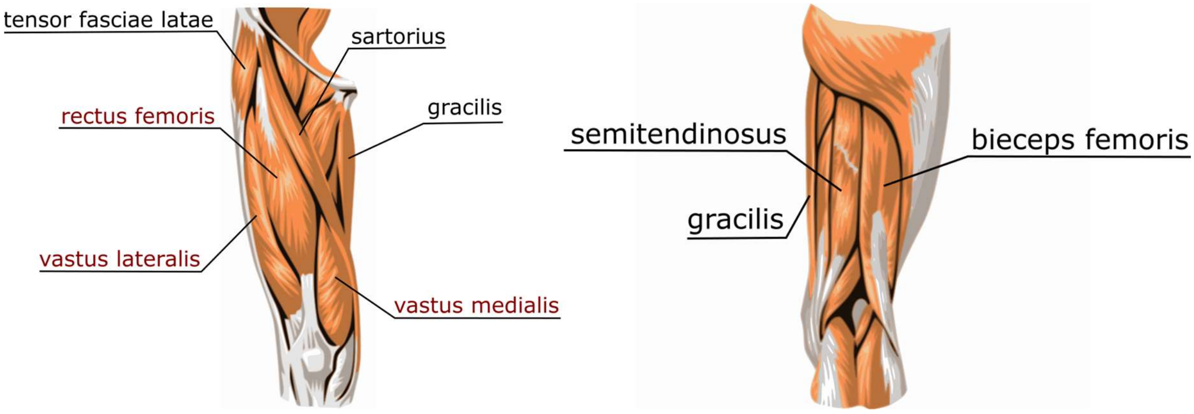

Figure 8: Superficial muscles of the thigh. The muscles in red text are pennate muscles, while the rest have fibres running parallel

3.2.2.2 Problematics of sEMG in the lower limb

Lower limb amputees that suffer from PLP have all sorts of stumps. Sometimes the stumps are very short and not all the muscles required by the targeted configurations listed in Table 3 are available. Other times parts of the stump are covered by scar tissue resulting from the amputation: the scar tissue increases the skin impedance, while pre-gelled adhesive electrodes do not stick well detaching easily. Not to mention the difficulty to localize the muscles with precision due to the thickness of subcutaneous tissue that often layers up on the stump, and to the anatomy of the muscles that might have been relocated during the amputation surgery. Finally, a major challenge is without any doubt to align the electrodes to the direction of the muscles fibres, especially in the quadriceps (pennate muscles).

In the perspective of a rehabilitative application used routinely, the electrode placement of bipolar electrodes on targeted muscles becomes difficult -or even impossible due to the lack of the required muscles- and time consuming. In order to make the process of placing the electrode easy for a patient who wants to use the system at home, alternative ways need to be explored.

3.2.2.3 Alternative electrode configurations

As a contribution of this Master's Thesis work, different configuration for electrode placement were proposed in Paper I. The configurations were then compared in two different studies in terms of SNR, offline accuracy in Paper I and real-time performance in a classification task in Paper II. The description of the electrode configurations is reported here:

- **Untargeted Monopolar Configuration (UMC):** The circumferential electrode is placed around the proximal third of the thigh and 16 Ag/AgCl pre-gelled electrodes placed below the band (distally), equally spaced around the thigh. The gap between the electrodes and band is approximately 4 cm. In a way similar to the Targeted Monopolar Configuration, differential measurements are recorded between each of the electrodes and the circumferential electrode. (Figure 9.a)
- **Targeted Monopolar Configuration (TMC):** For each pair of electrodes in the targeted bipolar configuration a third electrode is placed in between. A circumferential electrode made of conductive fabric (silver plated knitted fabric) is wrapped around the proximal third of the

thigh. Differential measurements are recorded between the eight electrodes and the average potential of the area covered by the circumferential. The configuration is considered targeted because the sEMG signals are supposed to come from physiologically appropriate muscles, which therefore need to be identified. The configuration is also defined as 'monopolar' due to the use of the common circumferential electrode which acts as a reference electrode because it covers a significantly larger area than that one covered by the Ag/AgCl pre-gelled electrodes. (Figure 9.b)

- **Targeted Bipolar Configuration (TBC):** Eight pairs of adhesive electrodes (disposable, pre-gelled Ag/AgCl, 1 cm diameter, and 4 cm inter-electrode distance) are placed over the following eight muscles: sartorius, tensor fasciae latae, vastus medialis, rectus femoris, vastus lateralis, gracilis, long head of the biceps femoris and semitendinosus. A stump long enough to identify all the required muscles is necessary. (Figure 9.c)

In all the three configurations the reference electrode is placed far, on an electrically neutral tissue: i.e. on the wrist, over the distal end of the ulna (Figure 9.e).

The two comparative studies, paper I and II, found the above described configurations to be successful in classifying the required motions without significant differences. However, the use of the UMC, where the electrodes are quickly applied around the proximal third of the thigh, was suggested as preferable for the implementation of a rehabilitative system that could be used daily and independently at home.

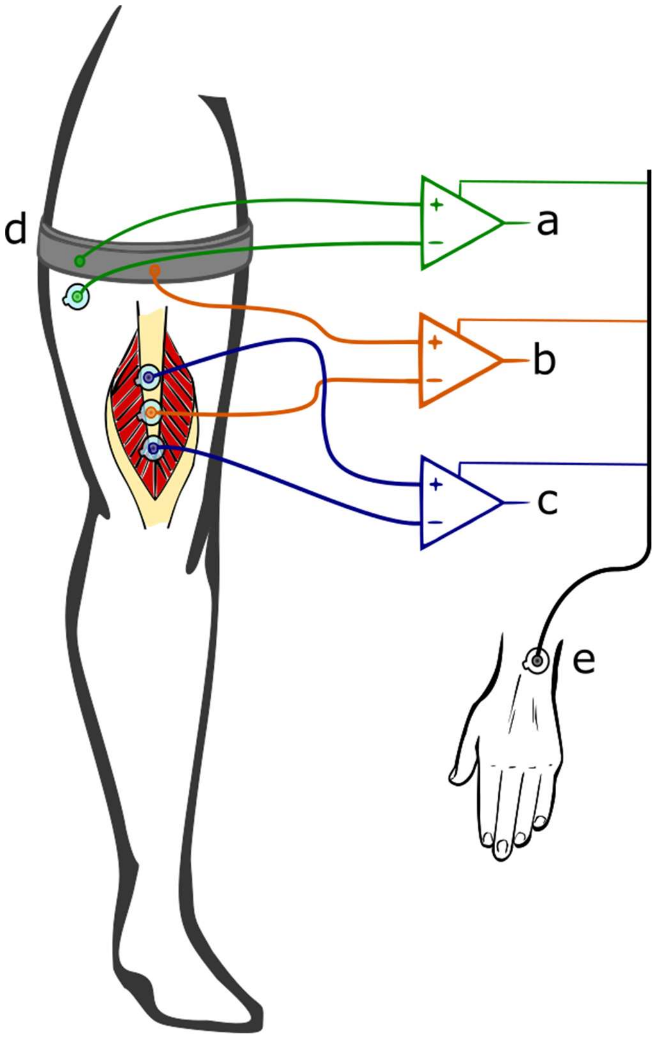

Figure 9: Sketch of the three electrode configurations, (a). Untargeted Monopolar Configuration, (b). Targeted Monopolar Configuration, (c). Targeted Bipolar Configuration. (d). Common circumferential electrode, (e). Reference electrode.

4

This chapter contains a description of the tools used to conduct the studies on the electrode configurations (Chapter 3) and the clinical investigation (Chapter 5). These tools consist in the software for MPR (BioPatRec) and the questionnaire used for phantom limb pain tracking.

4.1 BioPatRec

BioPatRec is an open source research platform for the analysis and pattern recognition of bioelectric signals [82]. The software is implemented in Matlab® and was first used for the development of advanced strategies for prosthetic control. Later, the system was also adopted for the treatment of PLP in an upper limb amputee patient showing promising results [5]. BioPatRec is a complete solution composed of different modules, depicted in the flowchart of Figure 10, reflecting the structure of the typical MPR control system reported in Chapter 3. The software can be used for both upper limb and lower limb as the modules from “Signal Recordings” to “Control Algorithms” don’t need any particular adaptation for one case or the other. Moreover, BioPatRec is already provided with virtual arm and leg to be used in the AR-VR environments. In conclusion, the only difference between using BioPatRec for MPR in lower or upper limb resides in the way the signals are acquired.
When it comes to the PLP treatment, the motions predicted by the pattern recognition algorithms don’t control a prosthesis, but they are used as commands for the AR-VR environments and a racing game provided within the software. The patients are required to move their phantom limb while receiving in real-time a visual feedback of the movement that they actually executed: in this way the patients improve the motor control over their phantom which in some cases has been associated with pain relief [83][84].

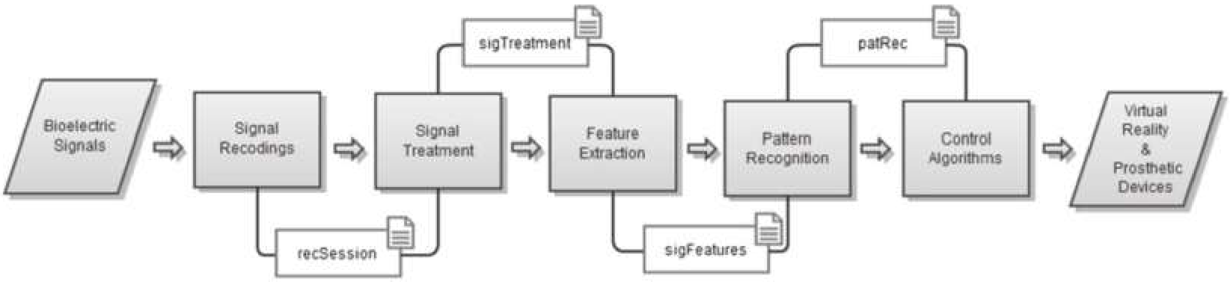

Figure 10: The structure of BioPatRec [82] .

4.1.1 Neuromotus

Neuromotus is the user friendly, stand-alone version of BioPatRec developed with the purpose of enabling the clinicians in rehabilitation centres to use it autonomously, without the need of technical help. However, the software is currently available only for upper limb rehabilitation and it can not be used for the clinical investigation presented in Chapter 5.

4.2 Pain tracking questionnaires

It is important to monitor the pain perception, not only throughout the entire length of the treatment, but also for a certain period post treatment in order to determine the long-term effects of the therapy. For this task, a pain tracking questionnaire has been implemented in a standalone software that consists of three parts, as described in [85]: Background Information, Pain Tracking and Pain Distribution. The progresses registered in the Pain Tracking and Pain Distribution parts are visualized through graphs computed by the software.

4.2.1 Background Information

The Background Information is completed once, at the enrolment in the treatment, and serves the purpose of gathering essential information about the patient such as patient demographics, previous treatments, medicines, and date, reason and location of the amputation.

4.2.2 Pain Tracking

To get a clear picture of the effects of the therapy, it is necessary to capture the many different aspects of the PLP. The different variables that are kept monitored at each treatment session with the questionnaire are briefly described below.

- **PLP, Stump Pain (SP), Phantom Limb Sensation (PLS) current magnitude:** The magnitude of these three variables is measured with a numeric rating scale (NRS) from 0 (no pain/lowest intensity) to 10 (worst possible pain/highest intensity).
- **Ability to move the phantom:** Analogously to the rating of the three variables described above, this variable captures ability at the present time to move and control the phantom limb. Again the intensity is described with NRS from 0 to 10 (full control over phantom motions).
- **PLP description:** The questions about the characterisation of the pain are based on the validated short form of the McGill pain questionnaire (SF-MPQ) which tries to encompass the different qualities that the experience of pain can have in an individual. The subject is asked to pick the descriptors of pain that best match the current PLP and rate their respective intensity with a Present Pain Intensity scale, which scores the pain from 0 (no pain) to 5 (excruciating pain)[86]. Associated with the pain descriptors, two indexes are also calculated: The Pain Rating Index (PRI) and the Number of Words Chosen (NWC). At every session the PRI is calculated as the sum of the scores of the different pain descriptors (highest score indicates worst pain), while the NWC is simply the number of pain descriptors that the patient associates with the current level of pain.
- **Medication and prosthetic monitoring:** These questions track any change in the use of a possible prosthesis or medication since these factors might influence the pain perception of the individual.
- **Pain intrusion in daily living:** As chronic pain interferes with the daily life activities, a reduction of the intrusion of pain indicates an improvement. In order to quantify the disruption caused by the pain, the patient is asked to rate with a NRS the interference with day-to-day activities, with the working life and with sleep.
- **PLP localization**: The location of pain can change over time, so the patient is asked to indicate the location of pain on a picture of the missing limb. The limb is divided in numbered regions and the subjects answer giving the number of the affected areas.
- **Telescoping:** It has been suggested that telescoping is correlated to the amount of cortical reorganization. However, mechanisms and consequences of this phenomenon are still unclear therefore monitoring the entity of telescoping, if present, is for sure of great interest.
- **Frequency of PLP:** Pain can be a constant sensation or can be experienced sporadically during the week regardless of its intensity: monitoring the frequency of the pain is an essential indicator for a comprehensive description.
- **Additional comments:** At the end of the pain tracking questionnaire the subject is able to leave additional comments about whatever he/she felt was not mentioned during the questionnaire or needed further clarification.

4.2.3 Weighted Pain Distribution (WDP)

Subjects suffering from chronic PLP often report their pain being fluctuating over time, experiencing different levels of pain even during the same day: the pain tracking questionnaire described above bases the pain intensity evaluation on a NRS which provide information regarding a single point in time. For this reason, Dr. Ortiz Catalan developed a pain distribution questionnaire named the Weighted Pain Distribution [5]. Here, the subject is asked to describe the course of pain over 24 hours estimating the amount of pain spent in each different pain level. The levels of pain used in this questionnaire belong to the Present Pain Intensity scale, where 0 corresponds to no pain and 5 to excruciating pain. The time of each selected level can be estimated in hours, minutes or even seconds and the hours of sleep are deducted from the total time since it is not possible for the subject to evaluate his/her experience of pain during the sleep. The portion of the total time obtained this way is the weight of the level. In practice, the WPD is calculated as the sum of the portion of time (0 to 100) times the pain score (0 to 5).

$$\mathrm{WPD} = \frac{\sum_{p=0}^{5}(p * t_p)}{\sum_{p=0}^{5} t_p}$$

5

This chapter presents and discusses in detail the clinical investigation carried out with the MPR/VR treatment presented in the previous chapters. One subject with trans-femoral amputation took part to the study which throughout 24 sessions.

5.1 Background information

A 70-years-old male sustained trans-femoral amputation on the right side approximately 35 years before this research due to trauma. He has been wearing the same kind of passive prosthesis ever since and he wears it every day as it is necessary for him to move around (with crutches).
The subject has experienced chronic PLP since the amputation, however the pain has worsened over the years. Moreover, none of the treatments tried before the enrolment into this study proved to be effective. Namely, he has a neuro-stimulator implanted in the spinal cord since ten years but the extent of the pain relief has decreased over time: at the time of the enrolment into the study, he would use the stimulation when the pain is unbearable to get only an instantaneous and partial break from the pain. The use of neurostimulation started years earlier, was steady at the start of the treatment and didn't bring any improvement on the general level of pain. For this reason, we didn't ask the patient to stop the stimulation treatment but decided to monitor it instead in order to analyse if there would be a reduction.
The pain was described as consisting of two components: a low-moderate intensity pain present mainly during the day; and a sustained-intensity, unbearable pain taking over during the evening and night. The strong pain usually left the subject restless: he could not sit on the couch and was forced to walk around in order to reduce the pain. Moreover, he reported to be unable to sleep more than two hours per night causing him to be extremely tired during the day.

5.2 Treatment procedure

The initial 15 minutes of the session were dedicated to pain monitoring using the questionnaires described in Chapter 4. Following this, the electrodes where placed on the stump: at the beginning of the treatment the UMC with 16 electrodes was used. However, after few sessions the muscles of the stump got visibly stronger making them easier to localize. Consequently, the number of electrodes was gradually reduced to eight and the preferred electrode configuration became the TMC. The location of the electrodes was found asking the patient to perform the desired movements and localizing the muscles by palpation. An example of the electrode placement used can be seen in Figure 11.
Once the electrodes were in place, the subject was instructed to perform a set of movements with the phantom limb, moving the phantom in a natural way (producing physiologically appropriate control). The set of motions were then recorded, and the signals were used to train the classifier (Linear Discriminant Analysis in One vs. One topology). The software used for the prediction of motor intent was BioPatRec.
Afterwards, real-time exercises were conducted: the patient was first asked to move the virtual leg freely for few minutes in order to get acquainted with it, and after to perform one (or few) Target Achievement Control (TAC) test. The TAC Test evaluates the performance of a given control algorithm by simulating the control and positioning of a virtual prosthetic device. Subjects are instructed to move a virtual prosthesis into a target posture and maintain it for a period of time. If the subject overshot the target posture or produced unnecessary movements these have to be corrected to achieve success [87]. A picture of the patient performing the TAC tasks can be seen in Figure 12.

Once the TAC tasks were completed, a set of different motions was recorded and the procedure repeated. At the beginning of the therapy the patient had poor control over phantom motion and the set of motions recorded usually included just one degree of freedom at a time (antagonist motions: i.e. knee flex and knee extend). Practice led to stronger and more selective muscle, resulting in more motion controlled at the same time.

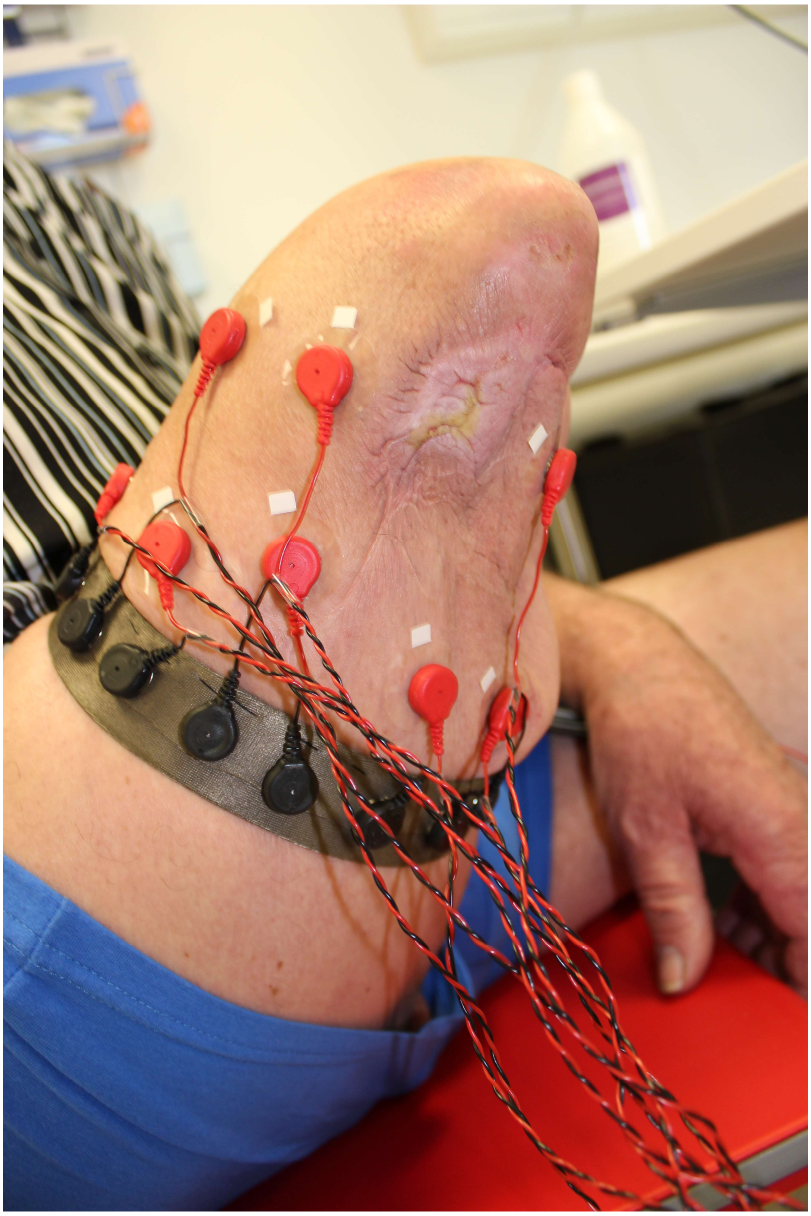

Figure 11: Example of the Targeted Monopolar Configuration (TMC) used for the treatment of the subject.

In each treatment session, the one or two degrees of freedom with best real-time accuracy are recorded again and used of two-three gaming exercises. Instead of controlling the movements of a virtual leg, the predicted motions are used as command to steer, accelerate and reverse a videogame car. A picture of the patient driving the racing car with his phantom can be seen in Figure 13. However, it is necessary to mention that the car game was very difficult and confusing for the patient to follow and it was therefore dropped out from the protocol after half of the sessions because he reported it as non-beneficial for himself.
At the time of the therapy, the augmented reality leg was not available yet therefore this part was skipped for the patient of the study currently described.
At the end of the session, the pain was monitored again with a short version of the questionnaire where only the intensities of PLP, SP, PS and PM were surveyed in order to capture any immediate change due to the treatment.
This protocol was applied twice a week starting in the end of January 2016. The subject took part to 24 treatment sessions for approximately three hours per session.

Figure 12 The patient performing the Target Achievement Control (TAC) test

Figure 13: The patient exercising with the videogame. In this example he controls steering with femoral rotation in/out and controls the acceleration/reverse with the keyboard

5.3 Results

The patient described an overall improvement of his condition during the entire length of the treatment. The extent of this improvement is however complex to describe since there are many aspects that must be taken under consideration.

Figure 14 shows the visual representation of WDP as it is registered at the beginning of each session: the general reduction of pain can be appreciated just with a quick glance, but it also catches the eyes the fact that the pain does not disappear completely after 24 sessions. Figure 15 represents the trend of the average numerical rating of the WPD.

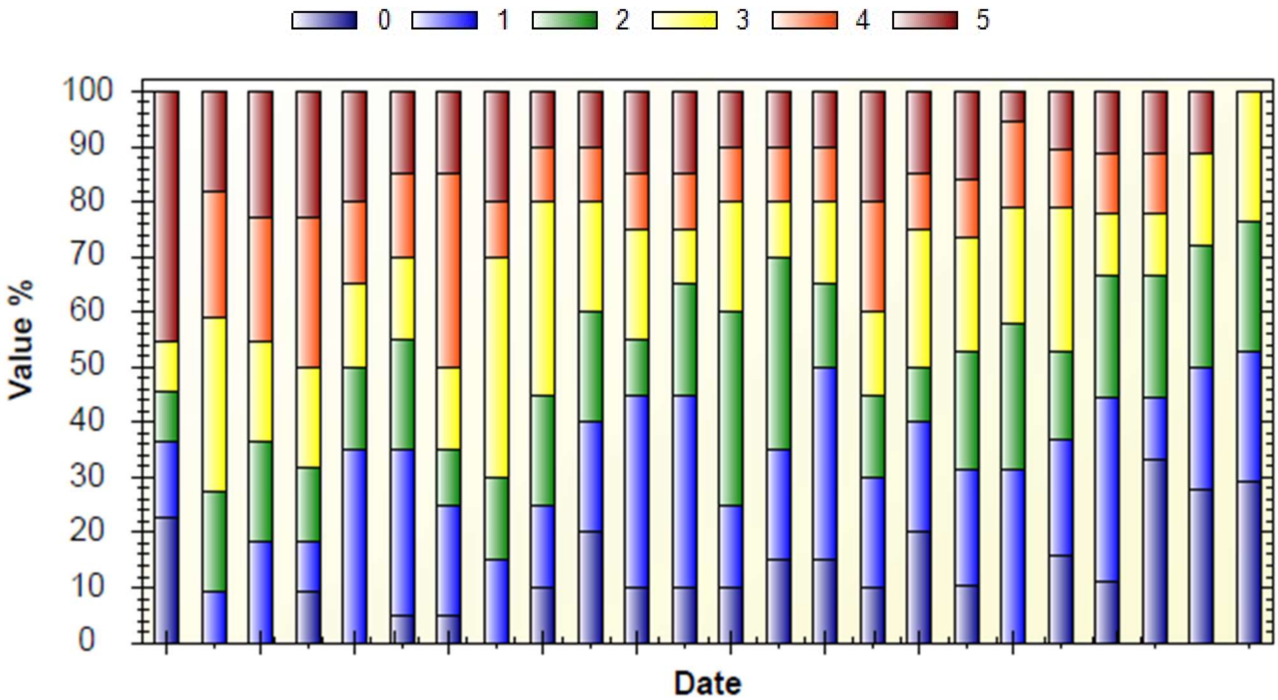

Figure 14 Weighted Pain Distribution (WPD) graph. Each bar represents a treatment session. The pain rating is from 0 to 5 where 5 (red) is the worst possible pain

A prolonged decrease of sustained-level pain was first witnessed after the second week and allowed him to begin sleeping longer (four hours per night compared to the two hours of before). The relief was mostly referred to the high-level pain present during the night and it can be observed in Figure 14 how the red/orange components (excruciating/horrible pain) of the histogram are gradually shrunk (till disappearing completely in the last session) making space for blue/light-blue components (no pain/mild pain). Interestingly, the green/yellow components (discomforting/distressing pain) seem to occupy a constant proportion of the waking time and correspond mostly to the pain that he perceived during the first part of the day.

It is easy to notice that the trend the trend of improvement is not constant from the graph of the mean value of the WPD in Figure 15. A slight rise of the time spent in pain can be seen around sessions 7-8, 13, 16 and were explained by the patient himself as pain associated by bad weather (he always feels his phantom as more painful in correspondence of poor meteorological conditions). In general, the main effect of the reduction of high-level pain is the drastic improvement in the quality of the evenings, when he could finally sit on the couch and watch the TV, and in the length of the sleep. After the ninth week of therapy the subject registered five hours of sleep per night, becoming six hours from the tenth week and seven at the last session. This resulted in better mood and higher energy level during the day as testified by the wife, the sons, the friends and the patient himself.

The subject showed slower reduction of the moderate pain perceived during the day: it is difficult to appreciate this improvement just by analysing the answers to the questionnaires. However, thanks to the comments freely provided by the patient, it is possible to understand the extent of the positive impact that this therapy had on his life. Before starting the therapy it was not possible for the patient to drive the car because of the pain, while towards the end of the treatment he attested to be able to

drive for more than 200 km. Moreover, both family and patient have observed a reduction in the use of the neuro-stimulator during the day.
The pain location remained constant throughout the entire length of the treatment (in the foot) and the phantom limb conserved the original size of a normal leg.
The intensities of PLP, PS, SP and PM registered with a NRS measurements are reported in and Figure 16 and Figure 17do not convey any remarkable information. As previously mentioned, the NRS measure is an estimation of a precise point in time. What we can see from the graphs is that PLP measured before and after the treatment was extremely constant during the 12 weeks of therapy and the intensity of pain corresponds with the mild-moderate pain that the patient described as persisting even after the sustained pain disappeared. SP also remained constant during the entire length of the treatment as it was constant the present of bruises on the stump due to the passive prosthesis. PS and PM are more variable, but their overall value is high corresponding with the fact that the patient had good control over the motions of his phantom limb.
Finally, Figure 18 reports a graphical representation of the pain descriptors of the SF-MPQ over the entire course of the treatment sessions: it can be noticed with a quick glance that the PLP loses qualities over time. In particular, at the beginning of the therapy, the subject would describe the PLP as being heavily throbbing, shooting, stabbing, gnawing, aching, heavy, splitting, tiring and exhausting, sickening, fearful and cruel. At the end of the treatment, the descriptors were limited to mild throbbing, stabbing, gnawing, hot-burning, aching. The NCW reflects the decrease of words used to describe the

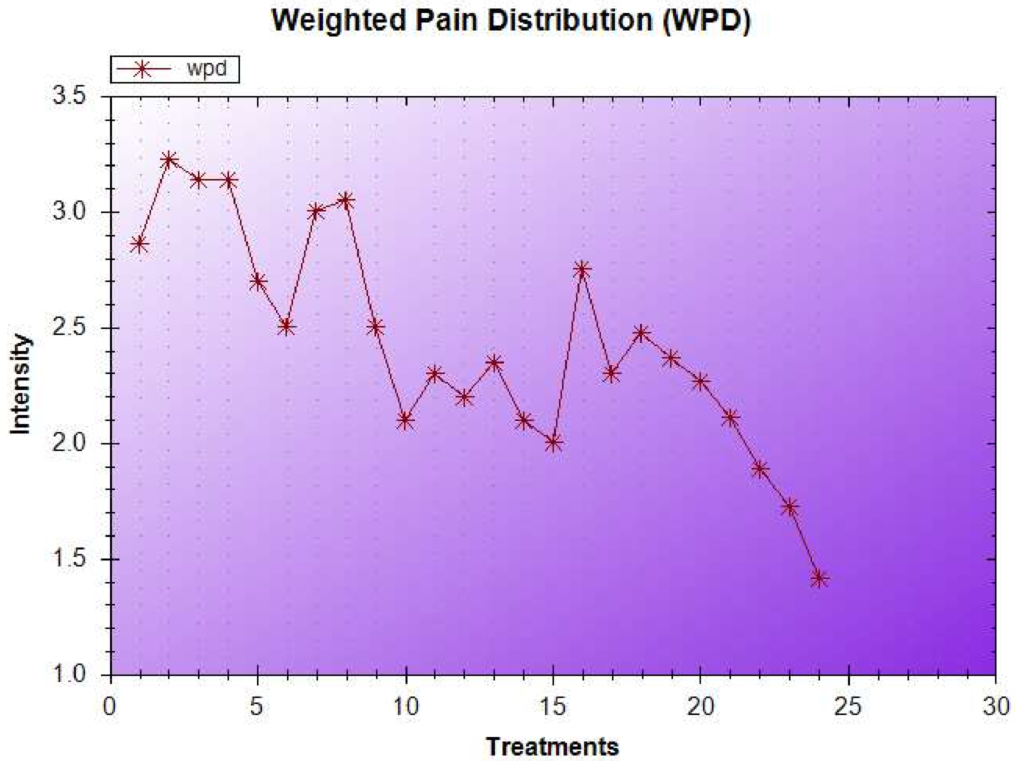

Figure 15: Average value of the WPD over the treatment sessions.

pain and it is shown in Figure 19 along with the graph of the PRI, which also shows a reduction over time.

5.4 Discussion

In this case study, a system for the PLP treatment of subjects who have undergone trans-femoral amputation was presented. This system was then tested in a subject with chronic PLP who had

unsuccessfully explored other treatments. Despite the fact that the pain has not disappeared completely, it is shown a remarkable improvement: not only were the most excruciating components of PLP eliminated, but more generally the quality of life of the patient has improved dramatically. Moreover, even the persistent pain was slowly decreasing. For that reason, it seems totally plausible that the pain could disappear completely after the long-term use of the system. On the other hand, it is worth to notice that the subject reported constant SP throughout the entire treatment and this was clearly due to the bruises caused by the compression of tissue by the passive prosthesis. The question of whether the SP could be involved in the maintenance of persistent mild/moderate PLP raises legitimately.
Furthermore, the car game used in the system proposed in [5] was too difficult for the patient and reported as unpleasant. For this reason, the game was used in a limited way and after half of the sessions, it was dropped. The patient continued the therapy using the VR and TAC test only and a second question that could be raised is whether VR alone is enough for the complete disappearance of PLP. On one side, one could argue that AR would provide a better visual feedback facilitating the embodiment with the virtual limb. On the other side, the lack of gaming could also be seen as the absence of a way to train dynamic motor control of the phantom limb (gaming forces the subject to move the phantom in fast paced and timely manner). All these questions wait for answers to disentangle the various factors that might contribute to PLP: SP, sensory feedback, motor control. The system proposed by [5] and partly implemented here for the lower limb provides therefore a powerful empirical tool to answer all these questions.
Finally, it is clear from the results of this case study that the measure of the intensities of PLP, SP, PS and PM in terms of NRS and VAS are not sufficient measures since they represent the value of the intensity at one point in time.

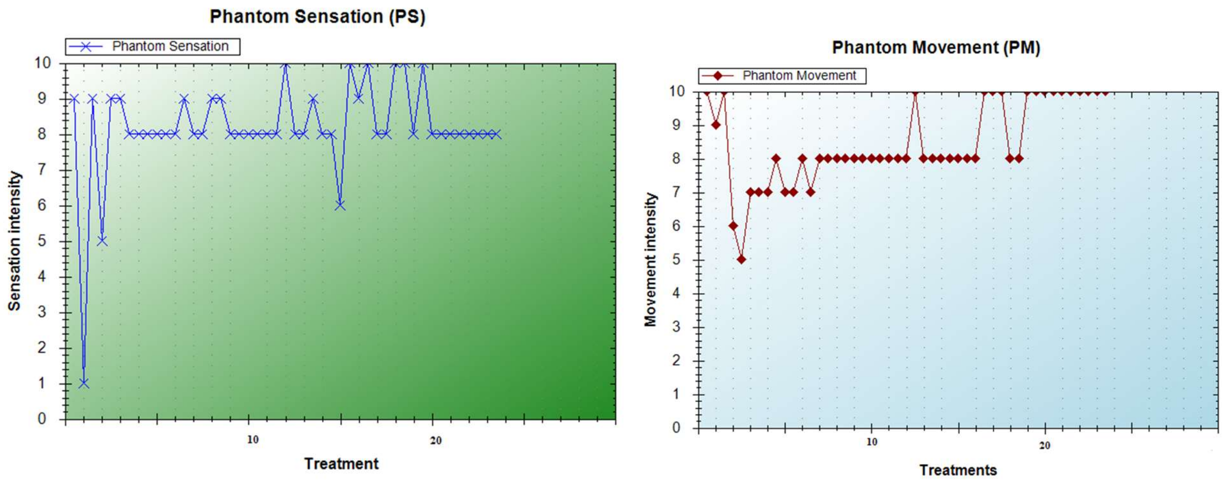

Figure 16: The intensities point registered at every session for phantom sensation (left) and phantom movement(right).

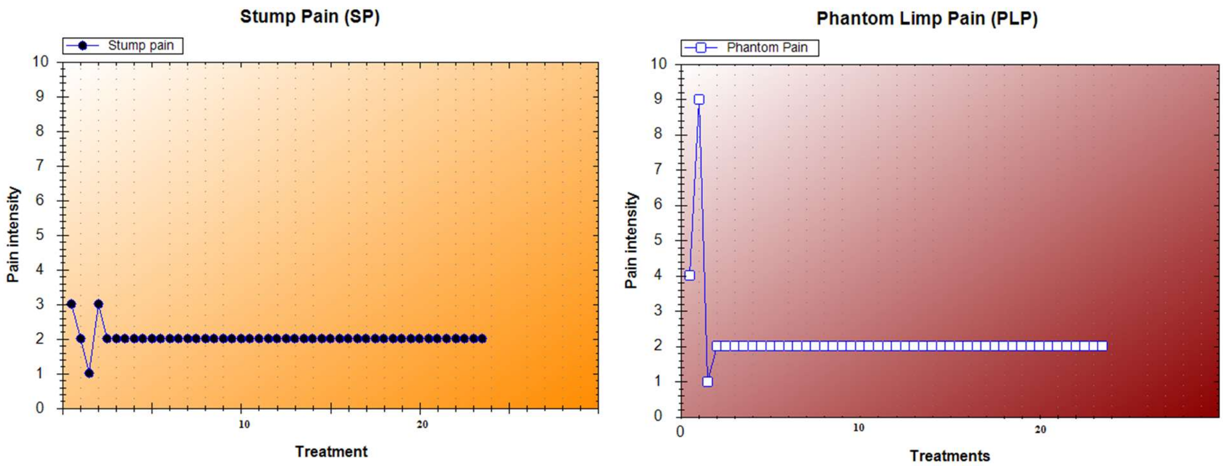

Figure 17: The intensities point registered at every session for stump pain (left) and phantom limb pain (right).

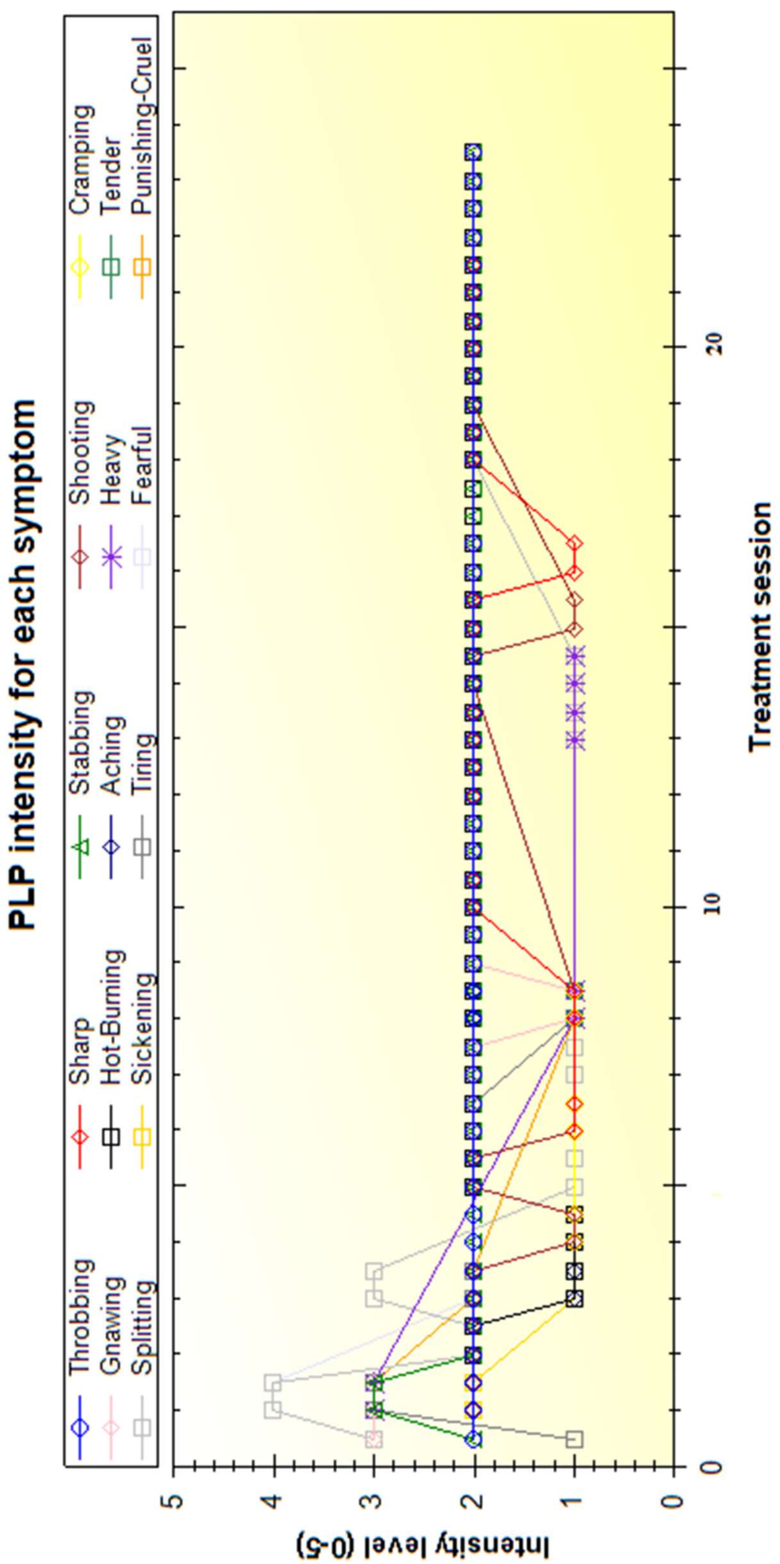

Figure 18: Graphical representation of the pain descriptors of the SF-MPQ over the entire course of the treatment sessions.

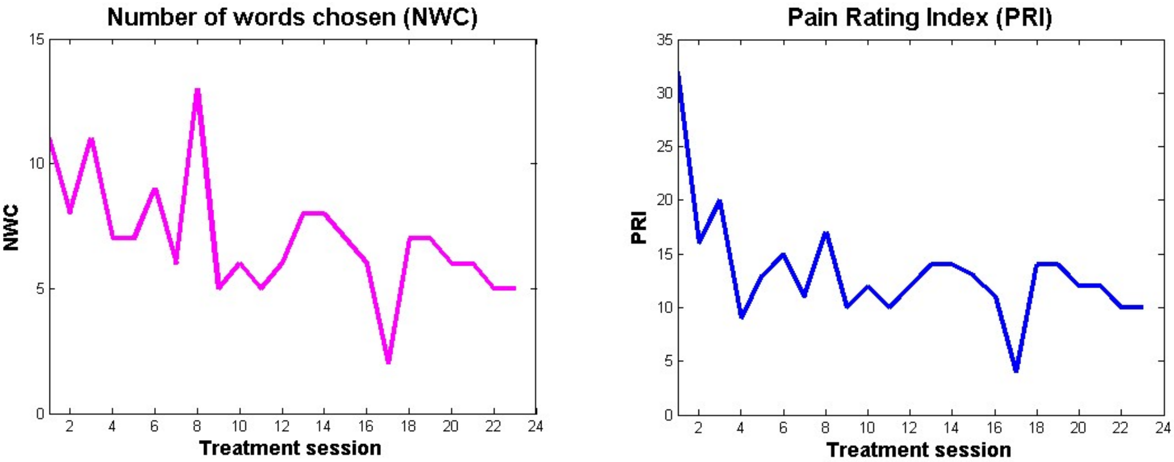

Figure 19: Graphs representing the NWC (left) and PRI (right) calculated from the pain descriptors and relative scores (shown in Figure 19) throughout the entire treatment,

5.5 Future work

As the development of Neuromotus proceed, AR and VR for the leg will be made available in the software making possible to undertake a controlled clinical trial on a large number of patients. However, the software development is not the only step needed before waging a large study. The results presented in the comparison of electrode configurations studies (Chapter 3 and Appendix) suggest the possibility of solution for the acquisition of MES signals made entirely of smart wearable textile. This electrode-system would make the correct electrode placement easy to achieve by clinicians and patients. For this reason, prototyping and testing of such a solution represent without any doubt one of the future objective for the creation of a successful system for the treatment of PLP. The final long term goal is that Neuromotus will be made available in large scale to help people with PLP from all over the world.

5.6 Conclusions

PLP is a condition difficult to treat that affects the majority of the individual with amputation. The majority of the amputees have undergone lower limb amputation(s) and the current case study introduces a first system based on MPR/VR and gaming for the treatment of lower limb amputees. The results of the case study, show promising results but also opened questions for further investigation. Clarification about the mechanisms that are at the base of this chronic pain condition is a major question for further research.

6

6.1 Summary of the papers

I. ***Classification of Non-Weight Bearing Lower Limb Movements: Towards a Potential Treatment for Phantom Limb Pain Based on Myoelectric Pattern Recognition.***
The work presented in this paper is the first step towards the goal of implementing a phantom limb pain (PLP) treatment for lower limb amputees based on MPR and augmented/virtual reality. In the study, we explored three different electrode configurations for acquiring electromyographic (EMG) signals: two targeted (bipolar and monopolar) and one untargeted (electrodes equally spaced axially). The targeted monopolar configuration yielded overall lower signal-to-noise ratios (SNR) but similar accuracy than those of the targeted bipolar configuration. The targeted bipolar and untargeted monopolar configurations were comparable in terms of SNR and offline accuracy when the same number of channels was used. The clear advantage of using the untargeted configuration is the easier and more practical electrode placement procedure.

II. ***Real-Time Classification of Non-Weight Bearing Lower Limb Movements: A Viable Alternative to Differential Recording for Rehabilitation Use.***
In this paper, we extended our previous investigation by increasing the number of subjects and by evaluating the real-time classification performance. The results showed that classification is possible without significant differences in all of the three configurations, but also highlighted that the use of the untargeted configuration can be the preferred for PLP treatment as it facilitates the electrode placement procedure.

References

[1] P. U. Dijkstra, J. H. B. Geertzen, R. Stewart, and C. P. van der Schans, “Phantom pain and risk factors: a multivariate analysis,” *J Pain Symptom Manag.*, vol. 24, no. 6, pp. 578–85, Dec. 2002.

[2] K. Ziegler-Graham, E. J. MacKenzie, P. L. Ephraim, T. G. Travison, and R. Brookmeyer, “Estimating the Prevalence of Limb Loss in the United States: 2005 to 2050,” *Arch. Phys. Med. Rehabil.*, vol. 89, no. 3, pp. 422–429, Mar. 2008.

[3] H. Flor, T. Elbert, S. Knecht, C. Wienbruch, C. Pantev, N. Birbaumer, W. Larbig, and E. Taub, “Phantom-limb pain as a perceptual correlate of cortical reorganization following arm amputation.,” *Nature*, vol. 375, pp. 482–4, Jun. 1995.

[4] T. R. Makin, J. Scholz, N. Filippini, D. Henderson Slater, I. Tracey, and H. Johansen-Berg, “Phantom pain is associated with preserved structure and function in the former hand area.,” *Nat. Commun.*, vol. 4, p. 1570, Jan. 2013.

[5] M. Ortiz-Catalan, N. Sander, M. B. Kristoffersen, B. Håkansson, and R. Brånemark, “Treatment of phantom limb pain (PLP) based on augmented reality and gaming controlled by myoelectric pattern recognition: A case study of a chronic PLP patient,” *Front. Neurosci.*, 2014.

[6] Ortiz-Catalan, M., Guðmundsdóttir, R.A., Kristoffersen, M.B., C. Zepeda-Echavarria, A., Caine-Winterberger, K., Kulbacka-Ortiz, K., Widehammar, K. Eriksson, A. Stockselius, C. Ragnö, Z. Pihlar, H. Burger, and L. Hermansson, “Phantom motor execution facilitated by machine learning and augmented reality as treatment for Phantom Limb Pain,” *Lancet*, vol. In Press, 2016.

[7] T. Mills, “From Land Mines To Lawn Mowers Prosthetic Rehabilitation Proceeds One Foot at a Time,” 2010. [Online]. Available: http://drtopher.blogspot.se/2010/03/from-land-mines-to-lawn-mowers.html. [Accessed: 12-Jun-2016].

[8] R. Melzack, “Phantom limbs and the concept of a neuromatrix,” *Trends Neurosci.*, vol. 13, no. 3, pp. 88–92, Mar. 1990.

[9] J. P. Hunter, J. Katz, and K. D. Davis, “The effect of tactile and visual sensory inputs on phantom limb awareness,” *Brain*, vol. 126, no. 3, pp. 579–589, Mar. 2003.

[10] L. Nikolajsen and T. S. Jensen, “Phantom limb pain.,” *Br J Anaesth*, vol. 87, no. 1, pp. 107–16, Jul. 2001.

[11] R. Melzack and J. D. Loeser, “Phantom body pain in paraplegics: evidence for a central ‘pattern generating mechanism’ for pain.,” *Pain*, 1978. [Online]. Available: http://www.ncbi.nlm.nih.gov/pubmed/273200. [Accessed: 13-Apr-2016].

[12] R. Melzack and P. R. Bromage, “Experimental phantom limbs,” *Exp. Neurol.*, vol. 39, no. 2, pp. 261–269, May 1973.

[13] R. G. Bittar, S. Otero, H. Carter, and T. Z. Aziz, “Deep brain stimulation for phantom limb pain.,” *J. Clin. Neurosci.*, vol. 12, no. 4, pp. 399–404, May 2005.

[14] S. Finger and M. P. Hustwit, “Five early accounts of phantom limb in context: Pare, Descartes, Lemos, Bell, and Mitchell,” *Neurosurgery*, 2003.

[15] N. J. Wade and S. Finger, “William Porterfield (ca. 1696-1771) and his phantom limb: an overlooked first self-report by a man of medicine.,” *Neurosurgery*, vol. 52, no. 5, pp. 1196-8-9, May 2003.

[16] T. S. Jensen, B. Krebs, J. Nielsen, and P. Rasmussen, “Phantom limb, phantom pain and stump pain in amputees during the first 6 months following limb amputation.,” *Pain*, vol. 17, no. 3, pp. 243–256, 1983.

[17] C. Jensen, O. Vasseljen, and R. H. Westgaard, “The influence of electrode position on bipolar surface electromyogram recordings of the upper trapezius muscle.,” *Eur. J. Appl. Physiol. Occup. Physiol.*, vol. 67, no. 3, pp. 266–73, 1993.

[18] C. M. Kooijman, P. U. Dijkstra, J. H. B. Geertzen, A. Elzinga, and C. P. van der Schans, "Phantom pain and phantom sensations in upper limb amputees: an epidemiological study," *Pain*, vol. 87, no. 1, pp. 33–41, Jul. 2000.
[19] L. Nikolajsen, S. Ilkjær, K. Krøner, J. H. Christensen, T. S. Jensen, S. Ilkjaer, K. Krøner, J. H. Christensen, and T. S. Jensen, "The influence of preamputation pain on postamputation stump and phantom pain.," *Pain*, vol. 72, no. 3, pp. 393–405, Sep. 1997.
[20] P. L. Carlen, P. D. Wall, H. Nadvorna, and T. Steinbach, "Phantom limbs and related phenomena in recent traumatic amputations.," *Neurology*, vol. 28, no. 3, pp. 211–7, Mar. 1978.
[21] S. M. Rajbhandari, J. A. Jarratt, P. D. Griffiths, and J. D. Ward, "Diabetic neuropathic pain in a leg amputated 44 years previously.," *Pain*, vol. 83, no. 3, pp. 627–9, Dec. 1999.
[22] T. S. Jensen, B. Krebs, J. Nielsen, and P. Rasmussen, "Immediate and long-term phantom limb pain in amputees: incidence, clinical characteristics and relationship to pre-amputation limb pain.," *Pain*, vol. 21, no. 3, pp. 267–78, Mar. 1985.
[23] W. R. HENDERSON and G. E. SMYTH, "Phantom limbs.," *J. Neurol. Neurosurg. Psychiatry*, vol. 11, no. 2, pp. 88–112, May 1948.
[24] J. Katz and R. Melzack, "Pain 'memories' in phantom limbs: review and clinical observations.," *Pain*, vol. 43, no. 3, pp. 319–36, Dec. 1990.
[25] P. Montoya, W. Larbig, N. Grulke, H. Flor, E. Taub, and N. Birbaumer, "The relationship of phantom limb pain to other phantom limb phenomena in upper extremity amputees.," *Pain*, vol. 72, no. 1–2, pp. 87–93, Aug. 1997.
[26] R. A. Sherman, C. J. Sherman, and L. Parker, "Chronic phantom and stump pain among american veterans: results of a survey," *Pain*, vol. 18, no. 1, pp. 83–95, Jan. 1984.
[27] B. D. Dickinson, C. A. Head, S. Gitlow, and A. J. Osbahr, "Maldynia: pathophysiology and management of neuropathic and maladaptive pain--a report of the AMA Council on Science and Public Health.," *Pain Med.*, vol. 11, no. 11, pp. 1635–53, Nov. 2010.
[28] D. M. Desmond and M. Maclachlan, "Prevalence and characteristics of phantom limb pain and residual limb pain in the long term after upper limb amputation.," *Int. J. Rehabil. Res. Int. Zeitschrift für Rehabil. Rev. Int. Rech. réadaptation*, vol. 33, no. 3, pp. 279–82, Sep. 2010.
[29] L. Nikolajsen, C. L. Hansen, J. Nielsen, J. Keller, L. Arendt-Nielsen, and T. S. Jensen, "The effect of ketamine on phantom pain: a central neuropathic disorder maintained by peripheral input.," *Pain*, vol. 67, no. 1, pp. 69–77, Sep. 1996.
[30] R. Melzack, R. Israel, R. Lacroix, and G. Schultz, "Phantom limbs in people with congenital limb deficiency or amputation in early childhood," *Brain*, vol. 120, no. 9, pp. 1603–1620, 1997.
[31] N. Birbaumer, W. Lutzenberger, P. Montoya, W. Larbig, K. Unertl, S. Töpfner, W. Grodd, E. Taub, and H. Flor, "Effects of regional anesthesia on phantom limb pain are mirrored in changes in cortical reorganization.," *J. Neurosci.*, vol. 17, no. 14, pp. 5503–8, Jul. 1997.
[32] V. T. Chang, R. S. Tunkel, B. A. Pattillo, and E. A. Lachmann, "Increased phantom limb pain as an initial symptom of spinal-neoplasia.," *J. Pain Symptom Manage.*, vol. 13, no. 6, pp. 362–4, Jun. 1997.
[33] R. Kuner, "Central mechanisms of pathological pain.," *Nat. Med.*, vol. 16, no. 11, pp. 1258–66, Nov. 2010.
[34] T. J. Coderre and J. Katz, "Peripheral and central hyperexcitability: differential signs and symptoms in persistent pain.," *Behav. Brain Sci.*, vol. 20, no. 3, pp. 404-19-513, Sep. 1997.
[35] H. Flor, L. Nikolajsen, and T. Staehelin Jensen, "Phantom limb pain: a case of maladaptive CNS plasticity?," *Nat. Rev. Neurosci.*, vol. 7, no. 11, pp. 873–81, Nov. 2006.
[36] M. Costigan, J. Scholz, and C. J. Woolf, "Neuropathic pain: a maladaptive response of the nervous system to damage.," *Annu. Rev. Neurosci.*, vol. 32, pp. 1–32, Jan. 2009.

[37] A. Karl, N. Birbaumer, W. Lutzenberger, L. G. Cohen, and H. Flor, “Reorganization of Motor and Somatosensory Cortex in Upper Extremity Amputees with Phantom Limb Pain,” *J. Neurosci.*, vol. 21, no. 10, pp. 3609–3618, May 2001.
[38] V. S. Ramachandran, D. Brang, and P. D. Mcgeoch, “Dynamic reorganization of referred sensations by movements of phantom limbs,” *NeuroReport Wolters Kluwer Heal. NeuroReport*, vol. 21, no. 21, 2010.
[39] M. Lotze, H. Flor, W. Grodd, W. Larbig, and N. Birbaumer, “Phantom movements and pain. An fMRI study in upper limb amputees.,” *Brain*, vol. 124, no. Pt 11, pp. 2268–77, Nov. 2001.
[40] A. J. Harris, “Cortical origin of pathological pain,” *The Lancet*, vol. 354, no. 9188. pp. 1464–1466, 1999.
[41] C. S. McCabe, R. C. Haigh, P. W. Halligan, and D. R. Blake, “Simulating sensory-motor incongruence in healthy volunteers: implications for a cortical model of pain.,” *Rheumatology (Oxford).*, vol. 44, no. 4, pp. 509–16, Apr. 2005.
[42] T. R. Makin, J. Scholz, N. Filippini, D. Henderson Slater, I. Tracey, and H. Johansen-Berg, “Phantom pain is associated with preserved structure and function in the former hand area.,” *Nat. Commun.*, vol. 4, p. 1570, Jan. 2013.
[43] R. A. Sherman, C. J. Sherman, and N. G. Gall, “A survey of current phantom limb pain treatment in the United States,” *Pain*, vol. 8, no. 1, pp. 85–99, Feb. 1980.
[44] C. Richardson, S. Glenn, M. Horgan, and T. Nurmikko, “A Prospective Study of Factors Associated With the Presence of Phantom Limb Pain Six Months After Major Lower Limb Amputation in Patients With Peripheral Vascular Disease,” *J. Pain*, vol. 8, no. 10, pp. 793–801, 2007.
[45] B. Subedi and G. T. Grossberg, “Phantom limb pain: mechanisms and treatment approaches.,” *Pain Res. Treat.*, vol. 2011, p. 864605, Jan. 2011.
[46] L. Nikolajsen, “Postamputation pain: Studies on mechanisms,” *Dan Med J*, vol. 59, no. 10, 2012.
[47] M. A. Hanley, D. M. Ehde, K. M. Campbell, B. Osborn, and D. G. Smith, “Self-Reported Treatments Used for Lower-Limb Phantom Pain: Descriptive Findings,” *Arch. Phys. Med. Rehabil.*, vol. 87, no. 2, pp. 270–277, 2006.
[48] W. M. Jenkins, M. M. Merzenich, M. T. Ochs, T. Allard, and E. Guíc-Robles, “Functional reorganization of primary somatosensory cortex in adult owl monkeys after behaviorally controlled tactile stimulation.,” *J. Neurophysiol.*, vol. 63, no. 1, pp. 82–104, Jan. 1990.
[49] M. Lotze, W. Grodd, N. Birbaumer, M. Erb, E. Huse, and H. Flor, “Does use of a myoelectric prosthesis prevent cortical reorganization and phantom limb pain?,” *Nat. Neurosci.*, vol. 2, no. 6, pp. 501–2, Jun. 1999.
[50] H. Flor, C. Denke, M. Schaefer, and S. Grüsser, “Effect of sensory discrimination training on cortical reorganisation and phantom limb pain,” *Lancet*, vol. 357, no. 9270, pp. 1763–1764, 2001.
[51] V. S. Ramachandran and E. L. Altschuler, “The use of visual feedback, in particular mirror visual feedback, in restoring brain function,” *Brain*, vol. 132, no. 7, pp. 1693–1710, Jul. 2009.
[52] B. L. Chan, R. Witt, A. P. Charrow, A. Magee, R. Howard, P. F. Pasquina, K. M. Heilman, and J. W. Tsao, “Mirror therapy for phantom limb pain.,” *N. Engl. J. Med.*, vol. 357, no. 21, pp. 2206–2207, 2007.
[53] M. MacLachlan, D. McDonald, and J. Waloch, “Mirror treatment of lower limb phantom pain: a case study.,” *Disabil. Rehabil.*, vol. 26, no. 14–15, pp. 901–4.
[54] M. Sumitani, S. Miyauchi, C. S. McCabe, M. Shibata, L. Maeda, Y. Saitoh, T. Tashiro, and T. Mashimo, “Mirror visual feedback alleviates deafferentation pain, depending on qualitative aspects of the pain: a preliminary report.,” *Rheumatology (Oxford).*, vol. 47, no. 7, pp. 1038–43, Jul. 2008.
[55] Flor H, Diers M, Christmann C, and Koeppe C, “Mirror illusions of phantom hand movements

brain activity mapped by fMRI," *Neuroimage*, vol. 31, p. 159, 2006.
[56] G. di Pellegrino, L. Fadiga, L. Fogassi, V. Gallese, and G. Rizzolatti, "Understanding motor events: a neurophysiological study.," *Exp. brain Res.*, vol. 91, no. 1, pp. 176–80, 1992.
[57] V. S. Ramachandran and D. Rogers-Ramachandran, "Sensations referred to a patient's phantom arm from another subjects intact arm: Perceptual correlates of mirror neurons," *Medical Hypotheses*, vol. 70, no. 6. pp. 1233–1234, 2008.
[58] E. E. Brodie, A. Whyte, and C. A. Niven, "Analgesia through the looking-glass? A randomized controlled trial investigating the effect of viewing a 'virtual' limb upon phantom limb pain, sensation and movement," *Eur. J. Pain*, vol. 11, no. 4, pp. 428–436, May 2007.
[59] K. O'Neill, A. DePaor, M. MacLachlan, and G. McDarby, "An Investigation into the performance of Augmented Reality for use in the treatment of Phantom Limb Pain in Amputees," in *7th Eur Conf Adv Assitv Tech Eur*, 2003.
[60] C. D. Murray, S. Pettifer, T. Howard, E. L. Patchick, F. Caillette, J. Kulkarni, and C. Bamford, "The treatment of phantom limb pain using immersive virtual reality: Three case studies."
[61] D. Desmond, K. O'Neill, A. De Paor, G. McDarby, and M. MacLachlan, "Augmenting the reality of phantom limbs: three case studies using an augmented mirror box procedure," *J Prosthet Orthot.*, vol. 18, no. 3, p. 74, 2006.
[62] H. Sveistrup, "Motor rehabilitation using virtual reality," *J. Neuroeng. Rehabil.*, vol. 1, no. 1, p. 10, 2004.
[63] J. Cole, S. Crowle, G. Austwick, and D. H. Slater, "Exploratory findings with virtual reality for phantom limb pain; from stump motion to agency and analgesia.," *Disabil. Rehabil.*, vol. 31, no. 10, pp. 846–54, Jan. 2009.
[64] F. Anderson and W. Bischof, "Augmented reality improves myoelectric prosthesis training," in *Proc. 9th Intl Conf. Disability, Virtual Reality & Associated Technologies*, 2012, pp. 1–9.
[65] R. Merletti and H. J. Hermens, "Detection and Conditioning of the Surface EMG Signal," in *Electromyography*, Hoboken, NJ, USA: John Wiley & Sons, Inc., 2005, pp. 107–131.
[66] K. Saitou, T. Masuda, D. Michikami, R. Kojima, and M. Okada, "Innervation zones of the upper and lower limb muscles estimated by using multichannel surface EMG.," *J. Hum. Ergol*, vol. 29, no. 1–2, pp. 35–52, Dec. 2000.
[67] C. Nordander, J. Willner, G. Hansson, B. Larsson, J. Unge, L. Granquist, and S. Skerfving, "Influence of the subcutaneous fat layer, as measured by ultrasound, skinfold calipers and BMI, on the EMG amplitude," *Eur. J. Appl. Physiol.*, vol. 89, no. 6, pp. 514–519, Aug. 2003.
[68] K. Roleveld, D. F. Stegeman, H. M. Vingerhoets, and A. Van Oosterom, "Motor unit potential contribution to surface electromyography," *Acta Physiol. Scand.*, vol. 160, no. 2, pp. 175–183, May 1997.
[69] G. E. Loeb and C. Gans, *Electromyography for experimentalists*. University of Chicago Press, 1986.
[70] D. F. Stegeman and H. J. Hermens, "Standards for surface electromyography: the European project 'Surface EMG for non-invasive assessment of muscles (SENIAM) .'"
[71] R. Reiter, "Eine neue Elektrokunsthand," *Grenzgeb. Med.*, vol. 1, no. 4, pp. 133–5, Sep. 1948.
[72] M. Asghari Oskoei and H. Hu, "Myoelectric control systems—A survey," *Biomed. Signal Process. Control*, vol. 2, no. 4, pp. 275–294, 2007.
[73] H. Huang, T. A. Kuiken, and R. D. Lipschutz, "A strategy for identifying locomotion modes using surface electromyography," *IEEE Trans. Biomed. Eng.*, 2009.
[74] D. Jin, J. Yang, R. Zhang, R. Wang, and J. Zhang, "Terrain Identification for Prosthetic Knees Based on Electromyographic Signal Features*," *Tsinghua Sci. Technol.*, vol. 11, no. 1, pp. 74–79, 2006.
[75] J. D. Miller, M. S. Beazer, and M. E. Hahn, "Myoelectric walking mode classification for

transtibial amputees," *IEEE Trans. Biomed. Eng.*, 2013.
[76] D. C. Tkach, R. D. Lipschutz, S. B. Finucane, and L. J. Hargrove, "Myoelectric neural interface enables accurate control of a virtual multiple degree-of-freedom foot-ankle prosthesis.," *IEEE Int. Conf. Rehabil. Robot.*, vol. 2013, p. 6650499, Jun. 2013.
[77] S. Au, M. Berniker, and H. Herr, "Powered ankle-foot prosthesis to assist level-ground and stair-descent gaits," *Neural Networks*, vol. 21, no. 4, pp. 654–666, 2008.
[78] A. J. Young, A. M. Simon, N. P. Fey, and L. J. Hargrove, "Classifying the intent of novel users during human locomotion using powered lower limb prostheses," in *2013 6th International IEEE/EMBS Conference on Neural Engineering (NER)*, 2013, pp. 311–314.
[79] H. A. Varol, F. Sup, and M. Goldfarb, "Multiclass real-time intent recognition of a powered lower limb prosthesis.," *IEEE Trans. Biomed. Eng.*, vol. 57, no. 3, pp. 542–51, Mar. 2010.
[80] T. Afzal, K. Iqbal, G. White, and A. Wright, "Task Discrimination for Non-Weight-Bearing Movements Using Muscle Synergies," 2015.
[81] L. J. Hargrove, A. M. Simon, R. Lipschutz, S. B. Finucane, and T. A. Kuiken, "Non-weight-bearing neural control of a powered transfemoral prosthesis," *J. Neuroeng. Rehabil.*, vol. 10, p. 1, 2013.
[82] M. Ortiz-Catalan, R. Brånemark, and B. Håkansson, "BioPatRec: A modular research platform for the control of artificial limbs based on pattern recognition algorithms.," *Source Code Biol. Med.*, vol. 8, no. 1, p. 11, 2013.
[83] E. E. Brodie, A. Whyte, and B. Waller, "Increased motor control of a phantom leg in humans results from the visual feedback of a virtual leg," *Neurosci. Lett.*, vol. 341, no. 2, pp. 167–169, May 2003.
[84] V. S. Ramachandran and D. Rogers-Ramachandran, "Synaesthesia in phantom limbs induced with mirrors.," *Proc. Biol. Sci.*, vol. 263, no. 1369, pp. 377–86, Apr. 1996.
[85] R. Á. Guðmundsdóttir, "Developing and testing of an electronic data collection system for the treatment of phantom limb pain," Chalmers University of Technology, 2014.
[86] R. Melzack, "The McGill Pain Questionnaire: Major properties and scoring methods," *Pain*, vol. 1, no. 3, pp. 277–299, 1975.
[87] M. Ann, J. Levi, A. Blair, M. S. Kuiken, and A. Todd, "Target Achievement Control Test : Evaluating real - time myoelectric pattern - recognition control of multifunctional upper - limb prostheses," pp. 1–6, 2016.
[88] "Using Grip Training To Hack The Nervous System And Improve Strength And Stability | PHYSIO ANSWERS." [Online]. Available: http://www.physioanswers.com/2014/06/using-grip-training-to-hack-nervous.html. [Accessed: 21-Oct-2016].
[89] M. Zahak, "Signal Acquisition Using Surface EMG and Circuit Design Considerations for Robotic Prosthesis," in *Computational Intelligence in Electromyography Analysis - A Perspective on Current Applications and Future Challenges*, InTech, 2012.
[90] JDifool, "Nervous system organization fr.svg - Wikimedia Commons," 2008. [Online]. Available: https://commons.wikimedia.org/wiki/File:Nervous_system_organization_fr.svg. [Accessed: 21-Oct-2016].

Appended Papers

Paper I

Classification of Non-Weight Bearing Lower Limb Movements: Towards a Potential Treatment for Phantom Limb Pain Based on Myoelectric Pattern Recognition.

Eva Lendaro and Max Ortiz-Catalan, *IEEE Member*

***Abstract*—Research in myoelectric pattern recognition (MPR) for the prediction of motor volition has primarily focused on the upper limbs. Recent studies in the lower limbs have mainly concentrated on prosthetic control, while MPR for lower limb rehabilitation purposes has received little attention. In this work we investigated the viability of a MPR system for the prediction of four degrees of freedom controlled in a near natural or physiologically appropriate fashion. We explored three different electrode configurations for acquiring electromyographic (EMG) signals: two targeted (bipolar and monopolar) and one untargeted (electrodes equally spaced axially). The targeted monopolar configuration yielded overall lower signal-to-noise ratios (SNR) but similar accuracy than those of the targeted bipolar configuration. The targeted bipolar and untargeted monopolar configurations were comparable in terms of SNR and offline accuracy when the same number of channels was used. However, the untargeted configuration tested with twice the channels yielded the best results in terms of accuracy. An advantage of the untargeted configuration is that it offers a simpler and more practical electrode placement. This work is the first step in our long-term goal of implementing a phantom limb pain (PLP) treatment for lower limb amputees based on MPR and augmented/virtual reality.**

I. Introduction

Electromyographic (EMG) signals contain information of neural commands sent from the central nervous system to muscles. Myoelectric pattern recognition (MPR) uses the combined activation of muscles to predict motor intention in the interest of controlling devices such as prosthetic limbs and exoskeletons. The relevance of this technique resides in the fact that it enables intuitive control over several robotic or virtual joints, making it useful not only for restoring the functionality of limbs [1], but also for rehabilitation of patients that suffer from phantom limb pain (PLP) [2], spinal cord injury [3] or stroke [4].

For decades, research in myoelectric control has been mainly focused on the upper limb [5]. Advances for the lower limb are relatively recent and have taken two distinct paths: prediction of movements in weight bearing and non-weight bearing conditions. A MPR system in weight-bearing situations detects the intended walking stage [6-7] and can be used to trigger mode transition in a microprocessor-controlled powered prosthesis [8-11]. MPR in non-weight bearing conditions has been accomplished offline [12] and in real-time [13]. Hargrove *et al.* demonstrated the discrimination of 8 leg movements (knee flexion/ extension, ankle plantarflexion/dorsiflexion, femoral rotation, and tibial rotation) in both able-bodied and amputee subjects using myoelectric signals from non-weight bearing contractions using nine residual thigh muscles [13].

To our knowledge no study has made use of MPR in the lower limb for rehabilitation purposes other than prosthetic control. In particular, we are interested in the decoding of motor volition to treat PLP in lower limb amputees, analogously to the work of Ortiz-Catalan *et al.* [2] where MPR was used for the physiologically appropriate control of a virtual arm while providing visual feedback via augmented and virtual reality (AR/VR). It is of crucial importance to the success of the proposed treatment that patients perform phantom motions in a natural way, focusing in particular on the portion of the phantom limb affected by the pain. Studies on PLP with a large number of subjects reported that the majority of them localize the pain distally e.g. in the feet/toes rather than in the knees [14-15].

The requirement of movements executed in a natural way means that distinguishable and repeatable patterns of muscular activation should be generated in amputee subjects by the same neural commands the missing limb would receive if still present. Bearing this in mind, when studying myoelectric pattern recognition on healthy subjects it is desirable that the patterns used for discriminating movements of the foot (i.e. ankle plantarflexion and ankle dorsiflexion) are not generated by the activation of thigh muscles owing to ground reaction forces as done in previous work [12-13].

In this work we investigated the viability of a MPR system for the prediction of four degrees of freedom controlled in a near natural way. We took a different perspective from previous work [12-13] by introducing the additional requirement that ground reaction of the foot is to be avoided. This is based on the hypothesis that it is still possible to obtain useful EMG patterns related to ankle activity even though none of the muscles involved in ankle motions are in the thigh. In order to achieve this, we explored three different electrode configurations for acquiring EMG signals from the lower limb in non-weight bearing movements and evaluated their performance in terms of signal-to-noise ratio (SNR) and offline MPR accuracy.

II. Methods

This study was conducted on one subject with unilateral trans-femoral amputation (72 years old and 35 years after amputation) and eight able-bodied subjects (6 males and 2 females, aged 24 to 28). The experiments were approved by the Västra Götalandsregionen ethical committee and all participants provided written informed consent.

A. Electrode placement

In order to prevent the feet from touching the ground, able bodied subjects sat on a raised seat, with the feet freely suspended. Electrodes were placed after the subjects were seated.

Experiment 1: EMG recordings were done simultaneously in two targeted electrode configurations (Fig. 1a and Fig. 1b)

Targeted bipolar configuration: Eight pairs of adhesive electrodes (disposable, pre-gelled Ag/AgCl, 1 cm diameter, and 4 cm inter-electrode distance) were placed over the following eight muscles: sartorius, tensor fasciae latae, vastus medialis, rectus femoris, vastus lateralis, gracilis, long head of the biceps femoris and semitendinosus.

Targeted monopolar configuration: For each pair of electrodes in the *targeted bipolar configuration* a third electrode was placed in between. Differential measurements between these eight electrodes and the average potential of the area covered by a single circumferential electrode made of conductive fabric (silver plated knitted fabric) were recorded. The configuration was named *targeted monopolar* due to the use of the common circumferential electrode which acts as a reference electrode.

Experiment 2: An *untargeted monopolar configuration* of 16 equally spaced electrodes was used with a common differential electrode similarly to *targeted monopolar* configuration. The gap between the electrodes and band was approximately 4 cm. (Fig. 1c).

The reference electrode was placed on the wrist contralateral to the active leg in both experiments. Each subject performed experiment 1 and 2 in randomized order.

B. *Recording session*

BioPatRec [16], an open source software for advance prosthesis control, was used to guide the subjects to perform the 8 movements: knee flexion, knee extension, ankle plantar flexion, ankle dorsiflexion, femoral rotation (internal and external), and tibial rotation (internal and external). The subjects were asked to perform the movements at a constant speed and approximately 70% of the maximal voluntary contraction. The amputee subject was requested to perform each movement as naturally as possible. Each movement was repeated three times during four seconds with equal relaxation intervals. The recording protocol is described in detail elsewhere [16]. The system used to acquire EMG in both experiments was an in-house developed amplifier (SAM_USB1) with embedded active filter (3rd-order Butterworth low-pass filter at 750Hz and a 1st-order high-pass filter at 1Hz). The system amplifies the signals with a gain of 200 and digitalizes them with 16 bits of resolution at 2 kHz sampling rate. Before proceeding to training the classifier, the subject performed two recording sessions to gain acquaintance with the recording protocol. Data from the third recording session were used to train a pattern recognition system and to compute classification accuracy and SNR.

C. *SNR*

The statistic ratio of signal and noise powers was calculated for every movement and the three different configurations were compared. The method followed to calculate the SNR is described in [17]. Briefly, the SNR is the ratio of signal power to noise power, where signal power is the integral over the RMS value of the largest signal recorded from the electrode array during a contraction, and noise power is the integral over the RMS value of the signal recorded at rest.

D. *Training of the classifier and offline accuracy*

The signals were first used to train the pattern recognition system and then compute the offline classification accuracy of each configuration using previously unseen data from the same recording session. The accuracy for the *untargeted* configuration (Experiment 2) was both calculated on a subset of eight channels (instead of 16) and on the complete set. The "rest" position was considered as a movement resulting in a classification task of nine patterns. The recording session was first preprocessed in order to reduce the information to a more suitable form for pattern recognition (feature vectors). In each movement repetition there are transient periods due to the delay between the prompt to execute the movement and the response from the subject, as well as a potential anticipatory relaxation. These transients were discarded by considering only the central 70% of the contraction time of each repetition. The resulting signals were segmented in overlapping windows of 200 ms, with 50 ms time increment producing 163 time windows assigned randomly to training, validation and testing (40%, 20% and 40%, respectively). The signal treatment chain is comprehensively described in [16]. Linear Discriminant Analysis in a One-Vs-One topology (LDA-OVO) was used for classification and the feature fed to the algorithm were the Hudgins' set (mean

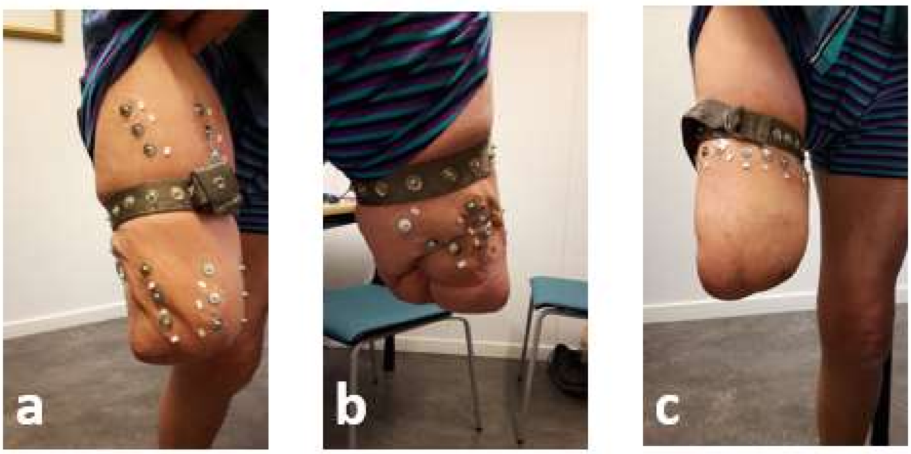

Figure 1: Photographs depicting the electrode placement. The electrode placement for Experiment 1 (targeted bipolar vs targeted monopolar configurations) is shown in picture a) front and b) back. Picture c) shows the electrode placement for Experiment 2 (untargeted monopolar configuration).

absolute value, wave length, slope changes and zero crossings).

III. RESULTS

The results are presented in box plots, where the edges of the box represent the 1st and the 3rd quartile, the "target" symbol represents the median value and the marker denotes the mean. The whiskers indicate the data range and the star marker is the data point from the amputee subject. Statistical significance, which is shown by the "*" marker was tested at 95% significance level using the Wilcoxon signed- rank test.

A. SNR per movement

The results of the SNR analysis are summarized in Fig. 2 where each box represents the distribution of the subject data for the particular configuration and movement. The *targeted monopolar* configuration performed worse than the other two configurations in most of the movements and on average ($p<0.05$). The SNR values for the *targeted bipolar* and *untargeted* configuration were found close to each other: the *untargeted* configuration had on average a marginally higher median and mean, however without a statistically significant improvement ($p=0.55$).

The SNR of the myoelectric signals from one amputee subject were also analyzed to gain insight on how the patient perform compared to the rest of the healthy subjects. These values, indicated in Fig. 2 by star markers, are consistently lower than those of healthy subjects in the *targeted bipolar* and targeted *monopolar* configurations. Interestingly in the *untargeted* configuration the amputee subject presented signals that fall into the range of those from healthy subjects. As expected, it was found that the weakest movements are the ones involving the ankle (plantarflexion and dorsiflexion) and for these movements the signals of the amputee subject were significantly stronger.

B. Offline Accuracy

The classification accuracy of the three different configurations was compared and the result of the analysis can be seen in Fig. 3. We found that the *targeted bipolar* and *targeted monopolar* configurations performed similarly, while the *untargeted* configuration with the eight-channel subset shows a marginal improvement without statistical significance ($p=0.1$). Using all of the 16 channels for the untargeted configuration was found to raise offline accuracy significantly over *targeted bipolar* and *targeted monopolar*. In a similar manner to the results presented in the SNR analysis, the signals from the amputee resulted in a better offline classification using the *untargeted* configuration.

IV. DISCUSSION

In this study three different electrode configurations for acquiring EMG data were explored aiming to determine if it is possible to classify naturally produced lower limb movements in four degrees of freedom. The classification of phantom lower limb movements in the condition of freely suspended foot is challenging due to weak signals related to the ankle. The main reason why the circumferential electrode was introduced was to eliminate the influence of alignment of the bipolar electrode pair to the muscle fiber orientation, which is known to be critical for optimal EMG recordings [18].
However, in the *targeted monopolar* configuration another factor must be considered, which is the increase of the distance between the differential electrodes resulting an increase of noise. These two effects can be noticed in Figure 2 where the SNR for the *targeted monopolar* presents generally lower values than those of the *targeted bipolar*: the use of the circumferential electrode provides a higher signal but such effect is undermined by the increase in noise due to the greater distance between electrodes. Similarly, the improved SNR by the *untargeted* configuration is explained by the proximity of the electrodes that renders less noise in the recording. The *untargeted* configuration yielded higher accuracy than the *targeted bipolar* and *targeted monopolar*, however this higher value is not statistically significant. One reason for this could be that eight electrodes do not provide sufficient coverage of the thigh. Increasing the number of channels to 16 provided a statistically higher offline accuracy.

Besides SNR and accuracy, there are secondary considerations useful for determining the preferred technique in a clinical application. Firstly, in the *untargeted* configuration the electrodes are easily and quickly applied as it is not necessary to localize particular muscles. This task is time consuming particularly since anatomical changes are

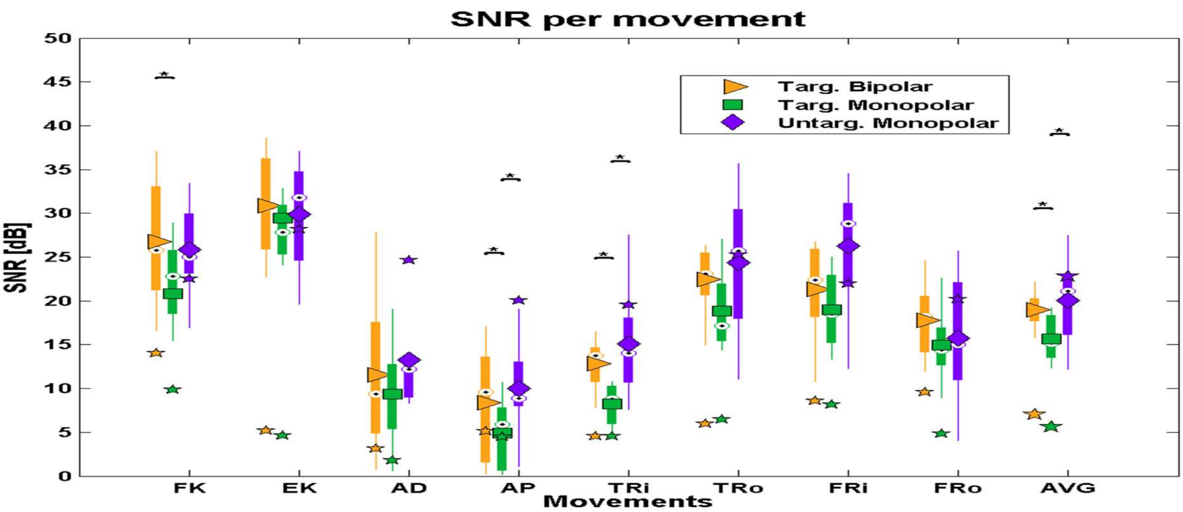

Figure 2: Comparison among configurations of the signal to noise ratio for each movement

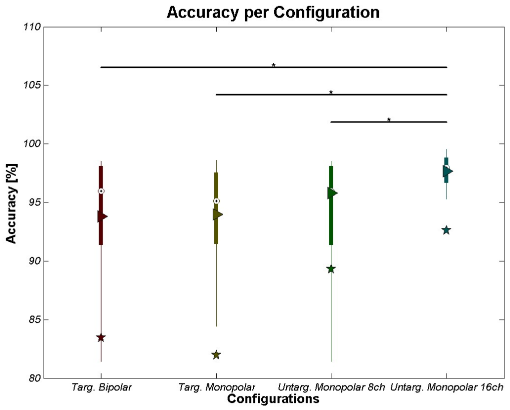

Figure 3: Comparison of classification accuracies

common after an amputation. Avoiding the need of careful electrode placement makes the system more suitable for independent home use. Secondly, the use of the circumferential electrode allows to use half of electrodes needed in a *targeted bipolar* configuration with the same number of channels. Lastly, the use of conductive fabric for the circumferential electrode opens possibilities for the development of solutions made entirely of wearable smart textiles, which would be easy to don and doff. These would adapt more easily to different anatomies and it would be possible to reuse.

The use of *targeted bipolar* and *untargeted* configuration is comparable in terms of SNR and offline accuracy when they use the same number of channels. Increasing the number of electrodes increments also the accuracy and might be necessary in early stages of our approach to PLP treatment. This work was limited to offline analysis and further work will be conducted to verify the results in real-time tests. Nevertheless, this study demonstrated the feasibility of decoding naturally produce leg movements isolating ground reaction forces, which is the first step towards our goal of implementing a phantom limb pain treatment based on virtual legs controlled by phantom movements.

REFERENCES

[1] D. Farina., N. Jiang, H. Rehbaum, A. Holobar, B. Graimann, H. Dietl, et al. “The extraction of neural information from the surface EMG for the control of upper-limb prostheses: emerging avenues and challenges,” *IEEE Trans. Neural. Syst. Rehabil. Eng.,* 2014, vol. 22, no.4, pp. 797–809.

[2] M. Ortiz-Catalan, N. Sander, M. B. Kristoffersen, B. Håkansson and R. Brånemark, “Treatment of phantom limb pain (PLP) based on augmented reality and gaming controlled by myoelectric pattern recognition: a case study of a chronic PLP patient,” *Front. Neurosci.* 2014, vol. 8, no. 24.

[3] J. Liu, P. Zhou, “A novel myoelectric pattern recognition strategy for hand function restoration after incomplete cervical spinal cord injury,” *IEEE Trans. Neural. Syst. Rehabil. Eng*., 2013, vol. 21, pp. 96–103.

[4] S. W. Lee, K. M. Wilson, B. A. Lock, D. G. Kamper, “Subject-specific myoelectric pattern classification of functional hand movements for stroke survivors,” *IEEE Trans. Neural. Syst. Rehabil. Eng.*, 2011, vol.19, pp. 558–566.

[5] M. A. Oskoei and H. S. Hu, “Myoelectric control systems—A survey,” *Biomed. Signal Process. Control*, 2007, vol. 2, no.4, pp. 275–294.

[6] H. Huang, T. A. Kuiken, R. D. Lipschutz, “A Strategy for Identifying Locomotion Modes Using Surface Electromyography,” *IEEE Trans. Biomed. Eng*., 2009, vol. 56, no. 1, pp. 65–73.

[7] D. Jin, J. Yang, R. Zhang; R. Wang, J. Zhang, "Terrain identification for prosthetic knees based on electromyographic signal features," *Tsinghua Science and Technology*, 2006, vol.11, no. 1, pp.74-79.

[8] S. Au, M. Berniker, H. Her, “Powered ankle-foot prosthesis to assist level ground and stair descent gaits,” *Neural Netw*., 2008, vol.21, no. 4, pp. 654-666.

[9] D.C. Tkach, R. D. Lipschutz, S.B. Finucane, L. J. Hargrove, “Myoelectric neural interface enables accurate control of a virtual multiple degree of freedom foot ankle prosthesis,” *Rehabilitation Robotics (ICORR), 2013 IEEE International conference On.,* 2013, pp. 1-4.

[10] A. J. Young, A. M. Simon, N. P. Fey, L. J. Hargrove, "Classifying the intent of novel users during human locomotion using powered lower limb prostheses," *Neural Engineering (NER), 2013 6th International IEEE/EMBS Conference on*, 2013, pp.311-314.

[11] H. Varol, F. Sup, M. Goldfarb “Multiclass real-time intent recognition of a powered lower limb prosthesis,” *IEEE Trans Biomed Eng*. 2010, vol. 57, no. 3, pp. 542-51.

[12] T. Afzal, K. Iqbal, G. White, A.B. Wright “Task discrimination for non-weight-bearing movements using muscle synergies,” *Conf Proc IEEE Eng Med Biol Soc*, 2015, 478-81

[13] L. Hargrove, A. Simon, R. Lipschutz, S. Finucane, and T. Kuiken, “Non- weight bearing neural control of a powered transfemoral prosthesis,” J. Neuroeng. Rehabil., vol. 10, no. 1, p. 62, 2013

[14] T. S. Jensen, B. Krebs, J. Nielsen, et al., “Phantom limb, phantom pain and stump pain in amputees during the first 6 months following limb amputation.” *Pain*, 1983, vol. 17, no. 3, pp. 243–256

[15] T. S. Jensen, L. Nikolajsen, “Phantom pain and other phenomena after amputation.” *In Textbook of Pain*, edn 4. Edited by Wall PD, Melzack R. Edingburgh: Churchill Livingstone, 1999, pp.799–814.

[16] M. Ortiz-Catalan, R. Brånemark and B. Håkansson, "BioPatRec: A modular research platform for the control of artificial limbs based on pattern recognition algorithms," *Source code for biology and medicine*, vol. 8, no. 11, 2013.

[17] E. Mastinu, M. Ortiz-Catalan, and B. Hakansson, "Analog Front-Ends comparison in the way of a portable, low-power and low-cost EMG controller based on pattern recognition”, *International Conference of the IEEE Engineering in Medicine and Biology Society (EMBC),* Milan, Italy, 2015

[18] G.E. Loeb, C. Gans, “Electromyography for Experimentalists.” *University of Chicago Press*, Chicago, 1986.

Paper II

Real-Time Classification of Non-Weight Bearing Lower Limb Movements: a viable alternative to differential recording for rehabilitation use.

Abstract

Strong evidence documents a correlation among the reorganization of the sensorimotor cortex taking place after an amputation, phantom limb pain and phantom limb mobility. This suggests that reacquisition of control over phantom movements is a promising therapeutic target. Myoelectric Patter Recognition (MPR) has been successfully used for this purpose on upper limb amputees by our group, however the use of MPR on lower limb in rehabilitation has never been attempted. In the present work we investigated the viability of a MPR system for the prediction of four degrees of freedom controlled in a near natural or physiologically appropriate fashion. We explored three different electrode configurations for acquiring electromyographic (EMG) signals: two targeted (differential and wide-differential) and one untargeted (electrodes equally spaced axially). We extend our previous investigation by increasing the number of subjects and by evaluating the real-time classification performance. The results showed that classification is possible without significant differences in all of the three configurations, but also highlighted that the use of the untargeted configuration can be the preferred for PLP treatment as it facilitates the electrode placement procedure.

Introduction

Following an amputation, the missing limb is often perceived as still attached to the body. The phenomenon, known as phantom limb, is accompanied by a wide range of sensory perceptions, different among individuals, but collectively referred to as phantom sensations (i.e. warmth, cold, kinesthesia, etc.) [1].

Frequently, in addition to phantom sensations, patients report pain in the missing limb: This condition, known as Phantom Limb Pain (PLP). The neural mechanisms at the base of the painful perception of a missing limb are not completely understood, making PLP a major clinical challenge due to the lack of effective treatments and to its large incidence [2], [3]. Amputation is known to lead to extensive reorganization of primary somatosensory (SI) [4] and motor (MI) cortices [5], where areas neighboring with the representation of the amputated limb will enlarge and invade the vacated cortex. Strong evidence suggests that the amount of reorganization correlates both with magnitude of PLP [6]–[8] and decrease of controllability of the phantom limb [9], which themselves are associated.

Even though the role of phantom mobility in PLP and cortical reorganization is still unclear; proofs of this relationship cannot be ignored. For instance, studies on movement disorders such as motor stroke or Parkinson's disease have shown that a disorganized cortical map corresponds to reduced motor control [10], [11] and treatments such as mirror therapy or phantom training can improve the phantom controllability as well as relieve from PLP [12]–[14]. For this reason, the reacquisition of control over voluntary movements of the phantom limb, thus reversing the maladaptive plasticity, poses itself as a promising therapeutic target.

In line with this working hypothesis, a study published in 2014 by Ortiz-Catalan et al. [15] presented a system where Myoelectric Pattern Recognition (MPR) was exploited to control virtual reality

(VR) and augmented reality (AR) upper limbs. On one hand, the use of MPR allowed the patient to control the virtual limb with physiologically appropriate muscles contractions. On the other hand, the VR and AR environments provided a visual feedback congruent with the phantom motion executed, therefore facilitating the training. The proposed system was then used in a clinical trial on 14 upper limb amputee patients and the promising results have underlined the need of making an analogous system available for lower limb amputees [16].

Since many decades, MPR has been vastly studied for the upper limb [17], while advances in the MPR for lower limb are relatively recent and mostly focused on improving the prosthetic control during weight bearing conditions [18]–[23]. In the context of implementing a PLP treatment however, the interest lies on MPR in non-weight bearing conditions since the patient should be able to exercise leg movements from sitting position.

MPR in non-weight bearing condition has been attempted offline [24] and real-time studies [25]. Notably, Hargrove et al. demonstrated the discrimination of eight leg movements (knee flexion/ extension, ankle plantarflexion/dorsiflexion, femoral rotation, and tibial rotation) in both able-bodied and amputee subjects recording surface electromyographic (sEMG) signals with bipolar electrodes placed over nine residual thigh muscles [25]. However, the procedure for electrode placement and signal collection adopted in the study could be a challenge in rehabilitative setting. First of all, depending on the level of the amputation not all the muscles might be available. Second, even when available, the muscles might not be easy to localize due to anatomical changes related to the amputation, making the precise identification of muscles an issue.

In a previous work we proposed two electrode configurations to acquire sEMG for MPR of non-weight bearing movements of the lower limb [26]. We compared these electrode configurations with the conventional bipolar targeted configuration in terms of Signal-to-Noise Ratio (SNR) and offline MPR classification accuracy. We found that placing the electrodes equally spaced around the proximal third of the thigh is a viable alternative to bipolar recordings from specific muscles with the advantage of facilitating the procedure over the latter.

In the present work, we extend our previous study [26] by increasing the number of subjects and evaluating the real-time classification performance.

Methods

Twelve able-bodied subjects (5 males and 7 females, aged 23 to 30), and two amputee subjects participated in the study. One amputee participant had a unilateral trans-femoral amputation (70 years old and 35 years after amputation), whereas the other had a unilateral trans-tibial

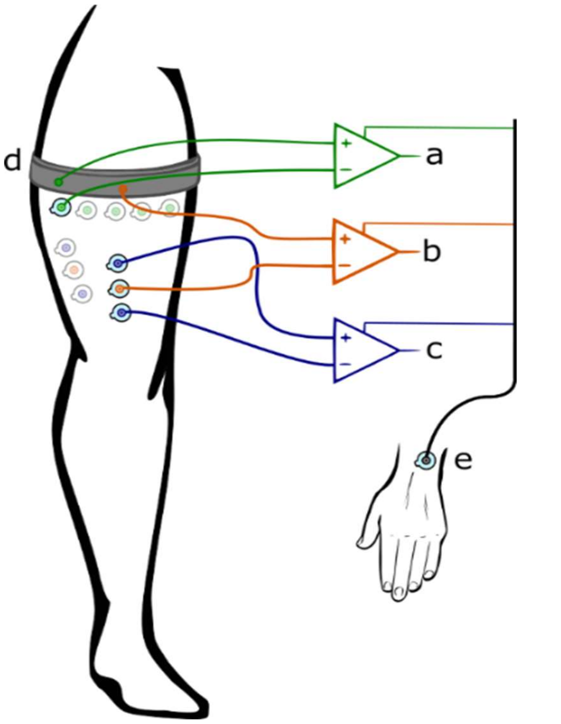

Figure 1: Sketch of the three electrode configurations. (a). Untargeted Monopolar Configuration, (b). Targeted Monopolar Configuration, (c). Targeted Bipolar Configuration, (d). Common Circumferential Electrode, (e). Reference Electrode

amputation (72 years old and 22 years after amputation). The trans-femoral amputee was trained in the use of the MPR system while the trans-tibial amputee was novice. All participants provided written informed consent prior taking part in the study. The study was approved by the Västra Götalandsregionen ethical committee.

The able-bodied subjects were divided randomly in two groups for distinct experiments. The amputee subjects performed both experiments in two different days. The two experiments consisted of a sEMG data collection phase to train the MPR system, followed by a second phase where the real-time performance was evaluated. The two experiments differed only in the electrode configuration employed to recorded the sEMG (Figure 1).

Electrode Placement

Able-bodied subjects sat on a raised seat allowing for their feet to hang freely. This precaution was taken to ensure that patterns used for discriminating movements of the foot (i.e. ankle plantarflexion/dorsiflexion) were not generated by ground reaction forces. In experiment 1, sEMG using a Targeted Bipolar Configuration (TBC) and a Targeted Monopolar Configuration (TMC) was acquired simultaneously, whereas in experiment 2) an Untargeted Monopolar Configuration (UMC) was used to recorded sEMG in two separate days.

- **TBC**: Eight pairs of adhesive electrodes (disposable, pre-gelled Ag/AgCl, 1 cm diameter, and 4 cm inter-electrode distance) were placed over the following eight muscles: sartorius, tensor fasciae latae, vastus medialis, rectus femoris, vastus lateralis, gracilis, long head of the biceps femoris and semitendinosus. The stump of the tranfemoral subject was long enough to identify all the muscles (Figure 1.b)
- **TMC**: For each pair of electrodes in the targeted bipolar configuration, a third electrode was placed in between. A circumferential electrode made of conductive fabric (silver plated knitted fabric) was wrapped around the most proximal third of the thigh. Differential measurements between the eight electrodes and the average potential of the area covered by the circumferential electrode were recorded. The configuration is defined as "monopolar" due to the use of the common circumferential electrode that acts as a reference for all the targeted ones (Figure 1.b)
- **UMC**: The circumferential electrode was placed around the most proximal third of the thigh and 16 Ag/AgCl pre-gelled electrodes placed below the band (distally), equally spaced around the thigh. The gap between the electrodes and the band was approximately 4 cm. In a similar way as for the Targeted Monopolar Configuration, differential measurements were recorded between each of the electrodes and the circumferential electrode. (Figure 1.a)

A reference electrode used for all recording configurations was placed on the contralateral wrist over the distal end of the ulna.

Recording session

The system used for the acquisition of sEMG was an in-house developed amplifier (SAM_USB1) with embedded active filter (3rd-order Butterworth low-pass filter at 750Hz, and 1st-order high-pass filter at 1Hz). The system amplified the myoelectric signals with a gain of 200 times, and digitalized them with 16 bits of resolution at 2 kHz sampling rate. Before proceeding to the data acquisition, sEMG signals from all the channels were checked in order to ensure the correct functioning of the device. Every subject performed as single recording session, which was done following the same procedure described below for both experiments. An open source software for prosthesis control based on MPR called BioPatRec was used for data acquisition, signal treatment, pattern recognition and real-time control [27].

The participants were instructed to follow a graphical user interface which showed the movement to be performed (Figure 2) along with a progress bar signaling the duration of each contraction. The recording session was conducted in the same way for both experiments, and the movements recorded were: knee flexion/extension, ankle plantarflexion/dorsiflexion, femoral rotation inwards/outwards and tibial rotation inwards/outwards. The amputee subjects were asked to execute the movements as naturally as possible using their phantom limb. sEMG for each movement was collected in three consecutive repetitions of four seconds each, where every repetition was followed by a period of four seconds of rest. The subjects were asked to execute the movements at approximately 70% of their maximal voluntary contraction. Before proceeding with the collection of the data actually used for the rest of the experiment, the subjects executed one recording session to get familiar with the system. The resulting recordings are available online in the repository of bioelectric signals of BioPatRec, under the label "8mov16chLowerLimb"[28].

Signal Treatment

The raw EMG signals were separated in contraction and resting periods. The data recorded during the contraction time tend to contain non-EMG information due to the delay between prompting and execution of a movement, as well as due to anticipatory relaxation. The impact of this irrelevant information was reduced by discarding 15% of the signal at the beginning and the end of the contraction time, which still allowed to preserve part of the transient EMG. The trimmed contraction periods were concatenated and then segmented in overlapping windows of 200 ms with 50 ms time increment. The segmentation produced a total of 163 overlapping time windows from which signal features were

Figure 2: Images shown in the graphical user interface to guide the recording session. The pictures illustrate the correct way to perform the movements. A) knee flexion and extension, B) ankle plantar flexion and dorsiflexion, C) femoral rotation, D) and tibial rotation.

extracted to form feature vectors. The feature vectors were then randomly assigned to training, validation, and testing sets in the following proportions: 40%, 20% and 40%, respectively. The feature vectors were formed by four time-domain features (mean absolute value, wave length, slope changes and zero crossings) for every channel [27].

Classifier training and real-time evaluation

The "rest" posture was considered as a movement resulting in a classification task of nine patterns. Linear Discriminant Analysis in a One-Vs-One topology (LDA-OVO) was used for classification [29]. Immediately after the classifier was trained, the real-time performance in each electrode configuration was evaluated by the Motion Test [30], as it is implemented in BioPatRec [27]. The Motion Test requests the subject to produce the trained movements in randomized order while evaluating the following metrics:

- **Selection time:** the time elapsed between the first prediction different from rest and the first correct prediction. The fastest selection time was possible at 211 ms. A new prediction was made every 50 ms.
- **Completion time:** the time elapsed between the first prediction different from rest (as in the selection time) and the 20th correct prediction. The fastest completion time was possible at 1.16s.
- **Completion percentage**: the percentage of motions that were completed; that is, the motions that have reached 20 correct predictions before the timeout10 s.
- **Real time accuracy:** it is calculated only for completed motions and it accounts for the number of predictions that were needed in order to obtain 20 correct predictions. For example, if the completion time took 25 time windows, thus producing 25 predictions from which 20 were correct, the real time accuracy would be 80%.

Each participant executed the motion test twice:

- Subjects taking part in experiment 1 performed one test in the TBC, while the other test in the TMC. The order of the two motion tests was randomized across subjects.
- In experiment 2, one test was executed with signals coming from a subset of eight channels (equally spaced around the thigh) of the original UMC, while the second test used all the 16 electrodes. Again, the order of the two tests was randomized across subjects.

Offline accuracy

Additionally, an offline analysis was done in order to compare the offline accuracies of the presented configurations (TBC, TMC, UMC with 8 channels and UMC with 16 channels). The signals were treated as described above, and the time windows were randomly assigned to training, validation and testing. The feature vectors in the testing set were used to compute the offline accuracy, which is the percentage of test data correctly predicted by the trained classifier. The classifier was trained 10 times per subject in order to calculate the average offline accuracy and its standard error.

Statistical analysis

This cross-sectional study compared

four different ways of placing electrodes (TBC, TMC, UMC with 8 channels and UMC with 16 channels) in healthy subjects and amputees, which were considered separately. The different configurations tested in experiment 1 and 2 are considered independent from each other. For this reason, the Kruskal-Wallis test was chosen to determine if there is any statistically significant difference among the 8 independent groups.

Results

Table 1 summarizes the mean values and the related standard errors for all the metrics. The results are also presented graphically in box plots (Figure 3-7): the line in the center of the box indicates the location of the median, the upper edge indicates the 3rd quartile, the bottom edge represents the 1st quartile, the circular marker denotes the mean and the whiskers indicate the data range. Along with every boxplot it is possible to see a square and a star marker: they represent the data points for the transtibial and the trans-femoral amputee subject respectively. Finally, Figure 8 shows the cumulative completion rate which reports the percentage of motions completed as a function of time.

The results showed no significant differences among any of the real-time performance indicators as well as the offline accuracy. Also, no significant difference was found between healthy subjects and amputees.

Discussion

The aim of the study was to further investigate the performance of three different ways of placing the electrodes in terms of real time performance and to demonstrate that the technique can be applied in the PLP treatment technology for trans-femoral patients.

Here we showed that classification is possible without significant differences in all of the three configurations. It is worth to notice that using 16 channels in the UMC

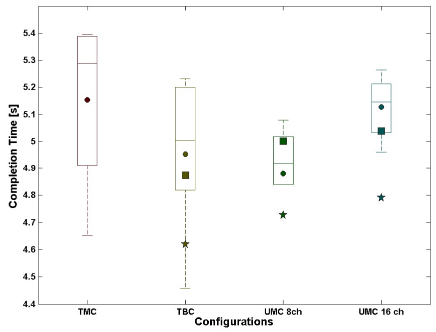

Figure 3: Completion Time

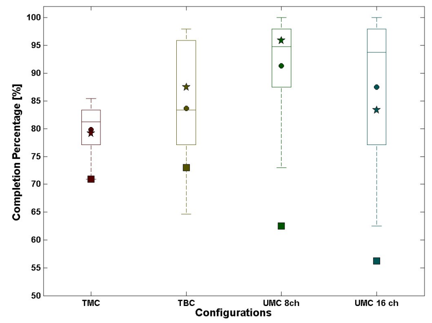

Figure 4: Completion Percentage

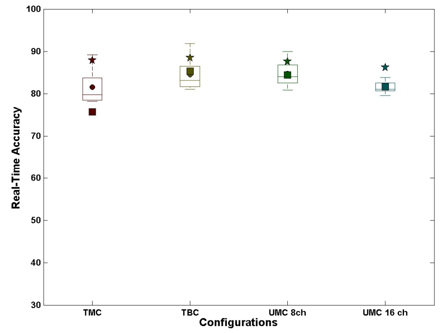

Figure 5: Real-Time Accuracy

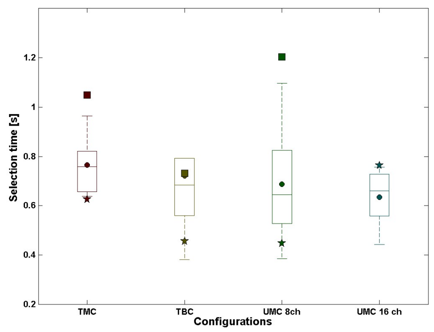

Figure 6: Selection Time

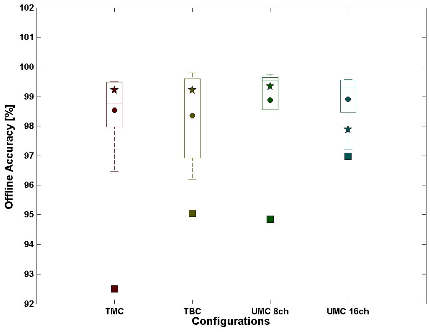

Figure 7: Offline Accuracy

does not give better results over the same configuration with just eight channels. Instead, the latter performs slightly but consistently better as it can be noticed from the mean values of the real time performance indicators reported in Table 1. This should not be surprising since it is known from the literature that the performance of a system that uses an excessive number of channels could lead to worse results because redundant information is fed to the classifier.

When performing MPR on healthy subjects it is desirable that the patterns used for classifying foot movements (i.e. ankle plantarflexion and ankle dorsiflexion) are not generated by the activation of thigh muscles owing to ground reaction forces. Contrary to previous work where both healthy subjects and amputees could control leg movements from sitting position [25], we took this factor into account by letting the healthy subjects sit on a raised chair with their feet hanging. The level of accuracy achieved for ankle motions in healthy subjects was above what forecast since the muscles that control the ankle are located below the knee. On the other hand, a study showed that phantom movements are accompanied by EMG activity from muscles that would have never contributed before amputation [31] explaining how it is possible. to perform phantom movements even when the physiologically appropriate muscles are lost Hence, a way to improve the quality of the MPR in amputee subjects would be to identify the muscle of the stump that are active during different phantom movements and place the electrodes over the identified muscles, making the electrode placement unique for each individual.

As it can be seen from the boxplots, the two amputee subjects performed quite differently. Even though the trans-tibial subject had intact thigh muscles, the trans-femoral subject performed better. The better performance is due to the training that the trans-femoral subject went through. It should be noted that the trans-tibial subject, who was a novice user,

Table 1: Performance metrics mean values (standard error)

	TMC		TBC		8 Ch		16 Ch	
Performance metric	**Amputee (n=2)**	**Healthy (n=6)**	**Amputee (n=2)**	**Healthy (n=6)**	**Amputee (n=2)**	**Healthy (n=6)**	**Amputee (n=2)**	**Healthy (n=6)**
Offline accuracy, %	95.9 (3.4)	98.5 (0.5)	97.1 (2.1)	98.3 (0.6)	97.1 (2.2)	98.7 (0.59)	97.4 (0.45)	98.7 (0.40)
Completion rate. %	75.0 (4.2)	79.8 (2.1)	80.2 (7.3)	83.7 (5.3)	79.1 (16.6)	91.3 (4.1)	69.8 (13.5)	87.5 (6.0)
Real time accuracy, %	81.7(6.1)	81.5 (3.0)	86.9(1.6)	84.6(2.9)	86,0(1.6)	84.7(2.3)	83,9 (2.3)	81,4(1.1)
Completion time, s	5.15 (0.35)	5.15 (0.12)	4.75 (0.13)	4.95 (0.12)	4.86 (0.14)	4.88 (0.08)	4.91 (0.12)	5.13 (0.05)
Selection time, s	0.84 (0.21)	0.77 (0.05)	0.59 (0.14)	0.72 (0.12)	0.83 (0.38)	0.69 (0.10)	1.25 (0.49)	0.88 (0.05)

reported painful phantom when performing the movements. An interesting further study would be to quantify the effect of training on the ability to move the phantom, its correlation to PLP and reorganization of motor cortex.

Besides real time performance and offline accuracy of the classifiers, there are secondary considerations useful for determining which should be the preferred technique for a clinical application. First of all, when dealing with patients with short stumps the TBC might not be an option as not all the muscles required for targeted configurations are available. Secondly, even when the muscles are available, the targeted electrode placement techniques can be difficult and time consuming because of the difficulty in identifying the muscles that can be due to excessive soft tissue, weak or relocated muscles. Thirdly, the use of bipolar electrodes requires special attention during the placement. For instance, it is advisable not to record differentially over the muscle belly or innervation zones because any small displacement of the sensors with respect to the innervation zones will give unstable or unreproducible signals [32]. Moreover, optimal sEMG signals are recorded with electrodes orientated parallel to the muscle fibers and therefore parallel to the direction of the action potential propagation [33]. However, in muscles like the quadriceps (muscles with pennation angle) the correct orientation of electrodes is impracticable. Both problems can be easily solved with a monopolar configuration as recording over the muscle belly gives large monopolar sEMG signals. This technique is also insensible to orientation of the fibers.

Altogether, the use of the UMC, where electrodes are quickly applied around the proximal third of the thigh, is a good solution if the ultimate goal is the implementation of a rehabilitation system which can be used daily and independently at home.

On a more speculative note, the successful use the circumferential electrode of conductive fabric opens possibilities for the development of solutions made entirely of wearable smart textiles, which would be easy to don and doff. It would adapt more easily to different anatomies and it would be possible to reuse.

Conclusion

This work demonstrates the possibility of using different techniques to acquire sEMG signals suitable for successful MPR of lower limb movements in non-weight bearing conditions. A preferred methodology for our rehabilitative application has been identified and future work will focus on further development the system and investigation of its efficacy in training the ability of moving the phantom limb and reducing the phantom pain

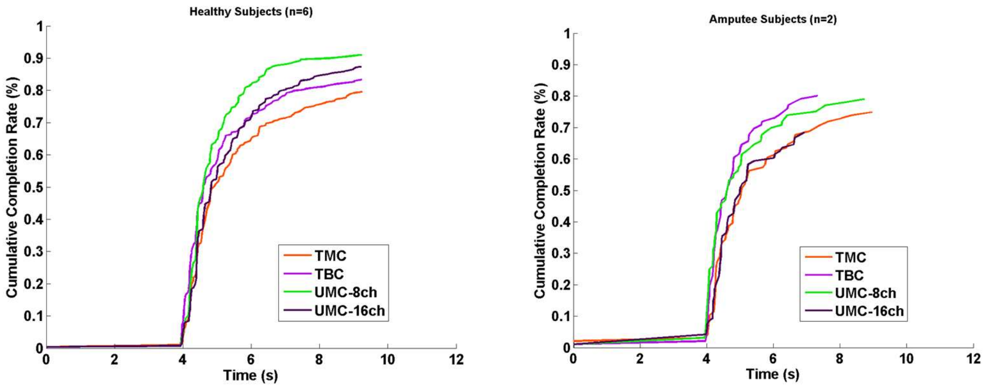

Figure 8: Motion completion percentage as a function of completion time for healthy subjects (left) and amputee subjects (right).

References

[1] V. S. Ramachandran and W. Hirstein, "The perception of phantom limbs," *Brain*, vol. 121, pp. 1603–1630, 1998.

[2] H. Flor, "Phantom-limb pain: characteristics, causes, and treatment," *Lancet Neurol.*, vol. 1, no. July, pp. 182–189, 2002.

[3] H. Flor, M. Diers, and J. Andoh, "The neural basis of phantom limb pain," *Trends Cogn. Sci.*, vol. 17, no. 7, pp. 307–308, 2013.

[4] T. Elbert, H. Flor, N. Birbaumer, S. Knecht, S. Hampson, W. Larbig, and E. Taub, "Extensive reorganization of the somatosensory cortex in adult humans after nervous system injury.," *Neuroreport*, vol. 5, no. 18, pp. 2593–2597, 1994.

[5] E. J. Hall, D. Flament, C. Fraser, and R. N. Lemon, "Non-invasive brain stimulation reveals reorganised cortical outputs in amputees," *Neurosci. Lett.*, vol. 116, no. 3, pp. 379–386, 1990.

[6] H. Flor, T. Elbert, S. Knecht, C. Wienbruch, C. Pantev, N. Birbaumer, W. Larbig, and E. Taub, "Phantom-limb pain as a perceptual correlate of cortical reorganization following arm amputation.," *Nature*, vol. 375, no. 6, pp. 482–4, Jun. 1995.

[7] A. Karl, N. Birbaumer, W. Lutzenberger, L. G. Cohen, and H. Flor, "Reorganization of Motor and Somatosensory Cortex in Upper Extremity Amputees with Phantom Limb Pain," *J. Neurosci.*, vol. 21, no. 10, pp. 3609–3618, May 2001.

[8] M. Lotze, H. Flor, W. Grodd, W. Larbig, and N. Birbaumer, "Phantom movements and pain. An fMRI study in upper limb amputees.," *Brain*, vol. 124, no. Pt 11, pp. 2268–77, Nov. 2001.

[9] E. Raffin, N. Richard, P. Giraux, and K. T. Reilly, "Primary motor cortex changes after amputation correlate with phantom limb pain and the ability to move the phantom limb," *Neuroimage*, vol. 130, pp. 134–144, 2016.

[10] J. Yao, A. Chen, C. Carmona, and J. P. A. Dewald, "Cortical overlap of joint representations contributes to the loss of independent joint control following stroke," *Neuroimage*, vol. 45, no. 2, pp. 490–499, 2009.

[11] D. Lindenbach and C. Bishop, "Critical involvement of the motor cortex in the pathophysiology and treatment of Parkinson's disease," *Neurosci. Biobehav. Rev.*, vol. 37, no. 10, pp. 2737–2750, 2013.

[12] B. L. Chan, R. Witt, A. P. Charrow, A. Magee, R. Howard, P. F. Pasquina, K. M. Heilman, and J. W. Tsao, "Mirror therapy for phantom limb pain.," *N. Engl. J. Med.*, vol. 357, no. 21, pp. 2206–2207, 2007.

[13] C. Mercier and A. Sirigu, "Training with virtual visual feedback to alleviate phantom limb pain.," *Neurorehabil. Neural Repair*.

[14] K. MacIver, D. M. Lloyd, S. Kelly, N. Roberts, and T. Nurmikko, "Phantom limb pain, cortical reorganization and the therapeutic effect of mental imagery.," *Brain*, vol. 131, no. Pt 8, pp. 2181–91, Aug. 2008.

[15] M. Ortiz-Catalan, N. Sander, M. B. Kristoffersen, B. Håkansson, and R. Brånemark, "Treatment of phantom limb pain (PLP) based on augmented reality and gaming controlled by myoelectric pattern recognition: A case study of a chronic PLP patient," *Front. Neurosci.*, 2014.

[16] Ortiz-Catalan, M., Guðmundsdóttir, R.A., Kristoffersen, M.B., C. Zepeda-Echavarria, A., Caine-Winterberger, K., Kulbacka-Ortiz, K., Widehammar, K. Eriksson, A. Stockselius, C. Ragnö, Z. Pihlar, H. Burger, and L. Hermansson, "Phantom motor execution facilitated by machine learning and augmented reality as treatment for Phantom Limb Pain," *Lancet*, vol. In Press, 2016.

[17] R. W. Wirta, B. R. SMEb Donald Taylor, B. S. E E F Ray Finley, and P. Dc, "PATTERN-RECOGNITION ARM PROSTHESIS : A HISTORICAL PERSPECTIVE—A FINAL REPORT a," *Nonr*, vol. 4292, no. 0, 1963.

[18] D. Jin, J. Yang, R. Zhang, R. Wang, and J. Zhang, "Terrain Identification for Prosthetic Knees Based on Electromyographic Signal Features*," *Tsinghua Sci. Technol.*, vol. 11, no. 1, pp. 74–79, 2006.

[19] H. Huang, T. A. Kuiken, and R. D. Lipschutz, "A strategy for identifying locomotion modes using surface electromyography," *IEEE Trans. Biomed. Eng.*, 2009.

[20] S. Au, M. Berniker, and H. Herr, "Powered ankle-foot prosthesis to assist level-ground and stair-descent gaits," *Neural Networks*, vol. 21, no. 4, pp. 654–666, 2008.

[21] D. C. Tkach, R. D. Lipschutz, S. B. Finucane, and L. J. Hargrove, "Myoelectric neural interface enables accurate control of a virtual multiple degree-of-freedom foot-ankle prosthesis.," *IEEE Int. Conf. Rehabil. Robot.*, vol. 2013, p. 6650499, Jun. 2013.

[22] A. J. Young, A. M. Simon, N. P. Fey, and L. J. Hargrove, "Classifying the intent of novel users during human locomotion using powered lower limb prostheses," in *2013 6th International IEEE/EMBS Conference on Neural Engineering (NER)*, 2013, pp. 311–314.

[23] H. A. Varol, F. Sup, and M. Goldfarb, "Multiclass real-time intent recognition of a powered lower limb prosthesis.," *IEEE Trans. Biomed. Eng.*, vol. 57, no. 3, pp. 542–51, Mar. 2010.

[24] T. Afzal, K. Iqbal, G. White, and A. Wright, "Task Discrimination for Non-Weight-Bearing Movements Using Muscle Synergies," 2015.

[25] L. J. Hargrove, A. M. Simon, R. Lipschutz, S. B. Finucane, and T. A. Kuiken, "Non-weight-bearing neural control of a powered transfemoral prosthesis," *J. Neuroeng. Rehabil.*, vol. 10, p. 1, 2013.

[26] E. Lendaro, M. O. Catalan, and I. Member, "Classification of Non-Weight Bearing Lower Limb Movements : Towards a Potential Treatment for Phantom Limb Pain Based on Myoelectric Pattern Recognition .," 2016.

[27] M. Ortiz-Catalan, R. Brånemark, and B. Håkansson, "BioPatRec: A modular research platform for the control of artificial limbs based on pattern recognition algorithms.," *Source Code Biol. Med.*, vol. 8, no. 1, p. 11, 2013.

[28] "Data Repository," *BioPatRec*. [Online]. Available: https://github.com/biopatrec/biopatrec/tree/Data_Repository.

[29] M. Ortiz-catalan, B. Håkansson, and R. Brånemark, "Real-Time and Simultaneous Control of Arti fi cial Limbs Based on Pattern Recognition Algorithms," vol. 22, no. 4, pp. 756–764, 2014.

[30] T. A. Kuiken, G. Li, B. A. Lock, R. D. Lipschutz, L. A. Miller, K. A. Stubblefield, and K. B. Englehart, "Targeted Muscle Reinnervation for Real-time Myoelectric Control of Multifunction Artificial Arms."

[31] K. T. Reilly, C. Mercier, M. H. Schieber, and A. Sirigu, "Persistent hand motor commands in the amputees' brain," *Brain*, vol. 129, pp. 2211–2223, 2006.

[32] R. Merletti and H. J. Hermens, "Detection and Conditioning of the Surface EMG Signal," in *Electromyography*, Hoboken, NJ, USA: John Wiley & Sons, Inc., 2005, pp. 107–131.

[33] G. E. Loeb and C. Gans, *Electromyography for experimentalists*. University of Chicago Press, 1986.