MECHANOMYOGRAPHY FOR NEUROMUSCULAR ELECTRICAL STIMULATION FEEDBACK APPLICATIONS IN PERSONS WITH SPINAL CORD INJURY

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ABSTRACT

Neuromuscular Electrical Stimulation (NMES)-evoked muscle contractions confers therapeutic and functional gains on persons with Spinal Cord Injury (SCI). However, the optimal efficacy of commercial NMES systems' application is inhibited by the imprecision in muscle force/torque production and rapid muscle fatigue. Evidence suggests that the application of a muscle mechanical response (force/torque) as a feedback to modulate the administration of NMES could optimize the efficacy of the technology by enabling muscle force regulation, and delaying the onset of muscle fatigue. Currently, a direct muscle force measurement is impractical and there is also lack of a reliable, electrical stimulus artifact-free and non-invasive proxy of muscle force to drive the NMES systems for enhanced controllability and clinical use. Attempts on the application of evoked-electromyography for this purpose remain debatable and clinically limited. As a viable alternative, this thesis proposes a non-invasive muscle force/torque measurement technique based on the mechanical activity of contracting muscles (Mechanomyography or MMG). This investigation was motivated by the knowledge that mechanomyography is immune from certain limitations of evoked-electromyography and provides direct information on muscle's mechanical responses to the electrical stimulation. Systematic literature survey revealed a lack of clear understanding of the relationship between mechanomyography and NMES-evoked torque production in a paralyzed muscle. Therefore, the present research introduces mechanomyography as a proxy of NMES-evoked torque in persons with SCI. At the outset, a hybrid procedure was developed to establish mechanomyography as a proxy of muscle force/torque in healthy volunteers and persons with SCI. This was used to investigate the pattern of incremental torque production and subsequently facilitated the estimation of the torque from mechanomyography using a computational intelligent technique based on Support Vector Regression (SVR) modelling. This thesis also demonstrated, in a clinical setting, the

validity of the mechanomyography as a relevant parameter for studying muscle fatigue during critical knee buckling stress *i.e.* standing-to-failure challenge in persons with SCI. Due to the peculiarity of the study participants/target population and the intended clinical application of NMES-supported standing, the quadriceps muscle group, widely reported for its relevance in studying the knee torque dynamics, was selected as the study site. Findings from these studies revealed that the mechanomyographic amplitude is highly correlated ($r > 0.95$; $P < 0.05$) to the muscle force in persons with SCI as it reliably tracked the muscle's motor unit recruitment pattern during NMES contractions. The SVR modelling results demonstrated a good predictive accuracy ($R^2 \geq 89\%$) with generalization capacity and suggested that the quadriceps' mechanomyography is a good indicator of NMES-evoked torque during knee extension tasks. Thus, the signal might be deployed as a direct proxy of muscle torque during leg exercise and functional movements in SCI populations. Additionally, the reliability (intraclass correlation coefficient range: 0.65-0.79; $P > 0.05$) of the mechanomyography during force production might be useful to evaluate the recovery or deterioration of motor unit activities following NMES supported exercise and as an alternative technique for monitoring the NMES-evoked muscle activity for practical control applications. Together, this thesis lays a foundation for the future implementation of MMG-driven NMES technologies.

ABSTRAK

Rangsangan kontraksi otot secara Stimulasi Elektrikal Neuromuskular (NMES) memberikan banyak faedah terapeutik dan fungsi berguna di kalangan pesakit saraf tunjang. Walaubagaimanapun, keberkesanan optimum yang ditawarkan oleh NMES komersil terhalang oleh penghasilan daya/tork otot yang tidak tepat dan keletihan otot yang berlaku begitu pantas berikutan pembalikan corak perekrutan motor unit semulajadi. Bukti menunjukkan bahawa penggunaan sistem maklumbalas terhadap tindakbalas otot (daya/tork dan keletihan) bagi mengawal stimulasi NMES boleh mengoptimumkan keberkesanan sistem NMES dengan adanya pengawalan daya otot dan melambatkan masa untuk berlakunya keletihan otot. Sehingga kini, tiada proksi kepada daya otot/tork otot yang boleh dipercayai, mudah dan tidak invasif untuk mendorong sistem NMES meningkatkan kadar kawalan dan kegunaan klinikal. Oleh itu, pelbagai percubaan telah dilakukan dengan menggunakan rangsangan-isyarat elektrik otot (EEMG), namun masih dipersoalkan dan terhad secara klinikal. Hal ini terdorong oleh isu-isu yang melibatkan kualiti isyarat yang tidak sempurna disebabkan oleh peluh yang terhasil akibat penggunaan otot yang terlalu kerap. Tambahan pula, artifak-artifak yang terdapat di permukaan stimulasi elektrikal menepui penguat EEMG dan teknik-teknik lazim bagi penghapusan/penindasan artifak tersebut masih belum disempurnakan. Sebagai alternatif, tesis ini mencadangkan satu teknik yang tidak invasif untuk mengukur tork berdasarkan aktiviti mekanikal dari kontraksi otot-otot (isyarat mekanikal otot atau MMG). Kajian ini didorong oleh fakta yang menyatakan bahawa isyarat MMG tidak mempunyai kekurangan seperti yang dinyatakan sebelum ini dalam EEMG yang mana ianya tersebar melalui tisu lembut dan memberikan maklumat terus dari mekanikal otot yang bertindakbalas dengan stimulasi elektrik, dan seterusnya memberikan lebih banyak maklumat yang berguna, terutamanya maklumat mengenai neuromuskular yang berkaitan dengan aktiviti otot-otot semasa stimulasi elektrik. Maklumat yang telah diperolehi dari

kajian literatur menunjukkan bahawa hubungan MMG dan penghasilan tork otot yang lumpuh semasa rangsangan-NMES kontraksi masih samar. Oleh itu, kajian ini merupakan satu cubaan unik dalam membina tork yang boleh dianggar atau teknik ukuran dari isyarat mekanikal otot dalam kalangan pesakit yang mempunyai kecederaan saraf tunjang semasa rangsangan kontraksi-NMES. Fokus pertama di dalam tesis ini ialah untuk membangunkan prosedur hibrid untuk menghasilkan MMG sebagai proksi kepada daya/tork otot, terutamanya dalam kalangan individu sihat dan yang mengalami kecederaan saraf tunjang. Ini digunakan untuk mengkaji corak penambahan membolehkan penghasilan tork otot berperingkat stabil, hasil dari tork dan seterusnya memudahkan membantu penganggaran tork otot dari isyarat mekanikal otot dengan menggunakan teknik pengiraan pintar – pemodelan Support Vector Regression (SVR). Tesis ini juga bertujuan untuk telah membuktikan bahawa dalam situasi klinikal, kesahihan isyarat MMG adalah satu parameter yang relevan dan optimum untuk kajian permulaan mengenai dalam mengkaji keletihan otot semasa pembengkokan lutut kritikal knee buckling stress, iaitu dalam keadaan berdiri-sehingga-keletihan di kalangan individu yang mengalami kecederaan saraf tunjang. Disebabkan oleh keunikan peserta dalam kajian ini/populasi sasaran dan tujuan aplikasi klinikal, sebagai contoh, berdiri dengan sokongan NMES, otot quadrisep telah dipilih untuk kajian. Kumpulan otot ini telah banyak dilaporkan kerana ianya relevan dengan kajian yang melibatkan dinamik tork lutut. Dapatan dari kajian ini menunjukkan bahawa amplitude isyarat MMG mempunyai hubungkait yang baik bagi penghasilan daya kerana kebolehpercayaannya dalam menjejak corak perekrutan motor unit semasa kontraksi-kontraksi otot rangsangan-NMES. Keputusan pemodelan SVR telah menunjukkan ketepatan ramalan cemerlang dengan kebolehannya dalam penyamarataan dan isyarat MMG dari otot quadricep dicadangkan sebagai indikator tork rangsangan-NMES yang bagus ketika latihan isometri extensi lutut. Berikutan itu, isyarat MMG telah dicadangkan sebagai proksi kepada ukuran tork otot semasa latihan kaki dan pergerakan-pergerakan berfungsi kepada populasi dengan kecederaan saraf tunjang. Di samping itu, tahap kebergantungan isyarat MMG dalam mengukur daya otot berkemungkinan besar berguna dalam menilai pemulihan atau kemerosotan aktiviti-aktiviti MU unit motor selepas latihan NMES dan bertindak sebagai alternatif untuk mengetahui aktiviti otot yang dirangsang NMES sebagai aplikasi kawalan praktikal. Secara keseluruhannya, tesis ini dapat menjadi menyandarkan asas kepada perlaksanaan teknologi NMES dorongan-MMG untuk masa depan.

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ANN : Artificial Neural Network

CNS : Central Nervous System

R^2 : Coefficient of Determination

EEG : Electroencephalogram

EEMG : Evoked-Electromyography

EMG : Electromyography

ENG : Electroneurogram

ε : Epsilon

FES : Functional Electrical Stimulation

Hz : Hertz

HF : High Stimulation Frequency

ICC : Intraclass Correlation Coefficient

η : Kernel option

λ : Lambda/hyper parameter

LF : Low Stimulation Frequency

mA : milliAmpere

µs : microseconds

MMG : Mechanomyography

MU : Motor Unit

NMES : Neuromuscular Electrical Stimulation

PT : NMES-evoked Peak Torque

PTP : Peak to Peak

r : Pearson's Correlation coefficient

PNS : Peripheral Nervous System

QOL	:	Quality of Life
QP	:	Quadratic Programming
C	:	Regularization parameter/factor
RBF	:	Radial Basis Function
RF	:	Rectus Femoris
RMS	:	Root Mean Square
RMSE	:	Root Mean Square Error
W	:	Shapiro-Wilk
SCI	:	Spinal Cord Injury
SD	:	Standard Deviation
SEM	:	Standard Error of Measurements
SVM	:	Support Vector Machine
SVR	:	Support Vector Regression
UMMC	:	University of Malaya Medical Centre
WHO	:	World Health Organization (WHO)

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CHAPTER 1: INTRODUCTION

1.1 Background

According to the World Health Organization (WHO), an estimated 250 to 500 thousand people suffer a spinal cord injury (SCI) each year (Bickenbach et al., 2013). Although the incidence rate of SCI is pronounced in the developed economy (Singh et al., 2014), the rate is on the rise in the developing countries including Malaysia (Ibrahim et al., 2013) and China (Yang et al., 2014). Based on the available data (Figure 1.1), there are consistent higher incidences of SCI among adult males—up to 80% of cases (Bickenbach et al., 2013). This has negative economic implications on the affected persons (and their family members) as there are over 60% unemployment rate in these populations, globally (Young & Murphy, 2009). For instance, within the affected population in Malaysia, not more than 57% could return to work post-acute care (Ramakrishnan et al., 2011).

Therefore, SCI drastically decreases the quality of life (QOL) of those affected due to a partial or total loss of functional capacity below their injury levels (Jacobs & Nash, 2004). This is often accompanied by secondary complications of a significant impairment to their physiological and cardiorespiratory performances which could lead to a marked degeneration of the affected neuromuscular functions (Davis et al., 2008; Hasnan et al., 2013). These changes are worsened by the sedentary lifestyle imposed by the impaired neuromuscular function due to the lack of appropriate physical exercise programs (Ragnarsson, 2007).

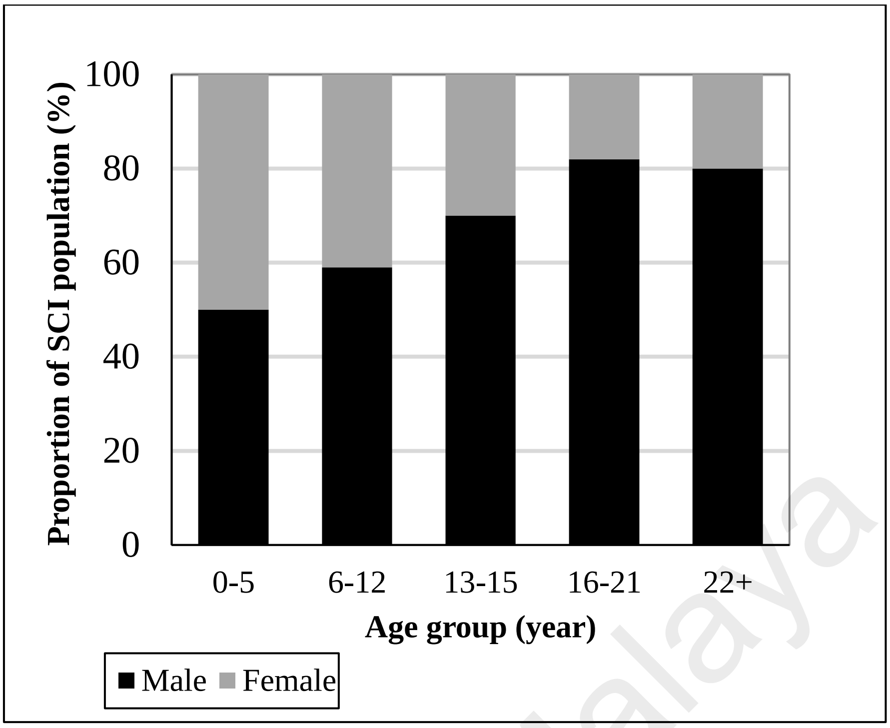

Figure 1.1: Incidence rate of SCI by gender and age group.
Adapted with permission from Vogel et al. (2012).

Depending on a number of factors such as the type of injury/lesion (upper motor neuron or lower motor neuron), severity of the injury, and user preference, neuromuscular electrical stimulation (NMES)-evoked muscle contraction has been generally recommended and validated for health promotion via exercise therapy and functional recovery in the affected populations (Hamid & Hayek, 2008; Ragnarsson, 2007). NMES applied via a pair of bipolar stimulating electrodes and over the human neuromusculature produces muscle contractions by depolarizing motor axons beneath the stimulating electrodes (Collins, 2007). Once the electrical stimulus amplitude exceeds the excitation threshold of the axons of the motor neuron, and through the principle of neuromotor plasticity (Martin et al., 2012; Singer, 1987), there will be elicitation of muscle contraction and force production (Reed, 1997). The product of the electrical stimulus-evoked muscle force and the muscle length or moment arm generates joint torques needed to execute functional tasks. Therefore, the foremost clinical objective of the NMES technology in restoring muscle functions is to substitute for the absence of motor function due to the lesion of the central nervous system (Vodovnik et al., 1981; Vrbová et al., 2008).

Although the NMES technology is gaining increasing popularity for its huge potentials in clinical rehabilitation applications (Peckham & Kilgore, 2013), the conventional control strategy of its stimulation parameters (frequency (Hz), current (mA) and pulse width (µs)) poses a significant drawback. For example, in most of the commercial surface NMES systems, users regulate the stimulation parameters manually via open-loop strategy. This is usually administered via "button presses" according to the users' perceived need. This strategy is highly subjective, enforces unnecessary constant stimulation intensity and thus, makes the outcome of the NMES suboptimal (Ragnarsson, 2007) and frustrating.

Automated NMES control strategy via closed-loop technology has recently become attractive (Ibitoye et al., 2016; Popović, 2014) to prolong muscle contraction, as several advanced simulations' results of the strategy have shown promise in enhancing the NMES utility and clinical prominence. This is due to the fact that the strategy is more effective, relevant and safer when compared to the traditional open-loop strategy (Braz et al., 2009). Basically, the closed-loop NMES strategy allows an efficient use of the technology as it automates the adjustment of electrical stimulus parameters throughout the entire duration of muscle contractions (Peckham & Knutson, 2005). However, one requirement of an automated NMES modulation is a reliable interpretation of the muscle response information generated as an indicator of neuromotor output following NMES-evoked contractions (Kimura et al., 2004; Peckham & Knutson, 2005; Popović, 2014). This is essentially required by the NMES controller to regulate muscle responses based on the muscle state.

Investigators (Hug et al., 2015; Scott, 2004) have identified the muscle force production following NMES-evoked contractions as an indicator of motor output. Therefore, muscle force could be used as a neural correlate of a muscle's motor performance. However, at the moment, a simple or artifact-free, direct and non-invasive measurement of muscle force production by individual muscle during NMES-evoked contraction is impractical (Erdemir et al., 2007; Popović, 2014). The estimation of the muscle force from other measurable muscle characteristics such as biopotentials has been promoted (Peckham & Knutson, 2005) as the control signal source for optimal performance of NMES systems.

Evoked-electromyography (EEMG) of a contracting muscle is the traditional source of NMES control signals as the signal is rich in muscle contraction and force information (Disselhorst-Klug et al., 2009; Thompson et al., 2011). However, the application of EEMG as an NMES control signal has a limited impact on the routine clinical practice. This is mainly due to the large size of stimulation artifact current in relation to the EEMG signal (Merletti et al., 1992; Yamaguchi et al., 2012) which has continued to challenge the reliability of the signal for the estimation of NMES-evoked muscle force (Popović, 2014). Practically, several strategies have been applied to decode the neural information in EEMG embedded in the electrical stimulation artifact but none has been so effective for clinical use (Chesler & Durfee, 1997; Hoffer et al., 1996; Popović, 2014). In addition, the sensitivity of the signal to the external electromagnetic interferences, variations in differential electrode positioning and skin impedance fluctuation due to perspiration (Yamamoto & Takano, 1994) often lead to the deterioration of EEMG signals and a compromise of its reliability on frequent use.

Furthermore, EEMG signal is unable to reflect changes in mechanical properties of muscle during fatigue stimulation (Orizio et al., 1999). With EEMG, muscle fatigue study is challenging as usually the signal continues to increase with increasing muscle's motor unit recruitment despite a decrease in the muscle effort/force due to muscle fatigue (Falla & Farina, 2008). Although EEMG reflects the degree of neural excitation responsible for the generation of muscle contractions and force, the muscle fatigue phenomenon, which EEMG may not discriminate from fresh contraction (Vøllestad, 1997), is also within the continuum of effective muscle contractions (Lei et al., 2011). Thus, quantification of NMES-evoked force production by EEMG alone during NMES-evoked contraction is deficient (Lei et al., 2011; Levin et al., 2000; Popović, 2014).

As a less complicated alternative, a mechanical activity of contracting muscles is gaining recent prominence as a proxy of muscle force. The surface measurement of the mechanical activity is called mechanomyography—MMG (Orizio, 1993; Stokes & Blythe, 2001). The rationale for investigating MMG signal as an alternative control signal source for NMES technology is as follows: (i) MMG is a mechanical "counterpart" of EMG for neuromuscular performance assessment (Croce et al., 2015; Orizio, 1993; Yuan-Ting et al., 1992), which summates the mechanical activity of active muscle fibre during contractions (Orizio et al., 1996) and in addition, reflects the peripheral adaptations in mechanical properties of muscle as reflected by muscle's dimensional changes (Cè et al., 2015) (ii) the signal readily propagates through the skin surface enabling a non-invasive recording of the muscle activity relevance for the estimation of the level of neural activation, and (iii) the MMG signal has been used to investigate motor unit (MU) activation strategy which is responsible for muscle contractions and force modulation (Beck et al., 2004; Orizio, 1993). Collectively, the highlighted MMG signal characteristics may allow a non-invasive estimation of muscle state as required for a closed-loop NMES operation to implement an automatic modulation of the stimulation parameters. An immediate question that may ensue following this preamble is, why is

MMG signal important in this setting? The study's motivation as illustrated in the following paragraphs answers this question.

1.2 Motivation for this Study

There is compelling evidence that a closed-loop control of NMES supported activity promotes the optimal utility of the technology in the clinical rehabilitation of persons with SCI. The lack of a direct, artifact-free, non-invasive and reliable proxy of muscle force from the stimulated muscles and affected limbs motivated this present study which sought to investigate the potential of MMG signals as a proxy of torque for NMES feedback applications.

However, in order to obtain an approximation of the functional capability and characteristics of NMES-evoked contractions of a muscle, its capacity to elicit isometric torque production must be assessed (Jaeger, 1986; Mohammed et al., 2012). Specifically, for the clinical application of NMES for therapeutic and functional gains, the use of muscle contraction signals (*i.e.*, biopotentials) for the assessment of muscle activity has been suggested (Peckham & Knutson, 2005; Wannstedt & Herman, 1978) for an effective joint control. This is required for neuromuscular training (Shields et al., 2006), in particular, during NMES supported knee extension, standing, and ambulation tasks. Therefore, a reliable measurement of muscle force, during these muscle activities, by a biopotential of muscle contraction origin for application as feedback control signals could significantly improve the functional outcomes of NMES-evoked contractions (Nataraj et al., 2010).

Although as a biosignal, several studies have evaluated the voluntary muscle performance using MMG signals (Barry et al., 1985; Beck et al., 2004; Ibitoye et al. 2014; Orizio, 1993), the specific interpretation and practical relevance of the signal parameters during NMES-evoked contraction of paralyzed muscles remain poorly understood.

Specifically, there is limited knowledge on the effects of muscle fibre type transformation and impaired muscle function following a SCI (Burnham et al., 1997) on the MMG characteristics of a muscle during intermittent and sustained NMES-evoked contractions. Understanding these may elucidate the relevance of the signal as a proxy of muscle force response for NMES control applications and consequently overcoming a technical challenge inhibiting the progress in NMES rehabilitation of muscles after SCI. This is based on the existing knowledge that the effect of muscle fibre transformation after SCI on the muscle force modulation and the associated muscle fatigue characteristics (Thrasher & Popovic, 2008) may be tracked by MMG signal responses (Kimura et al., 2004).

1.3 Research Objective

The main objective of this thesis was to develop a mechanomyographic-based NMES-evoked muscle force/torque estimation technique for feedback applications in NMES systems, particularly for use in persons with SCI. To address the main objective, the specific tasks carried out were:

- To develop a hybrid procedure to demonstrate MMG signal as a proxy of NMES-evoked muscle force in healthy volunteers.

- To deploy the developed procedure for studying the reliability of MMG signal as a proxy of muscle force during NMES supported knee extension task in persons with SCI.

- To demonstrate the potential relevance of MMG signal as a useful parameter for studying muscle fatigue during a critical knee buckling stress due to a sustained NMES-supported standing to fatigue failure task.

For a clear perspective, the experiments were designed to evaluate NMES-evoked contractions during common musculoskeletal assessment settings including knee extension activity against gravity and sustained standing (Clarkson, 2000). Therefore, the target muscle group was the quadriceps which has been well-established for its relevance in the study of knee torque dynamics during knee extension task, standing and ambulation training (Franken et al., 1993).

Based on this premise, the first specific objective aimed to develop a method to assess a healthy quadriceps muscle force via knee extension torque production during 'seated' NMES-evoked isometric quadriceps contraction using MMG signals. The objective was also meant to learn the adjustment required for the deployment of the same protocol in persons with SCI. The rationale for this study was based on the well-known knowledge of a healthy voluntary knee extension torque assessment and it is as follows:

The NMES-evoked muscle contraction increases with stimulation intensity as a result of an increase in the number of motor unit recruitment, to a certain critical level when the motor unit is fully recruited—a point preceding muscle fibre fusion and force saturation which may lead to a reduction in the muscle surface oscillation (Orizio et al., 1992). Specifically, the correlation between the MMG signal and the incremental NMES-evoked muscle force was examined. However, as the joint angle or muscle length influences the muscle force production (Pasquet et al., 2005; Rassier et al., 1999), the MMG responses to NMES-evoked muscle force at various knee angles could also be investigated. Based on this, the reliability of MMG signals as a proxy of muscle force was established, at incremental stimulation intensity levels, in order to mimic a typical practical clinical application of NMES-evoked muscle contractions for knee extension task. By this approach, the validity of the MMG signal to track muscle force production could be resolved while guiding the implementation of the same methodology in persons with neurological conditions.

The second specific objective is an application of the method developed in the first objective to study muscle response in persons with SCI. This is necessary as the MMG responses in healthy muscle may not adequately represent the situation in denervated or paralyzed muscle under neuromuscular provocation (Scott et al., 2007). This objective verified that the incremental NMES-evoked knee torque as measured by a commercial isokinetic dynamometer can be tracked by the MMG signal. Specifically, the experiment was conducted on persons with motor complete SCI; A and B according to the American Spinal Injury Association Impairment Scale (AIS, see Table 2.1 for details) (Kirshblum et al., 2011) during 'seated' NMES-evoked knee extension task for torque production via isometric quadriceps contractions. This mode of contraction is clinically relevant as NMES-evoked leg extension task involving short bouts of contractions and recovery periods has been suggested as an alternative modality to functional ambulation training in persons with SCI (Crosbie et al., 2009).

Subsequently, the data obtained from this experiment were used for knee torque estimation from MMG signal using a machine learning technique based on support vector regression algorithm. This was necessary to investigate whether the factors that influence muscle force modulation including stimulation intensity, knee angle, and the generated MMG signal could be intelligently combined to estimate the knee extensor torque. By this approach, the established positive correlations between the MMG signal and muscle force could be corroborated using a SVR model which is more robust, especially, in handling regression tasks, than the traditional regression methods (Yu et al., 2010).

In the two previously described specific objectives, the experiments were conducted in a laboratory and on an isokinetic dynamometer. The third specific objective was conducted in a rehabilitation gymnasium to examine the clinical relevance of the MMG signal as a muscle fatigue contraction sensor. The rationale for this experiment was to investigate whether MMG signal could track the paralyzed muscle activation pattern during a practical standing-to-failure task in persons with motor complete SCI. The quadriceps muscle failure as reflected by knee buckle served as an indication of muscle fatigue which is typically characterized by a torque reduction (Sayenko et al., 2015).

As the torque reduction is impractical or difficult to measure directly during NMES-supported standing tasks, a 30^0 drop in the knee angle was used as a critical fatigue failure indicator. This measurement together with the quadriceps' MMG signal responses over the contraction time allowed an investigation of whether MMG signals could be a reliable method for NMES-evoked muscle fatigue assessment. This approach was based on the knowledge that the muscle fatigue could be better assessed during NMES contraction as the limitation imposed by central nervous system (CNS), such as motivation, is absent (Vøllestad, 1997).

Collectively, the experimental settings adopted in this study was typical of clinical NMES applications for sustained muscle contractions to verify whether MMG signal could track the changes in motor unit recruitment strategy during fresh and fatigued contractions.

1.4 Research Significance

Findings from this thesis provide unique insights into the development of an NMES-evoked muscle force/torque measurement and tracking system using MMG signal in persons with SCI. Specifically, the thesis presents the technical assessment and implication of the MMG signal generated during NMES-evoked muscle contractions for applications in MMG-driven NMES systems. Such a system has the potential to impact the quality of life of many potential users, specifically from our rehabilitation program at the Department of Rehabilitation Medicine of the University of Malaya Medical Centre (UMMC) and in general, for other patients from among the affected population within Malaysia and beyond. Specifically, the following points summarize the significance of the thesis.

- ❖ The current open-loop mode of NMES technology has largely confined its application to research activities rather than its deployment for routine clinical use. The MMG signal proposed in this thesis as a stimulation artifact-free and non-invasive proxy of muscle force can be applied as a reliable NMES feedback signal source to promote the flexibility and efficacy of NMES technologies for routine clinical applications.
- ❖ The muscle force assessment method based on MMG signal, as proposed in this thesis, can be used to examine the level of NMES-evoked torque generation within and outside of laboratory and during NMES exercise for health benefits including minimizing muscle atrophy/wasting in paralyzed muscles (Panisset et al., 2016), promotion of neural repair (Young, 2015), healing of pressure ulcers (Lala et al., 2015) and prevention of secondary peripheral nerve deterioration (Lee et al., 2015) and joint contracture (Peckham & Kilgore, 2013) in persons with SCI.
- ❖ The thesis sought to provide a new knowledge on the potential application of MMG signals as a sensor to monitor the deterioration or improvement of motor control activity—responsible for muscle contractions following NMES-evoked contractions. This could guide clinicians and other allied health professionals administering NMES as a treatment option in rehabilitation and aid the development of effective rehabilitation interventions.
- ❖ The thesis also explores a novel approach for tracking muscle fatigue states during NMES supported standing based on the muscle's MMG signals and proposed the signal as a fatigue-failure predictor during critical functional tasks.

1.5 Research Scope

The reported studies are limited to the experimental investigations of the MMG signal as a proxy of NMES-evoked muscle force/torque during knee extension and standing tasks in healthy and spinally injured persons. The implementation of the proposed MMG signal as a feedback signal in a real-time NMES control setting was not investigated. The thesis also applied the computational intelligent approach of SVR modelling to predict torque from MMG signal/datasets. However, the predictive SVR model used was based on the standard SVR algorithm as the algorithm gave a good predictive accuracy. This was in agreement with the knowledge that SVR often demonstrate an impressive performance in comparison with other machine learning algorithms in related fields (Ameri et al., 2014; Meyer et al., 2003). Therefore, comparison of SVR with other modelling techniques was not covered in this thesis.

1.6 Thesis Organization

This thesis is an integration of three major separate but dependent studies. Each study is presented in a separate Chapter with subsections including the introduction, literature review, methodology, results, discussion and conclusion. As the thesis style is based on the article format, there may be certain unavoidable redundant information, particularly in introduction and literature review subsections of each Chapter. Also, included in each of these Chapters are the relevant theoretical background and assumption that informed the selection of the methodology adopted. The publication by the author that is related to each Chapter is included within the Chapter.

Chapter 2 provides the synthesis of an extensive background information to the research within this thesis. The Chapter specifically discussed the basic muscle physiology as well as neuromuscular principles of an impaired lower limb muscle function following a SCI. The Chapter also discussed the principle of NMES technology in evoking muscle contractions, its pattern of motor unit recruitment strategy and the limitations of the technology in order to identify the technical challenges militating against its optimal performance. As the literature revealed a research gap of a reliable, artifact-free, and non-invasive proxy of NMES-evoked muscle force, review of a machine learning modelling technique for an intelligent estimation of muscle force from MMG was also presented. The Chapter contains a synthesis of the author's four published review articles as listed under the introduction to Chapter 2.

Chapter 3 reports the procedure used to establish the MMG signal as a proxy of NMES-evoked quadriceps muscle force/torque in healthy volunteers. Moreover, the Chapter also presented the estimation of quadriceps muscles force from the MMG signal using support vector regression (SVR) modelling approach. The Chapter contains text from the author's published article:

Ibitoye, M. O., Hamzaid, N. A., Abdul Wahab, A. K., Hasnan, N., Olatunji, S. O., & Davis, G. M. (2016). Estimation of Electrically-Evoked Knee Torque from Mechanomyography Using Support Vector Regression. Sensors, 16 (7), 1115.

Chapter 4 presents the application of the procedure established in Chapter 3 to relate the MMG signals with NMES-evoked knee torque in persons with SCI. The Chapter contains text from the author's published article:

Ibitoye, M. O., Hamzaid, N. A., Hasnan, N., Abdul Wahab, A. K., Islam, M. A., Kean, V. S. P., & Davis, G. M. (2016). Torque and mechanomyogram relationships during electrically-evoked isometric quadriceps contractions in persons with spinal cord injury. Medical Engineering & Physics, 38 (8), 767-775

Chapter 5 reports the estimation of the paralyzed quadriceps electrically evoked muscle force from MMG signal using SVR modelling approach.

Chapter 6 describes the protocol for NMES-aided sustained standing to fatigue failure in persons with motor complete SCI. This was used to evaluate the validity of MMG signal as a proxy of muscle fatigue due to critical knee buckling stress during standing challenge task.

Chapter 7 summarizes the findings of this research study, discusses their implications and overall significance. Furthermore, the Chapter also enumerates the limitations of this study and provides suggestions for further investigations as applies to NMES control systems.

CHAPTER 2: LITERATURE REVIEW

2.1 Introduction

This Chapter reviewed related literature on muscle physiology and musculoskeletal impairment after a spinal cord injury (SCI), particularly for the benefits of the audience with an engineering background. The Chapter also discussed the neuromuscular electrical stimulation (NMES) technology as a popularly recommended rehabilitative intervention for persons after SCI while highlighting the major limitations of the NMES-evoked muscle contractions. The prominently identified limitations are (i) imprecision in torque production for effective functional applications and (ii) inherent rapid muscle fatigue probably due to a reversed or non-physiological recruitment of motor unit (Bickel et al., 2011).

Based on the available knowledge in the literature, optimal application of NMES for rehabilitative interventions warrants an automatic modulation of the stimulation parameters (Ibitoye et al., 2016). Therefore, NMES rehabilitation post-SCI has been discussed highlighting the need for biopotential sources for NMES feedback applications. Popular biopotential sources which have been used to assess the muscle performance (force/torque and fatigue) are also discussed to highlight the need for this thesis. Following the provision of a novel insight into the potential of a unique application of the muscle contraction characteristics (mechanomyography, MMG) as an NMES control signal, the Chapter concluded with a discussion on a machine learning modelling technique for muscle force/torque estimation using the MMG signal.

The literature discussed in this Chapter has been previously published, in part, in the following articles which were retrieved with permission from the publishers:

(i) Ibitoye, M. O., Estigoni, E. H., Hamzaid, N. A., Abdul Wahab, A. K., & Davis, G. M. (2014). The Effectiveness of FES-Evoked EMG Potentials to Assess Muscle Force and Fatigue in Individuals with Spinal Cord Injury. *Sensors*, 14 (7), 12598-12622.

(ii) Ibitoye, M. O., Hamzaid, N. A., Zuniga, J. M., & Abdul Wahab, A. K. (2014). Mechanomyography and Muscle Function Assessment: A Review of Current State and Prospects. *Clinical Biomechanics*, 29 (6), 691-704.

(iii) Ibitoye, M. O., Hamzaid, N. A., Zuniga, J., Hasnan, N., & Abdul Wahab, A. K. (2014). Mechanomyographic Parameter Extraction Methods: An Appraisal for Clinical Applications. *Sensors*, 14 (12), 22940-22970.

(iv) Ibitoye, M. O., Hamzaid, N. A., Hasnan, N., Abdul Wahab, A. K., & Davis, G. M. (2016). Strategies for Rapid Muscle Fatigue Reduction during FES Exercise in Individuals with Spinal Cord Injury: A Systematic Review. *PLoS One*, 11 (2), e0149024.

2.2 Motor Control in Human

Humans with intact neuromuscular function have controls over the performance of intended muscular activities via nervous system which controls the stimuli, perturbations and coordinates body activities (Hu et al., 2012; Rosenbaum, 2010). The nervous system is made up of (i) the central nervous system (CNS) which is composed of the brain and spinal cord, and (ii) the peripheral nervous system (PNS), that links the CNS with "various receptors and effectors" (Keijzer et al., 2013; Mackie, 1990). Typically, for motor and function coordination, there is typical information "signal pickup by sensory receptors" which is transmitted back and forth to the CNS through the PNS for processing (Keijzer et al., 2013) (Figure 2.1). However, injury to the spinal cord may lead to a malfunction of the sensory and/or motor function and coordination as a result of a partial or complete loss of motor or sensorimotor capability based on the severity of the injury (McDonald & Sadowsky, 2002; Valenzuela et al., 2016).

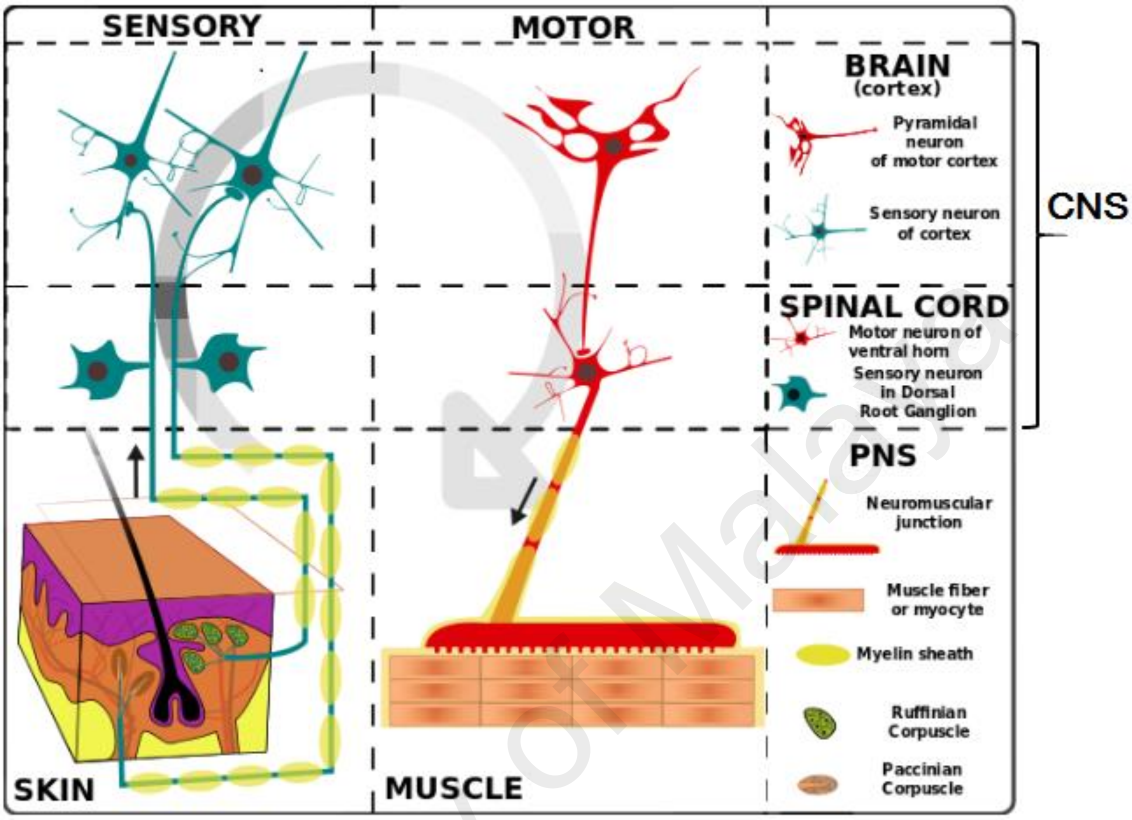

Figure 2.1: Basic representation of the nervous system function.
Adapted from JDifool and Looie496 (2009) according to the creative common license from Wikimedia.

2.3 Basic Skeletal Muscle Responses Post Spinal Cord Injury

An intact spinal cord propagates the motor and sensory information between the brain and the peripheral nerves that inerves muscles (Purves et al., 2001). This allows a voluntary movement coordination by the nervous system while the postural control and joint stability needed for skeletal movements for activity performance are normally supported by the skeletal muscle (Blottner & Salanova, 2015; Hogan, 1985). Following a SCI due to a disease or trauma to the spinal cord, there is usually partial or total loss of skeletal muscle functions. This is as a result of the disruption in the motor and sensory information below the injury level (Biering-Sørensen et al., 2009; Hamid & Hayek, 2008). As the human skeletal muscle which is responsible for movements and activities is innervated by spinal nerves accommodated within a particular segment of the spinal cord, injury to that segment logically translate to a loss of muscle activity below the injury site (Biering-Sørensen et al., 2009; Hamid & Hayek, 2008).

The rehabilitative technique or treatment options for the affected persons depends largely on the level (Figure 2.2) and severity or completeness of the SCI based on the injury classification. Table 2.1 describes the neurological injury classification according to the International Standards for Neurological Classification of SCI *i.e.* American Spinal Injury Association Impairment Scale (AIS) (Kirshblum et al., 2011; Waters et al., 1991). Furthermore, Figure 2.2 illustrates the relationships between the spinal cord segment and the supported functions.

Table 2.1: American Spinal Injury Association Impairment Scale (AIS) (Kirshblum et al., 2011).

Classification	Grade A	Grade B	Grade C	Grade D	Grade E
Injury completeness	Sensorimotor complete	Motor complete but sensory incomplete	Motor and sensory incomplete	Motor and sensory incomplete	Sensorimotor function is intact
Interpretation	Both motor and sensory functions are absent below the injury level and in the sacral segment S4-S5.	Only sensory function is preserved below the injury level and in the sacral segment S4-S5.	Motor function is intact below the injury level, with key muscles having muscle grade < 3	Motor function is intact below the injury level, with key muscles having Muscle grade ≥ 3	Normal neurological function

Note: Key muscles refer to the muscles below the injury level.

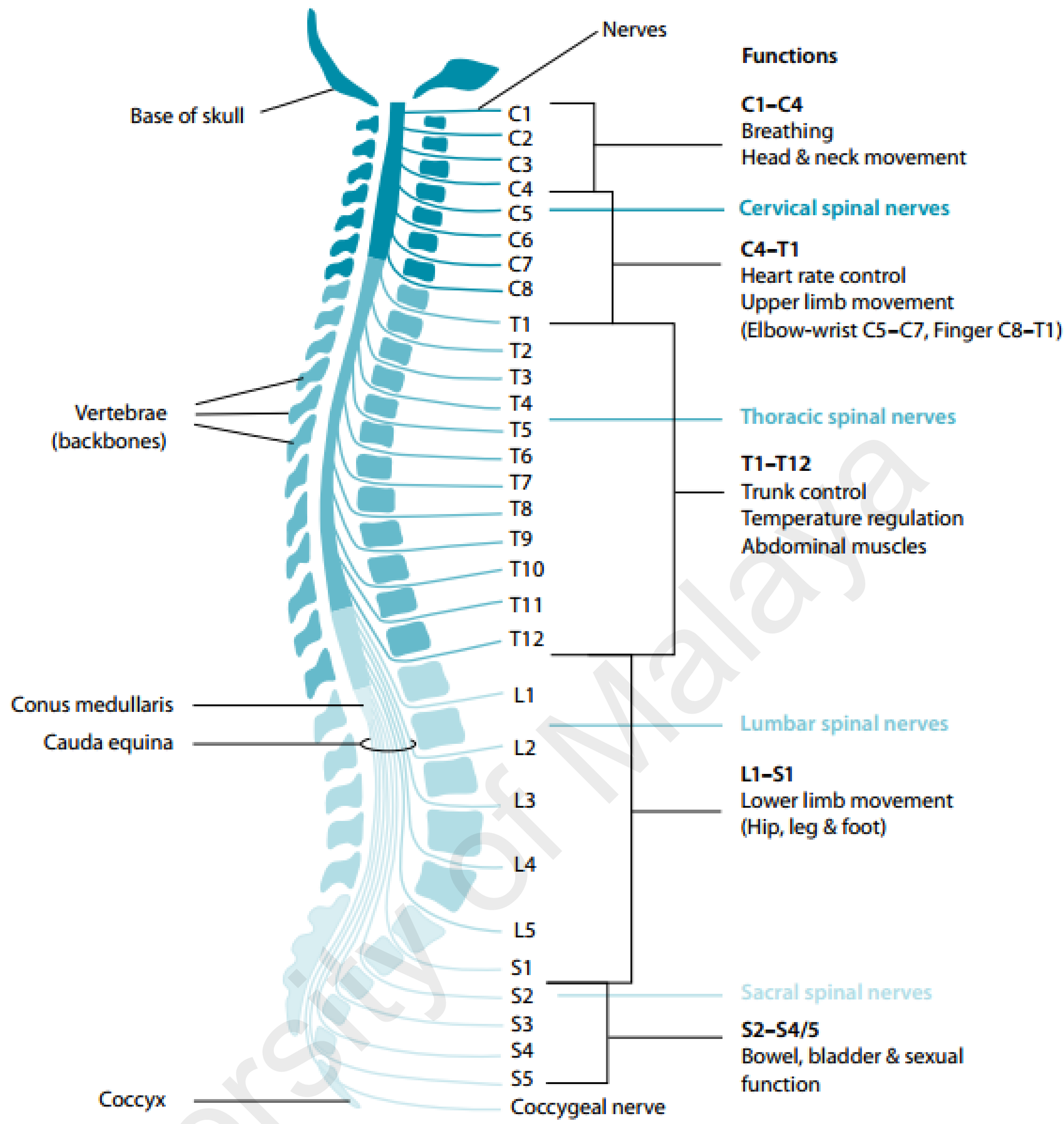

Figure 2.2: Classification of the levels of spinal cord injury according to the American Spinal Injury Association.
Reproduced from Bickenbach et al. (2013) under the general distribution terms of the World Health Organization.

Depending on the post-injury duration, SCI is also classified as acute (mostly while the affected persons is hospitalized for a primary rehabilitation intervention) and chronic (post-rehabilitation phase or community dwelling) (Curt et al., 1998) and a stage between the two is termed subacute (Fawcett et al., 2007). While there has been no definitive consensus on the demarcation of when an acute injury becomes chronic, chronic injury implies a relative stability in the body composition as compared to acute SCI (Hamid &

Hayek, 2008; Houle & Tessler, 2003). This knowledge is essential as there are differences between the physiological responses of a muscle in chronic and acute stages of SCI. Such responses are due to the variations in the duration of inactivity associated with the changes in the muscle metabolism, blood flow, and fibre composition (Peckham et al., 1976; Shields, 2002).

Consequently, the effect of this transformation confers different fatigue resistance capacities on the skeletal muscles during different post-SCI stages (Nguyen et al., 2011). For example, unlike during chronic SCI phase, an acutely denervated skeletal muscle might be characterized by an unusual muscle fibre composition—as indicated by the relative proportion of slow and fast myosin heavy chain isoform expression (Burnham et al., 1997). This is as a result of the alteration of fibre type morphology and histochemistry after SCI (Burnham et al., 1997; Gorgey et al., 2014). Therefore, there are different muscle force and fatigue temporal responses between an acutely-denervated versus chronically denervated muscle to a rehabilitative intervention and functional recovery.

Following a SCI, the main classes of muscle fibre types responsible for variations in the muscle responses are slow-twitch/fatigue resistant fibre and fast-twitch/fatigable fibre. Fast-twitch fibres' response to a contractile impulse is quicker than that of slow-twitch fibres, but at the expense of rapid onset of muscle fatigue. While slow-twitch fibres are more fatigue-resistant than fast-twitch fibres, response to a contractile impulse in slow-twitch fibres is slower in comparison with that of fast-twitch fibres (Bogdanis, 2012). Although the extent of muscle atrophy due to disuse and the level of physical exercise influence the ratio of the fibre types in skeletal muscle, alteration in the proportion of the slow-twitch fibre to fast-twitch fibre is a negative neuromuscular sequela to SCI (Round et al., 1993; Tanaka et al., 2013).

As a consequence of these morphological and histochemical adaptations, resistance to rapid fatigue is impaired in denervated or paralyzed skeletal muscles compromised by the upper motor neuron lesions in the spinal cord (Hillegass & Dudley, 1999). Accordingly, the power output and exercise capacity of the affected muscles are diminished due to the inactivity and unloading concomitant with post-SCI wheelchair confinement (Castro et al., 1999). This is clearly evident in the decline of the force-generating capacity of the muscle (*i.e.*, specific tension ($N \cdot cm^{-2}$)) (Hunter et al., 1998; Kluger et al., 2013).

Therefore, there is a significant influence of SCI on the muscle response and general health conditions of the affected persons (Davis et al., 2008; Noreau & Shephard, 1995). The common consequences of SCI includes: (i) disuse atrophy and consequently, osteoporosis with an increased risk of bone fracture, (ii) limited cardiorespiratory fitness due to sedentary lifestyle, (iii) decubitus ulcers, (iv) incontinence among various other physiological and biomechanical disorders (Davis et al., 2008). This justifies why returning the affected persons back to their "productive lives" has become a research priority (Boschen et al., 2003; Ditunno & Formal, 1994).

Thus, a recovery of the lost function or at least a preservation of muscle health integrity significantly impacts the quality of life of the affected persons. Evidence (Ditunno & Formal, 1994; Nash, 2005) suggests that rehabilitative interventions promote independence in "self-care" and "mobility" through exercise in the affected population. Thus, SCI-related health problems could be offset by therapeutic and functional rehabilitative interventions. One promising engineering technique that has been recognized and recommended for exercise is neuromuscular electrical stimulation assisted contractions. This technique has been used to offset sedentary lifestyle, and its complications, in the affected persons in order to improve their physical capacity (Hamid & Hayek, 2008; Ho et al., 2014; Jacobs & Nash, 2004).

2.4 Neuromuscular Electrical Stimulation

Neuromuscular electrical stimulation (NMES) is an engineering technique for artificially applying electrical current to the muscle or nerve to generate skeletal muscle contractions (Bajd & Munih, 2010; Hamid & Hayek, 2008). The technique is based on the discovery of Galvani and Volta (1793) which demonstrated muscle contractions with an electrical current propagation along muscle fibres. In clinical settings, NMES is used to activate skeletal muscle for rehabilitative purposes while the technique is used in research settings for the assessment of muscle performance and for the improvement of neuromuscular activation levels (Bickel et al., 2011).

Technically, NMES systems are made up of a "microprocessor-based electronic stimulator that coordinates the modus operandi of the stimulation. The system also has stimulation channels that communicate to individual pulses using pairs of stimulation electrodes connected to the neuromuscular system" (Hamid & Hayek, 2008; Papachristos, 2014) and a portable power source with a rechargeable battery (Ragnarsson, 2007). Figure 2.3 depicts the NMES scheme in open- and closed-loop configurations. Open-loop configuration is based on the manual bottom press while in a closed-loop configuration, proxies of muscle responses are inputs to the control interface from where the stimulator receives the command signals. The electrical stimulus pulses that are generated by the controller are delivered to the target muscle via pairs of stimulator electrode depending on the number of channels. This results in muscle contractions required for therapeutic and/or functional gains.

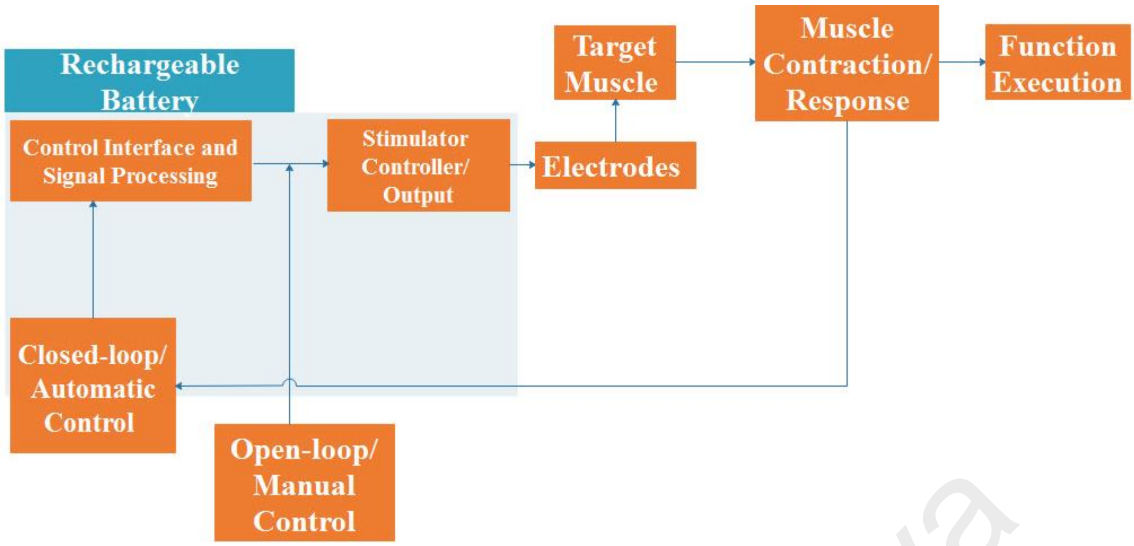

Figure 2.3: Basic component of a surface NMES system.

The stimulator generates a train of pulses (*i.e.*, similar to the neural twitches passing through the spinal cord to the peripheral nerves during voluntary contraction in an intact spinal cord) below spinal cord lesion to effect artificial muscle contractions (Durand et al., 2005; Hamid & Hayek, 2008). Specifically, the generated stimuli triggers action potentials in the peripheral nerves within the muscle fibres to activate muscle contractions (Rattay et al., 2003). The action potential, being “a fundamental unit of communication in the nervous system, is an electrochemical signal that travels along the neurons as a flux of ionic current between the extracellular and intracellular matrix” (Grill & Kirsch, 2000). Therefore, when NMES current is applied to a pair of stimulating electrodes affixed to the skin surface overlying sensorimotor structures, an electric field triggers action potentials along the nerve bundle, which leads to muscle contractions (Figure 2.4). This is effective as the released ions produce current in the tissue due to the transmission of action potentials along the axon to the peripheral nerve innervating the muscle (Durand et al., 2005; Grill & Kirsch, 2000).

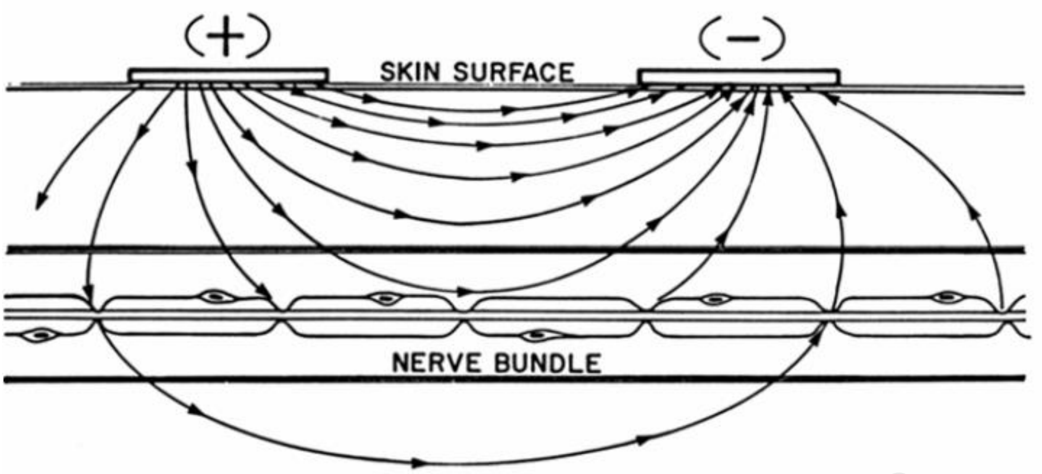

Figure 2.4: Electric field propagation and generation of the action potential to evoke muscle contractions during surface neuromuscular electrical stimulation. Reproduced from Bajd and Munih (2010) with permission from the publisher.

The propagation of the action potential along the nerve leads to muscle contractions through the activation of the PNS (Durand et al., 2005; Grill & Kirsch, 2000). The potency of the NMES is based on the system parameters' setting (intensity (current or voltage), pulse width and frequency; Figure 2.5) which determines the extent of muscle fibre recruitments, muscle contraction and consequently, muscle force generation (Bhadra, 2015). These electrical stimulation parameters are functions of the muscle force production while pulse frequency, specifically, affects the muscle fatigability (Ibitoye et al., 2016).

Evidence (Bickel et al., 2011) suggests that the NMES's recruitment pattern of motor unit (MU) is nonselective, spatially fixed and synchronous. This implies that the MUs are stimulated or activated at the same time without obeying the size principle of Henneman (1957). The size principle suggests that the normal physiological recruitment of MUs involves a progressive recruitment of slow twitch MUs before fast twitch MUs (Jabre & Spellman, 1996). This may justify why a stimulation frequency of 20 Hz and above, which is within the "physiologically relevant frequency of motoneuron discharge" (Al-Majed et al., 2000), is usually required for achieving effective electrical stimulus muscle contractions (Thompson et al., 2014). This is opposed to a voluntary MU activation strategy, which is asynchronous and requires a frequency range between 6 Hz and 8 Hz (Lynch & Popovic, 2008) for effective muscle contractions.

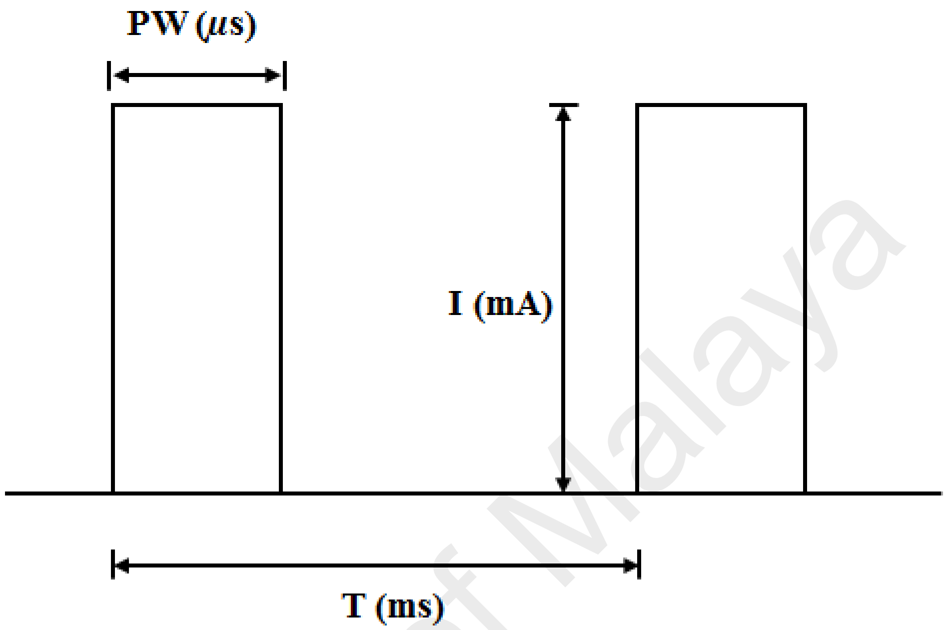

Figure 2.5: Stimulation parameters.
The period of stimulation (T (ms)) is the inverse of the frequency of stimulation (F (Hz)). PW (μs) stands for pulse width and I (mA) represents the stimulation current.

As earlier mentioned, the NMES is typically administered through pulses of electrical signals with specific parameters—current, pulse width, and frequency (Figure 2.5), using stimulating electrodes (Hamid & Hayek, 2008). These electrodes can be fixed to the skin surface non-invasively (transcutaneous), or surgically implanted and affixed to the muscle's motor point (epimysial), or implanted inside the muscle (percutaneous/intramuscular), or surgically wrapped around the nerve (helix or a cuff), or inserted (intraneural) within the nerve that innervates the muscle of interest (Popovic & Sinkjær, 2000; Ragnarsson, 2007).

Although implanted-based NMES electrode generally allows good muscle selectivity and promote excellent motor unit recruitment (Polasek et al., 2009), the technique may be characterized by infection, low user preference (Rohde et al., 2012) and has not been widely approved for clinical use (Peckham & Knutson, 2005). This has resulted in a limited "commercial success" of the technology (Peckham & Knutson, 2005). Conversely, while surface NMES technology is relatively safer and easier to use (Mangold et al., 2004), selective muscle contractions especially of deeper muscles is challenging. However, the modality is potentially appealing to the users and more commonly used in home and clinical settings (Keller & Kuhn, 2008; Ragnarsson, 2007). Therefore, based on the highlighted strengths of the surface stimulation modality, with consideration to the main objective of the present thesis and in accordance with previous related studies on knee extension (Gorgey et al., 2016; Hillegass & Dudley, 1999) and standing (Kralj & Bajd, 1989; Yarkony et al., 1990) tasks, surface stimulation was considered suitable and thus adopted for use in the various investigation performed in the present thesis.

On the mode of control of NMES system, the modulation of the stimulation parameters can be effected through an open-loop or closed-loop configuration (Ragnarsson, 2007). In an open-loop NMES modulation, the operation of the NMES system is dependent on the subjective users' perceived need. Therefore, information of the muscle state in terms of muscle force/joint torque and fatigue is absent and could not be compensated for. Other than being characterized by a sub-optimal muscle response, the modality predisposes a muscle to injury (Fitts, 1994). Although this type of NMES system is mostly available for therapeutic applications, its effectiveness for functional applications is limited as the modality overstimulates the muscle to ensure sufficient activation—a practice which leads to a rapid muscle fatigue (Hoffer et al., 1996).

Conversely, in a closed-loop NMES system, the real-time information on the muscle response/state such as muscle force or joint torque and fatigue status are automatically fed back to the NMES system by peripherally placed sensors to modulate or regulate the NMES operations (Peckham & Knutson, 2005). This type of NMES operation is more efficient, mostly required for functional activities and reduces “cognitive burden” of open-loop NMES systems—where the user is expected to be conscious of emerging perturbations (Hoffer et al., 1996).

By these two strategies, NMES provides muscle contractions for the restoration of movement or function (Bajd & Munih, 2010). The application of NMES therapy to promote the ‘restoration’ of purposeful function has been demonstrated in several studies (Doucet et al., 2012; Fouad & Tetzlaff, 2012; Scott et al., 2005). Useful clinical application of the NMES technology has been applied to maintain, improve or restore muscle trophism, promote health and augment functional outcomes after SCI (Collins, 2007; Deleys et al., 2015), in post-acute care, rehabilitation settings and exercise programmes (Fouad & Tetzlaff, 2012; Kebaetse et al., 2005; Mohr et al., 1997). In the next session, lower limbs rehabilitation applications of the NMES technology in post-SCI care is discussed.

2.5 NMES Assisted Rehabilitation in the Lower Limbs Post-SCI

NMES applied over the human neuromusculature produces muscle contractions by depolarizing motor axons beneath the stimulating electrodes (Collins, 2007). Previous neurophysiological studies have shown that the larger motor units’ axons are more readily depolarized, allowing preferential recruitment of fast twitch fibres during NMES-evoked contractions (Bickel et al., 2011; Blair & Erlanger, 1933). However, in persons with SCI, inactivity following wheelchair confinement leads to disuse atrophy and alters the normal physiological muscle response (Castro et al., 1999; Round et al., 1993). To preserve the integrity of muscle health in this population, NMES rehabilitative option exploits the adaptive potential of skeletal muscle fibres to increase loading effect on joints.

Therefore, there is strong evidence (Ho et al., 2014; Sadowsky et al., 2013) that NMES-evoked muscle contractions promote the recovery and/or preservation of health, and offset the secondary complications of the SCI (Griffin et al., 2009; Hasnan et al., 2013; Jacobs & Nash, 2004). Specifically, the NMES technology has shown promise in the rehabilitation of both the upper and lower limbs as well as human body functions mostly in persons with upper motor neuron lesions but intact peripheral nerve/lower motor neuron (Kern et al., 2007; Ragnarsson, 2007). In these persons, the affected muscles still retain the “ability” to contract and generate force (Biering-Sørensen et al., 2009).

However, depending on the type of paralysis, regaining standing and ambulation are typical important rehabilitative priorities in persons with paraplegia—those with lower limb and trunk paralysis (Ragnarsson, 2007) as well as those with low tetraplegia (Davis et al., 2001; Jaeger et al., 1989; Peckham & Knutson, 2005). NMES supported standing in these populations has been a major research concern for over five decades with the pioneer works of Kantrowitz (1963), Bajd et al. (1981) and Kralj and Bajd (1989). Therefore, standing and short distance ambulation represent major purposes of NMES application in the lower limbs (Peckham & Knutson, 2005) as the inability to stand or ambulate may disallow the affected persons the capacity to manipulate objects within their environments, transfer between places and have an equal level interaction (Davis et al., 1999; Peckham & Knutson, 2005).

Figure 2.6 represents an open-loop control of NMES administration for knee extension, standing, and ambulation training. In this case, the stimulation is triggered manually by a finger switch to effect knee lock in stance phase and unlocks the knee during swing phase in order to prevent collapse, while the NMES system consisting of about 16-channel stimulation via surface electrodes, moves the ankle. Evidence (Faghri et al., 2001) suggests that the NMES-assisted standing improves a joint range of motion, prevents orthostatic hypotension and circulatory hypokinesis and improves cardiorespiratory and metabolic functions for the promotion of the quality of life (Rohde et al., 2012). In addition, NMES supported standing may prevent disuse atrophy, promotes muscle strength and endurance, enhances cardiopulmonary status and tissue integrity to prevent pressure sore associated with inactivity (Triolo & Bogie, 1999).

Moreover, being a requirement (Davoodi & Andrews, 1999) for reaching and ambulation, standing allows persons with SCI to fulfill activity of daily living (Simpson et al., 2012). The need to channel research activities in line with this concern has continued to motivate research activity in this area of lower limb rehabilitation.

Leading among the NMES supported standing research priorities has been the strategies for “standing up”, “sit-to-stand” and “prolonged standing” during stance phase (Eng et al., 2001; Kern et al., 1999). These functional activities are often preceded by reconditioning of the involved muscles (Peckham & Knutson, 2005) through isometric knee extension exercise (Jaeger, 1986) and other strength conditioning modalities which could be used to promote the muscle resistant to rapid muscle fatigue for an extended contraction duration.

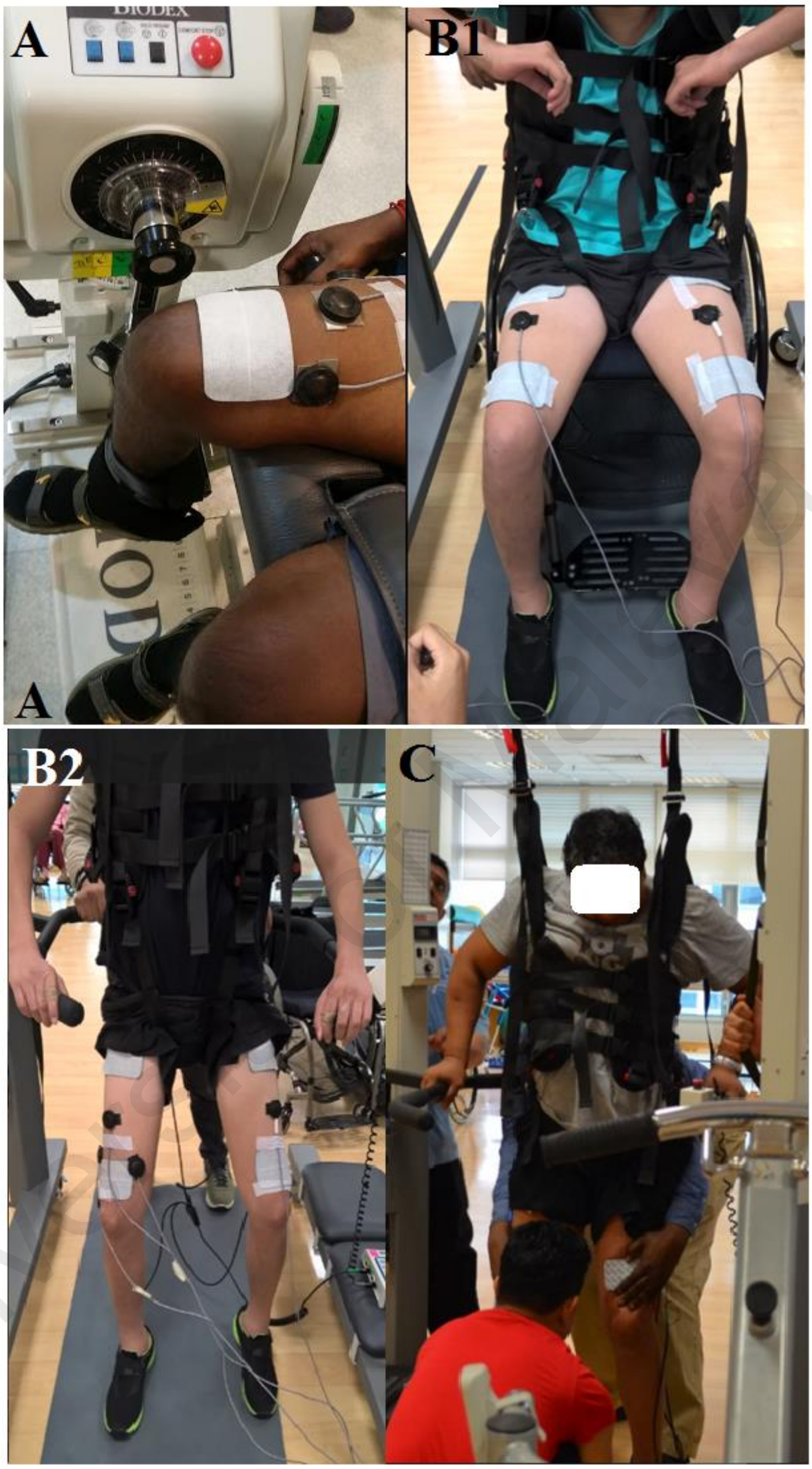

Figure 2.6: Typical NMES-assisted lower limb rehabilitation.
(A) The NMES assisted knee extension exercise for improvement of muscle strength and joint range of motion in preparation for standing tasks; (B1) The NMES supported sit-to-stand and (B2) standing tasks; and (C) An example of an NMES setting for ambulation training.

The specific population of SCI that possesses a good upper-limb strength which is required for standing may be trained for NMES supported standing to access objects and maneuver into places that are ordinarily inaccessible with a wheelchair (Davis et al., 1999). Standing has both functional (Triolo et al., 1992) and therapeutic benefits (Veltink & Donaldson, 1998). The functional standing task involves a stable and an upright posture while part of/or whole of upper limbs are used for object manipulations (Triolo et al., 1992). However, when the upper extremities are mainly used for postural control and stability, such a standing task is limited to therapeutic benefits. While the latter may be of limited clinical interest, its benefits are equally enormous (Veltink & Donaldson, 1998), particularly being a simple and cost-effective therapeutic exercise modality (Bajd et al., 1999). In both cases, standing benefits can fully be realized if it is considerably prolonged (Eng et al., 2001).

Currently, the dexterity of NMES supported standing is not comparable to that of voluntary standing in persons with intact neuromuscular function. For example, in terms of metabolic (energy) cost, the effort expended in NMES standing is estimated at 4 to 6 times higher than that of a normal voluntary standing (Graupe & Kohn, 1998; Jacobs & Nash, 2004; Kobetic & Marsolais, 1994). Additionally, an insufficient duration of NMES supported standing has been consistently reported and this is a limitation to the clinical efficacy of the NMES technology (Peckham & Gorman, 2004; Ragnarsson, 2007) for application in standing. Thus, the research interest to prolong the duration and improve the efficacy of NMES supported standing has been on the rise recently (Braz et al., 2015).

To understand the reason behind the inefficient outcome of NMES supported standing in persons with SCI, the knowledge of motor activities during voluntary recruitment of motor unit is vital. As earlier mentioned, voluntary muscle contraction obeys Henneman's size principle (Henneman, 1957; Henneman et al., 1965). That is, the recruitment order of motor units is from the smallest (slow twitch) to the largest (fast twitch). This has been interpreted as orderly recruitments of muscle fibres' motor units. This phenomenon naturally delays the occurrence of muscle fatigue during sustained maximal isometric contractions by allowing the "slowing" of motor unit firing rate— muscle wisdom (Boyas & Guével, 2011; Garland & Gossen, 2002). One of the exceptions to the Henneman's size principle, however, has been the recruitment pattern of NMES where a reversal of the size principle has been commonly reported (Bajd & Munih, 2010; Bickel et al., 2011).

In addition, the majority of evidence supports that the order of NMES-induced MU recruitment is non-selective (Bickel et al., 2011; Maffiuletti, 2010), the consequent of which is the exaggerated metabolic cost of NMES-evoked muscle contractions that lead to rapid muscle fatigue (Collins, 2007; Maffiuletti, 2010). This limits the duration of muscle contractions that NMES may evoke (Jaime et al., 2002). Therefore, while there are various therapeutic and functional benefits associated with lower limb rehabilitation (Thrasher & Popovic, 2008), the limitation imposed by rapid muscle fatigue demand that the NMES modulation is automated for optimal applications.

The effect of muscle fatigue is particularly significant as it is time-varying and affects the response of muscle, specifically, during high-intensity repetitive application of NMES for antigravity activities such as in standing-up and sustained standing where muscle fatigue may be evident in 60 secs of stimulation (Chesler & Durfee, 1997; Thrasher & Popovic, 2008). Consequently, there is an increased tendency for muscle injury associated with a prolonged muscle contraction due to the accumulated muscle fatigue (Fitts, 1994) without proper monitoring. Therefore, an automated NMES operation allows intelligent compensation for changes in the neurostimulated muscle response due to muscle fatigue and other perturbations.

However, one major limitation of the commercial NMES technologies is the lack of a reliable feedback signal source to gain muscle state information including the magnitude of the force/torque generation and fatigue contractions (Popović, 2014). This may justify why the available clinical NMES systems such as Parastep™ (Sigmedics, Inc., Fairborn, OH, USA) still rely on the manual control by hand switches for operation (Ethier & Miller, 2015). Till date, the development and validation of sensors to modulate and automate the stimulation pattern, during NMES-evoked muscle contractions in order to mimic the physiological coordination of muscular activities, is of interest and a wide knowledge gap (Ragnarsson, 2007). Indirect measure of neural activities including electromyogram (EMG), electroencephalogram (EEG), electroneurogram (ENG) (Sinkjaer et al., 2003) and mechanomyogram (MMG) which is the mechanical equivalent of EMG (Decker et al., 2010; Gobbo et al., 2006; Orizio, 1993) have been validated as physiological signals that is rich in neural information to decode functional intentions during muscle contraction.

These signals are generally promising in the design of biofeedback systems for NMES control applications in the research and clinical settings (Hatsopoulos & Donoghue, 2009). They may be deployed as a proxy of muscle contractions and the generated muscle force during fresh and fatiguing contractions or used to study the knee-joint dynamics (Sharma et al., 2009) for lower limbs rehabilitation. They may be utilized as biopotentials/signal sources for feedback applications to allow NMES systems to receive real-time muscle information and consequently modulate the activity of NMES controller to regulate the resulting muscle contractions for an effective muscle force production (Collinger et al., 2013; Loeb et al., 1980; Ragnarsson, 2007). The following section discussed certain physiological signals related to the neuromuscular system for NMES feedback applications.

2.6 Major Biopotential Sources for NMES Feedback Applications

2.6.1 Electromyography

The robustness, optimization, and safety of the future NMES applications appear to be dependent on the system's sensitivity to the electrical stimulus-evoked muscle force and reduction of fatigue occurrence. To access muscle state information during NMES applications as well as subverting the influence of non-physiological muscle response to the NMES, researchers (Ewins et al., 1988; Ibitoye et al., 2016; Sinkjaer et al., 2003) have recommended the use of various biopotentials as feedback signal sources for NMES control applications. One such biopotential is surface electromyography (SEMG)—electrical event accompanying muscle contractions (Akataki et al., 2004; Disselhorst-Klug et al., 2009). The SEMG measured from an activated muscle during NMES-evoked contractions is termed evoked EMG (EEMG). The signal is the summation of the motor unit action potential of the muscle fibres within the vicinity of the EEMG electrode (Fuglevand et al., 1992).

Based on its relative magnitude in comparison with other relevant biopotentials including nerve signals (electroneurogram, ENG) (Haugland & Sinkjaer, 1995) and brain signals (electroencephalogram, EEG) (Wolpaw et al., 2000), EEMG signals seemed to be mostly explored and favored as a biopotential for NMES feedback applications. This may be due to the fact that the EMG is about a thousand times larger in amplitude than the EEG (Thakor, 1999), substantially larger in amplitude than ENG (Rahal et al., 2000) and therefore, less difficult to interpret. Additionally, EEG and ENG require more critical process before they could be deployed to interpret neuromuscular functions due to the low information transfer rate (Wolpaw et al., 2000), low signal to noise ratio (Rahal et al., 2000) and high sensitivity to the body movement artifacts, eye blink and heartbeat (Niedermeyer & da Silva, 2005; Thakor, 1999). However, EEMG reliability and ease-of-use as an indicator of muscle activities is disputable and this continues to preclude its application as a biopotential or biofeedback signal for NMES control applications (Hoffer et al., 1996; Yamaguchi et al., 2012).

Although an indirect estimation of muscle force/torque production has been traditionally assessed by EEMG (Merletti et al., 1992; Thompson et al., 2011), sensitivity of the signal to the external electromagnetic interference, variations in differential electrode positioning and skin impedance changes due to perspiration (Yamamoto & Takano, 1994) presents a significant limitation (Castellini et al., 2014; Orizio, 1993). Therefore, the reliability of EEMG estimation of muscle torque generation during NMES-evoked contractions is debatable (Popović, 2014).

Unlike voluntary EMG signals the EEMG signals summate the synchronously firing motor units, with increasing electrical stimulus-evoked motor unit activation, there is also limited sensitivity of EEMG as an indicator of motor unit synchronization which could be used to determine the rate of muscle force development (Semmler, 2002; Yue et al., 1995). This is partly due to the inherent problem of the stimulation artifact *i.e.* an electrical current of larger amplitude that saturates the EEMG amplifier (Merletti et al., 1992; Popović, 2014; Yamaguchi et al., 2012).

Therefore, the trend of the investigations in utilizing EEMG signals to assess NMES-evoked muscle performance generally showed that investigators had to trade-off (i) aesthetics or a compact design for a rather complex electrical circuit to remove stimulation artifacts and (ii) transcutaneous/surface electrodes for invasive percutaneous/implanted stimulation electrodes for useful parameters of EEMG signals or M-wave to be derived (Ibitoye et al., 2014).

Although there have been recommendations on the strategies to reduce the influence of the stimulation artifact, many adjustments required to the EEMG amplifier, as well as the complication of the artifact blanking process explain why investigators continuous to look beyond EEMG as NMES feedback signal source (Chesler & Durfee, 1997; Hoffer et al., 1996; Popović, 2014). Thus, estimation of NMES-evoked muscle force during fresh and fatigue contractions by EEMG alone is deficient (Hoffer et al., 1996; Levin et al., 2000; Vøllestad, 1997). An estimation of muscle force/torque from other relevant muscle characteristics *i.e.* biopotentials of muscle activation, particularly, from physical sensors has recently become, necessary, viable and attractive.

2.6.2 Mechanomyography

Another relevant biopotential that has been used to monitor neuromuscular activities is mechanomyography (MMG), a mechanical equivalent of the EMG (Beck et al., 2004; Gordon & Holbourn, 1948; Marek et al., 2005). As with emerging techniques, various terminologies have been used to describe MMG based on the characteristics of the sensor used for the signal acquisition, namely: accelerometermyography (Lammert et al., 1976), muscle sound (Oster & Jaffe, 1980), acousticmyography (Barry et al., 1985), soundmyography (Orizio et al., 1989), vibromyography (Keidel & Keidel, 1989), phonomyography (Maton et al., 1990), among other terminologies, before the adoption of mechanomyography at the CIBA Foundation (now known as Novartis Foundation) Symposium in 1995 (Orizio, 1993; Stokes & Blythe, 2001) as the signal is mechanical in nature (Beck et al., 2007). The MMG signal refers to any of these terminologies, in the present thesis.

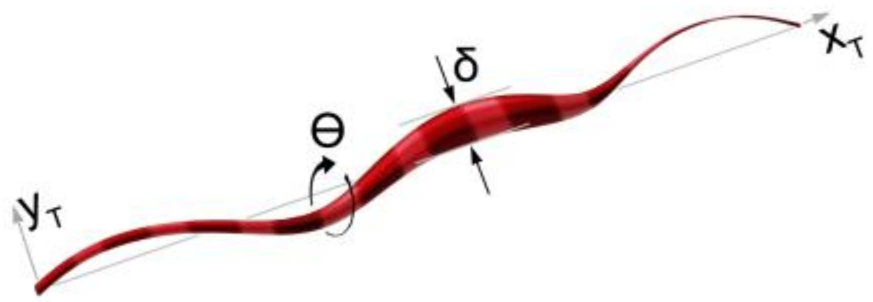

Figure 2.7: Basic principle of MMG generation during a muscle fibre contraction. Note that y_T, ɵ, and δ represent the lateral movement of the fibre, "axial twisting" as a variant of lateral vibration, and radial thickness in x_T direction, respectively. Reprinted with permission from Posatskiy (2011).

As a mechanical manifestation of muscle activation signals, evidence (Barry, 1987; Frangioni et al., 1987) suggests that the MMG signal is excited by "slow bulk movements of the muscle" fibre vibrations at the natural/ eigenfrequency of muscle or due to the pressure waves produced by muscle fibre dimensional changes (Orizio, 1993). Specifically, during "skeletal muscle contraction, the MMG is generated by three primary mechanisms (Figure 2.7): (i) a slow bulk movement of the muscle at the initiation of the contraction, (ii) smaller subsequent lateral oscillations occurring at the resonant frequencies of the muscle, and (iii) a pressure waves produced by dimensional changes of active muscle fibre" (Barry, 1987; Barry & Cole, 1990; Beck et al., 2007; Beck et al., 2004; Orizio, 1993).

Essentially, the MMG signal summates the activity of the muscle fibre's motor unit as each motor unit contributes to the pressure waves produced by the activated muscle fibres during muscle contractions (Orizio et al., 2003). The MMG measurement is predominantly captured by the lateral oscillation of muscle fibre during contraction (Akataki et al., 1999; Frangioni et al., 1987). The MMG signal may estimate MU activation strategy better than its "electrical counterpart" *i.e.* EMG (Akataki et al., 2004) as the formal propagates through soft tissues and may be richer in neuromuscular information pertaining to the activity of deeper muscles (Akataki et al., 2004; Orizio, 1993). The MMG signal can, therefore, be used to study the degree of motor units recruitment and their firing frequency (Orizio et al., 2003). Consequently, MMG is directly related to the two main force-generating mechanisms of human skeletal muscle—magnitude and pattern of motor unit recruitment and their firing rates/frequency (Beck et al., 2004).

MMG signal is commonly measured by a physical sensor such as an accelerometer (Orizio, 2004). It is interesting to note that unlike electromyography, the MMG signal is insensitive to electrical signal artifact (Yamaguchi et al., 2012) and impedance changes, and thus, suitable for muscle contraction measurements in the presence of electrical artifact noise, and could be subjected to a long time usage (Barry et al., 1986).

Currently, EEMG and MMG signals have been commonly used as control signal for NMES systems, but MMG signal modality has been gaining recent attention for its relevance for muscle activity detection for practical daily use "even in electrical noise" (Reza et al., 2005; Yamaguchi et al., 2012). For example, due to the convenience of MMG signal collection, its insusceptibility to skin impedance (Alves & Chau, 2010a), flexibility of its sensing technology (Ibitoye et al., 2014; Silva et al., 2005), and immunity from electrical stimulation artifacts associated with NMES (Orizio et al., 1999), the signal has been successfully used to classify muscle activity for specific application in controlling prostheses (Hong-Bo et al., 2009), and as a control signal for muscle machine interfaces (Barry et al., 1986; Silva et al., 2005).

Additionally, MMG acquisition requires a single point measurement averting the issues associated with the standardization of electrode spacing as needed for the common bipolar surface EMG configuration (Yamamoto & Takano, 1994). However, the muscle assessment and control applications of MMG signals have been mostly demonstrated under well-controlled laboratory conditions and in persons with intact neuromuscular function. There is a limited application of the signal in clinical settings and in persons with neuromuscular conditions.

Therefore, the use of the MMG signal as a reliable proxy of muscle force and fatigue during NMES contractions remains an open research question as several questions are unanswered. Considering the signal strength as earlier highlighted and if the signal's ability to track the muscle actions could be sufficiently validated in the research and clinical settings, there may be flexibilities in the applications of NMES technologies, with the ultimate goal of optimizing the utility of the technology. However, in order to utilize MMG as an NMES control signal, the signal features that reliably relate with muscle state are usually employed (Gobbo et al., 2006). The next session discussed the MMG measurement techniques and the extraction method of its predominant features in time and frequency domain.

2.7 Mechanomyography Measurement Techniques

The mechanical response of muscle fibre to contractions has been recently identified as a signature or indicator of the level of neural activation and a representation of muscle force production (Castellini et al., 2014). Such a mechanical response is related to the muscle surface oscillation or pressure waves generated by active muscle fibres' dimensional changes (Barry et al., 1986; Orizio, 1993). This oscillation has been referred to as the muscle MMG as the signal is a reflection of the mechanical activity of an activated muscle (Orizio, 1993). Essentially, the overall muscle dimensional changes due to the mechanical response of actin and myosin cross bridging formation following MU activation—for muscle force generation (Webb & Trentham, 2010) could be acquired in the form of MMG signal. As the MMG summates the motor unit contributions to muscle contractions (Orizio, 1993; Orizio et al., 1996), the signal has been used to study the motor unit activation strategies underlying muscle force modulation during low to high contraction intensity levels (Beck et al., 2004; Orizio et al., 1989).

During skeletal muscle contractions, the MMG signals may be acquired on the surface of the skin in the form of acceleration, vibration or sound signal (Orizio, 1993). Typically, the characteristics of a reliable MMG transducer/sensor includes the following: (i) high sensitivity in the muscle vibrational frequency range, *i.e.*, 1 Hz up to 250 Hz (Beck et al., 2005) and low sensitivity to random signals (noise); (ii) ease and standardization of the sensor attachment; (iii) biocompatibility and applicability in a clinical environment (Courteville et al., 1998), to mention only the major considerations. Although the MMG signals can be collected by a variety of physical sensors (Watakabe et al., 2003; Yungher et al., 2011), accelerometer-based sensors have been widely recommended due to their superior features, that have supported their suitability for integration into a neurostimulator, in comparison with other sensing modalities (Gobbo et al., 2006; Orizio, 2004).

To obtain MMG signals with acceptable integrity, the established technical guidelines used for the acquisition and processing of electromyograms are often adapted (Yuan-Ting et al., 1992). The uniformity of the MMG sensor's placement in relation to the intended signal site is crucial to ensure a reliable measurement. It has been previously demonstrated that different results may be obtained between trials if sensor position varies (Smith & Stokes, 1993). There is evidence (Frangioni et al., 1987; Stokes, 1993) that higher MMG signal magnitude/power could be collected over the muscle belly than the fascia at the muscle border or towards the tendon. This corroborates the significant relationship between the magnitude of the signal and the relative distance of the sensor from the muscle belly. However, there is an isolated report (Beck et al., 2009) on the high level of association between MMG signals collected with sensors' placement in different axis/plane on the same muscle. Therefore, MMG signal measurement in a single axis has been considered sufficient to interpret the neuromuscular activity during muscle contraction especially in a bipennate muscle such as "rectus femoris" (Beck et al., 2009).

Another consideration during MMG acquisition is ensuring the sensor firmness to the skin surface and contact pressure standardization to reduce the variability of the signal during repeated recordings (Smith & Stokes, 1993). The consistency of the signal response also depends significantly on the uniformity of the sensor location between trials and sensor firmness on the skin surface (Bolton et al., 1989). However, MMG signals are not influenced by changes in the skin impedance, and thus, may not require a rigorous skin preparation during acquisition (Alves & Chau, 2010a). Nevertheless, for an improved signal integrity, the standard practice for the signal acquisition may include the use of double sided adhesive tape to fix signal's sensor to the skin in order to ensure a constant pressure. Isolation of irrelevant muscles through an experimental setup on a standard testing device, such as a custom made or a commercial dynamometer, has been suggested to limit the effects of cross-talk and movement artifact (Beck et al., 2010).

In some experimental designs, investigators may seek a comparison between muscles, tasks and/or persons, thus, a normalization of the acquired signal has been recommended (Burden, 2010). This practice offsets the effect of inter-individual variability that may adversely influence the MMG signal integrity including differences in muscle mass, length, strength and the thickness of the tissue between the sensor and the participants' muscles. To eliminate the effect of these muscle variations, normalization to a reference level has been prescribed (Burden, 2010; Lehman & McGill, 1999).

Specifically, normalization constitutes a means of adjusting data to conform to a common scale for an objective averaging and analysis in order to validly compare between muscles, task and persons (Mathiassen et al., 1995). Moreover, normalization facilitates a comparison between electrode sites on the same muscle, two different muscles, and between test days (Lehman & McGill, 1999). Therefore, normalization is recommended to prevent erroneous conclusions especially if the test is meant to compare between trials, between electrode re-applications, between different muscles and persons (Burden, 2010).

In terms of the MMG signal collection, the cut-off frequency of the filter is flexible based on the type of sensor used, the muscle of interest and muscle action, but usually within 1 Hz and 250 Hz in most reported studies on human subjects (Beck et al., 2005). Theoretically, methodological and physiological concerns may dictate the signal sampling rate based on the site of the muscle of interest. A common compromise is to sacrifice the storage space for a high sampling rate during a signal acquisition process. A rule of thumb based on the Nyquist-Shannon sampling theorem goes thus; “for a reliable reproducibility and representation, a signal should be sampled at least twice the highest frequency content of the signal” (Shannon, 1949, 2001). This suggests that MMG signals should be sampled at least twice the highest recorded MMG signal frequency. However, the common sampling rate as found in the literature is 1000 Hz (1000 samples/s) or 2000 Hz (Cescon et al., 2008), presumably to check the aliasing effect which may be due to the hardware limitations.

Furthermore, oversampling enables a “sufficient accuracy of the MMG signals’ cross-correlation time measurements to detect a delay corresponding to the fastest transverse vibration in the muscular medium” (Ouamer et al., 1999). This approach has been used to demonstrate that MMG signal reflects the muscle response as a global resonant structure to the local fluctuations of pressure during voluntary contractions (Ouamer et al., 1999). However, if the concern is to select the highest possible sampling rate, there is usually a point at which sampling above a certain threshold has no additional advantage — “a point of diminishing return”. In order to save system storage, it is recommended that the sampling frequency is kept within the standard limits.

Taken together, a reliable MMG signal collection requires an appropriate selection of the signal analysis methods (Beck et al., 2005). As with other physiological signals’ collection procedures, it is equally pertinent that a clear and proper guide are given to the experimental participants in order to perform the experimental trials identically with each repetition through training and familiarization with the experimental protocols and equipment. As the MMG signals are inherently mechanical, the signal acquisition task may be facilitated because the signal can be collected without the need for a separate circuitry to eliminate the electrical noise interference in electrically stimulated contractions. Additionally, the signal acquisition may be performed with a single uniaxial electrode configuration unlike the simplest monopolar configuration of EMG (which is rarely used) with a separate reference electrode whereas bipolar and multipolar configurations of EMG require even more electrodes. These facts justify the reason for a simpler hardware requirements for MMG signal acquisition (Ibitoye et al., 2014; Silva et al., 2005) which in effect, may result in the cost effectiveness of the signal acquisition and processing (Fara et al., 2013; Silva et al., 2005).

2.8 Mechanomyography Parameters

2.8.1 Time Domain Parameters

One important feature of MMG is the time domain parameter or MMG amplitude characteristics. The quantification of the muscle force development (Orizio et al., 1989; Stokes, 1993), monitoring of muscle fatigue (Barry et al., 1985) and the examination of neuromuscular disorders (Orizio et al., 1997) have been widely delineated by the changes in the MMG time domain features which generally signifies changes in the motor unit recruitment during muscle contractions (Barry et al., 1985; Beck et al., 2004; Hu et al., 2007; Madeleine & Arendt-Nielsen, 2005; Orizio, 1993).

One important and predominant time domain feature of MMG is the root mean square (RMS) amplitude. Before the estimation of RMS amplitude from MMG signals, the digitally sampled and acquired time series MMG signal is rectified, smoothed and band-pass filtered (typically between 1 Hz and 250 Hz (Beck et al., 2005; Goldenberg et al., 1991; Smith & Stokes, 1993; Szumilas et al., 2015) depending on the type of sensors used, the need for muscle tremor reduction and the level of signal conditioning required) by a Butterworth filter. Butterworth filter has been commonly used for this purpose as it provides a good compromise between the attenuation and phase response by providing a "maximally flat magnitude response in the pass-band" (Fara et al., 2013; Murphy et al., 2008). Furthermore, in comparison with other common filter types, the pulse response of Butterworth filters is better than that of Chebyshev filters and its attenuation rate is better than that of Bessel filters (Fara et al., 2013; Murphy et al., 2008). These probably make Butterworth filter more suitable for use in MMG signal processing.

The RMS amplitude of MMG (MMG-RMS), as a measure of the magnitude of the varying value, is the square root of the mean square value defined for a specific time interval, T in secs. An important objective of RMS amplitude calculation is to obtain indices of muscle force (Sarlabous et al., 2013). Specifically, the amplitude of the MMG signal depends on the muscle fibre activations under tension (Watakabe et al., 2001), and it increases with increasing muscle force/effort based on the contraction level (Fara et al., 2013).

Thus, the signal amplitude may provide information on the level of muscle activation that may be required for functional tasks (Beck et al., 2005). The RMS feature of MMG correlates with muscle effort (Alves & Chau, 2010b) and has been used to estimate the level of muscle force/torque production (Lei et al., 2011). For example, Akataki et al. (2004) demonstrated an estimation of motor unit activation strategy underlying force generation by utilizing the MMG-RMS. Therefore, there is a significant relationship between the muscle force and MMG-RMS that may explain why MMG-RMS has been considered as the most reliable and useful parameter in the time domain (Basmajian & De Luca, 1985).

The commonly reported patterns of relationships between MMG-RMS amplitude and muscle force/torque production have been a parallel increase up to: 100% maximum voluntary contraction (MVC)/ effort (Beck et al., 2004; Coburn et al., 2005); and MMG amplitude reduction from 60-80% MVC to 100% MVC (Coburn et al., 2004; Maton et al., 1990; Orizio et al., 2003) due to a profound plateau or reduction in the muscle stiffness and the associated muscle force fusion—a manifestation of muscle mechanical changes during contraction (Orizio, 1993; Yoshitake et al., 2002). These patterns of relationships depend mainly on the type of muscle fibre and nature of muscle contractions/actions (Beck et al., 2005). In general, there have been consistent reports on the reduction or plateau in the response of MMG amplitude characteristics at high contraction intensity starting from around 60-80% MVC which has been suggested to be due to the fusion of muscle fibre or the effect of high contraction rate that reduces the MMG signal amplitude (Orizio, 1993; Yoshitake et al., 2002). This shows that MMG amplitude could be used to monitor MU recruitment strategy as the submaximal and maximum recruitment of MU could be monitored by the MMG signal amplitude.

Another important MMG amplitude characteristic is the peak-to-peak amplitude (MMG-PTP). The MMG-PTP is one of the metrics of the signal amplitude representing the distance between the signal’s peak or highest amplitude value and the trough or lowest amplitude value. Although not commonly used for a time series amplitude representation in MMG research, MMG-PTP has been adopted by a few isolated MMG studies (Gobbo et al., 2006; Orizio et al., 1999; Petitjean et al., 1998) where the variable was applied to monitor the changes in mechanical properties of a muscle during fatiguing voluntary (Orizio et al., 1999) and electrically-evoked contractions (Gobbo et al., 2006; Petitjean et al., 1998). For example, a consistent decrease or lack of recovery in the value of MMG-PTP amplitude has been used to indicate the reduction of muscle force during the period of stretching (Esposito et al., 2011), sustained contractions or muscle fatiguing contractions (Gobbo et al., 2006; Orizio et al., 2003).

Therefore, MMG amplitude could be used to monitor the persistent changes in the viscoelastic characteristics of muscle or series elastic component (tendon) which is manifested as the reduction in the force-generating capacity of a muscle, in particular, during muscle activity involving high level of contractions (Esposito et al., 2011) such as in fatiguing contractions. This relationship could be used to infer important characteristics about muscle tendon unit stiffness during voluntary or electrical stimulus strengthening exercise (Esposito et al., 2011). Additionally, as muscle fatigue has been described as a manifestation of the motor-neuro excitation failure or a reflection of the "impairment in the action potential propagation" (Sharma, Patre, et al., 2009), this evidence suggests that MMG amplitude could provide an important information on the muscle activation strategy during incremental voluntary or electrical stimulus-evoked fatiguing contractions (Orizio et al., 1999).

2.8.2 Frequency domain parameters

As some useful information in the MMG signal may not be ordinarily evident in time domain, frequency domain analysis of the signal has been suggested (Beck et al., 2004; Orizio et al., 1992). Different patterns in the spectral analysis during muscle contractions have been reported during various types of muscle actions (Beck et al., 2004). A shift in the frequency feature of MMG has been generally used to monitor muscle fatigue development and track the associated muscle activation pattern (Beck et al., 2007; Orizio et al., 1999). The magnitude of the changes is dependent on the type of muscle action, *i.e.*, dynamic (eccentric or concentric) or isometric (maximal or submaximal effort) and muscle mechanical characteristics including intramuscular fluid pressure and muscle stiffness (Beck et al., 2007). The measure of the magnitude and pattern of the MMG's spectral shift (compression or expansion) has been demonstrated (Beck et al., 2004; Orizio et al., 1992) by the frequency characteristics of the signal including peak frequency (PF), mean power frequency (MPF) and median frequency (MDF) (Beck et al., 2007; Orizio et al., 1990).

During voluntary contraction, the MPF is the most widely used frequency feature of the MMG signal compared to the PF and MDF. This is because the MPF is less affected by the method of analysis (Figini & Diemont, 1989; Stokes, 1993). Therefore, MPF has been an important metric for examining the mechanical changes underlying muscle contractions (Diemont et al., 1988). However, investigators (Yoshitake & Moritani, 1999) have also continued to explore the use of PF for the analysis of muscle response during electrical stimulus contractions. This may be due to that fact that the electrical stimulus contraction recruits motor unit synchronously (Orizio, 1993) and there seems to be no effect of incremental stimulation intensity on the MMG frequency content especially during unfused muscle contraction level (Yoshitake & Moritani, 1999).

Generally, the frequency content of the MMG signal reflects changes in the global firing rate of an unfused activated motor unit during muscle contractions (Ryan et al., 2008). Specifically, the frequency of MMG is closely related to the firing rates of the active motor units during voluntary (Esposito et al., 1996; Yuan-Ting et al., 1992) and NMES-evoked muscle contractions (Stokes & Cooper, 1992; Yoshitake & Moritani, 1999). While there are other domains for MMG signal analysis, this thesis limits the literature discussion to only the time and frequency domains analyses of MMG signal as these are the domains used in the present investigation. However, as MMG signal characteristics are insufficiently understood (Hu et al., 2007) in some of their area of potential applications, one such promising area is their application as a feedback signal for NMES systems.

2.8.3 Potentials of Mechanomyography as an NMES Feedback Signal

Although the potential use of MMG signal as a proxy of muscle force/ joint torque for NMES feedback applications has been poorly understood, the fact that the signal summate the muscle fibre twitches following NMES-evoked contractions has been well established (Barry, 1992; Orizio et al., 2003; Orizio et al., 1996). Given the complexity of the NMES-evoked recruitment of motor units, it is pertinent to investigate whether MMG signal could be a satisfactory representation of muscle force that has been evoked by electrical stimulation, with acceptable reliability. However, this may not be the only requirement for a signal to be a proxy of NMES-evoked muscle force as there is a need for the signal to be able to provide sensory information regarding muscle force modulation. In line with these requirements, the MMG signal has been suggested to be directly related to the two main muscle force-generating mechanisms; the magnitude and pattern of motor unit recruitment and their firing rates/rate coding (Beck et al., 2004).

Interestingly, by means of an electrical stimulation evoked muscle contractions, the generated MMG signal could be used to assess contractile properties of muscle fibre's motor unit (Orizio et al., 1997). This information may be useful to optimize the NMES-evoked contraction of a healthy, paretic or paralyzed muscle. An implementation of which could be through a feedback of muscle fibre contractile/muscle state information to the NMES system in order to automatically regulate the generated muscle force (Gobbo et al., 2006; Kimura et al., 2004). By this strategy, the pattern of neural activation of muscle force modulation could be tracked and used to efficiently modulate the NMES-evoked muscle force.

Additionally, being within the continuum of effective muscle contractions, muscle fatigue, a reflection of the inability of a muscle to sustain the required force or exercise intensity for a muscle action (Edwards, 1983; Fitts, 1994), may also be regulated by means of the muscle response feedback signal—MMG. This is clinically useful during sustained contractions of lower limb muscles such as in NMES supported knee extension exercise or standing where muscle fatigue may be evident within the first 60 sec of contractions (Thrasher & Popovic, 2008). Therefore, MMG has been identified as a good indicator of fresh and fatigued contractions as the signal could be used to monitor the mechanical changes during motor unit activation (Esposito et al., 1998; Orizio et al., 2003).

This knowledge is particularly useful in muscle force or joint torque control applications in NMES-assisted lower limbs rehabilitation as the control strategies that have been widely used have relied on external joint angle sensors or accelerometers (Peckham & Knutson, 2005). The investigation on the integration of sensors for NMES control is, therefore, an active area of research. This has been feasible by the recent progress in the development of control algorithms that allows an automated administration of the NMES systems (Peckham & Knutson, 2005).

As it is easy to measure and useful as a proxy of muscle force, MMG signal is potentially relevant as a modulating and control signal for NMES feedback applications (Gobbo et al., 2006). Additionally, the simplicity of the surface measurement and processing of MMG signal without the influence of stimulation artifact is another excellent advantage for the application of the signal as NMES feedback signal source.

Moreover, both the muscle force and MMG are mechanical output generated during muscle contractions. However, the predictive accuracy of MMG signals for NMES evoked muscle force, which is required for practical NMES systems, remains poorly investigated. As the MMG signal is a "summation of the mechanical activity of active muscle fibres" (Orizio et al., 2003), the summation may not be simple over the entire physiological range of muscle contractions (Orizio et al., 1996). This is mainly due to the development of fused contractions, in particular, during high contraction intensity (Yoshitake et al., 2002). On this basis, the problem associated with the signal pattern that may characterize the muscle response during electrical stimulus contractions (Crago et al., 1980; Durfee & Palmer, 1994; Rabischong & Chavet, 1997) warrants an application of a machine learning technique (Youn & Kim, 2010) for muscle force/ joint torque estimation from MMG signals.

2.9 Machine Learning Methodology

The application of machine learning or computational intelligent approach has been proposed for muscle force or joint torque estimation or prediction from other readily available muscle contraction signals as a direct and noninvasive measurement of muscle force is impractical (Erdemir et al., 2007). Based on the recent advancement in computer software applications and signal processing, a machine learning method uses developed algorithms by utilizing empirical data from sensors or databases to enable systems to generate programs or behaviors of themselves for estimation or prediction tasks (Al-Mulla et al., 2011).

Basically, a good machine learning method in a particular field of study is known to have an excellent estimation or predictive accuracy and a fast computational time for online implementation (Ameri et al., 2014). One example of machine learning algorithm which has increasingly been applied based on its strengths (Meyer et al., 2003; Vapnik et al., 1997) in medical applications (Ameri et al., 2014) is support vector machine through its extensions *i.e.* support vector regression and classification (Noble, 2006). As applied to the present thesis, an overview of the support vector machine methodology is discussed hereunder.

2.9.1 Support Vector Machine

Support vector machines (SVM) are based on the framework of statistical or supervised learning theory (Smola & Schölkopf, 2004; Vapnik, 1999a). Through training or learning by several examples, the SVM uses an algorithm to develop a model and by recognition of what has been learnt following the training, the algorithm can be used to solve a classification, prediction or estimation task. Although to the author's knowledge, SVM has not been previously used to estimate NMES-evoked muscle force, a related study (Ameri et al., 2014) on voluntary muscle contractions suggested that the technique could be applied to predict muscle force that is produced through electrical stimulus contractions. This view was supported by the fact that the SVM algorithms could be easily applied to perform various numerical computations (Smola & Schölkopf, 2004) including regression related tasks (Wu et al., 2007; Xue et al., 2009).

In order to implement SVM algorithm on a data instance with an input dataset (x), the mapping of the dataset is performed by projecting it by a function into a higher dimensional feature space $\phi(x)$ (Ameri et al., 2014). This process allows a linear estimation of the regression function $f(x)$ using the standard regression equation 2.1:

$$f(x) = w.\phi(x) + b \tag{2.1}$$

Where b denotes the "bias term" or "offset" which may be neglected following data preprocessing, w represents "weight vector" while the input data can be multivariate (Ameri et al., 2014; Cherkassky & Ma, 2004).

The solution of the optimization problem (described in detail in Chapter 3, equation 3.3 to 3.10) could explain how SVMs typically solve a regression problem and minimizes the estimation error. Based on this solution, the basic illustration of a standard SVR as applicable to the present thesis is as shown in Figure 2.8. The Figure illustrates the SVR methodology and specifically shows that the effect of errors may be unimportant once they are within ε-insensitive loss function zone. Additionally, the deviations are linearly penalized as revealed in the loss function graph, in which case the "Loss" serves as the "penalty" for deviations larger than ε (*i.e.*, data point outside allowable ε) using a non-negative slack variable ξ_i which represents upper and lower constraints on the system output (Granata et al., 2016; Yu et al., 2006).

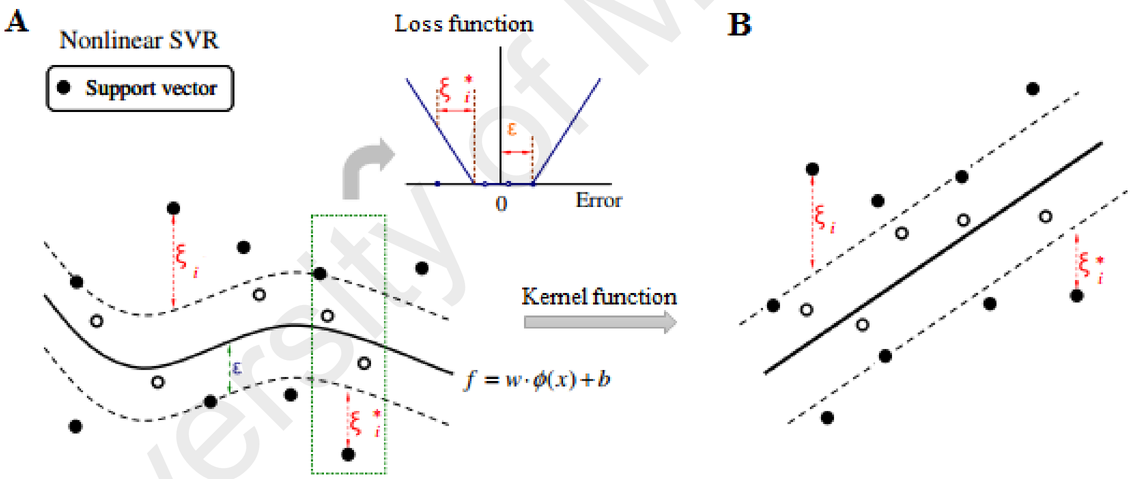

Figure 2.8: SVR methodology illustrated.
Adapted with permission from Yu et al. (2006).

For a non-linearly separable data in the input space, the idea of kernel function which represents "a dot product in some feature space" (Statnikov et al., 2011) has been introduced to transform such data into the feature space where the data could be linearly separable (Smola & Schölkopf, 2004). A description of such concept of SVR has been shown in Figure 2.8. Typically, the SVR projects a dataset from an original low-dimensional to a high-dimensional feature space (Noble, 2006) through some non-linear mapping selected *a priori* (Vapnik, 1999b)—kernel function through "kernel trick". This permit a construction of a linear model in the feature space (Figure 2.8B). Thus, the process allows the construction of an optimal separating hyperplane (Vapnik, 1999b) between classes of datasets in classification problems. However, in a support vector regression analysis problem, such a linear hyperplane is required to correlate the multi-dimensional input data points or support vectors to the output data points for an estimation or a prediction task to be performed.

The idea of ε-insensitive loss function introduced by Vapnik (1995) allows the SVM to be extended to support vector regression (SVR) (Smola, 1996), specifically, to solve regression or estimation problems (Fernandez, 1999), including those related to clinical estimation and predictions (Ameri et al., 2014). Essentially, the value of ε-insensitive loss function influences the number of support vectors that is used to construct a regression/predictive learning function (Cherkassky & Ma, 2004). The function measures the quality of an estimation (Vapnik et al., 1997) by controlling the "width of the ε-insensitive zone that is used to fit the training data" (Cherkassky & Ma, 2004; Vapnik, 1998). Together with the regularization parameter (C) (which is another user-defined parameter that indicates the tradeoff between the function's flatness and the amount of permitted error beyond ε- insensitive zone (Gupta, 2007)), ε determine the complexity of a regression model (Cherkassky & Ma, 2004).

Therefore, the selection of user-defined parameters including best kernel function $K(x_i, x_j) = \langle \phi(x_i).\phi(x_j) \rangle$ (Smola & Schölkopf, 2004) for a specific problem, to obtain a good generalization performance, is not normally direct and determines the performance of an SVR model (Cherkassky & Ma, 2004). Investigators (Noble, 2006; Smola & Schölkopf, 2004) have suggested many approaches such as "a statistically rigorous" method of using cross-validation for optimal selection of kernel parameters.

According to Vapnik (1999b), any function that obeys Mercer's condition can be used as a valid kernel function. A list of commonly applied kernel function is a shown in Table 2.2.

Table 2.2: Common kernel functions.

Kernel type $K(\overrightarrow{x_i} \cdot \overrightarrow{x_j})$	**Mathematical representation**
Linear	$\overrightarrow{x_i} \cdot \overrightarrow{x_j}$
Polynomial	$(\overrightarrow{x_i} \cdot \overrightarrow{x_j} + 1)^d$
Gaussian (RBF)	$\exp\left(-\gamma \left\Vert \overrightarrow{x_i} - \overrightarrow{x_j} \right\Vert^d \right)$
Sigmoid	$\tanh(\gamma \overrightarrow{x_i} \cdot \overrightarrow{x_j} + r)$

Where, γ, r, and d are kernel parameters.

Therefore, the SVR modelling has been judged a viable alternative prediction or estimation technique in comparison with both the traditional and other computational intelligence modelling methods (Meyer et al., 2003; Osuna et al., 1997) even with a small dataset (Zhao et al., 2015). For example, a recent evidence (Pochet & Suykens, 2006) also suggested that SVR outperformed the traditional logistic regression model showing a better generalization and higher performance in estimation or prediction tasks. In medical related prediction applications, for example, SVR has been reported with a better performance, as compared to multivariate linear regression, for prediction of tacrolimus blood concentration in patients with liver transplant (Van Looy et al., 2007), and as compared to an artificial neural network modelling for "simultaneous myoelectric control of multiple degrees of freedom in some upper limb muscles" activities (Ameri et al., 2014) at a computational speed that is useful for a real-time applications. In all, the uniqueness of the datasets used in the present study, based on the SCI participants as well as the area of application, is meant to advance the application of SVR modelling technique in the biomechanics research and in the rehabilitation of clinical populations.

2.10 Summary

This Chapter has reviewed the literature on muscle responses following a SCI and the NMES rehabilitation intervention that is often recommended. Furthermore, the Chapter highlighted the limitation of the NMES technology. Specifically, the application of NMES for lower limb rehabilitation as applied to the present thesis was also discussed to gain a useful insight into the limitation of the current NMES technologies. Major NMES feedback signal sources including EEMG and MMG were discussed with more attention to MMG due to its relevance to the main objective of the thesis. As the MMG signal has been recently promoted as a potential non-invasive and electrical stimulation artifact-free NMES feedback signal source, the synthesis of the available knowledge on the potential use of the signal as a feedback source was also presented. Furthermore, the Chapter discussed the useful parameters of the MMG signal that could be used to intelligently estimate muscle force using a SVR model.

Taken together, it could be inferred from the literature that there is a clear need for a reliable proxy of muscle force for implementation of a closed-loop NMES system—believed to promote the NMES technology among the clinicians and other allied professional administering the technology as a treatment option in rehabilitation. On this premise, the next Chapter (i.e. Chapter 3) is aimed at establishing the pattern of relationship between MMG signal responses and NMES-evoked muscle force/torque in healthy volunteers.

CHAPTER 3: DEVELOPMENT OF A HYBRID PROCEDURE TO ESTABLISH MECHANOMYOGRAPHY AS A PROXY OF NMES-EVOKED TORQUE

3.1 Introduction

This study sought to elucidate specifically the relationship between mechanomyographic (MMG) signals and torque production and to verify whether the motor unit activation strategy (recruited motor unit and their firing rates) could be tracked using MMG characteristics during incremental neuromuscular electrical stimulation (NMES)-evoked isometric contractions in healthy volunteers. The rationale for this study was that MMG signal measures muscle surface oscillation, due to the recruited muscle fibre's motor unit. This was based on the knowledge that electrically stimulated muscle contractions allows one to measure and analyze the MMG signal generated in a controlled settings as the contractions is mainly based on a "synchronous" recruitment of motor unit (Orizio et al., 2003).

This Chapter describes a method for NMES-evoked isometric torque assessment in healthy volunteers. Thereafter, an estimation of the knee torque from quadriceps muscle's MMG was demonstrated in eight healthy volunteers. The study described in this Chapter is being reproduced under the open access license from a published article by the author:

Ibitoye, M. O., Hamzaid, N. A., Abdul Wahab, A. K., Hasnan, N., Olatunji, S. O., & Davis, G. M. (2016). Estimation of Electrically-Evoked Knee Torque from Mechanomyography Using Support Vector Regression. *Sensors*, *16* (7), 1115.

While the preliminary finding from this study was accepted for an oral presentation at an IEEE Engineering in Medicine & Biology Society (EMBS) International Student Conference (ISC) 2016, Carleton University, Ottawa, Canada.

3.2 Literature Review

The magnitude of the muscle force or joint torque generated during NMES-evoked contractions has been used as a marker of physical performance in healthy volunteers (Brocherie et al., 2005; Parker et al., 2003), as well as a benchmark of functional recovery in persons with neurological conditions (Braz et al., 2009; Deley et al., 2015). To optimize NMES technology in therapeutic and functional applications, real-time information about the generated muscle force or joint torque, of the controlled limb, is vital (Braz et al., 2009; Popović, 2014). Such information is required; (i) to automate the neuromuscular stimulation characteristics based on the muscle state during the onset of fatigue, and (ii) to modulate muscle forces based on the requirements of the task (therapeutic or functional) to be performed, for example during sit-to-stand and sustained standing perturbations. However, joint torque is often impractical or impossible to quantify directly during real-time application of NMES (Popović, 2014). Estimation of joint torque from readily available muscle characteristics (e.g., biopotentials of nerve and/or muscle activation), particularly, from physical sensors has recently become both viable and attractive (Popović, 2014).

One such neuromuscular biopotential is mechanomyographic signal (MMG), which quantifies the mechanical equivalent of an electromyographic output generated during muscle contractions (Orizio, 1993). The signal originates from the skeletal muscle contractions due principally to the shortening of the muscle fibre length and an increase in its diameter (Farina et al., 2008). The activation of muscle fibres and their dimensional changes during muscle contractions creates pressure waves that can be detected on the skin surface and translated into an acceleration obtained by physical sensors, such as an accelerometer (Watakabe et al., 1998). The signal can reflect the extent of neuromuscular contractions (Yuan-Ting et al., 1992) and has gained recent popularity due to its close relationship with muscle force (Beck et al., 2004; Matheson et al., 1997). Specifically, the signal is directly related to the two main force-generating mechanisms of human skeletal muscle—magnitude and pattern of motor unit recruitment and their firing rates/frequency (Beck et al., 2004; Youn & Kim, 2010).

Moreover, due to the convenience of MMG signal collection, its insusceptibility to skin impedance (Alves & Chau, 2010a), flexibility of its sensing technology (Ibitoye et al., 2014; Silva et al., 2005), and immunity from electrical stimulation artifacts associated with NMES (Orizio et al., 1999), the signal has been successfully used to classify muscle activity for specific application in controlling prostheses (Hong-Bo et al., 2009), and as a control signal for muscle machine interfaces (Barry et al., 1986; Silva et al., 2005). In addition, during NMES-evoked muscle contractions, MMG signal has been used to track muscle fatigue in healthy volunteers (Gobbo et al., 2006). Thus, the signal may be used to estimate muscle force during voluntary and NMES-evoked muscle contractions (Ibitoye et al., 2014).

However, relating MMG signals as a direct proxy for NMES-evoked muscle force can be practically challenging due to the complexity and diversity of the recruitment of muscle's motor units (Hong-Bo et al., 2009; Orizio, 1993). Accordingly, the application of computational intelligence or machine-learning techniques for quantification of muscle force via joint torque from MMG signals has been proposed through statistical predictive modelling, and then validated during voluntary contractions (Xie et al., 2009; Youn & Kim, 2010).

The use of machine-learning techniques has recently shown promise in estimation, prediction and classification tasks. For example, Youn and Kim (2010, 2011) used an artificial neural network (ANN) model to estimate elbow flexion force from MMG during voluntary isometric contractions. The investigators obtained an estimation accuracy of up to 0.892 (Youn & Kim, 2010) and 0.883 (Youn & Kim, 2011) in terms of cross-correlation coefficient, and suggested the future application of other machine learning techniques including Support Vector Regression (SVR) for probable improvement of their model's estimation accuracy (Youn & Kim, 2011).

However, due to the advancement in the field of signal processing, several other computational intelligence regression techniques have been proposed with SVR yielding a good predictive and estimation accuracy, with often low Root Mean Square Errors (RMSE) (Shamshirband et al., 2014) and outstanding performance (Xie et al., 2009). Being an extension of a support vector machine learning technique, SVR is based on the principles of computational intelligence modelling that is built on the kernel method, whereby data are mapped into a higher dimensional space in order for the training dataset to be linearly separable to facilitate the regression analysis (Vapnik et al., 1997). SVR algorithms take into account the error approximation to a dataset with the ability to adapt and improve the estimation capability of a model (Shamshirband et al., 2014), particularly when the model is used to evaluate an additional dataset for the purpose of generalization (Jiang & He, 2012; Yang et al., 2009).

Moreover, SVR is robust in handling multivariate processes and offsets the limitation of traditional regression methods (Yu et al., 2010)—which cannot solve problems with high dimensional input dataset (Vapnik et al., 1997). Additionally, the SVR modelling only involves a solution to a "convex optimization problems", and unlike ANN model, it is not influenced by the "local minimal problem" (Ziai & Menon, 2011) and the network structure needs not to be defined (Shamshirband et al., 2015). Thus, the SVR algorithms could be used to build a generalized model and well suited for regression tasks (Vapnik et al., 1997). Based on these strengths, the technique has been successfully deployed in several fields of applications including physical therapy and rehabilitation engineering during voluntary muscle activation (Xie et al., 2009), medical diagnosis (GÜler & Koçer, 2005), and a host of other related fields. However, to the author's knowledge, SVR modelling has not been previously used to construct a joint torque estimation model, particularly, during electrically stimulated contractions.

The purpose of this study was, therefore, to apply SVR modelling to predict knee extensor torques from MMG signal characteristics during NMES-evoked incremental muscle contraction intensities. Since it has been suggested (Youn & Kim, 2010) that a combination of muscle contraction signals and related characteristics could compliment the estimation accuracy of joint torques, the input parameters (related to the muscle contractions) to the SVR model were chosen (MMG signals, level of electrical stimulation or contraction intensity, and knee angle) to estimate knee torque accurately. This information is particularly applicable to research areas where a real-time proxy of muscle force is sought.

3.3 Materials and Methods

3.3.1 Experimental Protocol

To validate the performance of the proposed SVR model, a calibrated commercial dynamometer (System 4; Biodex Medical System, Shirley, NY, USA) was used to record isometric knee torques produced by NMES-evoked muscle contractions of the knee extensors (Figure 3.1). Eight healthy male volunteers aged 23.4 (1.3) year (mean (SD)), body mass 70.4 (5.9) kg and height (1.72 (0.05)) m participated in this experiment. All participants were in good physical condition and were duly informed about the study protocol prior to giving their consents (see Appendix D or E). The study was approved by the University of Malaya Medical Ethics Committee (Approval No: 1003.14 (1)) as detailed in Appendix A.

As portrayed in Figure 3.1, the participants were set-up, as has been previously described by Brown and Weir (2001) for voluntary isometric knee torque measurements.

The dynamometer seat was adjusted so that each participant's lateral femoral condyle was aligned with the axle of the dynamometer (Bickel et al., 2004). To ensure consistency of body position and dynamometer lever arm, and for subsequent trials, notes were taken of each participant’s relevant anatomical positions.

Figure 3.1: Experimental set-up at 90° knee angle.
The set-up shows an arrangement of stimulation electrodes A cathode, B anode of Neuromuscular Electrical Stimulation, and C mechanomyographic signal sensor in a representative healthy participant.

3.3.1.1 NMES-Evoked Muscle Contractions and Knee Torque Measurements

A familiarization session, mimicking the actual test, preceded data collection to familiarize the participants to the study protocol and to habituate them to NMES-evoked knee extensors muscle contractions of maximally tolerable intensity. Thereafter, NMES of square-wave pulses at 30 Hz frequency and 400 μs pulse duration, and incremental current amplitude from 20 mA to 80 mA (in 10 mA increments; *i.e.*, seven different intensities of NMES or trial levels) was administered to elicit isometric torque of the knee extensors lasting 4 s (Orizio et al., 1992). Stimulation pulses were delivered through a commercial computer-controlled neurostimulator (RehaStim™, Hasomed GmbH, Magdeburg, Germany) using 9 × 15 cm^2 self-adhesive electrodes (Hasomed GmbH, D 39114, Magdeburg, Germany) on the dominant lower limb (Adams et al., 1993).

To preclude voluntary effort, the participants were carefully instructed not to assist or resist NMES-evoked muscle contractions. A similar stimulation protocol has been used for strength training with tolerable discomfort (Selkowitz, 1985) and without eliciting rapid muscle fatigue (Babault et al., 2001). During each trial, the NMES-evoked torque at maximum stimulation intensity (80 mA) was taken as the maximum NMES-evoked peak torque (PT).

The PT value was used to normalize the submaximal contraction levels across participants' data. The adopted stimulation electrode position has been recommended by Levin et al. (2000)—the anode electrode placed at "~ 5 cm proximal position to the patella and the cathode electrode at ~ 8 cm distal to the inguinal area over the rectus femoris (RF) muscle belly near the expected location of the motor points" (Figure 3.1). In order to accommodate the effect of joint angle on the magnitude of joint torque (Ebersole et al., 1998; Selkowitz, 1985), the experiment was conducted at three different randomized knee angles: 30°, 60°, and 90° (where 0° represented full knee extension). A duration of 48 h was allowed between each angle position, and there was a 10 min recovery between each trial to minimize potential muscle fatigue.

3.3.1.2 MMG Acquisition and Processing

Simultaneous with the NMES-evoked torque, MMG signals were collected using an accelerometer-based sensor (Sonostics BPS-II VMG transducer, sensitivity 50 V/g). As shown in Figures 3.1 and 3.2, the sensor was attached directly to the muscle belly (*i.e.*, at the midpoint between the inguinal crease and the superior border of the patella (Ryan et al., 2008) by means of double-sided adhesive tapes (3M Center St. Paul, MN, USA). The MMG signals were collected from the RF muscle as a simple representation of the knee extensors and a major contributor to the NMES-evoked knee torque production (Shinohara et al., 1998). The signals were collected at 2 kHz sampling frequency and were digitally band-pass filtered at 20–200 Hz (Goldenberg et al., 1991), amplified and stored by AcqKnowledge data acquisition and analysis software (MP150, BIOPAC Systems Inc., Santa Barbara, CA, USA) for offline analysis in the LabVIEW software environment (version 12.0, National Instruments, Austin, TX, USA) using custom written programs.

The peak torque values, MMG-root mean square (RMS) and peak to peak (PTP) amplitudes were obtained during NMES-evoked isometric contractions from 2 s epoch of the 4 s MMG and torque recordings (Katsavelis & Threlkeld, 2014) at each contraction level across the three joint angles. The selected 2 s epoch of the signals coincided with the middle position at which there was probable maximum muscle recruitment, without on-transients or off-transients due to rise in force at the beginning and the end of muscle contractions, respectively (Katsavelis & Threlkeld, 2014).

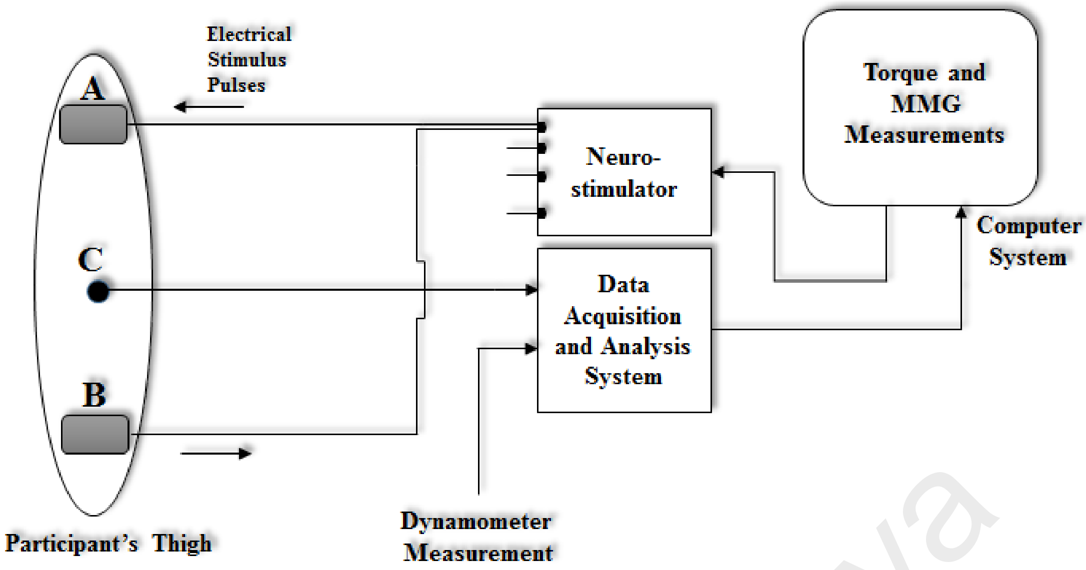

Figure 3.2: Schematic representation of the experimental setup. Stimulation electrodes (A) cathode, (B) anode NMES electrodes, and (C) MMG sensor.

To improve the model performance (Bray & Han, 2004), the MMG signals at each contraction level were normalized (by the equivalent value of the MMG signal at the highest stimulation intensity/ contraction level (80 mA)) and fed into the proposed SVR model for training. Previous investigations (Beck et al., 2004; Orizio, 1993) have validated the legitimacy of these MMG features for muscle force assessment, and, therefore, they were equally used as joint torque predictors in this study.

3.3.2 Support Vector Regression Modelling Approach

SVR algorithm was proposed in this study because of its optimal predictive performance even with a small dataset (Shin et al., 2005) and the ability to learn both linear and non-linear relationships between predictors and outcome variables. Such relationships have been used in establishing a pattern whereby unknown outcomes could be predicted accurately (Vapnik et al., 1997; Xie et al., 2009). Theoretically, SVR is derived from the statistical learning theory (Burges, 1998; Cortes & Vapnik, 1995) and employs ε-insensitive loss function (Vapnik et al., 1997) which measures the flatness of the generated pattern as well as maximum allowable deviations of the targets from the predicted values for all given training datasets $(x_1, y_1), ..., (x_k, y_k)$ with k number of samples (Gupta, 2007).

However, a function used for the SVR analysis should not only approximate the training data adequately but also predicts accurately the value of y for the future data x (Yang et al., 2009) for the purpose of generalization. Such a function, with $\langle w, x \rangle$ dot product in the space of R', is represented in linear form by Equation (3.1) for a set of training samples.

$$f(x,\alpha) = \langle w, x \rangle + b \tag{3.1}$$

where $w \in \boldsymbol{R}'$ and $b \in \boldsymbol{R}$

To establish the goal of SVR in ensuring the flatness of the Equation (3.1), small value of w is desired through minimization of the Euclidean norm $\|w\|^2$ (Smola, 1996) which makes the optimization problem of the regression to be governed by Equation (3.2):

$$\begin{aligned} &\text{minimize } \frac{1}{2}\|w\|^2 \\ &\textit{subject to} \begin{Bmatrix} y_i - \langle w, x_i \rangle - b \le \varepsilon \\ \langle w, x_i \rangle + b - y_i \le \varepsilon \end{Bmatrix} \end{aligned} \tag{3.2}$$

Equation (3.2) holds on the assumption (Pal & Goel, 2006) that there exists a function that is capable of providing error which is less than ε for all training pairs of the dataset. The slack variables $\left(\xi_i \text{ and } \xi^*_{\ i}\right)$, which represent the upper and lower constraints on the system output, are often introduced in order to permit some errors that are associated with real life problems (Burges, 1998; Pal & Goel, 2006). Therefore, Equation (3.2) is modified and presented as Equation (3.3).

$$
\begin{aligned}
&\text{minimize } \frac{1}{2}\|w\|^2 + C\sum_{i=1}^{k}\left(\xi_i + \xi^*_i\right) \\
&\textit{subject to} \begin{cases} y_i - \langle w, x_i \rangle - b \leq \varepsilon + \xi_i \\ \langle w, x_i \rangle + b - y_i \leq \varepsilon + \xi^*_i \\ \xi_i, \xi^*_i \geq 0 \quad \text{for all } i = 1, 2, \ldots\ldots, k \end{cases}
\end{aligned}
\tag{3.3}
$$

The regularization parameter *i.e.* C is one of the user-defined parameters and also indicates the tradeoff between the function's flatness and the amount of permitted error beyond ε- insensitive zone (Gupta, 2007). The optimization problem in Equation (3.3) is better solved, through the ε-insensitive loss function, by using Lagrangian multipliers $(\eta_i, \eta_i^*, \lambda_i \text{ and } \lambda_i^*)$ to transform the problem into dual space representation (Gupta, 2007; Vapnik, 1999a). Therefore, the Lagrangian for the Equation (3.3) is presented in Equation (3.4).

$$
\begin{aligned}
L = &\frac{1}{2}\|w\|^2 + C\sum_{i=1}^{k}(\xi_i + \xi_i^*) - \sum_{i=1}^{k}\lambda_i\left(\varepsilon + \xi_i - y_i + \langle w, x_i \rangle + b\right) \\
&- \sum_{i=1}^{k}\lambda_i^*\left(\varepsilon + \xi_i^* + y_i - \langle w, x_i \rangle - b\right) - \sum_{i=1}^{k}\left(\eta_i\xi_i + \eta_i^*\xi_i^*\right)
\end{aligned}
\tag{3.4}
$$

It is easier to locate the saddle point of the Lagrangian function defined in Equation (3.4) by equating the partial derivatives of the Lagrangian $\left(\text{with respect to } w, b, \xi_i \text{ and } \xi_i^*\right)$ to zero in order to obtain the expressions presented in Equations (3.5) – (3.7):

$$
w = \sum_{i=1}^{k}\left(\lambda_i^* - \lambda_i\right).x_i \tag{3.5}
$$

$$
\eta_i = C - \lambda_i \tag{3.6}
$$

$$
\eta^*_i = C - \lambda_i^* \tag{3.7}
$$

Thereafter, the optimization equation is maximized by substituting Equations (3.5) – (3.7) in (3.4) to arrive at Equation (3.8):

$$\begin{aligned} &\text{maximize } -\frac{1}{2}\sum_{i=1}^{k}\sum_{j=1}^{k}\left(\lambda_i^* - \lambda_i\right)\left(\lambda_j^* - \lambda_j\right)\left(x_j . x_i\right) - \varepsilon\sum_{i=1}^{k}\left(\lambda_i^* + \lambda_i\right) + \sum_{i=1}^{k} y_i\left(\lambda_i^* - \lambda_i\right) \\ &\textit{subject} \text{ to } \sum_{i=1}^{k}\left(\lambda_i^* - \lambda_i\right) = 0,\ 0 \le \lambda^*_i \text{ and } \lambda_i \le C \end{aligned} \tag{3.8}$$

The solutions (λ_i^* and λ_i) obtained from Equation (3.8) are substituted in Equation (3.1) and presented in Equation (3.9):

$$f(x,\alpha) = \sum_{i=1}^{k}\left(\lambda_i^* - \lambda_i\right)\left\langle x_i, x\right\rangle + b \tag{3.9}$$

However, since the concept of kernel function through ‘’kernel tricks’’ allows SVR to solve non-linear problems by mapping the original non-linear data into higher dimensional feature space where a linear model could be constructed (Lin et al., 2008), a proper selection of kernel function allows optimization of SVR performance (Lin et al., 2008). The regression function in feature space, after inserting the kernel function $K\left\langle x_i, x\right\rangle$, could be written as presented in Equation (3.10).

$$f(x,\alpha) = \sum_{i=1}^{k}\left(\lambda_i^* - \lambda_i\right)K\left\langle x_i, x\right\rangle + b \tag{3.10}$$

As the kernel functions help in transforming datasets into hyperplane (Lin et al., 2008), its variables determine the structure of high dimensional feature space which controls the complexity of the final solution. As applied in the present study, Equations (3.11) – (3.14) describe several kernel functions that are obtainable in the literature (Vapnik, 1999b) which include Polynomial, Linear, Gaussian (radial basis function (RBF)) and Sigmoid, respectively.

$$K(\overrightarrow{x_i}, \overrightarrow{x_j}) = (\overrightarrow{x_i} \cdot \overrightarrow{x_j} + 1)^d \quad (3.11)$$

$$K(x_i, x_j) = x_i^T . x_j \quad (3.12)$$

$$K(\overrightarrow{x_i}, \overrightarrow{x_j}) = \exp\left(-\gamma \left\| \overrightarrow{x_i} - \overrightarrow{x_j} \right\|^d\right) \quad (3.13)$$

$$K(x_i, x_j) = \tanh(\gamma x_i^T x_j + r) \quad (3.14)$$

where $\gamma, r, and\ d$ are kernel parameters and, $\overrightarrow{x_i}$ and $\overrightarrow{x_j}$ represent vectors in the input space—vectors of features computed from training or testing subset (Shamshirband et al., 2014).

3.3.2.1 Model Development

MATLAB software environment (Version 12, The MathWorks, Inc., Natick, MA, USA) using SVR coding was used for the computational aspect of this research work. Prior to the use of the dataset, the dataset was partitioned into two components to adhere to the SVR modelling approach (Shamshirband et al., 2014)—a machine-learning "training" subset and a "testing" subset in a ratio of 7:3, via stratified sampling to ensure effective random partitioning (Akbani et al., 2004). Specifically, 70% of the dataset was used for training and the remaining 30% was used for testing the SVR model via test-set cross-validation method. This allowed a regression analysis to be performed on the training dataset while estimating the future generalization accuracy, of the model, on the remaining testing subset. For further detail on the working principle of the proposed SVR model, readers are referred to Smola and Schölkopf (2004) and Vapnik et al. (1997).

3.3.2.2 Optimal Parameters Search Approach

The accuracy of an SVR model is dependent on the model parameters' selection (Shamshirband et al., 2014). However, due to the possibility of many different combinations of SVR parameters, it is often difficult to obtain optimal SVR parameters

(Cherkassky & Ma, 2004). To solve this problem systematically, and in order to obtain possible optimized parameters of SVR for an accurate estimation, a hybrid optimization search technique, which has been recommended (Rıza, 2009), was adopted and a test-set cross-validation technique was deployed (Owolabi et al., 2015).

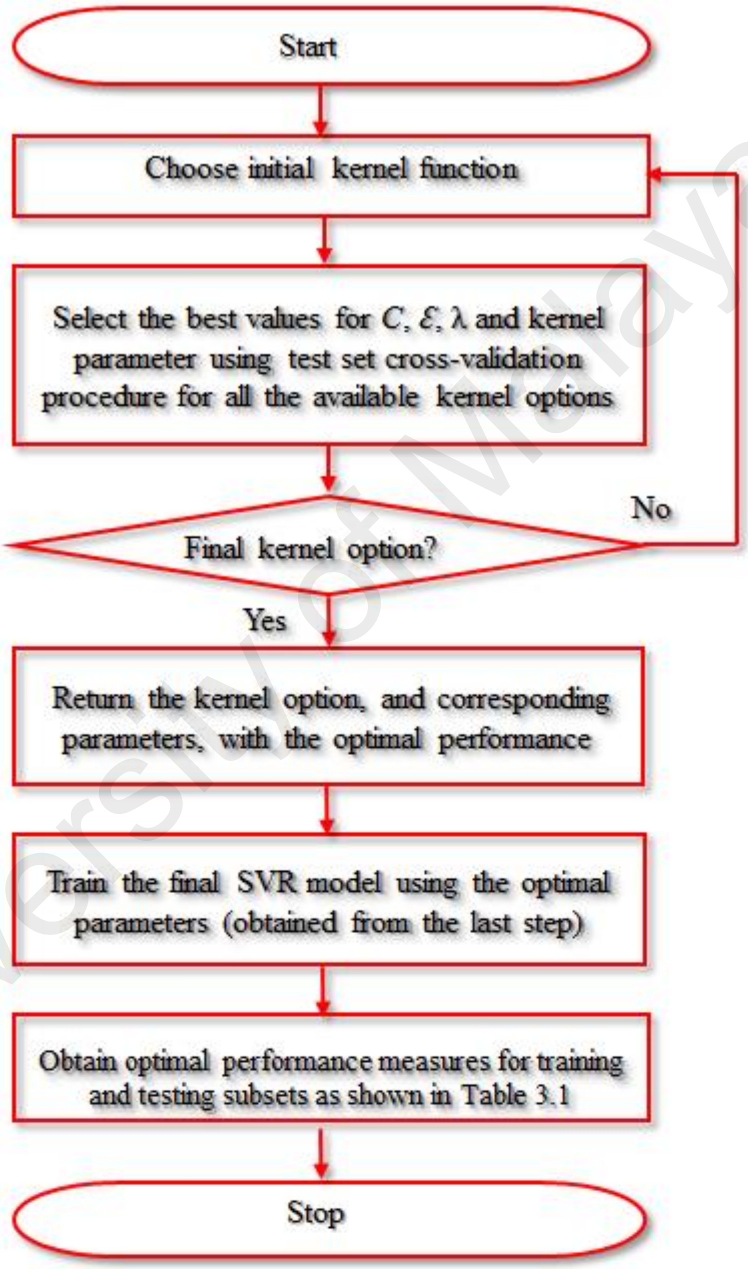

Figure 3.3: Flow chart of the procedure for obtaining optimal parameters, as shown in (Table 3.1), for the proposed SVR model.

The approach is as follows: for every partitioned training and testing subsets, the performance measures were noted for the SVR parameters values including the regularization parameter or factor C (bound on the Lagrangian multiplier), λ (conditioning parameter for quadratic programming (QP) methods), ε (epsilon) and η (kernel option) as well as the related kernel functions (Akande et al., 2015). Thereafter, this computational step was repeated for every available SVR kernel function with an incremental step of the parameters' values. Parameters' optimal values and the kernel function associated with the best performance measure were identified. The search procedures are presented summarily in Figure 3.3.

Table 3.1: Optimal parameters for the proposed Support Vector Regression model.

C	**879**
Hyper-parameter (Lambda)	2^{-15}
Epsilon (ε)	0.1205
kernel parameter	54
Kernel	Gaussian (RBF)

A mathematical implementation (Akande et al., 2015) of the test-set cross-validation technique is as described in Algorithm 3.1 as follows: $K_i(j)$ was defined where K contains all the available kernel functions (and i, j and k, are the indexes for the kernel functions) while iy, jy and ky represent the indexes for optimal kernel function. The total number of the available kernel function is represented by ni. The maximum values of C and η were assumed to be nj and nk, respectively. The recorded performance measures were stored in pf.

Algorithm 3.1: Optimal parameter search algorithm

$Initialization; iy = 0, jy = 0, ky = 0, qx = 0$
$for\ i = 1{:}ni$
$for\ j = 1{:}nj\ \ pf = f(K_i(j))$
$for\ k = 1{:}nk$
$pf = f\big(K_i(j)\big)$ [Performance measure for the present parameters combination]
$if\ pf\ is\ better\ than\ qx\ then\ qx = pf$
$iy = i, jy = j, ky = k$ $[storing\ the\ index\ of\ the\ best\ parameter]$
end
end
end

3.3.2.3 Model Statistical Performance Criteria

To evaluate the performance of the proposed model, common measures of association, between the actual and the estimated values, were employed, including correlation coefficient (r) and coefficient of determination (R^2) to quantify the "goodness of fit'', and Root Mean Square Error (RMSE) to quantify the error of estimate. For further details on their mathematical formulae, readers are referred to Youn and Kim (2011) and Olatunji et al. (2014).

3.4 Results and Discussion

Table 3.2 describes the actual experimental dataset used in this study. The results of the statistical analysis of the dataset are presented in Table 3.3. The suitability and applicability of the chosen dataset are revealed from the mean, maximum value, median, standard deviation, and minimum value. The MMG-RMS, MMG-PTP, level of electrical stimulation or contraction intensity, and knee angle obtained experimentally were the input to the SVR model to estimate the knee torque. Results of performance measures obtained from the training and testing subsets are as shown in Table 3.4.

To the author's knowledge, this is the first attempt to use an SVR modelling technique for NMES-evoked knee torque estimation from MMG signals. The outcomes of the developed SVR model (Table 3.4) indicated high correlation as well as low RMSE, and the model could, therefore, be adjudged as accurate. Moreover, high accuracy of the trained model, as evident by the coefficient of determination (R^2 = 94%), in predicting knee torque confirmed a reliable pattern between the predictors and the outcome which might be otherwise difficult to learn using the classical multiple linear regression method probably due to the concept of "curse of dimensionality" (Huang et al., 2006).

Table 3.2: Summary of the datasets.

Mechanomyographic signal (MMG) characteristics at seven Neuromuscular Electrical Stimulation (NMES) intensity levels, at three knee angles and their respective peak torque values.

Stimulation Intensity (mA)	Knee Angle								
	30°			60°			90°		
	PT	RMS	PTP	PT	RMS	PTP	PT	RMS	PTP
20	13.9 (3.7)	14.7 (9.9)	23.6 (16.4)	4.1 (0.7)	17.4 (18.4)	21.7 (23.0)	4.3 (5.7)	20.4 (20.0)	22.0 (26.9)
30	23.3 (19.7)	51.9 (22.4)	55.8 (24.7)	9.7 (8.5)	37.4 (21.2)	38.7 (19.5)	11.0 (10.2)	51.3 (30.0)	50.8 (30.6)
40	58.2 (23.6)	75.3 (29.5)	73.54 (19.1)	27.6 (24.2)	77.7 (36.6)	65.88 (19.2)	21.4 (15.0)	93.4 (45.4)	84.0 (34.1)
50	76.6 (19.3)	84.2 (15.2)	85.04 (14.9)	51.5 (26.2)	82.6 (27.3)	72.7 (14.9)	40.7 (18.5)	115.7 (39.6)	101.0 (33.8)
60	86.1 (20.2)	104.9 (22.5)	94.86 (18.2)	74.7 (19.2)	94.9 (30.4)	85.27 (14.7)	62.1 (12.3)	104.3 (29.0)	101.1 (28.5)
70	91.1 (21.5)	100.2 (6.2)	98.34 (5.7)	91.0 (8.2)	88.1 (9.7)	90.57 (14.4)	84.2 (12.3)	118.5 (22.0)	113.2 (10.7)
80	100.0 (0)	100.0 (0)	100.0 (0)	100.0 (0)	100.0 (0)	100.0 (0)	100.0 (0)	100.0 (0)	100.0 (0)

Abbreviations: Stimulation Intensity—level of electrical stimulation or contraction intensity, PT—Peak torque, RMS—Normalized MMG-RMS%, PTP—Normalized MMG-PTP%. Values are reported in mean (standard deviation) for N = 8.

Table 3.3: Statistical parameters of the datasets.

Input Parameters	Mean	Max	Median	Stdev	Min
Participants					
Weight (kg)	70.1	80	69	5.9	63
Age (years)	23.4	25	23.5	1.3	21
Stimulation intensity (mA)	50	80	50	20	20
Knee angle (°)	60	90	60	24.5	30
Normalized MMG-RMS%	77.8	188.1	86.9	40.0	4
Normalized MMG-PTP%	75.2	163.5	81.6	34.8	4.6
Peak torque	53.9	108.4	57.2	38	0

Table 3.4: Performance measures that determined the accuracy of the developed model.

Performance Measures	Training	Testing
r	0.97	0.94
R^2	94%	89%
RMSE	9.48	12.95

During the training period of the model, the estimated torques were positively correlated with the actual values drawn from the experimental data (actual vs. predicted values) for both the training (Figure 3.4A) and testing (Figure 3.4B) subsets.

In addition, the cross-plots of the “training’’ subsets (actual vs. predicted values) as shown in Figure 3.5 also confirmed the high accuracy of the “training” subsets. However, since the actual performance of any model is better accessed by the testing outcome (Gencoglu & Uyar, 2009), the accuracy of the developed SVR model was tested using 30% of the available data samples (*i.e.*, the reserved 30% that was not used for the model development). It was interesting to note that, the model also performed satisfactorily during testing phase with R^2 = 89%.

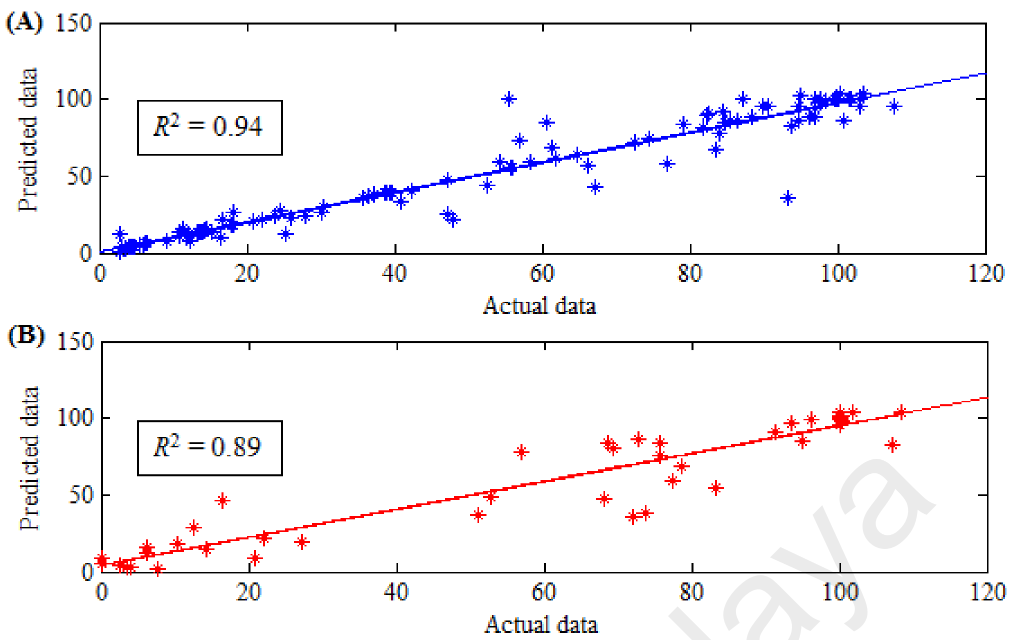

Figure 3.4: Plots of the correlation coefficients for the training (A) and testing; (B) subsets.

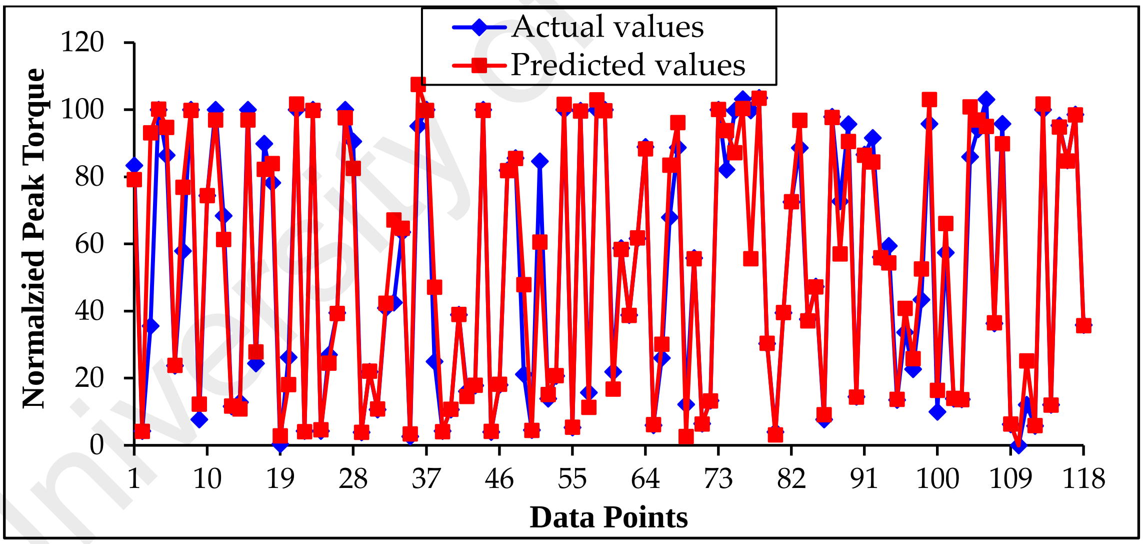

Figure 3.5: Cross plots of training sets—actual *vs.* predicted values.
The plots show the performance of SVR with Gaussian kernel for torque prediction on the training set.

This high correlation (r = 0.97; 0.94 for training and testing datasets, respectively) indicated that the estimated knee torque by the SVR model was very close to the actual experimentally recorded joint torque (from an isokinetic dynamometer) for each data sample. For better visualization and understanding of the outcome of this study, the crossplot of testing sets (actual vs. predicted values) has been portrayed in Figure 3.6. The level of accuracy in the testing phase (R^2 = 89%) of the model development indicates that the model is stable, efficient and not over-fitted. This was based on the suggestion of Tay and Cao (2001) that an overfitted model could perform excellently on the training set (r > 0.90) but will perform poorly on testing set (Tay & Cao, 2001). Therefore, the developed SVR model in this study achieved a good performance for both training and testing sets. These results are comparable to that of Youn and Kim (2011), where an artificial neural network model has been successfully used to estimate elbow force during voluntary contractions. Meanwhile, the potential of the SVR model for NMES-evoked joint torque estimation, which has not been previously documented, has also been demonstrated in the present study.

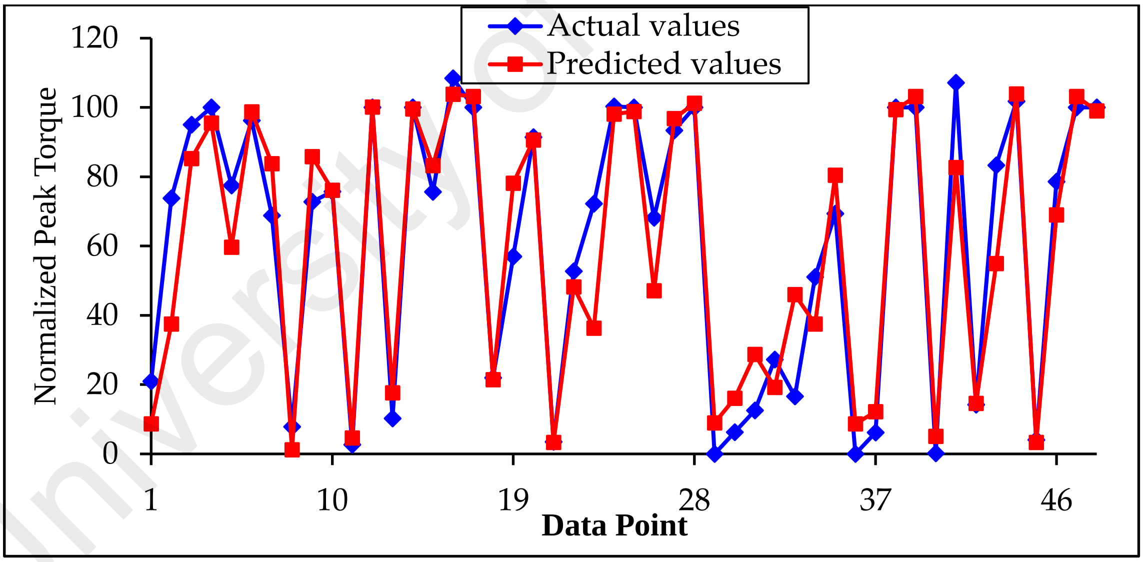

Figure 3.6: Cross plots of testing set—actual *vs.* predicted values.
The plots show the performance of SVR with Gaussian kernel for torque prediction on the testing set.

Moreover, Figures 3.5 and 3.6 portrayed the closeness of the predicted torque by the proposed SVR model to the actual experimental values. It could be noted that almost all the predicted points fit exactly on the experimental point or at least fits very closely to the target experimental point. Taken together, it could be inferred that the real-time knee torque information which is vital for the closed-loop implementation of NMES (Braz et al., 2009; Popović, 2014) in physical therapy and rehabilitation engineering might be reliably estimated by the proposed method. Nevertheless, the following limitations are acknowledged in the study design: the performance of the developed model is limited to the torque estimation during NMES-evoked isometric knee extension in healthy volunteers. In the future studies, the performance of the model will be verified using MMG signal and torque data from participants with neurological conditions. This will allow us to examine and improve the performance of the model, and to derive clinically relevant characteristics about the muscle force recruitment in the clinical populations.

3.5 Conclusion

Based on its previous estimation accuracy in relevant fields, SVR modelling was used in this study through the integration of relevant variables to predict NMES-evoked knee torque. The model was developed through training and testing via test-set cross-validation technique with the experimental dataset partitioned into training and testing subsets. Using the SVR methodology, the predicted knee torque was positively correlated with the actual values drawn from the experimental data for the training subset. Thereafter, to check the predictive ability of the model, the trained model was tested using the reserved testing subset that was not used in model development. The model performance was measured based on the correlation coefficient and RMSE. The outcomes from the developed SVR model showed an accurate prediction of the knee torque, characterized by a high coefficient of determination—up to 94% and 89%, and low RMSE of 9.48 and 12.95, for the training and testing cases, respectively. These results indicated a close similarity between the estimated joint torque by the SVR model and the actual experimental data obtained from the laboratory experiment. Additionally, the present study has uniquely shown that an SVR model could estimate NMES-evoked knee torque, generated by a synchronous modulation of muscle fibres' motor units (Gregory & Bickel, 2005), from MMG signal in healthy volunteers. Therefore, the good performance achieved in this study will motivate further studies in a similar direction to facilitate accurate estimations of torque using datasets from clinical populations—in which the NMES technology is more relevant, particularly among those with spinal cord injury. Moreover, since SVR models can be adapted for classification tasks (Cortes & Vapnik, 1995); in the future, the developed model will be used to classify fresh and fatiguing muscle contractions of knee extensors, from MMG signals, during standing and ambulation tasks. Such models might offset the need to contend with the stimulation artifacts (Braz et al., 2009; Popović, 2014) often encountered with the application of surface EMG signal as NMES feedback source.

CHAPTER 4: MECHANOMYOGRAPHY AS A PROXY OF MUSCLE FORCE DURING NMES-EVOKED KNEE EXTENSION TASK IN PERSONS WITH SCI

4.1 Introduction

Non-invasive estimation of muscle force is frequently sought in physical therapy and rehabilitation engineering. Therefore, the evaluation of muscle performance through torque production is used to grade the functional capability of a muscle in both healthy and neurologically impaired persons. The work reported in this Chapter was designed to apply the findings from healthy volunteers in persons with spinal cord injury (SCI). This was necessary because, although healthy volunteers' study was deemed required to investigate the feasibility of the MMG signal to study NMES-evoked muscle response and to learn about the safety of the experimental setting, such results cannot be generalized or directly applied to study the muscle activities in persons with SCI (Scott et al., 2007). This is as a result of the muscle paralysis in persons with SCI and the consequent characteristics of an unusual fibre typing or distribution which may influence their muscle responses to the neuromuscular provocation by electrical stimulation.

Therefore, this Chapter introduces a method for NMES-evoked isometric torque assessment in persons with SCI and quantifies the degree of association between MMG signals and isometric torque of the quadriceps muscle during incremental NMES-evoked muscle contractions at various knee angles. The Chapter also investigates the reliability of the MMG signals. The study described in this Chapter contains text from the author's published work reproduced with the permission from the publisher:

Ibitoye, M. O., Hamzaid, N. A., Hasnan, N., Abdul Wahab, A. K., Islam, M. A., Kean, V. S. P., & Davis, G. M. (2016). Torque and mechanomyogram relationships during electrically-evoked isometric quadriceps contractions in persons with spinal cord injury. *Medical Engineering & Physics*, 38(8), 767-775.

4.2 Literature Review

The study of motor unit (MU) recruitment to evoke force production is of clinical interest, particularly during NMES-evoked contractions of paretic or paralyzed muscles in neurological populations (Levy et al., 1990). Incremental MU recruitment during voluntary (Matheson et al., 1997; Orizio et al., 1989) and NMES-evoked contractions (Petitjean et al., 1998) has been used to describe muscle force modulation in healthy persons. However, while NMES-evoked contractions have been utilized for muscle force production in persons with SCI (Nash, 2005), the mechanical and morphological changes associated with muscle contractions in this population have been poorly understood.

To evaluate the effectiveness of NMES interventions, it is important to quantify electrical stimulus-evoked muscle force. In particular, understanding motor recruitment and muscle force characteristics could provide key insights about the contractile properties of the muscle (Elek & Dengler, 1995) and this has important implications for the use of NMES in rehabilitation. For example, measuring force or strength changes in persons with SCI can provide evidence of recovery or deterioration of motor output, as well as revealing the efficacy of rehabilitation interventions (Sisto & Dyson-Hudson, 2007). Beyond promoting the practical applications of NMES training in maintaining ‘muscle health’ (Shields et al., 2006), the ability to quantify an acute increase in muscle force production following NMES exercise (Hornby et al., 2009) could widen the application of this assistive technology in the clinical setting.

Traditionally, isokinetic dynamometers have been used to assess muscle force (via joint torque) in a research setting, and they quantify torque throughout the limb range of motion with acceptable reliability (Sisto & Dyson-Hudson, 2007). However, these devices lack portability and are relatively expensive and cumbersome to deploy for assessments in the clinical or home environment. The estimation of the muscle torque from other muscle characteristics, particularly bio-potentials, becomes an attractive option.

While an indirect estimation of torque production has been assessed using electromyography (EEMG) (Merletti et al., 1992; Thompson et al., 2011), the signal's sensitivity to the external electromagnetic interference and skin impedance changes as a result of perspiration (Yamamoto & Takano, 1994) presents significant limitations (Orizio, 1993). Additionally, the reliability of EMG estimation of muscle torque generation during NMES-evoked contractions remains debatable (Popović, 2014), largely due to the size of stimulation artifact current in relation to the EMG signal (Merletti et al., 1992). Thus, quantification of electrical stimulus-evoked force production by EMG alone during neurostimulation is deficient (Levin et al., 2000).

A mechanical "counterpart" of the electrical activity of active motor units as measured by EMG (*i.e.*, muscle mechanomyogram; MMG) has been proposed for muscle torque assessments (Alves et al., 2010; Beck et al., 2005). During skeletal muscle contractions, the generated MMG signal is a function of the following mechanisms: "(i) a slow bulk movement of the muscle at the initiation of the contraction, (ii) smaller subsequent lateral oscillations occurring at the resonant frequencies of the muscle, and (iii) dimensional changes of active muscle fibre" (Beck et al., 2005). Therefore, MMG reflects the mechanical activity of physiological phenomena underlying muscle contractions. MMG quantifies neuromuscular performance, and has been used to gain insights into muscle capability during voluntary (Beck et al., 2005) and NMES-evoked contractions (Petitjean et al., 1998).

In humans with intact neuromuscular functions, Petitjean et al. (1998) reported a positive linear relationship between MMG amplitude and MU recruitment (*i.e.*, muscle torque) during incremental NMES-evoked contractions of the first dorsal interosseous muscle (FDI). The authors suggested that the influence of the muscle fibre type may have been responsible for the pattern observed. Consequently, the MMG-torque relationship is both muscle fibre-type composition (Stokes & Dalton, 1991) and structure (Yoshitake & Moritani, 1999) dependent.

In addition, MMG frequency content provides information regarding the firing rates/frequency of the active motor units during voluntary and NMES-evoked contractions (Orizio et al., 2003). Therefore, simultaneous investigation of the time and frequency contents of MMG signal has been used to interpret motor control strategy that is responsible for muscle force modulation during voluntary (Beck et al., 2005) and NMES-evoked (Orizio, 1993) muscle contractions. Thus, the torque output during NMES-evoked muscle contractions depends on the degree of MU recruitment, their firing rates (Petitjean et al., 1998) and the contractile properties of the activated muscle (Yoshitake et al., 2002). Nonetheless, clear interpretation of the specific influence of MU recruitment and their firing rates on MMG characteristics during NMES-evoked contractions in persons with neurological conditions (*i.e.* SCI) has been minimally investigated.

Thus, the aims of this study were: (i) to quantify the degree of association between MMG signals and isometric torque of the rectus femoris (RF) muscle during incremental NMES-evoked muscle contractions at 30^0, 60^0, and 90^0 knee angles; and, (ii) to investigate the reliability of MMG signal recorded over RF muscles in persons with SCI. The quadriceps muscle group was selected because of its well-established relevance for the study of knee torque dynamics (Franken et al., 1993), could be readily stimulated in persons with SCI (Gerrits et al., 2005), and could be easily compared with existing data on voluntary contractions (Shinohara et al., 1998; Stokes & Dalton, 1991). RF was selected to represent the quadriceps group because it is the major contributor to the NMES-evoked quadriceps muscle torque production during knee extension (Richardson et al., 1998; Shinohara et al., 1998). To the author's knowledge, no previous studies have reported the relationship between MMG parameters and the quadriceps torque production during incremental NMES-evoked isometric contractions in persons with SCI.

It was hypothesized that the MMG signal would be a reliable proxy of incremental torque production since a positive linear relationship has been previously demonstrated in FDI, which is of comparable muscle fibre morphology to the quadriceps (Petitjean et al., 1998) with a predominance of type II fibres in this muscle group after SCI (Gerrits et al., 2005). Furthermore, a significant correlation between the MMG signal and muscle torque production would *a priori* support the validity of the signal as a proxy of muscle performance/torque, particularly when a direct measurement of torque might be impractical (Popović, 2014), such as in activities of daily living.

4.3 Materials and Methods

4.3.1 Participants

Nine chronic motor complete (American Spinal Injury Association Impairment Scale A and B) SCI (Kirshblum et al., 2011) participants with neurological lesions below C4 were recruited at the Department of Rehabilitation Medicine, University of Malaya Medical Centre (UMMC), Kuala Lumpur, Malaysia. Their written informed consent (see Appendix D or E) was obtained after a full disclosure of the rationale and procedures of the experiment in compliance with the University of Malaya Medical Ethics Committee's approval (Approval No: 1003.14 (1)) as detailed in Appendix A) based on the declaration of Helsinki. They were duly informed about the possible sources and discomforts of the dynamometer assessment and electrical stimulation and were advised of their rights of withdrawal from the study at any time. Persons with severe spasticity, joint contracture or lower motor neuron lesion that might adversely affect the production of modest quadriceps torque were excluded from participation. Also excluded were any participants who, as a result of incremental NMES current amplitude, produced no relative increase in their stimulus-evoked torque values.

Of the nine participants recruited at the outset, only seven successfully completed the full test battery. However, a further participant was excluded due to lack of increase in relative torque in response to increasing NMES current intensity. Therefore, the data of the remaining six participants (Table 4.1) has been included for analysis. All participants retained quadriceps spinal reflexes, and they could sit up on a dynamometer's chair with backrest. As part of clinical conditioning exercises (Bickel et al., 2004), at the time of the investigation, participants were already involved in NMES cycle training (2 to 3 times per week for at least 7 weeks) but were asked to refrain from the training for at least 48 hours before testing.

Table 4.1: Participants' Physical Characteristics

Participants	Gender	Age (y)	Body mass (Kg)	Height (m)	NLL	AIS	TSI (Yrs.)
1	M	49	79.6	1.74	T1	A	11
2	F	47	82.0	1.62	T4	B	24
3	M	28	62.4	1.71	C7	B	14
4	M	44	71.6	1.79	C6/C7	B	2.5
5	M	34	75.9	1.70	C6	A	17
6	M	33	44.0	1.71	C5/C6	A	13
Mean± SD		39.2±7.9	69.3±12.9	1.71±0.05			13.6±6.5

Abbreviation: NLL- Neurological lesion level, AIS- American Spinal Injury Association Impairment Scale, TSI- Time since injury, F-Female, M-Male.

4.3.2 Experimental Protocol

Participants were secured to a calibrated isokinetic dynamometer (System 4; Biodex Medical Systems, Shirley, NY, USA) by an inextensible restraining straps over the thigh, pelvis and the trunk to minimize extraneous movements (Brown & Weir, 2001) and to ensure only isometric contractions of the quadriceps could be performed (Bickel et al., 2004) as depicted in Figure 4.1. Based on safety considerations of not putting bone health at risk (Hartkopp et al., 1998), and to analyze the muscle torque in a range that will mimic functionally relevant mode such as in standing up, the maximal torque calculations based on the empirical data of Kagaya et al. (1995) was utilized. Those investigators suggested that the knee extensor moment/ torque should not exceed that required for NMES supported standing in persons with SCI.

Thus, careful attempts were made to keep the NMES-evoked muscle torque production within a range that would not risk bone integrity. Although none of the participants could be NMES-provoked to produce the maximum torque, the maximum torque production in each participant was limited to 75 Nm as suggested by Gerrits et al. (2005).

4.3.3 Familiarization

A familiarization session was conducted (at least a day prior to testing) to acquaint participants with the NMES-evoked isometric assessment procedures on the dynamometer. Thereafter, participants attended the laboratory on two different test days, separated by 48 hours, for each of the knee angles assessed, to quantify test-retest reliability.

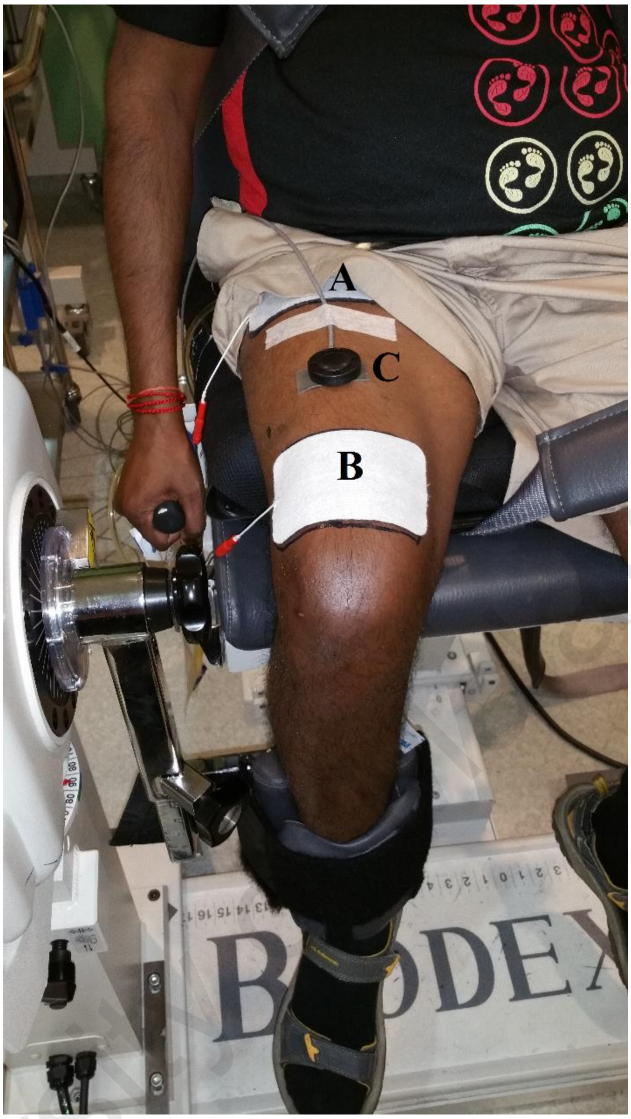

Figure 4.1: Experimental set-up showing the MMG and NMES electrode placement over the quadriceps muscle in a representative participant with SCI. Letters A and B are the cathode and anode electrodes, respectively, of the neuromuscular electrical stimulator while C represents the MMG sensor.

4.3.4 Stimulation Protocol

Through palpation and visual inspection, the isolated activation of knee extensors was ensured to establish that the muscle activation was primarily from quadriceps (Adams et al., 1993), using 9 cm×15 cm self-adhesive stimulating electrodes (Hasomed GmbH, D 39114 Magdeburg, Germany). The cathode NMES electrode was placed 8 cm distal to the inguinal area, over the RF belly near the expected location of the motor points (Botter et al., 2011), and the position of electrode was then slightly adjusted to a location whereby the maximal response, based on a palpable muscle response and force production, to the stimulation could be identified. The anode electrode was affixed 5 cm proximal to the patella as recommended by Levin et al. (2000). For both the distal and proximal anatomical landmarks, motor points represent the location where the motor branch of a nerve accesses the muscle belly whereby the maximal muscle force could be possibly obtained for a given electrical stimulus (Botter et al., 2011; Sung et al., 2003). Indelible marker was used to identify the electrode position for accurate placement between trials and testing days.

NMES was used to evoke isometric contractions of the knee extensors with the hip flexed at about 90^0, and the knee flexed to 90^0, 60^0 or 30^0 according to the study's protocol. NMES electrodes were connected to a neuromuscular stimulator delivering square-wave pulses of current amplitude between 50-120 mA. During each electrical stimulus-evoked contraction, a train of electrical stimulation (*i.e.*, repeated bursts of pulses at 30Hz, and 400μs pulse duration, with increasing stimulation amplitude (mA); RehaStim™, Hasomed GmbH, Magdeburg, Germany) was imposed to potentiate the quadriceps activation.

4.3.5 Measurements

4.3.5.1 NMES-evoked isometric torque measurement

Following submaximal warm-up trials wherein the muscle belly was palpated to ensure accurate MMG sensor fixation, 4s of randomly ordered NMES-evoked submaximal-to-maximal torque levels were imposed on the participants' quadriceps muscle at 30^0, 60^0, or 90^0 knee angles (0^0 = full knee extension). The incremental torque was evoked by stimulation intensity from 50 mA to 120 mA in 10 mA increments for each participant. Previous studies have shown that this protocol elicits optimized outcomes as it does not evoke premature muscle fatigue (Bickel et al., 2004). Torque production (Nm) was quantified in real-time by the dynamometer and data were 'gravity-corrected' by subtracting the passive torque produced by the leg mass affixed to the level arm. This was effected automatically following the positioning of the knee angle at 45^0 from the full knee extension angle (0^0) while each participant was instructed to remain relaxed. The recorded limb weight was automatically used by the dynamometer to "negate the gravity effect" on the collected torque data (Biodex (V.4X) operation manual). To eliminate any order effect, the administration of contraction intensities (mA) and knee angles were randomized. A 10-min recovery was allowed between trials to reduce the risk of cumulative muscle fatigue (Thomas et al., 2003).

4.3.5.2 MMG measurements

Simultaneously with the torque measurement, MMG signals from the RF were obtained using an accelerometer-based vibromyographic sensor (Sonostics BPS-II VMG transducer, compatible with Biopac MP150 platform, sensitivity 50 V/g) attached by means of double-sided adhesive tapes (3M Center St. Paul, MN, USA) (Barry, 1992) directly on the muscle belly (*i.e.*, at the midpoint between the inguinal crease and the superior border of the patella (Ryan et al., 2008)), in order to obtain the maximum muscle surface oscillation (Figure 4.1). Before attaching the MMG sensor, the skin was shaved (as needed) and cleaned with alcohol swabs. As it was sometimes difficult to identify the precise location of the quadriceps' muscle belly (due to muscle atrophy and adipose tissue thickening), the determination of the MMG sensor location was assisted by electrical stimulation of the muscle. During this procedure, a stimulation current amplitude of 50 mA (pulse width = 400μs, frequency = 30Hz) was administered to identify the probable muscle belly by visual inspection and palpation. This location was standardized for subsequent trials by indelible marker. An example of the pattern of MMG signals and the torque production during NMES-evoked muscle contractions is as shown in Figure 4.2.

4.3.6 Signal Processing

Signals were acquired and analyzed using AcqKnowledge data acquisition and analysis software (MP150, BIOPAC Systems, Santa Barbara, CA, Inc. USA) and a customized programme in LabVIEW (Version 12.0, National Instruments, Austin, TX, USA). The raw MMG signals were acquired at a sampling rate of 2 kHz and digitally band-pass filtered (20-200 Hz), to suppress the influence of artifacts associated with tremor and body movement (Goldenberg et al., 1991; Szumilas et al., 2015), for offline analysis. The peak torque (PT) obtained from a dynamometer was calculated for each NMES-evoked contraction level/stimulation intensity. The PT of the participants, MMG root mean square (MMG-RMS), peak-to-peak (MMG-PTP) amplitude and MMG frequency characteristic—peak frequency (MMG-PF) were extracted from the NMES-evoked isometric contraction measurement from 1 s epoch of MMG signal around the peak torque (location of probable maximum muscle recruitment) at each contraction intensity level.

The middle 1 s epoch was selected to avoid the on-transient due to a rise in force at the beginning and off-transient during the end of muscle contractions (Katsavelis & Threlkeld, 2014). The PT value and the MMG parameters at maximum stimulation intensity (120 mA) were used to normalize their relative submaximal values, at each knee flexion angle, to allow for comparison between participants.

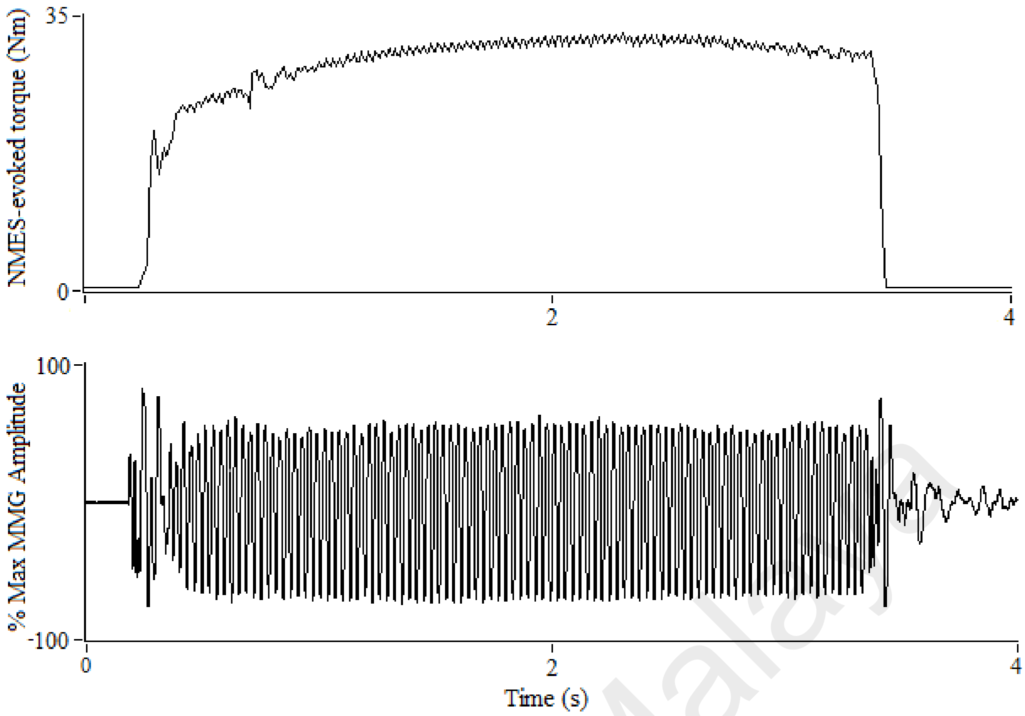

Figure 4.2: Simultaneous recordings of repetitive NMES-evoked torque and raw MMG signal from RF at stimulation current of 90 mA and 60^0 knee flexion angle from a representative participant.

4.3.7 Statistical Analysis

The test-retest reliability of measurements between days was quantified by intraclass correlation coefficient (ICC), using a two-way mixed effects model, and standard error of measurements (SEM%) (Weir, 2005) calculated as a percentage of relative mean values (*i.e.*, in order to examine the relative and absolute consistency of the parameters). Thereafter, paired samples *t*-tests were performed on the dependent variables to determine whether there was a significant mean difference between the test and retest scores. A data normality test was conducted using Shapiro-Wilk statistic, and the data were normally distributed except for a few (*i.e.*, peak torque at 60^0 knee angle) that were skewed probably due to the study's small sample size (Table 4.2).

Based on the recommendation of Munro (2005), the interpretation of the ICCs were as follows: >0.90, very high reliability; 0.70–0.89, high reliability; 0.50–0.69, moderate reliability. The significant association between the NMES-evoked torque vs. stimulation intensity, MMG-RMS vs. NMES-evoked torque, and MMG-PTP vs. stimulation intensity (at 8 levels of torque production) was investigated using Pearson's correlation coefficient (*r*) (Stokes & Dalton, 1991). Prior to the analyses, MMG data were expressed as a percentage of their values at maximum stimulation intensity level (Stokes & Dalton, 1991). A statistical software package (IBM SPSS for Windows Version 20, NY, USA) and Microsoft Office Excel 2013 (Microsoft, Redmond, WA, USA) were used for data analyses. A significant level of alpha (α) < 0.05 was set *a priori* for all statistical tests.

4.4 Results

After completing the full test battery and with one participant, out of seven, meeting exclusion criteria, six participants, whose physical characteristics appeared in Table 4.1, were included in the analyses presented herein.

4.4.1 Reliability

In Table 4.2, the ICC, SEM% and their respective probabilities for all the investigated parameters were presented. Based on the normative categories previously described, ICC ranged from "moderate to very high reliability" (*i.e.*, 0.65 to 0.97). For SEM%, the values ranged from 10.1 to 31.6% of their relative mean values. Paired sample *t*-tests indicated that there were no significant differences between the mean values of any parameters (P> 0.05).

Table 4.2: Test–retest reliability of torque and MMG measures. Probabilities (*P*-values) were obtained from paired *t*-test between trials. Standard error of measurements (SEM) was expressed as a percentage of mean values. Shapiro-Wilk (W) and its probability have been reported as a measure of normal distribution. PT represents NMES-evoked peak torque.

	Inter-day				
Knee angle	**Parameters**	**ICC**	**SEM%**	***P*-value**	**Shapiro-Wilk (W); *P*-value**
	PT	0.82	31.6	0.843	(0.961); 0.187
	MMG-RMS	0.79	15.5	0.080	(0.975); 0.504
30^0	MMG-PTP	0.72	17.1	0.064	(0.972); 0.414
	PT	0.97	11.4	0.996	(0.908); 0.001
	MMG-RMS	0.77	22.6	0.277	(0.947); 0.058
60^0	MMG-PTP	0.73	21.3	0.490	(0.964); 0.227
	PT	0.97	10.1	0.370	(0.082); 0.120
	MMG-RMS	0.65	18.2	0.091	(0.983); 0.720
90^0	MMG-PTP	0.67	15.7	0.219	(0.972); 0.412

4.4.2 Torque Production

Figure 4.3 illustrates MMG recordings at 50 mA (low torque production) and 100 mA (high torque production) and the corresponding spectra responses at 60^0 knee angle. Figure 4.4 shows significant (P< 0.05) positive relationships between NMES-evoked torques as a function of stimulation intensity (mA) for all the three knee angles.

4.4.3 MMG and Contraction Intensity

Figure 4.5 depicts significant (P< 0.05) positive correlations between the normalized MMG-RMS and NMES-evoked torque expressed in %PT (20, 40, 60, 80 and 100% PT) for 30^0, 60^0 and 90^0 knee angles at eight levels of contraction intensities (50, 60, 70, 80, 90, 100, 110, 120 mA).

In Figure 4.6, the relationship between MMG-PTP and stimulation intensity at the three knee angles were shown. There were statistically significant (P< 0.05) positive correlations between the two parameters at 30^0 (r= 0.792); 60^0 (r= 0.819); and 90^0 (r= 0.668) knee angles.

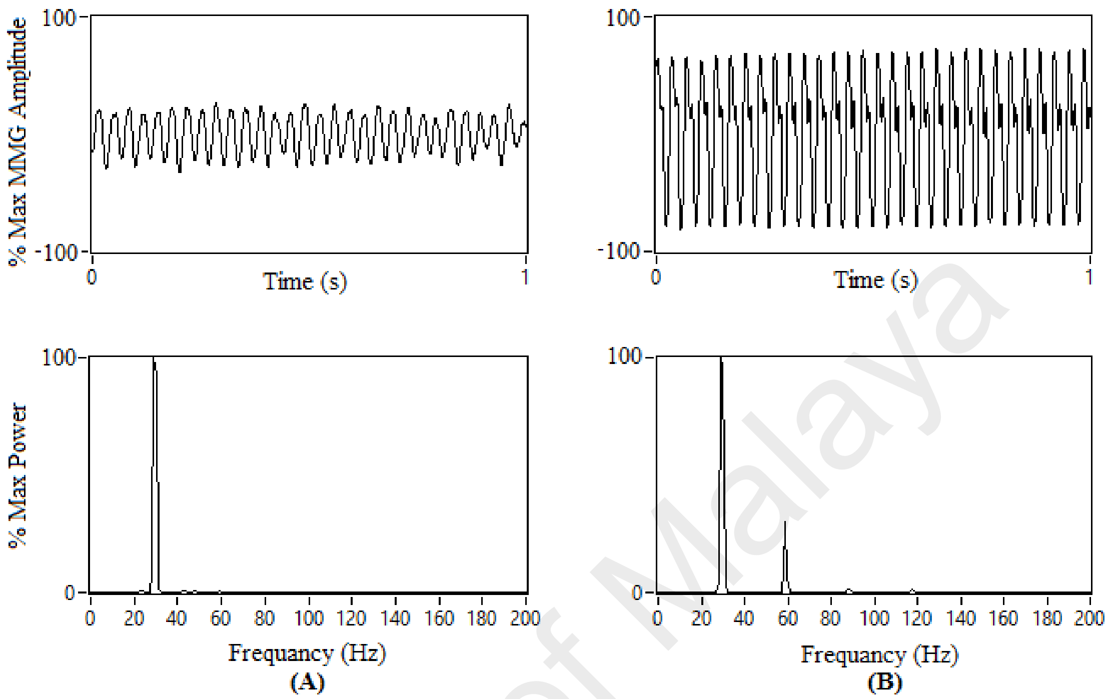

Figure 4.3: MMG recordings of RF at 50mA (A) and 100mA (B) neurostimulation current amplitude and the corresponding spectra at 60^0 knee flexion angle. The MMG-PF approximated the stimulation frequency of 30 Hz at both 50 mA and 100 mA contraction intensity levels, however, harmonics of the peak frequency characterizes the stimulation intensity of 100 mA.

4.5 Discussion

To the author's knowledge, this is the first study to investigate the degree of association between mechanomyographic characteristics and isometric NMES-evoked muscle torque in persons with motor 'complete' SCI. A moderate to very high test-retest reliability, together with strong, positive correlations between the MMG signal and contraction/stimulation intensity indicated that the underlying muscle mechanical changes could be reliably tracked by the MMG signal. This finding was in agreement with a previous investigation (Yoshitake et al., 2002) in healthy volunteers, and suggested the validity of the MMG signal to quantify muscle contractile properties and performance of paralyzed quadriceps muscle re-activated by NMES-evoked contractions.

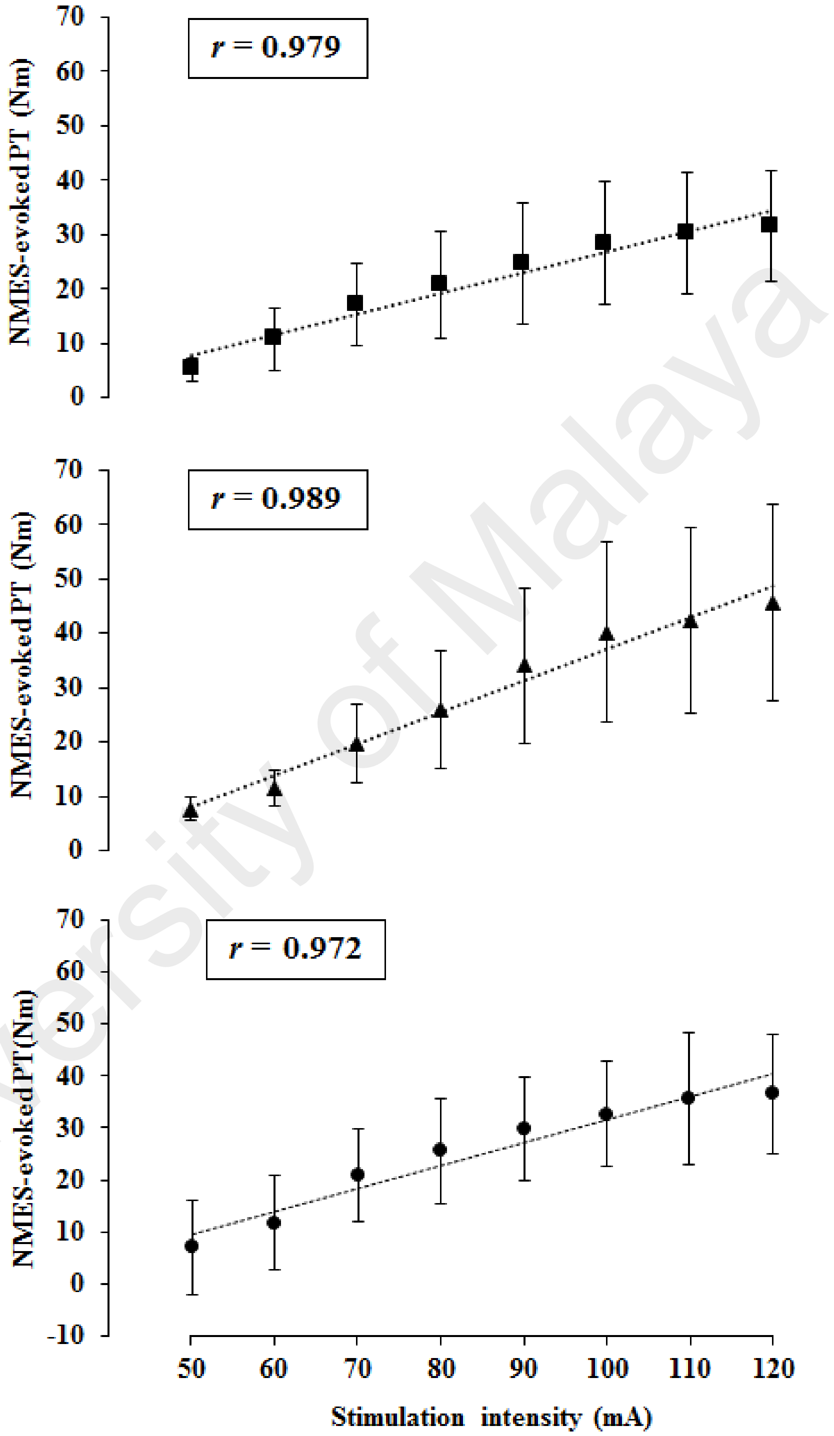

Figure 4.4: Correlations between the NMES-evoked torque and stimulation intensity (mA) during quadriceps contractions at 30^0 (■), 60^0 (▲) and 90^0 (●) knee angles.

Values are mean± SD at P < 0.05 significant level.

4.5.1 MMG Sensor Reliability

In the present study, two measures of MMG amplitude (MMG-RMS and MMG-PTP) demonstrated a comparable level of relative (ICC) and absolute (SEM) reliability (Table 4.2). Therefore, while MMG-RMS has been more widely used to ‘track’ muscle effort, MMG-PTP could similarly follow the underlying mechanical changes reliably during NMES-evoked contractions. This may justify why recent investigations (Cè et al., 2013; Gobbo et al., 2006) have adopted the MMG-PTP parameter to track NMES-evoked muscle fatiguing contractions in healthy volunteers. Additionally, based on the assumption (Currier, 1984; Pincivero et al., 1997) that ICC greater than 0.8 could be considered good enough for clinical applications, the findings from the present study provide an insight into the potential clinical efficacy of the MMG signal for real-time muscle performance grading during NMES-evoked contraction activities.

4.5.2 NMES-Evoked Torque Production

The NMES-evoked torque production was shown to be reliable between test days (Table 4.2) and varied among knee angles. This is in agreement with a previous investigation by Sinclair et al. (2006). The reduction in the torque production at the extreme knee angles may be due to a smaller active working range of muscle fibres—reduced fibre length (Gerrits et al., 2005). These results are in good agreement with those studies (Gerrits et al., 2005; Kulig et al., 1984; Sinclair et al., 2006), which suggested that muscle torque-generating capacity is knee angle dependent, in part due to the variation in fibre type composition following SCI and orientation as a function of the change in muscle length (Gerrits et al., 2005).

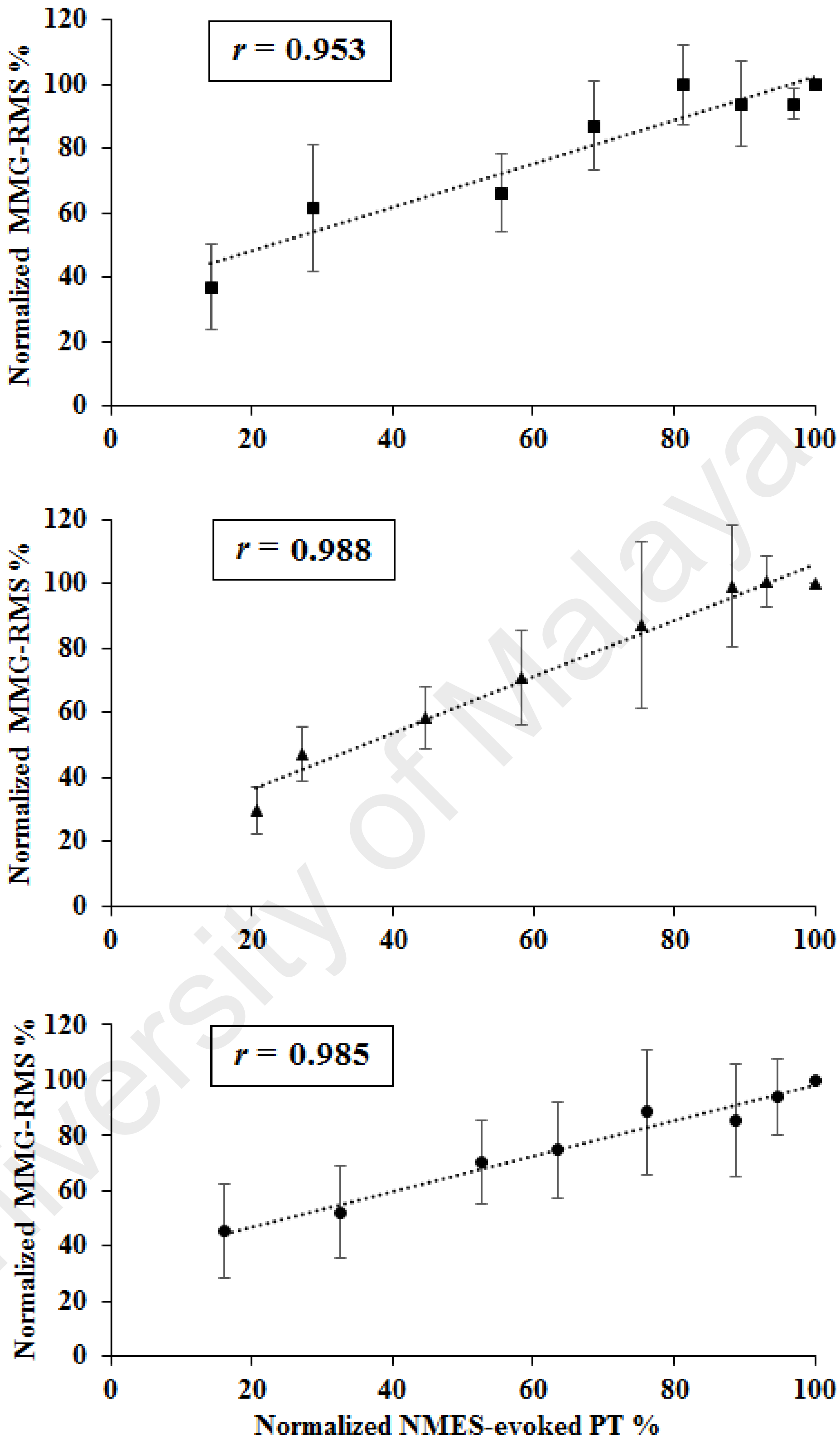

Figure 4.5: Correlations between the normalized MMG-RMS as a function of %PT during quadriceps NMES-evoked contractions at 30^0 (■), 60^0 (▲) and 90^0 (●) knee angles.

Data are eight levels of contraction intensities and values are mean ± SD at $P < 0.05$ significant level.

4.5.3 Mechanomyographic Responses to NMES-Evoked Isometric Torque

4.5.3.1 MMG amplitude

MMG-RMS provides physiological information about the activated MU recruitment of muscle fibres (Beck et al., 2005; Orizio et al., 2003). The MMG recordings during NMES-evoked torque production showed positive linear MMG versus torque relationships for the paralyzed quadriceps muscles. Previous studies (Barry, 1992; Beck et al., 2005; Gobbo et al., 2006; Munro, 2005; Petitjean et al., 1998; Yoshitake & Moritani, 1999) have demonstrated strong positive linear or non-linear correlations between MMG signal parameters and NMES-evoked isometric torque in healthy persons. To the author's knowledge, only a single investigation (Decker et al., 2010) has utilized MMG amplitude to quantify NMES-evoked contraction levels based on cycling ride time in quadriceps muscle of spinally injured persons. However, the present study has uniquely investigated the relationship between MMG amplitude and NMES-evoked isometric torque at submaximal-to-maximal contraction intensity levels in order to infer characteristics about torque production in a SCI population. Such information may be of a practical application during NMES supported sit-to-stand, standing, prolonged stance or stepping tasks where a direct measurement of muscle force/torque is necessary for fatigue estimation but it is impractical to measure with a dynamometer.

Although the torque values obtained in the present investigation were much lower when compared with the previously reported data on voluntary quadriceps contractions (Ebersole et al., 1998; Stokes & Dalton, 1991), MMG amplitude in the present study comparably tracked the incremental NMES-evoked torque production. This suggests that the sensitivity of MMG amplitude to the NMES-evoked muscle contractions is independent of the level of torque production. Furthermore, the pattern of MMG amplitude response was in good agreement with the previously reported patterns in healthy volunteers (Petitjean et al., 1998; Yoshitake & Moritani, 1999; Yoshitake et al., 2002).

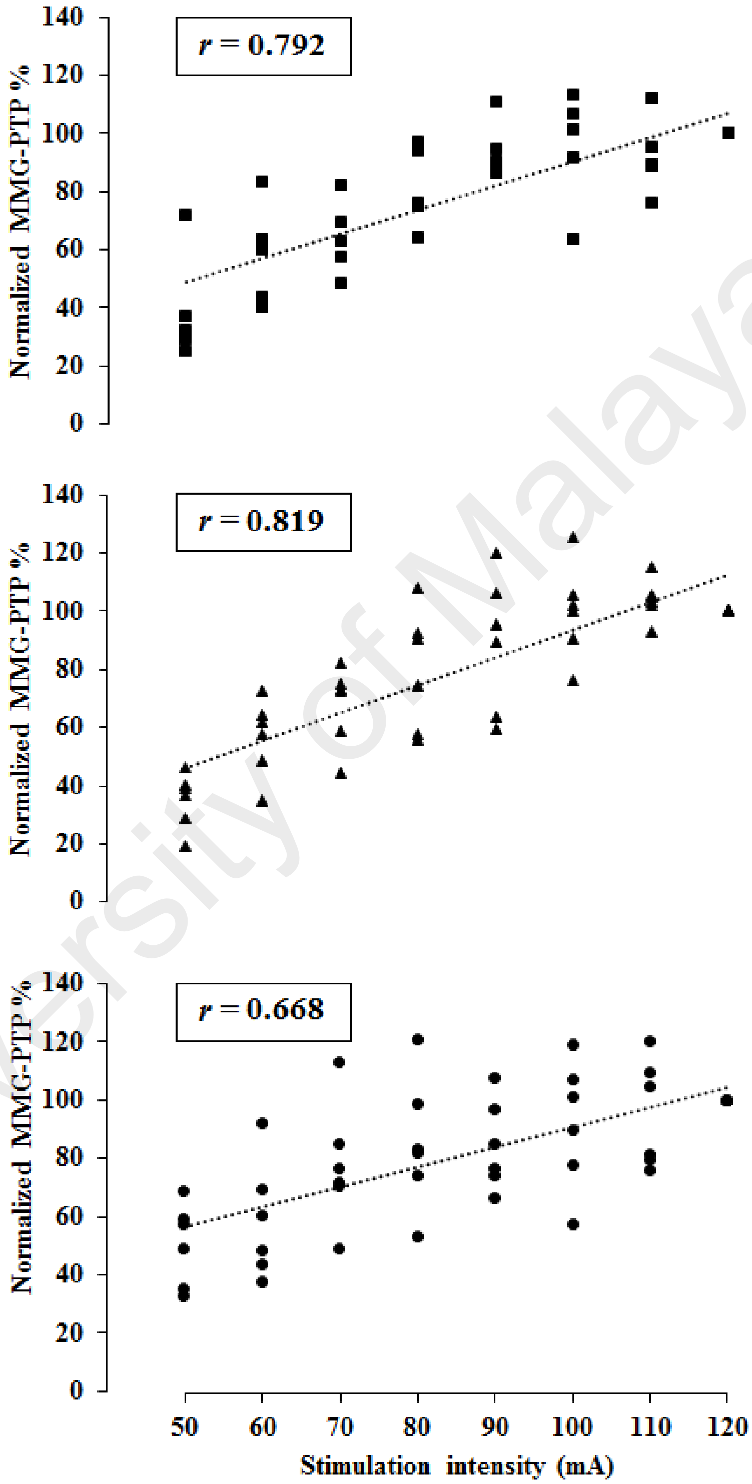

Figure 4.6: Correlations between the normalized MMG-PTP and stimulation intensity (mA) during quadriceps NMES-evoked contractions at 30^0 (■), 60^0 (▲) and 90^0 (●) knee angles.

Values are mean± SD at $P < 0.05$ significant level.

Specifically, MMG-RMS increased linearly up to 80 %PT (for the investigated knee angles) before the appearance of plateau due to the muscle stiffness and associated force fusion—a manifestation of muscle mechanical changes during contractions (Orizio, 1993; Yoshitake et al., 2002). This result suggests a possibility that MMG amplitude follows the contraction intensity independently of knee angle up to ~80 %PT. This might be sufficient for the implementation of a muscle performance feedback in situations where torque information is required to modulate NMES-evoked contractions in order to optimize its functional outcomes in persons with SCI as previously suggested by Gobbo et al. (2006).

Furthermore, MMG-PTP amplitude has equally been used to monitor the muscle mechanical changes *i.e.*, "the viscoelastic characteristics of the series elastic component" (Esposito et al., 2011) during NMES-evoked muscle contractions (Petitjean et al., 1998). Petitjean et al. (1998) has previously established a positive linear relationship between MMG-PTP and stimulation intensity in FDI and demonstrated that MMG-PTP could reflect the summation of the contracting MU. The authors suggested an orderly recruitment of the MU as the reason behind their observation. The present results confirm this finding and showed a comparable correlation between the MMG-PTP and stimulation intensity at the three knee angles investigated. In all, MMG-RMS and MMG-PTP may be used as conjoint proxies of muscle force.

4.5.3.2 MMG frequency

Unlike involuntary muscle contractions (Cescon et al., 2004), the increase in contraction intensity did not appear to influence the MMG peak frequency during NMES-evoked muscle contractions. At higher stimulation intensity/torque level, multimodal frequency characterized the MMG spectrum (Figure 4.3) and their values appeared to be the harmonics of the fundamental/peak frequency of the MMG signal. The apparent correspondence of the MMG peak frequency with the stimulation frequency (Figure 4.3) suggested that the MMG frequency may represent the MU firing frequency. This observation arose from the knowledge that the NMES-evoked muscle contraction is “synchronous” and because the participants of the present study had motor complete SCI, their muscle contractions were entirely involuntarily modulated. This implied that the recorded MMG signals were mainly generated by the synchronously recruited muscle fibres (Orizio, 1993).

This explanation is in good agreement with previous studies (Stokes & Cooper, 1992; Yoshitake & Moritani, 1999) which also demonstrated that the MMG peak frequency matched the stimulation frequency of contracting muscles. While a clearer interpretation of this pattern is beyond the scope of the present study, Stokes and Cooper (1992) and Yoshitake and Moritani (1999) have previously suggested that this phenomenon might be a function of the type of muscle, properties of the MMG transducer, and valid mainly during unfused contractions (Yoshitake & Moritani, 1999). In all, the MMG-PF may only approximate the NMES-evoked firing frequency of muscles at submaximal torque production levels of predominant fast twitch muscle fibre type, such as in denervated RF.

4.5.4 Influence of Knee Flexion Angles on Mechanomyographic Response

Although all the investigated knee angles revealed strong relationships between the MMG amplitude and NMES-evoked isometric torque, the pattern of the relationship was knee angle specific (Figure 4.5). This is in agreement with a previous investigation by Ebersole and co-workers (1998), whereby the relationship between the production of the quadriceps voluntary isometric torque and the associated MMG-RMS was knee angle dependent. Those investigators (Ebersole et al., 1998) suggested that such differences might be due to the variations in muscle stiffness or motor unit activation strategies as a reflection of length-tension relationship.

4.5.5 Correlations among MMG and NMES-Evoked Torque

Strong, positive correlations were observed between MMG-RMS and NMES-evoked torque, at all the three knee angles. The correlations might be attributed to the sensitivity of MMG amplitude to the incremental force modulation. This has a direct implication on the possibility of MMG to track the force modulation in paralyzed muscles with predominant fast twitch fibre type (Gerrits et al., 2005; Round et al., 1993) and supports the earlier suggestion (Yoshitake & Moritani, 1999) of examining muscle's cellular composition with MMG signal. This explanation is consistent with early voluntary isometric contraction studies of the quadriceps (Shinohara et al., 1998; Stokes & Dalton, 1991) which identified that the MMG-RMS of muscles with predominant type II fibre could increase up to 100% PT irrespective of the type of MMG sensor used (Shinohara et al., 1998).

Additionally, during NMES-evoked contractions of gastrocnemius muscles (type II fast twitch fibres predominant), a positive MMG-RMS linear relationship of up to 80% PT has also been reported in healthy volunteers (Yoshitake & Moritani, 1999). The present results with MMG-RMS attenuation at around 80% PT, reaffirmed those earlier findings and showed that comparable correlations could be obtained in paralyzed quadriceps muscle during NMES-evoked contractions.

4.5.6 Potential Clinical Applications

There is strong evidence (Crameri et al., 2002; Ibitoye et al., 2016; Jacobs & Nash, 2004; Panisset et al., 2016; Qin et al., 2010) that muscle deconditioning, due to "non-use", following SCI is attributed to a lack of physical activity in the affected populations. Therefore, during exercise, MMG signal might be used as a non-invasive measure of muscle effort to quantify the effectiveness of NMES training for neurological populations. Moreover, the signal might be used as a real-time proto-dynamometer to quantify muscle performance during activity of daily living—especially as a feedback signal to up-titrate NMES current amplitude, pulse duration or regulate stimulation frequency to optimize NMES activities. This finding also supports the suitability of MMG signal as a practical NMES control signal, as it only requires the calculation of MMG amplitude parameters for practical implementation (Gobbo et al., 2006). However, MMG responses to NMES-evoked torque production in other functionally relevant muscles, specifically of different fibre distribution, need to be investigated. Such information will give further insight into the physiological relevance of the signal.

Additionally, as the deconditioning is responsible for muscle fibre wasting which is manifested in the loss of muscle strength or functional capacity, there is current research interest in preserving muscle integrity not only for the promotion of muscle capacity but also for the prevention of secondary complication associated with disuse (Galea, 2012; Lam et al., 2010). Thus, the health benefits of the NMES incremental isometric contractions strategy used in this study may include; improvement of muscle tone, bulk/mass, strength and blood flow in order to offset spasticity, disuse atrophy and osteoporosis among other benefits. The collective clinical relevant of these benefits was to prepare the musculoskeletal system for a critical task such as standing and ambulation training (Kern et al., 2005).

The following limitations are acknowledged in the study design: (i) the findings were dependent on the protocol used, (*i.e.* modulating the current amplitude while keeping the pulse width and frequency constant) (ii) the NMES cycle training baseline of at least seven weeks was adopted based on the previous recommendation (Bickel et al., 2004), but a longer duration of training may have yielded different results, (iii) the investigation was based on a sample size (n) of six and some data distributions were non-normally skewed. Although the sample size was modest in comparison with other studies (Crameri et al., 2002; Sabatier et al., 2005) that have employed persons with motor complete spinal cord lesions, the size might have also affected the present findings so these should be interpreted with caution. Therefore, a larger test population is warranted in the future study to identify how broadly the present findings could be generalized.

4.6 Conclusion

The pattern of relationships between the MMG signals and NMES-evoked isometric contractions to study the motor unit recruitment strategy in motor complete paralyzed quadriceps have been demonstrated with an acceptable reliability of the MMG measurements. Useful insights inferred from these findings are: (i) MMG signals were sensitive to the incremental NMES-evoked muscle torque measured by a commercial dynamometer (*i.e.* a "gold standard"), and as a physically small sensor, the MMG could be a reliable proxy for these dynamometer measurements, (ii) MMG signals correlations with NMES-evoked muscle torque could be used to assess the paralyzed quadriceps mechanical changes during submaximal-to-maximal NMES-evoked muscle contractions. The application of MMG amplitude as a proxy of electrical stimulus-evoked isometric muscle force and relevance as a biofeedback source in NMES-evoked activities are evident. Whether these results could be generalized to other muscles and mode of contractions, specifically, during critical activities—such as NMES-supported standing, is a topic of further research. Testing of such hypothesis remains a promising perspective, particularly since automated NMES is clinically more relevant, effective and safe when compared with the traditional "user-controlled" approach (Braz et al., 2009).

CHAPTER 5: MUSCLE FORCE ESTIMATION FROM MECHANOMYOGRAPHY IN PERSONS WITH SCI

5.1 Introduction

In this Chapter, the dataset from the participants with spinal cord injury (SCI) was used to construct a model to estimate muscle force from MMG signals collected during NMES-evoked knee extension task. This was necessary for an intelligent torque estimation from the muscle response parameters associated with NMES-evoked torque production in order to avoid the "curse of dimensionality" which characterizes the traditional regression approaches (Huang et al., 2006). Thus, this Chapter demonstrated the performance and investigated the potential application of a statistical computational intelligent technique based on support vector regression (SVR) modelling for NMES-evoked muscle torque estimation from the quadriceps MMG signals of persons with chronic and motor complete SCI in whose NMES-evoked knee extension exercise is crucial (Hamzaid & Davis, 2009), particularly, for habituation and reconditioning in preparation for standing and ambulation training.

The study described in this Chapter has been prepared and ready for submission to IEEE Sensors Journal under the following heading:

> NMES-Evoked Knee Torque Estimation from Paralyzed Quadriceps Mechanomyographic signal Using Support Vector Regression Modelling.

5.2 Literature Review

Spinal Cord Injury is one of the catastrophic injuries of the nervous system which may lead to permanent neurological impairments (Hamid & Hayek, 2008). This is due to the manifestation of deficits in voluntary motor control and sensation, below the level of injury, that limits the performance of daily tasks and the overall activity level of those affected (Jacobs & Nash, 2004). Neuromuscular Electrical Stimulation (NMES)-evoked muscle contraction has been recommended for motor relearning and strength training in the affected population (Jacobs & Nash, 2004).

Conventionally, the NMES administration has been through manual control based on open-loop strategy (Peckham & Knutson, 2005). Although NMES technologies based on this approach have gained user preference probably due to their operational simplicity, their clinical efficacy is limited (Sun & Morrell, 2014). To implement a closed-loop NMES system, whereby the electrical stimulus parameters could be automated by the muscle responses for optimization of the NMES utility, it has been suggested (Peckham & Knutson, 2005) that the muscle state information is automatically fed back to the NMES system by peripherally placed sensors to modulate the NMES operations. This explains a recent surge in the research interest on reliable biopotential sensing modalities to monitor the physiological and mechanical responses of contracting muscles (Popović, 2014).

One such biopotential which has been recently promoted is mechanomyography (MMG)—the mechanical equivalent of muscle electromyography (Beck et al., 2004). The MMG signal is generated by a lateral movement of activated muscle fibres at the resonant frequency of the muscle, and it is reflected as the pressure waves produced by the dimensional changes of contractile elements of the muscle (Beck et al., 2004; Orizio, 1993). It is interesting to note that unlike electromyography, the MMG signal is insensitive to electrical signal artifact and impedance changes, and thus, suitable for muscle contraction measurements in the presence of electrical artifact noise, and could be subjected to a long time usage (Barry et al., 1986). The assessment of muscle contraction by MMG signal is primarily effected through changes in the time and/or frequency domain characteristics of the signal.

Although the signal has mostly been used as a proxy of muscle force during voluntary muscle contractions (Ibitoye et al., 2014), emerging evidence suggests its close relationship with NMES-evoked torque, mostly in healthy (Gobbo et al., 2006; Orizio, 1993; Petitjean et al., 1998; Stokes & Cooper, 1992; Yoshitake & Moritani, 1999) and rarely in persons with neuromuscular or neurological conditions (Hu et al., 2007; Ibitoye et al., 2016; Orizio et al., 1997). Therefore, the application of MMG signals for joint torque estimation during electrical stimulus contraction is rudimentary as it has only been investigated using traditional regression methodology.

The traditional regression methodologies are based on some assumptions that may be unsuitable for the characteristics of contemporary datasets (Vapnik, 1998). For instance, in situations where many factors contribute to a particular event that one intends to predict such as in a highly dimensional problem. Solving this kind of a problem by a traditional regression method would lead to a phenomenon termed "curse of dimensionality", whereby increasing the dimension of input dataset/independent variables requires an exponentially increasing number of terms to be solved (Huang et al., 2006). Additionally, real-life datasets may not be necessarily normally distributed and the assumption on which the traditional regressions rely will become violated. To evade these limitations as well as improve the torque estimation accuracy, statistical machine learning algorithms have been recommended (Huang et al., 2006; Vapnik, 1998).

The estimation of torque from MMG signals using machine learning modelling has recently been investigated in some upper limb muscles of healthy volunteers during voluntary contraction. For example, Youn and Kim (2010, 2011) studied the accuracy of an artificial neural network (ANN) model for elbow joints force prediction from MMG signals. The investigators reported estimation accuracies of up to 0.892 (Youn & Kim, 2010) and 0.883 (Youn & Kim, 2011) and suggested the future development of other machine learning techniques including Support Vector Regression (SVR) to improve the accuracy of their model. As an extension of a well-known Support Vector Machine (SVM) methodology, SVR depends on the statistical supervised learning theory (Vapnik, 1999b), as introduced by Vapnik et al. (1997), particularly for complex regression tasks (Vapnik et al., 1997; Wang et al., 2003). SVM minimizes a prediction risk through a 'trade-off' between the training error and confidence range (Schölkopf & Smola, 2002; Vapnik, 1998). The technique is particularly suitable for high dimensional problems even with small sample size datasets (Gupta, 2007; Shin et al., 2005).

Based on the extension of standard SVM algorithms, SVR has two basic phases of implementation, namely: (i) learning phase where a partitioned dataset is used to construct a mathematical model to represent a relationship between the actual/target and estimated parameters; and (ii) testing phase where the unused dataset for model development is used to assess the performance of the developed model (Vapnik et al., 1997). SVR often demonstrate an impressive performance, based on standard benchmarking tasks in comparison with other machine learning algorithms (Meyer et al., 2003). For instance, as compared to an ANN modelling, SVR has been used for a "simultaneous myoelectric control of multiple degrees of freedom" of some upper limbs muscle actions (Ameri et al., 2014), at a computational speed that is useful for real-time applications. Furthermore, our group (Ibitoye et al., 2016) recently reported an accuracy of 94% for NMES-evoked isometric knee extension torque estimation from MMG signal in healthy volunteers using SVR modelling. Therefore, SVR methodology has been gaining recent prominence for estimation and prediction problems in life sciences and medical fields (Van Looy et al., 2007).

To date, limited studies (Ibitoye et al., 2016; Youn & Kim, 2010, 2011) have investigated the application of machine learning techniques for torque estimation from

MMG signal. To the author's understanding, a torque estimation study using MMG collected during NMES-evoked contractions of paralyzed quadriceps has not been previously reported and the available information on healthy volunteers could not be extrapolated to interpret paralyzed quadriceps force responses (Scott et al., 2007).

Thus, the present study sought to investigate the estimation accuracy of an SVR model for knee torque estimation from the quadriceps MMG signal measured during incremental NMES-evoked knee extension task in persons with motor complete SCI. This knowledge has an important practical implication in a closed-loop NMES control settings, where a measurement of muscle response has been suggested as the preferred feedback signal (Ibitoye et al., 2016; Popović, 2014). This is based on the premise that MMG provides direct and immediate information on the response of the muscle to the electrical stimulation. Therefore, the information derived from the present investigation has a direct implication on the optimization of the efficacy of NMES applications in functionally relevant modes of muscle activity including knee extension, with short bouts of contraction and recovery periods (Crosbie et al., 2009), and standing tasks, where direct torque measurement may be required as an NMES modulating signal but impractical to measure directly.

The following section described the experimental investigation conducted to obtain the dataset used for the modelling task.

5.3 Materials and Methods

5.3.1 Experimental procedures

This study was granted ethical approval by the University of Malaya Medical Ethics Committee (Approval No:1003.14(1), as detailed in Appendix A). Eight chronic motor complete persons with SCI [lesion levels between C5 and T7 (mean (SD) age, 39.8 (10.7) years; stature, 1.7 (0.06) m; body mass, 67.9 (14.0) kg); time since injury, 10.9 (7.3)] volunteered for the NMES-evoked isometric knee extension trials, for torque production, to examine the accuracy of the SVR model. Participants' lower limbs were safely positioned on a calibrated commercial isokinetic dynamometer (Biodex 4, Shirley Corp., NY, USA) for torque measurement (Figure 5.1).

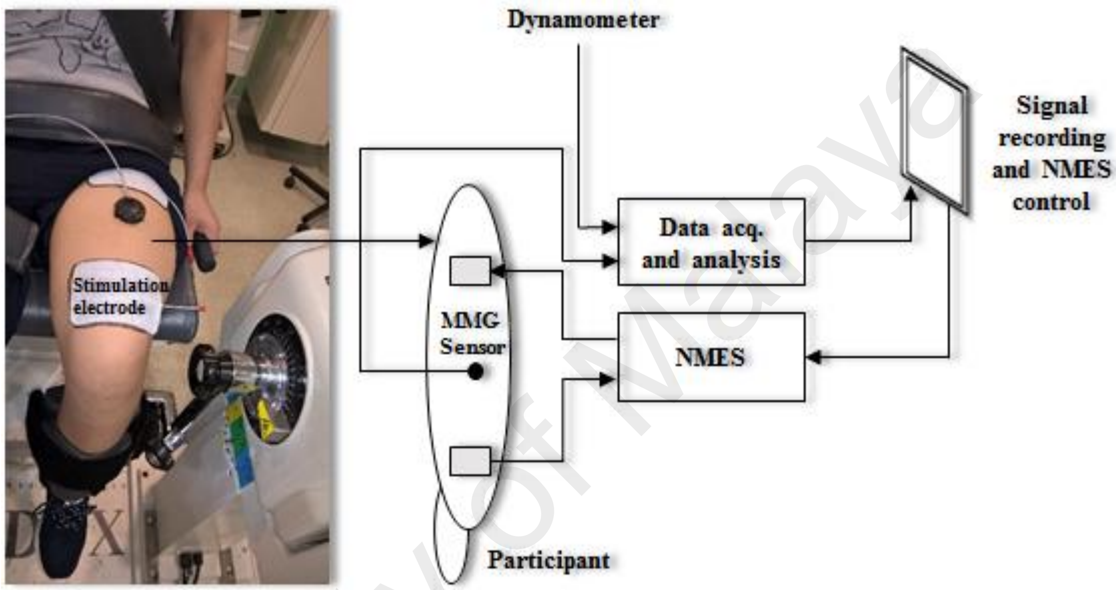

Figure 5.1: Sketch of the experimental setup for measuring the MMG signal and torque in a person with SCI.

To prevent extraneous movement, participants were firmly secured using dynamometer's thigh, trunk, and pelvic belts. In order to generate incremental torque values, the quadriceps muscle was stimulated with a current-controlled proprietary stimulator (RehaStim^{TM}, Hasomed GmbH, Magdeburg, Germany) at a constant frequency of 30 Hz and pulse width of 400 µs with an incremental stimulation current between 50 mA and 120 mA in steps of 10 mA (*i.e.* eight randomly ordered contraction intensity levels) for 4 s at each contraction intensity level.

The experiment was conducted at 60^0 and 90^0 knee angles. For an optimal muscle response, the stimulation electrodes were placed on the quadriceps muscle group as previously described in Ibitoye et al. (2016) based on the procedures of Botter et al. (2011) and Levin et al. (2000). In order to keep the bone health within a safe limit (Kagaya et al., 1995), the stimulation current was limited to 120 mA. To disallow probable rapid muscle fatigue, a 10 min recovery was allowed between trials and 48 hrs between knee angles.

5.3.2 Signal acquisition and analysis

While there are various sensors that could be used to measure MMG signal, accelerometers have been most widely utilized (Orizio, 2004). Therefore, the MMG signals of the Rectus Femoris (RF), as a simple representation of the knee extensor, were recorded with an accelerometer sensor (Sonostics BPS-II VMG transducer) compatible with the MP150 data acquisition system and simultaneously with the torque generated during NMES-evoked contractions. Using double-sided adhesive tape, the MMG sensor was fixed on the muscle belly of the RF. The MMG signals were digitized at 2 kHz and filtered between 20 and 200 Hz, to subdue the effects of muscle tremor and movement artifact (Goldenberg et al., 1991), with a 16-bit analog-to-digital converter using AcqKnowledge data acquisition and analysis software (MP150, BIOPAC Systems, Santa Barbara, CA, Inc. USA) and a customized programme in LabVIEW (Version 12.0, National Instruments, Austin, TX, USA).

To allow for maximal recruitment contractions in analyses, a middle 1 s epoch of the collected signal, while avoiding the on and off transients during the initiation and termination of muscle contractions, respectively, at each contraction level was retrieved for further analyses (Orizio et al., 1989). The MMG time domain parameters including root mean square (RMS) and peak to peak (PTP) amplitudes, that are related (Beck et al., 2004; Orizio, 1993) to the motor unit recruitment level and measures of motor output intensity were extracted for use as input variables to the proposed SVR model. The following section briefly describes the development of the proposed SVR model.

5.3.3 Development of the Support Vector Regression Model

The data obtained from the experiment thus far described was used to train the SVR model while the standard SVR coding in MATLAB software (Version 12, The MathWorks, Inc., MA, USA) was used to construct the model. To build an SVR model, the learning machine requires a training dataset of the form $(x_1, y_1),.........,(x_k, y_k)$ of continuous values. This dataset typically has an approximation function of the form:

$$f(x,\alpha) = \langle w, x \rangle + b \text{; where } w \in R^{'} \text{ and } b \in R \tag{5.1}$$

SVR finds a function $f(x,\alpha)$ that approximates the target data instance y_1 …., y_k. The function usually uses an error of approximation, as measured by Vapnik's alternative ε-insensitivity error function (Vapnik et al., 1997), to measure the maximum allowable deviation from the true value of the target data. That is, the permitted error on a training set should be kept within ε zone. Also, for the avoidance of over-fitting, the function $f(x,\alpha)$ should be "as flat as possible" (Statnikov et al., 2011). Thus, Smola (1996) has identified that minimization of the Euclidean norm $\|w\|^2$ is required to achieve the needed flatness of the equation (5.1).

Moreover, for a non-linear SVR model, the kernel function selection represents an important step in the regression performance as the models are robust and have the ability to explore a given dataset effectively via a nonlinear kernel function (Schölkopf & Smola, 2002) by mapping the input dataset or original features into a high-dimensional feature space. Thus, SVR, through 'kernel tricks' computes a regression function in a high dimensional feature space—where the input data are mapped via a nonlinear mapping function *i.e.* kernel function (Noble, 2006; Vapnik et al., 1997; Wang et al., 2003). The resulting decision function with kernel function $K\langle x_i, x \rangle$ is as shown in equation (5.2).

$$f(x,\alpha)=\sum_{i=1}^{k}\left(\lambda_i^*-\lambda_i\right)K\left\langle x_i,x\right\rangle+b \tag{5.2}$$

A detailed description and formulation of the solution to the resulting optimization problems could be found in Vapnik (1995), Smola and Schölkopf (2004) and Gupta (2007).

Table 5.1: Typical kernel functions.

Kernel type	Mathematical representation
Linear	$K(x_i,x_j)=x_i^T.x_j$
Polynomial	$K(\overrightarrow{x_i},\overrightarrow{x_j})=(\overrightarrow{x_i},\overrightarrow{x_j}+1)^d$
Gaussian (RBF)	$K(\overrightarrow{x_i},\overrightarrow{x_j})=\exp\left(-\gamma\left\Vert\overrightarrow{x_i}-\overrightarrow{x_j}\right\Vert^d\right)$
Sigmoid	$K(x_i,x_j)=\tanh(\gamma x_i{}^T x_j+r)$

Where, γ, r, and d are kernel parameters.

Table 5.1 presents the commonly used kernel functions based on the recommendation of Vapnik (1999b) and Schölkopf and Smola (2002). Two classical kernel functions namely gaussian and polynomial were evaluated in the present study based on their previous (Su et al., 2014) excellent performance in related fields. For example, a gaussian kernel based SVR model usually exhibits an excellent nonlinear predictive performance and has only a few parameter to be determined for implementation (Su et al., 2014). Polynomial kernel, being another commonly used kernel (Gupta, 2007), was also applied to the same dataset as a comparison to the gaussian kernel. Another important aspect of SVR modelling is the selection of certain user-defined parameters including the kernel parameters based on the selected kernel type, ε-insensitive zone and the regularization parameter (C) which regulates the regression or approximation function's flatness and the amount of permitted error beyond ε- insensitive zone (Gupta, 2007; Yu et al., 2006). The usual practice for the optimal selection of these parameters is described next.

5.3.4 Optimal parameters search approach

The selection of the optimized parameters is supposed to be automated, and computationally efficient. This process involves multiple iterations. Specifically, the time needed for the search or iteration is a function of the data size. The goal is to minimize the computational duration. This is necessary for an optimized estimation as the performance of an SVR model depends on the selection of optimal input parameters (Shamshirband et al., 2014; Vapnik et al., 1997). One approach to minimizing the computational duration is by using a partial dataset that could provide a near optimum model for support vector learning process (Hens & Tiwari, 2012). Therefore, to optimize the search for optimal kernel parameters to build the best model, a test-set cross-validation technique was used in the present study and its implementation is as described in Chapter 3 (Algorithm 3.1). Table 5.2 depicts the optimal values of parameters used to develop the final model.

Before use, the dataset was divided into two independent parts in compliance (Akande et al., 2015) with the SVR modelling approach *i.e.*, a training subset was 70% of the dataset and a testing subset was the remaining 30% of the dataset. This was done through test-set cross-validation method by stratified sampling approach for effective random partitioning (Akbani et al., 2004; Hens & Tiwari, 2012). Following this approach, a SVR analysis was performed on the training dataset and the generalization accuracy of the model was verified on the testing subset.

Table 5.3 presents the data used in the present study. Apart from being a common procedure for optimizing the performance of SVR (Ben-Hur & Weston, 2010), data normalization as applied to the current study also compensated for the probable variations in the participants' muscle response to the electrical stimulus intensity. Table 5.4 depicts the statistical analysis of the dataset.

Table 5.2: Optimal parameters for the proposed Support Vector Regression model.

Kernel	Gaussian (RBF)	Polynomial
C	879	879
Hyper-parameter (Lambda)	2^{-15}	2^{-15}
Epsilon (ε)	0.1205	0.1205
Kernel option	54	2

Abbreviations: C = the regularization parameter.

5.3.5 The statistical performance evaluation of the proposed model

In order to evaluate the performance or estimation accuracy of the proposed SVR model, the coefficient of determination (R^2) and root mean square error (RMSE) were utilized. Specifically, these measures were used to evaluate the goodness of fit of the relationship between the estimated and actual/target outputs as well as the error of estimation, respectively.

Table 5.3: Summary of the datasets.
MMG characteristics at eight NMES stimulation intensity levels, at two knee angles and their respective peak torque values.

Stim. Intensity (mA)	Knee angle					
	60^0			90^0		
	Torque	RMS	PTP	Torque	RMS	PTP
50	24.00(10.9)	32.67(13.9)	39.80(16.9)	20.55(8.5)	42.76(15.4)	49.44(11.3)
60	30.14(8.6)	48.73(8.9)	58.14(11.5)	38.04(12.5)	51.40(15.4)	57.76(16.7)
70	47.04(10.6)	56.55(8.8)	65.22(11.9)	56.90(10.3)	66.13(15.2)	74.51(17.0)
80	61.11(12.9)	69.54(13.0)	78.85(16.5)	67.67(12.1)	70.04(17.0)	88.24(21.3)
90	76.42(11.4)	83.77(23.3)	86.91(19.2)	78.61(8.5)	82.17(22.9)	77.76(18.0)
100	87.47(9.6)	96.18(17.6)	98.11(13.7)	88.44(6.4)	81.12(19.8)	77.96(19.1)
110	92.88(5.4)	100.88(6.8)	103.71(5.6)	95.16(3.8)	90.30(14.5)	91.22(17.0)
120	100.00(0)	100.00(0)	100.00(0)	100.00(0)	100.00(0)	100.00(0)

Abbreviations: RMS- Normalized MMG-RMS %, PTP- Normalized MMG-PTP%. Values are reported in mean (standard deviation).

Table 5.4: Statistical parameters of the datasets.

Input parameters	Mean	Max	Median	Stdev	Min
Participants					
Weight (kg)	67.9	82	73.8	14.0	44
Age (years)	39.8	58	39.0	10.7	25
Stimulation intensity (mA)	85	120	85	22.9	50
Knee angle (deg)	75	90	75	15	60
Normalized MMG-RMS%	73.3	128.2	72.5	26.0	15.7
Normalized MMG-PTP%	78.0	125.4	77.8	24.0	19.5
Torque	66.5	101.9	71.1	28.3	6.0

5.4 Results and Discussion

In this section, the dataset used for the experiment are described and the results of the SVR modelling are presented. A comparison between the two selected kernel functions (gaussian and polynomial) is also reported. Furthermore, the implications of the results are discussed. Finally, a conclusion on the findings of the study as well as its clinical implication is highlighted.

The present study assesses the predictive accuracy of SVR model to estimate the torque measured during an incremental NMES-evoked knee extension task using quadriceps MMG signals in persons with motor complete SCI. The input features to the proposed model were MMG signal amplitude (MMG-RMS and MMG-PTP), stimulation intensity, knee angle, participants' weight and age with the NMES-evoked torque as the target output. The results of the two kernel functions (gaussian and polynomial) were compared in terms of the estimation accuracy using the two partitioned datasets (training and testing) following the optimal selection of the SVR modelling parameters.

Figure 5.2 and 5.3 depict the relationship between the target/ experimental torque and estimated torque using both kernel functions for the training and testing cases, respectively. For the training case, R^2, measure of the estimation accuracy, of 95% (with RMSE = 6.28) and 92% (with RMSE = 7.99) were obtained with gaussian and polynomial kernels, respectively. However, in the case of the testing dataset, R^2 of 94% (with RMSE = 8.19) and 91% (with RMSE = 9.82) were obtained for the gaussian and polynomial kernel, respectively (Table 5.5). Moreover, Figures 5.2 and 5.3 show a slightly better performance of gaussian kernel in comparison with the polynomial kernel for both training and testing datasets, although both performances were comparably high.

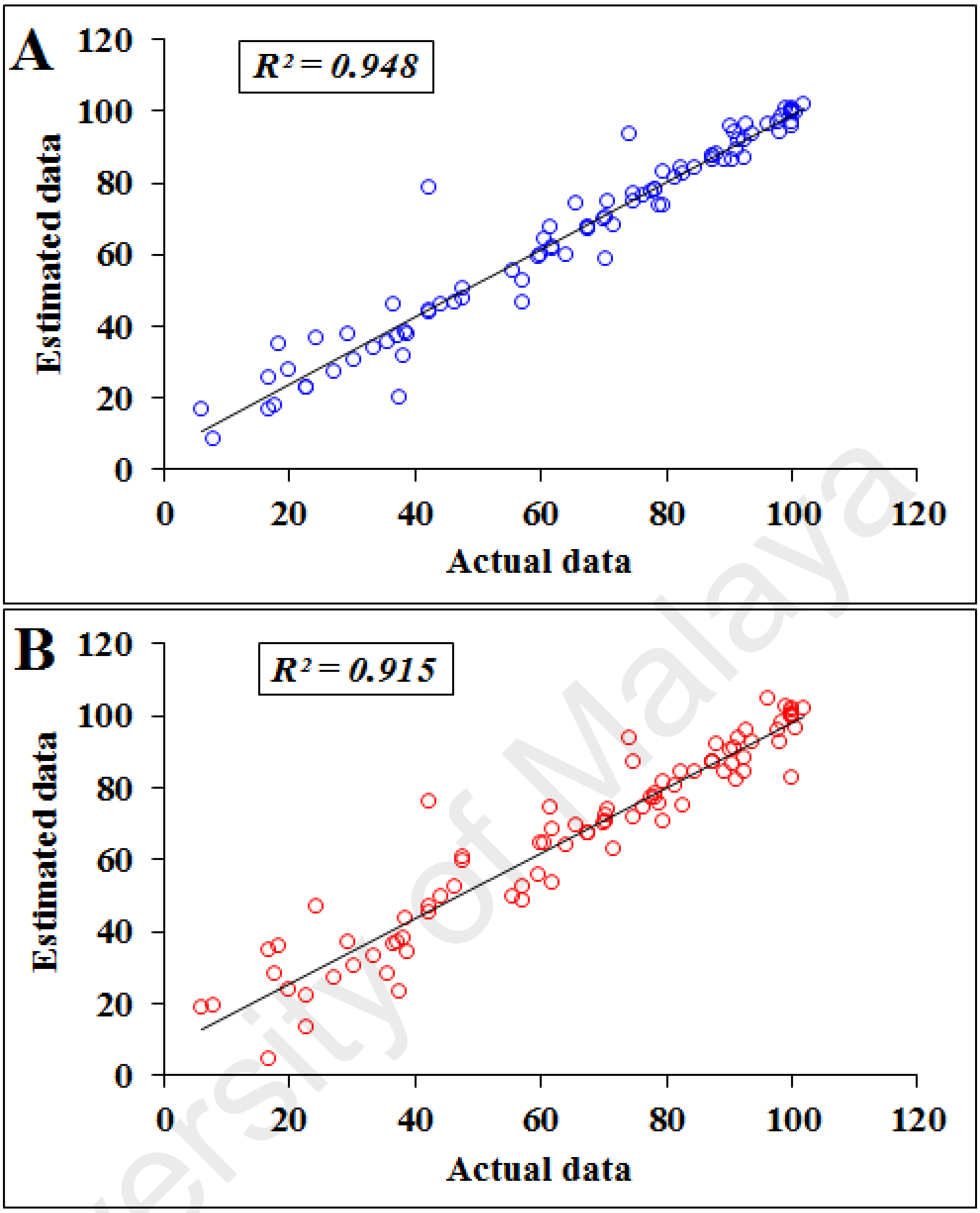

Figure 5.2: Relationships between the experimental/actual torque and estimated torque using gaussian (A) and polynomial (B) based kernel functions for training dataset.

Plots in Figure 5.4 (A and B) show a close relationship between the actual and estimated torque using the two kernel functions for training and testing subsets suggesting a comparable performance of the two kernels used in the present study. The plots revealed a slightly higher performance of gaussian kernel over polynomial kernel for torque prediction on both the training and testing subsets, although both kernels closely tracked the actual torque production.

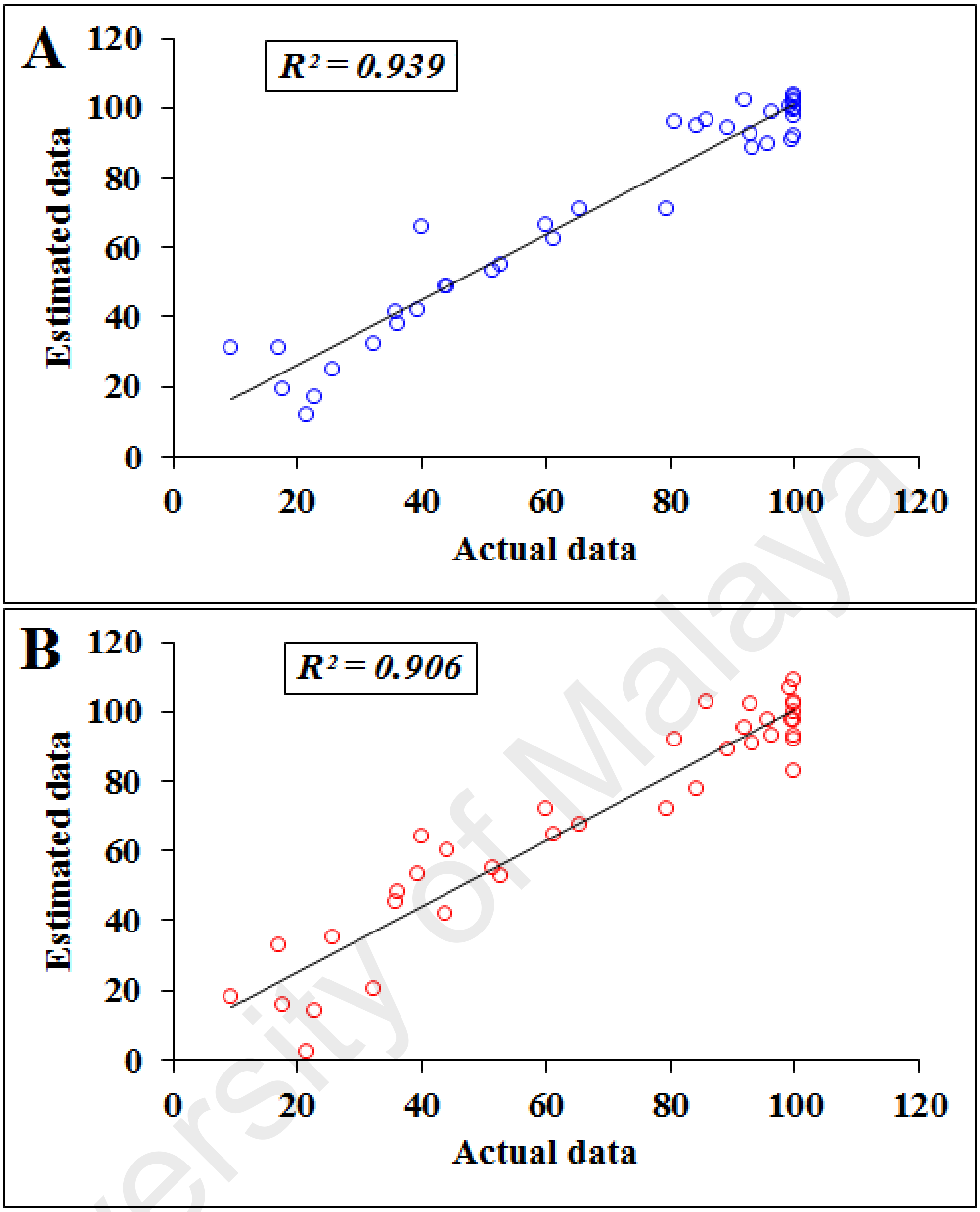

Figure 5.3: Relationships between the experimental/actual torque and estimated torque using gaussian (A) and polynomial (B) based kernel functions for the testing dataset.

Based on the results obtained, the SVR-based model could be used to estimate the NMES-evoked torque from MMG signal in persons with SCI. This finding introduces an alternative approach for torque estimation with potential applications in research, outdoor and clinical settings. Specifically, this technique may be applied to advance the clinical assessment of rehabilitation intervention outcomes with a miniature sensor such as an accelerometer used to measure MMG signal. Therefore, the knee torque estimation model proposed in this study could lend further guidance for the study and analysis of knee extension torque dynamics in SCI populations as a precursor for sit-to-stand, prolonged standing or ambulation training as the tracking of changes in mechanical muscle response to effect torque control requires that a joint torque must be accurately estimated.

Table 5.5: The accuracy of the developed model.

SVR Kernel	Training			Testing		
	r	***R***^{2}	**RMSE**	***r***	***R***^{2}	**RMSE**
Gaussian (RBF)	0.973	95%	6.28	0.969	94%	8.19
Polynomial	0.957	92%	7.99	0.952	91%	9.82

5.4.1 Clinical Implications

A number of approaches have been promoted for assessment of the strength improvement following NMES exercise. The isokinetic dynamometer that measures muscle strength gains via joint torque is laboratory based, not portable, and does not allow an integration to the electrical circuits for flexible NMES applications in the home and outdoors settings. With the findings of this present study, it may be possible that the mechanical muscle response to the electrical stimulus contractions as a marker of strength gain or deterioration (as revealed by the muscle's MMG), could be monitored. This may, therefore, strengthen clinical research with a tool that allows clinicians and other allied professionals to monitor the state of the electrically stimulated muscles. Furthermore, a predictive NMES-evoked torque control signal to automate NMES system may be derived from the MMG signal. This directly relates to the optimization of the efficacy of NMES systems as the proposed model could facilitate the controllability and versatility of the NMES utility. Moreover, as the electrical stimulation paradigm adopted in this study is similar to that used for routine clinical practice for knee extension strength training, it can be hypothesized that a similar model may be required for torque estimation during the application of NMES for critical tasks in persons with SCI.

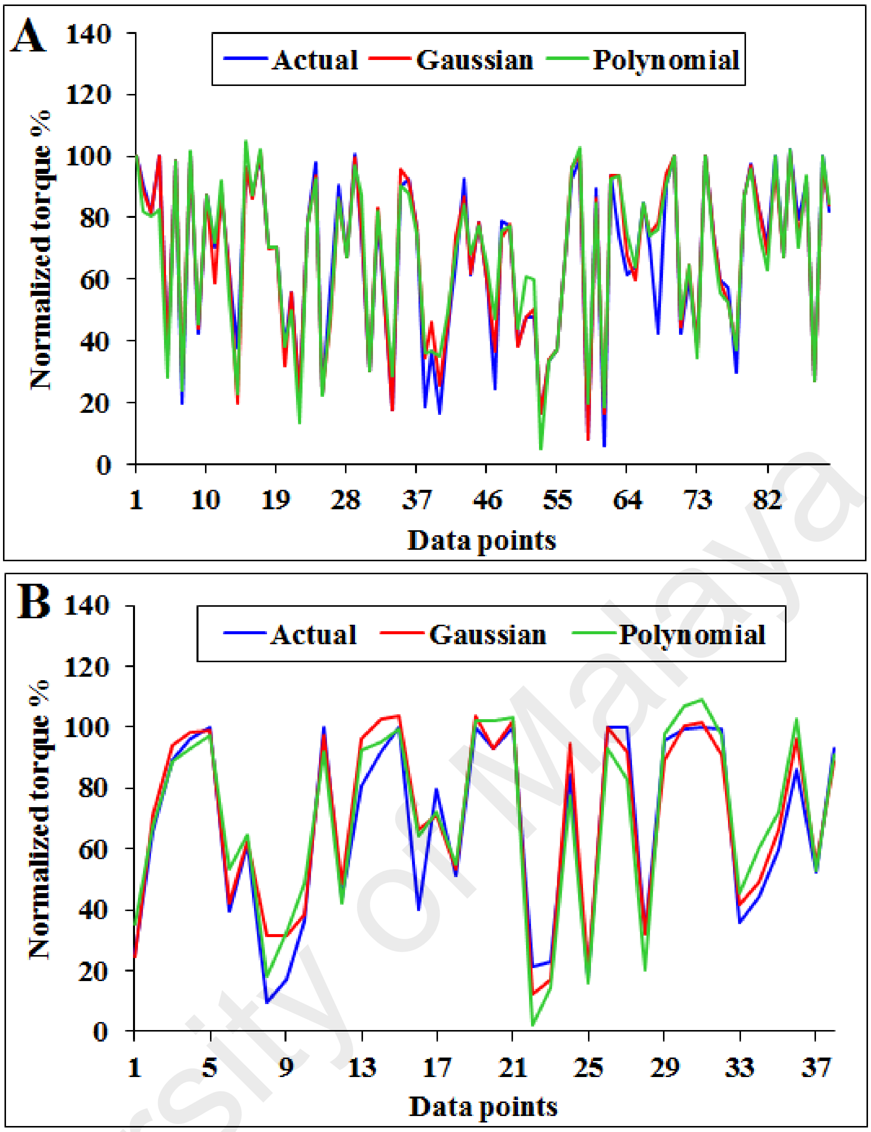

Figure 5.4: Plots of the actual versus predicted data points for (A) training and (B) testing subsets.

5.5 Conclusion

The present study has elucidated the application of SVR to estimate the NMES-evoked knee torque, as measured by an isokinetic dynamometer, using paralyzed knee extensors' MMG signals. The results revealed a good relationship between the actual knee torque production as obtained from a laboratory-based dynamometer and the MMG signals collected by an accelerometer-based sensor and other related parameters. This study has demonstrated that SVR is an alternative and viable computational tool for modelling the complex relationship between different parameters used in estimating the NMES-evoked muscle force/torque. Therefore, the proposed SVR model for knee torque estimation is a promising tool to access muscle force during real-time application of NMES where this cannot be otherwise estimated with a dynamometer. In the future studies, other related modelling algorithms will be considered in order to evaluate and improve the proposed model. In the meantime, the high accuracy obtained in this study has potential application in a variety of NMES related fields. For example, as a mechanomyographic based feedback signal for NMES controllers. As the ability to predict torque output response of electrically stimulated muscle has important implications for the use of NMES in rehabilitation, efforts are under way to apply the developed SVR model for prediction of muscle force production and fatigue during functionally relevant tasks such as NMES-supported standing in persons with neurological conditions. In all, these findings provide important new information with implication for the use of MMG signal in regulating the NMES parameters for optimal performance.

CHAPTER 6: MUSCLE FATIGUE TRACKING DURING NMES STANDING TO FAILURE CHALLENGE IN PERSONS WITH MOTOR COMPLETE SCI USING MECHANOMYOGRAPHY

6.1 Introduction

Up to this stage, it has been verified that mechanomyography could be used to investigate the recruitment pattern during isometric non-fatigued contractions where the recruitment order is somewhat or relatively simple (Orizio et al., 2003). The present Chapter reports the pattern of MMG signal to study motor unit recruitment during NMES sustained standing to fatigue failure challenge in persons with motor complete spinal cord injury (SCI). This study aimed to reveal the pattern of relationship between the MMG signals and fatigue contractions during a relatively complex and critical NMES-evoked muscle action. The experiment reported herein was conducted at the rehabilitation gymnasium of the Department of Rehabilitation Medicine, University of Malaya Medical Centre. The rationale for this study was to investigate the clinical relevance of the MMG signal by studying the relationship between the signal and muscle response's decay as indicated by knee buckling during fatigue contractions. One important implication of this study was to investigate the potential utility of the MMG as a muscle fatigue sensor useful as a control signal for NMES-supported standing in persons with SCI.

The study reported in this Chapter was taken from the following submitted journal article to the Medical and Biological Engineering and Computing under the heading:

Ibitoye, M. O., Hamzaid, N. A., Hasnan, N., Abdul Wahab, A. K., & Davis, G. M. (2017) Quadriceps mechanomyography reflects muscle fatigue during FES-sustained standing in adults with spinal cord injury: Case series proof of concept, under review in Medical and Biological Engineering and Computing.

6.2 Literature Review

Neuromuscular fatigue is generally defined as an exercise-induced reduction in muscle effort or ability to sustain muscle contractions (Fitts, 1994; Gandevia, 2001). During functional applications of Neuromuscular Electrical Stimulation (NMES), such as in upright stance, the agonist muscles are continuously under electrical stimulation-evoked contractions. This predisposes the stimulated muscles to rapid fatigue, which is the cause of standing failure (Brindley et al., 1979), manifested by a knee buckle.

Traditionally, muscle fatigue during functional electrical stimulation (FES)-supported standing has been monitored by a change in knee angle (Braz et al., 2009), and it is this decrease of knee angle that infers a reduction in the muscle's performance. Moreover, the phenomenon of muscle fatigue has also been investigated by monitoring changes of other characteristics, such as electromechanical indices (Blangsted et al., 2005), neurophysiology and metabolic responses (Levy et al., 1993). These have been often measured because a high stimulation intensity and prolonged muscle contraction are characterized by significant alterations in neuromuscular physiology, local muscle oxygenation, and metabolite concentrations (Allen et al., 2008; Cady et al., 1989). However, as "fatiguing contraction" lie within the continuum of effective muscle contractions (Scott et al., 2006), efforts to improve standing duration warrant the investigation of a possible proxy of muscle fatigue to directly grade muscle performance (Dugan & Frontera, 2000). A mechanical proxy of muscle performance may be used to titrate FES stimulation parameters in real-time for optimal task duration, such as upright stance, especially in persons with an increased susceptibility to rapid muscle fatigue after spinal cord injury (SCI).

Previous investigators (Bajd et al., 1982; Braz, Russold, & Davis, 2009; Ibitoye et al., 2016) have recommended some strategies to prolong the duration of FES-supported standing by delaying the onset of fatigue-failure. One traditional approach has been to maximally stimulate the knee extensors/quadriceps muscle with manual or open-loop FES control. Although this strategy is still popular since it can be readily deployed during a standing task with the assistance of caregivers, the approach provides a sub-optimal standing duration due to rapid muscle fatigue. However, more recent evidence (Braz et al., 2009; Popović, 2014) has suggested that automatic titration of key FES parameters based on the muscles' response might delay fatigability and increase standing duration in the SCI population. Based on this premise, research efforts to improve standing duration have focused on muscle response information, an indirect measure of muscle force and performance. However, issues such as cosmesis, reliability, and sensitivity of a muscle response sensor continue to inhibit the clinical acceptability of this approach.

Typically, when FES activates muscle fibers, there is excitation-contraction coupling due to depolarization of the motor nerve (Collins, 2007). The generated force, as a result of muscle shortening, can be obtained at the joint as a twitch torque (McMillan et al., 1990), a reduction of which characterizes muscle fatigue. Therefore, peak torque or maximal muscle effort has been proposed as a better descriptor of muscle fatigue (Russ et al., 2002), although impractical to measure directly during a real-time application of FES (Popović, 2014). There have been some previous useful attempts to utilize muscle electromyography (EMG) as an indirect indicator of muscle fatigue during surface (Chesler & Durfee, 1997; Li et al., 2014; Mizrahi et al., 1997) and implanted stimulations (Hayashibe et al., 2011). Unfortunately, electrical stimulation-evoked contraction is generally characterized by high stimulation artifacts that saturate EMG circuitry, and the option of artifact-blanking often complicates the retrieval of useful parameters of the evoked-EMG signal (Chesler & Durfee, 1997; Popović, 2014). This suggests a clear need for an alternative or complementary method to study muscle fatigue contraction, especially, during skin-surface repetitive FES contractions.

One promising technique to quantify muscle performance is mechanomyography (MMG) (Orizio et al., 1999). MMG signal is electrical stimulation artifact free (Yamaguchi et al., 2012) and has been identified as a useful method to detect impairments in excitation–contraction coupling (Søgaard et al., 2003) for muscle performance assessments (Herzog et al., 1994) during voluntary isometric fatiguing contractions. The MMG signal has been specifically identified as sensitive to muscle performance decrements due to the failure of excitation-contraction coupling during muscle fatigue (Blangsted et al., 2005). Being a mechanical counterpart of neuromuscular electrical activity (i.e. EMG) during muscle contractions, the MMG characterizes the intrinsic muscle mechanical properties (Shinohara et al., 1998). Thus, the MMG can reveal a fatigue-related impairment of the muscle's mechanical changes (Blangsted et al., 2005).

For example, during voluntary isometric fatiguing contractions, MMG amplitude has shown a consistent decay in upper extremities muscle groups (Barry et al., 1992; Madeleine et al., 2002). Furthermore, variations in the magnitude of MMG amplitude have been previously associated with a parallel reduction in force production during muscle fatigue of FES aetiology in healthy volunteers (Gobbo et al., 2006; Orizio et al., 1996). However, apart from the healthy populations investigated in earlier studies, the response of the MMG signal to electrical stimulation was only examined at submaximal levels, and these findings may not infer MMG signal characteristics in critical situations such as in prolonged standing in persons with a neurological impairment. Nevertheless, an important proof of concept could be objectively inferred from those previous studies that served to guide the present investigation.

The current study investigation was undertaken as a "proof of concept" using four case studies of adults with chronic motor-complete SCI. We sought to test the following hypotheses: (i) there would be an inverse relationship between MMG amplitude characteristics and duration of FES-evoked muscle contractions during a sustained standing-to-failure task in persons with SCI, and, (ii) the MMG amplitude would be sensitive to the variation in the electrical stimulation frequency during a standing challenge task. These objectives were meant to determine whether the MMG signal could be an adequate "fatigue-failure sensor" during a prolonged standing challenge task in four SCI case studies, to provide a justification for its potential application as a real-time muscle fatigue sensor worthy of further investigation. The quadriceps muscle performance during electrical stimulation was considered because it is the main agonist of sustained standing in persons with SCI (Rabischong & Chavet, 1997). While the rate of torque decrease remains the best index of muscle fatigue, it is often impractical to measure this during activities of daily living, so knee angle reduction and the quadriceps MMG amplitude response were used as proxies of muscle force diminution in relation to the knee buckle during standing (Mulder et al., 1990).

6.3 Materials and Methods

6.3.1 Participant

Four adults (3 males and 1 female) motor complete SCI participants were drawn from the inpatient and outpatient populations at the Department of Rehabilitation Medicine, University of Malaya Medical Centre, Kuala Lumpur, Malaysia. Their physical characteristics are presented in Table 6.1. Before participation, they were all screened to exclude; (i) severe contractures that could interfere with their ankle dorsiflexion, knee or hip extension (ii) pressure sores (iii) any other medical contraindications that might significantly affect their standing posture. Participants were limited to those with low tetraplegia and paraplegia for whom FES supported standing might be a realistic and achievable activity of daily living goal (Jaeger, 1992).

In addition, the participants were trained FES users and had gone through FES cycling exercise for at least 15 weeks previously (2 to 3 times per week) for muscle conditioning. However, since they were motor "complete" SCI, none of the participants could voluntarily produce muscle contractions to sustain standing. Although all participants were medically stable, a physiotherapist was present during testing to monitor vital signs throughout the duration of the study. The study was conducted based on the protocol approved by the University of Malaya Medical Ethics Committee (MECID.NO: 20164-2366) as detailed in Appendix B. Prior to the experiment, all participants who volunteered, endorsed written informed consent understanding the study activities, its risks and benefits, and had a discussion of the study protocol with the chief investigator.

Table 6.1: Participants' characteristics.

Variables	Characteristics
Age (yrs.)	41.8 (7.3)
Stature (m)	1.7 (0.04)
Body mass (Kg)	70.4 (15.4)
SCI level	T1, T4, C6 and C5/C6
Time since injury (yrs.)	17.3 (5.0)

Abbreviation: T – Thoracic level injury; C – Cervical level injury, (A) & (B) refer to AIS – American Spinal Injury Association Impairment Scale [31]. Reported values are mean (standard deviation).

6.3.2 Experimental design

6.3.2.1 Familiarization

Following a few days of standing training prior to testing sessions to screen for the possible occurrence of orthostatic hypotension and for their habituation to standing upright (Faghri & Yount, 2002), participants attended two sessions of different FES strategies separated by 2 days. On each visit, a particular frequency of neurostimulation (either a low stimulation frequency (LF) or high stimulation frequency (HF)) was administered twice with a minimum of 45 min rest to examine the consistency of standing duration within the stimulation protocol.

6.3.2.2 Test protocol

Based on the recommended stimulation frequency for standing from Kralj et al. (1986), two different stimulation frequencies (LF: 20 Hz and HF: 35 Hz), whose experimental implementation is as outlined in Appendix C, were used to verify whether the widely reported (Eser et al., 2003; Ibitoye et al., 2016) influence of stimulation frequency on muscle fatigability during stance (Crosbie et al., 2014) might also be reflected by the MMG characteristics. Thus, during FES-evoked contractions at both frequencies, the pulse width was held constant, while the current intensity was individualized as required to produce "near" full knee and hip extensions' standing in each participant (Crosbie et al., 2014). Specifically, the standing challenge test involved bilateral stimulation of the quadriceps and gluteus muscle groups during LF or HF, with pulse width of 300 μs sufficient to produce FES-supported standing in these individuals (Table 6.2).

Table 6.2: Stimulation current for FES-standing based on participants' responses.

Participant	I (mA) for low frequency protocol				I (mA) for high frequency protocol			
	R-Quads	L-Quads	R-Gluts	L-Gluts	R-Quads	L-Quads	R-Gluts	L-Gluts
1	100	100	80	80	100	100	80	80
2	120	120	96	96	120	120	96	96
3	100	100	80	80	100	100	80	80
4	80	80	64	64	80	80	64	64

Abbreviation: I (mA) - current amplitude, R-Quads - Right quadriceps muscles, L-Quads - Left quadriceps muscles, R-Glut s- Right gluteus muscles, L-Gluts - Left gluteus muscles.

Pairs of reusable self-adhesive surface stimulating electrodes (9 cm×15 cm; Hasomed GmbH, D 39114 Magdeburg, Germany) were affixed bilaterally over the quadriceps femoris and gluteus muscles as shown in Figure 6.1 (Note that the gluteus electrodes placement were not shown) and connected to a transcutaneous current-controlled neurostimulator (RehaStim^{TM}, Hasomed GmbH, Magdeburg, Germany). As previously recommended by Braz et al. (2015), the stimulation amplitude over the gluteus muscle group was set to 80% of that applied to the quadriceps muscle group (Table 6.2).

For the sustained standing task, the stimulation was continuous to provide repetitive contractions, and to stabilize the knee in full extension (Dalton et al., 1992). This resulted in substantial muscle fatigue (Levy et al., 1990) and consequent knee buckle in the participants. Each trial was terminated once the knee angle dropped by 30deg (Braz et al., 2015) from the vertical (180deg), as determined by the use of a goniometer (Figure 6.1). and this time point of knee buckle was defined as critical "fatigue-failure".

6.3.2.3 Standing challenge task

A modified version of a previously published (Braz et al., 2015) protocol was adopted for the present study. Pilot investigations revealed that this methodology could evoke full knee extension standing without a premature knee buckle. For safety, the standing protocol was performed using a safety harness (Biodex Offset Unweighing System, Biodex Medical Systems, Shirley, New York, USA) in the Physiotherapy Gymnasium. To allow participants to bear their full body mass during testing, the unweighing facility was not used and thus the safety harness provided no active support during standing, except trunk stabilization in participants with poor core strength.

The FES standing was achieved by a continuous bilateral stimulation of the quadriceps muscle to stabilize the knee extension while the stimulation of the bilateral glutei promoted full hip extension and a stable standing posture. Knee lock was achieved with electrical stimulation during sustained standing and the ankle joint was easily stabilized without stimulation of the plantar flexors (Bajd et al., 1982). FES-supported standing strategies, such as posture switching, was discouraged and the use of hybrid orthosis was avoided to mimic a real-life scenario, and to allow fatigue occurrence as necessary due to a continuous stimulation leading to fatigue-failure and knee buckling.

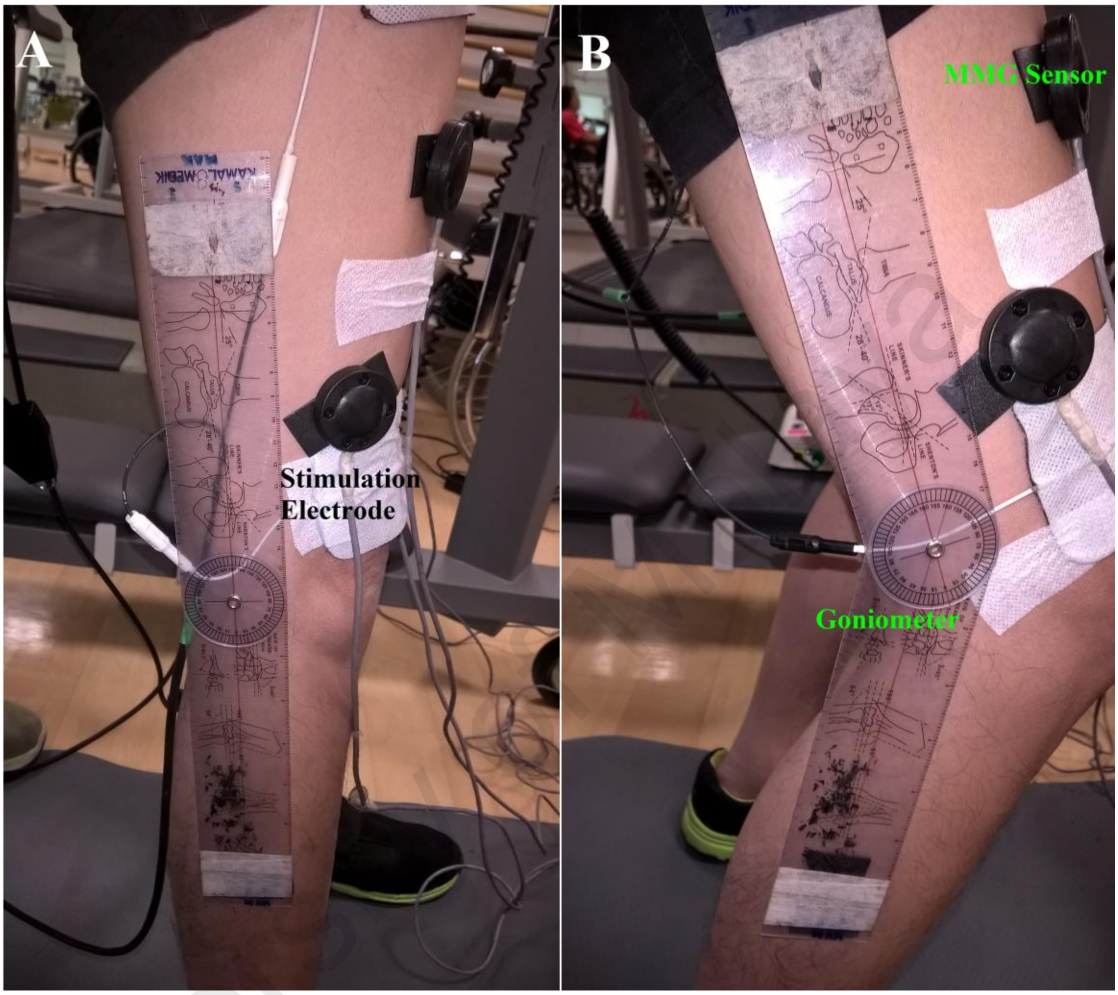

Figure 6.1: Experimental setup for the FES supported standing task.

Upright stance was attained and this was taken as the ability of each participant to bear up to ≥ 95% total body weight on their legs for a period of ≥ 1min (Jaeger et al., 1989). This was ensured by positioning the participants such that their centre of mass lay "almost" in the same plane as their feet (Figure 6.1) to promote stability (Braz et al., 2009). Ultimately, the stance duration was limited by rapid quadriceps muscle fatigue that led to knee buckling.

Based on previous recommendations (Chesler & Durfee, 1997; Thrasher & Popovic, 2008), a 70-s minimum duration of FES-supported standing was used to study MMG fatigue effects. In each participant, the stance time to fatigue-failure was noted to ascertain the duration of stance and its variability between participants and stimulation frequencies.

6.3.3 Mechanomyogram

Throughout the duration of FES-supported standing, MMG signals from the quadriceps muscle, due to its key role in "weight-bearing" during standing and walking (Mizrahi et al., 1985), were collected with an accelerometer-based vibromyographic sensor (Sonostics BPS-II VMG sensor on Biopac MP150 Acknowledge software platform, Goleta, USA). The sensor was attached using double-sided adhesive tapes (Barry, 1992) directly over the muscle belly. This was necessary to obtain the maximal muscle surface oscillation and to secure the sensor in place to ensure a constant pressure on the sensor-muscle interface (Bolton et al., 1989) (Figure 6.1). MMG signals were obtained unilaterally from the quadriceps, specifically RF. It had been earlier identified that bi-articular muscles (Jacobs & van Ingen Schenau, 1992) such as RF "have a unique role in controlling the distribution of net moments about the joints" (Kouzaki et al., 1999).

To extract the relevant MMG characteristics, the standing challenge continued until critical-fatigue failures, although fatiguing contractions were evident well before knee buckle at 30deg (Figure 6.1).

6.3.4 Signal processing

The raw MMG signals were digitized by a 16-bit analogue to digital converter, digitally band-pass filtered between 20 and 200 Hz and sampled at 2 kHz (MP150, BIOPAC Systems, Inc., Goleta, USA). The first 1 s segment of MMG signal was discarded due to the transient phenomenon associated with the initiation of isometric contractions (Orizio et al., 2003). Also excluded were some data segments (as there were early MMG amplitude rises in some instances) before the peak MMG amplitude was observed to accommodate only the muscle fatigue components in curve fitting and statistical analyses. The muscle contraction signal of the remaining segments up to the first 70-s of contraction was analyzed in 1 s epoch intervals for the assumption of non-stationarity to hold for the MMG signal (Beck et al., 2005). This was based on the assumption (Chesler & Durfee, 1997; Thrasher & Popovic, 2008) that muscle fatigue is typically evident by 60 s of sustained FES-evoked contractions, especially in persons with long-standing SCI. The MMG-RMS amplitude for each epoch was computed from the digitized signals in the time domain.

6.4 Data analysis

Prior to the data analyses, MMG-RMS amplitude values were normalized against their highest value across the two frequencies of stimulation in each participant to allow comparison between HF and LF. Based on previous recommendations by Rabischong and Chavet (1997) and Mizrahi et al. (1997), the relationship between MMG-RMS and time during the standing challenge were curve-fitted to a double exponential decay model comprising four parameters, as a single exponential gave a lower quality of fit, using the curve fitting tools available in the Matlab software (The MathWorks, Inc., Natick, MA, USA). The MMG fatigue data modelling is governed by Equation (6.1):

$$y = ae^{-bx} + ce^{-dx} \tag{6.1}$$

Whereby, y denotes MMG-RMS % and x represented the duration of standing challenge to fatigue failure (s). Parameters, a, b, c and d are the exponential regression model coefficients. Our selection of a case series proof of concept research design precluded parametric statistical analyses of curve-fitting. Coefficients of determination (R^2) and root mean square errors (RMSE) values were used to assess the performance of the model. As the present study's sample size was small, comparison of the standing duration between HF and LF strategies were examined by using a nonparametric Wilcoxon signed-rank test in SPSS software (Version 20, IBM SPSS for Windows, NY, USA). $P \leq 0.05$ was set as accepted level of statistical significance.

6.5 Results

6.5.1 MMG amplitude during muscle fatigue contractions

The mechanomyogram RMS characteristics followed an expected decline over the first 70 s of standing, coincidental with FES-induced muscle fatigue in the persons with motor complete SCI. Table 6.4 portrays the standing time for the participants under HF and LF stimulation protocols. In three of the cases, LF stimulation produced a longer standing time to critical failure-fatigue by 31-246 s, although this difference between HF and LF was not statistically significant ($P>0.05$).

Figure 6.2 shows the plots of MMG-RMS signal over time within the first 70 s of FES-supported standing. In general, MMG-RMS amplitude, as a proxy of muscle force decline over time, due to FES-evoked quadriceps fatigue, were well fit by a double exponential decay model (Equation (6.1); Table 6.3). The relationship ($MMG - RMS\ \% = ae^{-b*time}$ + $ce^{-d*time}$) yielded high coefficient of determination (R^2) between 0.85-0.99 with low room mean square errors (RMSE). Furthermore, "visual inspection" of Figure 6.2 revealed a close relationship between the experimental data (MMG-RMS) and the exponential decay model fit, albeit with some variability-scatter around the curve-fits. Although parametric statistical analyses of regression coefficients were not performed, there was an obviously faster MMG-RMS fatigue response during HF than LF, and both displayed a "fast" and "slow" components of MMG amplitude decline. This suggested a greater degree of fatigue during HF stimulation in comparison to that of LF stimulation, as detected by muscle mechanomyography.

Moreover, a longer standing duration during LF stimulation in comparison to HF stimulation, that was evident in three out of four participants (Table 6.4), represented a reasonable approximation of a practical standing task in persons with motor complete SCI (Braz et al., 2015).

Table 6.3: Exponential muscle fatigue regression model and goodness of fit coefficients.

Participant	Double Exponential Model			
	HF (a; b; c; d)	**R^2 (RMSE)**	**LF (a; b; c; d)**	**R^2 (RMSE)**
1	154.6; -0.063; 0.011; 0.095	0.98 (4.01)	-1.855e+6; -0.027; 1.856e+6; -0.027	0.99 (2.12)
2	102.7; -0.176; 9.875; 0.006	0.93 (3.88)	440.7; -0.059; -390.3; -0.092	0.96 (6.18)
3	137.6; -0.054; 0.026; 0.088	0.97 (4.61)	71.76; -0.041; 1.571; 0.026	0.97 (2.34)
4	160.4; -0.142; 18.140; -0.011	0.97 (3.91)	101; -0.028; 0.838; 0.048	0.85 (8.10)

Abbreviation: HF- High frequency; LF- Low frequency; RMSE: Root mean square error

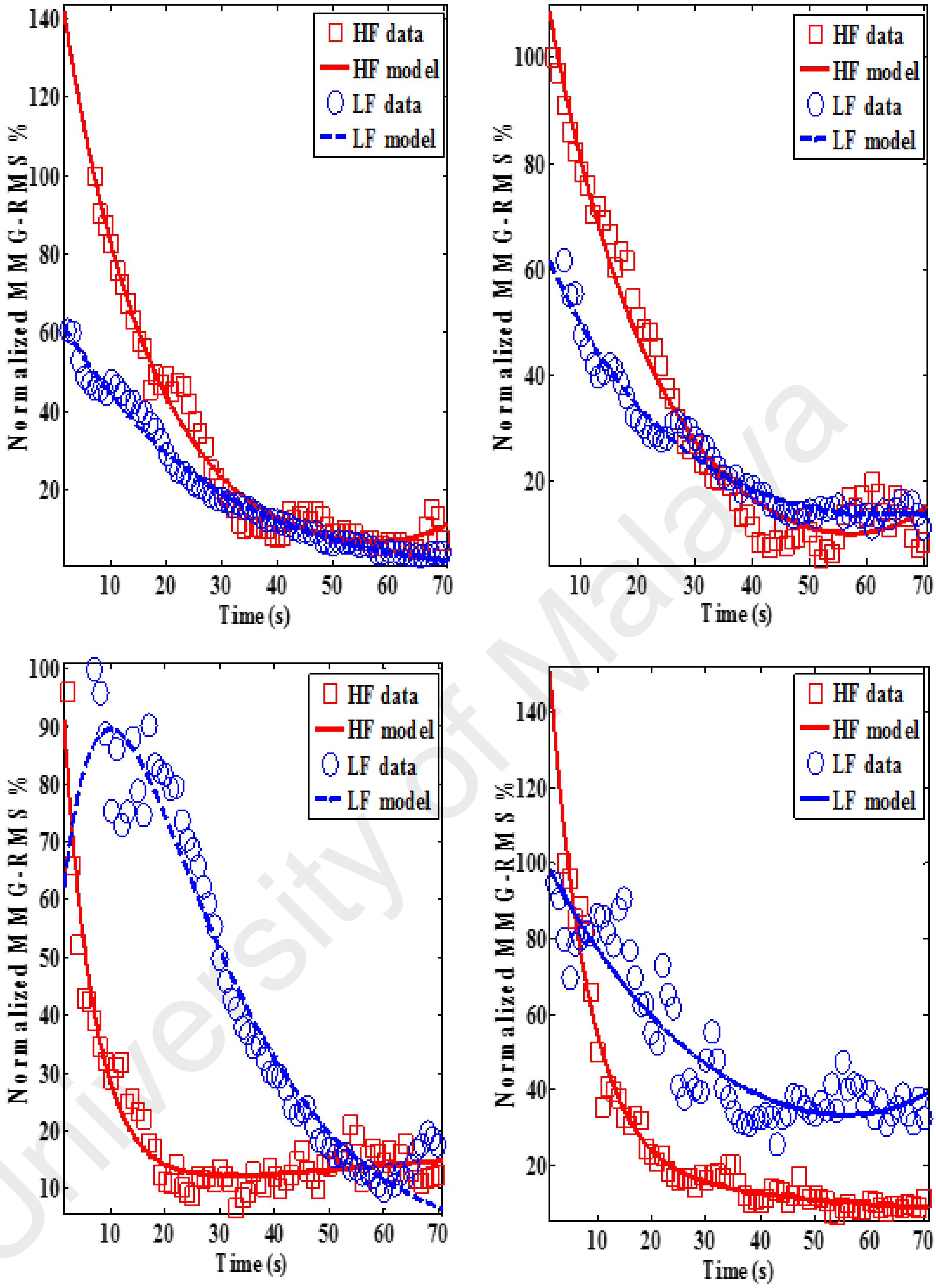

Figure 6.2: MMG-RMS amplitude versus standing time during LF and HF FES-evoked fatiguing contractions within the first 70 s.

Table 6.4: Total standing time to failure during the two stimulation protocols. The values reported for each participant represent the mean of two standing trials for each stimulation frequency.

Participants	Standing time (s)		
	HF (35 Hz)	LF (20 Hz)	Difference (LF-HF)
1	516.5	447.5	-69
2	233.5	479.0	245.5
3	102.5	186	84.5
4	72.5	103.5	31.0

Abbreviation: HF- High stimulation frequency; LF- Low stimulation frequency. The values reported for the HF and LF are mean values of two standing trials.

6.6 Discussion

This study investigated the manifestation of muscle fatigue in MMG amplitude characteristics during FES-supported standing until knee buckle, in order to study its application as a fatigue-failure proxy during a critical daily-living task in adults with motor complete SCI. The relationship between the MMG signal decline and time to quadriceps fatigue-failure was also explored between two disparate neurostimulation frequencies, known to produce different standing durations in this population (Kralj et al., 1986). In a case series of FES-trained individuals, who were capable of short-duration (~72 s) to long-duration (~516 s) stance, MMG-RMS displayed fatigue curves similar to those observed on a laboratory muscle torque measurement or dynamometer (Barry et al., 1992; Levy et al., 1990; Rabischong & Chavet, 1997; Russ et al., 2002).

6.6.1 Relationship between MMG amplitude characteristic and duration of sustained standing-to-fatigue failure

To quantify muscle performance in the present experimental context, MMG-RMS amplitude was employed. The MMG amplitude (Gobbo et al., 2006; Orizio et al., 2003) has been previously reported as an indicator of muscle fatigue as a change in MMG amplitude parameter are related to the motor unit activation pattern during FES-evoked muscle fatiguing contraction. Moreover, the MMG amplitude characteristics could reflect the failure in excitation-contraction coupling due to muscle fatigue (Fitts, 1994; Søgaard et al., 2003). In the present study, the main outcomes of muscle fatigue measurements were the reduction in knee angle (Figure 6.1) and a decline MMG-RMS over the time during FES-supported standing to failure. As evident from Figure 6.2, a decline of muscle force-generating capacity was apparent as early as the first 10 s of FES-evoked muscle contractions. Notably, the muscle fatigue profile in paralyzed quadriceps muscles could be accurately characterized by an exponential decay model (Figure 6.2, Table 6.3). This may suggest that denervated quadriceps muscle fatigue during standing may follow a double exponential behavior (Mizrahi et al., 1997; Rabischong & Chavet, 1997), with "fast" (more rapid) and "slow" (later onset) components, and that the associated knee angle reduction could be clearly mirrored by MMG amplitude responses. Specifically, MMG amplitude adapted quickly to the time variation in muscle responses during fatiguing contractions. Therefore, MMG signals could potentially provide an indication of muscle performance, and be used to monitor this during continuous repetitive neurostimulation-evoked contractions that might be required to effect prolonged standing in this population.

6.6.2 Effects of the stimulation frequency on the MMG response to muscle failure

Muscle fatigue is time-varying and it affects the response of a muscle to the FES-evoked contractions. In particular, during high-intensity repetitive application of FES for antigravity activities (Kralj et al., 1986) such as in standing-up and sustained stance where muscle fatigue could be manifested in about 60 s of muscle contractions (Thrasher & Popovic, 2008).

The results obtained, of a generally longer-standing duration in LF neurostimulation was comparable to the findings of Kralj and co-workers (1986), who identified that in comparison with an HF protocol, low stimulation frequency delayed the onset of muscle fatigue, but usually at the expense of muscle force production (Kralj et al., 1986). Our observations on the different stimulation protocols (HF and LF) clearly indicated the same pattern of contraction duration with a faster MMG amplitude drop in HF in comparison with LF protocol. This may suggest a higher rate of muscle force decay in the HF curve as mirrored by the MMG-RMS amplitude. Therefore, the present study compares favourably with those of Kralj and colleagues (1986) who identified a higher rate of force decay at high stimulation intensity levels while the changes of MMG-RMS as evident from the present study has been consistently described as a good measure of muscle fatigue (Søgaard et al., 2003).

Additionally, the shorter standing duration during HF (Table 6.4) (except for participant 1, probably due to his uncontrollable propensity for posture switching, as there was no special arrangement for body movement restriction to a particular plane (Jaime et al., 2002) was probably due to the greater quadriceps contraction forces produced by a continuous stimulation (Braz et al., 2015) at a relatively higher stimulation frequency. This has been attributed (Chou & Binder-Macleod, 2007) to the effect of contractile speed in relation to the frequency of stimulation. The higher the frequency, the higher the muscle force production, but at a reduced time for muscle to fatigue especially in muscle with predominantly fast fatigueable fibres (Ibitoye et al., 2016; Kralj et al., 1986). Moreover, this phenomenon might be due to an increase in muscle fibres' recruitment and the consequent increase in quadriceps oxygen demand (Braz et al., 2015) which suggests a reduction in muscle effort and an indication of a reduced motor activity.

The following limitations are acknowledged in the present study: based on the experimental setting, the muscle force reduction during the standing challenge, as well as the individual muscle power, a function of the rate of muscle force generation that is responsible for standing (Crosbie et al., 2014), could not be calculated. Nevertheless, the drop in MMG amplitude adopted in the present study to investigate muscle fatigue has been previously correlated (Gobbo et al., 2006) with muscle force during “seated” electrical stimulus fatigue contraction in healthy volunteers. Although the fatigue profile with an exponential function has been described, phases of the fatigue profile could not be identified based on our experimental data. Further studies that seek to address this limitation and rigorously validate the generalization ability of the model in larger study participants will be of clinical interest.

Second, although we chose to utilize a case series of SCI individuals with disparate FES-evoked standing times in this ‘proof of concept’ study, the authors were unable to undertake parametric statistical analyses of curve-fitting regression parameters of HF versus LF standing times through traditional repeated-measures analyses, due to the small sample size that we had selected.

6.6.3 Potential clinical implication

Although to date, the use of FES is commonly based on the manual control of stimulation intensity with the associated rapid muscle fatigue, an improved efficient control of stimulation parameters based on closed-loop modulation of FES parameters (pulse width, frequency, and current or voltage) is a focus of various research centres. This is partly due to the fact that other alternatives for restoration of motor function after a SCI including stem cell therapy are not currently available (Bryson et al., 2016). A realistic alternative is the application of a proxy of generated muscle performance in closing the loop of FES systems in order to promote the efficacy of the technology in clinical use. Therefore, tracking muscle fatigue pattern during FES-evoked contractions remains an important step in ensuring an efficient FES utility to improve muscle response as the fatigue profile has been derived by curve-fitting MMG-RMS of quadriceps muscles. Thus, the present finding offers a new knowledge on the probable application of the MMG signal as a simple fatigue tracking sensor.

Moreover, as fatigue profile modeling is vital to the optimization of skeletal muscle performance (Dugan & Frontera, 2000), MMG, which is stimulation artifact free (Yamaguchi et al., 2012), could be used to track muscle contraction during an FES-evoked fatigue failure task (Blangsted et al., 2005; Søgaard et al., 2003). This is unlike evoked-electromyography which may continue to increase with increasing motor unit recruitment even with a reduced muscle effort/force due to fatigue (Falla & Farina, 2008). The implication of this finding could be for the use of MMG signals in modulating the FES parameters, at least, as to implement a binary switch for FES system as the amplitude characteristics of MMG has been shown to change with FES-evoked fatigue contractions as previously proposed by Gobbo and colleagues (Gobbo et al., 2006) in healthy volunteers.

6.7 Conclusion

Although the results of the present investigation should be further verified in larger participant size with pathological muscle conditions, the study has shown that MMG signal could track the FES-evoked muscle fatiguing contractions. Specifically, the signal has been shown to monitor muscle fatigue development during repetitive contractions and over an extended contraction duration during FES-supported standing in persons with SCI. This result provided further evidence of the potential use of MMG as a proxy of fatigue with specific relevance in situations where an objective measure of muscle force may be needed, such as in biofeedback control of FES-evoked contractions to prolong the contraction duration. Furthermore, as a “known fatigue equation”, the exponential function has been shown as a relevant paralyzed quadriceps muscle fatigue model during FES-supported standing challenge. The MMG-RMS pattern during sustained isometric contractions of the quadriceps muscle due to fatigue is of particular relevance in using the signal as a muscle fatigue sensor in any related tasks that involved repetitive electrical stimulation contractions.

CHAPTER 7: CONCLUSION AND RECOMMENDATION

This Chapter summarizes the findings from various experiments and analyses conducted within this thesis. In addition, the relationship between each Chapter, limitations of the study and recommendation for future works are discussed.

7.1 Conclusion

This thesis is generally focused on the experimental investigation of the potential of mechanomyography (MMG) as a proxy of NMES-evoked muscle force/torque for NMES control applications. The findings from this thesis may also be useful for the application of MMG signal to monitor progress in NMES therapies or following NMES rehabilitative exercise interventions. As mentioned in the introductory Chapter of this thesis, three specific objectives were investigated to actualize the main objective.

- To develop a hybrid procedure to demonstrate MMG signal as a proxy of NMES-evoked muscle force in healthy volunteers.

Findings from Chapter 3 showed that the MMG signal is a promising NMES-evoked muscle force or torque proxy. Specifically, the support vector regression (SVR) estimation of NMES-evoked torque has been demonstrated using MMG signal in healthy volunteers. To the author’s knowledge, the proposed methodology represented a unique attempt to assess the knee extensor force via joint torque, though in a controlled laboratory setting.

- To deploy the developed procedure for studying the reliability of MMG signal as a proxy of muscle force during NMES supported knee extension task in persons with SCI.

Findings from Chapter 4 revealed that the MMG signal is highly correlated with the knee extensor torque and the relationship was also reliable. An important new information on the sensitivity of MMG signal to the muscle force modulation (*i.e.*, incremental motor unit recruitment) was evident. Moreover, in Chapter 5, an NMES-evoked torque estimation model was constructed from the paralyzed quadriceps MMG signals using SVR modelling with both gaussian and polynomial kernel functions. The finding from the Chapter demonstrated a good predictive accuracy of the proposed SVR model with capability for generalization. This provided further evidence for MMG signal as a proxy of NMES-evoked torque production during isometric knee extension tasks. Therefore, findings from Chapter 4 and 5 collectively provide an important new information with implication for the use of muscle contractions signal (MMG) to regulate NMES parameters.

- To demonstrate the potential relevance of MMG signal as a useful parameter for studying muscle fatigue during a critical knee buckling stress due to a sustained NMES-supported standing to fatigue failure task.

Findings from Chapter 6 preliminarily showed that the MMG signals might track the muscle fatigue development during a critical task such as NMES-sustained standing in persons with motor complete SCI. The finding suggested that MMG signals may be useful as a muscle fatigue sensor in situations where a real-time muscle force and fatigue measurement is impractical. Therefore, the signal has an important application in biomechanics research pertaining to the evaluation of the "potency" of muscle contractions to sustain standing or ambulation task.

Overall, the feasibility of the muscle MMG signal as a proxy of NMES-evoked torque in both healthy and motor complete spinally injured persons has been demonstrated, for the first time, without the need to contend with the issue of stimulation artifact that often characterizes the application of the prominent biopotential signal (*i.e.*, electromyography) which is used traditionally for an indirect muscle force/torque assessment. In addition, the present finding implied that the difficulty of a reliable NMES-evoked muscle force estimation may be resolved with a physically small sensor (MMG sensor) as compared to the "gold standard" and laboratory-bound isokinetic dynamometer for torque measurement. Next, the synergy between the chapters is enumerated.

(i) The critical systematic literature search conducted in Chapter 2 revealed the limitations of the application of current NMES technologies in the routine clinical practice. The foremost limitation established was the lack of flexibility in torque control which a non-invasive and artifact-free muscle signal source could improve through the application of the signal as NMES control signal. Therefore, to promote effective NMES therapies and for a wider clinical prominence of the NMES technologies, this thesis sought to resolve a number of issues concerning a reliable muscle signal (MMG) as a proxy of NMES-evoked torque for feedback applications.

(ii) The first experimental design as presented in Chapter 3 on healthy volunteers, revealed that the MMG signal could clearly track the incremental muscle force production or motor unit recruitment as measured by a commercial isokinetic dynamometer. The study also justified the feasibility of the experimental setting and allowed the conception of the adjustment required for the application of the same protocol to persons with SCI.

(iii) Based on the results obtained from the experiment conducted in Chapter 3 and apart from the adjustment made for the safety of the participants' musculoskeletal health, a similar experiment performed in persons with motor complete SCI as described in Chapter 4 demonstrated a reliable muscle torque measurement with MMG signal amplitude. Meanwhile, the frequency of MMG signal was shown to approximate the stimulation frequency and thus, suggestive of motor unit firing frequency.

(iv) In Chapter 5, an estimation of the torque production from MMG signal amplitude and other related parameters that may affect the torque production was conducted using a SVR model in persons with motor complete SCI. Being robust in handling multivariate input parameters, the SVR modelling results demonstrated a good torque predictive accuracy. Taken together, the results obtained from Chapters 4 and 5 showed that MMG signal (input to the model) could be successfully used to estimate the NMES-evoked muscle torque (output of the model) as these two variables (MMG versus torque) were found to be highly positively correlated.

(v) Based on the findings from Chapter 4 and 5, Chapter 6 demonstrated the potential application of MMG signal as a muscle fatigue sensor during a typical clinical critical task *i.e.* NMES supported standing. The preliminary results obtained in four persons with motor complete SCI showed that the signal could be used to track the muscle fatigue contractions. However, the advanced technique that may have been used to measure muscle force during NMES-evoked standing, such as inverse dynamics approach, is outside the scope of this thesis and its complexity for force estimation is absent in the proposed MMG signal modality. Therefore, the potential application of MMG signal to monitor muscle states during NMES-evoked fatigue contractions is another important knowledge derived from this study. Generally, the implication of these findings favours the implementation of a muscle mechanical response-controlled NMES technology as a measure of muscle activity can be used as a NMES control signal. Therefore, the present study is a part of the current research efforts to apply MMG signal as a muscle force sensor in order to facilitate the implementation of a flexible and portable NMES systems which could be used in the routine clinical rehabilitation practice.

The following are the descriptions of the thesis's accomplishments followed by detailed illustrations.

7.2 Contributions

To arrive at the conclusion, the following results highlight the specific contributions of the thesis:

(i) Findings from the first objective showed a good association between MMG signal amplitude and NMES-evoked torque as revealed by a high coefficient of determination (R^2) with a low RMSE using gaussian kernel function of SVR modelling. This finding suggested the legitimacy of using MMG signals as a proxy NMES-evoked muscle force in healthy volunteers and supported further investigation in persons with neurological conditions.

(ii) The second investigation revealed a high correlation coefficient (r) between the MMG amplitude characteristics and stimulation/contraction intensity versus NMES-evoked torque. This led to the study reported in Chapter 5, on torque prediction from MMG signal using SVR modelling, conducted on a wider study population. The study demonstrated a high R^2 and low RMSE across the study's participants. These findings have implications in some fields including biomechanics, rehabilitation medicine and rehabilitation engineering where NMES technologies are used as a mode of muscle performance improvement and rehabilitative intervention.

(iii) The implications of the aforementioned findings on the muscle fatigue tracking by MMG signal were demonstrated in the third objective in persons with motor complete SCI. Specifically, MMG signal was used to track the NMES supported standing until fatigue failure as indicated by knee buckle. Sustained quadriceps muscle contractions for 70 s duration between 80-120 mA stimulation intensity level resulted in a continuous muscle fatigue as reflected by a simultaneous decrease in MMG amplitude and the knee angle reduction over the contraction time. Having demonstrated the use of MMG signal to track muscle fatigue contractions, this study further supported the legitimacy of MMG signal as a feedback signal source for muscle state responses during NMES application for critical tasks such as in sustained standing in persons with SCI.

Collectively, these findings open the possibility of a paradigm shift in the perception of a possible wider application of NMES technology to improve function in a wide range of neurological disabilities. As the MMG signal has been demonstrated as a simple and non-invasive proxy of muscle force, the signal could be further explored to impact clinical decisions regarding NMES rehabilitation progression in clinical populations. Moreover, the application of MMG as an NMES control signal promises to improve the efficiency of the NMES technology and quality of life in persons with SCI. The overall results of this thesis suggest the feasibility of the MMG modality as an NMES feedback signal source and SVR as valid prediction algorithm.

Finally, a new method of NMES-evoked muscle force based on MMG signals has been presented, together with the hybrid procedure on the acquisition of torque production in both healthy and spinally injured populations. Moreover, in a selected group of SCI population, who are good candidates for NMES supported standing, *i.e.* those with low tetraplegia (C5-C8) and paraplegia (T1-T12) (Davis et al., 2001), this thesis has demonstrated the collection of MMG signal from their quadriceps muscles during NMES-evoked supported standing for potential application of the signal as fatigue failure sensor.

Therefore, it can be safely envisaged that the MMG signal as a muscle force and fatigue sensor for feedback applications has an important role in advancing the current status of NMES technologies, and therefore worthy of further investigations, either alone or in combination with other methods that could be used to sense muscle contraction responses.

7.3 Study Limitations

The author acknowledges the following limitations of the thesis: the MMG response during electrical stimulus contractions has been demonstrated using data from participants with motor complete SCI, whether the same procedure could be used to obtain a similar or better results in persons with other classes of neurological lesions was not verified. Additionally, the present investigations are based on the surface/transcutaneous electrical stimulation, the results may have limited application for functional application such as in ambulation training. Specifically, with surface stimulation approach, the activation of hip flexors required for an effective ambulation (Hardin et al., 2007) may not be directly stimulated (Thrasher & Popovic, 2008). Therefore, percutaneous or implanted stimulation approach may be of greater interest in relating MMG signal to NMES responses as this stimulation approach is characterized by an improved muscle selectively and ability to stimulate deeper muscles required for effective ambulation training (Hardin et al., 2007; Kobetic et al., 1997).

Nevertheless, as the present study is based on the experimental investigation of MMG signal as a proxy of NMES-evoked muscle force/torque, the methodology described herein could be considered mature enough for the validity of the MMG as a control signal for NMES systems. Therefore, this thesis provides a solid platform for the practical realization of a closed-loop NMES systems with muscle mechanomyographic signal as a potential feedback source.

7.4 Recommendation for Future Research

For more than five decades now, there have been increasing attempts on the application of NMES technologies for the restoration of the impaired or lost neuromuscular functions following a SCI. To date, the general principle of ensuring a safe activation of neuromusculature as well as the methods of generating stable muscle contractions have been established. However, integrating these commendable research efforts to provide effective therapeutic and functional gains that are clinically significant is still challenging. For example, open-loop NMES technologies have been more widely used, particularly for therapeutic exercise, which is of limited clinical relevance. While the closed-loop NMES technologies have proven to be of a better clinical relevance, their full realization remains an interesting open research question, particularly due to the lack of a non-invasive and reliable method of assessment of NMES-evoked muscle activities (Popović, 2014).

Based on this premise, NMES application is still perceived as an experimental procedure rather than a routine clinical practice (Thrasher & Popovic, 2008). Therefore, NMES technologies have been so far hesitant to fully restore the inactivity associated with SCI, identification of a reliable proxy of the response of neuromuscular activity to NMES-evoked muscle force has been suggested as a feedback source for NMES closed-loop control implementation. Thus, the result of this present investigation and related studies from other research centres will continue to be relevant to the implementation of an effective closed-loop NMES systems for the rehabilitation of persons with neurological conditions until the neural stem cell regenerative therapies, which has been proposed for neuroregeneration of axons, emerge (Bryson et al., 2016). Even with that, "NMES will still be needed to train stem cells to learn" (Popovic, 2012). Accordingly, advancing NMES technology to significantly impact the lives of persons with SCI is achievable rather than “waiting for science to find methods to regenerate axons within the injured spinal cord” (Ragnarsson, 2007).

Towards advancing the NMES technology, the present thesis has demonstrated the potential relevance of MMG as a biofeedback control signal for NMES feedback applications. However, being in early stage, the findings reported herein require further research. Specifically, in the development and implementation of MMG-based NMES technologies. Such research should focus on identifying an appropriate strategy for implementation, as well as determine how to optimally apply the neuromuscular information from the MMG signal to implement a closed-loop NMES systems. Such effort should also develop as well as integrate control algorithms that will allow an automation of muscle performance classification and pattern recognition. Moreover, such future studies may also elucidate the best modality for probable commercialization of this technology.

Following an adequate clinical progress, it can be surmised that a new generation of NMES systems will be available in the near future based on advances in MMG measurements and processes. Such a progress is expected to offer a substantial clinical benefit to promote the health of persons with spinal cord injury.

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1. **Ibitoye, M. O.**, Hamzaid, N. A., Abdul Wahab, A. K., Hasnan, N., Olatunji, S. O.; & Davis, G. M. (2016). Estimation of Electrically-Evoked Knee Torque from Mechanomyography Using Support Vector Regression. *Sensors*, 16(17), 1115. doi:10.3390/s16071115

2. **Ibitoye, M. O.**, Hamzaid, N. A., Hasnan, N., Abdul Wahab, A. K., Islam, M. A., Kean, V. S. P., & Davis, G. M. (2016). Torque and mechanomyogram relationships during electrically-evoked isometric quadriceps contractions in persons with spinal cord injury. *Medical Engineering & Physics*, 38(8), 767-775. doi:http://dx.doi.org/10.1016/j.medengphy.2016.05.012

3. **Ibitoye, M. O.**, Hamzaid, N. A., Hasnan, N., Abdul Wahab, A. K., & Davis, G. M. (2016). Strategies for Rapid Muscle Fatigue Reduction during FES Exercise in Individuals with Spinal Cord Injury: A Systematic Review. *PLoS One*, 11(2), e0149024. doi:10.1371/journal.pone.0149024

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7. **Ibitoye, M. O.**, Hamzaid, N. A., Abdul Wahab, A. K., Hasnan, N.; & Davis, G. M. (2017). Quadriceps mechanomyography reflects muscle fatigue during FES-sustained standing in adults with spinal cord injury: Case series proof of concept, Under Review in Medical and Biological Engineering and Computing.

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1. **Ibitoye, M. O.**, Hamzaid, N. A., & Abdul Wahab, A. K. (2014, January): Prospects of Mechanomyography (MMG) in Muscle Function Assessment during FES Evoked Contraction: A Review. In ***The 15th International Conference on Biomedical Engineering Volume 43 of the series IFMBE Proceedings***, James Goh (eds.) 524-526. Published by Springer International Publishing, Switzerland.

2. **Ibitoye, M. O.**, Hamzaid, N. A., & Abdul Wahab, A. K. (2014, January): Effects of Muscle Fatigue on FES Assisted Walking of SCI Patients: A Review. In ***The 15th International Conference on Biomedical Engineering Volume 43 of the series IFMBE Proceedings***, James Goh (eds.) 476-479. Published by Springer International Publishing, Switzerland.

3. **Ibitoye, M. O**, Hamzaid, N. A. (2013): Myoelectric Signal and FES-evoked Muscle Contraction: Muscle Force and Fatigue Assessments. In ***18th Functional Electrical Stimulation Society Annual Conference (IFESS), Spain 2013***, **pg.** 241-244.