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Dong, Jian

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BY
JIAN DONG

DISSERTATION SUBMITTED 2020

AALBORG UNIVERSITY
DENMARK

ON THE USE OF SUBDERMAL ELECTRICAL STIMULATION FOR RESTORATION OF SENSORY FEEDBACK

by

Jian Dong

AALBORG UNIVERSITY
DENMARK

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PhD supervisor: Prof. Winnie Jensen,
Aalborg University, Denmark

Assistant PhD supervisors: Associate Prof. Ernest Nlandu Kamavuako,
King’s College, London

Associate Prof. Strahinja Dosen and Assistant Prof. Bo Geng, Aalborg University, Denmark

PhD committee: Professor Johannes Jan Struijk (chairman)
Aalborg University

Associate Professor Christian Antfolk
Lund University

Dr. Antoni Ivorra Cano
IC, Universitat Pompeu Fabra

PhD Series: Faculty of Medicine, Aalborg University

Department: Department of Health Science and Technology

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CV

Jian Dong

Personal data

Nationality: China Gender: Male
Birth date: March 25, 1982

Education

- Aalborg University, Aalborg, Denmark
  Ph.D. of Biomedicine engineering, Electrical stimulation induced restoration of sensory feedback
  Sep. 2016 – Dec. 2019
  Jilin University, Changchun, China
  Master of Spine Surgery, Diagnosis and treatment of spine and spinal cord disease
  Feb. 2010 - Feb. 2012

Research and Working Experience

- Ph.D. student at Department of Health Science and Technology, Faculty of Medicine, Aalborg University
  Sep. 2016 - Dec. 2019
  Supervisors: Professor Winnie Jensen, Associate professor Ernest Nlandu Kamavuako, Strahinja Dosen and Assistant Professor Bo Geng
  Research projects: Electrical stimulation induced restoration of sensory feedback

- Master study, Department of Spine Surgery, The Third Affiliated Hospital of Jilin University
  Feb. 2010 - Feb. 2012
  Supervisor: Professor Xiaoyu Yang
  Research projects: Diagnosis and treatment of spinal cord diseases or disorders, Early management of acute traumatic spinal cord injury

ENGLISH SUMMARY

The lack of sensory feedback has been highlighted as an obstacle that limits the use of prosthetics. The use of invasive electrical stimulation such as peripheral nerve stimulation, spinal cord stimulation, and direct brain stimulation has been explored to provide sensory feedback through implantable electrodes. However, surgery is inevitable for placing these electrodes. Surface electrical stimulation has been studied intensively as a non-invasive peripheral nerve stimulation technique, but these electrodes are prone to high degree of variability owing to daily donning and doffing. In contrary, subdermal stimulation is minimally invasive, and is believed to be able to significantly decrease the energy consumption with less discomfort. However, the stability of subdermal stimulation (i.e., repeatability and variability) over time has not been systematically explored. In this thesis, it was hypothesized that sensory feedback evoked by subdermal electrical stimulation may have better stability, as evaluated through psychophysical measurements, and performance in closed-loop control systems over time than surface stimulation.

Four studies were conducted to test this hypothesis. **Study I** compared psychophysical properties between surface and subdermal stimulation under varying intensities and frequencies (20 and 100 Hz). **Studies II** and **III** tested the stability of the electrical stimulation delivered over time windows (8 h and 7 days) by surface and subdermal electrodes in healthy and amputee subjects. **Study IV** tested the performance of the surface and subdermal stimulation-induced sensory feedback in closed-loop control tests.

Results showed that subdermal stimulation is a more viable approach than surface stimulation for providing sensory feedback to amputees because overall, subdermal stimulation demonstrates similar stability and performance in closed-loop control over time as surface stimulation. In addition, subdermal stimulation has less energy consumption and is more comfortable than surface stimulation. Furthermore, this work provided insight into the properties of sensory feedback for practical applications and addressed the specific advantages of each stimulation modality, which may be used in future studies on sensory feedback design.

DANSK RESUME

Manglen på nervefeedback er en forhindring der begrænser brugen af proteser. Muligheden for anvendelse af direkte nerve stimulation via implanterede elektroder i perifere nerver, i rygmarven eller i hjernen til levering af sensorisk feedback, har været undersøgt. Ved disse teknikker er et kirurgisk indgreb uundgåeligt for at få placeret elektroderne inde i kroppen. Ikke-invasiv overflade stimulation har også været undersøgt som en alternativ mulighed, men denne teknik er sårbar overfor variabilitet idet at elektroderne skal dagligt skal sættes på og tages af huden. I modsætning til de nævnte teknikker er brugen af elektroder placeret lige under hudens overflade ('subdermal') mindre invasiv, og man mener at denne form for elektroder til levering af sensorisk feedback kan væsentligt nedsætte det nødvendige energi-forbrug og samtidigt føles mere behagelig under stimulationen. Men stabiliteten og variabiliteten af sensorisk feedback leveret via 'subdermal' stimulation over tid har ikke været systematisk undersøgt. I denne phd afhandling var hypotesen derfor at sensorisk feedback leveret via 'subdermal' elektroder kan opnå en bedre stabilitet målt via psykofysiske mål og via brug i lukket-sløjfe kontrol systemer over tid ift. sensorisk feedback leveret via overflade elektroder.

Fire studier blev gennemført for at teste denne hypotese. Studie I sammenlignede psykofysiske egenskaber af overflade og 'subdermal' stimulation ved forskellige intensiteter og frekvenser (20 og 100 Hz). Studie II og Studie III testede stabiliteten af den elektriske stimulation leveret med overflade og 'subdermal' stimulation over tid (8t og 7 dage) i både raske forsøgspersoner og hos amputerede. Stuide IV testede funktionaliteten af sensorisk feedack leveret via overflade og 'subdermal' stimulation i lukket-sløjfe kontrol system tests.

Resultaterne viste at 'subdermal' stimulation er en mere levedygtig tilgang til at levere sensorisk feedback end overflade stimulation til amputerede i fremtiden, i det at 'subdermal' kan generere den samme stabilitet og performance i lukket-sløjfe kontrol system tests over tid. Derudover kræver 'subdermal' stimulation mindre energi og føles mere behagelig. Arbejdet i denne afhandling frembragte nye oplysninger om egenskaberne ved sensorisk feedback i applikationer og de specifikke fordele for hver stimulations teknik som kan bruges i fremtidige studier med fokus på sensorisk feedback design.

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Finally, I am especially grateful to my wife Wei Liu for her patience and endless support and to my parents and parents-in-law, who supported me without any complaint. This thesis is dedicated to my lovely son, Louie Dong, whose arrival motivated me to complete my Ph.D. work.

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ABBREVIATIONS

ACRONYM	**ABBREVIATION**
DT	Detection threshold
PT	Pain threshold
DR	Dynamic range
JND	Just noticeable difference
WF	Weber fraction
CORR	Correlation of coefficient
RMSE	Root mean square error
TD	Time delay
CoV	Coefficient of variation
EMG	Electromyography
TIME	Transversal intrafascicular multichannel electrode
LIFE	Longitudinal intrafascicular electrode
USEA	Utah slanted electrode array
FINE	Flat interface nerve electrode
CWRU	Case Western Reserve University

1. INTRODUCTION

In 2005, an estimated 1.6 million amputees were living without an upper or a lower limb in the United States. The number of people with limb loss was speculated to rise to 3.6 million by the year 2050 (Ziegler-Graham et al., 2008). The main reason for amputation is vascular diseases, followed by, trauma, malignancy of the bone and joints, and congenital limb deficiency (Dillingham et al., 2002).

A devastating impairment on quality of life is often followed by limb loss, and the affected persons' physical, psychological, and vocational aspects are challenged (Graczyk et al., 2018b). Basic social activities such as greeting, grooming, artistic expression, and syntactical communication cease to exist, thereby requiring tremendous psychological support and physical recovery. Artificial prosthesis was invented and employed to manage limb loss throughout history; this is the earliest recorded solution in the Vedas a Indian book written in Sanskrit dated from 3500 to 1800 BC, which state that Queen Vishpla wore an iron leg to walk and return to the battlefield (Grimmer & Seyfarth, 2014). A prosthesis is defined as an artificial device that replaces a missing body part and further restores the lost motor and sensory function of the amputated limb, which could presumably improve the quality of life of the amputee.

The anthropomorphic and most advanced prostheses that can mimic functions of real hands have been developed in the past decade (Johannes et al., 2011). However, lack of sensory feedback is an obstacle that limits the users' clinical acceptance of such prostheses (Li et al., 2015; Saal & Bensmaia, 2015); this is a challenge in current commercially available prostheses (Graczyk et al., 2018b). Consequently, only visual and audio cues are available to supplement feedback information to the user. However, visual and audio feedback alone are insufficient to provide the required information (exteroceptive and proprioception information) during hand grasps and manipulations. Tactile feedback can provide the supplementary information (exteroceptive and proprioception information) to the amputees. Integration of sensory feedback in a closed sensory-motor loop could substantially enhance the accuracy of motor control and embodiment of bionic hands (Saal & Bensmaia, 2015). To this aim, the sensor data extracted from prostheses could be encoded via neural stimulation and transferred to the central nervous system to communicate the prostheses' state information (Figure 1) (Grimmer & Seyfarth, 2014). Furthermore, this specific approach could also be used in rehabilitating motor control and somatosensations in amputees (Saal & Bensmaia, 2015). The approach can be described as a sensory substitution system (Kaczmarek et al., 1991), comprising a sensor for collecting the information (e.g., size, weight, and texture) of the touched/grasped object, a coupling system for translating the information into electric signals, and a stimulator for transferring the electric signals to perceptual organs in the skin, peripheral nerves, or central nervous system. For instance, the amputee subject could obtain the extent of prehensor opening or the magnitude of the grasp force according the coded electric signals (electrical pulse trains) (Riso, 1999). In (Clemente et al., 2016), grasp force control and motor coordination were systematically improved by transfering electric signals through intrafascicular electrodes implanted into the subject's median and ulnar nerves; in (Tan et al., 2014), long-term stable natural touch sensations were obtained and the functional performance (pulling the stem of a cherry without crushing it) was improved by transferring electric signals through cuff electrodes implanted on the subject's median, ulnar, and radial nerves.

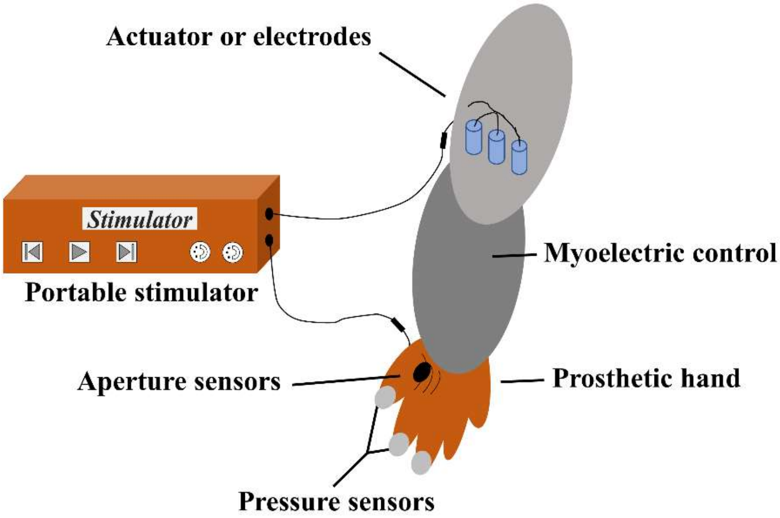

Figure 1 Components of a prosthesis equipped with sensory feedback.

In general, mechanical or electrical stimulation are available to provide sensory feedback (Antfolk et al., 2010; Dhillon & Horch, 2005; Kaczmarek et al., 1991) to amputees. In the case of electrical stimulation, the elicited tactile sensations can be adjusted within the dynamic range by modulating the stimulation parameters, without wearing bulky components (e.g., actuators) needed for mechanical stimulation. Surface electrodes (non-invasive), subdermal electrodes (minimally invasive), cuff electrodes (invasive), intrafascicular electrodes (invasive), or intracortical electrodes (invasive) (Bensmaia & Miller, 2014) can be used for providing electrical sensory feedback. The intracortical electrode, peripheral nerve cuff electrode, and intrafascicular electrode were not explored in this thesis owing to their invasive nature, which may not be acceptable to all patients (Benz et al., 2016; Li et al., 2015). Therefore, the subdermal electrode (minimally invasive) and surface electrode (non-invasive) were selected as the main topics in the current thesis. A minimally invasive operation is defined as a medical operation or procedure with less tissue damage than open surgery or a small incision together with less pain and complications (Jin et al., 2019; Scriba et al., 2013). In addition, subdermal stimulation may be an interesting approach for providing sensory feedback compared with surface stimulation, as it produces similar sensations (Geng et al., 2018) using a lower current to activate the neuronal membranes, thereby optimizing energy consumption (Polasek et al., 2009). Moreover, although surface electrode stimulation has been explored for providing sensory feedback in previous studies (Kaczmarek et al., 1991; Szeto & Saunders, 1982), the usability (e.g., stability across time and closed-loop control) of surface and subdermal stimulation has not been systematically explored to the best of our knowledge.

Furthermore, psychophysical assessment was employed in this thesis, as it is a method that can be used to assess sensations and perceptions in addition to evaluating the subject's ability for detecting a stimulus or invariably discriminating between similar stimuli (Dagnelie, 2008).

The focus of this Ph.D. thesis was to investigate a novel method for delivering sensory feedback through psychophysical assessments, centered on subdermal electrical stimulation, and compare it to surface electrical stimulation.

2. STATE-OF-THE-ART

2.1. BACKGROUND OF ELECTRICAL-STIMULATION-INDUCED SOMATIC SENSATIONS

2.1.1. TYPE OF SOMATIC SENSATIONS FOR RESTORING PROSTHETIC CONTROL

Two subsystems are involved in the human somatic sensory system: mediating the sense of touch using receptors in the skin and mediating the proprioception (the sense of limb position and movement) using receptors in muscles, tendons, and joints (Barha et al., 2016). Under physiological conditions, information regarding the shape, size, and texture of grasped objects and the slipping of objects can be transmitted in the form of somatic sensations (touch and proprioception) to our brain (Johansson & Flanagan, 2009). These sensations (sensory feedback) do not exist in amputees. The lack of sensory feedback has been cited as a challenging aspect in current commercially available prostheses (Graczyk et al., 2018b). Therefore, the restoration of somatic sensations in amputees is crucial to improve the performance of a prosthesis (Johansson & Flanagan, 2009).

In general, electrical feedback (e.g., that provided by a surface electrode), vibration feedback (e.g., that provided by vibration motors), and mechanical feedback (e.g., that provided by force and torque applicators) can be applied on the skin of the residual limb to provide somatic sensations in a non-invasive manner. The relative information of touch (contact), hand aperture, hand rotation, and grasping force can be converted into electric siginals, and these signals can be conveyed to the skin through electrical or mechanical stimulation (Markovic et al., 2018). The messages regarding grasping force and hand aperture have been described as major feedback by myoelectric prosthesis users (Peerdeman et al., 2011). This information can be delivered by tactors and/or coin motors placed on the skin, and improvement in grasping performance has been reported in the relevant literature (Muijzer-Witteveen et al., 2015).

2.1.2. SENSATIONS INDUCED BY ELECTRICAL STIMULATION

A comprehensive study using electrocutaneous stimulation on human sensory nerves reported that evoked sensations include vibrating, pricking, or stinging and can vary in intensity from just perceivable to extremely painful (Adrian, 1919). The electrical properties, the electrode, and the state of the skin under the electrode are all parameters that can affect the quality and intensity of the evoked sensations. Pulse amplitude (Adrian, 1919), pulse duration, and pulse frequency are the three primary influencing factors on perceptual sensation induced via electrical stimulation (Jelinek & McIntyre, 2010). Painless sensations such as tingling, itching, vibration, buzzing, touch, pressure, and pinching are caused when the currents are increased just up to the perception threshold, whereas sharp stinging sensations and burning are caused when higher currents are applied (Garnsworthy et al., 1988; Kaczmarek et al., 1991; Robert, 1982). Based on different frequencies, warmth can be induced by direct current (dc) without muscle contractions, whereas unpleasant tingling/prickling sensations with muscle contractions can be induced using low-frequency AC current (Dalziel & Mansfield, 1950; Katims et al., 1987; Prausnitz, 1996). However, to the best of our knowledge, specific sensations (e.g., warmth and hardness) are yet to be used for providing sensory feedback in the current prosthesis system. Such specific sensations are presumed to enrich the content of feedback sensations (compared to touch and hand aperture only) and provide motivation for using prostheses.

2.1.3. ELECTRODES FOR PROVIDING ELECTRICAL STIMULATION

Transcutaneous electrical stimulation is one way of providing sensory feedback that has been used in physical therapy or prostheses by activating excitable tissue using surface electrodes or other forms of electrodes. At the least, a pair of electrodes is needed to generate a potential gradient electrical current (Keller & Kuhn, 2008). Note that electrical impedance should be considered when implementing transcutaneous electrical stimulation; this impedance comprises two parts: the impedance of the tissue between the two electrodes and the impedance of the skin directly under the electrode (Pfeiffer, 1968). Under the condition of applying a smaller stimulating electrode in addition to a larger "neutral" electrode, the located stimulus effect near the smaller electrode is induced by the higher current density of the stimulating electrode (Pfeiffer, 1968).

Different types of electrodes have been tried/used for providing sensory feedback. The invasive intraneural electrode (Davis et al., 2016; Oddo et al., 2016; Raspopovic et al., 2014; Valle et al., 2018) and cuff electrode (Ortiz-Catalan et al., 2014; Tan et al., 2014), minimally invasive (Geng et al., 2018; Riso et al., 1989; Riso et al., 1991), and non-invasive electrodes (Chai et al., 2015; D'Anna et al., 2017; Dosen et al., 2017; Kaczmarek et al., 1991) (Table 1) have been used to successfully regain tactile feedback in upper limb amputees; however, only preliminary invasive studies have been conducted to restore proprioceptive feedback with the results exhibiting only limited functional benefits (Dhillon & Horch, 2005; Horch et al., 2011; Pistohl et al., 2015; Schiefer et al., 2016).

Table 1 Invasive, minimally invasive, and non-invasive electrodes for providing sensory feedback

	Modalities	Location	Longevity	Products
Invasive	Intraneural electrode	Transverse intrafascicular or longitudinal intrafascicular electrodes (e.g., ulnar or radial nerve)	30 days to 7 months	TIME, LIFE, USEA
	Cuff electrode	Encircle nerves (e.g., median or ulnar)	Up to 10.4 years	FINE, CWRU spiral electrode

Minimally invasive	Subdermal electrode	Underneath the skin	Months to years	Wire electrode, disk electrode
Non-invasive	Surface electrode	Surface of the targeted skin (e.g., forearm skin)	Disposable	Ambu 700

TIME: Transversal intrafascicular multichannel electrode; LIFE: Longitudinal intrafascicular electrode; USEA: Utah slanted electrode array; FINE: Flat interface nerve electrode; CWRU: Case Western Reserve University (spiral nerve cuff electrode); and Ambu 700: Self Adhesive Surface Electrode.

Intraneural electrodes contain transverse intrafascicular and longitudinal intrafascicular electrodes. Transversal intrafascicular multichannel electrode (TIME) (Boretius et al., 2010) and Utah slanted electrode array (USEA) are the two representatives of transverse intrafascicular electrodes. TIME (Figure 2A) was developed by (Boretius et al., 2010) and designed to traverse the targeted nerve fascicles. A strip-like, folded polyimide substrate mounted with several aligned platinum electrodes was threaded through the fascicles using a needle. TIME has been threaded into the ulnar nerve to provide sensory feedback for controlling a prosthesis (Raspopovic et al., 2014). USEA (Figure 2B) was developed based on the Utah electrode array with electrodes of different lengths enabling the electrodes to reach most of the fascicles (Branner et al., 2001). Furthermore, multiple percepts (sensory feedback) were evoked for improving the control of sophisticated prosthesis by implanting microelectrode arrays (e.g., USEA) into transradial amputees' median or ulnar nerve over one month (Davis et al., 2016).

The longitudinal intrafascicular electrode (LIFE) (Figure 2C) used a wire with Teflon or metalized Kevlar fiber-coated for insulation and one to several contact sites along the wire for recording signals or stimulating the nerve fibers (Lefurge et al., 1991). The wire was threaded into the nerve along with the targeted fascicle guided by a round needle. An electrode named the distributed intrafascicular multi-electrode (DIME) comprising six LIFEs has been developed for successfully recording or stimulating various nerve fibers (Thota et al., 2015).

The cuff electrode was designed to encircle the nerve for non-invasive nerve recording or stimulation. The Flat interface nerve electrode (FINE) and Case Western Reserve University (CWRU) electrode (spiral nerve cuff electrode) are the two most known cuff electrodes. FINE (Figure 2D) was designed as a flat tunnel to flatten the nerve, enabling larger area of contact to the nerve fascicles (Tyler & Durand, 2003). Spatial resolution can be improved through different methods based on this design (Wodlinger & Durand, 2009; Yoo & Durand, 2005). CWRU (Figure 2E), the spiral nerve cuff electrode, comprises several electrodes embedded within a self-curling sheath. CWRU was designed to be self-sizing to encircle the target nerve post implantation using the self-curling sheath composed of biocompatible materials (Naples et al., 1988). The spiral nerve cuff electrode was reported to be functional for stimulating peripheral nerves up to 11 years post-implantation without serious adverse effects and medical complications (Christie et al., 2017).

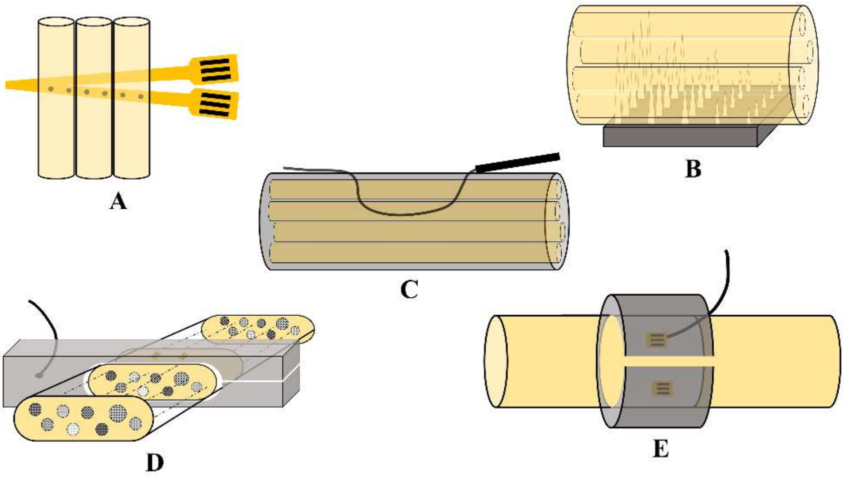

Figure 2 Schematic of invasive electrodes with target nerves. A, TIME; B, USEA; C, LIFE; D, FINE; E, CWRU.

2.1.4. TYPES OF SUBDERMAL ELECTRODES

Subdermal electrodes were developed including wire electrodes (Anani et al., 1977; Scharf et al., 1973), coiled wired electrodes (Riso et al., 1991), and subdermal disk electrodes (Riso et al., 1991). A subdermal electrode composed of Ag-Ag/Cl has been verified to remain implanted in the skin over days and weeks for intensive care unit monitoring (Ives, 2005) without any side effects e.g., infections. Moreover the safety of stainless-steel coiled wire electrode when left in place for several months to years has been ascertained (Riso et al., 1991).

2.2. PSYCHOPHYSICS FOR EVALUATING INDUCED SENSATIONS

The scientific approach to explore the relationship between stimulus and sensation is called psychophysics (Gescheider, 1997a). This study has been defined as the assessment of the relationship between sensations in the psychological domain and stimuli in the physical domain after the publication of Fechner's *Elements of Psychophysics*. The core of psychophysics is the concept of a sensory threshold that constitutes both an absolute threshold or detection threshold (DT) and difference threshold. DT was defined as the stimulus value at which 50% trials (stimuli) can be detected by the subject and the difference threshold was defined as the units of stimulus that changed to produce a just noticeable difference (JND) sensation. In addition, sensations can be generally described by intensity, quality, extension (location), and duration having four dimensions: with cutaneous sensation, the dimension of quality may be characterized by pain, warmth, or itching, and the dimension of location may be local, radiating, or referred. A local location implies that the sensation just appeared on the stimulation site of the skin, a radiating location implies that the sensation spreads out from the stimulation site to nearby sites of the skin, and a referred location implies that the sensation appeared at a non-stimulated site on the skin.

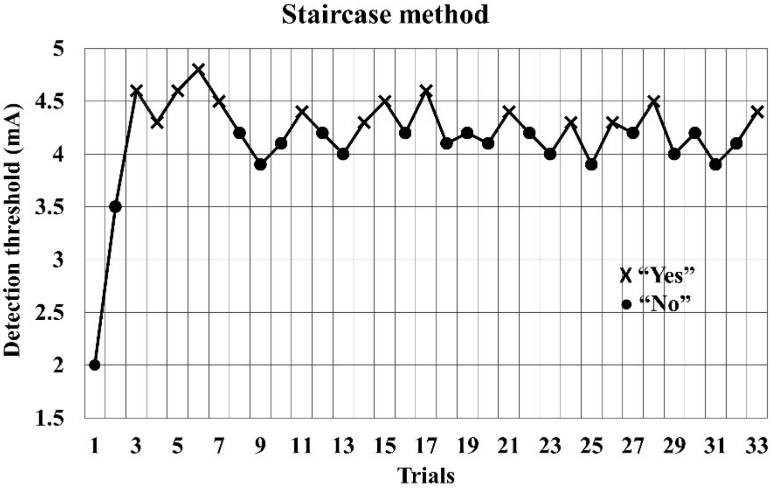

Figure 3 Illustration of the staircase method. Data from one detection threshold determination of our experiment.

Classical psychophysical methods of threshold measurement involve the method of constant stimuli, the method of limits (up-and-down or the staircase method and the forced-choice method), and the method of adjustment (Gescheider, 1997b). The method of constant stimuli is the procedure of randomly applying a group of stimuli (typically of 5-9 different intensities) in the experiment with each stimulus presented more than 100 times. The lowest intensity is not detected, and the highest intensity is detected by the subject most times. Then, the success rate in detecting are recorded and plotted as a psychometric function. The threshold is finally estimated at the 0.5-point (50% success rate in detecting the stimulus) level of the psychometric function. The method of limits involves sending a series of ascending or descending stimuli around the threshold. The subject is asked to report whether he/she perceived the ascending stimuli to decrease compared to the reference stimulus and vice versa. The values of the stimulus at the answers of shifts (from yes to no or from decreasing to increasing and vice versa) are collected and averaged as the threshold. There are two variations of the method of limits called the up-and-down or staircase method (Figure 3) and the forced-choice method. The staircase method involves sending a set of stimuli with the intensity of which increases or decreases in steps. The subject is asked to answer whether he/she perceived the stimulus using the answers "yes" or "no." The stimulus increases by one step if the answer is "no" and vice versa. The value at which the answer shifts is recorded, and then the average of all the values at the shifts is considered the threshold. The forced-choice method involves sending several specific observations containing only one correct answer. The subject is asked to select the correct answer. The method of adjustment involves setting the stimulus' intensity considerably higher or lower than the threshold. Then, the subject is asked to reduce the stimulus' intensity to start disappearing or to improve the intensity to start presenting.

The method of limits is an efficient measurement approach (less stimuli is applied in this method than other psychophysical methods) that typically provides sufficient results under proper control. For instance, in the staircase method, except the first few stimuli, the following stimuli are quite near the "real threshold" (Cornsweet, 1962) and every stimulus contributes to the final calculation of the "real-threshold". Furthermore, the staircase method is used more extensively owing to its lesser time consumption compared to the method of constant stimuli, even though it is less precise than the method of constant stimuli. In the method of adjustment, the delivered stimuli are ambiguous and are thus less clear compared to the stimuli used in the staircase method. However, note that the subject is aware of the staircase procedure along with time, even when it does not happen in the beginning. The forced-choice method has always been believed to provide robust measurements compared to others. However, considering the time constraints in our experiment combined with several trials in each session, the staircase method was used in the experiments conducted herein.

Finally, some limitations of psychophysics have been considered, e.g., i. psychophysics rarely explains the mechanism of behavioral outputs controlled by motor systems; and ii. the subject's motivation is definitely omitted in "forced choice" designs, resulting in forced answers of yes or no, thereby dismissing the qualitative nature of human perception (Read, 2014).

2.3. ASSESSMENT OF PROSTHESIS PERFORMANCE AND ACCEPTANCE

With regards to the performance of the prostheses, the reduced performance time and improved performance accuracy (Schiefer et al., 2016) on finishing a task are the two major aspects for performance evaluation (Latash, 2012; Raveh et al., 2018a; Raveh et al., 2018b). Better performance improves the confidence and embodiment of the amputee when using the prostheses (Schiefer et al., 2016), which further improves the acceptance of the prostheses. The users' feedback is also important as it indicates clinical acceptance (Li et al., 2015) of the prostheses for long-term use. This clinical acceptance may improve if the prosthesis provides intuitive sensory feedback (improvement in accuracy), in terms of the prosthesis being light, comfortable, and convenient for daily use (Biddiss & Chau, 2007). As stated by (Benz & Civillico, 2017), users wish to have lightweight prostheses to decrease fatigue of the arm, shoulder, and back. The difficulty in performing precise hand or finger movements is also becoming a concern (Benz & Civillico, 2017). In addition to fatigue, power consumption should be considered in the case of transradial prostheses, as enough power should be available for a whole day's use without any recharge (Cipriani et al., 2010). A survey conducted by (Peerdeman et al., 2011) analyzed user-centric needs of prostheses based on a workshop and literature review. In that workshop, a multidisciplinary group contributed their perspectives on developing user-acceptable prostheses. Five points were highlighted therein: 1) providing continuous and proportional feedback; 2) providing position feedback; 3) providing interpretable stimulation (feedback) in an easy and intuitive manner; 4) providing unobtrusive feedback for both the wearer and others; and 5) providing adjustable feedback.

3. OUTLINE OF THE PH.D. WORK

Millions of amputees are living without upper or lower limbs and the quality of their life is profoundly affected by the limb loss in terms of the individual's physical, psychological, and vocational aspects. Naturally performing common daily tasks has been facilitated through the use of modern scientific technology, i.e., sophisticated myoelectric prostheses, such as the Michelangelo hand which comprises flexible thumb, index and middle fingers, and the Bebionic hand which comprises an individual motor in each finger that can move and grasp in a coordinated manner (Kashef et al., 2020). However, the prostheses mentioned above either lack sensory feedback or the amputee is excluded from the sensory feedback closed-loop, which are drawbacks of modern prostheses. Adding sensory feedback in a closed sensory-motor control is believed to substantially enhance the accuracy of motor control and embodiment of the prostheses.

Electrical stimulation has been proposed as a possible method of providing such sensory feedback to amputees (Isaković et al., 2016). Apart from the invasive approaches (Bensmaia & Miller, 2014), surface and subdermal electrical stimulation may be more accepted by amputees owing to their non-invasive or minimally invasive nature. However, surface stimulation has some disadvantages (the frequent reapplication of electrodes, inconsistent evoked sensations, and unpleasant sensations), because of which subdermal stimulation was selected and accessed for providing sensory feedback in this thesis compared to surface stimulation.

Specifically, the usability (e.g., stability across time and closed-loop control) of surface and subdermal stimulation as sensory feedback was compared and assessed through psychophysical measurements and their performance in closed-loop control system.

3.1. HYPOTHESIS

The present work hypothesizes that sensory feedback evoked via subdermal electrical stimulation may have better stability over time (owning to less repositioning error) as evaluated through psychophysical measurements and closed-loop control system performance, when compared with sensory feedback delivered through surface stimulation.

3.2. SPECIFIC RESEARCH QUESTIONS

To address the above-mentioned hypothesis, three specific research questions were formulated.

1. How different are sensory perceptions evoked through subdermal stimulation from those evoked via surface stimulation?

2. How stable are the sensations induced via subdermal stimulation compared to those induced via surface stimulation over time?

3. How does sensory feedback delivered through subdermal stimulation and surface stimulation influence the subject's performance in a real-time closed-loop system?

Four studies were then designed and conducted to address the above stated questions.

Study I assessed perceptual properties through psychophysical measurements of subdermal stimulation in comparison to surface stimulation.

Studies II and III explored the repeatability and variability of psychophysical measurements of subdermal stimulation during varying time periods (8 h and 7 days) in both healthy and amputee subjects. Finally, in **Study IV**, a closed-loop online tracking system was formulated as the ultimate goal is to use surface or subdermal stimulation as sensory feedback in a real closed-loop prosthesis with amputees.

The work conducted herein has resulted in the following four publications and manuscripts.

Study I

Published in IEEE Transactions on Neural Systems and Rehabilitation Engineering:
"**Psychophysical evaluation of subdermal electrical stimulation in relation to prosthesis sensory feedback**."
Geng, Bo[1]; Dong, Jian[1]; Jensen, Winnie[1]; Dosen, Strahinja[1]; Farina, Dario[2]; Kamavuako, Ernest Nlandu[3]
1. Center for Sensory-Motor Interaction, Department of Health Science and Technology, Aalborg University, 9220 Aalborg, Denmark
2. Department of Bioengineering, Imperial College London, London SW7 2AZ, U.K.
3. Centre for Robotics Research, Department of Informatics, King's College London, London WC2R 2LS, U.K.

Study II
Submitted to the Journal of IEEE Access:
"**The short-term repeatability of subdermal electrical stimulation for sensory feedback**."
Dong, Jian[1]; Kamavuako, Ernest Nlandu[2]; Dosen, Strahinja[1]; Jensen, Winnie[1]; Geng, Bo[1]
1. Center for Sensory-Motor Interaction, Department of Health Science and Technology, Aalborg University, 9220 Aalborg, Denmark
2. Centre for Robotics Research, Department of Informatics, King's College London, London WC2R 2LS, U.K.

Study III

Published in IEEE Transactions on Neural Systems and Rehabilitation Engineering:
"**The variability of psychophysical parameters in surface and subdermal stimulation: A multiday study in amputees.**"

Dong, Jian[1], Geng, Bo[1], Niazi, Imran Khan[2], Amjad, Imran[3], Dosen, Strahinja[1], Jensen, Winnie[1], Kamavuako, Ernest Nlandu[4]

1. Center for Sensory-Motor Interaction, Department of Health Science and Technology, Aalborg University, 9220 Aalborg, Denmark
2. New Zealand College of Chiropractic, 1060 Auckland, New Zealand
3. Riphah College of Rehabilitation Sciences, Riphah International University, H-8/2 Islamabad, Pakistan
4. Centre for Robotics Research, Department of Informatics, King's College London, London WC2R 2LS, U.K.

Study IV

Under preparation, to be submitted to Frontiers in Neuroscience:
"**Performance of surface and subdermal stimulation feedback in online closed-loop control**."

Dong, Jian[1]; Geng, Bo[1]; Jensen, Winnie[1]; Kamavuako, Ernest Nlandu[2]; Dosen, Strahinja[1].

1. Center for Sensory-Motor Interaction, Department of Health Science and Technology, Aalborg University, 9220 Aalborg, Denmark
2. Centre for Robotics Research, Department of Informatics, King's College London, London WC2R 2LS, U.K.

4. METHODOLOGICAL APPROACH

A summary of the methodological approaches applied in each study is provided in Table 2.

Table 2 Methodological approaches

	Study I	Study II	Study III	Study IV
Subjects	16 healthy subjects	14 healthy subjects	8 upper-limb amputees	8 healthy subjects
Electrodes	Ambu Neuroline 700 surface electrode; Fine-wire subdermal electrode	Ambu Neuroline 700 surface electrode; Fine-wire subdermal electrode	Ambu Neuroline 700 surface electrode; Fine-wire subdermal electrode	Ambu Neuroline 700 surface electrode; Fine-wire subdermal electrode
Stimulation sites	Ventral and dorsal sides of the forearm	Dorsal side of the forearm	Dorsal side of the forearm	Ventral and dorsal sides of the forearm
Stimulation parameters	Symmetric, biphasic, rectangular waveform Pulse width of 200 µs with changing amplitude	Symmetric, biphasic, rectangular waveform Pulse width of 200 µs with changing amplitude	Symmetric, biphasic, rectangular waveform Pulse width of 200 µs with changing amplitude	Fixed stimulus amplitude Continuously changing pulse width
Test period	Instant test	3 repetitions over 8 h	7 sessions over 7 days (once per day)	8 trials with each trial lasting 90 s
Psychophysical methods	Method of limits, staircase procedure	Method of limits, staircase procedure	Method of limits, staircase procedure	Method of limits
Experimental measurements (Section 5.1-5.3)	DT, PT, PT/DT, JND, quality of sensation, intensity, comfort, and sensation location	DT, PT, PT/DT, JND, quality of sensation, intensity, comfort, and sensation location	DT, PT, PT/DT, JND, quality of sensation, intensity, comfort, and sensation location	CORR, RMSE, and TD
Data analysis	Paired t-tests or Wilcoxon signed-rank test	One-way repeated measures ANOVA or Friedman test	One-way repeated measures ANOVA or Friedman test, Coefficient of variation	Paired t-tests or Wilcoxon signed-rank test

DT: detection threshold; PT: pain threshold; PT/DT: dynamic range; JND: just noticeable difference; CORR: correlation of coefficient; RMSE: root mean square error; and TD: time delay.

4.1. SUBJECTS

Sixteen healthy subjects were recruited for **Study I**, 14 for **Study II**, and 8 for **Study IV**. All 38 subjects provided informed consent. None of the subjects experienced visible broken skin or any infections in the stimulation area. They all joined both the surface and subdermal stimulation experiments. **Studies I**, **II**, and **IV**, were approved by the North Denmark Region Committee on Health Research Ethics (N-20160021).

Nine male upper-limb amputees were recruited from the Railway General Hospital, Rawalpindi, Pakistan for **Study III.** One subject was excluded from **Study III** as the subject’s pain threshold could not be estimated even when a high stimulation amplitude was applied, and the unwanted muscle twitch was evoked. All eight amputees received both surface and subdermal stimulation. **Study III** was approved by the Ethical Committee of Riphah International University (N-ref# Riphah/RCRS/REC/000121/20012016).

4.2. ELECTRODES

Ambu Neuroline 700 (Figure 4A), a self-adhesive gelled electrode, was used in the experiments for surface stimulation. Ambu Neuroline 700 is primarily manufactured and designed for intraoperative monitoring, surface electromyography, nerve conduction studies, electronystagmography, electro-oculography, polysomnography, evoked potentials, and as a reference electrode, used for stimulating or recording in previous studies (Geng et al., 2018; Kamavuako et al., 2014). The solid gel of Ambu Neuroline 700 is soft, flexible, and can maintain comfort and electrical conductivity when placed outside the hair zone. Ambu Neuroline 700 is a Ag/AgCl electrode with a duck-foot shape for ensuring excellent adhesion. It is 20 × 15 mm in size with a lead length of 10 - 200 cm.

The fine-wire electrode (subdermal electrode, Figure 4B) was designed and manufactured in the laboratory of Aalborg University to collect electromyography (EMG) signals (Kamavuako et al., 2014) and provide sensory feedback (Geng et al., 2018) in the laboratory. Teflon-coated stainless steel (A-M Systems, Carlsborg WA, diameter 50 μm) is used for fabricating the fine-wire electrode. The stainless steel is placed in a sterile 25-gauge hypodermic needle’s tube with a 5-mm tip uninsulated for electrical conductivity and a 5-mm tip bent as a hook for electrode anchoring under the skin. The wire electrode can be inserted into the skin with the help of the hypodermic needle and the hooked tip can be fixed/secured under the skin tissue after gradually withdrawing the hypodermic needle.

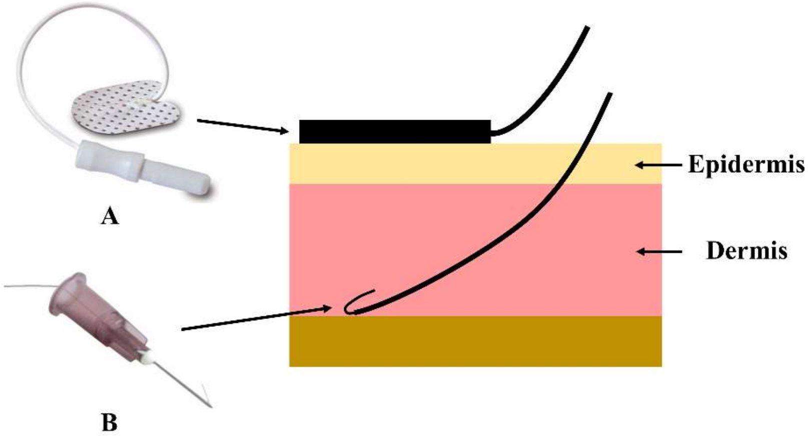

Figure 4 Surface and subdermal electrodes and their positions with respect to the dermis.

4.3. SELECTION OF STIMULATION SITE(S)

The stimulation site was chosen to be in the middle of the ventral and/or dorsal forearm because the aim of the present work was to restore sensory feedback for transradial upper-limb amputees, which constitute up to 65% of the amputated population (Esquenazi, 2015).

In **Studies I** and **IV**, stimulation was applied both to the ventral and dorsal sides of the forearm, as the aim of **Study I** was to explore the perceptual properties of the stimulation (perceptual properties are used in **Studies II** and **III**), and the ventral and dorsal sides' sensory feedback were needed by the subjects in **Study IV** to control the joystick in two directions.

In **Studies II** and **III,** only the dorsal side of the forearm was stimulated as one location was enough to evaluate the repeatability and variability of subdermal stimulation with respect to surface stimulation. Furthermore, the dorsal side was chosen because the dorsal side of the forearm exhibited a higher degree of reliability.

4.4. SELECTION OF STIMULATION PARAMETERS

A symmetric, biphasic, rectangular waveform with a pulse width of 200 µs was used as the basic waveform in **Studies I**, **II**, and **III** as this waveform has the lowest total charge compared to other commonly used waveforms (Kantor et al., 1994). Utilizing low charge influences the overall power consumption, which can minimize the electric components (e.g., battery), thus ultimately lowering the weight of the prosthesis.

The stimulation intensity was adjusted by changing the current amplitude in **Studies I**, **II**, and **III**. A frequency lower than 100 Hz was used in **Study I** as these frequencies have previously been found to be the most useful in sensory communication (Szeto et al., 1979). Based on the results of **Study I**, 20 and 100 Hz stimulation frequencies were selected and used to evaluate the repeatability and variability of sensation quality in **Studies II** and **III**. The stimulation in the first three studies was produced using a constant current stimulator (ISIS Neurostimulator, Inomed; Emmendingen, Germany). However, this stimulator was not used in **Study IV** as it cannot produce continuously changing amplitude in real-time for an online closed-loop system (**Study IV**). Therefore, another customized stimulator (TremUNA, UNASystems, Serbia, SR) was employed in which the sensation intensity was changed by the pulse width, but not the current amplitude.

4.5. TEST PERIOD

In **Study I**, the tests were instant, wherein the subjects were asked to report their sensations right after the delivery of stimulation for providing basic sensation properties induced through surface and subdermal stimulation. In **Study II**, the tests were repeated three times over 8 h to obtain the stability (repeatability) of the induced sensations via surface and subdermal stimulation. In **Study III**, the tests were repeated 7 times across 7 days to measure the stability (variability) of the evoked sensations over time via surface and subdermal stimulation. In this manner, the basic properties of the evoked sensations in **Study I** were tested and used over different time periods (8 h to 7 days in **Studies II** and **III**) by evaluating their stability, providing insight into the long-term use of the stimulation modalities in the future. In **Study IV**, the test was conducted during a 90-s closed-loop control task using a joystick to control a system while the electrotactile stimulation provided sensory feedback on the system state. The closed-loop performance of surface and subdermal stimulation feedback was compared. The ultimate goal is to use the feedback in a closed-loop prosthesis system, which is expected to improve the embodiment and confidence in using prostheses (Saal & Bensmaia, 2015).

4.6. PSYCHOPHYSICAL METHODS

The method of limits and its variation, the staircase method (Gescheider, 1997b), were used in **Studies I, II**, and **III**. The motivation and goal of using the staircase method have been stated in **Section 2.2**. To determine pain threshold (PT), the method of limits was employed. Wherein the ascending single pulse stimuli in steps of 0.3-0.8 mA for surface stimulation and 0.1-0.4 mA for subdermal stimulation were presented to the subjects from non-painful intensity, and stopped when the painful sensation was perceived. This procedure was repeated 3 times and the 3 stimulus amplitudes at the painful sensation were averaged as the PT. The staircase method was used to determine DT in **Studies I, II**, and **III**. First, the method of limits with ascending stimuli in step sizes of 0.3-3 mA for surface stimulation and 0.1-0.3 mA for subdermal stimulation were used to estimate an approximate DT before the staircase method.

Second, a lower to approximate DT stimulus was employed as the start of the staircase method. A series of ascending stimuli in steps of 0.03-0.05 mA for surface stimulation and 0.01-0.03 mA for subdermal stimulation were delivered to the subject until he/she detect the stimulus. Followed by the delivery of a goups of decending stimuli until he/she can not detect the stimulus and this sequence reversed again. The sequence continued and terminated until 10 transition-points were reached or 30 stimuli were presented. Finally, by excluding the first three transition-points, DT were estimuated as the average of stimulus amplitudes of the remaining transition-points.

4.7. EXPERIMENTAL MEASUREMENTS

The measurements of DT, PT, dynamic range (PT/DT), JND, sensation quality, intensity, comfort, and sensation location were assessed in this thesis. Note that the provided sensory feedback intensity must be neither higher over the PT, nor lower below the DT. The PT/DT was the range that the stimulus can be worked within, with a bigger PT/DT indicating that there is a larger range for modulation of sensory feedback parameters. Furthermore, JND represents the sensitivity of the sensory system toward detecting the stimulus changes, wherein a smaller JND implies a higher resolution in detecting rich sensory feedback. The sensation quality, intensity, comfort, and sensation location were assessed via a questionnaire presented after each delivered pulse train. The sensation quality included 12 words that are normally used to describe electrical stimulation, of which pleasant sensation is preferred to provide sensory feedback. In addition, low-intensity and high-comfort stimulus was demanded by the subjects. The preferred sensation location depended on the specific context of delivered feedback, e.g., local sensation was needed when touching a static object (modality-matched feedback).

4.8. CLOSED-LOOP CONTROL PERFORMANCE

The tracking performance of electrical-stimulation-induced sensory feedback, the relative absolute error, rate of correct recognition, amount of transmitted information, and delay time have been used as evaluation aspects in 1979 (Anani & Körner, 1979). In this thesis, **Study IV** was conducted to evaluate the performance of the delivered sensory feedback induced by surface and subdermal electrical stimulation in an experimental closed-loop control system. The electrical-stimulation-induced sensory feedback was to be finally employed in a closed-loop system of the prosthesis. Hence, in the study, the subjects were asked to track a moving object presented on a computer screen using a joystick, while the electroctile feedback transmitted the tracking error through the intensity of the perceived stimuli (Figure 5). The object (blue square) moved along a line following a pseudorandom multi sine wave trajectory and electrical stimulus was delivered if the object moved away from the middle of the line (the red dot) and vice versa (no stimulus was presented when the object moved to the middle). The intensity of the stimulus was proportional to the deviation of the object from the middle line. The subject was asked to move joystick so that the object remains at the middle of the line. Therefore, the subject was supposed to compensate the stimuli (i.e., to reduce the stimulation intensity), and hence the task is called compensatory tracking. Finally, the correlation coefficient (CORR), root mean square tracking error (RMSE), and time delay (TD) of the tracking (between the generated and desired trajectory) were used to evaluate the performance of the surface and subdermal electrical stimulation feedbacks. Therein, CORR assessed the shape similarities, RMSE assessed the absolute deviation, and TD assessed the time shift between the generated and desired trajectory. High CORR and low RMSE and TD indicate improved tracking performance (i.e., better control of the prosthesis).

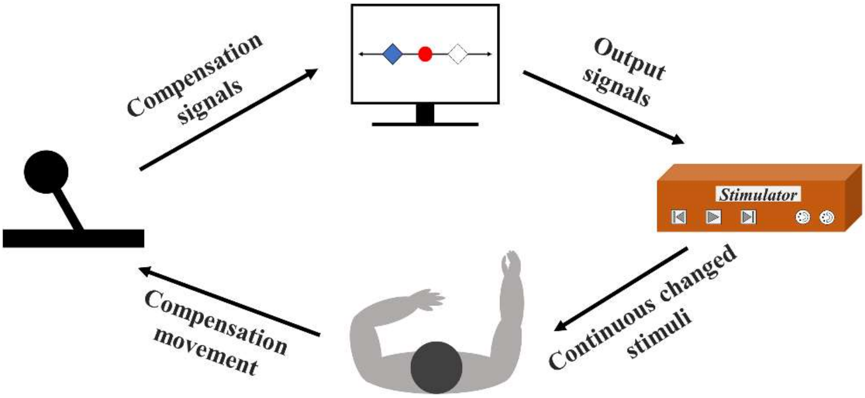

Figure 5 Experimental setup of ***Study IV****.*

4.9. DATA ANALYSIS

One-way repeated measures ANOVA (the Friedman test was performed if the data did not follow normal distribution) was used to evaluate the repeatability of the experimental measurements in **Study II** and the systematic change (the mean measurements across days) in **Study III**. The coefficient of variation (CoV) was used to evaluate the variability (intrinsic variability) of experimental measurements across the 7 days in **Study III**. With regard to the repeatability and variability in different studies, the measurements were expected to be stable across time for providing sensory feedback. Moreover, the nonsignificant difference in ANOVA was defined as stable in **Study II** and lower CoVs in the paired sample t-test was defined as stable in **Study III**.

In **Study II**, the term “repeatability” was defined to represent stability as only three sessions were performed and the CoV of the experimental measurements was unsuitable to be used; in contrast, in **Study III**, seven sessions were performed, and therefore, the term “variability” was defined to represent stability and the CoV was used. A paired t-test (Wilcoxon signed-rank test was performed if the data did not follow normal distribution) was used to compare the difference (e.g., DT and PT in

Study I, CoVs in **Study III**, and CORR and RMSE in **Study IV**) between surface and subdermal stimulation. In **Study IV**, the data was presented in CORR, RMSE, and TD as these parameters were normally used to evaluate the feedback performance in an online closed-loop system.

5. SUMMARY OF THE MAIN RESULTS

This thesis compared the usability (e.g., stability across time and performance in closed-loop control) of surface and subdermal stimulation sensory feedbacks. The overview of the aims, methods and main findings of the four studies are presented in Table 3:

Table 3 Overview of the aims and main findings of the four studies

	Aim	Methods	Main findings
Study I	To investigate the perceptual properties of subdermal and surface stimulation for inducing sensory feedback	Psychophysical measurements	1. Subdermal stimulation had a large PT/DT (dynamic range), low JND, and was more comfortable than surface stimulation (e.g., at 100 Hz of the ventral forearm). 2. Surface stimulation induced more "muscle twitch" and "movement."
Study II	To explore the repeatability (Section 4.9) of sensory feedback applied through subdermal and surface stimulation	Psychophysical measurements 8 h	1. Subdermal stimulation created more repeatable DT, induced less "muscle twitch," "movement," and "referred" sensation than surface stimulation. 2. Surface stimulation induced repeatable PT and WF.
Study III	To study the variation of psychophysical measurements of subdermal and surface stimulation	Psychophysical measurements 7 days	1. Surface stimulation induced less variation for DT, PT, DR, and intensity (at 100 Hz). 2. Systematic change was only found for PT in both surface and subdermal stimulation.
Study IV	To analyze the performance of inducing sensory feedback through subdermal and surface stimulation in a closed-loop control system	Closed-loop control Change in CORR, RMSE, and TD	1. Subdermal stimulation showed a training effect. 2. The performance of surface stimulation was better than subdermal stimulation as it owned a higher CORR and lower RMSE.

DT: detection threshold; PT: pain threshold; PT/DT: dynamic range; JND: just noticeable difference; CORR: correlation of coefficient; RMSE: root mean square error; and TD: time delay.

5.1. STUDY I: PSYCHOPHYSICAL EVALUATION OF SUBDERMAL ELECTRICAL STIMULATION IN RELATION TO PROSTHESIS SENSORY FEEDBACK

Study I investigated the perceptual properties of subdermal stimulation with respect to the surface stimulation (contribution to addressing **Research question 1** of the present thesis). Specifically, the perceptual properties of surface and subdermal stimulation related to sensory feedback of prostheses were studied in healthy subjects on both ventral and dorsal forearms. The measurements included DT, PT, JND, and induced sensation quality, comfort, intensity, and sensation location.

The results showed that subdermal stimulation induced low DT and PT, high PT/DT, and a small JND. The low DT and PT of subdermal stimulation means that low electric current is needed to produce the sensory feedback, and therefore, the electric elements within the prosthesis can be produced with light weight. **Study I** identified that subdermal stimulation could produce similar sensation quality as surface stimulation and superior energy efficiency. In contrast, surface stimulation induced more frequent "muscle twitches" and "movements" at high frequencies (100 Hz) than subdermal stimulation and the "pinprick" sensation was induced more frequently in subdermal stimulation than surface stimulation. Furthermore, single-pulse surface stimulation induced higher intensity on the dorsal forearm at thrice the DT and less comfort on the ventral forearm at 100 Hz.

The results agreed with the hypothesis (**Research question 1**) and encouraged us to conduct **Studies II** and **III** (evaluation of stability across time).

5.2. STUDY II: THE SHORT-TERM REPEATABILITY OF SUBDERMAL ELECTRICAL STIMULATION FOR SENSORY FEEDBACK

Study II evaluated the repeatability of experimental measurements (similar to **Study I**) in 8 h (contribution to address **Research question 2** of the present thesis), as the consistency and repeatability (stated in section 4.9) of the evoked sensation by external stimulation is the basis of the prostheses' use with sensory feedback (Zhang et al., 2007). Frequencies of 20 and 100 Hz were applied in **Studies I** and **II** because frequencies lower than 100 Hz have been previously shown to be more useful in sensory communication (Szeto et al., 1979) and these frequencies were identified to produce more reliable sensations (Dong et al., 2017).

The results showed that subdermal stimulation elicited more stable (stated in section 4.9) DT, maybe due to the fact that the impedance of the electrode-skin interface for the surface electrode changed during the time of placement because of gel impregnation and sweating. In contrast, surface stimulation elicited more stable PT and JND than subdermal stimulation, implying that calibration should be performed with subdermal stimulation before using the prostheses. The other measurements such as DR, resolution, sensation modality, intensity, and comfort were found to remain constant over time for both surface and subdermal stimulation. Subdermal stimulation was found to induce more comfortable sensations, better localization (less induced referred sensations), and fewer unwanted sensations (e.g., muscle twitch and movement).

The results of **Study II** demonstrate that some of the experimental measurements of surface and subdermal stimulation such as DR, resolution, sensation modalities, and intensity were stable across 8 h for the two modalities. The results neither support the hypothesis nor oppose it in terms of stability. However, subdermal stimulation was overall found to be superior to surface stimulation based on its results from **Study I** (e.g., efficient and compact way, long-term implant). Furthermore, we do not know if this tendency will also be observed in amputee subjects (the sensory feedback would finally be employed to help the amputee subjects). **Study III** was therefore conducted based on these considerations.

5.3. STUDY III: THE VARIABILITY OF PSYCHOPHYSICAL PARAMETERS IN SURFACE AND SUBDERMAL STIMULATION: A MULTIDAY STUDY IN AMPUTEES

Study III assessed the variability of experimental measurements of subdermal stimulation with respect to surface stimulation across 7 days (longer-term compared to **Study II**) with amputees (contribution to address **Research question 2** of the present thesis) as the goal was to use the feedback in the long-term for amputees. In **Study III**, the 7 days of experimental measurements (DT, PT, DR, JND, and evoked sensations) were studied for variability evaluation (CoV).

Subdermal stimulation showed more variability (intrinsic variability) in DT, PT, DR, and intensity at 100 Hz compared to surface stimulation, but without variability in other measurements (JND, quality of sensation, and location). However, no systematic change was found for the mean of any experimental measurements except PT. This may be because the amputees showed adaptation following the days of surface and subdermal stimulation (Graczyk et al., 2016; Graczyk, et al., 2018a). Therefore, a tradeoff exists between the intrinsic variability (CoV) and better usability (e.g., efficiency and compactness, long-term implant).

The limitation here is that the placement/implantation period of surface and subdermal electrodes were not the same (the surface electrode was changed each day and the subdermal electrode was implanted for 7 days), according to the practical application for surface electrode and the superior part of subdermal stimulation (long-term use).

5.4. STUDY IV: PERFORMANCE OF SURFACE AND SUBDERMAL STIMULATION FEEDBACK IN ONLINE CLOSED-LOOP CONTROL

Sensory feedback should be continuously provided as human beings continuously need to adjust their movements according to the sensory feedback to achieve any perfect action. Therefore, an online closed-loop control system (**Study IV**) (answer to **Research question 3** of the present thesis) was designed and implemented based on the results of **Studies I, II,** and **III**. The results showed that surface electrical stimulation had better performance in terms of CORR and RMSE, whereas the subdermal electrical stimulation had a training effect in RMSE. Therefore, we concluded that both surface and subdermal feedback are viable options for sensory feedback approaches as they both have their own advantages (surface stimulation performed better in CORR and RMSE, whereas subdermal stimulation showed its ability in training effect in RMSE). However, there was no difference for TD between surface and subdermal stimulation in the current study. The results of this study need to be investigated in longer-term (months or years) studies with healthy subject and amputees.

6. DISCUSSION

6.1. SUBDERMAL ELECTRODES AS AN ALTERNATIVE ROUTE FOR PROVIDING SENSORY FEEDBACK

This thesis focused on evaluating the use of subdermal stimulation in comparison to surface stimulation for providing sensory feedback in closed-loop prostheses application. Subdermal stimulation may be an interesting alternative approach for providing sensory feedback as it can produce similar sensation (Geng et al., 2018) (**Study I**) compared to surface stimulation while using lower current to activate the neuronal membranes which will be lowered the power consumption. The subdermal electrode can be implanted under the skin for a long period of time (months and even years), while the surface electrode (Ives, 2005) needs to be replaced every 12 to 24 h to maintain the impedance interface. Finally, the subdermal electrode is considered to be less invasive than a fully implanted electrode (e.g., cuff electrodes, intrafascicular electrodes, and intracortical electrodes (Bensmaia & Miller, 2014)), which may be a reason for amputees to select subdermal stimulation. Furthermore, subdermal stimulation, which uses smaller electrical fields than surface stimulation, would not interfere with the Electromyography (EMG) signals typically used for prosthesis control (Riso et al., 1989). However, even if we did not observe any side effects, such as inflammation caused by the electrodes in our four experiments, subdermal stimulation is still an invasive approach with the risk of inflammation. In addition, the maximum implant period in our studies was just 7 days, and the goal period of implantation was months or even years, which will increase the risk of infections that need to be identified in the future. In short, subdermal stimulation through a wire electrode may reproduce the lost sensation of an amputee in an efficient manner based on the results of **Study I**. Finally, this technology can be applied to other related fields for producing reading and mobility aids for the blind or tactile vocoders of deaf people.

In addition, the accuracy and repeatability of electrical sensory feedback produced by chronic subdermal electrodes should be tested further to enrich the knowledge of perceptual properties of the electrode for long-term (months and even years) application. Furthermore, stimulators embedded with an adjustable stimulation waveform and impedance monitoring have been developed to reduce the variability of the perceived sensory intensity (Cornman et al., 2017; Kajimoto et al., 2014). These stimulators are expected to be manufactured in small size, which can be seamlessly integrated into a prosthesis (Akhtar et al., 2018).

6.2. ATTACH TIME PERIOD OF THE ELECTRODES

The comparison of surface and subdermal stimulation was not actually based on the same attach time. Although we placed the surface electrode for the entire duration of the 8-h study that same with subdermal electrode (i.e., **Study II)**, the surface electrode was changed every day (each session) in **Study III**, whereas the subdermal electrodes were attached for 7-day. However, the impedance of the surface electrode likely changed owing to gel impregnation and sweating for 8 h, which was indicated by the decreasing DT during the 8 h. In contrast, the surface electrode was changed every day in **Study III** as the period of placement for the surface electrode was assumed to be from 12 to 24 h to maintain the impedance interface (Ives, 2005). Interestingly, surface stimulation showed less variation for DT and PT compared to subdermal stimulation in **Study III**. This may be because the impedance of the surface electrode did not vary as it was changed every day and therefore evoked more stable DT and PT or there were micromotions of the subdermal electrode when it was placed under the skin continuously for 7 days. In Riso's study (Riso et al., 1989), contrary to our results obtained in **Study III**, two of the three subdermal wire electrodes showed excellent stability at the current threshold during the 100 days post-implantation and the threshold pulse width of the subdermal disk electrode did not change systematically even after tissue encapsulation (in the first few weeks post-implantation). However, the subdermal electrodes were implanted in only one subject and the obtained results were not based on comparison to other types of electrodes (e.g., surface electrode).

6.3 SUBJECTS

Scientific medical research is generally performed in the order of healthy subjects and then disabled subjects (amputees). The same order was employed in this thesis. The amputees' experiment was designed and adjusted based on the results of the healthy subjects. To obtain the perceptual properties of surface and subdermal stimulation, healthy subjects were recruited for **Study I** and **II**, following which amputee subjects were recruited for **Study III** (**Section 4.1**). Finally, healthy subjects were recruited in the closed-loop study (**Study IV**) as the goal is to use the feedbacks in closed-loop prosthetic systems. The results of the healthy subjects and amputees varied, which may be due to the following reasons: 1) the different test period (**Study II** was conducted over 8 h and **Study III** was conducted over 7 days); 2) physical differences caused by the amputation (Ehde et al., 2000); and 3) psychological differences in the amputees following a period of postamputation (Gallagher & MacLachlan, 1999).

6.4. PHYSIOLOGY OF SURFACE AND SUBDERMAL STIMULATION

It has been shown that different types of nerve fibers will be activated by different electrical stimulation types (Sang et al., 2003). In general, large myelinated fibers (Aα and Aβ) will be activated first, followed by the smaller myelinated fibers (Aδ), and the unmyelinated fibers (C) (Johansson & Vallbo, 1979; Micera & Navarro, 2009). With surface stimulation, cutaneous Aδ fibers (pain-sensing) can be preferentially activated by small surface electrodes compared to Aβ fibers (touch sensing), and the stimulation site must have a thin stratum corneum (Mørch et al., 2011). In the case of subdermal stimulation, the subdermal electrode (similar size as our subdermal electrode) was relatively much bigger than the size of the nerve fibers; therefore, many cutaneous nerve fibers were activated together and sensations similar to those of surface stimulation were evoked (Riso et al., 1989). In the studies conducted in this thesis, a small surface electrode was used, and pain sensation (mediated by Aδ fibers) was not evoked as lower stimuli (lower than PT) were used in all experiments. Therefore, we assume that only Aβ fibers were activated during the surface and subdermal stimulation and possibly Aα fibers were activated in some cases, as some subjects reported muscle twitches in **Study I**. Furthermore, there are proprioceptors innervated in Aβ fibers (Johansson & Vallbo, 1979; Micera & Navarro, 2009), which can provide proprioception information to the amputee under specific coding stimulation. However, this was not explored in the present work. A better understanding of how electrical stimulation activates the different types of nerve fibers would be beneficial for interpreting our results and designing an artifical sensory feedback paradigm.

6.5. ACCEPTANCE OF THE PROSTHESIS

To the best of our knowledge, even with a highly sophisticated prosthesis, the users' clinical acceptance of the prosthesis remains low partly owing to lack of sensory feedback (Li et al., 2015; Saal & Bensmaia, 2015). Therefore, the prosthesis should provide intuitive sensory feedback, should be light, comfortable, and convenient for daily use (Biddiss & Chau, 2007).

In this thesis, subdermal stimulation was assessed and was expected to improve clinical acceptance as the electric components can be produced smaller in weight (lower current was needed to evoke sensations similar to those of surface stimulation) and as it can induce more comfortable sensations than surface stimulation (**Study I**). The light weight could substantially benefit the prostheses users in terms of minimizing the subdermal implants with only a microincision during implantation (improving the acceptance), which has been rated as an important reason for prostheses rejecters not using the prostheses (Biddiss & Chau, 2007). In addition, a wireless subdermal electrode is an option in the future for long-term implantation under the skin that could reduce the risk of infections caused by the subdermal electrode. Furthermore, surface stimulation elicited "muscle twitches" and "movements" more frequently at high frequencies (100 Hz), which can be referred to as a type of discomfort. In **Studies II, III**, and **IV**, both surface and subdermal stimulation showed advantages in terms of stability, performance, or training effect. However, subdermal stimulation was superior than surface stimulation with respect to these advantages.

6.6. SENSATION EVALUATION

The non-uncomfortable and stable (time stability) sensations were preferred for the application of sensory feedback with amputees clinically. Subdermal stimulation produced similar results in most sensation qualities compared to surface stimulation

(**Study I**), the uncomfortable sensations ("muscle twitches" and "movements") were induced more frequently at 100 Hz for surface stimulation in **Studies I** and **II.** Furthermore, the elicited sensations were more localized (less referred sensations) for subdermal stimulation (**Study II**). To this end, subdermal stimulation is more desirable for the application of sensory feedback.

With some of the induced sensations (e.g., pressure, vibration, tinging, movement, pinprick, and warmth), differences were found between surface and subdermal stimulation. We imagine that these differences can be used in different applications. For example, in the modality-matched feedback, the specific sensation can be provided to the amputee when the specific sensation is detected by the sensor, which could eventually lower the errors in the grip-force control of the myoelectric hand (Patterson & Katz, 1992). Although sensations such as vibration, pressure, tapping, pain, and tightening have been induced through USEA electrodes implanted into the median and ulnar nerves (George et al., 2019) and pulsing pressure, light moving touch, tapping, and vibration have been induced through cuff electrodes placed on the ulnar, median (FINE), and radial nerves (CWRU) (Tan et al., 2014), the modality matched-feedback using these specific sensations is still not employed. Therefore, we believe that the performance of the prothesis will improve when stable modality-matched feedback (e.g., subdermal electrical-stimulation-induced sensations) can be employed in the future.

The specific electrical stimulation parameters (e.g., frequency, duration, intensity, temporal patterns, and localization) must be selected and combined to produce specific natural perceptions (Bensmaia & Miller, 2014). Additionally, the user must have the ability to distinguish the combination of every studied sensory feedback after it is transferred to the user (Perruchoud et al., 2016). Furthermore, the optimal touch and proprioceptive signal (sensory feedback) should have the ability to mimic the proprioception occurring in natural body movements: sufficient signal information should be offered to accomplish the expected movement without requiring additional sensory inputs (Sherman et al., 1989).

7. CONCLUSIONS

Herein, electrical stimulation has been proposed as a method of providing sensory feedback to amputees suffering from sensory deficit and disabilities (limb amputations) (Riso et al., 1989). The usability of cuff electrode stimulation (Saal & Bensmaia, 2015) and intracortical stimulation (Stocking et al., 2019) (invasive approach) has been explored in the past. However, the usability of subdermal stimulation (minimally invasive) has not been extensively investigated in the literature, showing its advantages over surface stimulation (non-invasive), which has been identified in the past (Kaczmarek et al., 1991; Szeto & Saunders, 1982). Therefore, the usability of subdermal stimulation as a novel way of sensory feedback was assessed in this thesis and compared to surface stimulation. Subdermal electrical stimulation was hypothesized to be superior to surface electrical stimulation for use as a sensory feedback modality.

The experimental measurements revealed that subdermal stimulation has a larger dynamic range (PT/DT). It also produces a more comfortable sensation than surface stimulation at 100 Hz and induces relatively less “muscle twitch” and “movement,” which is not preferred when delivering sensory feedback. Surface stimulation was found to produce more repeatable results with pain threshold (PT) and Weber fraction (WF), as well as less variation with the detection threshold (DT), PT, and intensity at 100 Hz. However subdermal stimulation was found to produce more repeatable results with DT. During the online closed-loop evaluation, surface stimulation exhibited better performance with respect to the correlation of coefficient (CORR) and root mean square (RMSE). In contrast, subdermal stimulation showed a training effect in RMSE over time.

Subdermal stimulation performed better in perceptual properties (**Study I**) but generated mixed results in stability across time (**Studies II** and **III**) and the performance of closed-loop evaluation (**Study IV**). However, subdermal electrical stimulation via fine-wire electrode may be a novel route for providing sensory feedback approach based on systematic evaluation of advantages and disadvantages as the subdermal electrode can be implanted and used wirelessly through modern technology. In contrast, other feedback approaches have their own drawbacks (frequent mounting and removal of the surface electrode, invasiveness of direct peripheral nerve stimulation, and intracortical stimulation). However, the online closed-loop study of subdermal stimulation feedback in a real prosthesis during some functional tasks requires further investigation in the future.

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