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Towards Wearable Neuroprostheses for Hand Function Restoration

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Abstract

Regaining hand function is the primary demand among people with spinal cord injury. Among the interventions available, functional electrical stimulation is preferred for its ease of use and non-invasiveness. However, realizing a complete hand function is still challenging, as these systems must overcome the physiological limitations of non-invasive stimulation, including selectivity and discomfort. Hence, this thesis aims to improve the applicability of wearable stimulation systems to facilitate complex hand function tasks by addressing these limitations. Also, to improve them through electrode designs and material technologies, which can offer improved stimulation performance favoring prolonged usage.

Firstly, a scanning routine identified the motor points of flexors and extensors across the forearm. Later, a machine learning-based clustering algorithm grouped these motor points, which aided in deriving a generalized catalog that streamlined electrode placements.

Secondly, optimal stimulation parameters that elicited controlled and comfortable levels of muscle contraction were identified using isokinetic dynamometry. Additionally, the influence of stimulation-induced fatigue was assessed under tetanic contraction. By varying the stimulation parameters and the corresponding motor points of the target muscles, the likelihood of personalized digit/wrist control was demonstrated.

Furthermore, the potential for electrode designs with a simple 2D geometry having improved stimulation performance was shown using both model-based and experimental assessments.

Lastly, a conformable electrode array-based sleeve, suitable for the stimulation of forearm muscle groups was fabricated using a multi-layered screen-printing process. Herewith, the conductivity of a silicone-based elastomer was altered by the addition of carbonaceous material. Further characterization studies revealed that electrodes with an optimal ratio of
carbon black infused within these elastomers tend to maintain their stimulation performance after several stretching cycles.

By selectively eliciting digit control through motor point-based stimulation, exerting controlled digit forces by varying stimulation parameters, and synergistically activating muscle groups via distributed electrodes, the viability for realizing complex hand function tasks was demonstrated. Furthermore, this thesis also establishes the potential for improving stimulation performance by modifying the electrode geometry and the viability of fabricating a conformable electrode array-based sleeve. Ultimately, utilizing these electrode designs and advanced fabrication techniques can pave the way for comfortable and cost-effective wearable stimulation systems.

All experimental procedures in this study that involved human participants were subjected to ethical approval, which was endorsed by the University of Auckland Human Participants Ethics Committee (UoAHPEC-020096).
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Table of Contents

Acknowledgments ........................................................................................................ iii
Table of Contents ........................................................................................................ iv
List of tables ................................................................................................................ vi
List of figures ................................................................................................................. vii
List of abbreviations ..................................................................................................... ix

1. Introduction ................................................................................................................. 1
  1.1 Spinal cord injury and motor deficits ................................................................. 1
  1.2 Motivation .............................................................................................................. 3
  1.3 Objectives ............................................................................................................. 5
  1.4 Organization of thesis ......................................................................................... 9

2. Literature review .......................................................................................................... 12
  2.1 Introduction to tNMES ...................................................................................... 12
  2.2 Functional grasping using neuroprostheses ....................................................... 14
  2.3 Challenges and limitations ................................................................................ 23
  2.4 Summary ............................................................................................................. 25

3. Hand function assessment system ............................................................................. 26
  3.1 Introduction .......................................................................................................... 27
  3.2 System design and identification ........................................................................ 29
  3.3 Discussion ............................................................................................................ 33
  3.4 Summary ............................................................................................................. 34

4. Motor point cataloging ............................................................................................... 35
  4.1 Significance of motor point cataloging .............................................................. 36
  4.2 Challenges in generalizing motor point catalogs .............................................. 37
  4.3 Electrophysiological identification of motor points ......................................... 38
  4.4 Data Clustering and Analysis ............................................................................ 44
  4.5 A generalized motor point catalog ................................................................... 49
  4.6 Discussion ............................................................................................................ 59
  4.7 Summary ............................................................................................................. 62

5. Characterizing muscle stimulation ............................................................................ 63
  5.1 Significance of characterizing evoked muscle activity ...................................... 64
  5.2 Evaluating muscle contraction .......................................................................... 67
  5.3 The response of an electrically stimulated muscle ......................................... 70
List of tables

Table 2.1 Bionic glove from the University of Alberta. ................................. 17
Table 2.2 NESS H200 (Hand master) from NESS Ltd., Israel. ...................... 17
Table 2.3 OrthoJacket, a BMBF funded EU project. ................................. 18
Table 2.4 Hyper TERERE, Spanish Ministry of Science and Innovation. .. 18
Table 2.5 MUNDUS Project using RehaStim from Hasomed GmbH. ........ 19
Table 2.6 A BCI-FES system from Battelle Memorial Institute................ 19
Table 3.1 Range of motion and forces entered by hand, [121] ................. 31
Table 4.1 Metrics derived for motor point characterization ....................... 42
Table 4.2 Pseudocode for normalizing the electrode location ................. 43
Table 4.3 Pseudocode for gaussian mixture clustering of a bivariate data ... 46
Table 4.4 Maximum voluntary contraction for various muscle groups ........ 49
Table 4.5 Properties of motor point clusters for flexor muscle groups ....... 53
Table 4.6 Properties of motor point clusters for extensor muscle groups .... 54
Table 5.1 Stimulation of forearm flexors for digit and wrist control. .......... 74
Table 6.1 Properties of tissue layers ....................................................... 89
Table 6.2 Dynamics of ion channels along the Node of Ranvier ............... 93
Table I.1 Material properties of the muscle-tendon complex .................. 170
List of figures

Figure 1.1 Functions of the Spinal cord and the impact of its injury. ..................2
Figure 2.1 Transcutaneous stimulation of a muscle at its motor point. .............13
Figure 2.2 Transcutaneous stimulation for hand function restoration. ............16
Figure 2.3 Grasp synthesis with electrode array-based stimulation. ...............20
Figure 2.4 Demonstration functional grasps using neuroprostheses ...............22
Figure 3.1 Hand function assessment system ...........................................29
Figure 3.2 The sensorized glove and electrode array-based sleeve ...............30
Figure 3.3 The voltage bridge circuit-schematics for the flex sensor ..........31
Figure 3.4 [a] Current-controlled stimulator and its accessories. [b] Customizable biphasic stimulation waveform. ........................................32
Figure 4.1 Methodological identification of motor points and clustering .......39
Figure 4.2 Normalizing the electrode location based on anthropometric measures .........................................................................................43
Figure 4.3 Minimum evocable contraction for various muscle groups ..........50
Figure 4.4 Motor point clusters for flexor muscle groups ..........................51
Figure 4.5 Motor point clusters for extensor muscle groups .......................52
Figure 4.6 Stimulation zones for flexor and extensor muscle groups ..........55
Figure 4.7 Distribution of inter-electrode distances across the forearm muscles. ...............................................................56
Figure 4.8 A roll-out plot showing the displacement of motor points ..........58
Figure 5.1 [a] Strength-duration and [b] pain-duration curve for a single monophasic pulse. ...............................................................70
Figure 5.2 [a] Strength-duration and [b] pain-duration curve for a tetanic stimulation. ................................................................................71
Figure 5.3 MVIC levels for [a] twitch and [b] tetanic stimulation along with the sensation of discomfort as VAS scores normalized between 0-1 ..........72
Figure 5.4 Stimulation sites for flexor muscle groups ..................................73
Figure 5.6 [a] Demonstration of spherical grasp and [b] electrode placements. ..................................................................................76
Figure 5.7 [a] Demonstration of hook grasp and [b] electrode placements. 77
Figure 5.8 [a] Demonstration of cylindrical grasp and [b] electrode placements. .........................................................................................77
Figure 5.9  [a] Demonstration of jaw chuck and [b] electrode placements. ...... 78
Figure 5.10  [a] Demonstration of tip grasp and [b] electrode placements. ...... 78
Figure 5.11  Digit and wrist motion during [a] spherical, [b] hook, [c] cylindrical, [d] jaw chuck, and [e] tip grasp. Here, the flexion of Thumb (T), Index (I), Middle (M), Ring (R), Little (L), and wrist (W) are reported. 80
Figure 6.1  The equivalent electrical circuit for the myelinated nerve. ........ 90
Figure 6.2  Thin layer approximation for membrane currents ............... 98
Figure 6.3  Evaluation of the FE-based myelinated nerve fiber. ............. 101
Figure 6.4  Transcutaneous stimulation of motor nerve fiber ............... 102
Figure 6.5  The SDC, comparing model and experimental data. ............. 104
Figure 7.1  Electrode geometries considered ...................................... 118
Figure 7.2  Computational model for transcutaneous stimulation of motor and sensory nerve fibers ......................................................... 120
Figure 7.3  Measures of stimulation selectivity .................................... 124
Figure 7.4  Activation volume under varying electrode geometry .......... 125
Figure 7.5  Measures of stimulation comfort ....................................... 126
Figure 7.6  Measures of stimulation safety ......................................... 128
Figure 7.7  Current density distributions under the electrode surface. .... 129
Figure 8.1  Multi-layered screen printing of an electrode array sleeve. .... 140
Figure 8.2  Conductivity across different weight ratios of CB + Ecoflex .... 141
Figure 8.3  Searchability across different CB:Ecoflex ratios .................. 142
Figure 8.4  [a] Average surface thickness and [b] thickness profile obtained using Stylus Profilometry ................................................. 144
Figure 8.5  SEM images for a 1:8 weight ratio of CB:Ecoflex ............... 145
Figure 8.6  [a] Electrode array-based sleeve fabricated using multi-layered screen printing. [b] Cross-section of the sleeve showing four different layers of Ecoflex and CB+Ecoflex ................................................. 145
Figure 10.1  A framework for neuroprosthetic control of hand function .... 161
Figure I.1  Model for transcutaneous neuromuscular stimulation .......... 166
Figure I.2  Properties of the muscle-tendon complex ........................... 169
Figure I.3  Comparing of model-predicted and experimentally SDC ....... 170
Figure I.4  Muscle contraction with an increase in active stress development 171
List of abbreviations

ADL  Activities of Daily Living
AHP  Afterhyperpolarization
AV   Activation Volume
BDF  Backward Differentiation Formula
BIC  Bayesian Information Criterion
BMI  Body Mass Index
CB   Carbon Black
CE   Contractile Element
CI   Confidence Interval
CT   Computer Tomography
DAP  Depolarizing Afterpotential
DCS  Double Cable Structure
DoF  Degrees of Freedom
ECF  Extracellular Fluid
EM   Expectation-Maximization
EMG  Electromyography
FCU  Flexor Carpi Ulnaris
FE   Finite Element
FES  Functional Electrical Stimulation
GMM  Gaussian Mixture Model
IE   Index Digit Extension
IED  Inter-Electrode Distance
IER  Inter-Epicondylar Radius
IF   Index Digit Flexion
IMU  Inertial Measurement Unit
INP  Internode
ISR  Inter-Styloid Radius
JUX  Juxtaparanode
LE   Little Digit Extension
LF   Little Digit Flexion
ME  Middle Digit Extension
MEC  Minimum Evocable Contraction
MEP  Motor Entry Point
MF  Middle Digit Flexion
MRI  Magnetic Resonance Imaging
MTC  Muscle-Tendon Complex
NoR  Node of Ranvier
PAF  Peri-Axoplasmic Fluid
PD  Precision Disk
PDF  Probability Density Function
PE  Passive Element
PN  Paranode
RE  Ring Digit Extension
RF  Ring Digit Flexion
RI  Recruitment Index
ROM  Range of motion
SCI  Spinal Cord Injury
SDC  Strength Duration Curve
SSA  Small Surface Area
TE  Thumb Extension
TF  Thumb Flexion
TG  Tripod Grasp
tNMES  Transcutaneous Neuromuscular Electrical Stimulation
VAS  Visual Analog Scale
WE  Wrist Extension
WF  Wrist Flexion
WRD  Wrist Radial Deviation
WUD  Wrist Ulnar Deviation
1. Introduction

1.1 Spinal cord injury and motor deficits

The spinal cord serves its primary function as the relay center between the brain and the rest of the body. Additionally, the spinal circuits regulate autonomic function [1]. Physiologically, each section of the spinal column is associated with different body functions, Fig. 1.1. As most bodily functions depend on the spinal column, any damage to the spinal cord can be a devastating one. Spinal cord injury (SCI) obstructs normal motor function. The success of treatments with SCI is not on par with stroke; the permanent disability, along with other physiological limitations, makes SCI hard to diagnose and creates a socio-economic burden to an individual. A report by the National SCI Database (2001) reports that the burdening health cost and inability to return to work compels people with SCI to rely on federal assistance [3].

SCI has a global incidence of 10–83 cases per million people [2], with United States (40.1 per million), Estonia (35.4 per million), Japan (39.4 per million), and New Zealand (49.1 per million) showed the highest rates. The incidence of SCI in New Zealand was much higher than in Australia (14.5 per million) and Fiji (10 per million) [4]. The Disability Support Services of New Zealand reports motor vehicle accident as the prime cause for 40% of SCI occurrence, with a new case being registered once every five days. With reports showing approximately 30 per million instances of SCI and 130-180 victims diagnosed every year, the government of New Zealand has inclined to take evasive action. By formulation of an action plan, the Ministry of Health has recognized the need for drastic changes with its existing model of Medical intervention and support structure for diagnosing people with SCI [5]. Also, the Accident Compensation Corporation of New Zealand has reported managing 1500 SCI victims and has acknowledged their higher use of health and associated support services.
Likewise, CatWalk - New Zealand has urged an investment for additional research on SCI interventions to cut down the country’s $820 million annual healthcare budget for SCI, which can benefit victims from spending on $6.2 million each on healthcare.

Motor deficits of the upper or lower extremity resulting from SCI severely impact one’s quality of living by impeding their independence. SCI is diverse in its nature and severity; hence, only with a patient-specific approach, a treatment modality can impart functional benefit that facilitates recuperation. Commonly deployed interventions include surgical restoration [6]–[8], Functional Electrical Stimulation (FES)-based therapy [9]–[13], robot-assisted therapy [6], [14]–[16], and occupational therapy [3], [17]. Considering the diversity of the condition, often hybrid approaches that combine one or more of the abovementioned interventions are preferred [18]. Among contemporary therapies, FES was recognized as a viable intervention amid patients and clinicians, as no other treatment modality offered the same level of functional restoration. Moreover, FES is often coupled with functional augmentative surgeries to realize maximum practical benefit [19], [20].

Figure 1.1 Functions of the Spinal cord and the impact of its injury.
1.2 Motivation

Chronic motor deficits increase dependency by obstructing one's functional capabilities. Hence, gaining functional independence is the primary demand among them. With a common occurrence of over 50 % of SCI at the cervical level, it is predominant that upper extremity functions are often impaired. Likewise, regaining arm/hand function was considered most valuable [22]. Another study emphasized upper extremity deficits as devastating, and the preference of 42% of people with SCI to regain hand function [23]. People with paraplegia around 44-76% were more likely to retrain, and not trade-off existing arm/hand function tasks for other improved functions [24]. Over 77% of respondents also preferred hand function, when studying 565 members with tetraplegia for the impact and priority needs [25].

The abovementioned studies indicate the priority demand among people with SCI to reclaim upper extremity functions and to regain functional independence. Additionally, studies have emphasized the mismatch of interest between patients and researchers, demanding the need to assess and understand the functional requirements of the patients first [22], [26]. Only 5 to 20 % stroke or SCI survivors realize complete recovery of their upper extremity functions [21]. Hence, assistive interventions can be highly beneficial to them to aid in their activities of daily living (ADL) and can simultaneously impart therapeutic benefit [27], [28]. Moreover, with repeated practice and by minimizing the involvement of a therapist, their suitability for home-based rehabilitation is improved.

The upper extremity predominantly relies on hand function for most activities in a workplace, which includes grasping and manipulation tasks. Moreover, during object manipulation, the force generated by multiple digits is larger when compared to single-digits [29]. This thesis advocates the use of a non-invasive form of FES, the transcutaneous neuromuscular electrical stimulation (tNMES), to reanimate lost hand function. Hence, to
realize complex hand function tasks, tNMES must achieve selective digit control and facilitate its coordination, with controlled force exertion. The inherent limitations of tNMES, such as selectivity and discomfort, limit the realization of complex hand function tasks. Despite, achieving a minimum viable ADL-grasps can complement normal hand function. Such grasps included the power sphere, medium wrap, lateral tripod, lateral grasp, tripod grasp, and precision disk, identified for their high frequency of occurrence in real-life situations [30], [31].

Simultaneously activating multiple electrodes placed over the target muscle can coordinate the stimulation of more than one muscle. Electrode arrays can realize such a feat in coordinated muscle activation, also offering the advantage of selective activation and easy reconfigurability. Often sophisticated programs scan for the stimulation site and record the outcome to create a lookup table, which is later used to imitate predefined hand function tasks [33], [34]. During forearm movements, the electrodes tend to displace away from the motor point; due to this deviation, selective muscle targeting is obstructed [35]. Moreover, improper adhesion of the electrodes to the skin surface can be discomforting. To facilitate prolonged usage of such electrode arrays, they must be flexible and adaptable to the forearm morphology. By having a low form factor, these devices can enable the user to induct therapy while performing their ADL. Likewise, they can dynamically adapt to choose a specific electrode in an array to acquire the best muscle response, allowing a non-expert to operate the device effectively in a home environment. Considering these factors can improve the usability of electrode arrays, which, in turn, promote its utility for home-based rehabilitation.
1.3 Objectives

Given the priority need for restoring hand function, returning innate functionality similar to a biological hand is essential [22]–[25]. Although contemporary FES systems could emulate meaningful grasps, these systems are incapacitated to deliver digit coordination and force control [13], [36]. Primarily, transcutaneous stimulation must facilitate targeted muscle activation by overcoming the highly redundant and multi-articular nature of the human hand. Here, charges are delivered across the skin, which activates the sensory nerve fibers (epidermis of the skin), thus creating discomfort. Another setback is the reverse order of muscle recruitment following electrical stimulation, the rapid onset of fatigue suppresses force generation along time and hinders sustained muscle contractions. Moreover, patients with neurological deficits preferred an assistive technology that can be less cumbersome and personalizable, which can aid with their ADL in a home-based setting [27], [37]. Hence, this thesis aims to improve surface stimulation technology from both physiological and technological standpoints.

Mainly, motor point-based stimulation can elicit fine digit control by selectively activating individual muscle groups. However, existing information on motor point locations is based on anatomical charts that lack generalization and are unreliable [38]–[40]. Also, during forearm rotation, the motor points tend to displace with respect to the skin surface. Although manually searching these motor points for every individual seems to be reliable, such a routine is time-consuming. Moreover, coordination of fingers and thumb motion mediates hand manipulation tasks for ADL. Controlled force exertion across multiple digits are crucial for object manipulation, as the total force exerted with multi-digits is higher than individual digits. Thus, in addition to fine digit control, achieving its coordination is decisive to reanimate complex hand function tasks. Multi-digit coordination is intricate enough that several motor points of muscle groups must be synergistically activated. Herewith, factors such as
selectivity of target muscles [41], accompanied pain [42]–[44], the onset of fatigue, and the inter-subject variability in choosing optimal stimulation parameters must be considered. To effectively utilize FES for realizing complex hand manipulation tasks, these factors must be regulated. Hence, the physiological standpoints included motor point-based stimulation [35], [45]–[47] and parametric control [13], [48], [49].

Commercial electrodes are bulky and have a large form-factor, which tend to constrain most of the forearm movements and can be far from desirable. Moreover, the sensation of discomfort during transcutaneous stimulation has caused low user acceptance [50]. Wearable neuroprostheses must be less cumbersome, personalizable, and comfortable to favor prolonged usage. The performance of stimulation electrodes is improved by modifying the electrode surface [51]–[53], or by adding current redistribution layers [54]–[56]. Since several subject-specific factors influence stimulation performance, these electrodes must be tailored to an individual. Moreover, the demand is to realize a conformable and easy to conceal (low form-factor) electrode array-based sleeve, with simple electrode designs and a straightforward fabrication process. Hence, the technological standpoints to improve existing surface stimulation technology included advances with distributed electrodes, in terms of design, the choice of materials, and its fabricability [32].

Additionally, this thesis demands a myriad of assessments specific to each chapter. Hence, an assessment system to quantify several aspects of electrical stimulation must be designed. The system must localize motor points, characterize the input-output response to external stimulation, and assess electrode configurations for selective, comfortable, and optimal muscle contractions. Under static conditions, these systems can use a fixed load cell to characterize the muscle response to the external situation [57]–[60]. For dynamic interactions, sensorized gloves [61]–[64] or interactive objects [65]–[67] are preferred.
Considering the above, the core objectives of this thesis include:

**1.3.1 Development of an assessment system**
- To develop a hand assessment setup that can evaluate several aspects of electrical stimulation of forearm muscles while facilitating hand function tasks.
- To feature an XY-gantry system that localizes motor points.
- To include dynamometry and electromyography to assess muscle contraction.
- To bring in a sensorized glove for kinetic and kinematic measures of hand function.

**1.3.2 Cataloging the motor points of forearm muscles**
- To electrophysiologically identify the motor points of flexors and extensors of forearm muscles.
- To generate a generalized catalog by clustering the motor point locations.
- To characterize motor points of flexors and extensors of forearm muscles, based on their location, recruitment, and displacement.

**1.3.3 Characterizing the stimulation of forearm muscles**
- To characterize the response of an electrically stimulated muscle by varying the stimulation waveform parameters across different muscle groups.
- To assess stimulation-induced fatigue and discomfort.
- To derive optimal stimulation parameters, which can sustain desired force levels while performing for ADL-based tasks.
- To demonstrate five ADL-based grasps, spherical, hook, cylindrical, jaw chuck, and tip grasp.
1.3.4 Modeling for transcutaneous nerve stimulation

- To develop a computational model of the forearm that features transcutaneous nerve stimulation using the Finite Element Method.
- To embody the stimulation of the median nerve branch innervating the flexor muscles of the forearm.
- To validate the model based on experimentally obtained excitability indices.

1.3.5 Assessing the influence of electrode geometry

- To extend the previously developed computational model (Section 1.3.4) of the forearm to include the stimulation of both motor and sensory nerve fibers.
- To assess the influence of electrode geometry on stimulation performance using both model-based and experimental evaluations.
- To derive optimal electrode design that offers improved stimulation performance while stimulating the forearm muscles.

1.3.6 Fabricating a wearable electrode array-based sleeve

- To develop a wearable electrode array-based sleeve infused with carbon-based silicone elastomers, that is conformable, lightweight, and easy to use; fabricated using the multi-layered screen-printing process.
- To characterize the conductivity, stretchability, and surface profile of the stimulation electrodes across different weight ratios of the base materials (Carbon black infused, silicone-based elastomer).
1.4 Organization of thesis

A detailed research work that has been carried out to complete the above-stated objectives. Based on the high-level objectives, this thesis was divided into two main sections. The first section included the physiological advances in achieving selective digit control, and coordination for ADL grasps. The second section included improvements to existing transcutaneous stimulation technology in terms of electrode designs and material technologies. Accordingly, the thesis is organized as follows:

**Chapter 2** briefly discusses the principles of tNMES, emphasizing the importance of motor point-based stimulation. Following this, wearable neuroprostheses aimed at hand function are introduced. Here, the advantages of array-based stimulation over conventional single electrode-based stimulation are compared, and wearable devices that use array-based stimulation to restore hand function tasks were reviewed. Furthermore, this section discusses functional grasps that repeatedly contribute to ADL, stimulation mapping algorithms, the paradigm for neuroprostheses mediated grasp, and reviews existing studies that have successfully restored grasp functions among people with SCI. The last section of this chapter identifies current gaps in the literature, emphasizing the physiological challenges in stimulating forearm muscles for hand function tasks and limitations with existing wearable stimulation technologies.

**Chapter 3** describes the development of a hand grasp assessment system that included a sensorized glove, test bench platform, dynamometry, electromyography (EMG) acquisition, and interactive objects. The setup facilitated isokinetic dynamometry and an XY-gantry system that was used to locate and assess the response motor point-based stimulation in Chapter 4. The isokinetic dynamometry and EMG were used to determine the muscle response to varying stimulation parameters and stimulation-induced fatigue, respectively, in Chapter 5. The sensorized glove mounted flex
sensors and force sensors that measured digit motion and force exerted during ADL-based grasps. Lastly, the setup facilitated excitability measures that were carried out in Chapters 6 and 7.

**Chapter 4** describes the electrophysiological identification, localization, and characterization of motor points across the flexor and extensor muscles of the forearm. Experimental procedures on motor point tracing and the resulting muscle response were evaluated using the experimental setup described in the previous chapter. The identified sites were grouped using Machine learning-based clustering algorithms. Following this, the centroids and confidence regions of the clusters were derived. To further validate the generalizability of such clusters, physiological correlations and cross-validation tests were performed. By establishing the generalizability of motor point catalogs, their implications for fine digit control and stimulation mapping algorithms were discussed further.

**Chapter 5** extends the applicability of precise digit control to hand manipulation tasks; wherein, systematic analysis of stimulation parameters to achieve controlled levels of muscle contraction was carried out. This analysis was done following the motor point identification from the previous chapter. Here, digit control and coordination were achieved by synergistic activation of various muscle groups through spatially distributed electrodes. Additionally, to favor prolonged usage, stimulation-induced fatigue and discomfort were assessed, which aided in deriving optimal and safe stimulation protocols that are crucial to sustaining desired force levels while performing for ADL-based tasks.

**Chapter 6** presents a computational model that represents the stimulation of the median nerve branch, innervating the flexor muscles of the forearm. Here, equations for voltage-dependent membrane currents were derived. Then, these equations were coupled with the volume conductor-based forearm and were solved simultaneously for a transient-external stimulus using the finite element method. By capturing the spatial and temporal distribution of the electric field across realistic morphologies, the model
served as a testbed to improve electrode designs. The applicability of this model was extended to tNMES, by coupling the nerve excitation with the contraction of muscle fibers as in Appendix I.

**Chapter 7** describes the model-based and experimental assessments that were performed to evaluate the influence of electrode geometry on stimulation performance. For model-based evaluation, the computational model from the previous chapter was extended to include sensory nerve fibers in the skin layers. The stimulation performance was assessed in terms of selectivity, comfort, and safety. Also, psychophysical and excitability measures on healthy participants were derived concurrently to the model predictions. Here, electrode geometry influenced the current density distributions on the skin surface, which in turn affected the stimulation performance. Accordingly, electrode geometries that offer high perimeter gain tend to have improved performance. Implications from this chapter to aid with easy to fabricate and personalized electrode designs were discussed further.

**Chapter 8** describes the viability of fabricating conductive layers infused with silicone-based elastomers using the multi-layered screen-printing technique. Here, different weight ratios of carbon black and Ecoflex™ were prepared, and their conductivity, stretchability, and surface morphology were characterized. The best performing weight ratio was identified and later used to fabricate the electrode array. Lastly, the viability of the fabrication technique for the realization of comfortable, wearable, and cost-effective wearable stimulation systems was discussed.

The last two chapters discuss the overall research work and summarize the contributions of this thesis, conclusions, and the proposed future work.
2. Literature review

The implications of Functional electrical stimulation (FES) have been as early as 1961; wherein, quantifiable function outcomes from FES improved the independence of stroke victims [68]. Since then, electrical stimulation has been used for neuromuscular disorders, pain management, motor control, and other associated therapies. Stimulation is administered by transcutaneous (surface) or by percutaneous or by implanted electrodes, restores motor function [69]. Percutaneous or implantable electrodes favor selective activation of muscle groups for fine and precise movements with high reliability and reproducibility. However, implanted or percutaneous systems are costly, and not all patients are comfortable with surgical procedures. Hence, transcutaneous stimulation is preferred for being less cumbersome and non-invasive, favoring both clinical and home-based rehabilitation.

2.1 Introduction to tNMES

Among FES modalities [70], transcutaneous neuromuscular electrical stimulation (tNMES) is preferred to elicit muscle contraction. tNMES is a non-invasive technique that targets the motor nerves to initiate muscle contraction. For deploying tNMES, the motor units must be intact. A motor unit comprises muscle fibers that are innervated by respective motor nerve axons, Figure 2.1. The stimulation electrodes are placed on the surface of the skin; wherein, the induced electric field penetrates through several layers of tissues to reach the target nerve at their motor points. A motor point represents the region on the nerve trunk wherein the peripheral nerve branches itself into a muscle to form individual motor units. The notion behind motor point-based stimulation is to target the nerve branch that innervates most of a muscle. Muscle fibers are at different depths; hence, higher stimulation intensities are required to activate deeper motor nerve fibers. Stimulating a motor point causes depolarization along these motor nerve fibers. This depolarization creates an action potential that propagates
along the terminal nerve branches to reach the neuromuscular junction. At this junction, the chemical neurotransmitter acetylcholine is released to cause muscle-level depolarization, which consequently resulting in muscle contraction. Hence, the number of nerve axons being excited can directly influence muscle recruitment.

Figure 2.1 Transcutaneous stimulation of a muscle at its motor point.

Stimulating more axons consequently activates more muscle fibers, resulting in high contraction levels. Compared to direct muscle stimulation, muscle contraction achieved through motor point-based stimulation requires less excitation energy. Due to low excitation currents, there is also a significant reduction with discomfort [45]. Moreover, motor point-based stimulation improves muscle fiber recruitment, reduces neuromuscular fatigue [47], and has a rehabilitative impact [40]. Although motor point-based stimulation is highly regarded for its benefits, during tNMES only superficial motor points (those close to the skin surface) can be targeted with less discomfort. Increasing the charge density to target deeper motor points can cause co-contraction of neighboring muscles and may induce discomfort. Due to poor control over the dosage [40] and the influence of tissue layers on the distribution of electric field [71], optimal motor point stimulation is arduous using tNMES. Hence, in Chapter 4, the motor points of the forearm muscles were identified, localized, and clustered to derive a generalized catalog that can simplify electrode placements for motor point-based stimulation.
2.2 Functional grasping using neuroprostheses

Recently, transcutaneous stimulation has seen drastic improvements with the advent of electrode arrays [72]. The use of an electrode array simplified the modulation for electrode shape, size, position, and customize stimulation parameters for each electrode entity [72]–[74]. It offers selectivity and can adapt to electrode displacements. Moreover, it facilitates coordinated digit activation by synergistic activation of muscle groups. Hence, wearable neuroprostheses utilize electrode arrays on the forearm muscles to facilitate functional grasps. Neuroprostheses consists of an electrode array, a stimulator, an input transducer, and a control unit [75]. Here, the user initiates control signals that select and instigate grasp patterns. The control signal is typically acquired from a retained voluntary motion or by using advanced brain-machine interfaces [76]. Following this, a coordinated stimulation pattern activates the muscles in a sequence that delivers a functional grasp. These devices reduce the dependency of patients on therapists and help them to perform their activities of daily living with much more independence.

2.2.1 Benefits of electrode arrays

The benefits of electrode array-based stimulation have motivated many investigators to test its efficacy across several applications [33], [77], [78]. Electrode arrays offer the following advantages:

**Selective and diverse activation:** The forearm has a tightly packed musculature; hence, selectively targeting a muscle is arduous. Moreover, to achieve hand function tasks, more than one muscle group must be stimulated simultaneously. As motor point-based stimulation can selectively elicit muscle contraction, electrodes distributed in an array can adequately enfold these motor points. If the area of activation is larger than a single electrode within the array, switching several electrodes can virtually cover the desired area. Thus, electrode shapes can be modified specifically to the activation site. Moreover, anode and cathode can be
switched across the array elements to regulate the electric field under the active electrode surface. By modulating the size, shape, position, and stimulation parameters, electrode arrays can accommodate diversity in muscle groups [79]–[81].

**Dynamic Adaptations:** Change in the relative position of stimulation sites about the forearm surface may affect the stimulation performance. One of the significant drawbacks with the single electrode is the inability to compensate for the changes when the electrode displaces from the target site, which can activate unwanted muscle areas. However, electrode arrays can compensate for such changes [82], as individual electrodes in an electrode array are distributed spatially; hence, shape over the stimulation area (virtual electrodes) and can be adjusted dynamically to such displacements. This allows for easy repositioning, and the system can effortlessly be calibrated after donning and doffing.

**Improved Electrode-Skin Interface:** Electrode arrays are flexible and, if conformable (stretchable), can mimic the shape of the forearm. Hence, it tends to improve the electrode-skin contact, regardless of the uneven texture or displacements in the forearm [83].

**Favour Asynchronous Recruitment:** Electrodes in an array-type configuration are distributed along the forearm surface. By sequentially stimulating these electrodes, asynchronous stimulation, i.e., the physiological order of motor unit recruitment, can be mimicked. This stimulation strategy has been demonstrated to reduce muscle fatigue, which is otherwise impossible to achieve using single electrode-based stimulation [84], [85].

**Ease of use:** Here, the electrodes are integrated into a fabric sleeve. Moreover, they can be easily calibrated after repositioning. Hence, a significant amount of time needed for installation or set-up of the device is avoided. Thus, allowing a non-expert to use the device for home-based rehabilitation [82].
2.2.2 State of the art

Wearable neuroprostheses may reduce the dependency of patients on therapists, giving them much more independence to perform their activities of daily living. When used in conjunction with user-initiation, it serves as a promising tool for rehabilitation, as voluntary movements of patients are often used to control muscle contraction in achieving the activities of daily living (ADL). Additionally, the application of tNMES tends to enhance the kinematic ability and improve coordination of the impaired motor function and has also shown a reduction in muscle tone and spasticity [86]. Studies have utilized these benefits of transcutaneous stimulation in restoring hand function tasks among people with paralysis from spinal cord injury (SCI), as in Table 2.1 - 2.6. Such devices include the Bionic glove [36], NESS H200 [12], [13], OrthoJacket [9], Hyper TERERE [10], and MUNDUS [11]. The most recent advancement has been reported to achieve truly continuous control of graded muscle activation in a paralyzed human using a Brain control interface (BCI) controlled tNMES-based system [87].

![Figure 2.2 Transcutaneous stimulation for hand function restoration.](image)

[a] A typical bipolar stimulation; wherein, an electric field is applied across the two electrodes. [b] An electrode array to selectively activate the forearm muscles [33]. [c] A BCI-controlled FES system with electrode array-based stimulation facilitating ADL tasks [88]. Figures [a], [b] © [2019] IEEE. Reprinted, with permission [33], [88].
Table 2.1 Bionic glove from the University of Alberta.

<table>
<thead>
<tr>
<th>Type</th>
<th>Channels</th>
<th>Pulse Width</th>
<th>Amplitude</th>
<th>Frequency</th>
</tr>
</thead>
<tbody>
<tr>
<td>tNMES</td>
<td>3</td>
<td>50-200 µs</td>
<td>25-35 mA</td>
<td>20-30 Hz</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Source</th>
<th>Waveform</th>
<th>Battery</th>
<th>Control</th>
<th>Approval</th>
</tr>
</thead>
<tbody>
<tr>
<td>Constant current</td>
<td>Rectangular</td>
<td>-</td>
<td>Proportional wrist movement</td>
<td>Commercially available</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Pathology</th>
<th>C6 and lower-level tetraplegia from SCI</th>
</tr>
</thead>
<tbody>
<tr>
<td>Description</td>
<td>The system had a stimulator mounted on to a sleeve on the forearm, which was connected to self-adhesive electrodes. Active wrist movements were detected to stimulate respective muscles for hand opening and closing.</td>
</tr>
<tr>
<td>Effectiveness</td>
<td>The system was effective in improving the tenodesis grasp for subjects with intact control of wrist movements. It was an effective replacement over implantable and costly systems, gaining a long-term acceptance among 30% of its users.</td>
</tr>
<tr>
<td>Advantages</td>
<td>Being a prototype, its cost-effectiveness ratio was high, and it had limited applicability, which demands intact voluntary functions.</td>
</tr>
<tr>
<td>Disadvantages</td>
<td></td>
</tr>
</tbody>
</table>

Reference(s) Prochazka, Gauthier, Wieler, & Kenwell, 1997; [36]

Table 2.2 NESS H200 (Hand master) from NESS Ltd., Israel.

<table>
<thead>
<tr>
<th>Type</th>
<th>Channels</th>
<th>Pulse Width</th>
<th>Amplitude</th>
<th>Frequency</th>
</tr>
</thead>
<tbody>
<tr>
<td>tNMES</td>
<td>4</td>
<td>10-500 µs</td>
<td>&lt; 150 mA</td>
<td>18/36 Hz</td>
</tr>
</tbody>
</table>

<table>
<thead>
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<th>Waveform</th>
<th>Battery</th>
<th>Control</th>
<th>Approval</th>
</tr>
</thead>
<tbody>
<tr>
<td>Constant voltage</td>
<td>Sinusoidal (11Khz)</td>
<td>Biphasic/symmetric</td>
<td>Push-button</td>
<td>FDA Approved</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Pathology</th>
<th>C5 or C6 level tetraplegia from SCI or Hemiplegia from stroke</th>
</tr>
</thead>
<tbody>
<tr>
<td>Description</td>
<td>The device replicated a wrist-hand orthosis; enclosed within were the stimulation electrodes that activated the thumb and the fingers. The system ran preprogrammed sequences of stimulation for hand opening/closing, which was controlled by the user with a push button.</td>
</tr>
<tr>
<td>Effectiveness</td>
<td>It demonstrated an improved grasp functionality. Moreover, it improved muscle strength and reduced contractures of fingers.</td>
</tr>
<tr>
<td>Advantages</td>
<td>It helps an individual with ADL.</td>
</tr>
<tr>
<td>Disadvantages</td>
<td>The device received a general dissatisfaction for limited grasp patterns and poor performance</td>
</tr>
<tr>
<td>Reference(s)</td>
<td>Alon &amp; McBride, 2003; Snoek et al., 2000; [12], [13]</td>
</tr>
</tbody>
</table>
### Table 2.3 OrthoJacket, a BMBF funded EU project.

<table>
<thead>
<tr>
<th>Type</th>
<th>Channels</th>
<th>Pulse Width</th>
<th>Amplitude</th>
<th>Frequency</th>
</tr>
</thead>
<tbody>
<tr>
<td>tNMES</td>
<td>4</td>
<td>50–200 µs</td>
<td>25 – 35 mA</td>
<td>20–30 Hz</td>
</tr>
</tbody>
</table>

<table>
<thead>
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<th>Source</th>
<th>Waveform</th>
<th>Battery</th>
<th>Control</th>
<th>Approval</th>
</tr>
</thead>
<tbody>
<tr>
<td>Constant</td>
<td>Rectangular</td>
<td>-</td>
<td>-</td>
<td>Research</td>
</tr>
<tr>
<td>current</td>
<td>Biphasic/asymmetric</td>
<td>-</td>
<td>-</td>
<td>Prototype</td>
</tr>
</tbody>
</table>

**Pathology**
SCI (ideal for subjects with limited force-generating capacity)

**Description**
The system was a combination of an orthosis, a surface stimulator, and sophisticated sensor systems. The orthosis improves joint stabilization, whereas the sensors tend to drive the stimulator based on user-intents and provided feedback on the joint positions and muscle activity.

**Effectiveness**
The system was effective in its adaptive approach regarding the electrode placement for stimulation, and the use of sensors helped in quantifying the neurological recovery.

**Advantages**
The use of active orthosis, in conjunction with the stimulation, can even assist people with minimal force-generating capacity.

**Disadvantages**
The major disadvantage with the system was the inability of the sensors to distinguish voluntary from evoked muscle activity to quantify spasticity and fatigue.

**Reference(s)**
Schill et al., 2011; [9]

### Table 2.4 Hyper TERERE, Spanish Ministry of Science and Innovation.

<table>
<thead>
<tr>
<th>Type</th>
<th>Channels</th>
<th>Pulse Width</th>
<th>Amplitude</th>
<th>Frequency</th>
</tr>
</thead>
<tbody>
<tr>
<td>tNMES</td>
<td>32</td>
<td>-</td>
<td>-</td>
<td>-</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Source</th>
<th>Waveform</th>
<th>Battery</th>
<th>Control</th>
<th>Approval</th>
</tr>
</thead>
<tbody>
<tr>
<td>Constant</td>
<td>Rectangular</td>
<td>-</td>
<td>-</td>
<td>Research</td>
</tr>
<tr>
<td>current</td>
<td>Biphasic/asymmetric</td>
<td>-</td>
<td>-</td>
<td>Prototype</td>
</tr>
</tbody>
</table>

**Pathology**
Stroke and SCI

**Description**
The 32 channel electro-stimulator was based on a new current source that deployed a linear closed-loop transconductance amplifier. The device also provides enhanced switching capacities to support multiple electrodes.

**Effectiveness**
Had improved channel switching capacities for multiple muscle activation.

**Advantages**
The stimulator had a portable and flexible design; wherein, it was capable of generating custom stimulation waveform, aimed to explore novel stimulation algorithms and patterns.

**Disadvantages**
The distributed concept also demands new stimulation algorithms and patterns to reach the desired goals.

**Reference(s)**
Brunetti, Garay, Moreno, & Pons, 2011; [10]
Table 2.5 MUNDUS Project using RehaStim from Hasomed GmbH.

<table>
<thead>
<tr>
<th>Type</th>
<th>Channels</th>
<th>Pulse Width</th>
<th>Amplitude</th>
<th>Frequency</th>
</tr>
</thead>
<tbody>
<tr>
<td>Robotic Exo + tNMES</td>
<td>8</td>
<td>20-500 µs in steps of 10 µs</td>
<td>0 – 130 mA in 65 steps</td>
<td>10-50 Hz in steps of 5Hz</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Source</th>
<th>Waveform</th>
<th>Battery</th>
<th>Control</th>
<th>Approval</th>
</tr>
</thead>
<tbody>
<tr>
<td>Constant current</td>
<td>Symmetric biphasic, rectangular</td>
<td>up to 10 Hrs</td>
<td>Computer-controlled</td>
<td>Clinically approved</td>
</tr>
</tbody>
</table>

Pathology Description: The system was highly sophisticated with a lightweight exoskeleton, an active hand orthosis, a stimulator (RehaStim™), and user-initiation facilitated using EMG, BCI, and Eye-tracking.

Effectiveness: The modularity of the system was utilized to configure the needs of the user and was effective in delivering arm reaching and hand functions.

Advantages: It enhanced the functional assistance for motor system impaired individuals for their activities of daily living.

Disadvantages: The major con of the system is its complexity and sophistication, which demands technical assistance and maintenance.

Reference(s): Pedrocchi et al., 2013; [11]

Table 2.6 A BCI-FES system from Battelle Memorial Institute.

<table>
<thead>
<tr>
<th>Type</th>
<th>Channels</th>
<th>Pulse Width</th>
<th>Amplitude</th>
<th>Frequency</th>
</tr>
</thead>
<tbody>
<tr>
<td>tNMES</td>
<td>140</td>
<td>500 µs</td>
<td>0 – 20 mA</td>
<td>20 Hz</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Source</th>
<th>Waveform</th>
<th>Battery</th>
<th>control</th>
<th>Approval</th>
</tr>
</thead>
<tbody>
<tr>
<td>Constant current</td>
<td>Monophasic rectangular</td>
<td>up to 10 Hrs</td>
<td>BCI driven</td>
<td>-</td>
</tr>
</tbody>
</table>

Pathology Description: Using the BCI-FES system, a single participant was able to generate a continuum of force levels between 0.3 - 0.7 lbs.

Effectiveness: The system depicts a recent advancement to facilitate SCI individuals to regain more natural control for performing fine motor tasks.

Advantages: Stimulation was controlled by the user. Moreover, 140 individual electrodes in the array provided fine digit control.

Disadvantages: The major con of the system is its complexity and sophistication, which demands technical assistance and maintenance. Moreover, the installation of the BCI-based system involves surgical procedures.

Reference(s): Friedenberg et al., 2017; [87]
2.2.3 Achieving functional grasping

Neuroprosthetic devices that feature an electrode array facilitates hand function tasks in four stages, as in Figure 2.3. Firstly, sites that elicit several flexion and extension movements of the digit/wrist is obtained [89]–[91]. Secondly, the input-output recruitment curve that relates stimulus input and the resulting muscle contraction are obtained [92]–[94]. As the electrodes are distributed along the forearm surface, automated mapping algorithms can facilitate these two steps [72], [77], [95].

![Figure 2.3 Grasp synthesis with electrode array-based stimulation.](image)

Thirdly, to achieve grasp control, user-initiated inputs are obtained, typically using a push-button or through physiological signals [96], [97]. Lastly, based on the type of grasp, appropriate electrodes are activated, and stimulation parameters are adjusted to achieve required muscle contraction levels [92], [98]–[100].

The stimulation mapping algorithms identify personalized stimulation sites and parameters, that compensates for variability among users, in terms of differences in impairments and anatomy. Out of several combinations, in order to find the optimal electrode configuration and stimulation parameters, the triggered grasps patterns are compared and compensated against a grasp template (an ideal grasp response) [77], [94]. Studies have implemented stimulation mapping algorithms using: a rule-base, that synthesized stimulus map for various grasp patterns [101]; an optimization algorithm, that automatically determined electrode
configurations and stimulation intensity for various movements [95]; a self-learning algorithm, that modeled stimulation parameters as a function of electrode location and finger forces, that self-adapts to any disruptions to obtain an optimized stimulation profile [90], [102]; a novel EMG-based, to identify appropriate electrode configurations without any kinematic data [100].

During grasp control, the user must command the grasp intuitively. Accordingly, studies have implemented several control strategies that facilitated grasp control based on user command. Model predictive control [103], mathematical models [104], and self-learning artificial neural networks [105] were commonly used to coordinate muscle contraction of several digits that realized grasp and release functions. The ultimate goal in using FES for grasp restoration is by manipulation of electrical parameters and selective stimulation of muscle groups the user will be able to dictate and control the strength of the grasp, wherein patients with motor deficits can regain their ability to hold or manipulate objects.

By following one or more of the above strategies, studies have demonstrated key grip, palmar grasp, and other precision grips, [12], [13], [83], [106]–[108]. Here, different stimulation parameters and control strategies were applied across people with varying levels of paralysis from SCI. The existence of a large number of studies demonstrating ADL grasps using transcutaneous stimulation, Figure 2.4, offers a promising start to explore the viability for complex hand function tasks. In these studies, [12], [13], [83], [106]–[108], several grasps assessments were additionally carried out to evaluate the mediated recovery and improvements to hand function.
A complete hand function embodies grasps that vary from power to precision, and complex in-hand manipulation tasks. However, it is worth mentioning that not all these hand function tasks necessarily contribute to ADL. For hand function recovery, grasps that are very crucial to performing ADL, which offers the independence to carry out tasks like brushing, eating, opening, must be considered. Studies have also derived crucial grasps based on 33 unique sets of prehension form over 211 grasps found on literature [31]. The chosen set of ADL grasps signified prehension form power to precision category and had a high frequency of occurrence in real-life situations. These grasps included the power sphere, medium wrap, lateral tripod, lateral grasp, tripod grasp, and precision disk. The implication being these grasps are fundamental to normal hand function. Realizing only these grasps can enable a ‘functionally viable hand,’ as they can aid most of the ADL tasks.
2.3 Challenges and limitations

Although electrode array-based stimulation has delivered several advances for both upper and lower limb functions. The complexity lies in stimulating the forearm muscles for restoring complete hand function. Considering the priority need for people with SCI to regain their hand function, it is equally essential to identify, address, and overcome limitations faced by electrode array-based stimulation to reanimate complex hand function tasks. Table 2.1 – 2.6 reports prominent studies that used transcutaneous stimulation to restore hand function. Despite this, they had limited applicability in terms of usability and control in eliciting several grasps to represent a near-normal hand function. Moreover, most of these devices demand technical assistance and maintenance. These factors must be addressed, which, in turn, promote its utility for home-based rehabilitation as an assistive intervention.

The intricate musculature of the forearm contributes to the higher DOF associated with hand function. To realize fine digit control and its coordination, target muscles must be selectively stimulated, wherein coordinated activation of several muscles can deliver ADL-based grasps. Although electrode arrays offer the advantage of selective activation and easy reconfigurability, sophisticated scanning and calibration routines are still needed to identify the target sites and record the muscle response. Moreover, these target sites with respect to the skin surface tend to displace under forearm rotation or movements, which obstructs the selectivity. However, no studies have comprehensively identified such sites or characterized their response to stimulation and displacement to forearm movements. Moreover, this knowledge solely dictates the capabilities and design of electrode arrays and their control. With such information, the scanning times for recalibration, or electrode placements can be improved significantly.
Hand contributes to grasping and manipulation tasks. Common ADL-based tasks predominantly involve coordinated stimulation of the digits and wrist. As in Fig. 2.3 the second step in grasp synthesis is to characterize the stimulation of forearm muscles in terms of their stimulation comfort, muscle recruitment, and effects of fatigue. These outcomes are dictated by several factors that include electrode configuration, stimulation type, stimulation waveform, and the characteristics of the target grasp. Moreover, such a characterization is crucial in achieving controlled levels of muscle contraction. Similar to the identification of the target sites for a specific muscle, such individual-specific characterization on muscle response is often performed by scanning algorithms. Ideally, these characterizations can help to deliver a highly selective, comfortable, and desired muscle contraction for specific grasp outcomes.

The inherent limitation of transcutaneous stimulation is poor selectivity and induced discomfort. Based on their practicality and usability, wearable electrode arrays that use transcutaneous electrodes are highly preferred. Moreover, these electrodes are used for prolonged stimulation delivery meant for therapeutic and assistive implications. Hence, improving their stimulation comfort is considered equally important. Several studies have aimed to enhance the stimulation performance of such transcutaneous electrodes in terms of selectivity and comfort, either by modifying the electrode surface [51]–[53] or by adding current redistribution layers [54]–[56]. Moreover, commercial electrodes are sophisticated in terms of their design; they are bulky and have significant trade-offs in their performance. Additional factors such as easy wearability, being lightweight, and low-form factor must also be considered with electrode designs based on the users’ perspective. Hence, electrodes with improved stimulation performance that accommodates easy fabricability and the ability to tailor their performance or outcomes for personalized electrode designs are in demand.
2.4 Summary

The main aim of this thesis is to improve existing wearable surface stimulation technology. Hence, this chapter introduces the principles of tNMES and electrode array-based stimulation. Additionally, the paradigm for neuroprostheses mediated grasp is discussed. Reviewing existing studies identified the gaps in the literature, emphasizing both physiological and technological challenges with current systems. Moreover, individual chapters discuss these limitations in detail, that can be followed upon every chapter. In summary, these challenges included 1) the derivation of a generalized catalog to identify target sites that elicit several hand function tasks, 2) the need for characterization of an electrically stimulated muscle to facilitate controlled force exertions with ADL-based grasping and manipulation tasks, 3) the need to improve stimulation performance of transcutaneous electrodes in terms of their stimulation selectivity and comfort, and 4) the demand to improve the design, wearability, and fabrication to develop personalizable electrode arrays.
This chapter presents the development of a hand function assessment system to evaluate several facets of electrical stimulation of forearm muscles. This hardware setup enabled experimental assessments throughout this thesis. The system had a test bench platform, dynamometry, EMG acquisition, sensorized glove, and interactive objects. In the following chapters, this setup was used to locate and assess the motor points along the forearm; determine the stimulation-induced fatigue; measured the digit motion and forces exerted during ADL-grasps; evaluate the nerve excitability during transcutaneous stimulation.
3.1 Introduction

As a viable intervention to restore upper limb functions, evaluating the neurophysiological function mediated by transcutaneous neuromuscular electrical stimulation (tNMES) will aid in the development of better devices, its optimization, and to assess the mediated recovery. This thesis presents and undertakes a diverse assessment of neuromuscular function; hence, to perform all necessary measures, the hardware setup developed in this chapter served as a one-stop platform.

Given the tightly packed musculature of the forearm, identification of an optimal motor point and an electrode configuration is arduous [41], [102]. Furthermore, more than one stimulation site and electrode configuration can elicit a similar response. Hence, targeting the forearm muscles to identify, localize and characterize the motor points and their electrode configurations must be carried out like a methodical process, wherein the assessment setup must facilitate fast scanning times and standardization of outcome [35], [41], [102].

During external stimulation, its influence and the resulting muscle contraction can be quantified based on the contact forces exerted using a dynamometer under isometric conditions [48], [112]. Similarly, studies have used dynamometry to measure wrist torque and prehensile grasp forces [57], [60]. Although they are suitable for larger forces such as the wrist torque or isometric digit forces, they are not suitable for low-level grip forces that involve object manipulation tasks.

Quantitative investigations on hand function can be summed up into four categories. Firstly, to evaluate fine motor control, finger movements along with grip force are studied [60], [113]. Secondly, the relation between grip force and the load is studied by assessing the grip necessary to counteract the physical load while holding an object [58], [65]. Thirdly, to study unconstrained manipulation, dynamic gripping is assessed. Lastly, the force-generating capacity is assessed by studying the power grip [114]. To
facilitate such measures while performing manipulation tasks, both kinetic and kinematic aspects of digits and the objects being grasped must be evaluated [58].

Studies have measured the position and forces of digits and fingers using a measurement system that mounted load cells [57], [115]. However, these systems were static, which facilitated assessments only for a prefixed hand or forearm orientations. As an alternative to such static assessment systems, sensorized gloves can promote robust and dynamic measures while performing manipulation tasks. Sophisticated systems included the use of fiber optics-based sensors, motion capture devices, such as the Vicon [8–10] and the inertial measurement sensors, which gave the position and orientation of each digit in a 3D space used [58], [62], [65], [116], [117]. Still, these devices are cumbersome, need constant calibration, and are technically challenging to operate in a non-laboratory-based setting. However, the incorporation of lightweight, compact sensors that have robust measurement outcomes, and low power consumption can make them ideal for hand function assessments.

With the above motivations, the main objective of this chapter is to develop and present a physical system for assessing several aspects of electrical stimulation while facilitating hand function tasks. As in Section 1.3.1, the following objectives were accomplished in this chapter.

• To feature an XY-gantry system that localizes motor points under three forearm orientations
• To include dynamometry and electromyography to assess muscle contraction.
• To bring in a sensorized glove for kinetic and kinematic measures of hand function.
3.2 System design and identification

The entire system was custom-built, which consisted of a test-bench platform with dynamometry and electromyography, a sensorized glove, and interactive objects.

3.2.1 Hardware setup

A custom-made setup was devised to position/orient the forearm while the participants sat in a comfortable position, Figure 3.1. Given the prolonged nature of experiments, adjustable and padded arm support further improved participant’s comfort. The anthropometric information on the length of the forearm, length span of the wrist, length of fingers was considered for the design of the test bench, and the glove [118], [119]. The setup also featured several adjustments that could improve the suitability of the user, as indicated by blue arrows in Figure 3.1. At the wrist level, a mechanism facilitated controlled pronated, supinated, and neutral positions, insert in Figure 3.1.

Figure 3.1 Hand function assessment system
The setup featured an XY-gantry that gave electrode positions about the forearm surface. The setup had two SS25LA Dynamometers (BIOPAC Systems, Inc., California) that evaluated the muscle response to subsequent stimulation. One dynamometer measured the forces exerted by the thumb and wrist and the other measured forces across the four digits. The positions of these sensors were adjusted to suit the user. Force measurements from these dynamometers sampled at 1 kHz were recorded using Biopac MP 36 (BIOPAC Systems, Inc., California). The Biopac MP 36 amplifier also enabled electromyography (EMG) measures. The interactive objects represented the objects that were used in daily living [30], [120].

### 3.2.2 Sensorized glove

The sensorized glove facilitated the kinetic and kinematic measures of hand manipulation tasks. It consisted of a fabric glove with several sensors mounted using a 3D printed assembly. The glove mounted flex sensors, force sensors, and IMUs that measured digit motion, fingertip forces, and hand orientation during activities of daily living (ADL)-based grasp, respectively, Figure 3.2a.

![Figure 3.2](image1.png)

**Figure 3.2** The sensorized glove and electrode array-based sleeve
The glove included unidirectional, resistance-based flex sensors (Spectra-Symbol, Salt Lake City, USA). Several flex sensors measured the flexion of five digits, flexion of the wrist, and the abduction of the thumb, also, the extension of the wrist. Each digit had two flex sensors that measured the range of motion at its respective proximal and medial phalanges. The outputs were then normalized based on the ROM of their respective phalanges to give the percentage of flexion/extension between 0 – 100, Table 3.1. A voltage-divider circuit was used to measure the varying resistances across the sensors, Figure 3.3.

**Table 3.1** Range of motion and forces entered by hand, [121]

<table>
<thead>
<tr>
<th>Wrist</th>
<th>Abduction</th>
<th>Adduction</th>
<th>Flexion</th>
<th>Extension</th>
</tr>
</thead>
<tbody>
<tr>
<td>Thumb</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>FL</td>
<td>EX</td>
<td>AB</td>
<td>AD</td>
</tr>
<tr>
<td></td>
<td>60</td>
<td>60</td>
<td>15</td>
<td>15</td>
</tr>
<tr>
<td>Digit</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>FL</td>
<td>EX</td>
<td>AB</td>
<td>AD</td>
</tr>
<tr>
<td></td>
<td>30</td>
<td>90</td>
<td>35</td>
<td>35</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Metacarpophalangeal joint</th>
<th>Distal phalanges</th>
<th>Carpometacarpal joint</th>
</tr>
</thead>
<tbody>
<tr>
<td>FL</td>
<td>FL</td>
<td>FL</td>
</tr>
<tr>
<td>EX</td>
<td>EX</td>
<td>EX</td>
</tr>
<tr>
<td>FL</td>
<td>FL</td>
<td>FL</td>
</tr>
<tr>
<td>EX</td>
<td>EX</td>
<td>EX</td>
</tr>
<tr>
<td>AB</td>
<td>AB</td>
<td>AB</td>
</tr>
<tr>
<td>AD</td>
<td>AD</td>
<td>AD</td>
</tr>
</tbody>
</table>

AB-Abduction, AD-Adduction, FL-Flexion, EX-Extension

![Figure 3.3](image) The voltage bridge circuit-schematics for the flex sensor.
The capacitance-based force sensors (Singletact™, Pressure Profile Systems Inc., USA) at the fingertips gave a pre-calibrated output that measured fingertip forces up to 50 N. Also, the IMU was mounted on the posterior side of the hand, which prevented any interruption to the user while handling or grasping objects. A DAQ-device collected the outputs from all the sensors and was processed in LabVIEW 8.6 (National Instruments, TX, USA).

3.2.3 Stimulation electrodes

The ADL-based grasps were mediated by dynamic control over the forearm muscles using an electrode array-based sleeve, Figure 3.2b. The sleeve had several reconfigurable 3 × 3 pads of Ag-AgCl-based disposable snap electrodes, that covered the desired forearm regions.

3.2.4 Stimulation hardware

The stimulation was delivered through a current-controlled stimulator, Rehastim™ (Hasomed GmbH), Figure 3.4a. The stimulator had eight channels to deliver customized stimulation and supported various pulse generation modes, Figure 3.4b. The stimulation parameters can be regulated, with amplitude, up to 130 mA, pulse-width, up to 500 µs and frequency up to 50 Hz, using a PC via the ScienceMode2.

![Figure 3.4](image)

**Figure 3.4** [a] Current-controlled stimulator and its accessories. [b] Customizable biphasic stimulation waveform.
3.3 Discussion

The setup was developed to facilitate assessments that were needed to achieve the proposed objectives of this thesis (Section 1.3.1). The entire system was custom-built, which consisted of a test-bench platform that mounted sensors for isokinetic dynamometry and electromyography.

The assessment setup enabled to position/orient the forearm; this allowed motor point identification under controlled pronated, supinated, and neutral positions in Chapter 4. Following motor point-based stimulation, to directly quantify muscle tension, isometric contact forces of the digits and the wrist were measured using the two dynamometers mounted on the setup. Moreover, motor points along the forearm surface were traced using a special motor point pen, that was mounted on the XY-gantry. The gantry system within the setup facilitated to localize and assess the response of motor point-based stimulation.

Similarly, in Chapters 4, 5, and 6, the dynamometry was used to determine the muscle response to varying stimulation parameters. Evoked force exertions were normalized based on the strength of isometric contractions using maximum voluntary isometric contractions (MVIC).

Also, in Chapter 5, the influence of stimulation-induced fatigue was studied across the forearm muscle groups, here, EMG was used to quantify the onset of fatigue, by measuring the fall in muscle contraction levels over time. Furthermore, the sensorized glove, which mounted flex sensors and force sensors, measured digit motion and force exerted during ADL-based grasps.

Lastly, the setup was able to position the forearm comfortably for extended periods, that enabled psychophysical, recruitment (muscle) and excitability measures to assess the stimulation performance of several electrode geometries in Chapters 6.
3.4 Summary

A hand grasp assessment setup that can evaluate several aspects of electrical stimulation across the forearm muscles was developed successfully in this chapter. The entire system and its elements were custom-built, which consisted of a test-bench platform with dynamometry and electromyography; a sensorized glove; and interactive objects. The test-bench platform featured an XY-gantry scale that was used to locate and assess the response motor point-based stimulation. Also, the sensorized glove mounted flex sensors, force sensors, and IMUs that measured digit motion, fingertip forces, and hand orientation during ADL-based grasps, respectively. The system was exclusively designed for neuroprostheses mediated grasp, but it can be extended to generic grasp and object manipulation-based research. In the upcoming chapters, this step enabled the identification and location of motor points; optimal electrode placements for bipolar stimulation; studying the influence of electrical stimulation on muscle contraction, the influence of stimulation-induced fatigue, assess the performance of stimulation electrodes and finally to evaluate ADL mediated grasps evoked through electrical stimulation. Measuring functional outcomes is an essential step in that direction as both a research and an evaluation method.
4. Motor point cataloging

Motor point-based stimulation is crucial to activating a target muscle selectively. Hence, in this chapter, sites that elicited flexion and extension of the digits and the wrist were electrophysiologically identified across the forearm muscles. Here, machine learning-based clustering algorithms were used to derive a generalized map of stimulation zones available for selective control of various muscle groups. Clustering the motor points and cataloging them simplified electrode placements for fine digit control, which accomplished several ADL-based grasps in the following chapter.
4.1 Significance of motor point cataloging

Complete hand function is an ensemble of fine and coordinated digit movements. As the viability of fine digit control through stimulation of forearm muscles have been established [41], [102], [122], the subsequent step is to advance coordination in digit control, which can be achieved by stimulation of various muscle groups through electrode arrays [123].

With the advent of electrode array-based stimulation, dynamic control over various muscle groups is made possible. Furthermore, the size and shape of active electrodes can be customized, which offers the flexibility to dynamically adapt to change in electrode displacement due to forearm movements [33]. Electrode arrays offer a myriad of advantages when compared to single electrode-based stimulation (Section 2.2). Although these advantages make electrode arrays integral to wearable neuroprostheses, their capabilities and design solely depend on the prior knowledge on innervations regions, motor point displacement (of forearm movements), and stimulation profiles [33], [110]. The ideology behind electrode array design is to facilitate control over all available stimulation zones by complying with the anatomical characteristics of the forearm.

Anatomical charts are the basis for motor point locations [38]–[40]. Still, motor point locations from these charts lack generalization and are unreliable [39], [46]. Furthermore, limb/joint movements, e.g. wrist pronation/supination, can displace these motor points [102], [111]. Hence, motor point identification is recommended prior to every study; however, a manual search is often time-consuming and discomforting to the user [40]. For studies deploying electrode array-based stimulation, subject-specific maps of these stimulation sites are automatically extracted using special algorithms [77]. However, the effectiveness of such algorithms relies on baseline information obtained from manual search-based techniques; wherein, their location and displacement profiles are necessary beforehand to minimize the search space and the time involved.
4.2 Challenges in generalizing motor point catalogs

The motor unit recruitment during a bipolar stimulation is dependent on the position of the active electrode, the stimulation parameters, and the distance between the two electrodes for the given limb configuration [124], [125]. Existing studies that use monopolar stimulation for motor point tracing often grade the muscle response visually though skin palpitation [39], [126], or by kinematic measures [122]. When considering bipolar stimulation-based motor point identification, to examine the underlying recruitment (for muscle response), the impact of electrode configuration, along with other contributing factors, must be considered. With two active electrodes, the bipolar configuration can yield a myriad of combinations to stimulate a motor point. Examining such characteristics can further aid in choosing an optimal electrode pair configuration and stimulation parameters, that elicits movement closest to an ideal hand response.

Currently, the lack of a comprehensive understanding of bipolar stimulation limits its application to wearable transcutaneous stimulation systems. By expanding the work of [39], [41], [126], this chapter aims to characterize the motor points based on their location, displacement, and recruitment characteristics under bipolar stimulation. Equally, this work aims to standardize the protocol for identification and characterization of motor points, which is lacking in literature specific to transcutaneous neuromuscular electrical stimulation (tNMES). Due to the varying nature of nerve-branching patterns and the availability of more than one motor point for each muscle [127], such identification is highly subject-specific. To improve the generalization of findings and to further address the concerns raised by [40] regarding the misconceptions about motor point-based stimulation, physiological correlations (using cadaver-based data) for the identified motor points were performed to validate this method, and the impact of electrode configuration when using bipolar stimulation.
4.3 Electrophysiological identification of motor points

The fundamental objectives of this chapter are to identify the motor points of the flexor and extensor muscles, which are responsible for wrist and individual digit control, towards realizing complete hand function. Also, to cluster those motor points into probable stimulation zones and to validate their physiological correlations. Furthermore, to understand the recruitment characteristics.

4.3.1 Participants

The study included eleven healthy male participants (27.3 yrs±4.0 yrs, BMI 24.8±3.0). Data from nine participants served as the training set ($n_{\text{train}}$=9) and two for validation ($n_{\text{test}}$=2). Participants considered for the study had no history of medical conditions, that were contraindicative to electrical stimulation, or deficits/injury to the hand.

4.3.2 Experimental setup

A custom-made setup (Chapter 3) was devised to characterize the motor points and to position/orient the forearm, thus enabling motor point identification under controlled pronated, supinated, and neutral positions, Figure 4.1a. The experimental setup featured an XY-gantry system that gave electrode positions about the forearm surface, which simplified the localization of motor points. Further to locating the motor points, the muscle response to subsequent stimulation was graded using isokinetic dynamometry. Accordingly, the isometric forces were measured using two SS25LA Dynamometer (BIOPAC Systems, Inc., California). One dynamometer measured the forces exerted by the thumb and wrist, and the other measures forces across the four digits. The positions of these sensors were adjusted to suit the user. Force measurements from these dynamometers sampled at 1 kHz were recorded using Biopac MP 36 (BIOPAC Systems, Inc., California).
Figure 4.1 Methodological identification of motor points and clustering.

[a] Experimental setup for motor point identification and isokinetic dynamometry. A customized stimulation waveform from a current-controlled stimulator was used to evoke a motor point. [b] The vertex points of 60 X 60 mm grids were marked for reference electrode positions; accordingly, the tracing electrode was traversed along the forearm. [c] Using GMMs, the motor point locations were grouped into clusters. [d] Clustered motor points represented as stimulation zones. By constraining participants' forearm under pronation, supination, and neural positions, the motor points were scanned using the interlaced scanning routine as in [b]. © [2019] IEEE. Reprinted, with permission, from [35].
Motor point stimulation was achieved using RehaStim™ 2 (Hasomed GmBH, Magdeburg, Germany). The output from the stimulator was a biphasic, current-controlled waveform. Using the ScienceMode Protocol (Hasomed GmBH, Magdeburg, Germany), the stimulation parameters were customized to evoke motor point stimulation, Figure 4.1b. Two electrodes, a reference electrode, DENIS01526 (UniMed Electrode Supplies, Surrey, UK) of 15 x 20 mm, and a tracing electrode, Compex motor point pen (Compex Medical SA, Switzerland) of ø 4 mm administered the bipolar stimulation. Given the prolonged nature of the study, adjustable and padded arm support further improved the participant’s comfort.

4.3.3 Experimental Procedures

Participants were seated in a comfortable position, and their arm was engaged in the setup. For a given orientation of the forearm, the objective was to systematically extract a profile featuring the motor point locations, their response, and electrode configurations. Motor points were also traced in the neutral position to assess their displacement to change in forearm orientation [102], [122]. Due to the characteristic limitation of transcutaneous stimulation, as explained earlier, only the superficial extrinsic muscles were stimulated. Accordingly, motor points that elicit flexion and extension of digits, along with flexion, extension, ulnar, and radial deviation of the wrist, were identified. The effectiveness of tNMES based stimulation must be determined by muscle tension [128]. To directly quantify muscle tension, isometric contact forces were measured. Information collected on motor point locations and their isometric force responses were standardized across the participants. Maximum voluntary isometric contraction (MVIC) was taken as the average of two maximum force exertions over a ten-second window was used to standardize the isokinetic force responses. Similarly, anthropometric measures on the length and radius of the forearm were used to normalize the motor point locations.
Movements considered for flexor muscle groups included thumb flexion (TF), index digit flexion (IF), middle digit flexion (MF), ring digit flexion (RF), little digit flexion (LF), wrist flexion (WF), and wrist ulnar deviation (WUD). Similarly, for the extensor muscles included thumb extension (TE), index digit extension (IE), middle digit extension (ME), ring digit extension (RE), little digit extension (LE), wrist extension (WE), and wrist radial deviation (WRD).

A current-controlled, symmetric biphasic stimulation waveform with a pulse width of 280µs, a fixed inter-pulse delay of 100µs, a pulse stimulation frequency of 50Hz were used. The stimulation parameters were chosen by considering the refractory period of skeletal muscles, 0.4 – 1 ms, and the fusion frequency for tetanic contraction [128]. By keeping the frequency and pulse width a constant, the stimulation amplitude was varied until motor point-based stimulation evoked a muscle response. For every participant, the lowest stimulation amplitude was chosen as a trade-off between their comfort and a substantial muscle contraction, which is referred to as the stimulation threshold throughout this chapter. As polarity has no effect when using symmetric bipolar stimulation [129], at a given instance, any one of the electrodes can stimulate a motor point, and the other becomes a return electrode. This yields several configurations that can have similar motor responses. Thus, it is vital to assess the impact of electrode configuration on the excitability of a motor point under bipolar stimulation. In this study, by keeping one electrode stationary, the other was traced over the forearm surface. Reference positions for the stationary electrodes were marked using a template, as in Figure 4.1b. For each reference position, the tracing electrode was traversed in an interlaced fashion along the entirety of the forearm surface.

For a valid muscle response, both the electrode positions and the forces were recorded. Electrode positions were localized in reference to anatomical landmarks [41], [130]. Similarly, a medial line bifurcating the forearm was drawn, Figure 4.1b. It joined the midpoint of the line connecting the radial
and ulnar styloid process and the midpoint of the line connecting the medial and lateral humeral epicondylar regions, each representing the radius of the forearm at the styloid process and the epicondylar region, respectively. The medial line represented the x-axis that runs along the forearm. Due to its bifurcation by the medial line, the line along the forearm radius represents the y,-y -axes. Electrode positions are referenced to these lines and were recorded as coordinates (XA, YA – for tracing electrode; XB, YB – for reference electrode). As these locations are subject-specific, they cannot be readily analyzed. Subject-specific electrode positions were normalized based on anthropometric measures ($\bar{X}A, \bar{Y}A$), as in Figure 4.2. For all pooled subjects the ratio$I_{ISR}$ was 0.6 and for the pro-supinated position the ratio$I_{IER}$ was 0.45; accordindly, Table 4.2 was used for normalizing the electrode position.

Similarly, the muscle tension under isometric conditions was standardized based on the MVIC. MEC represented the ratio of force exerted to its MVIC when the stimulation threshold was applied. Furthermore, based on the stimulation parameters and electrode locations, the interelectrode distance (IED), charge density, and recruitment index (RI) were derived as metrics to further characterize the nature of stimulation, as in Table 4.1.

**Table 4.1** Metrics derived for motor point characterization

<table>
<thead>
<tr>
<th>Metric</th>
<th>Notation</th>
<th>Formulation</th>
<th>Unit</th>
</tr>
</thead>
<tbody>
<tr>
<td>Normalized x-axis location</td>
<td>$\bar{X}A$</td>
<td>$\frac{X}{L_{\text{forearm}}}$</td>
<td>-</td>
</tr>
<tr>
<td>Normalized y-axis location</td>
<td>$\bar{Y}A$</td>
<td>$\frac{Y}{f(YA,ISR,IER)}$</td>
<td>-</td>
</tr>
<tr>
<td>Inter-electrode distance</td>
<td>$I_{ED}$</td>
<td>$\sqrt{(XB - XA)^2 + (YB - YA)^2}$</td>
<td>mm</td>
</tr>
<tr>
<td>Minimum evocable</td>
<td>$MEC$</td>
<td>$\frac{Isokinetic force}{MVIC}$</td>
<td>%</td>
</tr>
<tr>
<td>contraction</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Charge density*</td>
<td>$\rho$</td>
<td>$\frac{Amplitude}{PW \cdot IED}$</td>
<td>C $\cdot$ m$^{-1}$</td>
</tr>
<tr>
<td>Recruitment Index</td>
<td>$RI_{\text{Muscle}}^k$</td>
<td>$\frac{\sum_{n=1}^{k}(MEC/\rho)/N^k}{\max_{\text{Muscle}} (MEC/\rho)}$</td>
<td></td>
</tr>
</tbody>
</table>

*Linear charge density considered; k-mixture components as in section 2.4; N-Number of observations; © [2019] IEEE. Reprinted, with permission, [35].
Due to indifference in polarity with bipolar configuration, only the electrode that is close to the target nerve tends to stimulate a motor point [131]. In this case, the electrode proximal to the motor point becomes the active electrode, and the other becomes the return electrode. Accordingly, for various electrode configurations, the active electrode positions were considered to be the electrode that was on the target muscle.

**Figure 4.2** Normalizing the electrode location based on anthropometric measures

**Table 4.2** Pseudocode for normalizing the electrode location

```
Initialize electrode(X,Y)

alpha = 180 - (90 + tan\(^{-1}\)(1 - ratio\(_{ER}^{SP} \cdot IER)/FL))

scaled\(_{y-axis}\) = (FL/tan\(\alpha\)) + ratio\(_{ER}^{SP} \cdot IER\)

norm\(_{X}\) = (electrode \((X)/FL\) \(\times 100\)

norm\(_{Y}\) = (electrode \((Y)/scaled\(_{y-axis}\)) \(\times 100\)
```

end
4.4 Data Clustering and Analysis

Following the systematic evaluation, motor points were identified as coordinates along the forearm surface. Studies have often used descriptive statistics to localize these motor points [39], [41], [126]. Due to large variations within a population, motor point locations are non-linear and can also have missing data. Often homogeneity tests were done to rank the quality in data. The reliance of such statistical-based methods, on the nature of distribution and significant sample size, often limit the generalization of inferences drawn and may yield an unreliable outcome. This limitation instigates the need for techniques that identify underlying patterns in the data. Cluster analysis is one of such techniques that aim to partition data into groups of clusters. Similarly, a set of motor point locations \(\{\tilde{x}_n, \tilde{y}_n\}\) can be clustered into ‘\(k\)’ groups. Most clustering algorithms use their own similarity measure to partition data and group them.

By using metrics inherent to these algorithms, further analysis of data can be made. Accordingly, confidence ellipse (the area surrounding the data points of a given cluster) and its centroid were inferred. Although region boundaries can be drawn using means and standard deviations, it fails to account for the density and shape of data, which makes such an estimation untenable.

A generative probabilistic model-based clustering approach called the Gaussian Mixture Model (GMM) was used in this study [132]. GMMs are a branch of machine learning-based clustering algorithms that use probability distributions while categorizing data. Primarily, GMMs represent the given data as a mixture of Gaussian components (4.1). For each mixture component, the probability of generating every element within the distribution was computed first. The obtained model-specific probability is then used to assign data into clusters.
Such a distribution $p(x)$, is given as the weighted sum of $k$ mixture components, with each component having its weight ($\pi_k$), mean ($\mu_k$) and covariance ($\Sigma_k$).

\[
p(x) = \sum_{k=1}^{k} \pi_k(x|\mu_k, \Sigma_k)
\] (4.1)

While fitting a mixture of Gaussian distributions to the given data (with $N$-observations), the goodness of fit is quantitatively measured using the log-likelihood as in (4.2). By maximizing this likelihood, optimal parameters $\{\pi, \mu, \Sigma\}$ that represent each mixture component were derived iteratively. Furthermore, the weights of each mixture components ($\pi_k$) are also computed, which is the direct implication of density estimation.

\[
\ln p(x|\pi, \mu, \Sigma) = \sum_{n=1}^{N} \ln \left( \sum_{k=1}^{k} \pi_k N(x|\mu_k, \Sigma_k) \right)
\] (4.2)

For a given training set data (motor point locations), the data is inclusive of directly observed variables $\{\tilde{x}_n, \tilde{y}_n\}$ and latent variables [133]. These latent variables are hidden and can represent characteristic features of the training data. In GMMs, the latent variables represent the attributes of the mixture components that were used to generate each observation $\{\tilde{x}_n, \tilde{y}_n\}$. Contrary to popular clustering algorithms that use distance metrics to categorize data, using these latent variables, GMMs categorize data based on their attributes to fit a mixture component. Thus, the joint distribution $p(x,z)$ is represented as the product of the marginal distribution of latent variables $p(z)$ and the conditional distribution of the observed variables and the latent variables $p(x|z)$.

In this study, the expectation maximization (EM) algorithm was used to fit a gaussian mixture model to the motor point locations, Table 4.3. The EM is an iterative learning technique, wherein the objective is to find the optimal parameters $\theta = \{\pi_k, \mu_k, \Sigma_k\}$ that can maximize the log-likelihood, as explained earlier. The EM algorithm is shown in Figure 4.1c. During the expectation set up, for a given set of parameters $\theta$, the relative densities (responsibilities) are calculated for each component until they reach a convergence threshold.
The optimization criterion is to maximize the log-likelihood of estimated parameters $\theta$, to fit the component distribution. Using the latent variables, the component that generated each observation is inferred.

Rather than assigning data points strictly to each cluster (hard clustering), GMM based clustering assigns data points to each cluster based on their probability estimates. The information on the output class labels is known. Hence, the clusters were generated within each movement group. Herewith, the primary objective of clustering is to fit confidence ellipses and obtain cluster characteristics. The modeling approach for GMM-based clustering is shown in Figure 4.1c. Such a model was implemented using the Statistics and Machine Learning toolbox™ in MATLAB 2017a (The MathWorks, Inc., United States). Here, the motor point locations specific to each movement group were given as inputs for clustering. As these motor point locations are coordinates of $x,y$ along the forearm surface, the data represents a bivariate distribution wherein their covariances become an essential feature.

Table 4.3 Pseudocode for gaussian mixture clustering of a bivariate data

<table>
<thead>
<tr>
<th>Input $data_{in} = {electrode_{X_{\text{muscle}}}, electrode_{Y_{\text{muscle}}}}$</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>routine GMM fitting</strong></td>
</tr>
<tr>
<td>Initialize $k_{in}, \theta = {\pi_k, \mu_k, \Sigma_k}$, Iterations do</td>
</tr>
<tr>
<td>for k do</td>
</tr>
<tr>
<td>for covariance ${\text{type, sharing}}$ do</td>
</tr>
<tr>
<td>Fit GMMs</td>
</tr>
<tr>
<td><strong>Expectation step</strong> $q(x) = p(x</td>
</tr>
<tr>
<td><strong>Maximization step</strong> $\theta = \arg\max_{\theta} \sum_{n=1}^{k} {q(x) \ln \cdot p(x</td>
</tr>
<tr>
<td>end</td>
</tr>
<tr>
<td>end</td>
</tr>
<tr>
<td>while convergence do</td>
</tr>
<tr>
<td>find $GMM_{opt}{k_{opt, \theta_{opt}}} \rightarrow \min (BIC \ or \ AIC)$</td>
</tr>
<tr>
<td>end</td>
</tr>
<tr>
<td><strong>end routine GMM clustering</strong></td>
</tr>
<tr>
<td>train $GMM_{opt}$</td>
</tr>
<tr>
<td>estimate component probability $data_{in}$</td>
</tr>
<tr>
<td>assign cluster labels</td>
</tr>
<tr>
<td><strong>end routine</strong></td>
</tr>
</tbody>
</table>
Firstly, several GMMs that fit the Gaussian mixtures based on the number of predefined clusters \(k_{in}\) and random \(\theta\) were obtained. As GMMs are highly susceptible to initial conditions, a fixed k-means++ based initialization [134] was used across all models. Upon convergence, using the Bayesian information criterion (BIC), the model that best fits the distribution was determined [132]. These model parameters represent the optimal number of clusters \(k\) with respective weights \(\pi_k\) and covariance properties \(\Sigma_k\). By fitting this GMM to our given data distribution, the probability density function (PDF) for each of \(k\) mixture components were known.

Thus, the identified stimulation locations were clustered based on their membership (relative) probabilities to lie in any of those \(k\) components. Ultimately, the inverse of chi-squared \(\chi^2\) was applied to each component PDF to estimate their confidence ellipse with 95% CI. Each of these \(k\) confidence ellipses, which represent a probable stimulation zone.

Further to deriving the stimulation zones, its physiological significance and generalization (traceability) were also assessed. Each stimulation zone represents one of the \(k\) mixture components with a muscle group. The physiological validity of each component was ensured by comparing it against the motor entry point (MEP) identified from cadaver studies [127], [135]. As each \(k\) component has its own PDF \(p^k(\theta)\), the posterior probability \(p(\theta|\text{MEP})\) represents the likelihood of finding the MEP \(p(\text{MEP}|\theta)\) within the respective stimulation zone as given by (4.3).

\[
p(\theta|\text{MEP}) = \frac{p(\text{MEP}|\theta)p(\text{MEP})}{p^k(\theta)} \tag{4.3}
\]

Also, the test for generalization was done by comparing each \(k\) component distributions obtained from the training participant set \(Q^k_{\text{muscle}}\) with the test participant set \(T^k_{\text{muscle}}\). The Hellinger distance \(h\) was used as a measure to quantify the degree of divergence between the two distributions [136].
For probability distributions, the Hellinger distance between \((Q, T)\) is given by (4.4).

\[
h_{(Q,T)} = \frac{1}{\sqrt{2}} \| \sqrt{Q} - \sqrt{T} \|_2
\] (4.4)

As a final step, an atlas of stimulation zones that can best elicit a motor point-based stimulation for each muscle group was derived. A single muscle may have more than one \(k\) component. However, an ideal stimulation zone was regarded as the one with high physiological significance and can easily be traced. Accordingly, each stimulation zone was graded based on their component weights \((\pi^k)\), recruitment index \((RI^k)\), generalizability \((h_{(Q,T)})\) and its physiological validity \((p(\theta | MEP))\). Based on the weighted average of these parameters specific to each mixture component \(k\), optimal clusters were ranked (4.5). Wherein the optimal stimulation zone retains the best trade-off among these factors.

\[
\text{rank} = \arg \max_{k \in \text{muscle}} (\pi^k, RI^k, p(\theta | MEP), \min(h_{(Q,T)}))
\] (4.5)
4.5 A generalized motor point catalog

The length of the forearms from all participants was 275.5±17.0 mm. The forearm radius at the inter-styloid process at the neutral position was 41.7±3.0 mm, and the pro-supinated position was 55.6±4.0 mm. The inter-epicondylar radius was 90.6±6.0 mm. The MVIC measures across participants for various muscle groups are shown in Table 4.4.

Table 4.4 Maximum voluntary contraction for various muscle groups

<table>
<thead>
<tr>
<th>Group</th>
<th>TF</th>
<th>IF</th>
<th>MF</th>
<th>RF</th>
<th>LF</th>
<th>WF</th>
<th>WUD</th>
</tr>
</thead>
<tbody>
<tr>
<td>MVIC</td>
<td>16.1</td>
<td>15.6</td>
<td>15.1</td>
<td>9.0</td>
<td>6.3</td>
<td>27.0</td>
<td>18.0</td>
</tr>
<tr>
<td>(N)</td>
<td>±7.0</td>
<td>±5.0</td>
<td>±5.0</td>
<td>±3.0</td>
<td>±2.0</td>
<td>±15.0</td>
<td>±8.0</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Group</th>
<th>TE</th>
<th>IE</th>
<th>ME</th>
<th>RE</th>
<th>LE</th>
<th>WE</th>
<th>WRD</th>
</tr>
</thead>
<tbody>
<tr>
<td>MVIC</td>
<td>8.7</td>
<td>6.8</td>
<td>6.3</td>
<td>6.3</td>
<td>4.3</td>
<td>17.9</td>
<td>17.2</td>
</tr>
<tr>
<td>(N)</td>
<td>±2.0</td>
<td>±2.0</td>
<td>±2.0</td>
<td>±2.0</td>
<td>±2.0</td>
<td>±6.0</td>
<td>±8.0</td>
</tr>
</tbody>
</table>

4.4.1 MEC to Evaluate Motor Point-Based Stimulation

The threshold to elicit motor point-based stimulation was different across subjects. Accordingly, with an average stimulation intensity of 6.1±1.0 mA, 7.2±2.0 mA, and constant stimulation parameters, motor point-based stimulation was achieved across flexor and extensor muscles. As the muscle responses were standardized, various muscle groups were directly compared. The quantiles in the data, along with their kernel densities, are illustrated as violin plots in Figure 4.3. Motor point-based stimulation was able to achieve 21.3±15.0 % MEC and 29.6±17.0 % MEC across the flexor and extensor muscles. For flexor muscles maximum MEC of 34.2±17.0 % (5.64±1.0 mA) was achieved for RF and the lowest MEC of 14.6±11.0 % (6.24±2.0 mA) for TF. Also, for extensor muscles, maximum MEC of 41.9±20.0 % (7.8±2.0 mA) was achieved for LE, and the lowest MEC of 17.6±12.0 % (6.9±2.0 mA) for WE.
4.4.2 Motor point clusters and their physiological significance

Using GMMs, the motor point locations represented as the pooled training set data for each muscle group were clustered. Such clusters obtained for flexor and extensor muscles are depicted in Figure 4.4 and Figure 4.5. GMM-based clustering uses membership probabilities as a similarity measure to categorize such motor point locations.

Accordingly, the GMM contours in Figure 4.4 and Figure 4.5 represent the motor point locations within any of the k-clusters. The probability is very strong at the center, and it weakens as it moves away from its centroid (*). Due to varying covariances, each of the k-clusters has a unique shape, size, and direction. The nature of covariance that best fits a Gaussian mixture to given distribution was determined based on the model evaluation criterion (BIC). All GMMs contours bound the experimental data with a 95% confidence interval.

By fitting an ellipse to each cluster, its properties such as major axis, minor axis, angle of deviation from the major axis, eccentricity, and area...
were calculated. Further to cluster analysis, the physiological correlations of each cluster were analyzed. For every movement group in Figure 4.4 and Figure 4.5, their own MEPs are represented by triangles ($\Delta$).

Such MEP locations were derived from cadaver-based studies [127], [130], [137]. MEPs that remain within the confidence region of any of the $k$ clusters were denoted by green triangles. Except for LE, WRD most of the physiological MEPs fall within the experimentally derived clusters. As the PDF for each cluster group is known, by calculating the posterior probability of an MEP with respect to each cluster, its physiological correlations were evaluated. Clusters for TF, MF, WF of flexor muscles and TE, IE, ME, RE, WE of extensor muscles have the highest posterior probability, as in Table 4.5 and Table 4.6.

![Motor point clusters for flexor muscle groups](image)

**Figure 4.4** Motor point clusters for flexor muscle groups

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Furthermore, cross-validation of the training set clusters against the test set clusters is shown in Figure 4.4 and Figure 4.5. The training set data is represented by red makers. The overlapped distribution indicates the likelihood of test subject data to lie within any one of the $k$ training set clusters. To quantitatively assess this likelihood, the average divergence of each test set cluster against the training set clusters were estimated using the Hellinger distance metric (4.4).

When considering distance as a divergence metric, two similar distributions must have a distance of zero, and it increases as the likelihood decreases. The clusters for both flexor and extensor groups agree well with the test group data as well as the physiological MEP, indicating the viability of eliciting a motor point stimulation, in support of their generalizability.
The properties of each cluster, their confidence regions, recruitment index, posterior probabilities of MEPs, and cross-validation through Hellinger distance are presented as tables. By assessing these properties designated to each cluster, they were ranked based on (4.5), as seen in Table 4.5 and Table 4.6. Furthermore, GMMs specific parameters ($k_i$, $\Sigma_k$) can also be added to (1), which can change the number, shape, and orientation of the clusters.
### Table 4.6 Properties of motor point clusters for extensor muscle groups

<table>
<thead>
<tr>
<th>Group</th>
<th>Cluster properties</th>
<th>Properties of confidence ellipses</th>
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<th>Cross-validation</th>
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### 4.4.3 Stimulation Zones - Traceable Motor Point Locations

Stimulation zones are clusters of motor points with confidence boundaries and graded properties (4.5). From a data clustering perspective, the pooled motor point locations can be categorized into $k$-clusters. However, an optimal cluster should represent a highly generalizable and traceable motor point location. Accordingly, Figure 4.6 represents the stimulation zones, which are optimal motor point clusters that were ranked ‘1’ based on (4.5).
4.4.4 Recruitment Characteristics for Bipolar Stimulation

Although several factors affect motor unit recruitment, the charge density was the only externally controllable factor. The average stimulation threshold for flexor muscles was $6.3 \pm 1.3 \text{ mA}$, and the extensor muscle was $7.4 \pm 1.5 \text{ mA}$. As the stimulation amplitude was kept minimal throughout this study, the recruitment demand was compensated by the IED.

Further to clustering, the motor point data were categorized into 30% [0-30%], 60% [30-60%], and 100% [60-100%] MEC, with which the respective IEDs were analyzed. Fig 4.7 shows the quantile distribution of IEDs for 30%, 60%, and 100% MEC for flexor and extensor muscles. For both flexor and extensor muscles, the maximal MEC (60-100%) was exerted if the IED was smaller.
Figure 4.7 Distribution of inter-electrode distances across the forearm muscles.
This was also further corroborated by correlation analysis, wherein, the Pearson correlation coefficient \( r \) was negative for both flexor \( r = -0.29 \) and extensor muscles \( r = -0.24 \). Hence an optimal electrode configuration when using bipolar stimulation can be regarded as the set of electrode locations with smaller IEDs that can evoke comfortable and substantial muscle contraction.

The motor point locations directly represent the active electrode positions; accordingly, the return electrode positions that can evoke maximal MEC (60-100\%) for each muscle group. Out of various scanned configurations, these electrode combinations embody the return electrode locations, where the IED was minimal for each muscle group. Choosing any return electrode position within the radius of minimal IED can evoke substantial muscle contraction.

Pronation and supination are typical forearm movements that tend to displace the motor points along the direction of rotation. Although deep motor points are less susceptible to forearm rotation, superficial motor points, and motor points that are proximal to the wrist are often displaced. The displacement of motor points for pronation and supination were quantified based on their shifts from the neutral position. Accordingly, the magnitude of the displacement was evaluated based on the shifts in their centroids between the neutral position and the displaced position.

### 4.4.5 Displacement of Motor Points for Forearm Positions

The displacement of centroids for various muscle groups from their pronated and supinated positions is shown in Figure 4.8. The extensor muscles responsible for TE, IE, ME, and the flexor muscles responsible for TF and MF were displaced during the forearm movements. These muscles were along the median line of the forearm, which were subjected to maximum displacement. With a mean shift of 144\% along the radius of the forearm, maximum displacement was seen in ME muscles.
Figure 4.8 A roll-out plot showing the displacement of motor points.

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4.6 Discussion

One of the prevailing problems with wearable neuroprostheses is the lack of adequate information on motor point catalogs [33], [94], [123], that limit such systems from restoring a complete hand function. The study conducted in this chapter was the first of its kind to characterize motor points based on their location, recruitment, and displacement, which has direct implications for such systems. This can significantly decrease the setup time, and calibration often performed towards subject-specific customization. Also, the stimulation zones derived from this study can assist clinicians with electrode placements for functional electrical stimulation-based therapy.

In accordance with previous studies, a high level of variability with the availability and the localization of motor points was observed across subjects. Hence, the problem of localizing motor points and their generalization was the interest of this study. When deploying bipolar stimulation, the optimal location to simulate a motor point was dependent on the electrode configuration, and the stimulation parameters. Hence, several combinations of sites that elicited motor point-based stimulation for various electrode positions were obtained. The advantage of this scanning routine enabled us to cluster the stimulation sites in deriving a generalizable map. Also, considering a comparatively larger cohort size (n=9) that gave the study a statistical advantage over existing studies [39], [41].

Manual search-based cataloging involves prolonged sessions; hence, studies are often performed with a limited number of subjects [41]. Also, the inter-subject variability of motor point locations [126] further limits any statistically significant result. Although several motor point catalogs exist, due to the limiting factors, such catalogs are not readily generalizable. Moreover, the data on motor points have non-linearity, and conventional statistical-based techniques are limited from deriving any significant
inference from such data. By demonstrating the feasibility of extracting meaningful information from the underlying patterns within motor point clusters, the abovementioned limitations have been addressed in this study using the generative clustering approach. The generative approach, based on GMMs clustering is good with handling missing data and outliers [133], such as the motor point data. Commonly used clustering techniques (k-means), partition data into clusters based on hard assignments. On the contrary GMMs-based clustering performs a soft assignment based on the membership probabilities [132]. Additionally, based on the data distribution properties, density estimation is accounted, while fitting a Gaussian mixture model [132].

Representing motor point locations based on probability contours (PDF) along with their density estimates ($\pi^k$) improves the generalization and a novel approach towards motor point cataloging. Prior to clustering, the GMMs fits are evaluated based on the model evaluation criterion. Also, confidence intervals (95% CI) were assigned to each cluster after clustering; these steps improved the statistical rigor with the inferences being drawn [132]. Thus, the use of probabilistic generative clustering (GMMs) was emphasized in this study.

Furthermore, the importance of stimulation zones also stems from their ranking (5). For simplicity, equal weights were chosen for this study. Thus, each stimulation zone retains the best trade-off among its component weights ($\pi^k$), recruitment index ($RI^k$), generalizability ($\tilde{h}_{(Q,T)}$) and its physiological validity ($p(\theta|MEP)$). Further to embody generalizable motor point clusters, ranking the stimulation zones can open the potential for deriving application-specific stimulation zones. Wherein, a stimulation zone can have a higher recruitment index (suited for inducing therapeutic benefits) or be more generalizable (restoring hand function using assistive devices). Furthermore, GMMs specific parameters ($k_{in}, \Sigma_k$) can also be added to (1), which can change the number, shape, and orientation of the clusters, which can better accommodate electrode array designs [33].
Also, the Hellinger distance demonstrated the similarity between the trained GMMs cluster and clusters form test data. However, this method of validation is different from the conventional cross-validation techniques that are used to train ML-based classifiers. In our study, an unsupervised clustering on the experimentally derived motor point locations was done. Hence, similar cross-validation cannot be performed. Moreover, the data from the test-subjects cannot be considered an ideal output class, against which the GMMs clusters were trained. Furthermore, the GMMs-based clustering had an inbuilt performance evaluation criterion based on loglikelihood (2) and BIC. Hence, a similarity measure, which could be analogous to conventional cross-validation techniques was used. This enabled us to demonstrate that the trained GMMs cluster was able to generalize previously unknown data, i.e., the clusters of test data. Additionally, a future work that assess the stimulation performance of using the map derived from motor point clusters will further corroborate the study’s claim towards its generalizability.

As the polarity effect is indifferent with bipolar stimulation, multiple electrode configurations can have the same functional outcome. For a given bipolar electrode configuration, any electrode (active or return) can activate a motor point. This effect was inferred in the study. Accordingly, the raw experimental data was processed, such that the electrode that lies with the target muscle was considered the active one and the distant electrode to be the return electrode. This further implicates the importance of placing one of the electrodes close to the motor point or along the path of charge flow [126]. Also, a comfortable and isolated muscle contraction [102] can be achieved by keeping the IED to a minimum [45]. This property was due to the inverse proportionality of IED and its effect on overall current density.
4.7 Summary

The viability of fine digit control has been demonstrated through motor point-based stimulation, which enabled targeted and isolated activation of muscle groups. Transcutaneous stimulation systems aim to restore hand function by enabling dynamic control over motor point-based stimulation. Wherein, their design and control algorithms are formulated based on a priori knowledge on the location of these motor points. Often, anatomical charts and manual search techniques are used to extract the individual-specific stimulation profile. Such information being heterogenous, they lack standardization and reproducibility. These limitations were addressed in this chapter by identifying, localizing, and characterizing the motor points across the forearm muscles. Sites that allowed motor point-based stimulation were identified among nine healthy participants. These sites were clustered using Machine learning-based clustering algorithms, following which their centroids and confidence regions were derived. Moreover, such experimentally derived clusters had physiological correlations, and further cross-validation was also in agreement with two test subjects. Thus, demonstrating the generalizability achieved by clustering motor point locations. With current literature lacking such data, the novelty of this chapter lies in the representation of baseline information on location, shape, and the recruitment of stimulation zones available for selective control of various muscle groups using bipolar stimulation.
5. Characterizing muscle stimulation

In the previous chapter, the motor points of forearm flexor and extensor muscles were identified. Such identification is crucial to facilitate fine digit control. However, to extend the applicability of precise digit control to hand manipulation tasks, the determinants of force generation must be understood to evoke optimal muscle contraction during ADL tasks. Accordingly, the influence of transcutaneous stimulation on muscle contraction, stimulation comfort, and stimulation-induced fatigue was quantified. Finally, by varying the stimulation parameters, and the motor points, the likelihood of personalized digit/wrist control was demonstrated.
5.1 Significance of characterizing evoked muscle activity

Disability from upper extremity paralysis resulting from Spinal cord injury (SCI) affects one’s quality of living. Regaining complete hand function gives them the independence to carry out activities of daily living (ADL) as the hand contributes to 90% of upper extremity functions involving manipulation tasks. Likewise, the primary demand among SCI victims was to recoup hand function [22], [25], [138]. Any form of grasp, ranging from power to precision, can be mediated by coordinated fingers and thumb motion with controlled force exertion. Moreover, the conformity and the total force exertion is comparatively higher with digit coordinated grasps. Hence, achieving fine digit control and its coordination is decisive, given the priority need for hand function tasks. Although Functional electrical stimulation (FES)-based systems have demonstrated to restore grasp/release [12], [36], [44], [107] and upper extremity functions [11], [109], complex hand function tasks have not yet realized. Moreover, multi-digit coordination is a complex task that requires the synergistic activation of several muscle groups. Major factors that limit transcutaneous stimulation from realizing hand function tasks are the selectivity of target muscles [41], the accompanied pain [42]–[44], the onset of fatigue, and the inter-subject variability in choosing optimal stimulation parameters.

Muscles of the forearm must be stimulated to facilitate hand function tasks. Since the forearm muscles are tightly packed, stimulation must be targeted; any spillover may activate adjacent muscle groups resulting in its co-contraction. Advances with distributed electrodes have improved the capabilities of conventional FES-based stimulation. With the ability to dynamically control more than one muscle group, these electrodes also facilitate targeted muscle activation. Additionally, to selectively elicit flexion/extension of digits, electrode placements [122] and motor-point catalogs (Chapter 4) [35] have also been derived. Hence, achieving a selective digit control using transcutaneous electrodes is relatively simplified.
Varying levels of force must be exerted while performing hand manipulation tasks. However, the inherent limitation of stimulation-induced fatigue complicates the applicability of FES-based systems. Regardless of the recruitment demand, fatigue onsets from the synchronous activation of motor units as both slow-and fast-twitch fibers are excited. The fatigue response of large muscle groups such as the quadriceps, biceps brachii has been well documented [112], [139]–[141]. However, such characterization is lacking for forearm muscle groups. Ideally, stimulation must be highly selective, comfortable, and evoke desired muscle contraction. Parameters of the stimulation waveform, including its amplitude, pulse-width, and frequency, and the electrode properties, including its surface area and inter-electrode distance, are externally controllable factors that influence the stimulation performance.

Muscle recruitment, the onset of fatigue, and stimulation comfort can be regulated using the previously mentioned, externally controllable factors. By facilitating random recruitment order, which is asynchronous, the rippled force generation and muscle fatigue with surface stimulation can be compensated [139], [142]–[144]. Also, the use of low frequencies in combination with longer pulse duration with high voltages can maximize motor unit recruitment with reduced metabolic demand [112]. Also, for both healthy and people with SCI, low-frequency asynchronous stimulation had superior fatigue reduction, when compared to any other form of stimulation [145]. Optimal pulse duration can significantly render comfortable muscle contraction. Accordingly, a pulse-width of 300µs was more suitable for forearm muscles when compared to low pulse-widths of 50µs. Also, the frequency of stimulation affects the type of muscle contraction and muscle tension [70]. A safe stimulation with a frequency of 20-50 Hz is recommended, which is based on the normal motor unit discharge rate during volitional activity [146]. Any frequency greater than 70 Hz can cause neuromuscular junction failure.
Moreover, forearm muscles have varying innervation depth, innervation ratios, and musculature, making the influence of these parameters highly specific to the muscle type. Increasing the stimulation amplitude to achieve higher muscle contraction of deep nerve fibers can be discomforting. Alternatively, increasing the stimulation frequency to achieve higher contraction levels can result in a rapid onset of fatigue. Thus, for prolonged usage, both stimulation-induced fatigue and discomfort must be studied. Such measures can aid with deriving optimal and safe stimulation protocols that are crucial to sustaining desired force levels while performing for ADL-based tasks.

Hence, the goal of the chapter is twofold: 1) To systematically assess the influence of stimulation parameters while exerting varying muscle contraction levels across a forearm muscle. Muscle contraction was characterized based on twitch, tetanic, and fatigue responses along with stimulation comfort. 2) To demonstrate the synergistic activation of muscle groups in facilitating ADL-based activities based on the previously obtained parameters to have controlled force exertion.
5.2 Evaluating muscle contraction

5.2.1 Participants

The study was conducted on four healthy participants (3M+1F, 29.2±1.1 yrs., 172.5±5.6 cm, 82.5±5.5Kg). Participants included for the study had no orthopedic impairment of the upper limb and no history of medical conditions contraindicative to electrical stimulation. The study was approved by the university’s ethics review board, and all participants gave informed consent before experimentation. Hand dominance can affect the motor unit firing behavior; hence, all experimental procedures were performed on the non-dominant forearm [147]. Accordingly, four left-forearms were considered.

5.2.2 Experimental setup

The hand grasp assessment setup that was described previously in Chapter 3 was used. While the participants sat in a comfortable position, the custom-built setup constrained the position of their forearms. The stimulation was delivered through a current-controlled stimulator, Rehastim™ (Hasomed GmbH). The stimulator had eight channels to deliver customized stimulation and supported various pulse generation modes. For this study, a single monophasic rectangular pulse and a symmetric biphasic pulse-train were used. A self-adhesive, pre-gelled, Ø24 mm electrode, CDE0241026 (UniMed Electrode Supplies, Surrey, UK), was used to deliver the stimulation. The size of the electrode was empirically chosen to have good selectivity. Also, the Motor point pen ™ (Compex SA, Switzerland) was used for motor point identification. The ADL-based grasps were mediated by dynamic control over the forearm muscles using an electrode array-based sleeve. The sleeve had several reconfigurable 3 x 3 pads of Ag-AgCl-based disposable snap electrodes, that covered the desired forearm regions.

In addition to dynamometry, the muscle activity was also recorded using the electromyography while performing electrically evoked isometric
contractions. Disposable Ag–AgCl electrodes (Kendall™, Covidien, USA) was placed on the forearm surface to measure muscle activity. Force measurements from the dynamometers and the EMG signals were recorded at 1 kHz and 10 kHz, respectively, using the Biopac MP 36 (BIOPAC Systems, Inc., California).

5.2.2 Experimental procedures

Two experimental procedures were carried out in this study. Firstly, the muscle response to electrical stimulation was characterized. Secondly, optimal stimulation parameters were derived to facilitate seven ADL-based grasps.

Muscle contractions were measured in terms of percentage of maximum voluntary isometric contraction (MVIC), taken as the peak force during three consecutive voluntary contractions (~5 s contraction separated by 60 s of rest). While performing muscle contractions, participants were asked to rate their discomfort using a ten-point visual analog scale (VAS), with 0 corresponding to “no pain” and 10 corresponding to “the worst possible pain.” For all protocols, the stimulation amplitude was varied between 0 – 20 mA, with one mA increments. For a reliable VAS score evaluation, participants were habituated to varying levels of stimulation before the experimental procedures.

The flexors of the wrist, while eliciting muscle contractions at 20% MVIC was studied. Accordingly, the Flexor digitorum superficialis and Flexor digitorum profundus muscles were stimulated at their motor points. Following a scanning routine, the respective motor points were identified.

Firstly, using a single monophasic pulse (twitch stimulation), the excitability was measured. For 300 µs pulse-width, the minimum current required to elicit a noticeable sensation and a muscle twitch were recorded as sensory and motor thresholds, respectively. Then, the pulse-width was varied between 100 and 500 µs with 50 µs increments and the twitch responses, and the sensation of discomfort was measured for 20 % MVIC.
Secondly, using a symmetric biphasic pulse train (tetanic stimulation),
tetanic responses were measured across the muscle for 20 % MVIC along
with the VAS scores. Here, the frequency was kept constant at 20 Hz. The
stimulation frequency of 20 Hz was considered after the minimum fusion
frequency for muscle contraction, and the pulse-width of 300 µs has been
widely used for the stimulation of forearm muscles. A safe stimulation, with
a frequency of 20-50 Hz, was administered [146], [148]. The characteristic
change between pulse width and force as a function of Muscle recruitment
was dependent on the stimulation amplitude, muscle length, and the
electrode location. During tetanic stimulation, every muscle contraction was
sustained for 3-5 seconds.

Lastly, using the same protocol as above, the fatigue responses were
measured. However, stimulation discomfort was not studied this time.
Here, the time taken for the peak electromyography (EMG) signal to fall to
50% of its amplitude was measured. The muscle contraction levels were
measured using the amplitude of EMG signals. The EMG signals were post-
processed using a Butterworth filter with a cutoff frequency of 20-500Hz,
and later the comb filter was used to remove the stimulation artifacts [106],
[149].

Following the characterization study, five ADL-based grasps, spherical,
hook, cylindrical, jaw chuck, and tip grasp were demonstrated. The
implication being these grasps are fundamental to normal hand function.
Achieving these grasps can enable a ‘functionally viable hand’ [150].
5.3 The response of an electrically stimulated muscle

All the participants were able to successfully elicit the flexion of the wrist through motor point-based stimulation. The motor threshold, identified as a noticeable twitch for a 300 µs stimulation, was 6.6±2.4 mA. However, no observable change was noticed for the sensory threshold, and it was consistent for all participants by 2 mA.

Following the excitability measures, the twitch response to elicit 20 % MVIC is shown in Figure 5.1a. The amplitude required to elicit the target response increased with decreasing pulse-width. The longest pulse-width, 500 µs demanded 16.3±0.4 mA and the shortest pulse-width, 100 µs demanded 30.5±1.7 mA. A pulse-width increase from 100 to 500 µs decreased the stimulation amplitude by 46.7 % to elicit the target MVIC. For a single monophasic pulse, the total charge per phase is lower; hence, to recruit more motor units, higher stimulation amplitudes were noticed.

Figure 5.1b shows the discomforting sensation reported via the VAS. Lower pulse-width demanded higher stimulation amplitudes, and hence, the sensation of discomfort was higher. Hence, the sensation of comfort increased with increasing pulse-width.

![Figure 5.1](image_url) [a] Strength-duration and [b] pain-duration curve for a single monophasic pulse.
The tetanic response to elicit 20 % MVIC is shown in Figure 5.2a. Unlike twitch response, the tetanic response is formed by the fusion of several muscle contractions that resulted in the flexion of the wrist. Hence, the intensity of the stimulation was comparatively less. Also, the amplitude required to elicit the target response increased with decreasing pulse-width. With a constant pulse frequency of 20 Hz, the longest pulse-width, 500 µs demanded 8.5±2.3 mA and the shortest pulse-width, 100 µs demanded 13.7±2.4 mA. Compared to the twitch response, there was a 47.6 % and 54.9 % reduction in stimulation intensity for 500 and 100 µs, respectively.

Also, the VAS scores followed a similar trend; wherein, longer pulse-widths were less discomforting. However, the range of the VAS scores (4-7) was lower when compared to the twitch response (6-8). This implicates that due to incomplete contractions during a twitch response, more current is required to sustain the muscle contraction level. The stimulation amplitude directly influences the strength of muscle contraction by affecting motor unit recruitment. Furthermore, high intensities also consequently stimulate the superficial sensory fibers causing severe discomfort.

![Figure 5.2](image-url)  
**Figure 5.2** [a] Strength-duration and [b] pain-duration curve for a tetanic stimulation.
The plots comparing muscle contraction levels while sustaining 20 % MIVC for twitch and tetanic responses are shown in Figure 5.3a and b, respectively. Here, for both stimulation types, longer pulse-widths deliver a comfortable stimulation. However, to yield a similar muscle response, tetanic stimulation demanded less stimulation amplitude.

![Graphs showing muscle contraction levels and sensation of discomfort](image)

**Figure 5.3** MVIC levels for [a] twitch and [b] tetanic stimulation along with the sensation of discomfort as VAS scores normalized between 0-1.

The time taken for the muscle contraction to drop to 50 % of the desired MVIC level was calculated as a measure of onset of fatigue. Accordingly, 10 and 20 % MVIC were considered. When compared against volitionally sustained muscle contraction, electrical stimulation resulted in the onset of fatigue. Accordingly, the time taken for 10% MVIC to fall to 5% MVIC was 54.0±7.0 s, and for 20 % MVIC to fall to 10 % MVIC was 44.0±3.0 s.

Moreover, it was evident that for low force demands (10%), fatigue was comparatively delayed. However, higher contraction levels (20%) resulted in faster fatigue.
5.4 Digit coordinated grasps

Previously identified motor points in Chapter 4 simplified the tracing for stimulation sites. Here, motor point-based stimulation enabled selective activation for digit and wrist flexion, Table 5.1. Several sites that elicited motor point-based stimulation for a single subject are shown in Figure 5.4. Here, an amplitude varying (1-10 mA) monophasic pulse, with a pulse-width of 300 µs was used to identify the motor points. The most prominent muscles were Flexor digitorum superficialis & Flexor digitorum profundus; being the prime driver for the flexion of digits 2-5, it had the largest concentration of stimulation sites. Nevertheless, due to proximity, segregating the flexion of the middle from the Index finger and the Ring finger was a demanding task. The muscles for various movements of the wrist and thumb were readily available. Moreover, even the pronation of the forearm was achieved in all subjects by stimulating the PT muscle. Achieving fine control over the flexion of forearm muscles, as in Table 5.1, demonstrated the viability of realizing complex and near-normal hand function. It is worth noting that the location of electrodes was susceptible to the forearm orientation, and displacements in the electrode position altered the recruitment properties or activated the neighboring muscles.

![Figure 5.4 Stimulation sites for flexor muscle groups](image)

73
Table 5.1 Stimulation of forearm flexors for digit and wrist control.

| Thumb flexion | The flexion of thumb was achieved by placing one electrode on the motor point over the muscle belly of Flexor Pollicis Longus and the return electrode over the tendinous area of the Flexor digitorum superficialis or Flexor digitorum profundus. Achieving flexion of thumb with electrode over the forearm region does not intrude in-hand manipulation tasks. |
| Thumb abduction | The abduction of thumb was achieved by placing one electrode on the motor point over the belly area of APB and the return electrode over the muscle belly of Flexor digitorum profundus far away from the active electrode. However, placing an electrode over the palmar region of the hand can obstruct in-hand manipulation tasks. |
| Index flexion | Positioning the electrode for index flexion was arduous, as most of the co-contraction of other digits were evident, which was either accompanied by thumb flexion or by the flexion of the middle digit. However, flexion of the index was achieved using two combinations, either by placing the electrodes between the distal tendon distal and the muscle belly of Flexor digitorum profundus or by placing the electrodes between the proximal tendon and the muscle belly of Flexor digitorum profundus. |
| Middle flexion | Achieving the flexion of the middle digit was effortless. Low stimulation amplitudes elicited distinct middle flexion. However, increasing the stimulation amplitude resulted in the flexion of the wrist. The active electrode was placed on the muscle belly of the Flexor digitorum profundus, and the return electrode over the tendinous region or away from the muscle belly. |
The flexion of the ring digit was delicate to achieve as the same muscle is responsible for flexion of the middle, ring, and little fingers. Nevertheless, effective control over its flexion was achieved by placing the active electrode on the medial part of the Flexor digitorum superficialis belly, and the return electrode away from the active electrode over the tendonious region or the epicondylar region.

The flexion of the little digit was achieved by placing the active electrode over the far medial side of the Flexor digitorum superficialis, and the return electrode over the lateral tendonious region of Flexor digitorum superficialis. Although the little digit offered the least significance to ADL tasks, for power grasp, it offers conformity over the objects being held.

Stimulation for flexion of the wrist was easily achieved. Here, flexion of the wrist was achieved by the stimulation of Flexor digitorum superficialis. Ideally, the electrode locations were similar to middle flexion; however, at higher stimulation amplitude, it consequently flexed the wrist.

Wrist adduction was achieved by stimulating the FCU. The return electrode was on the Brachioradialis and the active electrode over the muscle belly of FCU. This configuration yielded the optimal deviation of the wrist.

Following the characterization study, to deliver a comfortable and sustained level of muscle contraction, tetanic stimulation was preferred. Suitably, for a fixed stimulation frequency of 20 Hz, the stimulation amplitude was varied between 8 to 15 mA. Also, the pulse width was held
at 300 µs. Electrode placements from Table 5.1 were used to elicit flexion of the digits or the wrist. Accordingly, to demonstrate common hand manipulation tasks, five ADL grasps, spherical, hook, cylindrical, jaw chuck, and tip grasp, were demonstrated, Figure 5.5 - Figure 5.9. These grasps signified prehension from power to precision. Here, two or more muscles were activated simultaneously to realize these grasps. Desired muscles were simultaneously activated using an electrode array-based stimulation.

Spherical grasp was achieved by simultaneous activation of digits 1-5, Figure 5.5. Two stimulation channels were used. Firstly, the flexion of thumb was achieved, using electrodes A and B, which stimulated the flexor pollicis brevis muscle. Secondly, the flexion of digits, 2-5 were achieved by stimulating the Flexor digitorum profundus muscle. A higher stimulation amplitude of 12-15 mA was used to activate a large area of the muscle group, through electrodes C and D, that flexed the digits.

![Figure 5.5](image-url) [a] Demonstration of spherical grasp and [b] electrode placements.
Figure 5.6 [a] Demonstration of hook grasp and [b] electrode placements.

Figure 5.7 [a] Demonstration of cylindrical grasp and [b] electrode placements.
Figure 5.8 [a] Demonstration of jaw chuck and [b] electrode placements.

Figure 5.9 [a] Demonstration of tip grasp and [b] electrode placements.
The Hook grasp was achieved with a single channel stimulation, Figure 5.6. The active electrode A was placed over flexor digitorum profundus and the return electrode B over the region where all flexor tendons of digits 2-5 met. This expertly flexed the digits, which facilitated the hook grasp.

For cylindrical grasp, two channels were used simultaneously. The grasp required the flexion of digits 2-5 and the abduction of the thumb. The electrode pair A-B abducted the thumb, and the second electrode pair C-D flexed the digits 2-5. Here, the active electrode A was located over the belly area of Adductor pollicis muscle, and the return electrode B over the flexor digitorum profundus. For the second channel, the active electrode C was placed over the flexor digitorum profundus, and the return electrode D was placed over the region where all flexor tendons of the four digits converged.

For jaw chuck, three active channels were used. Being a precision grasp, the activation required low stimulation amplitudes (7-9 mA), as increasing the stimulation intensity caused the co-contraction of muscles. Here, both the flexion and abduction of the thumb, along with the flexion of the index, were needed. The first channel, A-B, abducted the thumb (adductor pollicis), the second channel, C-D, flexed the thumb (Flexor pollicis longus), and the third channel, E-F, flexed the index (Flexor digitorum profundus).

Tip grasp was similar to hook grasp, and it was a precision grasp. Here, two active channels were used. One channel abducted the thumb, with active electrode A, over the adductor pollicis muscle, and the other channel, with active electrode C, over the Flexor digitorum profundus flexed the index. Although similar to the Jaw chuck, performing a flexion of the thumb can laterally force the object to move away from the tips of thumb and index. Hence, only the thumb abduction was performed. The abduction of thumb gave the necessary support to hold the object, and the flexion of the index provided the prehension.
The sensorized glove (Section 3.2) was used to measure the digit/wrist motion and the digit tip forces. After a successful grasp, the digit/wrist joint motion as captured by the flex sensors for spherical, hook, cylindrical, jaw chuck, and tip grasp for a single subject are shown in Figure 5.10. Here, the deflection was reported from the fully flexed baseline positions of wrist and digits. Although the digit tip forces were not reported here. The implications of capturing digit/wrist motion can aid with closed-loop control over hand function tasks.

**Figure 5.10** Digit and wrist motion during [a] spherical,[b] hook, [c] cylindrical, [d] jaw chuck, and [e] tip grasp. Here, the flexion of Thumb (T), Index (I), Middle (M), Ring (R), Little (L), and wrist (W) are reported.
5.5 Discussion

By characterizing an electrically stimulated muscle, optimal and safe stimulation protocols that are crucial to sustaining desired force levels were derived. Moreover, the applicability of fine digit control was extended to hand manipulation tasks, wherein muscle groups were synergistically activated to achieve grasps that varied between the power to precision. In addition to modulating the size, shape, and position of individual electrodes in an electrode-array, altering the stimulation parameters can aid in sustaining desired force levels while performing for ADL-based tasks.

For hand function tasks and to control forearm muscles, most studies have opted stimulation pulse-widths between 100 to 600 µs [48], [151], [152]. Hence, in this study, a similar operating range was used to characterize the muscle response. The sensory threshold for a single monophasic pulse was 2 mA. However, a minimum of 6.6±2.4 mA was required to elicit a motor response. Hence, at higher stimulation amplitude sensation of discomfort cannot be avoided due to the activation of sensory nerve fibers on the skin.

Parameters of the stimulation waveform, including its amplitude, pulse-width, and frequency, and the electrode properties, including its surface area and inter-electrode distance, are externally controllable factors that influence the stimulation performance and the resulting muscle response. In most cases, the readily available parameter for control might be the properties of the stimulation waveform.

With a limited number of studies assessing the impact of stimulation waveform on forearm muscles for object manipulation tasks, this study has characterized the muscle response to twitch and tetanic contractions. This chapter demonstrated that that twitch contraction demanded higher stimulation intensities when compared to tetanic stimulation. Moreover, the demand for higher stimulation amplitudes can cause adverse effects like discomfort [43], [53], [153], stimulation-induced discomfort, and faster
fatigue [37], [48], [154], [155]. Although tetanic stimulation was comforting, only a 20 Hz frequency was considered for the study; the increase in frequency can lead to rapid muscle fatigue. Using a frequency of 20 Hz had less differences in fatigue that can suitably be used for fine finger coordination and object manipulation tasks.

Additionally, this study has also shown that muscle fatigue has a significant impact during evoked stimulation. Although the onset of fatigue cannot be avoided, studies have shown that by combining low-frequency stimulation with longer pulse-width can reduce muscle fatigue [155], [47], [85], [144], [156]. Nevertheless, decreasing the stimulation frequency below the fusion frequency of the muscle can cause ripples in force production, which can yield a very coarse outcome and induced discomfort. Also, the effect of stimulation-induced fatigue must mostly be assessed during object manipulation tasks to quantify their effect on ADL.

Most studies have reported that finger movements were coupled, and consequently, single-digit control is arduous to achieve [74], [109], [157]. However, by systematically identifying the motor points of flexors and extensors, and by using optimal stimulation parameters, this study has demonstrated fine digit control and movements of the wrist. Demonstration of such a selective muscle activation can effectively reproduce several hand function tasks.

Following digit control, it's coordinated activity to elicit several functional grasps were also demonstrated using an electrode array-based stimulation; wherein, the electrodes were distributed along the forearm surface. Desired electrodes were activated to synergistically activate more than one muscle group that enabled five ADL-based grasps, spherical, hook, cylindrical, jaw chuck, and tip grasp. Accurate grip force control is essential in performing activities such as grasping of fragile objects, resistance to external forces, and when applying movement to the object. Moreover, through parametric control, the force exerted by the digits on the objects being manipulated can be controlled.
5.6 Summary

In this chapter, electrically evoked muscle contractions across the forearm muscle groups were characterized. Accordingly, the influence of transcutaneous stimulation on muscle contraction, stimulation comfort, and stimulation-induced fatigue was quantified. Experiments were performed on four healthy participants; wherein, stimulation was delivered to the flexors of the wrist. Moreover, to extend the applicability of precise digit control to hand manipulation tasks, the determinants of force generation were used to evoke optimal muscle contraction. Based on the optimal parameters obtained, seven ADL-based hand function tasks were also demonstrated. Here, digit control and coordination were achieved by synergistic activation of various muscle groups through spatially distributed electrodes. Characterization of forearm muscles, as performed in this study, has implications for closed-loop FES control, as controlled digit forces are required to perform hand manipulation tasks.
6. Modeling nerve stimulation

In the previous two chapters, the viability for a highly selective, digit-coordinated grasps was demonstrated. Additionally, this thesis also aims to improve the surface stimulation technology for prolonged usage in facilitating hand function tasks. Evaluating the physiology of neuromuscular stimulation and the stimulation performance of transcutaneous electrodes is crucial to derive optimal stimulation protocols and for the design of wearable electrode arrays, respectively. Moreover, these models can complement the testing time and discomfort imparted to the users. Hence, in this chapter, a computational model of the forearm under tNMES was developed; wherein, the physiological validity of the model was assessed based on the excitability of motor nerve fibers innervating the forearm muscles.
6.1 Significance of modeling tNMES

tNMES has gained popularity in recent years for its ease of use, non-invasiveness, and functional outcome [12], [44], [87]. For people with neuromuscular deficits, transcutaneous neuromuscular electrical stimulation (tNMES) facilitates the stimulation of muscles at their motor points to recuperate their lost motor function. Functional outcomes of such stimulation procedures are often evaluated directly on patients, which are time-consuming and discomforting [43], [45], [53], [71]. As an alternative, computational models enable a safe and convenient way to test a myriad of stimulation protocols, thus reducing the patient’s time and discomfort [53], [71], [158], [159]. Such models have been used to assess the impact of electrode profiles [53], [71], [158], [160], the influence of geometry on volume conductor representations [161], [162], the validity of axonal models [162], to predict motor activation [163] and to estimate the thresholds for tactile sensation [163], [164].

Despite their broad applicability to tNMES research, to accommodate complex neurophysiological outcomes, contemporary models lack a holistic representation for the nerve-tissue interactions by accounting for the spatiotemporal distribution of electric fields across realistic geometries [165], [166]. In this regard, the foremost limitations faced by tNMES models that this study aims to address are discussed as follows.

Firstly, established concepts in neurostimulation consider the neuronal membranes in an isolated infinite medium. This medium is assumed to be iso-potential; hence, the extracellular field across the neuronal membranes are linearly interpolated [165]–[167]. Although such simplification is prevalently used, its applicability is limited to simple geometries and homogenous material properties [168]. When deploying tNMES, this assumption is not pertinent as the electric field permeates tissue layers with varying electrical properties that are geometrically composite [163]. Moreover, studies have shown that the anisotropy of skin layers [169],
muscle tissue [161], [162], [170], and extraneural tissues [171], [172] impacts nerve activation. Incidentally, the depth of the target nerve and the electrode size had the most influence on chronaxie values [162]. While modeling these composite of tissue layers, the electric field is often solved using the quasi-static Maxwell’s equations [71], [161], [173]. Under transient conditions, the dielectric property of tissues influences the electric field permeation, which brings the quasi-static assumption in neglecting the capacitive effects into question as it introduces errors of up to 16% [173]–[175]. Thus, accurate estimation of three-dimensional current and the electric field distribution within the tissue layers becomes integral to tNMES modeling [163], [166], [176].

Secondly, ignoring the dynamics of ion channels by assuming linear (passive) neuronal elements tend to impart prediction errors up to 23.6% [176]. The structural and biophysical properties of a nerve fiber determine their excitability and recovery cycle characteristics [169], [177]. Accordingly, the explicit modeling of nodal and internodal regions with a sub-myelinic conductive path was a significant contributor to the longer chronaxie values under tNMES [162].

Thirdly, the inherent shortcoming of the two-stage approach, which arises from decoupling the nerve from its surrounding tissue. Because the electric field through various tissue layers is calculated first, and the resulting electric field is later applied to analytical nerve models, the two-stage approach cannot accommodate dynamic interactions between the two [165], [166]. Physiologically, two-way interaction exists between the nerve fibers and its exogenous tissues. Electric fields induced within these tissues can affect the nerve fibers, and the resulting nerve activation can equally influence the surrounding tissues. Devoid of dynamic interactions with its surrounding tissues, computing the membrane potential for a nerve can yield inconsistent results [166], [168], [178]. The two-stage method also neglects ephaptic interactions among neuronal elements [179], which can limit the model’s accuracy when considering bundled axons [176].
In conclusion, existing modeling methods must be improved to accommodate explicit biophysical representations of the nerve fiber, to quantify the nerve-tissue interactions based on the spatiotemporal distribution of electric fields, and to allow the transient analysis of the neuronal response to extracellular stimulation as a self-consistent scheme [166], [168].

Studies have proposed analytical formulations to directly calculate the membrane potentials of unmyelinated axons under exogenous stimulation [167]. However, their excitation was modeled from a perspective of near-field stimulation, limiting their capabilities to simple geometries and homogenous material properties. Calculating membrane currents across biophysically intricate nerve models and the electric field across composite tissues involves differential equations that are to be solved numerically.

Among such methods, the Finite element (FE) analysis overcomes methodological limitations with conventional techniques and can be used for a range of physical field problems [166], [180]. With its advantage for handling complex geometries and materials with varying electrical properties, the FE method has been extensively used to quantify the neuronal response to exogenous stimulation [162], [165], [168].

Moreover, the viability for modeling unmyelinated [165], [168], [170], [181], and myelinated axons [182] using the FE approach has been demonstrated. The FE method allows for a discretized geometry approximation, which is crucial to capture the effect of nerve excitation based on the spatial and temporal distribution of the electric field in a medium [165]. In this way, inconsistencies that arise from spatial interpolations can be avoided [159]. Hence, the application of FE modeling to transcutaneous stimulation of myelinated axons is promising for tNMES-based studies.

The structural morphology of the nerve exits on a microscale relative to the exogenous tissues, deploying the FE method can yield meshes that are
computationally intensive. As an alternative, hybrid models involving 1D nerve embedded within 3D volume conductors have been proposed to accommodate scalability [165], [166], [168], [180]. Multi-compartmental modeling can be used to extend this scheme to realize elaborate nerve geometries. This chapter adopted this approach to model the stimulation of a myelinated nerve fiber under a composite of tissue layers.

6.2 Finite element modeling for tNMES

In the proposed model, the response of a multi-layered compartmentalized active myelinated nerve fiber to a transient-external stimulus from an induced electric field inside a volume conductor-based forearm was computed using the FE method. A continuum description for the model was achieved by enabling a bidirectional coupling between the nerve fiber and its exogenous tissue layers. The methodological implementation for each of these strategies is briefed in the following sections. The model was built around the median nerve innervating the forearm muscles; hence, the model’s response was compared against experimental data from five healthy participants for its validation.

Passive elements surrounding the nerve fiber represented the tissues of the forearm and the nerve. The impact of using an accurate anatomical representation for the forearm was deemed to be insignificant in earlier studies [161], [162]. Hence, an equivalent cylindrical geometry was used. The length of the forearm was 35 cm, and the thickness and dielectric properties for each of the tissue layers are given in Table 6.1. The properties of muscle and neural tissues were considered anisotropic [71], [162]. Also, the stimulation electrode geometry and their IED were modeled to match the experimental protocol.
The muscle is commonly innervated by 2 to 4 branches of the median nerve [127], [135], [185]. Here, the foremost nerve branch that intercepts the muscle at a depth of 7.1 to 16.8 mm from the skin surface was considered [186]. Histology-based studies have shown that this nerve branch originates from a single nerve fascicle [185] and has a circular topology with a diameter of 0.5 mm [183].

The modeled nerve branch had a single nerve fiber embedded in the extracellular matrix of endoneurium [171], [185], which was subsequently bounded by the perineurium. The thickness of perineurium was 4% of the fascicular diameter [172]. Based on nerve conduction studies, the diameter of a single nerve fiber was modeled for 10 and 14 µm [187]. The structural morphology and excitation dynamics of these nerve fibers were representatives of the MRG-type [177], due to its physiologically accurate double cable structure (DCS) of α-MNs and good agreement with experimental results [162], [163].

### Table 6.1 Properties of tissue layers

<table>
<thead>
<tr>
<th>Material</th>
<th>Thickness</th>
<th>Conductivity</th>
<th>Permittivity</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>µm</td>
<td>Sm⁻¹</td>
<td></td>
</tr>
<tr>
<td>Conductive Gel</td>
<td>500†</td>
<td>0.0556†</td>
<td>1</td>
</tr>
<tr>
<td>Skin</td>
<td>1500</td>
<td>0.0014</td>
<td>6000</td>
</tr>
<tr>
<td>Fat tissue</td>
<td>2500</td>
<td>0.0303</td>
<td>25000</td>
</tr>
<tr>
<td>Muscle</td>
<td>Axial</td>
<td>33500</td>
<td>120000</td>
</tr>
<tr>
<td></td>
<td>Radial</td>
<td>0.3333</td>
<td>40000</td>
</tr>
<tr>
<td></td>
<td></td>
<td>0.1111</td>
<td></td>
</tr>
<tr>
<td>Bone</td>
<td>6000</td>
<td>0.0200</td>
<td>3000</td>
</tr>
<tr>
<td>Marrow</td>
<td>6500</td>
<td>0.0800</td>
<td>10000</td>
</tr>
<tr>
<td>Endoneurium</td>
<td>Axial</td>
<td>240[183]</td>
<td>72.3[184]</td>
</tr>
<tr>
<td></td>
<td>Radial</td>
<td>0.0571[172]</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>0.0833[172]</td>
<td></td>
</tr>
<tr>
<td>Perineurium</td>
<td>10</td>
<td>0.0021[172]</td>
<td>4.97[184]</td>
</tr>
</tbody>
</table>

Parameters adopted from [162] unless specified; †Experimentally measured.
Figure 6.1 The equivalent electrical circuit for the myelinated nerve.

The Node of Ranvier is unmyelinated, allowing it to directly interact with the extracellular medium, whereas the internodal regions have an additional layer of periaxonal fluid, which is encapsulated by an insulating myelin sheath. The current flow at the central node is the difference in voltage between the neighboring nodes and the resistance across them.
The nerve fiber length spanned 21 node of ranvier (NoR), with each node-to-node segment constructed from four regions with distinct biophysical properties: the unmyelinated NoR; and the three myelinated internodal regions: the paranode (PN), Juxtaparanode (JUX), and internode proper (INP), that were arranged in the following order: NoR, PN, JUX, 6×INP, JUX, PN. The presence of two core conductors in a fiber model represents a DCS [177], [188]; however, as an extension to the DCS, an additional layer for the extracellular fluid was included. In this way, each compartment of the nerve fiber contained three radial fluid layers: the axoplasmic fluid, peri-axoplasmic fluid (PAF), and the extracellular fluid (ECF) within which longitudinal currents travel along. Each fluid layer was encapsulated by a neuronal membrane that facilitated transverse currents across the nerve: the Axolemma, the Myelin sheath, and the Basal lamina shrouded the axoplasm, PAF, and ECF, respectively.

The equivalent electrical circuit for the nerve segment is shown in Figure 6.1. Every segmental region had distinct membrane properties and morphology; thus, the electrical activity across them was solved using compartment-based modeling [165], [180]. These compartmentalized regions were linked to its neighbors by a longitudinal axoplasmic resistance ($R_i$), along the PAF by a longitudinal peri-axoplasmic resistance ($R_p$) and along the ECF by the resistance of extracellular fluid ($R_e$). The current flux along individual compartments contributed to the overall membrane currents as denoted by green and blue arrows for respective axial and radial currents in Figure 6.1.

The morphology of every compartment was assumed to be symmetric, which resulted in the calculation of the membrane potentials at the geometric center of each compartment. Representative equations that relate axial and radial currents for each compartment are derived in the following sequence:
Firstly, the longitudinal axoplasmic current, entering \((I_{i-1,i})\) and leaving a node \((I_{i,i+1})\) and the radial current flowed across the membrane as axolemma current \((I_a)\) were considered. The axolemma current was the sum of ionic current \((I_{a,ion})\) and capacitive current \((I_{a,cap})\). Applying Kirchhoff’s law around this node to combine all currents entering and leaving the node (6.1):

Membrane current is the sum of respective ionic and capacitive currents,

\[
I_{a,ion}^n + I_{a,cap}^n = I_{i,i-1,n}^n + I_{i,i+1,n}^n
\]

\[
I_{a,ion}^n + C_a \frac{\partial V_a^n}{\partial t} = \left( \frac{V_{i-1}^n - V_i^n}{R_{i-1}} \right) - \left( \frac{V_{i+1}^n - V_i^n}{R_i} \right)
\]

The longitudinal axoplasmic resistance was assumed to be uniform across each compartment, implying a constant cross-sectional area and resistivity, which simplifies to (6.3):

\[
C_a \frac{\partial V_a}{\partial t} + G_a (V_a - V_{rest}) = \frac{1}{R_i} (V_{i-1} - 2V_i + V_{i+1})
\]

For a compartment with an axoplasmic diameter \(d_a\) and length \(\Delta x\), \(R_i = \frac{4\rho_i \Delta x}{\pi d_a^2}\) with \(\rho_i\) the axoplasmic resistivity, \(G_a = g_a \pi d_a \Delta x\), with \(g_a\) the axolemma conductivity, and \(C_a = c_a \pi d_a \Delta x\), with \(c_a\) the axolemma capacity. Substituting these terms into (6.3) yields (6.4):

\[
c_a \frac{\partial V_a}{\partial t} + G_a (V_a - V_{rest}) = \frac{d_a}{4\rho_i} \left( \frac{V_{i-1} - 2V_i + V_{i+1}}{\Delta x^2} \right)
\]

Using the finite difference approximation, when \(\Delta x \to 0\), (6.4) becomes (6.5), wherein, the transmembrane potential \((V_a)\) was calculated as the difference between the intracellular \((V_i)\) and periaxonal potentials \((V_p)\) [189].

\[
c_a \left( \frac{\partial V_i}{\partial t} - \frac{\partial V_p}{\partial t} \right) - \frac{d_a}{4\rho_i} \left( \frac{\partial^2 V_i}{\Delta x^2} \right) = -G_a (V_i - V_p - V_{rest})
\]

The ionic currents for NoR and JUX were due to the opening and closing of ion channels (6.7). Whereas PN and INP had only passive membrane
currents. The NoR contained fast sodium \((Na_f)\), persistent sodium \((Na_p)\), slow potassium \((K_s)\) and nodal leakage channels. Whereas, the JUX contained fast potassium \((K_f)\) channels and passive membrane conductance. The ionic current \((i_{ion})\) of each ion channel was the product of the maximum single-channel conductance \((\tilde{g}_{ion})\), gating variables \((\omega_{ion})\) and the deviation of \(V_a\) from its Nernst potential \((E_{ion})\) as in (6.6).

\[
i_{ion} = \tilde{g}_{ion} \omega_{ion} (V_a - E_{ion}) \tag{6.6}
\]

\[
\frac{d\omega}{dt} = \alpha_\omega (1 - \omega) - \beta_\omega \omega \tag{6.7}
\]

The Nernst potential for sodium \((E_{Na})\), potassium \((E_K)\) and leakage channels were 50, -90, and -90 mV, respectively, and the nodal leakage conductance was 0.007 Scm\(^{-2}\). Based on their voltage-dependent rate constants \(\alpha_\omega\) and \(\beta_\omega\), the activation dynamics for various ion channels were determined from Table 6.2.

### Table 6.2 Dynamics of ion channels along the Node of Ranvier

<table>
<thead>
<tr>
<th>Ion channel</th>
<th>Gating variable</th>
<th>(\alpha_\omega)</th>
<th>(\beta_\omega)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Fast sodium</td>
<td>(m^3)</td>
<td>(\frac{6.57 + (V_a + 21.4)}{1 - e^{-\frac{(V_a + 114)}{10.3}}})</td>
<td>(\frac{-0.304 + (V_a + 25.7)}{1 - e^{-\frac{(V_a + 114)}{10.3}}})</td>
</tr>
<tr>
<td></td>
<td>(h)</td>
<td>(\frac{-0.34 + (V_a + 114)}{1 - e^{-\frac{(V_a + 114)}{11}}})</td>
<td>(\frac{12.6}{1 + e^{-\frac{(V_a + 31.8)}{11}}})</td>
</tr>
<tr>
<td>Persistent sodium</td>
<td>0.01</td>
<td>(\frac{0.035 + (V_a + 27)}{1 - e^{-\frac{(V_a + 27)}{10.2}}})</td>
<td>(\frac{-0.00088 + (V_a + 34)}{1 - e^{-\frac{(V_a + 34)}{10}}})</td>
</tr>
<tr>
<td>Slow potassium</td>
<td>0.08</td>
<td>(\frac{0.3}{1 + e^{-\frac{(V_a + 83)}{5}}})</td>
<td>(\frac{0.03}{1 + e^{-\frac{(V_a + 90)}{4}}})</td>
</tr>
<tr>
<td>Fast potassium</td>
<td>0.04</td>
<td>(\frac{0.0462 + (V_a + 83.2)}{1 - e^{-\frac{(V_a + 83.2)}{14}}})</td>
<td>(\frac{-0.0824 + (V_a + 66)}{1 - e^{-\frac{(V_a + 66)}{10.5}}})</td>
</tr>
</tbody>
</table>

\(\alpha_\omega\) and \(\beta_\omega\) represent gating parameters at 37\(^0\)C [177]
Secondly, currents along the PAF were considered. At this node, the longitudinal current consisted of current entering \((I_{p-1,p})\) and leaving \((I_{p,p+1})\) the node through the periaxonal space. The radial current consisted of the axolemma current, expressed as the sum of ionic currents \((I_{a}^{\text{ion}})\) and capacitive currents \((I_{a}^{\text{cap}})\) entering the node, and the total myelin current, expressed as the sum of ionic currents \((I_{m}^{\text{ion}})\) and capacitive currents \((I_{m}^{\text{cap}})\) leaving the node. Applying Kirchhoff’s law at this node yielded (6.8):

\[
I_{p}^{k,k+1} + I_{m,cap}^{k} + I_{m,ion}^{k} = I_{a}^{k} + I_{p}^{k-1,k}\tag{6.8}
\]

\[
\frac{(v_{c}^{k} - v_{c}^{k+1})}{(r_{p}^{2} + r_{p}^{2} + r_{p}^{2})} + C_{m}^{k} \frac{\partial v_{m}^{k}}{\partial t} + G_{m} v_{m}^{k} = \left(\frac{v_{c}^{k-1} - v_{c}^{k}}{r_{p}^{2} + r_{p}^{2} + r_{p}^{2}}\right) - \left(\frac{v_{c}^{k} - v_{c}^{k+1}}{r_{p}^{2} + r_{p}^{2} + r_{p}^{2}}\right) + \left(\frac{v_{c}^{k-1} - v_{c}^{k}}{r_{p}^{2} + r_{p}^{2} + r_{p}^{2}}\right)
\]

(6.9)

Based on the implementation, all values of the surface area must be declared w.r.t ratio of surface areas. Where \(R_{p}^{k} = \frac{4 \rho_{p} \Delta x_{p}^{k}}{\pi d_{p}^{k}}\); \(G_{m}^{n} = \frac{\alpha_{m}^{n}}{2N} \pi d_{m}^{k} \Delta y\);

\[
C_{m}^{k} = \frac{c_{m}^{k}}{2N} \pi d_{m}^{k} \Delta y
\]

\[
\frac{(v_{c}^{k} - v_{c}^{k+1})}{(r_{p}^{2} + r_{p}^{2} + r_{p}^{2})} + (C_{m}^{k} \pi d_{m}^{k} \Delta y) \frac{\partial v_{m}^{k}}{\partial t} + (g_{m}^{k} \pi d_{m}^{k} \Delta y) v_{m}^{k} = \left(\frac{v_{c}^{k-1} - v_{c}^{k}}{R_{p}^{2} + R_{p}^{2} + R_{p}^{2}}\right) - \left(\frac{v_{c}^{k} - v_{c}^{k+1}}{R_{p}^{2} + R_{p}^{2} + R_{p}^{2}}\right) + \left(\frac{v_{p}^{k-1} - v_{p}^{k}}{R_{p}^{2} + R_{p}^{2} + R_{p}^{2}}\right)
\]

(6.10)

Dividing by \(\pi d_{m}^{k} \Delta y\)

\[
\frac{(C_{m}^{k})}{(2N)} \frac{\partial v_{m}^{k}}{\partial t} = \left(\frac{d_{m}^{2}}{4 \rho_{m} d_{m}^{2}} \left(\frac{\partial v_{m}^{k}}{\partial t} \Delta y^{2} \right)\right) + \left(\frac{d_{m}^{2}}{4 \rho_{m} d_{m}^{2}} \left(\frac{\partial v_{m}^{k}}{\partial t} \Delta y^{2} \right)\right) - \left(\frac{g_{m}^{k}}{2N}\right) v_{m}^{k}
\]

(6.11)

If \(\Delta y \to 0\), the finite difference second-order approximation gives,

\[
\left(\frac{C_{m}^{k}}{2N}\right) \frac{\partial v_{m}^{k}}{\partial t} = \left(\frac{d_{m}^{2}}{4 \rho_{m} d_{m}^{2}} \left(\frac{\partial v_{m}^{k}}{\partial t} \Delta y^{2} \right)\right) + \left(\frac{d_{m}^{2}}{4 \rho_{m} d_{m}^{2}} \left(\frac{\partial v_{m}^{k}}{\partial t} \Delta y^{2} \right)\right) - \left(\frac{g_{m}^{k}}{2N}\right) v_{m}^{k}
\]

(6.12)

Where \(V_{a}^{k} = v_{i}^{k} - v_{p}^{k} - v_{rest}^{k}\); \(V_{m}^{k} = v_{p}^{k} - V_{e}^{k}\)

Based on the number of lamellae \(N_{m}\) and the diameter of the myelin sheath \(d_{m}\), the myelin capacitance \(C_{m} = \frac{c_{m}}{2N_{m}} \pi d_{m} \Delta x\), with \(c_{m}\) the myelin
capacity, and myelin conductance \( G_m = \frac{g_m}{2N_m} \pi d_m \Delta x \), with \( g_m \) the myelin conductivity was calculated. The diameter of the periaxonal space was \( d_p \), and \( \rho_p \) the peri-axoplasmic resistivity. The transmyelin potential was the difference between periaxonal (\( V_p \)) and extracellular potentials (\( V_e \)) [189]. Substituting these terms into (6.12) yields (6.13):

\[
\frac{c_m}{2N_m} \left( \frac{\partial V_p}{\partial t} - \frac{\partial V_e}{\partial t} \right) - \frac{d_p^2}{4 \rho d_m} \left( \frac{\partial^2 V_p}{\partial x^2} \right) = -\frac{g_m}{2N_m} (V_p - V_e) + \frac{d_a}{d_m} \left( c_a \left( \frac{\partial V_i}{\partial t} - \frac{\partial V_p}{\partial t} \right) - g_a (V_i - V_p - V_{rest}) \right)
\]

Thirdly, currents along the ECF was calculated. Here, the longitudinal current consisted of the currents entering (\( I_{e-1,e} \)) and leaving the node (\( I_{e,e+1} \)). And the radial currents consisted of the respective membrane currents across the basal lamina (\( I_{b}^{cap}, I_{b}^{ion} \)) and the myelin sheath (\( I_{m}^{cap}, I_{m}^{ion} \)).

\[
I_{b}^{cap} + I_{b}^{ion} = I_{m}^{cap} + I_{m}^{ion} + I_{e-1,e} + I_{e,e+1}
\]

Similar to (6.13), but with \( c_b \) and \( g_b \) the capacity and the conductivity of the basal lamina, respectively, and \( d_f \) and \( \rho_e \), the diameter and resistivity of the ECF, respectively, the current densities in the ECF are given by (6.15). This layer was grounded to the tissue layers using \( V_c \).

\[
c_b \left( \frac{\partial V_e}{\partial t} - \frac{\partial V_i}{\partial t} \right) - \frac{d_f}{4 \rho e} \left( \frac{\partial^2 V_e}{\partial x^2} \right) = -g_b (V_e - V_c) + \frac{d_a}{d_f} \left( c_a \left( \frac{\partial V_i}{\partial t} - \frac{\partial V_p}{\partial t} \right) + \frac{g_m}{2N_m} (V_p - V_e) \right)
\]

As, (6.5), (6.13) and (6.15) are represented as a system of coupled equations, changes in \( V_c \) directly influences \( V_b, V_m \) and \( V_a \) respectively.

The specific capacitances of the axolemma and myelin sheath were \( c_a = 2 \) \( \mu \)Fcm\(^{-2} \) and \( c_m = 0.1 \) \( \mu \)Fcm\(^{-2} \), respectively, and the conductance of axolemma along the PN, JUX, INP were 0.001, 0.0001 and 0.0001 Scm\(^{-2} \), respectively. The specific conductance of myelin at the internodal regions was 0.001 Scm\(^{-2} \), the resistivity of axoplasm and PAF were both 70 \( \Omega \)cm,
and that of ECF was $1 \times 10^9 \, \text{M} \Omega \text{cm}^{-1}$. The capacitance of basal lamina was zero and, its conductance was $1 \times 10^9 \, \text{S} \text{cm}^{-2}$. The resting membrane potential ($V_{\text{rest}}$) was -80 mV. In the model implementation (Supplementary material), all electrical quantities were specified relative to the diameter of the fiber.

The computational model was split into two domains. The electrode-skin interface, forearm tissues, and the extraneural tissues constituted the volume-conductor domain ($\Gamma_c$), while the nerve fiber constituted the intracellular domain ($\Gamma_i$). The $\Gamma_c$ was modeled as a 3D geometry, within which the 1D nerve fiber was embedded. Equations for potential distribution within $\Gamma_c$ and that of the voltage-dependent membrane currents were derived and were later solved using the FE method with appropriate boundary conditions.

The composite of tissues in $\Gamma_c$, with respective conductivity ($\sigma_e$) and permittivity ($\varepsilon_0$) were solved using Maxwell’s equation (6.16), which takes the form of the Poisson equation [174], wherein the capacitive effects were included, but the inductive effects were assumed to be negligible. By establishing a continuity of currents at the interface of each medium, and by accounting for any internal current sources ($Q_i$), the $\Gamma_c$ was solved as a volume conductor. Neural membranes that undergo activation process contributes to $Q_i$. Three boundary conditions were applied to $\Gamma_c$: the peripheries representing the air-tissue interface were insulated (6.17); external current density ($i_{\text{ext}}$) as the Neumann boundary condition was applied to the active electrode (6.18), and the reference electrode was grounded using the Dirichlet boundary condition (6.19). The unit normal at the boundaries of each are denoted by $n_c$.

\[-\nabla \cdot (\sigma_c \nabla V_c + \varepsilon_0 \varepsilon_r \nabla \frac{\partial V_c}{\partial t}) = Q_i \] (6.16)

\[n_c \cdot (\sigma_c \nabla V_c) = 0 \] (6.17)

\[-n_c \cdot (\sigma_c \nabla V_c) = i_{\text{ext}} \] (6.18)
\( V_c = 0 \) \hspace{1cm} (6.19)

The nerve fiber was placed directly under the cathode at depths of 7.1 and 16.8 mm. The membrane currents along the 1D nerve segment were computed by solving (6.5), (6.13), and (6.15). The nerve edges were insulated, and the initial conditions (6.20) and (6.21) were applied. Also, the longitudinal currents along the axoplasm, PAF, and ECF were continuous across the interconnected compartments.

\[ V_i = V_{\text{rest}} \] \hspace{1cm} (6.20)

\[ V_p = V_e = 0 \] \hspace{1cm} (6.21)

The contact between the basal lamina of \( \Gamma_i \) and the endoneurium of \( \Gamma_c \) establishes an interface between the two domains. Equations to represent a continuum description were solved at this interface. As the nerve fiber was embedded within the volume conductor, using (6.19), the influence of the permeated electric field was directly included in the membrane potential. Additionally, to model the influence of nerve fiber on the volume conductor, the bidomain formulations were used [165], [166], [168], [179], [181].

Based on the current conservation relationship, the current leaving the \( \Gamma_i \) must be equal and opposite to the current entering the \( \Gamma_c \). Accordingly, (6.23) was derived, wherein \( n_c \) and \( n_i \) are vectors normal to the boundary in domains \( \Gamma_c \) and \( \Gamma_i \), respectively, \( J_b \) is the basal lamina membrane current perpendicular to \( \Gamma_i \) which crosses the basal lamina and enters the exogenous tissue layers at \( \Gamma_i \cap \Gamma_c \), and \( \beta \) is the surface to volume ratio. As the nerve fiber was implemented as 1D segments, the membrane current entering the volume conductor was implemented as a line-source [166], [168], [180].
Figure 6.2 Thin layer approximation for membrane currents

The intracellular domain ($\Gamma_i$) is separated from the extracellular domain ($\Gamma_e$) by neuronal membranes. Using the bidomain formulation, they can be approximated as thin layers wherein the continuity of current is ensured along the boundaries of each domain. At the Node of Ranvier (NoR) (green), the membrane current is due to the axolemma current ($I_{a}$) that enters the $\Gamma_e$. However, for the internodal region (blue) in addition to the $\Gamma_i$ and $\Gamma_e$, there is an intermediary periaxonal space ($\Gamma_p$). Due to its double cable structure, the axolemma current leaves as myelin current ($I_{m}$). This is applicable across the internodal compartments of PN, JUX, and INP.

\[
V_b = V_e - V_c 
\]

\[
-n_c \cdot \sigma_c \nabla V_c = n_i \cdot \sigma_i \nabla V_i = -\beta \cdot J_b, \text{ at } (\Gamma_i \cap \Gamma_c) 
\]

It is noted that the volume conductor was affected by two current sources: one from the externally applied current density (6.18); and one from the basal lamina membrane current ($\beta \cdot J_b$). The nerve fibers were modeled after $\alpha$-MNs, wherein, the myelinated regions contained low-density membrane currents, separated by NoR with high-density membrane currents that entered the extracellular fluid. The contribution of myelinated regions to $J_b$ being smaller, the line-source condition was applied only along the NoR.
In conclusion, solving the entire system required the solution of the Poisson equation (6.16) governing the volume conductor potential, the non-linear equations for voltage-dependent membrane currents (6.5), (6.13) and (6.15), and the bidomain formulation (6.23) to quantify the effect of membrane currents on the volume conductor potentials. The abovementioned problem represents a coupled system wherein the analytical solution is hard to achieve, given the inclusion of various boundary conditions, materials with anisotropic properties, and hybrid geometry. Thus, the model was solved using the finite element methods. Since 1D nerve elements were used in the model, the bidomain formulation was simplified to a monodomain formulation.

The model was implemented using the commercially available FE package, COMSOL Multiphysics, Version 5.4 (COMSOL, Inc., MA, USA). The computational model was discretized using tetrahedral Lagrange-quadratic finite elements. However, the perineurium being a thin layer, swept meshes were used. Also, a mesh convergence study was performed to congregate with optimal mesh density. The model was solved under transient conditions for ~760000 DoF, using a fully coupled, direct solver (PARDISO). The implicit BDF scheme with adaptive time-stepping was used to vary the step-integration time between 1 to 10µs.

The model was developed around the motor branches of the median nerve, which innervate the forearm flexor muscles. Therefore, for experimental validation, the SDC was obtained from motor point-based stimulation of the foremost median nerve branch entering the Flexor digitorum superficialis muscle on five healthy human participants (29±2.0yrs, BMI 23.9±1.8). Before conducting experimental procedures, informed consent was obtained from all participants. It was ensured that the participants considered for the study had no history of medical conditions that were contraindicative to electrical stimulation. The study was approved by the University of Auckland Human Participants Ethics Committee.
Motor thresholds were obtained by varying the amplitude and the pulse-width of stimulation, delivered via a current-controlled stimulator, RehaStim™ 2 (Hasomed GmBH, Magdeburg, Germany). Stimulation pulse was applied across the skin surface through two rectangular electrodes CDE0241026 (UniMed Electrode Supplies, Surrey, UK), each with ø 24 mm. The active electrode was placed over the motor point [35], while the ground electrode was maintained with an interelectrode distance (IED) of 75 mm. The experimental protocol involved the administration of a single monophasic cathodic stimulation pulse, with amplitude varied between 0 - 25 mA in increments of 1 mA, and, for each amplitude, the pulse-width was varied between 100 - 500 µs [162], [190] in increments of 50 µs. The lowest stimulation amplitude, for each pulse-width that elicited a visually distinguishable twitch in the Flexor digitorum superficialis muscle or wrist flexion, was considered a positive indication of muscle excitation and was recorded as the motor threshold. The motor thresholds were then plotted against the stimulation pulse-width representing the SDC. Finally, the Weiss equation [191], [192] was fit to the SDC to obtain their respective chronaxie (τ_{ch}) and rheobase (I_{rh}).

Prior to the validation of the tNMES model, six of the neurophysiological measures in [177] were evaluated from the standalone nerve fiber with 10 and 14um diameters using a point source stimulation in a semi-infinite medium: shape and size of the propagating action potential; conduction velocity; current-distance relationship; SDC evaluated across nine electrode positions (inset, Figure 6.3d) [177]; threshold tracking via threshold electrotonus; and, recovery cycle. The stimulation waveform was varied based on the test-type, and the point source was placed directly above the middlemost NoR, among 21 interconnected nerve segments. The axial and radial conductivities of the semi-infinite medium were 0.33 and 0.083 Sm⁻¹, respectively, taken from the dorsal column of a cat [177]. For the tNMES model, the nerve fiber was placed within the forearm directly below the cathode, at depths of 7.1 and 16.8 mm from the skin surface.
6.3 Physiological validity of the model

The standalone nerve fiber with 10 and 14 µm fiber diameters reproduced a wide range of experimental results [177].

Figure 6.3 Evaluation of the FE-based myelinated nerve fiber.

In response to a stimulus threshold, the nerve fiber produced action potentials that propagated along with the nerve segments, Figure 6.3a. The nerve fibers had the depolarizing-afterpotentials (DAP) and the after-hyperpolarization (AHP) that are crucial to α-MNs. Also, the conduction velocity was linearly dependent on the fiber diameter [177], Figure 6.3b. Changes to electrode-axon distance had a non-linear relationship with the stimulus threshold that fits within experimental data [177], Figure 6.3c. The strength-duration curve (SDC) for nine electrode configurations broadly matched the reported chronaxie (50-150 µs) [193] and rheobase (0-25 µA) [177] values, Figure 6.3d.

**Figure 6.4** Transcutaneous stimulation of motor nerve fiber

The model shows the stimulation of a nerve fiber embedded within the forearm tissues, and the tetrahedral mesh elements used to discretize the computational domain. [a] The volume of tissue activation represented as an iso-potential surface. [b] Transmembrane potential ($V_a$), [c] Basal lamina current ($J_b$) along the middlemost nodal region upon successful excitation.
The chronaxie was shorter if the axon was close to the stimulation source. Threshold tracking via threshold electrotonus produced changes in the stimulus threshold, measured during and after the conditioning pulse, as observed in experimental data [177], Figure 6.3e. Finally, excitability changes during the recovery cycle exhibited periods of increased and decreased excitably, as observed in experimental data [177], Figure 6.3f. By validating the response of the standalone nerve fiber for various excitability indices, it was further incorporated into the tNMES model.

The proposed tNMES model, with the excitation of nerve fiber placed directly below the stimulation electrode, is shown in Figure 6.4. The volume of tissue activated under the cathode that envelopes the nerve fiber is shown as an iso-potential surface in Figure 6.4. Due to the proximity of the middlemost nodal region to the electrode, initial depolarization in this region caused an action potential that propagated along the length of the fiber. The resulting membrane currents crossed the nerve fiber as $J_b$, Figure 6.4, [189], and entered the endoneurium, influencing the volume conductor potential [167].

Figure 6.5 shows the mean and standard deviation for the SDC data from five healthy participants (solid line with bars), overlaid with the mean +/- variance for the SDC data obtained from model prediction of fibers placed at depths of 7.1 and 16.8 mm (solid line +/- shaded region), where the grey shaded region indicates an overlap of SDC data on 10 and 14 µm diameter fibers. The model showed good agreement with experimental data and was able to fit the experimental range, 352±153 µs. It was evident that larger fibers were recruited first, and the depth of the nerve influenced the chronaxie and rheobase values. Shorter chronaxie values of 308 and 360 µs were noted at a depth of 7.1 mm for 10 and 14 µm, respectively. As the depth increased to 16.8 mm, the chronaxie values were longer, 348, and 394 µs for 10 and 14 µm, respectively. Moreover, for model predicted values, a steep increase in stimulation threshold was noticed for shorter pulse-widths, similar to findings in [162].
Figure 6.5 The SDC, comparing model and experimental data.

The strength-duration curve comparing experimental data against the model’s prediction on two fiber diameters placed at varying depths. The grey shaded region represents the overlap of data from 10 and 14um fiber diameters.
6.4 Discussion

The three foremost limitations with current modeling approaches were addressed in this chapter. The proposed FE implementation of an active myelinated nerve fiber and its bidirectional interaction with the volume conductor was demonstrated in this study. Moreover, the presented model is a novel implementation of a myelinated nerve fiber, which introduces a triple cable structure with compartmental representations for nodal and internodal regions modeled using experimentally established parameters [177]. A holistic approach to combining microscopic neural events with macroscopic extracellular field distribution in a volume conductor, by coupling the two at their boundary, was demonstrated, which is crucial to compute a physiologically valid outcome for neuroprosthetic applications such as tNMES [162], [166]–[168], [182]. This feat was achieved by successfully integrating three main strategies – the theory of volume conduction, compartment-based modeling, and the bidomain formulation – which were solved using the FE method. This enabled the computation of electric field distribution in a volume conductor and the resulting neuronal response simultaneously for a transient-external stimulus.

Implementation of a nerve fiber without proper biophysics or the use of the second-order difference of the extracellular voltage can be inadequate for determining neural activation [176]. Hence, a physiologically valid triaxial myelinated nerve fiber was modeled in this tNMES study. Accordingly, equations (6.5), (6.13), and (6.15), representing the fiber voltage-dependent membrane currents, were derived and solved. The dielectric properties of tissue layers also influence the time-course and amplitude of stimulus waveform, which demands an accurate calculation of the electric field. Hence, the Poisson equation (6.16) was solved to calculate the electric field in a composite of tissue layers.

To improve upon existing models, detailed biophysics of the nerve in conjunction with non-linear field changes was considered. However, for
nerve activation models that are spatially distributed within a composite of geometrically complex mediums having directional and or frequency-dependent conductivity, such as the tissue layers of the forearm, the equations describing this system become complex enough to be solved analytically. In the proposed model, in addition to the model equations, intricate boundary conditions and the highly coupled nature of system equations used to establish a continuum description for nerve-tissue interactions must also be solved for time-varying conditions. By approximating shape functions as solutions to these equations, and by dividing them into discrete elements, the FE method enables transient analysis. The FE method also implements a discretized geometry approximation, which was found to be crucial to capture the effect of nerve excitation based on the spatial and temporal distribution of the electric field and avoided inconsistencies due to spatial interpolations in earlier studies. For these reasons, the FE approach was used for tNMES modeling in this study.

By neglecting the extracellular component, classical cable theory-based modeling cannot accommodate the influence of external fields on membrane potentials. Hence, in this study, the excitation of the nerve was modeled by accounting for the extracellular potential gradient \( \partial V_{\text{exx}} \). Conventionally, intracellular charge injection drives the whole cell membrane to the same potential. However, due to the discretization of the model domain, as in this study, the spatially driven potential gradient can have a significant impact on the mechanism of excitation along the compartmentalized nerve fiber. It is hypothesized that this mechanism of excitation is physiologically alike.

Motor point-based stimulation is commonly used to facilitate muscle contraction. Excitation of a motor point implies the stimulation of the terminal nerve branch rather than the nerve trunk. As the anatomical and biophysical properties of motor points are different from that of the nerve trunk, comparatively shorter chronaxie values were reported for motor
point-based stimulation [191]. Hence, to appropriately model the motor point-based stimulation of the median nerve in accordance with the experimental protocol, a single fascicle structure of the target nerve branch entering the Flexor digitorum superficialis muscle was included in this study.

The nerve fiber was modeled after the MRG-type model for its ability to reproduce a wide range of neurophysiological outcomes [177]. The MRG-type model has been extensively used in tNMES-based studies and shown good agreement with experimental results [162], [163]. The FE implementation of the triaxial compartmentalized myelinated nerve fiber produced matching results with earlier modeling studies for all of the evaluated excitability indices, Figure 6.3. Moreover, the nerve fiber diameters selected for modeling were 10 and 14 µm, as their respective conduction velocities 56 and 93 ms\(^{-1}\) were similar to nerve conduction studies on forearm muscles [187].

The excitability of the nerve fibers under transcutaneous stimulation was experimentally validated by comparing its SDC against data obtained on five healthy participants. Controllable factors in the experimental protocol – the electrode size and inter-electrode distance – were kept constant. Also, the external stimulation was delivered as a current-controlled pulse, which was intended to reduce the effect of skin impedance across subjects [162]. The depth of the nerve, being the most significant contributor to chronaxie values, needed to be estimated experimentally. Hence, the depth of the nerve, based on common innervation patterns was varied for 7.1 and 16.8 mm in the model.

The SDC obtained for these nerve depths represented a range of probable excitability characteristics, which were compared against experimental data. The rheobase for motor point-based stimulation, 3.4±0.9 mA, was within the model predicted range, 4.8±3.5 mA. Similarly, the model predicted that the chronaxie values of 353±31 µs were within the experimental range. These values were similar to reported chronaxie
values, 330 - 410 μs [190], [191], and rheobase values, 4 – 6 mA [191], [192]. An increase in electrode-fiber distance typically resulted in longer chronaxie values. For both the fiber diameters, the model predicted chronaxie values were within the acceptable reported range, 200-700 μs [162], [192], which further emphasizes the model’s applicability to tNMES-based studies. Moreover, changes in chronaxie between the model predicted and experimental values can be attributed to intra-subject variability in the thickness and dielectric properties of fat [71] and muscle tissues [158], [162].

The FE approach has the potential to improve on the existing state-of-art modeling for extracellular stimulation of neuronal systems. Incorporation of the three implemented strategies – the theory of volume conduction, compartment-based modeling, and the bidomain formulation – can also be applied to study stimulation protocols, improve electrode designs, and assess a wide range of neurophysiological outcomes for tNMES. Moreover, FE modeling offers the flexibility to include morphological details of both the nerve and the surrounding tissues. With current advances in CT and MRI imaging techniques, tissue morphology and nerve branching can be included to derive personalized tNMES models, without explicitly modeling them [194]. In addition to neurophysiological evaluation of nerve function, the volume conductor-model can be evaluated for 3D currents, electric field distribution, and activation volume, which are often assessed in tNMES-based studies.

By demonstrating the interaction of nerve with its surrounding tissues, the model proves its capability in emulating micron-level interactions across neuronal elements, paving the way for advanced coupled nerve-tissue electrostimulation models [167], [178]. By including fascicular morphology with appropriate nerve fiber distribution, gradient activation of bundled nerve fibers can be studied, as the number of nerve axons being excited can be a good predictor of muscle recruitment [162].
Limitations were encountered in replicating results produced by the MRG-type nerve model. Primarily, the shape of the action potential tended to feature a DAP with higher than normal amplitude. In order to reduce its influence in affecting the overall shape of the action potential, the $K_f$ channels at the JUX were included in the FE model, which reduced the amplitude and duration of DAP and subsequently affected the supernormal period [177].

The nerve fiber was represented as a 1D geometry to reduce the underlying computational cost of meshing the nerve’s structural features, which would otherwise be excessive given that the structural morphology of the nerve exits on a microscale relative to the exogenous tissues [167]. An alternative to overcome the accommodation of features with vastly different spatial scales is a 3D neurite with thin-film approximation [168].

To further simplify the model, only a single nerve fiber with interconnected nerve segments were considered. However, the conductivity of endoneurium tissue surrounding the nerve tissue was inclusive of the combined conductivity of nerve fibers and the extraneural connective tissue [171], [172]. This enabled us to assume a single homogeneous fiber distribution within the fascicle of interest, whereas the fiber distribution was likely heterogeneous and variable across subjects.

Intended to model the twitch response, only monophasic stimulation was applied in the study. However, to evaluate neural response to pulse train-based stimulation, the frequency-dependent effects must be included [195]. Furthermore, the line source approximation was applied only along the NoR, under the assumption that the myelinated regions contained low-density membrane currents.
6.5 Summary

In this chapter, a computational model that accommodated a holistic representation of the nerve-tissue interactions for a transient-external stimulus featuring transcutaneous nerve stimulation was developed. The proposed model represented the stimulation of the median nerve branch innervating the flexor muscles of the forearm. The model was able to predict the time-dependent effects of external stimulation and the resulting neuronal response. The model predicted excitability characteristics were compared against the data from in-vivo experimentation on human participants. Accordingly, the determinants of the strength-duration curve, rheobase, and chronaxie for the coupled nerve-tissue model had close correlations with in-vivo measures. Furthermore, the excitability indices for the triaxial compartmentalized myelinated nerve fiber implemented using the FE method showed good agreement with experimental data from the literature. The validity of the proposed model encourages its use in neuroprosthetic applications involving the stimulation of myelinated axons. With the capability to capture the spatial and temporal distribution of the electric field across realistic morphologies, the model can serve as a testbed to improve stimulation protocols and electrode designs with subject-level specificity.

Also, to represent the physiological processes of tNMES, as an extension of the model developed in this chapter, a new model is proposed in Appendix I. Here, the activation of a myelinated nerve with a volume conductor was coupled to a parameterized Hill-type muscle model. Wherein, the active stress developed during muscle contraction was later integrated into a constitutive muscle model. The model predicted muscle forces for an externally induced transient stimulation. As a continuum representation for neuromuscular stimulation, the proposed model can be used to evaluate several tNMES-based protocols.
7. Design of stimulation electrodes

In the previous chapter, a physiologically valid computational model for transcutaneous nerve stimulation was developed. In this chapter, the applicability of such a model was extended by adding sensory nerve fibers along with the motor nerve fibers. The extended model facilitated the assessment of the influence of electrode geometry on stimulation performance. Additionally, experimental assessments were also carried out. Based on experimental and model-based inferences, of small surface area electrodes with improved selectivity and comfort were derived.
7.1 Factors affecting simulation performance

Transcutaneous surface stimulation electrodes are integral to wearable neuroprostheses that aim to restore dormant hand function. Prevalent for their non-invasiveness, ease of use, reusability, and reconfigurability, these electrodes are utilized for personalized and home-based rehabilitation [32], [72], [87]. However, transcutaneous delivery of charges offers poor control over its dispersion as the spillage may activate neighboring muscles in addition to the targeted ones. Also, the induced discomfort poses a significant limitation as these electrodes are used to deliver prolonged stimulation for therapeutic and assistive implications [32], [52], [196]. Furthermore, high current density profiles on the electrode surface can invoke electrochemical reactions that can cause inflammations and skin burns upon extended usage [197], [198].

The sensation of discomfort is due to the activation of nociceptive sensory nerve fibers in the skin. Sensory nerve fibers are activated at stimulation thresholds lower than that of the motor nerve fibers [199]. Consequently, the requisite for higher stimulation thresholds when targeting deeper motor nerve fibers, in turn, activates more sensory nerve fibers along with off-target motor nerve fibers due to the large volume of an excitable electric field [53], [200].

For transcutaneous stimulation, the permeation of the electric field in a composite medium such as the forearm depends on the nature of the stimulation waveform [51] and the biophysical properties of the tissue layers [159], [174]. Still, the electrode-skin impedance and the electrode properties primarily steer the current density distributions on the electrode surface [200], [201]. High current density regions along the electrode peripheries are typical to stimulation electrodes. Referred to as edge effects, they tend to cause inefficient stimulation and can lead to mild inflammatory responses and small puncture burns [52], [197].

Besides, the penetration of high-density current into the dermo-
epidermal regions induce pain sensation [164]. Either by modifying the electrode surface [51]–[53] or by adding current redistribution layers [54]–[56], optimal current density distribution is achieved. Although these methods have also reported delivering safe stimulation, modifying the structural features of the electrode surface complicates the fabrication process and its characterization in deriving optimal electrode designs [15]. Moreover, the performance of conductive hydrogels that are used to redistribute the currents is highly non-linear, subjective, and deteriorates over time [202], [203].

The choice of muscle dictates the electrode size [51], [53]. The forearm muscles being tightly packed, electrodes with small surface area (SSA) are chosen for selective activations [32], [53], [160]. SSA electrodes have a high current density profile that creates localized high current density regions, which are discomforting [52], [164]. Considering the importance of realizing hand function tasks by facilitating targeted muscle activation over the induced discomfort, wearable neuroprosthetic devices still use SSA electrodes to stimulate the forearm muscle groups [32], [72], [87]. Improving the performance of SSA electrodes can expand its applicability by delivering selective, comfortable, and safe stimulation [52], [160], [204].

With a lack of comprehensive studies assessing the influence of electrode geometries for wearable neuroprostheses design, studies on cardiac pacing [198], [205], and neurostimulation [206]–[209] have reported several advances using high perimeter electrodes. Hence, improving the electrode performance for functional electrical stimulation (FES) by changing its geometrical aspects is of interest to this study. A diverse assessment of electrode geometries on SSA electrodes can help with improved electrode designs suited for the stimulation of forearm muscles. Perimeter increase in electrode geometries tend to improve the current density distribution both for near-field [205], [210], [211] and far-field stimulations [209], [212].
Amidst the reduction in maximum peak current, these geometries can prevent skin burns by minimizing faradaic reactions [211]. Moreover, studies have reported high perimeter-based geometry to outperform typical electrode shapes [209], [213]. Also, for transcranial stimulation, concentric and ring-like geometries had better performance over conventional electrodes [206], [207]. Additionally, a consensus can be reached that the performance of simple Euclidean geometries is very similar, as reported for circular or rectangular or elliptical [160] and clover or fan-shaped geometries [198].

Hence, the primary objective of this chapter was to demonstrate that electrode geometry can influence stimulation performance in terms of selectivity, comfort, and safety. Also, to identify suitable electrode designs for SSA electrodes that can offer improved stimulation performance when compared to the conventional circular geometry.
7.2 Electrode designs and evaluation

To assess stimulation performance, current density, and field distribution profiles must be obtained. In place of sophisticated *in-vivo* or *in-vitro* assessments, computational models can be a plausible alternative to predict such profiles [53], [160], [214]. Hence, a physiologically valid computational model to assess the performance of several electrode geometries was implemented. This model was derived and extended from the previous chapter. In addition to these model-based predictions, psychophysical and excitability tests were also carried out on healthy participants.

7.2.1 Modeling for transcutaneous nerve stimulation

The tissues of the forearm represented a three-dimensional volume conductor with a 35 cm long cylindrical geometry [162], Figure 7.2. The electric field within the volume conductor was calculated using (7.1) with respective conductivity ($\sigma_e$) and permittivity ($\varepsilon_0$) for each layer and appropriate boundary conditions imposed. Local inhomogeneities in the skin layers were not considered in the model [162], [164]. The thickness and dielectric properties of the forearm tissues were modeled after [162]. A cylindrical geometry was chosen for the volume-conductor as the impact of using an accurate anatomical representation for the forearm was deemed to be insignificant in earlier studies [162]. To assess the impact of discomfort while eliciting muscle contraction, the forearm volume conductor included the sensory (A$\delta$) and the motor (A$\alpha$) nerve fibers as 1D elements, Figure 7.2. The volume conductor potential ($V_e$) was then coupled with the activation of these fibers at the skin level and at the muscle level, respectively.

$$-\nabla \cdot (\sigma_e \nabla V_e) - \nabla \cdot \left( \varepsilon_0 \varepsilon_r \frac{\partial V_e}{\partial t} \right) = 0 \tag{7.1}$$

The A$\delta$ nociceptive fibers respond to perceptive or noxious electrical stimuli [215], [216]. To estimate the perceived discomfort, passive A$\delta$
fibers were included in the model. These nerve fibers were 35 µm deep from the skin surface, signifying the epidermal depth, and were oriented perpendicular to the forearm curvature [164], [215], [217]. To represent a patch of skin under the electrode surface with an area of ~88 cm² [164] the model included forty-nine 3.25 mm long Aδ fibers distributed in a 7 x 7 grid, wherein the fibers were 15.6 mm apart. The branching morphology of Aδ fibers was disregarded due to the underlying computational demands when using the finite element (FE) method.

Four Aα fibers, each 100 µm apart that were distributed along the vertices of a square within a 200 µm thick endoneurium, represented the motor nerve. Also, a thin layer of perineurium bounded the endoneurium that had a thickness of 4 % the fascicular diameter. To signify its innervation into the Flexor digitorum superficialis muscle, the nerve was placed under the active electrode at 12.4, 14.6, and 16.8 mm [186].

The geometric and biophysical properties of the Aα fibers were modeled after the MRG-type fiber [177]. The model included the activation dynamics for the nerve fibers at 37°C. The nerve fibers had a diameter of 14 µm, considered after forearm nerve conduction studies [187]. With 21 node-to-node segments, the nerve fibers ran along the forearm for 280 mm. The model was able to fit the reported experimental range for transcutaneous nerve stimulation [162], [218] with a chronaxie of 575±61 µs and rheobase of 2.3±0.5 mA that ensured the validity of results.

The model was discretized using the FE method that captured the nerve response to spatial and temporal changes for an externally induced electric field, implemented in COMSOL Multiphysics®, 5.4 (COMSOL, Inc., MA, USA). Unlike two-stage models [162], differential equations for voltage-dependent membrane currents of Aα fibers were solved concurrently with the electric field distribution in the volume conductor. Localized mesh refinement was carried out to accommodate diverse spatial scales in the model. Moreover, the meshing routines were kept consistent across the electrode geometries.
The model was solved as tetrahedral quadratic Lagrange elements for \( \sim 8 \times 10^5 \) DoF, via the implicit backward differentiation scheme under transient conditions using a fully coupled, direct solver (MUMPS) with adaptive time stepping.

### 7.2.2 Electrode design and fabrication

All electrodes had a constant surface area of 450 mm\(^2\). The surface area was derived upon two requirements; firstly, to activate deep nerve fibers (innervating the Flexor digitorum superficialis) under a fat thickness of 2.5 mm [53] and secondly, to fit the SSA-type suitable for stimulation of forearm muscle groups. The circular geometry is still the gold standard for electrode design and is widely used for peripheral nerve stimulation. Hence, twelve different electrode geometries, in addition to the circular one was assessed, Figure 7.1. They were based on established 2D geometries that offered an increase in the perimeter that could potentially avoid edge effects [205] and improve the charge injection [211]. Based on the increase in perimeter from the circular geometry, they were categorized into groups of low (0-100%), medium (100-200%), high (200-300%) and very high (>300%) perimeter gain with each category encompassing three unique geometries. All the electrode designs avoided very sharp edges that can worsen the edge effects [202].

The low-gain group included a circular geometry with a serpentine perimeter, a ring-type, and a modified lemniscate geometry. A typical lemniscate includes a figure-eight geometry; however, this was modified to avoid the infinitesimal surface area at its geometric center. Also, the rectangular and elliptical geometries were disregarded. Although they fit within this category, their performance was very similar to the circular one or imparted no significant change [45], [160].

The medium-gain group included a quartet of reuleaux triangles, a second-order Sierpiński square, and a concentric geometry. The high-gain
group included an octet of rouleaux triangles, a concentric geometry with serpentine perimeters that were extended from the previous group.

![Figure 7.1 Electrode geometries considered](image)

**Figure 7.1** Electrode geometries considered

*Electrode geometries included: circular serpentine (I), modified lemniscate (II), ring (III), reuleaux quartet (IV), 2\textsuperscript{nd} order sierpiński (V), concentric (VI), reuleaux octet (VII), concentric serpentine (VIII), 4 x 4 electrode array (XI), 3\textsuperscript{rd} order sierpiński (X), 3\textsuperscript{rd} order Hilbert curve (XI) and spiral (XII)-types.*

The very high-gain group included a third-order Sierpiński square, a third-order Hilbert curve, and a spiral geometry. Also, a 4 x4 electrode array with circular electrodes gave a high perimeter gain.

The electrode prototypes were fabricated via toner transfer technique and a subsequent etching process. This method represented an economical and relatively straightforward fabrication process. Firstly, electrode designs were printed on a glossy photo paper using a laser printer. The patterned photo paper was firmly attached to a single-sided copper-clad laminate and
passed through a laminator at 80ºC for at least five times to transfer the toner onto copper clad laminate.

Following this, the hot copper-clad laminate was immersed in water for a few minutes to dissolve the starch layer. The transferred toner patterns formed a resistive mask on the copper-clad laminate sheets. Finally, the patterned copper-clad laminate was dipped into 20 wt/v % of Sodium peroxidisulfate solution for 30 min to etch the copper, wherein, the non-masked regions were subsequently etched, leaving the desired electrode patterns. The sample was rinsed with water and cleaned with acetone to remove the toner residues. The final patterned electrodes were cut to a dimension of 45 x 45 mm.

**7.2.3 Model-based evaluation of stimulation performance**

Concurrent to the experimental protocol, the Aα fibers were excited until the depolarization elevates the transmembrane potential \( \geq 20 \, \text{mV} \). Upon successful activation, metrics for selectivity, comfort, and safety were derived from model predicted current density and electric field distributions.

Firstly, the topology of the electric field in the volume conductor quantified the electrode’s selectivity. Activation volume (AV) is a lobe of tissues under the active electrode with the same electric field potential (isosurfaces) that signified potential areas of neuronal excitability [219]. AVs are widely used in volume conductor-based models [153], [219], [220]. The iso-potential value for an AV was determined to be the minimum voltage amplitude needed to depolarize the nerve fiber, which was unique to the fiber diameter, stimulus duration, and electrode configuration (shape, size, and inter-electrode distance) [153], [219]. The activation volume was calculated using a quadratic interpolation using the FE package.
A highly selective AV when targeting deep Aα fibers must resemble a hemi-ellipsoid [219], [220]. Hence, the properties of this hemi-ellipsoid were used as metrics that quantified electrode selectivity. Accordingly, the surface area \( S_{AV} \), the surface eccentricity \( e_{AV} \), the activation depth \( d_{AV} \) and the topological volume \( V_{AV} \) of the isosurface directly under the active electrode were determined.

Secondly, the excitation of Aδ fibers quantified stimulation comfort. Since the Aδ fibers were modeled as passive cables that lacked ion-channel dynamics; their excitation was assessed using the activating function along the direction of the nerve fibers [164], [196], [209], [215]. The activating function: second-order differentiation of extracellular voltage, provided a qualitative estimation on nerve excitation. Regions of positive activating function were considered to be active nerve fibers. Based on the number of active sensory fibers and the magnitude of the activating function, the stimulation comfort was quantified.

Thirdly, the current density profiles were analyzed to estimate the
stimulation safety. Stimulation induced skin burns were concluded to have electrochemical origin [197]. Regions of high current density where high voltage gradients co-existed tend to cause electroporation [198]. These hotspots were identified as potential areas that could induce skin damage [200], [221]. Also, the non-uniformity of the current density under the electrode surface was calculated. As in (7.2), $k$ is expressed with, $J_{\text{max}}$, the maximum current density, $J_{\text{min}}$, the minimum current density and $J_{\text{avg}}$, the average value of current density [54], [200].

$$k = \frac{J_{\text{max}} - J_{\text{min}}}{J_{\text{avg}}}$$  \hfill (7.2)

**7.2.4 Experimental evaluation of stimulation performance**

Experimental procedures were carried out on twelve healthy participants (9M+3F, aged 31.75±6.27yrs, BMI 22.82±2.65) who had no contraindications to electrical stimulation. The University of Auckland Human Participants Ethics Committee approved this study, and all participants gave informed consent. The intent was to assess the electrode performance while enabling the wrist flexion. The procedures were performed on the volar side of a non-dormant forearm; wherein, the participants sat in a comfortable position with their forearms constrained onto a testing platform in a pronated position [35]. After preparing the skin, a tracing routine identified the motor points that elicited the contraction of Flexor digitorum superficialis [35]. The active electrode was placed directly above this motor point. While the geometry of the active electrode was varied, the reference electrode had a fixed circular geometry, which was held 80 mm away from the motor point. A constant pulse-width (300 $\mu$s) monophasic cathodic stimulus delivered via current-controlled stimulator, RehaStim™ 2 (Hasomed GmbBH, Germany), evoked muscle contractions. This method enabled a reliable measure for both sensory and motor thresholds [222].

Only the stimulus amplitude was varied between 0 – 20 mA with one mA increments. The platform also mounted a dynamometer (Biopac Systems
Inc., USA) that measured the strength of isometric contractions. The average of three voluntary force exertions gave the maximum voluntary isometric contraction (MVIC) level, which was then used to normalize evoked force exertions.

The single-blinded study design was adopted to mask the electrode geometries from the participants. The average of two trials quantified the overall stimulation performance. For each trial, the order of electrode groups was changed. Nevertheless, the electrodes within each group were sorted with an increasing perimeter. Before conducting trials on performance evaluation, increasing stimulus was delivered using circular and spiral electrodes for the participants to accommodate varying levels of stimulation. The abovementioned steps were taken to overcome experimental bias.

Each experimental trial followed the identification of sensory and motor thresholds, followed by the evaluation of stimulation performance. The minimum current required to elicit a noticeable sensation and a muscle twitch, respectively, were recorded as sensory and motor thresholds. Secondly, the participants qualitatively rated the stimulation comfort while eliciting a submaximal muscle contraction (>=10 % MVIC) using verbal descriptors and a 10-point visual analog scale (VAS).

The verbal descriptors expressed the pain sensation as ‘no sensation’ (=1), ‘Dull,’ ‘Prickling,’ and ‘Pressing’ with an intensity scale (‘mild’=1, ‘medium’=2 and ‘severe’=3) [223]. While evaluating the stimulation comfort, to compare the VAS and the verbal descriptors directly, the verbal descriptors were converted into a 10-point scale, termed as the pain index. With increasing order of discomfort, the numbers one to ten were assigned to the verbal descriptors. For every session, each verbal descriptor was multiplied with the intensity level to get a numeric estimate.
7.3 Geometry affecting electrode performance

All electrode geometries considered in this study evoked muscle contractions at > 10 % MVIC with varying comfort levels. Measures on stimulation performance to quantify the selectivity, comfort, and safety were corroborated by both model-based and experimental data as follows:

The experimental and model-predicted motor thresholds are presented, Figure 7.3a. The experimentally derived motor threshold 6.33±0.13 mA had no significant difference across electrode geometries. The model-predicted threshold of 6.57±1.59 mA for circular geometry was similar to the experimental one. However, for other electrode groups, the threshold varied between 7.82±1.88 to 8.61±1.74 mA.

The AV influencing a motor nerve at 16.8 mm from the electrode surface represented as a hemi-ellipsoidal lobe, Figure 7.3b. Across the three nerve depths, the circular electrode had the smallest AV, 12607±2521 mm³. For other electrode groups, the AV increased from 14 to 25 % along with the increasing perimeter. This effect was consequent of the higher motor thresholds, as reported earlier, Figure 7.3a. Also, there was a linear correlation between stimulation amplitude and AV ($r=0.71$, $p<0.05$). The largest activation volume, 17288±3971 mm³, was produced by the Hilbert geometry (at 9.53±1.8 mA).

Here the aim was to quantify selectivity based on the surface to volume ratio. Lower surface to volume ratio tends to avoid the charge spillage preventing the co-contraction of neighboring muscles. The model predicted circular geometry to have the largest surface to volume ratio, and it decreased with an increase in electrode perimeter, Figure 7.3c. However, the activation depth of circular geometry was 4.2 % higher when compared to other electrode geometries.

Experimentally, all electrodes evoked muscle contraction at $\geq$10% MVIC with 10.66±0.17 mA. Although the stimulation amplitude was similar across all electrode groups, due to higher AVs when compared to circular
electrodes, other groups evoked 19.73 % more contraction, Figure 7.3d. Circular electrodes evoked 12.06±2.42 % of MVIC (at 10.83±1.66 mA), and the very high-gain group evoked the maximum muscle contraction of 16.32±0.83 % of MVIC (at 10.68±0.11 mA). When comparing the evoked muscle contraction against the electrode perimeter, there was a linear increase in MVIC with perimeter ($r=0.83$, $p<0.05$).

**Figure 7.3** Measures of stimulation selectivity

[a] Comparing experimental (boxes) and model-predicted (circles) motor thresholds. [b] The activation volume for a circular electrode representing an isopotential surface of 19.7 V. [c] The surface to volume ratio of the activation volumes as predicted by the model across the electrode groups. The error bars represent motor nerve stimulation at depths of 12.4, 14.6, and 16.8 mm. [d] Experimentally evoked muscle contraction expressed as % MVIC.
In a similar work [153], the AVs for circular, rectangular, elliptical, ring, spiral, and array-type geometries were compared, Figure 7.4. Here, for the same activation threshold, the current density and AV profiles for circular, rectangular, and elliptical geometries were similar.

![Activation volume under varying electrode geometry](image)

**Figure 7.4** Activation volume under varying electrode geometry


The model-predicted values for the percentage of active sensory fibers are shown, Figure 7.5a. The circular geometry had the largest activation of sensory nerve fibers, and the activation decreased along the electrodes with an increasing perimeter. The % of activation had a high variability across the high perimeter groups; however, the circular geometry, even with low variability, had a high percentage of fiber excitation. At the motor threshold, the model-predicted circular geometry to have 72.79±0.96 % of sensory fiber activation and the lowest activation of 64.4±3.98 % was for the very-high perimeter gain.

The distribution of charges under the electrode surface influences the activation of sensory nerve fibers in the skin; hence, the surface eccentricity of the AV was used to quantify this effect, Figure 7.5b. The
eccentricity of the AV surface was the least for the circular geometry, 0.41±0.27. All electrodes exhibited a higher eccentricity than the circular one. Due to the elliptical nature of lemniscate geometry, its eccentricity of 1.22 significantly affected the overall eccentricity of the low-gain group.

![Graph showing measures of stimulation comfort](image)

**Figure 7.5 Measures of stimulation comfort**

[a] Percentage of active sensory fibers. [b] Surface eccentricity of the activation volume. The errorbars in [a], [b] represent motor nerve stimulation at depths of 12.4, 14.6, and 16.8 mm. The pain index [c] and VAS scores [d] while evoking muscle contraction >=10% MVIC. The electrode geometries included circular (c), circular serpentine (I), modified lemniscate (II), ring (III), reuleaux quartet (IV), 2nd order sierpiński (V), concentric (VI), reuleaux octet (VII), concentric serpentine (VIII), 4 x 4 electrode array (XI), 3rd order sierpiński (X), 3rd order Hilbert curve (XI) and spiral (XII)-type.
Psychophysical tests to evaluate the stimulation comfort across the electrode geometries using the pain index and the VAS, as in Figure 7.5c, b, respectively, were performed. A one-way ANOVA was performed across the varying perimeter groups against the circular one. A significant difference \((p<0.05)\) in pain index with medium-gain \((4.75)\), high-gain \((4.64)\), and very high-gain \((4.3)\) groups against the circular one \((6.06)\) was observed. Also, a significant difference \((p<0.05)\) in VAS score with low-gain \((4.81)\), medium-gain \((4.81)\), high-gain \((4.88)\), and very high-gain \((4.54)\) groups against the circular one \((5.9)\). Values in bracket represent the group means.

Examining the frequency of verbal descriptors and their intensity revealed that the participants felt a medium level prickling for across all geometries. However, spiral and 3\(^{rd}\) order sierpiński geometries induced a mild level pressing sensation.

The uniformity of current and electric fields across the electrodes was compared in Figure 7.6. It is evident that the lowest non-uniformity is for the circular electrodes. Electrodes that had a geometry very similar to the circular one such as the modified lemniscate (II), reuleaux quartet (IV), concentric (VI), reuleaux octet (VII) formed a cluster with low non-uniformity coefficients. However, the fractal electrodes, including the 2\(^{nd}\), 3\(^{rd}\) order sierpiński (V, X), and the sharp-edged circular serpentine (VIII) geometries had very high non-uniformity. Figure 7.6 also overlays the average current density as a color contour, and the size of the markers normalized based on the activating function. The average current density was highest for the spiral (XII) shape, and other electrode geometries had a very similar current density profile.

Stimulation comfort and selective activation are two significant limitations with transcutaneous electrodes deployed for the restoration of hand function. Although large electrodes are preferred for comfortable stimulation [43], [204], considering the tightly packed nature of forearm muscles, they cannot facilitate selective activation.
**Figure 7.6 Measures of stimulation safety**

Plot comparing the model-predicted non-uniformity coefficient of current density and the electric field across electrode groups. The colorbar represents the average current density on the respective electrode surface. And the size of the makers indicates a normalized value of the activating function ranged between $3428$ to $60327 \text{ V/mm}^2$. Electrode geometries include circular serpentine (I), modified lemniscate (II), ring (III), reuleaux quartet (IV), 2nd order sierpiński (V), concentric (VI), reuleaux octet (VII), concentric serpentine (VIII), 4 x 4 electrode array (XI), 3rd order sierpiński (X), 3rd order Hilbert curve (XI) and spiral (XII).

The current density distributions for circular, rectangular, elliptical, ring, spiral, and array-type geometries were compared, in a similar work [153]. All electrode shapes had a high current density at their edges, marked by arrows. The current density distribution was also affected by the location of the return electrode. As in Figure 7.7, the current density for array-type geometry was strong on the side-proximal to the return electrode when compared to their edges.

Concurrent to the AVs, the current density profiles for circular, rectangular, and elliptical geometries were similar. The spiral geometry had a strong
current density at its terminals. Although high current density regions are seen across all electrodes for the array-type geometry, its magnitude was comparatively less.

Figure 7.7 Current density distributions under the electrode surface.

7.4 Discussion

Stimulation comfort and selective activation are two significant limitations with transcutaneous electrodes when facilitating hand function tasks. Although large electrodes are preferred for comfortable stimulation [43], [204], considering the tightly packed nature of forearm muscles, they cannot facilitate selective activation. Hence, SSA electrodes are preferred for forearm muscles. With such electrodes distributed along the forearm surface, dynamic control over these muscle groups facilitates several hand function tasks [72], [87]. Commercial electrodes are typically larger, and they claim to have improved stimulation performance; wherein, they are optimized for general purpose use [52]. Moreover, its multi-layered construction makes the electrode design cumbersome. Hence, improving the stimulation performance of electrodes by exploiting its geometry provides a promising venture to develop simple and highly personalized electrode designs with a significantly low-profile form factor.

Accordingly, in this study, using both model-based and experimental conclusions, it was shown that electrode geometry can influence stimulation performance. Furthermore, this study provides the firsthand evidence by assessing a comprehensive geometry of SSA electrodes suited for transcutaneous stimulation of forearm muscle groups. Moreover, by using SSA electrodes, it was shown that regardless of their high current density profiles, varying the electrode geometry can improve the stimulation comfort. The implications of this study are not limited to forearm-muscle stimulation but can be applied to any form of non-invasive electrostimulation such as pain management with spinal cord injury, defibrillation electrodes, and transcranial stimulation.

To conduct the aforementioned model-based analysis on the current density and the electric field distribution profiles, here, a novel computational model that assessed the excitation of sensory and motor nerve fibers was developed. The validity of the model-based inferences with
experimental data also urges its usage for electrode designs and optimization studies involving transcutaneous stimulation.

The discrepancies with the model-predicted and experimentally obtained motor threshold (Figure 7.3a) can be attributed to the nerve orientation, geometric, and dielectric properties of the tissue layers [214], [215]. The demand for a higher motor threshold for electrodes with increasing perimeter naturally increased its AV. Moreover, due to varying motor thresholds, the AVs across the electrodes cannot be directly compared. Hence, the ratio of surface to volume to quantify selectivity was used. The surface to volume ratio also decreased along the electrodes with perimeter, as in Figure 7.3c. The higher surface to volume ratio of circular geometry suggests that all other electrodes achieved comparatively higher selectivity.

Also, the circular geometry activated the nerve fibers until the depth of 15.2±1.82 mm; wherein, all other electrodes achieved similar activation at 14.8±0.08 mm. Moreover, for a similar stimulation amplitude, with a lower activation depth, the magnitude of evoked muscle contraction increased along with the perimeter size. This effect can be attributed to two effects, either due to larger AV or due to a higher magnitude of the electric field. Studies have also reported that electrodes with a large perimeter to surface ratio can have high charge injections [209], [211]. Since the surface to volume ratio of AV decreased along the perimeter, this effect was due to the higher magnitude of the electric field gradient.

Although larger electrodes usually are preferred for comfortable stimulation, they are not suitable for forearm muscles. The high current density profiles of SSA electrodes are prevalently known to be discomforting. However, in this study, it was demonstrated that SSA with varying electrode geometries achieved higher stimulation comfort when compared to circular geometry.
The influence of electrode geometry on the sensory threshold was insignificant, as all electrode geometries evoked a sensation at 2 mA, experimentally. FES-based systems must elicit a minimum muscle contraction at 10% MVIC to signify activities of daily living. Hence, measures of stimulation comfort, the VAS score, and the pain index were obtained while evoking >=10% MVIC. With increasing order of the electrode perimeter, higher levels of muscle contraction were achieved with less discomfort. Furthermore, all groups had a significantly lower score than the circular one indicating an improved level of comfort. Similar to the 4 x 4 electrode array used in this study, using distributed sources has reported achieving improved comfort [213]. As predicted by the model that the circular electrode activated a larger population of sensory fibers, the experimental VAS and pain index were also higher. Except for the spiral and 3rd order Sierpiński, all electrode geometries evoked a medium level prickling sensation regardless of varying levels of comfort.

As in Figure 7.7, the spiral geometry had a very high current density profile, and the 3rd order sierpiński has the highest non-uniformity of current density; these effects were reflected in the experiments, as they evoked a mild pressing sensation. A limitation when opting for a very-high gain perimeter is that the non-uniformity of current density also increased. In general, sierpiński, Hilbert, spiral, and serpentine geometries have acute edges, that are common sources of high current density. As these spots could potentially induce skin damage [200], [221], it could be a trade-off. However, given the advantage of improved stimulation comfort, their designs can be optimized to improve the uniformity of current density, or the use of charge-balanced waveform can potentially avoid such adverse effects that result from charge accumulation [52], [199].
7.5 Summary

Ease of use and non-invasiveness has made transcutaneous stimulation a pervasive approach for restoration of hand function. Still, limited targetability and induced discomfort pose a significant impedent for its clinical translation. Modifying the distribution of currents on the electrode surface can potentially improve stimulation performance. Accordingly, this chapter aims to assess the impact of electrode geometry to improve selectivity and comfort of small surface area electrodes that are suited for forearm muscles. The stimulation performance for twelve electrode geometries was assessed using a computational model that represented the transcutaneous stimulation of sensory and motor nerve fibers. Following this, psychophysical and excitability measures on healthy participants were derived concurrently to the model predictions. Here, the impact of electrode geometry on stimulation performance was demonstrated. Accordingly, electrode geometries that offer high perimeter gain tend to have improved performance. Implications from this chapter can aid with easy to fabricate and personalized electrode designs. Moreover, the applicability of wearable neuroprostheses can be improved by integrating these optimized electrode designs with advanced material technologies.
8. Development of a wearable electrode array

In this chapter, the viability of fabricating conductive layers infused in silicone-black based elastomers using the multi-layered screen-printing technique is demonstrated. The viability of the fabrication technique and the electrode designs encourage the realization of comfortable, wearable, and cost-effective wearable stimulation systems.
8.1 Introduction

The advent of electrode arrays has facilitated dynamic control over forearm muscle groups to achieve ADL using FES [33], [52], [72], [91], [159], [224]. Moreover, electrode array-based stimulation offers several advantages over single electrode-based stimulation, Section 2.2.1, which are integrated into a wearable sleeve. This makes them easy to use, that can be donned and doffed easily and allows for easy recalibration after repositioning [88], [90], [91], [98], [212]. Nevertheless, for home-based rehabilitation to assist people in their daily activities, personalizable and cost-effective electrode arrays must be realized.

Early designs for a wearable sleeve integrated conductive rubber-based electrodes into an orthosis or a fabric [9], [36]. However, these devices had several limitations in producing selective activation. They were bulky and tended to constrain the forearm movements [225]. However, recent advances with screen printing [73], [226], and textile technologies [196] have developed electrode arrays that are flexible and deliver comfortable stimulation. Furthermore, whole body garment-based designs were also proposed for several functional modalities [227]. Adequate research is being conducted for the development of flexible and lightweight electrode array designs [32]. In addition to challenges, choosing appropriate material for the stimulation electrode, considering optimal designs and materials for the traces and connections are also equally important.

Metal electrodes are entirely obsolete; they are discomforting and can cause electrochemical reactions on the skin surface. Still, they are often covered with a biocompatible fabric to improve its usage [52]. Since they are not flexible, they lack conformity on the forearm surface. Commercial electrodes have a multi-layered construction, with highly resistive layers infused with metal electrode meshes. Due to the current redistribution layers, they offer considerable comfort and are widely used for clinical and home-based rehabilitation. However, due to the multi-layered construction,
they are bulky and cannot be easily incorporated into electrode arrays [51], [52], [153]. Textile technologies that use woven materials integrate wire meshes, and gauzes seem straightforward and have the potential to be incorporated into existing fabrics. It should be noted that bulky, thick, molded-type electrodes are not as flexible and have limited use as they cannot be conformed over the forearm surface. Since these electrodes do not have a low profile, they make the wearing uncomfortable and unsuitable for use under clothing, or bandages, and the like.

The applicability of electrode arrays can be improved by considering designs that can be derived from the shape and size of the stimulation zones in Chapter 4. Moreover, several subject-specific factors influence stimulation performance; hence, these electrodes must be tailored to an individual. Most importantly, these electrodes should be flexible, stretchable at the same time maintain the conductivity; thus, comfortable stimulation can be delivered. Considering the above factors, electrode arrays fabricated using screen printing offers stretchability, they are lightweight, and the fabrication process facilitates rapidly customizable electrode designs.

Infusing silicone-based elastomers with conductive materials like carbon black can offer the required stimulation performance and can still be stretchable. Moreover, screen printing of such silicone-based elastomers has achieved several strides for wearable electronics [228], [229]. Moreover, the demand is to realize a conformable and easy to conceal electrode array-based sleeve, with simple electrode designs and a straightforward scalable fabrication process. Hence, this chapter aims to leverage the advantages of silicone-based elastomer electrodes by coupling with the multi-layered screen-printing process, wherein the traces and the electrodes are together integrated into a conformable electrode array-based sleeve.
8.2 Methods

The base material for the electrodes was a silicone-based elastomer infused with carbon black. Here, the conductive property of the silicone-based elastomer was modified by the addition of carbon black and was fabricated into electrode arrays using the multi-layered screen-printing process. The dimensions of the sleeve were considered after the forearm anthropometry [230].

Moreover, the stimulation electrodes had a geometric surface area of 79 mm² with simple circular geometry. The sleeve had 21 electrodes distributed in a 7 x 3 array. The gap between the electrodes was 150 mm, considered after [159]. In this study, five different weight ratios, 1:7, 1:8, 1:9, 1:10, and 1:11 of CB + silicone-based elastomer were prepared. With further characterization, the ratio that offered the best performance was later used to fabricate the electrode array.

8.2.1 Materials and preparation

Here, Ecoflex™ 00-30 (Smooth-on Inc., PA, USA) was used as the silicone-based elastomer that served as the stretchable medium. For the conductive element, 50 nm particle size CB powder, Vulcan® XC72R (Fuel Cell Store, TX, USA) was used. The concentration of CB in Ecoflex (base mixture) primarily steered the conductivity and printability of the electrode arrays. The base mixture was prepared by meticulously by blending CB and Ecoflex at the desired weight ratios.

Mixing was done in a pressurized glove box to prevent the agglomeration of CB into lumps. The uncured mixture was homogenized using a planetary centrifuge mixer (Mazerustar KK-50S) and was later degassed. Also, no thinners (Silicone oil) was added to regulate the viscosity of the base mixture.
8.2.3 Characterization

Different weight ratios of the base mixture were characterized for conductivity, and surface morphology. The novelty of this work is to develop a stretchable electrode array-based sleeve that can conform to the forearm surface, Figure 8.1k. Hence, the conductivity of the electrodes was also assessed under stretching cycles.

For conductivity measurements, 20 x 20 mm samples were prepared for all weight ratios. The sheet resistance of the electrode samples was then measured using a four-point probe. Herewith, currents were applied, and the voltage changes were measured using the Keysight b2902a precision source/measure unit (Keysight Technologies, CA, USA).

Also, the conductivity was measured under several stretching cycles. Here, a custom-built rig measured the change in resistance for various strain levels. Samples of 3 x 1 cm were prepared for all weight ratios considered. Wherein, one end of the sample was held stationary, and the other end was mounted on to a motorized stage. The samples were stretched up to 500% its original length and were relaxed, at the rate of 0.005 ms\(^{-1}\), and the resistance was measured using the Agilent 4263B LCR meter.

The surface morphology of the samples was observed using a scanning electron microscope. To improve the visibility of grain size at higher magnification levels, the samples were predeposited with gold. In addition to microscopic imaging, the roughness profile of the samples was evaluated using Stylus Profilometry (Bruker Dektak XT).

For each weight ratio, all characterization for conductivity, change in resistance with stretching, and surface profilometry, three measurements were obtained, which were then averaged for final comparisons.
8.2.2 Fabrication

The screen-printing process followed the infusion of the base mixture through patterns on a stencil, which was deposited over a substrate. After curing, the desired patterns were developed [229]. However, this process was done in multiple stages to incorporate both the stimulation electrodes and the traces. The aim was to develop a thin and light-weight sleeve, wherein only the stimulation electrodes are exposed, and the traces are embedded within the sleeve. Several stages involved in the fabrication process is illustrated in Figure 8.1.

Firstly, the samples were characterized by several weight ratios (Section 8.3). Blending one part of CB into eight parts of silicone-based elastomer yielded the best stimulation performance. Accordingly, the base mixture was prepared. Secondly, as in Figure 8.1b, pristine Ecoflex was prepared by mixing 1A:1B by weight; it was degassed and poured into a mold to form the substrate of the sleeve. It was allowed to cool on a leveled surface at room temperature (23 °C) for nearly 4 hours.

Thirdly, the first layer of the stencil was placed on the cured substrate, and the base mixture (1:8; CB:Ecoflex 00-30) was evenly poured and was smeared using a squeegee. It was ensured that the base mixture was spread along, that it covered the entire patterns of the stencil. The squeegee was daubed on only done direction; this was done to yield a good quality of patterning. Removing the stencil left the desired patterns that formed the traces for the electrode, Figure 8.1e. The pattern was cured in a temperature-controlled oven at 60°C for 8 hours.

Following this, another thin layer of the pristine layer of Ecoflex was layered, applied, and cured, Figure 8.1h. This layer prevented the traces from contacting the skin surface. It also served as a protective coating that maintained the integrity of the trace layers. Lastly, the base mixture was again patterned and cured to form the exposed electrodes, Figure 8.1j.
Figure 8.1 Multi-layered screen printing of an electrode array sleeve.
8.3 Characterization

Conductivity was measured in terms of sheet resistance for the weight ratios, 1:7, 1:8, 1:9, 1:10, and 1:11 of CB + Ecoflex, Figure 8.2. The mean and standard deviation across four measurements for each sample is shown as an error bar in Figure 8.2. Sample with 1:11 weight ratio had the maximum sheet resistance of $5.92 \pm 0.59$ MΩ, and the lowest sheet resistance was for 1:8, $13.44 \pm 0.25$ kΩ. It was an apparent decrease in sheet resistance with increasing weight amount of Ecoflex, and the conductivity gain was due to the addition of CB. Moreover, the samples with a 1:7 weight ratio were too rough to get reliable conductivity measurements. Hence, it was discarded from further characterization.

![Figure 8.2 Conductivity across different weight ratios of CB + Ecoflex.](image)

This study aims to develop a stretchable (conformable) electrode array-based sleeve. Hence, it was crucial to assess the performance of these electrodes under cyclic stretching. The change in resistance for the weight ratios, 1:8, 1:9, 1:10, and 1:11 of CB + Ecoflex when stretched up to 500% its original length was compared in Figure 8.3. The plots represent the averaged values across three separate stretching cycles performed on three different samples.
The weight ratios 1:8, 1:9, 1:10 had a comparatively similar profile. However, the resistance drastically changed under cyclic stretching for the 1:11 weight ratio. The change in resistance, taken as the ratio of resistance at the current strain level to the resistance at resting length, was the lowest, with a factor of 4.5, for the 1:8 weight ratio. Similarly, for the weight ratios, 1:9 and 1:10, the change in resistance was 5.7 and 7.8, respectively.

Furthermore, for the 1:11 weight ratio, the change in resistance was worsened at 400 % stretch to a factor of 7.3 and reached a maximum value of 26.6 at 494 % its original length. Inference can be derived that the integrity of bonding between the CB infused with the elastomer was lost at this weight ratio. Moreover, CB infused within elastomers suffer from discontinuities during the curing process or homogenization. With higher weight ratios of Ecoflex as in 1:11, this effect might have been amplified, which contributed to the drastic changes in resistance after the 400 % strain limit.
The surface morphology of samples with different weight ratios observed using stylus profilometry is shown in Figure 8.4a,b. Here, every sample was prepared using a stencil that was 0.1mm thick. An increasing trend in surface roughness was observed with the concentration of CB. The maximum thickness of 10151.50 ± 1417.77 µm was observed for the weight ratio of 1:7. And the smallest thickness of 351.62 ± 12.21 µm for the weight ratio 1:11.

The mean surface profiles for weight ratios, 1:8 and 1:9 were very similar, with a thickness of 1314.54 ± 712.21 µm and 1132.83 ± 62.71 µm, respectively. However, the weight ratio of 1:8 had a higher deviation in thickness across the profiling length when compared to the sample with the 1:9 weight ratio. Since 1:7 and 1:8 had similar thickness across the sample, their mean thickness was grouped and compared against the other two weight ratios. Here, the removal of CB concentration (1:11 weight ratio) decreased the surface thickness by 71.2 %, and its addition (1:7 weight ratio) drastically increased the surface thickness by 730 % increase.

Moreover, the surface roughness along the profiling length for several weight ratios are shown in Figure 8.4b. Similarly, the size of the peaks and troughs were huge for samples with a 1:7 weight ratio and was comparatively uniform for a 1:11 weight ratio. Furthermore, the weight ratio 1:7 being very coarse; previously, it could not deliver a robust conductively measurement. Hence, both the weight ratios 1:7 and 1:11 were disregarded for being too coarse and smooth, respectively.

Although the surface roughness of the 1:8 weight ratio was higher when compared to 1:7, this unevenness in the electrode surface could favor electrode-skin adhesion. Moreover, this weight ratio had the lowest change in resistance under cyclic stretching, which was considered a crucial factor in deriving stretchable stimulation electrodes.
Figure 8.4 [a] Average surface thickness and [b] thickness profile obtained using Stylus Profilometry.

The surface morphology of the sample with a ratio of 1:8 CB:Ecoflex was observed using an SEM, Figure 8.5. In accordance with Stylus Profilometry, the surface of the sample was comparatively rough, scale 150µm [a], with further magnification [b], scale 50 µm, discernible size of particles can be seen, that left large peaks and trough as in Figure 8.4.
Based on the characterization studies, the weight ratio of 1:8 was chosen to have optimal stimulation performance and the desired surface roughness to establish a good electrode-skin adhesion. Figure 8.6a shows the final sleeve fabricated using the multi-layered screen-printing process (Section 8.2.2). Also, a cross-section of the sleeve reveals several layers, Figure 8.6a, that included the pristine Ecoflex layer (I), that served as the substrate and provided structural support to the sleeve. This layer was 2 mm thick, wherein the other layers (II, III, and IV) were 0.5 mm thick.
8.4 Discussion

In this chapter, the viability of fabricating a stretchable electrode-array based sleeve was demonstrated. The sleeve was designed to suit the stimulation of forearm muscle groups. In addition to the fabrication of a stretchable electrode array-based sleeve, the multi-layered screen-printing technique also facilitated the holistic fabrication of stimulation electrodes and their traces using the same base material. With a relatively cost-effective fabrication process, highly customizable electrode array-based sleeves can be realized.

Two requirements primarily influenced the sleeve’s design. Firstly, the sleeve, stimulation electrode, and its traces must be conformable. That can adapt to forearm movements for improved user comfort. Secondly, the stimulation electrodes within the sleeve must have a recommended resistance between 1 to 100 KΩ, which matches the resistance of the human skin. [52] Hence, to make the electrode inherently stretchable, a silicone-based elastomer was used. However, having poor electrical properties, the conductivity of the silicone-based elastomer was altered, adding functional materials. Accordingly, the conductive properties of a silicone-based elastomer, Ecoflex™00-30, was modified by the addition of CB. The ratio of CB and Ecoflex™ influences the conductivity and printability of the composite. Different weight ratios of the base mixture were characterized for conductivity, and surface morphology. And the weight ratio with 1:8 was identified to have optimal stimulation performance and was later used to fabricate the stretchable electrode-array based sleeve.

Here, Ecoflex™ 00-30 was the choice of material for its stretchability and biocompatibility. As a commercially available material, Ecoflex has been used for a wide range of applications into sensing and actuation [231], [232]. Moreover, they are easy to work with and are relatively inexpensive. The addition of CB altered the conductive properties of Ecoflex by maintaining its stretchability. The use of carbon-based material into
stimulation electrodes is prevalent [52]. Compared to other carbon-based materials, CB has been extensively researched [233]–[235]; wherein, its characteristics are well known [236]. Moreover, it is inexpensive and can easily be dispensed into other materials without any pre-treatment.

Different weight ratios of the CB and Ecoflex were characterized for conductivity, and surface morphology. This study considered weight ratios of 1:7, 1:8, 1:9, 1:10, and 1:11, that were chosen based on preliminary experimentation; considering the dispersion of CB, and the expected electrode impedance. Among the weight ratios, 1:7 performed very poorly due to a very coarse dispersion of CB. Optimum sheet resistance was identified for weight ratios, 1:8 (13.44±0.25 kΩ), and 1:9 (17.96±0.65 kΩ). It was vital to assess the resistance of the stimulation electrode under stretching; the least change in resistance was observed for the 1:8 weight ratio (factor of 4.5).

Additionally, the problem of discontinuities during the curing process or homogenization was noticed among samples with a higher weight ratio of Ecoflex (1:11). Due to this effect, drastic changes to resistance values were observed, stimulation delivered via such electrodes can have adverse effects for stimulation-induced burns or discomfort. Also, the surface morphology was altered by the addition or removal of CB. The surface was comparatively rough for the 1:8 weight ratio; however, this can be leveraged, as the uneven surface could favor improved electrode-skin adhesion. Considering the above factors, the sleeve and the traces were fabricated with a 1:8 weight ratio of CB and Ecoflex to derive the desired conformable electrode array-based sleeve.

As shown in Figure 8.6, several layers of CB:Ecoflex and pristine Ecoflex were bonded using the multi-layer screen-printing process. Compared to other fabrication techniques, screen-printing is widely used for being cost-effective and straightforward [226], [228], [233], [237], [238]. Intricate patterns can be made with relatively simple, with masking stencils and a squeegee. Here, the patterned materials were kept under higher than
normal temperature to accelerate the curing process. However, it can also be cured in a normal room temperature, which obviates the need for temperature-controlled ovens. Also, both the electrodes and the traces were fabricated using a single fabrication process. The fabrication method is simple, applicable for large-scale production, highly customizable, and can support a wide variety of materials. Also, the fabrication base materials that were considered here, like CB and Ecoflex, were cheap.

Previous attempts on stretchable fabric for electrotherapy have been proposed [239]; however, they have not been implemented to electrode array-based stimulation. Moreover, electrode arrays fabricated through screen printing [226], and garment-based [196] have been proposed. Although they were able to demonstrate flexible designs, this work here is the first of its kind to develop a stretchable (conformable) array that included cost-effective materials and a fabrication technique that coupled the electrode and trace elements in a single fabrication step. Nevertheless, using the improved design principles [232] and further optimizing the weight ratios and other functional properties of the base materials, long life wearable sleeves with improved stimulation performance can be realized.

This chapter has successfully demonstrated the viability of a stretchable electrode array, suitable for the stimulation of forearm muscles, and also identified a potential fabrication method for the same. However, as the next phase, as future work, further testing on participants, and assessing the electrode performance can ascertain its applicability.
8.5 Summary

The viability of fabricating conductive layers infused with silicone-based elastomers using the multi-layered screen-printing technique was demonstrated. Herewith, the conductivity of the silicone-based elastomer was altered by the addition of carbon black. The resistivity, stretchability, and surface morphology of different weight ratios of CB and Ecoflex™ were assessed. An optimal ratio of carbon black infused within the elastomers tends to maintain their stimulation performance after several stretching cycles were identified and later used to fabricate the electrode array. In addition to the fabrication of a stretchable electrode array-based sleeve, the multi-layered screen-printing technique also facilitated the holistic fabrication of stimulation electrodes and their traces using the same base material, which is straightforward and a comparative cost-effective fabrication process. The viability of the fabrication technique and the electrode designs encourage us to realize comfortable, wearable, and cost-effective, functional systems in healthcare applications.
9. Discussion and outlook

This thesis aimed to improve the applicability of wearable stimulation systems to facilitate complex hand function tasks. Firstly, a generalizable motor point catalog was derived, which simplified electrode placements for fine digit control. Secondly, digit control and coordination were achieved by synergistic activation of various muscle groups; wherein, parametric control over the stimulation waveform facilitated controlled force exertions for ADL grasps. Thirdly, using both model-based and experimental assessments, electrode designs with improved selectivity and comfort were derived. Lastly, the viability of fabricating conductive layers infused with carbon-black based elastomers using the multi-layered screen-printing technique. The overall discussion on each chapter for its applicability to wearable neuroprostheses are as follows: The summary of the overall work and the thesis is reflected in this chapter.

9.1 Motor point cataloging

Based on the movements considered in this study (Flexion, extension of digits and wrist; abduction and adduction of the wrist), fine digit control and its coordination can be achieved through spatially distributed electrodes [89], [240]. Wearable neuroprostheses targeted specifically for dexterous hand function could utilize the stimulation zones from this study towards the design of electrode arrays and stimulation mapping algorithms (Section 2.3). Moreover, the characterization of motor points based on their location, recruitment, and displacement can significantly reduce the calibration and setup time when using electrode array-based stimulation.

Often control algorithms are implemented to activate pre-indexed electrode positions to get a suitable response. As these maps are highly subject-specific and due to lack of a priori information on motor point location [33], [94], [123], exhaustive search is performed to create a stimulation map [77], which is a long process and discomforting to the user.
On the contrary, with stimulation zones derived from this study, ideal electrode locations towards a targeted muscle response can easily be inferred from forearm anthropometry. Instead of an exhaustive search, the probability of muscle activation with the designed stimulation zone is much higher. This has the potential to render sophisticated mapping algorithms obsolete. Considering the symmetricity of motor point locations [39], [41], with simple mapping routines, highly personalized stimulation maps can be achieved from the baseline information derived from this study. Although bipolar stimulation is often ignored for electrode array-based stimulation for having multiple stimulation configurations that demand complex switching circuits [225], the viability for targeted control when using bipolar configuration outweighs this limitation.

Furthermore, suitable electrode configurations involving both active and return electrode can be derived, which also simplifies the use of bipolar stimulation techniques. As seen in Table 4.5 and Table 4.6, the parameters characterizing a motor point cluster are entirely new to the field, as similar studies offer only inferential outcomes on these motor point locations. With topological parameters like the area, eccentricity, and angle of deviation readily available for every motor point cluster, the overall design of electrode arrays can also be optimized. With subject-specific topology on probable activation zones that can be predetermined, electrode arrays can be printed only along the active area, which can significantly reduce the number of electrodes and the switching circuits.

Displacement of motor points to various forearm movements traditionally poses a limitation to wearable surface stimulation systems, which was also addressed in this thesis. As the information on the mean displacement of muscle groups has been derived, such information can be incorporated into stimulation mapping algorithms, which could obviate the need for removing or repositioning of stimulation electrodes under various forearm movements. Thus, reducing the time taken for rescanning scanning the displaced stimulation sites.
9.3 Characterizing muscle stimulation

To extend the applicability of precise digit control to hand manipulation tasks, the determinants of force generation must be understood. Such a characterization is crucial to applications involving closed-loop control with FES while performing hand manipulation tasks. Hence, in Chapter 5, electrically evoked muscle contractions across the forearm muscles were characterized. Accordingly, the influence of transcutaneous stimulation on muscle contraction, stimulation comfort, and stimulation-induced fatigue was quantified. Experiments were performed on four healthy participants; wherein, stimulation was delivered to the flexors of the wrist. The resulting twitch, tetanic, and fatigue responses were recorded under muscle contraction levels of 20% MIPC. Based on the results, it was evident that pulse width was an important determinant for the comfort of stimulation. As pulse-width and intensity are directly proportional to the depth of penetration, after an optimal pulse width, the force for muscle contraction gets saturated, but the stimulation pain keeps increasing. Also, care must be taken when choosing between twitch and tetanic stimulations, based on the application of interest. In this study, stimulation levels to achieve controlled levels of muscle contraction, with minimal discomfort to the user, were obtained. Also, the viability for controlled force exertion and complex grasps demonstrates to extend the limitation of FES, in realizing a near-natural hand function. Although electrically stimulated muscle fatigues faster, its effect seems insignificant for ADL tasks. Based on the optimal parameters obtained, seven ADL-based hand function tasks were also demonstrated. By varying the stimulation parameters and site of inoculation (motor points), the likelihood of personalized digit/wrist control has been demonstrated. By extending this construct, in realizing complex ADL grasps, the study has shown that ‘functionally viable hand’ deemed achievable. By understanding the characteristics, different stimulation techniques that can help in achieving near volitional contraction can be derived.
9.3 Modeling nerve stimulation

Using the FE implementation, the interaction of an active myelinated nerve fiber and its bidirectional with the volume conductor-based forearm was demonstrated. The present model is a novel implementation to incorporate a triple cable structure of a myelinated nerve fiber. The inclusion of compartmental representations for nodal and internodal regions modeled using experimentally established parameters [177] helped in the demonstration of several electrophysiological evaluations.

The FE approach has the potential to improve on the existing state-of-art modeling for extracellular stimulation of neuronal systems. Incorporation of the three implemented strategies – the theory of volume conduction, compartment-based modeling, and the bidomain formulation – can also be applied to study stimulation protocols, improve electrode designs, and assess a wide range of neurophysiological outcomes for tNMES. Moreover, FE modeling offers the flexibility to include morphological details of both the nerve and the surrounding tissues. With current advances in CT and MRI imaging techniques, tissue morphology and nerve branching can be included to derive personalized tNMES models, without explicitly modeling them [194]. In addition to neurophysiological evaluation of nerve function, the volume conductor-model can be evaluated for 3D currents, electric field distribution, and activation volume, which are often assessed in tNMES-based studies.

By demonstrating the interaction of nerve with its surrounding tissues, the model proves its capability in emulating micron-level interactions across neuronal elements, paving the way for advanced coupled nerve-tissue electrostimulation models [167], [178]. By including fascicular morphology with appropriate nerve fiber distribution, gradient activation of bundled nerve fibers can be studied, as the number of nerve axons being excited can be a good predictor of muscle recruitment [162].
Additionally, as an extension to the above model, by utilizing a similar modeling approach, a computational model for tNMES was developed in Appendix I. Here, the aim was to extend the capability of an FE-based nerve excitation model to accommodate subsequent muscle contraction that embodies neuromuscular stimulation by coupling an active nerve fiber with a constitutive muscle fiber model. Both the nerve and the muscle elements were embedded in a volume conductor of the tissue layers. The model was solved under transient conditions, wherein an external stimulus created a distributed electric field to excite the nerve fibers that subsequently initiated muscle contraction. The validity of the model was further verified against experimental data on nerve excitability. The model was able to predict the stress developed during muscle contraction, which contributed to the total force exertion. The proposed model is a novel attempt towards a continuum description for neuromuscular stimulation, that can be deployed to test various stimulation protocols and assessing their physiological outcome.

In-vivo testing for evaluation of stimulation procedures is time-consuming and discomforting. As an alternative, the presented models can be used to assess neuronal response for stimulation protocols and to improve electrode designs in tNMES, and, additionally, for evaluating neurophysiological outcomes by accommodating micron-level nerve-tissue interactions. With the capability to capture the spatial and temporal distribution of the electric field across realistic morphologies, the model can serve as a testbed to improve stimulation protocols and electrode designs with subject-level specificity.
9.4 Design of stimulation electrodes

When facilitating hand function tasks, transcutaneous electrodes have limited selectivity and cause discomfort. To improve the selective activation of the forearm muscles, the SSA electrode is preferred. However, due to a small surface area, they tend to have high current densities and can be discomforting. Furthermore, these electrodes are integral to wearable electrode array-based sleeve that facilitates several hand function tasks [72], [87]. Hence, improving the stimulation performance of such SSA electrodes exploiting its geometry provides a promising venture to develop simple and highly personalized electrode designs with a significantly low-profile form factor.

An ideal stimulation electrode must be able to facilitate selective and comfortable stimulation while eliciting submaximal muscle contraction. SSA electrodes are highly selective; however, it might be challenging to activate deep muscles as higher current densities can be discomforting. Nevertheless, it was shown that by altering the geometry of SSA electrodes, comfortable stimulation while evoking a submaximal muscle contraction can be achieved. With each electrode geometry having a unique current density and field distribution profile, the size and shape of the AV varied with electrode geometry. Thus, customizing the AV based on the electrode geometry can: maximize the efficiency of the charge delivered to the tissue, that in turn, maximizes the surface to volume ratio of an AV - to maintain a comfortable stimulation [203], [209]; also, can favor anatomical features of a target muscle to evoke submaximal contraction.

Commercial multi-layered electrodes are bulky and have a large form factor. Hence, they tend to constrain most of the forearm movements and can be far from desirable. However, achieving comfortable stimulation by changing the surface geometry emphasizes the potential for simple, single-layered electrodes. The new geometries assessed here favor breathability and conformity, which are also crucial for long time usage. Very high-gain perimeter electrodes, although demonstrated to be comfortable, the
presence of high current density regions and the non-uniform spread of current density poses a significant trade-off. Still optimizing their designs to improve the current density profile can potentially overcome such adverse effects. Influencing the electrode performance by altering the electrode geometry can result in highly personalized, easy-to-fabricate, and cost-effective electrodes for wearable neuroprostheses. Moreover, when combined with advances in stimulation techniques [9,10,19], electrode configurations [9,23], material properties [3,6,23,38], and interface layers [3,11,34] the performance of these electrodes can further be boasted.

Metal electrodes are not recommended for transcutaneous stimulation due to several adverse effects [52]. Still, altering the surface geometry of such electrodes gave a considerable improvement in stimulation performance. The sensation of discomfort during transcutaneous stimulation is one of the major hurdles for prolonged usage. When such designs are coupled with functional materials that are optimal for stimulation electrodes, their advantages can further be leveraged.

In addition to the improved electrode designs, here, a novel computational model that included both the activation of sensory and motor nerve fibers was proposed. This model was an extension of the computational model on transcutaneous nerve stimulation that was introduced in Chapter 5. In-vivo testing on electrode designs and optimization can be arduous and cumbersome. However, the model proposed here that activates both sensory and motor nerve fibers pose a promising avenue to improve such electrode designs and perform further optimization. Furthermore, the physiological validity of these models has been established. Hence, changing the model parameters to suit the physiology of users can enable rapid and personalized electrode designs for improved stimulation performance.
9.5 Development of a wearable electrode array

Electrode-array based stimulation facilitates dynamic control over the forearm muscles with improved selectively, making them inevitable for the restoration of hand function. Still, the translation of such systems from a research-based setting to a clinical/home-based setting depends on several factors such as their user acceptance, ease of use, customizability, stimulation performance, and cost-effectiveness. The viability of fabricating conductive layers infused with silicone-based elastomers using the multi-layered screen-printing technique was demonstrated in Chapter 8. This can potentially address the above-mentioned factors to improve the applicability of wearable surface stimulation systems.

Recent advances with screen printing [73], [226], and textile technologies [196] have developed electrode arrays that are flexible and deliver comfortable stimulation. However, no attempts have been made to develop stretchable and lightweight electrode array designs [32]. Stretchable electrodes can be more natural and ergonomic. They can conform over the forearm surface without restraining the forearm movements. Moreover, it can be easily concealed under any garment and can favor prolonged usability. Innately, electrode arrays can compensate for repositioning and allows a non-expert to use the device in a home-based setting. These advantages can gain user acceptance.

As briefed in Section 2.3, to facilitate personalized stimulation. The shape and size of the stimulation zones must be accommodated into electrode-array designs. Also, based on the mediated recovery, the properties of the stimulation electrodes can be altered by the therapist. Moreover, the stimulation performance of the electrodes can deteriorate over time. These factors demand the need for inexpensive materials and an economical and rapid fabrication technique. Also, the fabrication process can suit low-temperature conditions.
This paper presents the rationale, design, and proof of concept for a conformable wearable electrode array-based sleeve. In addition to challenges in choosing the appropriate material for the stimulation electrode, considering optimal designs and materials for the traces and connections are also equally important [241]. Conformability of the electrodes is very important for user comfort and to compensate for the displacement of motor points following forearm rotation. Moreover, the study previously done on the displacement of motor points under forearm rotation has shown that the stimulation of motor points can only displace up to 100%. The reason for considering 500% strain in the thesis is to improve the durability of the electrode array-based sleeve as it may be exposed to several donning on and off. Still, the weigh ratios 1:8,1:9 had an integral performance way above the physiologically valid displacement.

The addition of CB to Ecoflex can open several opportunities, in addition to the conductivity, the roughens of the electrode surface can be altered, which was demonstrated with SEM and stylus profilometry results. The most crucial properties of a stimulation electrode are surface morphology, and electrical properties, both of which can be altered by the addition of the stimulation electrodes like the carbon black. This can lead to rapidly customizable stimulation electrodes.

Additionally, the change in resistance during stretching can be used to sense the direction of shear, thus avoiding any external sensor to be embedded. Moreover, carbon black-based Ecoflex sensors have been proposed for sensing EMG or biopotential recordings [238]. Furthermore, the use of Ecoflex has made the electrode-array, biocompatible. Given the rapid fabricability of the electrodes, it can be altered to fit any forearm, and the sleeve designs can be improved to accommodate breathability.
10. Conclusions

By selectively eliciting digit control through motor point-based stimulation and synergistically activating muscle groups via distributed electrodes, the feasibility for realizing complex hand function tasks was demonstrated. Furthermore, this thesis also establishes the potential for improved stimulation performance by modifying the electrode geometry, and the viability of fabricating a conformable electrode array-based sleeve. Using these advanced fabrication techniques and improved electrode designs, comfortable, wearable, and cost-effective stimulation systems can be realized. The principal findings of this research are summarized below:

This thesis has systematically identified the superficial motor points across the flexor and extensor muscles. Dynamic stimulation over these motor points can facilitate dexterous manipulation. Furthermore, the potential for using machine learning-based clustering algorithms to extract optimal and highly generalizable motor point catalogs was also demonstrated. The traceability and physiological correlation of stimulation zones represent a highly generalizable data that can be used towards the design of electrode arrays, stimulation mapping algorithms and aid clinicians with electrode placements for patient-specific treatments.

Also, the influence of transcutaneous stimulation on muscle contraction, stimulation comfort, and stimulation-induced fatigue was quantified. Such a characterization is crucial to applications involving closed-loop control with functional electrical stimulation (FES) while performing hand manipulation tasks. Based on the optimal parameters obtained, seven activities of daily living (ADL)-based hand function tasks were also demonstrated. Wherein, the muscle groups were synergistically activated using an electrode array-based stimulation. These grasps being fundamental to ADL; this study has shown that ‘functionally viable hand’ deemed achievable. By extending this construct, complex hand function tasks with controlled force exertions can be accomplished.
Also, a physiologically valid computational model for transcutaneous nerve stimulation has been developed. The excitation of a triaxial, compartmentalized, active myelinated nerve model, as influenced by the electric field distribution from a volume conductor-based forearm, was solved under transient conditions using the finite element approach. Assessment of the nerve fiber model for several excitation indices produced values that fit experimental data reported in the literature. In addition, the coupled nerve-tissue model was validated against experimental data on five healthy subjects. The presented model can be used to assess neuronal response for stimulation protocols and to improve electrode designs in transcutaneous neuromuscular electrical stimulation (tNMES), and, additionally, for evaluating neurophysiological outcomes by accommodating micron-level nerve-tissue interactions.

Furthermore, a comprehensive assessment of several electrode geometries that can potentially improve stimulation performance was performed. Both model-based analysis and experiments, the influence of high perimeter electrodes to deliver a selective and comfortable stimulation were demonstrated. The implication of the study can be used to design application-specific electrode designs that can have translative applications in a wide variety of electrotherapy and electrostimulation-based applications. In place of sophisticated electrodes, optimizing surface geometry can streamline electrode designs for wearable neuroprostheses.

Lastly, a conforable electrode array-based sleeve was fabricated using a multi-layered screen-printing process. The addition of carbon black to the silicone-based elastomer altered its conductivity that resulted in a stretchable stimulation electrode. Also, the weight ratio of carbon black infused within the elastomers, that gave an optimal stimulation performance was obtained. The fabrication process facilitated the fabrication of both the stimulation electrodes and the traces that can conform over the forearm surface.
10.1 Future work and directions

The additional demand among people with SCI was to have an assistive intervention that can be used in a home-based setting. This thesis has demonstrated the viability of functional grasping and potentially to have controlled force exertions that can lead to restoring complete hand function. Additionally, advances to existing stimulation technology that can deliver comfortable, and personalizable systems were also demonstrated.

Hence, the future directions for this thesis would involve the development of an assistive framework, that can engage users, and also help them to achieve autonomy to perform their ADL tasks. Such a framework is shown in Figure 10.1. On a high-level, the framework represents a user-controlled closed-loop FES system that synergistically activates muscle groups for hand function tasks. Since open-loop control for FES is prone to external disturbances and has been proven to be inefficient [242].

Figure 10.1 A framework for neuroprosthetic control of hand function
Moreover, compared to fixed parametric stimulation, error compensation of amplitude, pulse-width, and frequency has improved muscle contraction for non-isometric contraction. When finger contact with the desired object is made, the grasp force is increased to the optimal level, using both our prior knowledge about the object and information from the tactile sensors of the fingers gathered during the interaction. Corrective actions are applied to different frictional conditions in order to provide an optimal grip force that is normally.

In order to facilitate this, FES-control must be facilitated that it can be easily integrated with any type of user-control interface. Compared to other interfaces, myoelectric control is better for speed of operation and in delivering natural control [243]. Moreover, muscle synergies exploit the musculoskeletal dynamics for effective and optimal motor control with its modularity; it simplifies a computationally redundant problem. The viability for a synergy based control interface utilizing low-dim signals to control a high dimensional system has been demonstrated by [244]. Hence, coupling these systems can realize a framework for an assistive intervention.
Publications list

Peer-reviewed journal articles


Peer-reviewed international conference papers


Dataset contributions

Appendix I: Modeling for tNMES

I.1. Introduction

Despite advances in computational models in the field of electrical stimulation, it is quite challenging to develop a representative model for transcutaneous neuromuscular electrical stimulation (tNMES), given its intricate physiology. In Chapter 6, a novel approach for the FE-based nerve excitation model was proposed, developed, and validated. As an additional application of this FE-based model, the nerve excitation stage was coupled to a constitutive muscle fiber model that embodied transcutaneous neuromuscular stimulation.

In this representation, both the nerve and muscle elements were embedded in a volume conductor of the tissue layers. The model was solved under transient conditions, wherein an external stimulus created a distributed electric field to excite the nerve fibers that subsequently initiated muscle contraction. The validity of the model was further verified against experimental data on nerve excitability. The model was able to predict the stress developed during muscle contraction, which contributed to the total force exertion. The proposed model is a novel attempt towards a continuum description for neuromuscular stimulation, that can be deployed to test various stimulation protocols and assessing their physiological outcome.

Driven by electrophysiological indices, computational models on tNMES could replicate neuromuscular function at the subject-specific level. In this way, such tools can aid in understanding the physiological recruitment and neuromuscular response to various stimulation protocols [162], [181], [247]. This could potentially reduce evaluation times on patients and can serve as a test-bench to validate motor control strategies. However, a complete biophysical representation of neuromuscular stimulation is very challenging.
Such modeling needs to embody (i) the spatial distribution of electric field inside tissue layers [162], (ii) excitation of nerve fibers based on the spatially distributed electric field [248], (iii) the excitation-contraction coupling to transduce nerve activation into corresponding muscle fiber recruitment [249] and (iv) the contraction dynamics to dictate the whole muscle response [249]–[251]. Separate studies have modeled these representations. So far, an integral approach has not been attempted for tNMES.

Two-step models are used to predict the nerve response to external excitation [162]. Herewith, the spatial distribution of the electric field within tissues is solved as volume conductors, and the excitatory field is later applied to analytical nerve models. However, these models have limited applicability as the calculation of field distribution, and the resulting excitatory response secedes (Section 6.1). The constitutive representation is widely adopted in biomechanics towards full-scale muscle modeling. Active stress development that initiates muscle contraction is modeled based on macroscopic, phenomenological models like the Hill-type [246] or microscopic models based on cross-bridge sliding, like the Huxley-type models [247], [251]. The choice of the two methods varies based on their applicability and computational limitations [252]. To couple the previously mentioned nerve activation with the muscle models, depolarization of a muscle fiber is modeled based on the alterations in its calcium ion concentration with respect to the transient excitatory nerve response [247], [249], [251]. Coupling the physiological process of nerve recruitment into these models is actively researched [251].
I.2. Methods

Three-dimensional modeling represents a compelling approach to include the geometrical and biophysical features of the neuromuscular system for deriving personalized models. Furthermore, the above-mentioned physiological mechanisms and their transient behavior are represented by differential equations; hence, to accommodate such a modeling feat with reduced computational complexity, the FE approach is favored [162], [247], [251], [252]. Accordingly, a model that can predict muscle forces for a transient external stimulation using the FE approach was developed.

This chapter presents a methodological approach in deriving a neuromuscular multi-scale model using the FE approach. To couple individual elements that represent tNMES, the excitation of an active myelinated nerve fiber in a volume conductor of tissues was coupled with a constitutive muscle model with its active stress generation characterized by the Hill-type formulations.

Figure I.1 Model for transcutaneous neuromuscular stimulation.

[a] A stylized representation of the neuromuscular model. [b] Electrical equivalent of the compartmentalized myelinated nerve model. [c] Biomechanical equivalent of a muscle with active and passive elastic components.
The entire computational model was implemented using COMSOL Multiphysics, Version 5.4 (COMSOL, Inc., MA, USA). The model represented the transcutaneous stimulation of the median nerve for its consequent contraction of the Brachioradialis muscle upon excitation. The forearm tissues and the Brachioradialis muscle were modeled as 3D geometry [162], [250], Figure I.1. Additionally, the median nerve with its axons was modeled as 1D elements to reduce the computational complexity.

Firstly, the tissue layers were idealized as volume conductors with respective conductivity ($\sigma$), permittivity ($\varepsilon_0$). Using Poisson's equation for electrical conduction (I.1), the spatial distribution of the electric field as a potential gradient $(V_e)$ was calculated for the externally induced stimulation $(J)$.

$$-\nabla \cdot (\sigma \nabla V_e - \varepsilon_0 \frac{\partial V_e}{\partial t}) = J \tag{I.1}$$

The axons of the nerve fiber were modeled based on an established myelinate nerve [248]. Each nerve axon was compartmentalized with 21 interconnected nodal and internodal segments. The nerve fiber was at a depth of 12 mm from the skin surface with twenty five of such 10 $\mu$m compartmentalized nerve axons distributed within 20 $mm^2$ [162]. The current density across each compartment of the nerve segment was computed as (I.2), based on the membrane capacitance ($C_m$), conductance ($G_m$) and the resistivity of the intracellular fluid ($R_i$) (Figure I.1). The potential gradient, $V_e$ from the volume conductor is directly coupled into (I.2), thus perturbations to the intracellular potential ($V_i$) can depolarize the nerve causing an action potential.

$$c_m \left( \frac{\partial V_i}{\partial t} - \frac{\partial V_e}{\partial t} \right) = \frac{g_a}{4\rho_i} \left( \frac{\partial^2 V_i}{\partial x^2} \right) - g_a (V_i - V_e - V_{rest}) \tag{I.2}$$

This action potential can further depolarize the motor-end plates of several muscle fibers within a motor unit (Figure I.1). Activation of motor units depends on its type [246], stimulation amplitude (recruitment) [162] and frequency (tetanus) [245]. Here, only the recruitment-based activation
was considered. Hence, a scale factor ($S_f$) was introduced in (I.5). Based on the innervation ratio and the number of constituent muscle fibers within Brachioradialis [245], the total muscle contraction was graded based on the number of nerve axons being excited. Based on the transmembrane potential ($V_a$), the motor unit activation was considered (I.3). Also, the dynamics between nerve activation and the resulting depolarization for subsequent muscle activation was included (I.4) [253].

$$u(t) = \begin{cases} 0, & \text{if } V_a < 20 \text{ mV} \\ 1, & \text{if } V_a \geq 20 \text{ mV} \end{cases} \quad (I.3)$$

$$\dot{a}(t) = \frac{u-a}{\tau_a(u,a)} \quad (I.4)$$

An MTC has the muscle fiber arranged in series with the tendon. The Hill-type model was used to represent the MTC, Figure I.1c. The muscle component included the active CE and the passive connective tissue element, PE. The force generated by the muscle ($F^m$) depended on the (i) respective passive force-length relationships of CE [254] and PE [249] elements $f^\text{CE}_{fl}(\bar{L}^m)$ and $f^\text{PE}_{fl}(\bar{L}^m)$, Figure I.2a. (ii) dynamic force-length relationship of the CE [254], $f^\text{CE}_{fv}(\bar{v}^m)$, Figure I.2b and (iii) muscle activation $a(t)$. Thus $F^m$ was the sum of active and passive forces (I.5).

As the hill-type parameters are scalable to model different muscle types, they were characterized for Brachioradialis. Accordingly, the optimal muscle length ($\bar{L}^m$), tendon stack length ($l^t_s$) and pennation angle ($\alpha^m$) were determined [249], [250]. The maximum muscle force ($F^m_0$) was estimated from the muscle’s cross-sectional area and its specific tension [250].

$$F^m = F^m_0 S_f \left[ \left( f^\text{CE}_{fl}(\bar{L}^m) f^\text{CE}_{fv}(\bar{v}^m) \dot{a}(t) \right) + f^\text{PE}_{fl}(\bar{L}^m) \right] \quad (I.5)$$

$$f^\text{CE}_{fl}(\bar{L}^m) = \begin{cases} -4(\bar{L}^m - 1)^2 + 1, & 0.5 \leq \bar{L}^m \leq 1.5 \\ 0, & \text{otherwise} \end{cases} \quad (I.6)$$

$$f^\text{CE}_{fv}(\bar{v}^m) = \begin{cases} \frac{\arctan(\bar{v}^m - 0.5)}{\arctan(5)} + 1, & \bar{v}^m < -10s^{-1} \\ \frac{\pi}{4 \arctan(5)} + 1, & -10s^{-1} \leq \bar{v}^m \leq 2s^{-1} \\ \frac{\pi}{4 \arctan(5)} + 1, & \bar{v}^m > 2s^{-1} \end{cases} \quad (I.7)$$
The 3D MTC was modeled as cylindrical geometry with the muscle connected to a tendon. The material properties [255] of MTC are given in Table I.1. The mechanical behavior of the muscle upon its activation $\dot{a}(t)$ from the previous sections was assigned to the MTC. Further to this, the model was solved for its displacement, and the von Mises stress was obtained.

**Figure I.2** Properties of the muscle-tendon complex

[a] Normalized force-length relationship for active and passive muscle elements.
[b] Normalized force-velocity relationship for the active muscle element.

External stimulation was implicated into the model using the Neuman boundary condition applied at the active electrode, the reference electrode was held as ground using the Dirichlet boundary condition, and the lateral edges were insulated. The model was validated based on experimental data from two subjects. Through motor point-based stimulation [35], the Brachioradialis muscle was evoked for wrist flexion. A monophasic stimulation with amplitude varied from 1-30 mA, and the pulse-width between 100-500 µs was delivered via transcutaneous electrodes. The stimulation was delivered via a current-controlled stimulator, RehaStim™

$$f^{PE}_{l_i}(\hat{l}^m) = \frac{e^{10(\hat{l}^m-1)}}{e^5}, 1 \leq \hat{l}^m \leq 1.5$$ (I.8)
(Hasomed GmbH, Magdeburg, Germany). The strength-duration curve was measured to quantify nerve excitation to transcutaneous stimulation and, the twitch response was also recorded using a dynamometer [162]. The twitch response was normalized based on the MVIC.

**Table I.1 Material properties of the muscle-tendon complex**

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<th>Poisson’s ratio $-$</th>
<th>Density $kgm^{-3}$</th>
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<td>1.162</td>
<td>0.4</td>
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<tr>
<td>Tendon</td>
<td>1.6</td>
<td>0.49</td>
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The activation of nerve fibers and the resulting muscle contraction were represented by a collection of coupled differential equations. The computational domain was discretized into finite elements using tetrahedral and edge mesh elements. A mesh convergence study resulted in 300000 mesh elements that were solved using a fully coupled, direct solver as a time-dependent study. The model was studied by simulating the experimental protocol.

**Figure I.3** Comparing of model-predicted and experimentally SDC
Based on the spatial distribution of the electric field, the number of nerve axons being excited varied. Fig. I.3 shows the comparison of model predicted excitability against experimental data. Although the time constants for model predictions fall within the acceptable range [162], the discrepancy was due to the choice of nerve model [162], [248]. Wherein, the rheobase for the model [248] was four times of experimental data.

The experimentally obtained twitch responses were <10% of MVIC. The transient-external stimulus applied to the model recruited several nerve axons that initiated muscle contraction. After solving the active stress development with the hill-type formulations for various recruitment levels, the resulting muscle contraction was evaluated for its deformation. A visual representation of muscle displacement is shown in Fig. I.4. Stresses were induced due to the stretching of muscles. Moreover, the maximum stress of 17 MPa was developed when $F_0^m$ was at its maximum.

![Figure I.4 Muscle contraction with an increase in active stress development](image-url)
The proposed model reproduces critical traits of tNMES, such as the interactions between a spatially distributed electric field, nerve activation, and the resulting muscle contraction, modeled as a fully coupled system of differential equations. Also, the choice of constitutive 3D muscle utilizing the Hill-type model was computational efficiency and to accommodate a parameterized muscle model with their macroscopic-whole muscle level responses: the force-length and the force-velocity relation [252]. Here, the active stress developed in the muscle was coupled with the deformation response of the muscle. As a continuum representation for neuromuscular stimulation, the proposed model can be used to evaluate several tNMES-based protocols.

As future work, the model’s capability can be expanded to predict muscle response to frequency-induced stimulation effects based on the calcium accumulation dynamics at the muscle fiber level. In this way, the model can predict muscle response to different stimulation protocols. Also, higher stimulation frequencies will dramatically increase the muscle output to its maximum, causing fatigue. Inclusion of frequency-dependent muscle activation and the effects of fatigue can aid with the identification of suitable stimulation parameters needed to achieve desired force output.

The inclusion of McNeal-type fiber [248], gave large chronaxie values (Figure 1.3) which was identified as a limitation. However, the choice of McNeal-type fiber was to simplify the underlying computation as it does not include explicit representation of nerve segments. Still, Section 6.2 introduces modeling methods for a triaxial myelinated nerve fiber, inclusion of such models can accommodate several electrophysiological evaluations and overcome limitations with McNeal-type fiber.
References


R. Bestel, R. Appali, U. van Rienen, and C. Thielemann, “Effect of Morphologic Features of


“Current Density Imaging and Electrically Induced Skin Burns Under Surface Electrodes,”


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Chapter 4 entitled 'Motor point cataloging'
N. RaviChandran, K. Aw, and A. McDaid, "Characterizing the Motor points of Forearm Muscles for Dexterous Neuroprostheses," in IEEE Transactions on Biomedical Engineering. DOI: 10.1109/TBME.2019.2907926 (Accepted).

<table>
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The undersigned hereby certify that:
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- that the candidate wrote all or the majority of the text.

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Chapter 6 entitled 'Modeling nerve stimulation'
N. RaviChandran, J. Hope, K. Aw, and A. McDaid, "Finite element modeling for excitation of nerve axons under transcutaneous stimulation," in Journal of Neural Engineering

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<td>James Hope</td>
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Chapter 7 entitled 'Design of stimulation electrodes'

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<td>Mei Ying Teo</td>
<td>Fabrication of electrodes and contributed to the manuscript</td>
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