



PHD THESIS

IMPERIAL COLLEGE LONDON

DEPARTMENT OF BIOENGINEERING

Modeling the Neurophysiology of Tremor to Develop a Peripheral Neuroprosthesis for Tremor Suppression

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Abstract

Pathological tremor is an involuntary oscillation of the body parts around joints. Pharmaceuticals and surgical treatments are approved approaches for tremor management; however, their side effects limit their usability. The main objective of this study is, therefore, to design a closed-loop non-invasive electrical stimulation system that could suppress tremor without serious side effects.

We started our system design by investigating *motor unit* (MU) behaviors during postural tremor via decomposition of high-density surface *electromyography* (EMG) recordings of antagonist pairs of wrist muscles of *essential tremor* (ET) patients. The common input strength that influences voluntary and tremor movements and the phase difference between activation of motor neurons in antagonist pairs of muscles were assessed to find the correlation of the motor unit activity during different tasks. We observed that, during postural tremor, the motor units in antagonist pairs of muscles were activated with a phase difference that varies over time. An online EMG decomposition method and a phase-locked-loop system were, therefore, implemented in our tremor suppression system to real-timely discriminate motor unit discharge timings, track the phase of the motor unit activity and use that real-time phase estimation to control the stimulation timing. We applied sub-threshold stimulation to the muscle pairs in an out-of-phase manner. The system was validated offline with the data recorded from 13 ET patients before it was tested with an ET patient to prove the concept.

Since the spinal cord is the termination of the afferent neurons from the peripheral nervous system and connection to the central nervous system and motor neurons, we hypothesized that electrical stimulation at the spinal cord could also modulate tremor-related neural commands. Russian currents with a 5 kHz-carrier frequency modulated with a slow burst at tremor frequencies were used with sub-threshold intensity to stimulate at C5-C6 cervical spine of 9 ET patients. The reduction of the tremor power was observed via an analysis of the wrist angle recorded using an accelerometer.

We present, in this thesis, two electrical stimulation approaches for tremor suppression via the peripheral nerves and spinal cord, providing options for patients to utilize based on their preference.

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Nomenclature

<i>ACC</i>	Accelerometer
<i>ACh</i>	Acetylcholine
<i>ADL</i>	Activities of daily living
<i>ANS</i>	Autonomic nervous system
<i>BB</i>	Biceps brachi
<i>CMAP</i>	Compound muscle action potential
<i>CNS</i>	Central nervous system
<i>CP</i>	Charge pump
<i>CST</i>	Cumulative spike train
<i>DBS</i>	Deep brain stimulation
<i>DCN</i>	dorsal column nuclei
<i>DelA</i>	Anterior deltoid
<i>ECR</i>	Extensor carpi radialis
<i>EEG</i>	Electroencephalography
<i>EMG</i>	Electrocardiography
<i>EPSP</i>	Excitatory postsynaptic potential
<i>ESCS</i>	Epidural spinal cord stimulation
<i>ET</i>	Essential tremor
<i>FCR</i>	Flexor carpi radialis
<i>FDI</i>	First dorsal interosseous
<i>iEMG</i>	Intramuscular electromyography

IPSP Inhibitory postsynaptic potential

MEG Magnetoencephalography

MEP Motor evoked potential

MU Motor unit

MUAP Motor unit action potential

PD Parkinson's disease

PFD Phase/Frequency detector

PIC Persistent inward current

PLL Phase-locked loop

PSD Power spectral density

PT Parkinsonian tremor

ROA Rate of Agreement

rTMS Repetitive magnetic brain stimulation

SCI Spinal cord injury

sEMG Surface electromyography

SNS Somatic nervous system

tESS Transcutaneous electric stimulation

TMS Transcranial magnetic stimulation

VCO Voltage control oscillator

VIM Nucleus ventralis intermedius

Statement of Originality

I certify that the content of this thesis represents my own work, except where otherwise acknowledged.

Gonthicha Puttaraksa

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Chapter 1

Introduction

1.1 Motivation of the thesis

Tremor is one of the common symptoms many people experience in their everyday activities [Lyons and Pahwa, 2005]. Our arms would shake when holding a heavy stack of books; our fingers would tremble when we tried to insert a thread into a needle. We may sometimes feel shaking when we are alert or excited. These symptoms are typical effects of fatigue, modulation of muscle force to fine movements, or side effects of chemical reactions of the brain to hormones produced during different states of human emotions. With this occasional symptom, we are able to move freely and have control over our bodies. However, if the tremor is not due to fatigue or any external stimuli, it could be due to impairment in the nervous system [Louis and Vonsattel, 2008, Raethjen et al., 2007]. The causes of tremors could involve genetics [Thenganatt and Louis, 2012], dysfunction of cells in the brain, or abnormality in the pathways of the cortico-muscular system [Louis, 2012, Helmich et al., 2013, Shilla et al., 2012]. Tremor could occur at specific body parts such as the head, jaw, neck, arms, and legs. People with pathological tremors experience difficulty in *activities of daily living* (ADL), such as drinking, eating, and writing which would not only affect their physical health but could trigger social and mental health problems [Zesiewicz et al., 2005]. Tremor could build social anxiety and depression in turn, worsening the tremor in a vicious circle [Monin et al., 2017, Jhunjhunwala and Pal, 2014, Louis, 2010]. Pathological tremor occurs not only in the elderly but also younger, and it is prone to worsen with age [Gutierrez et al., 2016]. Tremor would contaminate the movement during rest or when the person performs kinetic movement or hold a posture. ET, for example, is one of the most common tremors that occur during posture or movement [Louis, 2005, Hess and Pullman, 2012].

There is no permanent treatment for tremors. Only symptoms could be mitigated by using pharmacotherapy or invasive surgeries [Louis, 2012, Deuschl et al., 2011, Zesiewicz et al., 2002].

In order to treat tremor, insight into the causes and origins of the tremor should be thoroughly understood. Advanced technologies of neuroimaging such as Magnetic Resonance Imaging and Positron Emission Tomography allow elucidation of the change in the central nervous system and its pathways in tremor patients [Louis and Vonsattel, 2008], which brought benefits to the development of tremor treatments such as medicines to help increasing lacked chemical substances in the brain, increase activation of loss cells or enhance the connection between lesion regions causing the abnormality [Zesiewicz et al., 2002]. Advance in surgical procedure allows the implementation of assisting devices such as pacemaker to tremor treatment. Invasive surgery to implant electrical thalamic stimulation is the most effective method to treat tremors; however, it may cause risks of inflammation, infection, and sides effects in movement and speech problems [Iorio-Morin et al., 2020]. Non-invasive tremor management has become a topic researchers are focusing on to avoid the serious side effects of the surgery.

By recording the electrical activity of the tremorous muscles, we are now able to estimate backward their neural commands, thanks to the advances in EMG and signal processing techniques [Dideriksen et al., 2011b]. The EMG and inertial sensors, including accelerometers or displacement sensors recordings, are meaningful data to diagnose, distinguish, and implement a tremor management system [Elble, 2003, Hagan, 2012, Elble and McNames, 2016, Widjaja et al., 2009, Maneski et al., 2011, Dideriksen et al., 2017]. Recent EMG recording techniques, intramuscular and surface recording via single or multiple electrodes, open the door for cortico-muscular connectivity assessment [Merletti and Farina, 2009, Farina and Merletti, 2008, Muceli et al., 2019, Holobar et al., 2010]. High-density surface electrodes or multichannel intramuscular electrodes and decomposition techniques provide an ability to discriminate the activity of individual MUs located in the muscle of interest [Holobar and Zazula, 2003, Negro et al., 2016, Muceli et al., 2015, Holobar et al., 2010, Merletti et al., 2008, Barsakcioglu and Farina, 2018, Clarke et al., 2020]. Analysis of MU activities may elucidate cortical-related command and tremor pathology. By decomposing the EMG into MU spike trains, we were able to investigate the MU activity during voluntary movement and compare them with those during the tremor [Farina and Holobar, 2016, Holobar et al., 2012, Gallego et al., 2015a, Puttaraksa et al., 2019].

In this Ph.D. study, we aim to understand the behavior of the MUs producing tremorous movement of upper limbs and possible influence promoting the pathology to design a real-time closed-loop system for tremor suppression based on the decomposed EMG. As muscle force is modulated mainly by the electrical potential of motor neuron pools, electrical stimulation at a different intensity of the tremor-related pathways might be able to interrupt the process of tremor generation. We, therefore, have utilized surface electrical stimulation of the nerves related to motor control in the design of our tremor suppression system as it is non-invasive and is possible to build in as a small device providing a better appearance. The electrical stimulation could be delivered above [Prochazka et al., 1992, Maneski et al., 2011, Gallego et al., 2013] or below [Dosen et al., 2015, Dideriksen et al., 2017] the motor threshold, which is the stimulation intensity necessary for

muscle fiber activation. The stimulation at a high intensity above the motor threshold (also called efferent stimulation) can directly activate the efferent nerve fibers connected to the muscle fibers. In contrast, the sub-threshold or afferent stimulation uses an intensity lower than the motor threshold to trigger the afferent nerve fibers, which are multi-synaptic to the brain, spinal cord and muscle fibers. To counteract the tremor, we hypothesized that the interference of the afferent feedback loops (part of the tremor generation system) by sub-threshold electrical stimulation might be able to cancel out the tremor via the stretch reflex mechanism by increasing excitability of inhibitory interneurons located in the spinal cord. To control the timing of the stimulation device, we used a frequency and phase detector to help tracking the phase of the muscle activity during the tremor. Since the spinal cord is where the *central nervous system* (CNS) connects to *peripheral nervous system* (PNS) and motor neurons synapse with muscle fibers, modulation of this conjunction may influence MU behavior during the tremor. We further hypothesized that the disturbance of the spinal cord using different levels of high-frequency carrier electrical stimulation at sub-threshold intensity would modulate the power of the tremor through increment of excitation or inhibition effects on tremor pathways. This study would be useful for creating a novel tremor managing method in the future.

1.2 Objectives of the thesis

The objectives of the thesis are divided according to three main as follow

1. Study of tremor physiology via analysis of MU firing patterns decomposed from high-density surface EMG recording from antagonist pair of the wrist muscles of ET patients during the postural tremor.
 - We used power spectrum analysis to investigate components that contribute to the spectrum of MU spike trains during tremor.
 - We investigated the proportion of tremor-related common inputs to motor neuron pools within agonist muscles or between antagonist pairs of muscles using coherence analysis at the voluntary and tremor frequency bands. In this way, we could determine the proportions of common and independent inputs to muscles.
 - We estimated the phase of muscle activation during tremor using the Hilbert Transform. The Hilbert Transform applied at voluntary and tremor frequency bands revealed the behavior of motor neuron pools involved in voluntary movement and tremor separately.
2. Design of a closed-loop tremor suppression system using MU spike train based control of sub-threshold electrical stimulation.
 - Online EMG decomposition technique has been used to obtain real-time MU spike trains, which is a key to controlling stimulation timing. It allows us to control the system based

on current muscle activities in real-time.

- We implemented a *phase-locked loop* (PLL) system to track changes of MU spike trains in real-time and used it as a control signal for the stimulator.
 - Each system component was validated using offline EMG recordings of 13 ET patients. MU spike trains decomposed online were compared with those decomposed offline using a standard technique using Rate of Agreement Analysis. The estimated phase of muscle activity from the PLL system was compared with the phase calculated from Hilbert Transform.
 - The tremor suppression system was tested with an ET patient to prove the concept.
3. Study of influences of transcutaneous cervical spinal cord stimulation on tremor activity using Russian currents at different frequencies.
- We investigated changes in wrist tremor amplitudes recorded by an accelerometer while increasing spinal cord stimulations at C5-C6 using power spectrum analysis.
 - We compared instantaneous phases of tremor oscillations and phases of the stimulations to investigate the entrainment behavior of the stimulation to the tremor-related neural inputs.

1.3 Structure of the Thesis

The thesis is organized into six chapters according to the objectives.

- | | |
|------------|---|
| Chapter 1. | is a brief introduction of the thesis and thesis objectives. |
| Chapter 2. | provides background and current aspects of the related topics that inspired this thesis project, including the physiology of muscle and force generation, connections between cortico-muscular system, technology for EMG recordings, physiology of tremor, and its mechanism. |
| Chapter 3. | describes the physiological study of the tremor based on the analysis of MU spike trains decomposed from recorded EMGs of ET patients during postural tremor. This chapter has been published in [Puttaraksa et al., 2019] . |
| Chapter 4. | describes the development of non-invasive tremor suppression. We proposed implementation of the PLL system to the system in this chapter with experimental data recorded from an ET patient. Each component of the system including an online decomposition and phase estimation via the PLL system were validated offline using decomposed EMGs recorded from ET patients before the prove of concept was done. This chapter has been published in [Puttaraksa et al., 2022] . |

Chapter 5.	describes spinal cord stimulation procedure using high-frequency carrier stimulation on ET patients and the analysis of their tremor oscillation recorded by EMG and accelerometer.
Chapter 6.	is the conclusion of this thesis. Limitations, future works and possible improvement of the tremor suppression system is suggested.

Chapter 2

State of the art

2.1 Physiology of motor control

Movements are generated by neural commands from the nervous system. The human nervous system consists of the CNS and the PNS. The brain, one part of the CNS, can be divided based on its functions into different areas including cerebrum or cerebral cortex, cerebellum, diencephalon covered by the cerebellum and brain stem. These regions are important in generating and facilitating neural components supply for the control of force, movements and reflexes. Different ascending and descending pathways lay across upper part of the body to link information between the brain and spinal cord which further convey the information to skeletal muscles. For example, spinothalamic and (posterior and anterior) spinocerebellar tracts are important ascending pathways sending sensory information captured by receptors on the skin, muscle spindle and tendons from spinal cord to thalamus and cerebellum, respectively. Conversely, the descending pathways such as corticospinal, vestibulospinal, rubrospinal, and reticulospinal tracts send motor commands from the brain to the spinal cord (Figure 2.1). These tracts are involved in various functions to control muscle movements and postures. The system of neurons that links the cerebral cortex through a direct contact to the skeletal muscles and is responsible for voluntary movement is called *somatic nervous system* (SNS) while the system of neurons that originate from the brain stem are responsible for autonomic control of the muscle is called *autonomic nervous system* (ANS).

The descending inputs from the cerebral cortex (motor cortex and premotor cortex) are transferred via interneurons [Fetz et al., 2002] and motor neurons of the brain stem and spinal cord through the corticospinal tract, major motor pathways to control voluntary, highly skilled, and functional movements. The motor neurons, then, send signals to muscle fibers via neuromuscular junction (synapses) with the help of neurotransmitters such as glutamate, glycine, or GABA [Dum and Strick, 1996] and finally, elicit muscle contractions. The pathway systems can be disynaptic,

involving a single interneuron between the brain and muscle, or polysynaptic, which involve more than one interneuron. In sophisticated movements, the control of the muscles may involve not only the descending pathways from the SNS and ANS but also the ascending pathways through spinocerebellar and spinothalamic tracts to adjust and correct the current movement to the desired position. Specifically, a motor neuron is not only synapsed by descending inputs from the CNS but also by several interneurons connected from sensory afferents such as Ia and Ib feedback loops (Figure 2.1). A motor neuron could receive thousands of synapses on its dendrites, and the inputs from these synapses could excite (having *excitatory postsynaptic potential* (EPSP) effect) or inhibit (*inhibitory postsynaptic potential* (IPSP) effect) the activity of the muscle fiber it innervates [Rekling et al., 2000, Heckman and Enoka, 2004].

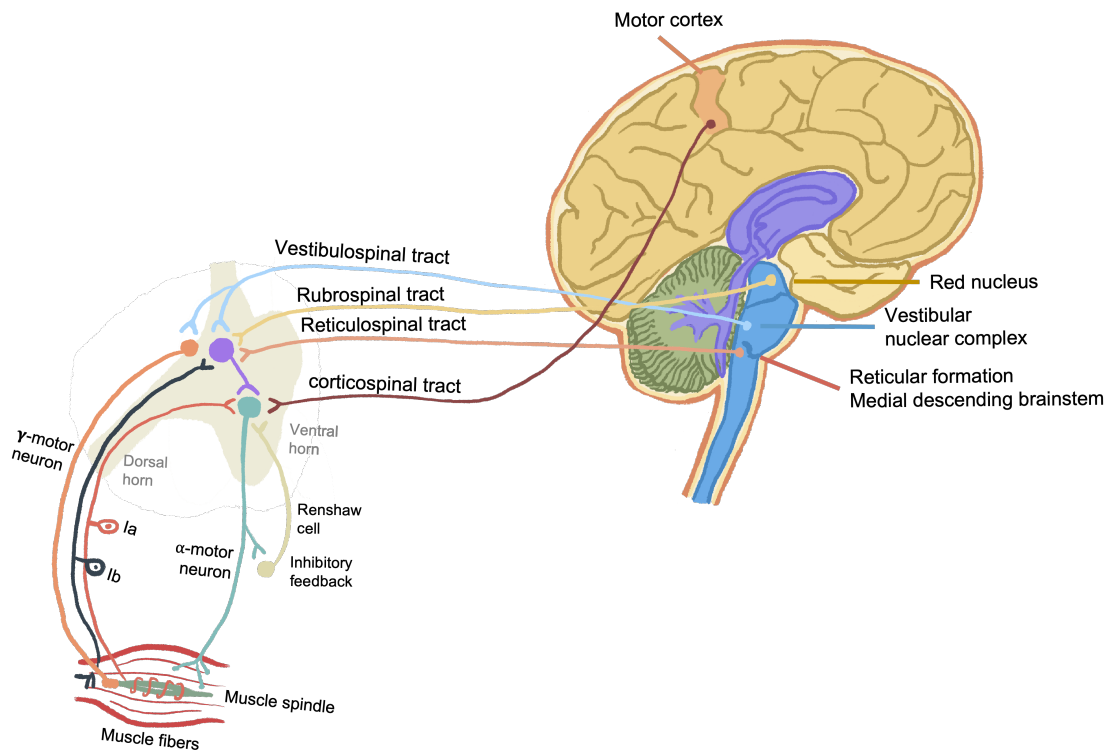


Figure 2.1: Simplified illustration of projection of cortico-muscular tracts from upper motor neurons to lower motor neurons. The upper motor neurons have their axons pass through the corticospinal tract, vestibulospinal tract, reticulospinal tract, or rubrospinal tract before they synapse to interneurons (purple line), alpha-motor neuron (green line), or gamma-motor neuron (orange line) which directly innervates muscle fiber and intrafusal muscle fibers (within muscle spindle), respectively. The muscle spindle, a proprioceptor located within a muscle, detects changes in muscle length, sending sensory input back to the brain via group Ia afferent. Similarly, the Golgi tendon also senses muscle tension back to the brain via group Ib afferent.

2.1.1 Important tracts link the CNS to muscles.

- **Corticospinal tract**

The corticospinal tract includes corticobulbar, lateral corticospinal and anterior corticospinal tracts. The corticospinal tract is also called the pyramidal tract, as the tracts pass through the medial pyramids of the medulla oblongata. The corticospinal tracts receive inputs from the primary motor and premotor cortex, pass through the internal capsules and medulla before separating into lateral and anterior tracts at the pyramids, and terminate at the spinal cord. While the lateral corticospinal tract crosses over to the other side of the pyramids before synapses to the motor neurons at all levels of the spinal cord, the anterior corticospinal tract does not cross the pyramids but synapses to motor neurons at the lower level of the spinal cord in order to separately control upper and lower limbs. The tracts located in more lateral portions primarily control more skilled, learned, voluntary movements [Welnarz et al., 2017].

- **Vestibulospinal tract**

The vestibulospinal tract is an ANS; it medially descends signals from the brainstem and travels along the spinal cord white and grey matter. It is responsible for the automatic control of the muscle. The vestibulospinal tract originates in the vestibular nuclei in the medulla and plays an essential role in activating the anti-gravity muscles in response to the imbalance of the body. The vestibular nuclear complex receives sensory input from the vestibular apparatus in the inner ears about the head position, body position, and balance and compensates for the disturbance by exciting the anti-gravity musculature such as gastrocnemius and soleus muscles that control ankle joint flexion to maintain the body upright [Hibino, 1980].

- **Reticulospinal tract**

The reticulospinal tract originates from cells in the reticular formation located in the pons and medulla. It is laterally and medially travels along the spinal cord white and grey matter. The reticulospinal tract plays an essential role in regulating muscle tone, body stabilization, and maintaining anti-gravity postures. In addition, the reticulospinal tract involves alpha-gamma co-activation of motor neurons and modulating stretch reflex sensitivity.

- **Rubrospinal tract**

The rubrospinal tract originates from the red nucleus located in the midbrain. It also plays an important role in controlling extensor and flexor muscles and hand movement.

Upper motor neurons from these tracts synapse to lower motor neurons in the anterior grey column of the spinal cord. The lower motor neurons only discharge an action potential (motor neuron firings) when the summation of the electrical potential at the pre-synaptic inputs exceeds

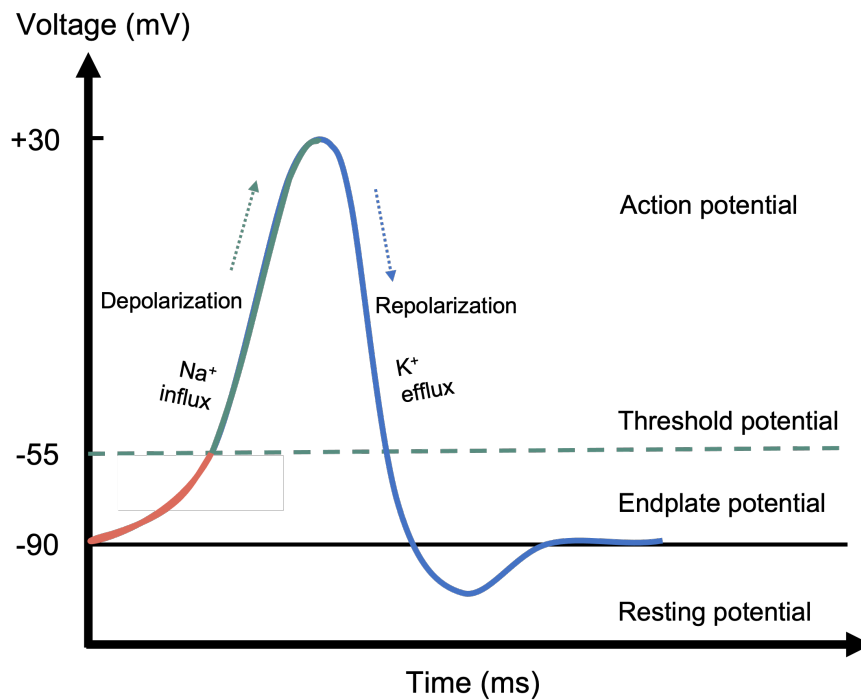


Figure 2.2: Depolarization and repolarisation processes of an action potential. The depolarization of the cell membrane potential only occurs when there is a sufficient EPSP to reach the threshold potential at -55mV (dashed line). When the action potential threshold is reached, voltage-gated Na^+ channels are opened, allowing Na^+ to flow into the membrane, increasing the membrane potential to $+30\text{ mV}$ producing an action potential. Repolarization occurs when the voltage-gated Na^+ channels are inactivated, and the voltage-gated K^+ channels are opened, allowing K^+ release from the cell membrane reducing the membrane potential before it recovers back to its resting state at -90mV .

the activation threshold or recruitment threshold. The recruitment threshold is a value of force at which the MU begins to discharge action potentials (Figure 2.2)) [Lucas, 1909]. The action potential, then, propagates along the motor neuron axon, whose length is wrapped by myelin sheaths, reaching the axon terminal where the voltage-gated sodium channels are located (Figure 2.4). At around -55 mV , the voltage-gated sodium channels are opened, allowing Na^+ ions to diffuse in the axon membrane generating depolarization that opens the next voltage-gated sodium channels until reaching the synaptic bulb. At approximately $+30\text{mV}$, the voltage-gated calcium channels are opened, and the Ca^{2+} ions flow in signaling the neuron to release neurotransmitters contained in synaptic vesicles [Schiaffino and Reggiani, 2011]. The neurotransmitter is called *Acetylcholine* (ACh) crosses the synapse (synaptic cleft) and induces an electrical charge to the postsynaptic cell (sarcolemma). [Hodson-Tole and Wakeling, 2009] has reviewed the function of the neurotransmitters involved in the transmission of action potentials to muscle fibers, its safety factor, and the effect of their modulation. Specifically, the Ca^{2+} helps activate proteins: Synaptotagmin, Synaptobrevin, Snap25, and Syntaxin on the synaptic vesicles and synaptic bulb membrane to bind to each other

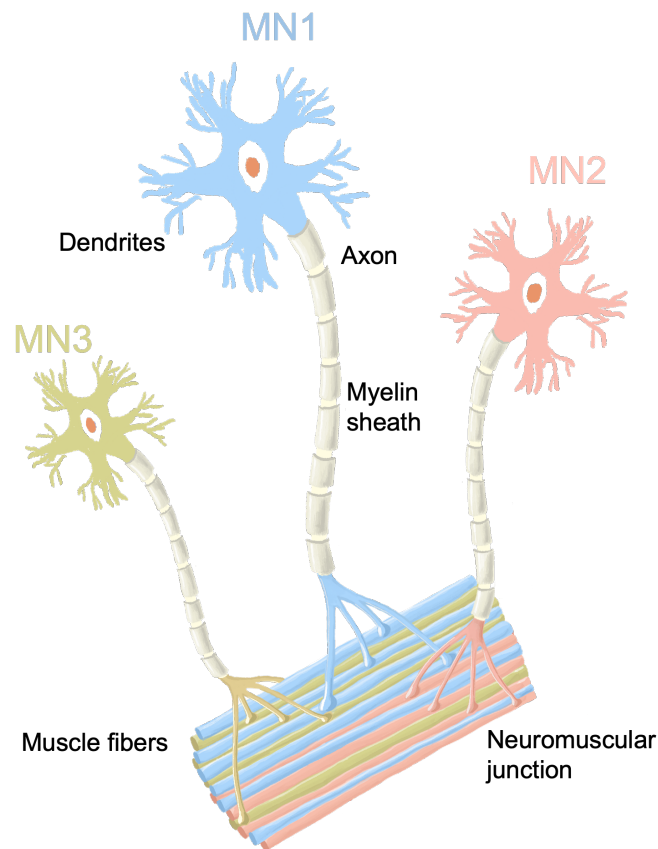


Figure 2.3: Sketch of a group of three MUs (1:blue, 2:orange and 3:green). Each MU consists of a lower motor neuron whose dendrites connect to upper motor neurons at the spinal cord (not shown in this figure) and axon connect to a group of muscle fibers. An action potential propagates along its axon covered by myelin sheath to muscle fibers and induces muscle fiber action potentials through the neuromuscular junction. Within a muscle, groups of fibers in different MUs are distributed over the muscle to ensure sufficient control even when some of the MUs are destroyed.

until they fuse, causing the release of the ACh. ACh in the synaptic cleft is bonded on the muscle sarcolemma (lipid bilayer muscle fiber membrane) by ACh specific receptors called Nicotinic (located at the motor endplate). The ACh opens ionotropic synaptic channels allowing Na^+ ions from extracellular fluid to flow into the muscle fiber membrane and depolarizes the membrane to generate an endplate action potential (or muscle fiber action potential). This potential depolarizes the sarcolemma down to the transverse tubule and evokes the sarcoplasmic reticulum to release Ca^{2+} it stores for excitation-contraction coupling through a coupling between voltage-gated Ca^{2+} channels called Dihydropyridine on the surface of the transverse tubule and ryanodine receptors on the sarcoplasmic reticulum membrane [Dulhunty et al., 2002] (Figure 2.5). Ca^{2+} and adenosine triphosphate induce interaction of the contractile proteins: thick and thin filaments (actin-myosin cross-bridges moving toward thin filament) and finally, elicit muscle contraction [Gordon et al., 2001, Bloch and Gonzalez-Serratos, 2003]. When the muscle fiber membrane potential reaches +30mV, the transverse tubule repolarizes and inactivates the voltage-gated Ca^{2+} channels on the

sarcoplasmic reticulum to store the Ca^{2+} . The thick and thin filaments are detached, leading to the release of excitation-contraction coupling (Figure 2.5). The muscle then goes to its resting stage.

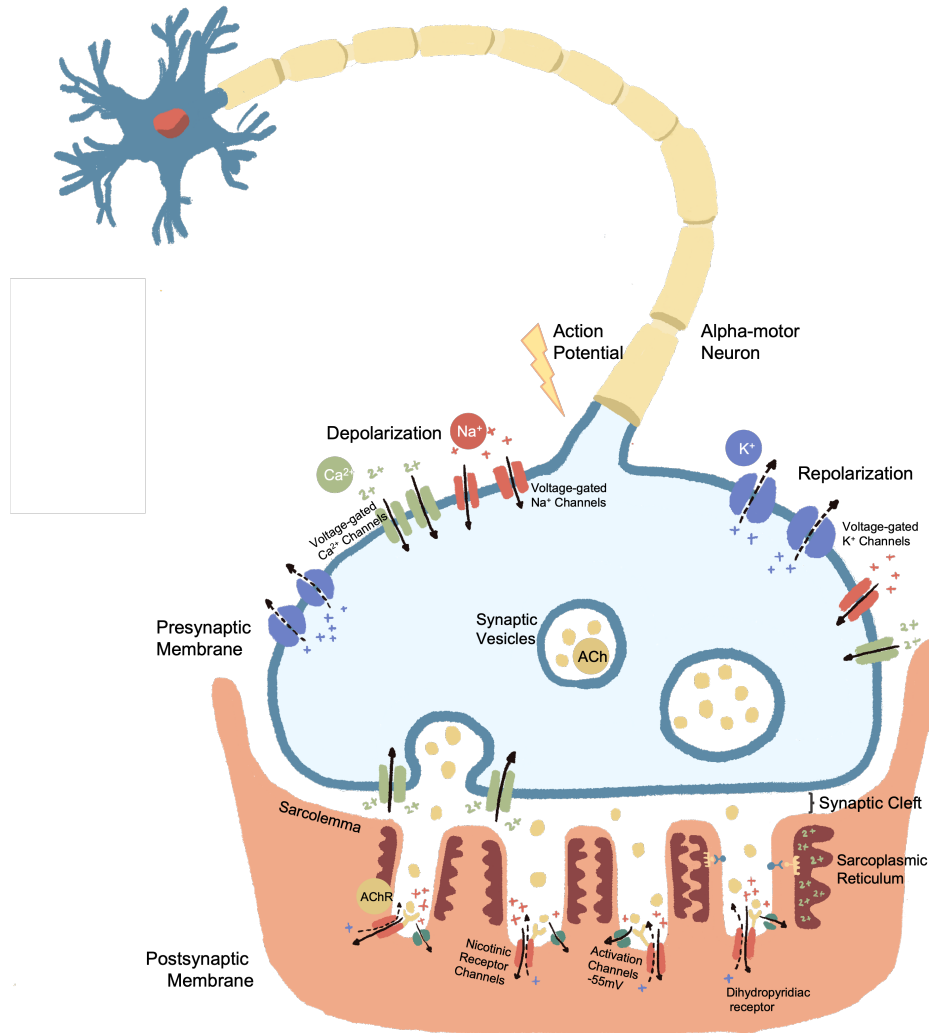


Figure 2.4: The synaptic transmission of an action potential at the neuromuscular junction. A motor neuron innervates muscle fibers (postsynaptic membrane) at the motor endplate. The synapse between the two membranes occurs between the synaptic cleft. The alternate flow of Na^+ , K^+ , and Ca^{2+} allow modulation of the cell membrane potential, which influences the release of vesicles containing Acetylcholine, the neurotransmitter attached to a specialized receptor located on the membrane of postsynaptic muscle fibers. This attachment allows depolarization of the postsynaptic membrane, inducing the generation of muscle fiber action potential. The sketch was adapted from [Gonzalez-Freire et al., 2014]

Apart from the ionic mechanism involved in motor neuron potential regulation, monoaminergic input also plays an important role in depolarizing and maintaining the polarizing state of the motor neurons. Interneurons that are sensitive to neurotransmitters such as Serotonin, Nore-

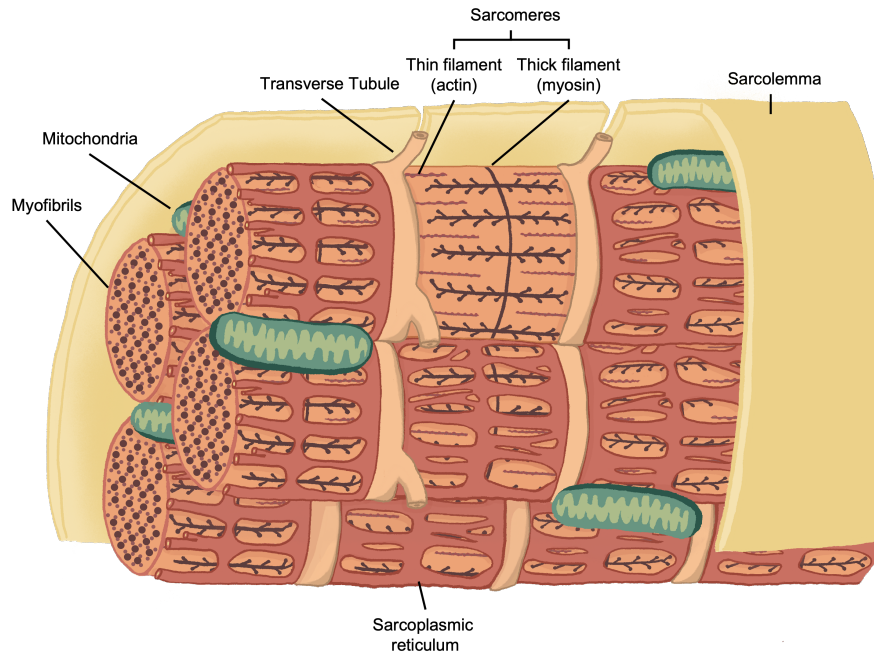


Figure 2.5: Sketch of skeletal muscle components. Myofibrils, which can be divided into myosin (thick myofibrils) and actin (thin myofibrils), are essential components for muscle shortening and contraction generation. A muscle unit containing these two myofibrils is called Sarcomeres and is divided by Z lines (black line). Actin-myosin cross-bridges occur here via the release of Ca^{2+} and Adenosine triphosphate to simultaneously shorten the length of muscle cells to generate muscle contraction. The sketch was adapted from [Korfage et al., 2005, Tsianos and Loeb, 2017]

pinephrine are commonly found in the brain stem, and hypothalamus [Binder et al., 2020, Vitrac and Benoit-Marandmarienne, 2017]. When Norepinephrine is captured by norepinephrine neurons, the depolarization of the neuron is preserved by remaining voltage-gated channels on the membrane opened and prolonging the potential state of the neuron (persistent depolarization). This potential is sufficient to dominate the neuron behavior by increasing the baseline current of the cell membrane, facilitating it to discharge an action potential easier (increasing gain) when a current from the ionic mechanism arrives. If the monoaminergic input is high enough, the neuron potential remains above the firing threshold producing self-sustained firing (persistent inward current) without additional synaptic inputs before inhibitory input is injected and returns the neuron to resting-state [Lee and Heckman, 2000, Heckman and Enoka, 2004, Heckman et al., 2008].

All the neural inputs that successfully activate muscle contractions are called neural drive to muscle [Negro and Farina, 2011]. A single alpha-motor neuron (lower motor neuron) can innervate a branch of muscle fibers that allocates over a muscle. Depending on its size, a muscle could contain tens to thousands of muscle fiber branches and can be innervated by a group of motor neurons located in the ventral horn of the spinal cord grey matter. The group of motor neurons innervating a single muscle is called a motor neuron pool [Burke et al., 1977]. Branches of the muscle fibers innervated by the motor neuron pool are randomly distributed all over the muscle to ensure that

damage to a single motor neuron in the pool will not severely affect the overall function of the muscle. An alpha-motor neuron and the group of muscle fibers it innervates constitute a functional unit called a MU [Liddell and Cherrington, 1925, Enoka, 1995] (Figure 2.4). An action potential produced by a MU induces an action potential in all the fibers it innervates. MUs are, therefore, an interface between the final output from the spinal cord and the actual muscle function [Farina and Merletti, 2008, Farina and Holobar, 2016, Heckman and Enoka, 2004].

The CNS regulates the level of force produced by a muscle by alternating the number of MUs recruited and their firing rate (rate coding) [Macefield et al., 1996, Gordon et al., 2001]. A study has shown that there is a one-on-one communication between single action potential and a muscle twitch (force evoked by a single action potential) [Katz and Ricardo Miledi, 1965]. To produce a tetanic force, sufficient presynaptic inputs are required to activate a larger number of MUs to produce continuous muscle fiber action potentials (MU firings) and increase their firing rates [Adrian and Bronk, 1928, Adrian and Bronk, 1929]. In general, MUs are orderly recruited based on size recruitment principal [Henneman, 1957]. Small MUs (small soma of alpha-motor neurons and diameter of its axon) are recruited first as they have a lower recruitment threshold and require lower stimulation intensity. Larger MUs are then orderly recruited using a higher potential to reach their recruitment threshold. While the size of the MUs is proportional to the stimulation intensity needed to recruit them, [De Luca and Erim, 1994] and the series of his studies [De Luca et al., 1996, De Luca and Contessa, 2012] revealed that the size of the MUs recruited is inversely proportional to their firing rates. Therefore, investigating the sequence of the MUs recruitment and their firing patterns could reflect the composition of synaptic inputs involved in the neuromuscular control system. Study of MU characteristics such as the MU types and their firing patterns, hence, facilitated the understanding of the underlying mechanism of movements [Fuglevand et al., 1993].

2.1.2 Size principle

The level of force produced by a muscle is significantly influenced by the number and size of the MUs recruited [Henneman, 1957]. The size of a MUs is determined by 1) size of the motor neuron soma, 2) diameter of its axon, 3) the number of muscle fibers the motor neuron innervates, and 4) diameter of the muscle fibers. Specifically, larger axons could provide a greater number of synaptic endings branched from the axons allowing activation of a greater number of muscle fibers; hence, higher force [Henneman et al., 1965]. Animal studies have shown that there was a strong correlation between innervation ratio and MU size with the maximal force it produced [Rafuse et al., 1997, De Zepetnek et al., 1992, Grinnell and Trussell, 1983, Kanda and Hashizume, 1992]. Assessment of EPSP produced by stimulation of homogeneous and heterogeneous Ia afferent of cat tibialis anterior and medial gastrocnemius showed that the level of EPSP is inversely related to motor neuron size implying the orderly recruitment during increasing force [Dum and Kennedy, 1980]. Using the McComas method, a method for the number of MU estimation based on the EMG

measurement of a MU after receiving increasing nerve stimulation [McComas et al., 1971], it is found that there were an average of 1400 muscle fibers per MU of human biceps brachii and 1600 - 2000 fibers in the vastus lateralis of 8 female and 8 male subjects, respectively [Miller et al., 1993]. Small MUs, such as in the first lumbrical muscle, contains only around 100 muscle fibers, whereas a larger muscle, as the gastrocnemius, could contain around 2,000 muscle fibers per MU [Duchateau and Enoka, 2022]. The muscle force level is also determined by the diameter of an axon which is proportionally scaled with its neuron soma [Henneman et al., 1965]. As the conduction velocity of an axon is a direct function of its size [Gillespie and Stein, 1983]. The small diameter axon has low conduction velocity due to the small conductive membrane area (containing the low number of voltage-gated Na⁺ channels). Thus, the force produced is lower than a larger diameter axon.

Recruitment threshold of a MU is determined by the MU size [Deuschl et al., 2011]. The recruitment threshold is the level of force necessary for a MU to start its first firing. The MU contains small neurons; hence, small-diameter axons are called low-threshold units [Henneman et al., 1965] and are recruited first during slow contraction before larger neurons (high-threshold unit). This recruitment of MUs in order of size is called the size principle. Since the low-threshold MUs are small, the force they can produce is weak [Henneman et al., 1965]. Therefore, the size of MUs is distributed in different types of muscle based on their functions. For example, in slow-twitch and fatigue-resistant muscle or type S muscle, small MUs (fewer than 30 axon branches) which can produce the weakest force can be found, whereas larger MUs (more than 80 axon branches) providing fast and strong contraction can be found in fast-twitch and fatigue-resistant muscles (type FR), and fast-twitch and fatiguing muscles (type FF) [Enoka, 1995]. However, a muscle could contain a combination of these three types of muscle fibers [Wallinga-De Jonge et al., 1985]. As the MUs are recruited with the size principle, i.e., the type S fibers usually are recruited first, followed by Type FR and FF when the force increases, the recruitment sequence allows smooth movement, optimizes precision of force gradation, promotes fatigue resistance, and prolongs energy efficiency. The recruitment threshold of a MU could be reduced if a rapid and strong force is needed like in ballistic contraction [Desmedt and Godaux, 1978], especially the MUs in slow-contraction muscles, to facilitate the contraction. When the force gradually reduces, the MUs are de-recruited in inverse order of their recruitment [Henneman et al., 1965]. However, it was suggested that the MUs may not always be orderly recruited by their size but could have specific patterns of recruitment depending on the tasks (task-specific) [Laine et al., 2014]. In addition, cutaneous stimulation could also modify the order of MU recruitment [Hodson-Tole and Wakeling, 2009].

In general, MUs are recruited from low- to high-threshold units to exert a higher force while concurrently increasing the firing rate of the recruited MUs [De Luca and Hostage, 2010]. When all of the MUs in the muscle are recruited, and the recruitment threshold limit of the muscle is reached but the force produced is not sufficient, the increased neural command will modulate the MU discharge rates (rate coding) of the already active MUs to increase the muscle force.

2.1.3 Rate modulation of the MU discharge (Rate coding)

The discharge rate of a motor neuron varies in proportion to the number of synaptic inputs it receives, and the variation of the discharge rate regulates the level of force produced by the muscle fibers [Adrian and Bronk, 1928, Fuglevand et al., 1999]. Adrian and Bronk investigated the discharge of a single motor neuron innervating the diaphragm, phrenic nerve, of an anaesthetised rabbit using a capillary electrometer and valve amplifier. Their experiment shows that increased stimulation frequency doubled the suction pressure caused by the diaphragm before reaching plateau pressure. The plateau of force exertion reflects a limitation of one motor neuron discharge. This corresponds to their next experiment involving the recording of the tibialis anticus reflex tension after varying mechanical stimulation in cats and tricep muscle fibers recording during the varying degree of voluntary contraction using concentric needle electrodes [Adrian and Bronk, 1929]. However, increasing the force does not alter the amplitudes of the action potential (“all or none”) but only the discharge rate. In addition, during higher force exertion, synchronisation of action potential from multiple active motor neurons is observed, showing recruitment of a group of neurons to perform a specific task [Deuschl et al., 2011].

There is a clear relationship between peak force and the rate coding of MUs. This relationship is approximately sigmoidal. Under the force-frequency curve, it may be divided into three regions. At low frequencies, the force generated is deficient, producing only discrete muscle twitches. After the frequency increases, the generated force rises rapidly, approaching its maximum where the frequency also reaches its peak and remains plateau [Fuglevand et al., 1999, Lee et al., 2009]. The force-frequency curve varies according to the properties of the muscle, such as muscle length and contractile activity.

2.1.4 Non-linearity and linearity of motor neuron pools

It is known that there is a one-on-one mechanism between a motor neuron’s axon and a muscle fiber it innervates. Specifically, a single action potential propagating through the axon will elicit a single muscle fiber contraction. Therefore, the neuromuscular junction, the synaptic gap between the axon and innervated zone on muscle fiber, is a linear gateway for a successive neural drive to a muscle. However, the motor neuron whereby those axons are branched receives more than one synaptic input from presynaptic neurons. The motor neuron can only elicit an action potential if the summation of all the synaptic inputs exceeds its recruitment threshold. These synaptic inputs include 1). ionotropic inputs, which could have excitatory or inhibitory effects on the motor neurons, and 2). the influence of persistent inward current modulated by release of neurotransmitters [Heckman et al., 2008]. The regulation of the neuron potential by these inputs, together with variation in properties of different types of motor neurons, makes the MU system non-linear [Negro and Farina, 2011, Farina and Negro, 2015]. The non-linearity of individual

motor neurons can be reduced by grouping motor neurons that receive the same synaptic inputs (common inputs) to create a motor neuron pool. Action potential discharges of a motor neuron pool could be considered linear to the net synaptic inputs if the number of MUs in that group is large enough. Specifically, the discharges of MUs are not individually controlled by the CNS, but they are controlled as a group. The independent inputs projected to individual MUs can be filtered out, and only the common inputs are enhanced and influence the action potential trains of the motor neuron pool to modulate the force required [Gallego et al., 2015a, Puttaraksa et al., 2019] (Figure 2.6).

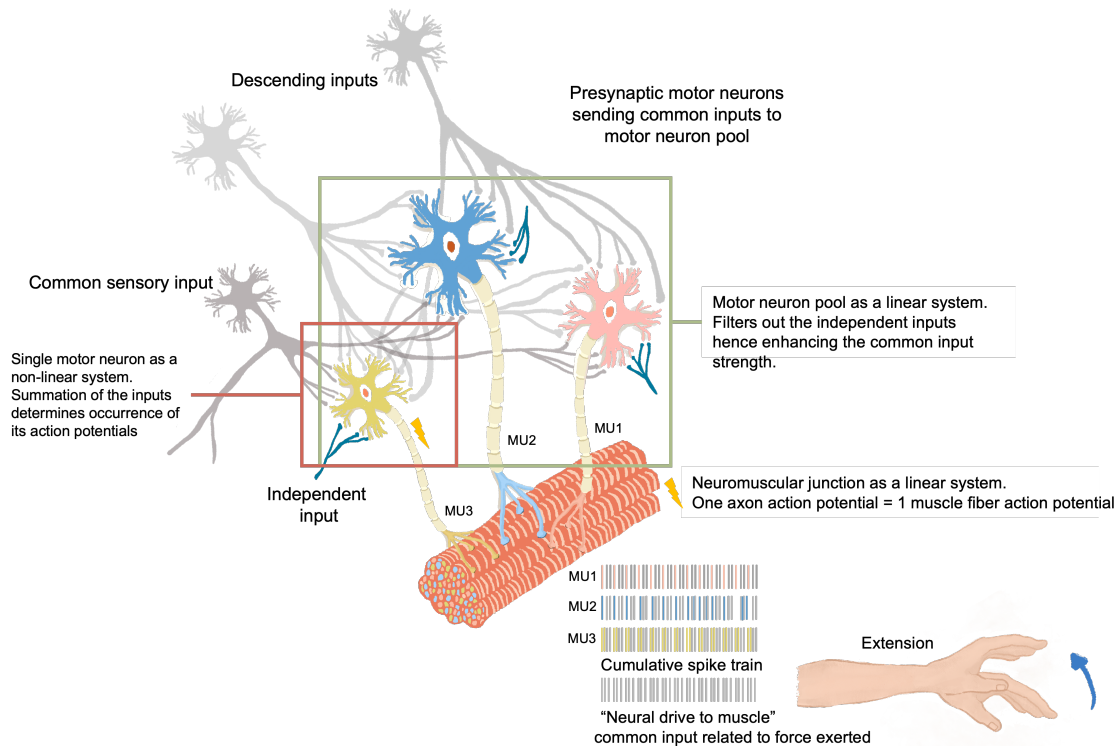


Figure 2.6: Non-linearity and linearity of motor neuron pools. A single MU is a non-linear system. The summation of projecting inputs to the motor neurons is not proportional to the MU discharge patterns. However, a group of motor neurons (motor neuron pool) increase its linearity as they emphasize the influence of the shared inputs while filtering out the noise or independent inputs projected to individual MUs. Similarly, the neuromuscular junction is a one-on-one connection between MU action potentials and muscle fiber action potential making the system linear. Thus, the motor neuron pool and a group of the muscle fibers they innervate could be accounted for as a linear system. Recording of the MU spike trains that are successfully transferred to the muscle represents the common inputs from the CNS. The neural drive to muscle then modulates the level of force exerted.

2.1.5 Muscle fiber action potential

Similar to the way electrical potential is transmitted and propagated through the axon of a neuron, muscle fiber action potential is induced in the neuromuscular junction. The muscle fiber action potentials bilaterally propagate along the muscle fibers via an ionic mechanism away from the innervation zone or motor endplate toward tendons. The muscle fiber action potential is a summation of depolarization due to the influx of action potential in tubular and repolarization due to efflux of K^+ through sarcolemma. Therefore, the net muscle fiber action potentials have a triphasic-like shape with a similar amplitude of positive and negative potentials, followed by a slow decaying potential called afterpotential. The amplitude of the muscle fiber action potential is determined by the conduction velocity and size of the muscle fibers. The summation of action potentials of muscle fibers belonging to a motor neuron is a *motor unit action potential* (MUAP). Superposition of muscle fiber action potentials due to spatial potential distribution or different conduction velocities of each fiber creates complex and irregular MUAP shapes. Since the neuromuscular junction is a highly reliable synapse [Heckman and Enoka, 2004, Deuschl et al., 2011], recordings of the muscle fiber action potentials provide a direct connection to the MU discharge timing and patterns that produce the current force, which is also called successive neural drive to the muscle. Electronic measurement of the muscle fiber action potentials is, therefore, a link to elucidate the neural mechanism behind that movements [Gasser and Newcomer, 1921].

2.1.6 Electromyography

The electrical activity of skeletal muscles can be recorded using minimally invasive or non-invasive electrodes. The recording of the electrical activity of a muscle is called electromyography recordings or electromyogram (EMG). The EMG has been used to quantify muscle force, study the physiology and pathology of the MUs, measure the innervation zone to the tendon endings, estimate muscle-fiber conduction velocity, length, and orientation of the fibers. Although electrical responses in a muscle fiber give an accurate measurement of muscle fiber action potentials responded to the motor neuron action potentials, interpretation of the EMG recording should be made with caution. This is because the shape of the EMG is not a direct measurement of the summation of each motor fiber action potential but is influenced by the action potentials of different muscle fibers having various conductive velocity properties. The EMGs are also influenced by the muscle-electrode distance and the degrees of synchronization of the MU discharges, which could lead to a superposition of MUAPs. The EMG, therefore, accounted only as a global representative of the muscle activity captured under the electrode area. Biological tissue such as skin and fat have different conduction properties that low-pass filter the sum of the detected MUAPs blurring the features of the EMGs [Farina and Rainoldi, 1999]. Thus, the EMG features such as their amplitudes and frequency are significantly influenced by the types, sizes, and locations of the electrodes.

- **Intramuscular Electromyography**

Intramuscular Electromyography (iEMG) is one of the EMG recording techniques where the recording electrodes are inserted into a muscle. Recording the EMGs through intramuscular wires or needle electrodes is a standard approach for accessing MUAPs features that are beneficial for diagnosing muscle disorders and assessing the principle physiology of MUs, such as MU size, order of recruitment and firing pattern [Merletti and Farina, 2009]. It can also be used to assess the internal structure of muscle fibers, such as its conduction velocity [Rubin, 2012]. Because of the small distance between the electrode and the muscle fibers, the intramuscular recordings are not substantially influenced by the tissue filtering (volume conductor) [Farina and Rainoldi, 1999]. Monopolar needle electrodes, for example, are the simplest needle electrodes. Its core is stainless steel coated with Teflon; its bared tip is referenced to another electrode attached to electrical silent areas such as bone and tendon. However, having a reference electrode distance to the needle and a wider detection area of the electrode tip introduces noise from the surrounding muscle fibers to the recorded EMGs.

A concentric needle electrode was introduced to improve the signal-to-noise ratio and selectivity of the monopolar needle electrodes. It was first used to record a single MU activity in the human triceps brachii muscle [Adrian and Bronk, 1929]. The electrode needle consists of a steel cannula filled with copper or platinum wire which is cut at the tip into an oval shape. The shaft of the needle acts as a reference electrode, while the tip of the wire acts as an active electrode. The small gap between two electrodes inserted underneath the muscle fibers allows the measurement of the potential difference of the fibers next to the electrode areas [Tankisi et al., 2020]. Further development of the concentric needle electrodes into bipolar concentric needle electrodes has improved the quality of the detected signals and selectivity of the electrodes, which is necessary for individual MU identification from superimposed action potential recordings.

It is worth noting that different properties and sizes of the needle electrodes significantly affect the acquired MUAP morphology, and iEMG may become inappropriate at high force levels as small movements of the electrodes during the increment of muscle force could change MUAP shapes and could be painful for the subject. In addition, despite having high selectivity of MU detection, the small detection size of the needle electrode limits the number of MU detected [Merletti and Farina, 2009].

A more recent model of the intramuscular electrode is made of flexible fine wire called indwelling electrode [Basmajian and Stecko, 1962]. This electrode consists of a pair of fine nylon-coated wires placed in a hypodermic needle. After injection of the electrode, the wire is left within a muscle, and the needle is withdrawn. The wire is attached securely to the muscle with a hook at the end of the wire. These electrodes are less likely to displace during high force contractions, improving the quality of the recorded signals. The fine wire electrodes could also reduce pain during muscle contraction compared with the needle electrodes. Since

intramuscular electrodes provide high selectivity for MU recording, the number of detected MUs is limited. A novel multi-channel micro-fabricated intramuscular wire electrode was developed to maximize the number of identified MUs. By increasing the recording sites, more action potential of more MUs can be detected [Farina and Merletti, 2008, Muceli et al., 2015, Muceli et al., 2019].

- **Surface Electromyography**

Unlike intramuscular electrodes, *surface electromyography* (sEMG) has poor MU selectivity. It records the summation of muscle fiber action potentials of a much greater number of MUs underneath the electrode area. Although the volume conduction of muscle-skin tissue allows electrical recording over the skin, the action potential recorded are severely low-pass filtered by the effect of fat and skin conduction properties [Farina and Rainoldi, 1999] causing difficulty in distinguishing action potential shapes of different MUs (i.e. the detected action potentials from different MUs may overlap) [Merletti and Lo Conte, 1992, Merletti and Muceli, 2019, Farina et al., 2004, Stegeman et al., 2000]. The large area of the surface electrodes could detect cross-talk, which is MUAPs that belong to adjacent muscles or muscles located deeper into the interest muscles. Contamination of the cross-talk in the EMGs could lead to errors in the interpretation of the EMG features [De Luca and Merletti, 1988]. In addition, the information contained in surface EMG is not a perfect representative of MU activity as there are cancellations between negative and positive phases (amplitude cancellation) of the overlapped muscle fibre action potentials due to volume conduction of the muscle-skin tissue [KG, Keenan, Farina D, Maluf KS, Merletti R, 2005, Farina et al., 2004, Farina and Rainoldi, 1999]. Although surface electrodes are easy to apply compared to intramuscular electrodes, the quality of EMG signals significantly depends on recording positions and configurations (monopolar or bipolar recordings). High-density surface electrodes, therefore, were developed to overcome the volume conductivity effect of the regular surface electrodes (bipolar electrodes). Based on spatial filtering and spatial sampling of multi-location recording, the high-density surface electrodes counteract the low-pass filtering effect of the volume conductor and increase the selectivity of the recordings [Blok et al., 2002]. High-density surface electrodes comprise about a hundred tiny electrodes closely arranged in an array, embedded on a flexible silicone rubber [Drost et al., 2006, Farina and Merletti, 2008, Holobar et al., 2010, Merletti et al., 2008]. They can be monopolar electrodes referencing a common ground electrode distant to the electrode array. The high-density surface electrodes are useful in investigating propagation velocity of muscle fiber action potential, detection of innervation zone via bipolar recordings or differential of monopolar recordings, estimation of MU firing rate, morphology of the MUAPs and MU discharge patterns. The surface MUAPs can also be estimated using spike-triggered average where the decomposed discharge timings are used as the triggers for the sEMG averaging [Farina and Merletti, 2008, Merletti and Farina, 2009]. In addition, the high-density sEMG can be used to access pathology of MUs such as in Parkinsonism, and ET patients [Drost et al., 2006, Holobar et al., 2011, Puttaraksa et al., 2019] via assessment of their MU discharge

patterns using advanced decomposition techniques such as convolution kernel compensation [Holobar and Zazula, 2003, Holobar and Zazula, 2007] and independent component analysis [Negro et al., 2016, Chen et al., 2016, Cichocki and Amari, 2002]. Real-time decomposition of EMG was also developed, giving an equivalent performance to the offline algorithm [Clarke et al., 2020, Barsakcioglu and Farina, 2018].

Mathematical model of multi-channel EMG signal can be described as a convolutive mixture of impulse responses of filters (MUAP shape, h_{ij} having L -sample long)) with a series of MU discharge timing (MU spike trains, s_j) as describe in eq. 2.1 (Glaser et al., 2013).

$$x_i(n) = \sum_{j=1}^N \sum_{l=0}^{L-1} h_{ij}(l) s_j(n-l) + \omega_i(n), \quad i = 1, \dots, M, j = 1, \dots, N \quad (2.1)$$

Where x_i is the i th EMG channel at time sample n , ω is the white zero-mean Gaussian noise at channel i , N and M are number of MUs (sources) and EMG channels, respectively. The eq. 2.1 can be written in a matrix form by extending the vector in eq. 2.1 and can be expressed as

$$\mathbf{x}(n) = \sum_{l=0}^{L-1} \mathbf{H}(l) \mathbf{s}(n-l) + \boldsymbol{\omega}(n) \quad (2.2)$$

where $\mathbf{x}(n)$ is a vector of n th sample of M th EMG channel, and $\mathbf{s}(n)$ is a vector of n th sample of N th MU spike trains, which are extended to their R and $L-1$ delayed versions, respectively. The extended length R should be larger than $N/M \times L$ [Holobar and Zazula, 2007, Negro et al., 2016].

$$\begin{aligned} \mathbf{x}(n) &= [x_1(n), x_2(n), \dots, x_M(n)]^T \text{ is extended to} \\ \bar{\mathbf{x}}(n) &= [x_1(n), x_1(n-1), \dots, x_1(n-R), \dots, \\ &\quad x_M(n), x_M(n-1), \dots, x_M(n-R)]^T \end{aligned} \quad (2.3)$$

$$\begin{aligned} \mathbf{s}(n) &= [s_1(n), s_2(n), \dots, s_N(n)]^T \text{ is extended to} \\ \bar{\mathbf{s}}(n) &= [s_1(n), s_1(n-1), \dots, s_1(n-L-R+1), \dots, \\ &\quad s_N(n), s_N(n-1), \dots, s_N(n-L-R+1)]^T \end{aligned} \quad (2.4)$$

$$\begin{aligned} \boldsymbol{\omega}(n) &= [\omega_1(n), \omega_2(n), \dots, \omega_M(n)]^T \text{ is extended to} \\ \bar{\boldsymbol{\omega}}(n) &= [\boldsymbol{\omega}_1(n), \boldsymbol{\omega}_1(n-1), \dots, \boldsymbol{\omega}_1(n-R), \dots, \\ &\quad \boldsymbol{\omega}_M(n), \boldsymbol{\omega}_M(n-1), \dots, \boldsymbol{\omega}_M(n-R)]^T \end{aligned} \quad (2.5)$$

Whereas $\mathbf{H}$ which has the size of $M \times N$ is a mixing matrix of MUAPs from all MUs.

$$\mathbf{H} = \begin{bmatrix} \bar{h}_{11} & \cdots & \bar{h}_{1N} \\ \vdots & \ddots & \vdots \\ \bar{h}_{1M} & \cdots & \bar{h}_{MN} \end{bmatrix} \quad (2.6)$$

With each $\bar{h}_{ij}$ is expressed as

$$\bar{h}_{ij} = \begin{bmatrix} h_{ij}[0] & \cdots & h_{ij}[L-1] & 0 & \cdots & 0 \\ 0 & \ddots & \ddots & \ddots & \ddots & \vdots \\ \vdots & \ddots & \ddots & \ddots & \ddots & 0 \\ 0 & \cdots & 0 & h_{ij}[0] & \cdots & h_{ij}[L-1] \end{bmatrix} \quad (2.7)$$

Figure 2.7 illustrates a convolution of mixing matrix (MUAPs) and MU spike trains observed by a number of EMG channels explained in 2.2. From this model, the MU spike trains ($\mathbf{s}(n)$) can be discriminated from the EMG signals using the independent component analysis techniques [Cichocki and Amari, 2002] if the MU spike trains are not synchronized or the convolution kernel compensation (CKC) algorithm which is a more robust algorithm used to decompose the surface EMG into contributions of individual MUs [Holobar and Zazula, 2003, Holobar and Zazula, 2007, Holobar et al., 2010, Holobar et al., 2012]. Basically, the algorithm estimates the transformation of the individual MUs that contributes to the observed

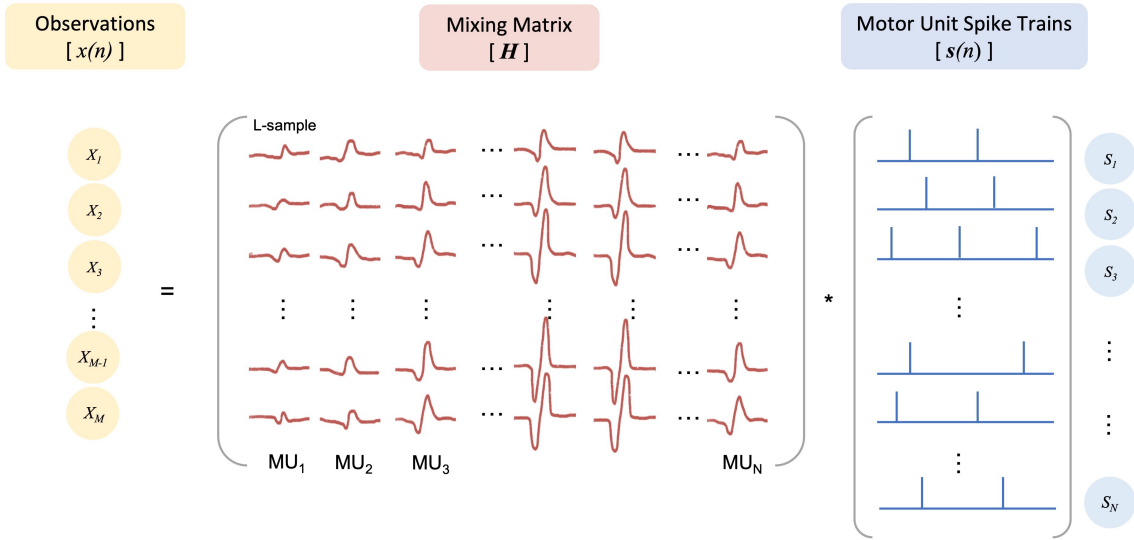


Figure 2.7: Signal generation. The signal observed by M EMG electrodes is a convolution of mixing matrix $\mathbf{H}$ with N MU spike trains. A MU spike train is a binary sequence of zeros and ones where ones reflect the MU firing times and zeros are the silent period of the MU. The vector $\mathbf{s}(n)$, therefore, is the discharge pattern of the N motor neurons. Mixing matrix $\mathbf{H}$ is a matrix of MUAPs with L -sample length of N MUs that are measured by M EMG electrodes. EMG recordings, therefore, are the contribution of several MUs underneath the electrodes.

EMG (mixing matrix $\mathbf{H}$). The estimated transformation is, then, inversely applied to the new-coming EMG to discriminate the MU spike trains.

2.2 Physiology of tremor

Tremor, the most common movement disorder, is characterized by rhythmic oscillations of body parts around joints [Lyons and Pahwa, 2005]. It is commonly recognized as a pathological tremor if the tremor has a frequency ranging from 1 to 25 Hz, with high oscillatory amplitude. In contrast, physiological tremor is a low amplitude oscillation inherently present in healthy muscle activation at an approximate frequency of 10 Hz [Hess and Pullman, 2012, Zhang et al., 2009, Elble, 2009]. The pathological tremor is a symptom associated with neurological disorders, such as *Parkinsonian Tremor* (PT) and ET, which are chronic and progressive diseases [Burne et al., 1987, Lyons and Pahwa, 2005]. It is suggested that the generation of pathological oscillations is associated with dysfunction of cells in the cerebellum, basal ganglia circuits, abnormality in the release of neurotransmitters such as GABAergic [Louis, 2012, Helmich et al., 2013], and neurodegeneration of cells in the cerebellum such as swelling or loss of Purkinje cells [Shilla et al., 2012]. Pathological tremors can be assessed by measuring involuntary oscillations of body parts (particularly the limbs). For example, in *Parkinson's disease* (PD) patients, degeneration of a neurotransmitter called dopamine causes an abnormal descending input from the brain to muscles, leading to involuntary movements of the limbs [Lyons and Pahwa, 2005, Brown et al., 2001]. PT and ET can be distinguished by their characteristics, such as their sources, peak frequencies, and conditions presented [Raethjen et al., 2000, Zhang et al., 2017]. Features of the PT and ET can be quantified using the acquisition of EMG, accelerometer, gyroscope, or force recordings and analyzed by time and frequency-domain methods [Widjaja et al., 2008, San-Segundo et al., 2020, Hagan, 2012, Elble and McNamers, 2016, Deuschl et al., 2011]. Among different types of pathological tremor, ET is the most common tremor disease, affecting 4% of people aged over 50 [Wenning et al., 2005, Louis and Ferreira, 2010]. The ET prevalence has been reported to increase with age. It could reach approximately 22% of people aged over 95 [Louis, 2012].

2.2.1 Essential Tremor

ET originates from abnormal neuronal oscillations at cerebellar and thalamocortical pathways, degenerative changes in the form of brainstem Lewy bodies [Louis, 2009], and abnormalities of basal ganglia [Elble, 1996, Helmich et al., 2013, Shilla et al., 2012, Raethjen et al., 2007, Hua et al., 1998, Pedrosa et al., 2012]. ET could also be related to degeneration of inhibitory neurotransmitter GABA and reduction in GABA receptors as using medication such as primidone and topiramate, which is used for increasing GABAergic transmission, could treat ET [Deuschl et al., 2011]. The

involvement of the CNS in generating tremor in ET has been supported by analysis of the brain and muscle correlation. Schnitzler and his team [Schnitzler et al., 2009] has shown significant cerebro-muscular coherence of *magnetoencephalography* (MEG) recorded from primary motor cortex and EMG recorded from *extensor digitorum communis* (EDC), the *first dorsal interosseus* (FDI), and the *flexor digitorum superficialis* (FDL) muscles. Consistent with MEG-EMG coherence, a cortico-muscular coherence study using *electroencephalography* (EEG) and EMG of wrist flexor and extensor muscles revealed maximum coherences over the contralateral sensorimotor cortex [Hellwig et al., 2001]. The relation of cortical center in ET was also supported by the power spectrum analysis of EMG and accelerometer recordings before and after applying loads to the affected limb. The results showed that the load added did not alter the dominant frequency of ET, implying the involvement of the central oscillator [Elble et al., 1987, Homberg et al., 1987, Elble, 1996].

The basic characteristic of ET is that it occurs during voluntary muscle contraction with frequency ranging from 4 to 12 Hz [Louis, 2005, Hess and Pullman, 2012] without other neurologic symptoms. 95% of ET patients experience this type of tremor called action tremor. Action tremor can be divided into postural tremor, and kinetic tremor [Lorenz and Deuschl, 2007, Louis, 2013, Pigg et al., 2020]. Postural tremor occurs while maintaining a posture of body parts against gravity, whereas the kinetic tremor occurs during active movements. ET commonly affects the upper limbs but also occurs in the head, face, jaw, voice, trunk, and lower extremities [Elble, 2013, Schrag et al., 2000, Laine et al., 2015]. Tremor severity could increase with age [Gutierrez et al., 2016]. These impair ADL such as drinking, eating, and writing [Zesiewicz et al., 2005]. In addition, ET patients and their close others have a risk of experiencing psychological symptoms such as depression, anxiety, daily stress, social phobia, and could induce problems in cognitive, concentration, and memory aspects [Monin et al., 2017, Jhunjhunwala and Pal, 2014, Louis, 2010]. The Fahn-Tolosa-Marín tremor rating scale is a common scale used to estimate tremor severity in ET [Deuschl et al., 1998, Fahn et al., 1988] and later, Essential Tremor Rating Assessment Scale has been validated and growing in popularity as it provides a larger score range which is more suitable for patient with severe ET [Swartling, 2016, Ondo et al., 2018].

Misdiagnosis of ET with other types of tremor, including PT and enhanced physiological tremor, has been reported [Schrag et al., 2000, Jain et al., 2006]. Although the PT commonly occurs at rest within the 3 to 6 Hz frequency range when the affected body part is fully supported, it can also be combined with action tremor at 8 to 12 Hz due to fatigue or anxiety, which leads to difficulty in distinguishing ET from PT. Differentiation of ET and PT is out of the topics of this thesis. Further information, such as their diagnosis criteria and common misperceptions, can be found in [Thenganatt and Louis, 2012]. Briefly, it is firmly supported that PT is a neurodegenerative disease arising from the death of dopaminergic nigrostriatal neurons, causing abnormal oscillations in the loop linking the cortex, basal ganglia, and thalamus [Elble, 2009]. Its tremor amplitude is enhanced by reflex pathways, and mechanical properties of the body parts [Ross, 1986, Hess and Pullman, 2012].

2.2.2 Causes of the tremor

Tremor movements are associated with abnormality in CNS, and PNS [Allum et al., 1978]. Possible causes of the tremor include the following

1. Central Oscillator

The central oscillator is a group of neurons within a nucleus of brain regions that acts as a pacemaker sending involuntary oscillation down to subcortical regions. The nuclei such as in the primary motor cortex, sensorimotor cortex, *nucleus ventralis intermedius* (VIM) of the thalamus and spinal cord [Lyons and Pahwa, 2005, Shaikh et al., 2008], send independent information to the peripheral loop until reaching the skeletal muscles. Normally, a pre-synaptic neuron transfers its potential to post-synaptic neurons when the summation of excitatory or inhibitory action potentials at its membrane reaches the firing threshold. However, if the firing is followed by a prolonged hyperpolarization induced by insufficient external inhibition or increment of the neuron excitation or rebound potential of reciprocally innervated neurons, the change in the membrane properties of these neurons could cause an irregular burst of action potentials inducing oscillations. This irregular burst could be rhythmically repeated and generate continuous oscillations of tremor [Shaikh et al., 2008].

It has been suggested that the central oscillation is independent of the sensory feedback or peripheral mechanical reflex mechanisms and can be identified using spectral analysis of the EMG. The tremor in ET is partially related to the central oscillator as the spectrum of the EMG at the tremor frequency was not changed even when the mechanical resonance of the limb was changed by added load [Elble, 1996, Deuschl et al., 2001, Helmich et al., 2013]. The rationale that ET tremor is related to the central oscillator is also supported by corticomuscular coherence, specifically in the contralateral lateral central area and the primary cortical areas [Raethjen et al., 2007], and coherence analysis of the oscillatory activity of the thalamic ventralis intermediate nucleus and the tremor frequency of peripheral limbs [Elble, 1996, Hua et al., 1998, Deuschl et al., 2001, Lyons and Pahwa, 2005]. In addition, [Hellwig et al., 2001] has observed clear tremor-related activity in the electroencephalogram (EEG) from some of their tremor patients.

Although the influence of the central oscillator on ET has been widely recognized, the studies of [Raethjen et al., 2007], and [Sharifi et al., 2017] have suggested a limited role and dynamic involvement of the central oscillator and suggested involvement of other subcortical centers in the occurrence of the tremor. They found that the cortico-muscular coherence of the ET patients enrolled in the study significantly fluctuated over time regardless of the tremor intensity during the same task. Raethjen and team have found an intermittent loss of corticomuscular coherence at the tremor frequency even though there was a strong tremor during the recordings, whereas the coherence at the 15-30 Hz (physiological tremor) is

consistent even when the power of EMG spectra at this frequency is absent. This suggested that the tremor may only be intermittently influenced by the central oscillator and is partially the output of a sophisticated oscillatory network. On the other hand, the physiological tremor may mainly be determined by cortical activity. However, they confirmed the involvement of the central oscillator as there was a delay of cortico-muscular coherence that is corresponded to fast corticospinal pathways and feedback of the tremor signal from muscle to the CNS. A study using *repetitive magnetic brain stimulation* (rTMS) delivered over the primary motor cortex demonstrated the involvement of modulation in the central oscillator as it increased action tremor power in healthy individuals [Rogasch and Todd, 2013].

2. Mechanical properties of the joint

Muscles and joints act as the mass and spring system oscillating at a certain resonance frequency of the limb. The frequency of the spring oscillation is inversely proportional to the system's mass (e.g. 2.8), and the gain, which is the property of the spring, can be accounted as peripheral feedback control gain of the limb modulated by muscle contraction and stiffness of the joint [Deuschl et al., 2001]. The muscle mass, therefore, determines the frequency of the limb oscillation; for example, the shoulder joint has a frequency of 0.5 - 2 Hz, the elbow 3 - 5 Hz, the wrist 8 - 12 Hz, and the finger joint 17 - 30 Hz [Hallett, 1998]. Any perturbation of a mechanical system causes it to oscillate at its resonance frequency [Lakie et al., 2012]. In humans, one substantial perturbation is the ballistocardiac impulse [Marsden et al., 1969]. In the pure mechanical tremor, the frequency of the limb oscillation will decrease when increasing the weight of the limb (adding external loads), but the spectrum of the EMG will not change as the tremor occurs only because of the resonance of the disturbance [Elble, 1996, Lakie et al., 2012].

$$\text{Frequency} = \sqrt{K/\text{Inertia}} \quad (2.8)$$

Where K is a constant of stiffness of the joint.

3. Modulation of tremor via reflex loops

Oscillation of a body part involves an alternation of agonist and antagonist muscle contractions. This alternate contraction is related to reflex mechanisms involving sensory afferent neurons, interneurons, and alpha-motor neurons. The most straightforward and well-known loop is the stretch reflex loop. This loop involves propagation of potentials from muscle spindle through Ia afferent neuron and mono-synapses onto an alpha-motor neuron and inhibitory interneuron in the spinal cord. The axon of the alpha-motor neuron activates the agonist muscle fibers while exciting the inhibition interneuron to inhibit the activation of antagonist muscle fibers [Elble et al., 1987, Stiles and Pozos, 1976]. The reflex loops operate over time and may oscillate at frequencies inversely proportional to the loop delay. The tremor purely related to the mechanical reflex is dependent on the external loads added.

Specifically, the frequency and amplitude of mechanical reflex tremors are determined by the elastic properties of the body. Therefore, the spectrum of the EMG and the limb oscillation are shifted according to the properties of the limbs.

The nonlinear nature of the oscillation system causes a massive effect on a little change in the system, and the sum of these causes will not be directly estimated as the causes of the tremor Figure 2.8. Several studies have designed computational models of the neuro-musculoskeletal system to study the physiology of tremors, and the dependency of each possible component influencing tremor [Zhang et al., 2009, Dideriksen et al., 2011a]. They have integrated the central oscillators, peripheral mechanisms (stretch reflex and Golgi tendon reflex, and modulation of Renshaw cells),

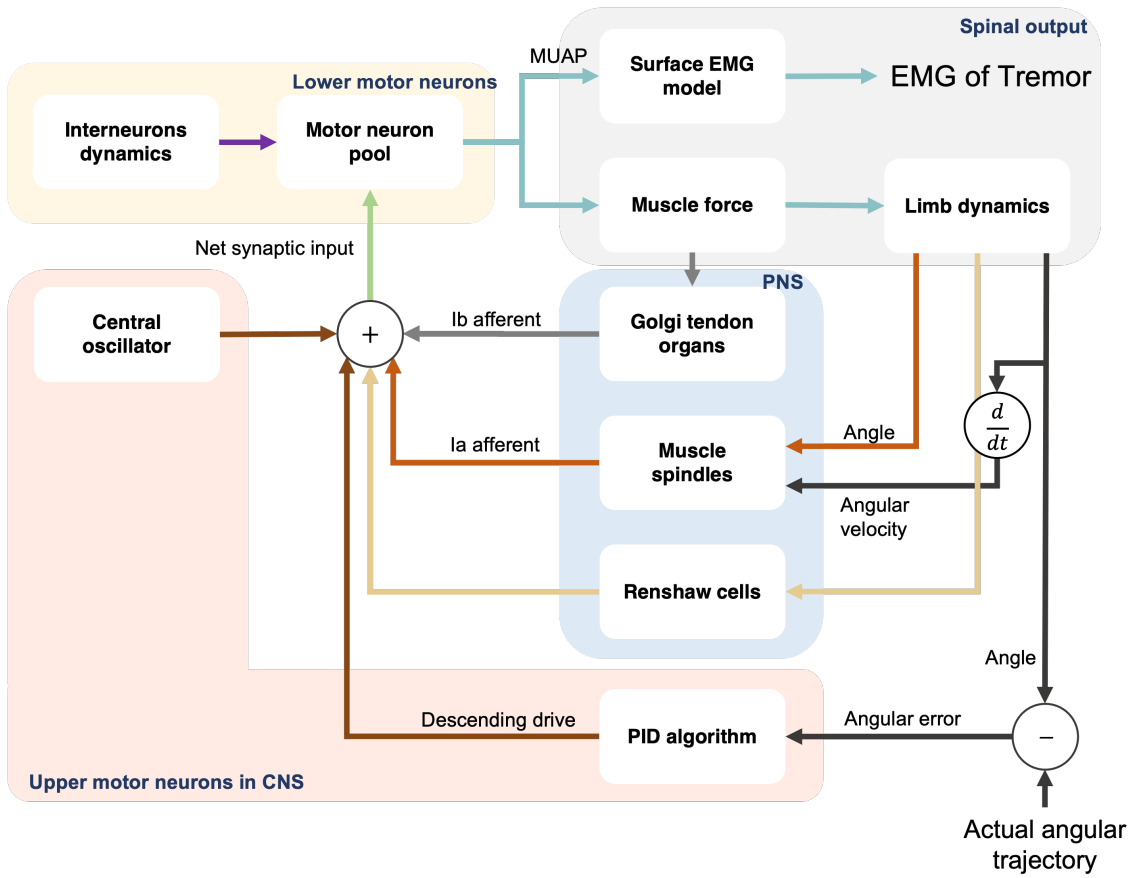


Figure 2.8: Simplification of tremor generation mechanism and EMG generation adapted from [Zhang et al., 2009, Dideriksen et al., 2011a]. The model consists of 1) the CNS sends a descending drive to adjust the limb's position to the desired place and the central oscillator in the brain to the motor neuron pool (group of lower motor neurons), 2) the PNS includes the Golgi tendon, muscle spindles, and Renshaw cells, providing sensory information through group Ia and Ib afferents about limb dynamics such as changes in muscle length, velocity, and force, 3) Interneurons dynamic receiving an inhibitory signal from antagonist muscle and 4) model of surface EMG generation to estimate EMG of tremor based on MU action potentials and muscle force model that would modulate limb position and angle.

and reciprocal inhibitions between an antagonist pair of muscles with the motor neuron and limb dynamics models. [Dideriksen et al., 2011a] also added a surface EMG model to the system allowing observation of the effect of each component on the EMG. The development of this model has advanced the understanding of the tremor system to the creation of novel tremor suppression technologies. In Chapter 3, we used time and frequency domain analysis to study the synaptic inputs common to a pair of antagonist muscles and the phase of the muscle activity during postural tremor in ET patients. It has been confirmed that tremor-related components are common to both muscles, and their phases vary over time as an influence of limb oscillation and reflex loops [Puttaraksa et al., 2019]. The tremor model has suggested several functional aspects for designing a non-invasive and non-pharmacological tremor suppression system.

1. Disturbance of limb dynamics determines the limb oscillations by providing adjustment in muscle spindle and Renshaw cells.
2. It has confirmed that afferent and reflex loops play a crucial role in modulating the tremor

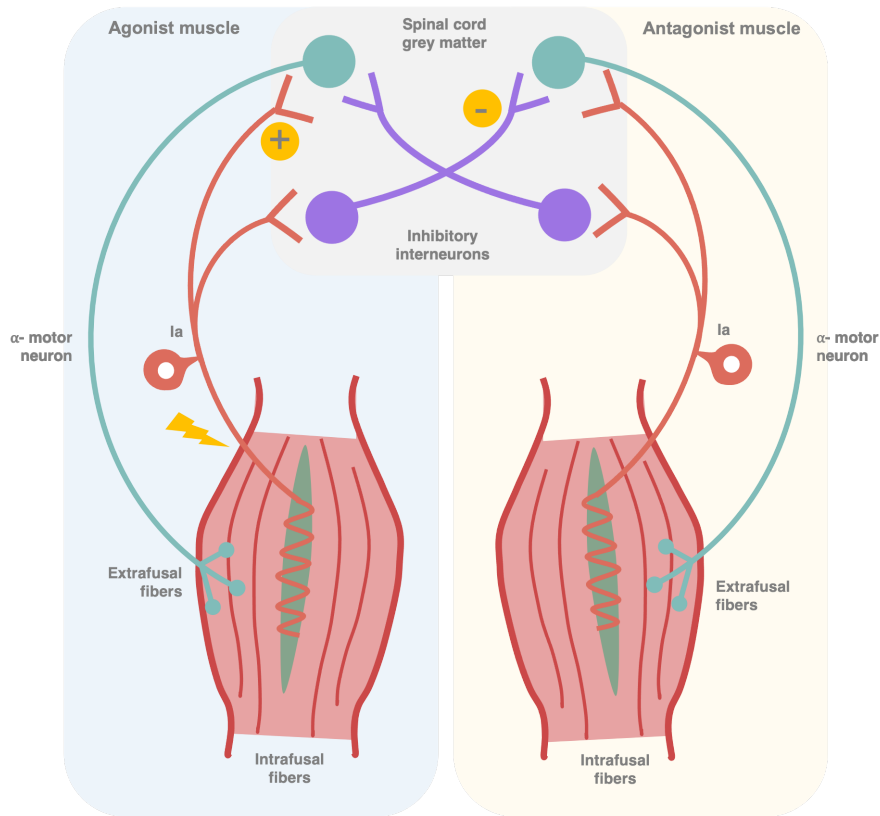


Figure 2.9: Reflex mechanism of agonist-antagonist pair of muscles. Muscle spindles in intrafusal fibers send information about muscle length and velocity changes via Ia afferent neurons. This neuron is monosynaptically connected to an alpha-motor neuron innervating muscle fibers in agonist muscle and synapses to an inhibitory interneuron connected to an alpha-motor neuron in antagonist muscle. Excitation of a muscle inhibits its antagonist muscle activation allowing joint flexion or extension.

amplitude.

3. Locally increases or decreases of the influence of each tremor component could modulate the net synaptic input generating tremor.
4. Mechanism between an antagonist pair of muscles provides a gap for tremor suppression techniques by disturbance of interneurons projecting to antagonist muscles or increase excitation of motor neuron of agonist muscle.

Based on these aspects, some studies have disturbed the tremor system by using active electric motors as in an orthosis system [Rocon et al., 2007, Herrnstadt and Menon, 2016], adding weight to the distal part of the affected limb in the form of a wrist cuff or holding weighted utensil such as a weighted spoon. [Rocon et al., 2007] has shown that tremors can be mechanically suppressed using external skeletons in the form of anthropomorphic robots. Although significant tremor amplitude reduction has been reported using the systems mentioned above, the reduction was observed only in patients whose tremor is not related to an impairment in the CNS. Particularly, Parkinson's patients reported no benefit from the weight system [Meshack and Norman, 2002]. The orthosis and weighted system also produce discomfort, and its bulky appearance creates difficulty in everyday usage. Concerning the real-life usability and cosmetic of suppression devices, researchers have been focusing on implementing a *functional electrical stimulation* (FES), which has an ability to activate muscle fibers electrically [Prochazka et al., 1992, Widjaja et al., 2009, Grimaldi et al., 2011, Zhang et al., 2011]. The FES at the level that it could elicit a muscle response has been used to stimulate both agonist-antagonist muscles to create stiffness of a joint and, in turn, reduces tremor amplitude (co-contraction) [Gallego et al., 2013]. FES was also used to stimulate the antagonist muscle of the active muscle in an opposite phase manner (out-of-phase stimulation) to produce force in the antagonist muscle, which could pull back the limb to the opposite side of the tremor [Dideriksen et al., 2017, Dosen et al., 2015, Muceli et al., 2019]. Using electrical stimulation to directly activate and create muscle force (motor threshold level) provides significant benefits for tremor suppression as it could reduce tremor amplitude from 50 - 85% [Prochazka et al., 1992, Maneski et al., 2011], however, continuous stimulation of a muscle at its twitch level could generate fatigue and pain in the muscles. Therefore, the trend of recent research focuses on investigating the effects of sub-threshold electrical stimulation of the muscle nerves related to the tremor-affected muscles. The EMG was implemented in an open-loop stimulation system to reduce the delay of stimulation timing that is usually produced by the use of inertial sensors [Dideriksen et al., 2017, Dosen et al., 2015].

Figure 2.9 illustrates the reflex mechanism of agonist-antagonist pair of muscles which is a feedback loop. The mechanism involves proprioceptors, muscle spindles in charging muscle stretch detection. Increasing excitation of Ia afferent neurons, which is determined by muscle spindles in intrafusal fibers of an agonist muscle, induce activation in Ia inhibitory interneuron which consequently inhibits activation of its antagonist muscle [Day et al., 1984, Lloyd, 1946b, Lloyd,

1946a]. [Lloyd, 1946b] has demonstrated that afferent stimulation of agonist muscle could inhibit activation of motor neuron innervating antagonist muscle of the same joint in hind limbs of a cat. Electrical stimulation was used to study the efficacy of synaptic transmission of the afferent pathway to the muscle by measuring H-reflex. The H-reflex or Hoffmann-reflex is a muscle reflex response due to external stimuli. An action potential generated from electrical stimulation at the Ia afferent neurons is transferred to a group of motor neurons of its agonist muscle and generates a muscle twitch. The H-reflex, therefore, is noticeable in the EMG measured during the stimulation. In addition, an increase in direct stimulation of peripheral nerve could directly activate efferent fibers or motor neurons to elicit a muscle response, M-wave response, which can also be recorded

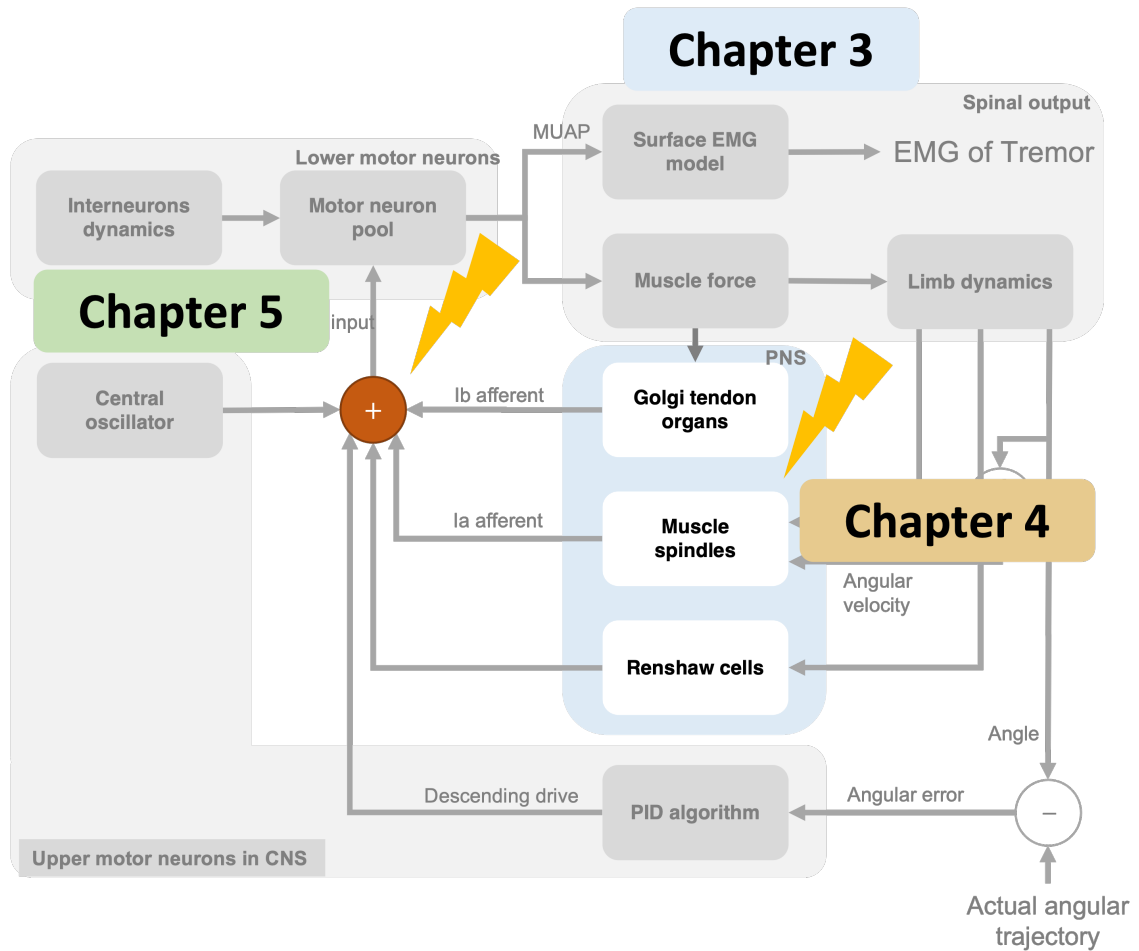


Figure 2.10: The outline of this thesis illustrated according to the tremor model. In Chapter 3, MU spike trains decomposed from sEMG recordings of ET patients were investigated to elucidate the neural activity during the tremor. Electrical stimulation for tremor suppression system, then, was designed and validated in the following chapters. The yellow flash symbols indicate the targets of electrical stimulation we investigated. In Chapter 4, the afferent stimulation was used to modulate reflex mechanisms that we hypothesized could interfere and cancel out the tremor. In Chapter 5, the stimulation target was the cervical spine aiming to observe the stimulation effect on cortical and sub-cortical regions.

by EMG [Palmieri et al., 2004]. A study of [Day et al., 1984] has demonstrated via analysis of H-reflex recordings that humans also have this inhibitory mechanism similar to animals. They observed inhibition of the H-reflex of the wrist flexor muscles when the median nerve supplying the wrist extensor muscles were stimulated at 75% of motor threshold level. They suggested that this antagonist inhibitory process was 0.95 ms longer than the central synaptic delay of H-reflex, which was due to an additional synapse of the inhibition interneuron. Based on the reflex mechanisms, it is hypothesized that stimulation of nerve fiber in an agonist muscle at the time that its antagonist muscle would activate could inhibit that activation and cancel out the tremor. From these aspects, in our closed-loop tremor suppression system, we decided to choose the electrical stimulation at subthreshold intensity, delivering an out-of-phase muscle activation. In order to increase the suppression performance of current stimulation techniques, we hypothesized that estimating stimulation timing from phases of MUAP trains decomposed from high-density surface EMG recordings directly could enhance the accuracy of the time estimated. In order to track the change in phases of tremor signals, we utilized a phase-lock loop system to real-time estimate the phase of agonist and antagonist muscles. The design and validation of the proposed closed-loop system were discussed in Chapter 4.

Electrical stimulation of cortical and subcortical regions such as at primary motor cortex [Nguyen et al., 1998, Moro et al., 2011] and the spinal cord [Fénelon et al., 2012, Thiriez et al., 2014, Russo et al., 2018] has been suggested to be beneficial for improving pain, muscle strength, and tremor. Since the spinal cord acts as conjunction where the upper-limb motor neurons are connected with motor nerves and can be non-invasive stimulated without severe risk of side effects, spinal cord electrical stimulation at the cervical level may determine the tremor activity in the upper limb. We tested this hypothesis by measuring the tremor oscillation of ET patients using an accelerometer during the postural tremor and reported the observation in Chapter 5 (Figure 2.10).

The following chapters will be our main result chapters answering the questions introduced in the first section of the thesis, starting from the physiological study (Chapter 3) to the design of a closed-loop tremor suppression system (Chapter 4) with the hypothesis in the modulation of tremor activity at the PNS. Furthermore, in Chapter 5, the tremor modulation via spinal cord stimulation is presented.

Chapter 3

Voluntary and tremorogenic inputs to motor neuron pools of agonist/antagonist muscles in essential tremor patients

Designing a noninvasive peripheral electrical stimulation that could accurately counteract the oscillations of the tremor and not interfere with the voluntary movement requires an insight into the characteristics and behaviors of the MUs specifically during the tremor. The significant features of the tremor-affected MUs may include MU firing rates, the dominant frequency of the oscillation of the motor neuron pools, and the timing of the MU activation. The phase difference between activation of antagonist pair of muscles is also crucial for determining the correlation between the muscles generating tremor.

In this chapter, the MU activity during postural tremor was investigated using MU spike trains decomposed from high-density surface EMG of the tremor-affected upper limb of ET patients. The MU spike trains were analyzed in order to elucidate the behavior and mechanism of neural drive to antagonist pair of muscles of the tremor patients. The chapter is presented in order of Abstract, Introduction of the roles of common inputs to voluntary movement and tremor oscillation, and signal processing techniques to assess the strength of these common inputs, Material and Methods, Statistical Analysis, Results, and Discussion. Part of this chapter was published in [\[Puttaraksa et al., 2019\]](#).

3.1 Abstract

Pathological tremor is an oscillation of body parts at 3–10 Hz, determined by the output of spinal motor neurons, which receive synaptic inputs from supraspinal centers and muscle afferents. The behavior of spinal motor neurons during tremors is not well understood, especially in relation to the activation of the multiple muscles involved. Recent studies on patients with ET have shown that antagonist motor neuron pools receive shared input at the tremor frequency. In this study, we investigated the synaptic inputs related to tremor and voluntary movement and their coordination across antagonist muscles. We analyzed the spike trains of MUs identified from high-density sEMG from the forearm extensor and flexor muscles in 15 patients with ET during the postural tremor. The shared synaptic input was quantified by coherence and phase difference analysis of the spike trains. All pairs of spike trains in each muscle showed coherence peaks at the voluntary drive frequency (1–3 Hz, 0.2 ± 0.2 , *mean $\pm$ SD*) and tremor frequency (3–10 Hz, 0.6 ± 0.3) and were synchronized with small phase differences ($3.3 \pm 25.2^\circ$ and $3.9 \pm 22.0^\circ$ for the voluntary drive and tremor frequencies, respectively). The coherence between motor unit spike trains of antagonist muscle groups at the tremor frequency was significantly smaller than intramuscular coherence. We predominantly observed in-phase activation of MUs between agonist/antagonist muscles at the voluntary frequency band ($0.6 \pm 48.8^\circ$) and out-of-phase activation at the tremor frequency band ($126.9 \pm 75.6^\circ$). Thus motor neurons innervating agonist/antagonist muscles concurrently receive synaptic inputs with different phase shifts in the voluntary and tremor frequency bands.

3.2 Introduction

3.2.1 Common inputs and tremor generation

The neural source of muscle contraction is ultimately the output from the pools of spinal motor neurons, and the summation of inputs to these neuron pools is essential for modulating the muscle activity [Negro and Farina, 2011, Farina et al., 2010, Farina and Holobar, 2016].

As mentioned in the second chapter, the occurrence of tremor may involve the combination of inputs from several neural pathways, including corticospinal pathways and feedback from afferent fibers, these descending and ascending inputs can be shared (common inputs) to all the motor neurons in a motor neuron pool or independently projected to individual motor neurons (independent inputs) resulting in variation of the tremor [Nordstrom et al., 1992, Holobar et al., 2011, Negro and Farina, 2011, Negro et al., 2016, Gallego et al., 2015b]. The presence of the common inputs to motor neurons determines correlation in the motor neuron discharge patterns [Negro and Farina, 2012]. Relative strength of the common inputs to motor neuron pools can be indirectly inferred with time-domain (synchronization) [Dietz et al., 1976, Bremner et al., 1991, Hua et al., 1998]

or frequency domain (coherence) analysis [Rosenberg et al., 1989, Halliday et al., 1995, Hellwig et al., 2003, Christakos et al., 2009, Raethjen et al., 2009]. The coherence analysis is a meaningful method used to describe the frequency spectrum and synchronization of two signals or discharge patterns of motor neurons either within a muscle or across muscles. To investigate into possible central oscillator from the CNS, coherence analysis has been previously applied to quantify the correlation between cortical inputs and spinal motor neuron outputs (corticospinal coherence) using simultaneous recordings of EEG and EMG [Hellwig et al., 2003, Raethjen et al., 2007]. Recent studies also applied this analysis to pairs of motor neurons or motor neuron pools of different muscles to reveal their population behavior [Holobar et al., 2011, Negro and Farina, 2012, Gallego et al., 2011] and to assess the contribution of peripheral feedback loops to tremor [McAuley and Marsden, 2000, Raethjen et al., 2000, Holobar et al., 2012]. The results of these studies suggested that tremorgenic movements may be generated by a single oscillator [Raethjen et al., 2007, Dideriksen et al., 2015], abnormal oscillations in the cerebello-thalamo-cortical pathway [Benito-León and Louis, 2006], potentially involving the basal ganglia [Louis, 2005, Lyons and Pahwa, 2005]. [Raethjen et al., 2007] has suggested that tremor-related common input may come from the cortical oscillator in the motor cortex. Their corticomuscular coherence analysis at the tremor frequency shows that the tremor frequency and the frequency of the corticomuscular coherence remain unchanged even when loads are applied on the tremor-affected limb, implying less influence on limb mechanical component tremor. The involvement of the central oscillator and the limb mechanism in tremor generation was also supported by [Elble, 1996, Deuschl et al., 2001] where they suggested that the corticomuscular delays were a direct corticomuscular transmission. In addition, the tremor remains even when the corticomuscular coherence at the tremor frequency has vanished (intermittent absence of cortical oscillations) showing that the tremor could be persisted by other mechanisms such as resonance of limb oscillations due to the limb properties, and the reflex loops [Deuschl et al., 2001, Lakie et al., 2012].

In addition, it is suggested that the cortical inputs that are common to the motor neuron pool influence more on the motor unit activity than the interference of independent inputs [Negro and Farina, 2011]. Coherence analysis has also been used to assess the extent of common synaptic input to agonist muscles in healthy subjects [Negro and Farina, 2012], revealing that only a small subset of MU spike trains is sufficient to sample the common synaptic input. However, because MUs of tremor-affected muscles fire in bursts and are prone to be more synchronized than those of healthy subjects [Gallego et al., 2015b, Holobar et al., 2012], this hypothesis also has to be validated in individuals with pathological tremors.

The study of [Negro et al., 2016] has proposed a method to quantify the proportion of the common input in a low-frequency bandwidth. An analytical model was created to fit experimental data to a least-square curve, then used to estimate the proportion of common input. Moreover, the study described in [Laine et al., 2015] used the partial coherence analysis to further investigate the strength of shared and unique inputs to the vastus lateralis and vastus medialis muscles during

different levels of isometric knee extensions.

Recent simulation and experimental studies on the phase difference (delays) between motor neuron activities in antagonist muscles revealed that the phases during tremors were modulated by the intensity of the supraspinal tremor oscillator to each muscle and the difference in the strength of the voluntary command to each muscle [Gallego et al., 2015a]. However, the investigation of motor neuron activities in the very low-frequency band (voluntary drive) has not been thoroughly investigated. This is due to limitations in the coherence analysis applied to sEMG signals. The EMG model proposed in [Farina et al., 2004] has shown that the low-frequency components of oscillatory inputs are filtered out (high-pass filtered) in the coherence measurement when using raw sEMG signals. Although EMG rectification may preserve more low-frequency oscillations compared to raw EMG, the cut-off frequency also depends on additional factors, including the duration of the MU action potentials (selectivity of the electrodes) and the degree of amplitude cancellations [Negro et al., 2015]. On the contrary, an analysis of MU spike trains, which are not affected by these two factors, maybe a more appropriate tool to investigate the behavior of muscles at the voluntary drive frequency during tremor.

Since muscle contraction is ultimately caused by the output from the pools of spinal motor neurons, the accurate identification of the timings of motor neuron activity provides an important window into tremor pathophysiology [Holobar et al., 2011, Gallego et al., 2011]. The discharge timings of MNs can be assessed in vivo during natural movements by decoding EMG signals into MU firings (MU spike trains) [De Luca and Forrest, 1972, Merletti and Farina, 2009, Muceli et al., 2015]. Recently, methods for MN analysis have been substantially advanced by techniques based on high-density surface EMG electrodes [Drost et al., 2006, Farina and Holobar, 2016, Merletti et al., 2008] and blind source separation of the resulting multichannel EMG recordings [Chen et al., 2016, Holobar and Zazula, 2003, Holobar and Zazula, 2007, Negro et al., 2016]. These approaches allow identification of the activity of relatively large MN populations.

Therefore, the aims of this study were i) to concurrently investigate the behavior of MNs receiving voluntary command and tremor inputs, ii) to estimate the strength of these inputs shared between agonist-antagonist muscles by means of coherence analysis, iii) to investigate changes in the coherence magnitude at the tremor and voluntary drive frequencies as a function of the number of MU spike trains.

3.3 Material and methods

3.3.1 Patients

The data were collected from 15 ET patients (6 females; age, 69.5 ± 9.9 years) with a diagnosis of definite ET according to the criteria of the Tremor Investigation Group and the consensus of the Movement Disorder Society Group [Deuschl et al., 1998]. According to the Fahn-Tolosa-Marin scale, the mean score of the tremor severity in the most affected limb was 32.1 ± 11.3 (range 15–50). Eight patients had left tremor predominance and one had tremor that equally affected both limbs (bilateral). All procedures were approved by the Ethical Committees at the University Hospital “12 de Octubre” (Madrid), which guaranteed compliance with the Declaration of Helsinki. Written (signed) informed consent was obtained from all enrollees.

3.3.2 Task

The patients were seated on a comfortable armchair with their forearms fully supported and they were asked to stretch their hands out against gravity with palms down in order to evoke postural tremor. The EMG signals were recorded for 40 s – 4 min depending on the time the patient felt comfortable with the task. The EMG signals were acquired from both forearms using four grids of 64 surface electrodes, arranged in five rows and 13 columns (one electrode missing in a corner) with 8 mm interelectrode distance, placed over the wrist flexor and extensor muscles. The electrode grids were centered above the flexor carpi radialis and extensor digitorum communis, respectively. A soaked wrist strap was worn and acted as a common reference. Before attaching the electrode grids, the recording area on the forearms was shaved, lightly rubbed using abrasive paste, and cleansed with water. Analog EMG signals recorded from the electrode grids were amplified and band-pass filtered (EMG-USB2; OT-Bioelettronica, Italy) between 10 to 750 Hz before being converted to digital signals at 2048 Hz sampling frequency by a 12-bit analog-to-digital converter. The data were stored in a database for further offline analysis using MATLAB.

3.3.3 EMG decomposition

The convolution kernel compensation algorithm [Holobar et al., 2010, Holobar and Zazula, 2003, Holobar and Zazula, 2007] was used to discriminate the spike train of each MU and to express it as a sequence of binary values (0 or 1) at the MN discharge times. The decomposition accuracy was estimated by using the pulse-to-noise ratio (PNR) [Holobar et al., 2014]. Only the recordings from which at least two MUs were identified with $\text{PNR} > 26$ dB and firing in a time interval ≥ 30 s (see below) were retained for further analysis. The MU spike trains from forearms with predominant

tremor (2 muscle groups) of 14 patients fulfilled these criteria and were included in the analysis. To increase the sample size, we included an additional patient who had bilateral tremor with MU spike trains from three muscle groups (flexor and extensor muscles of the left wrist and extensor muscles of the right wrist) meeting the criteria. MU spike trains were therefore extracted from 31 muscle groups. The time interval in which the firing rate of each MU was $\geq 60\%$ of the maximum firing of the same MU was selected for further analysis. This corresponded to 30 s for 11 patients and 60 s for the remaining 4 patients.

3.3.4 Pools of MUs

The neural drive to a muscle was represented by the pooled cumulative discharges of all the MUs whose spiking activity was detected [Farina et al., 2014, Gallego et al., 2015a]. This summation of the spike trains is called *cumulative spike train* (CST). For the intramuscular correlation analysis, the MUs detected in a muscle were divided into two groups with the sizes of maximum half number of MUs (i.e., if 11 MUs were detected, they were divided into 2 CSTs comprising 5 MUs and 6 MUs) that were summed to create two CSTs. Similarly, for the intermuscular correlation analysis, the two CSTs were generated from all the activated MUs in the flexor and extensor muscles, respectively. For this analysis, the maximum number of MUs in each CST depends on the smaller number of MUs of either extensor or flexor muscles. Every possible combination of MU grouping to generate the CSTs was analyzed, and the results were averaged.

3.3.5 Tremor and voluntary drive

Coherence analysis was performed on the CSTs using nonoverlapping Hanning windows with 0.125-Hz resolution. Coherence was calculated according to the following equation:

$$C_{xy}(f) = \frac{|\overline{G_{xy}(f)}|^2}{\overline{G_{xx}(f)} \cdot \overline{G_{yy}(f)}}, \quad (3.1)$$

where $\overline{G_{xy}(f)}$ is the averaged cross-spectral density between the CSTs x and y using Welch's method, $\overline{G_{xx}(f)}$ and $\overline{G_{yy}(f)}$ are their corresponding autospectral densities averaged using Welch's method, and f is the frequency of interest. The peak frequency in the coherence spectrum within the tremor (3–10 Hz) and voluntary drive (1–3 Hz) frequency ranges were considered as the dominant tremor frequency and dominant voluntary drive frequency, respectively. The dominant tremor frequency represents the frequency of the tremor oscillator that is common to the MN pool [Gallego et al., 2015a].

3.3.6 Phase difference between neural drives

The Hilbert-transform was used to calculate the instantaneous phases from 30-s intervals of filtered CSTs at ± 1 Hz with respect to the DTF to observe the phase difference between MU activities at the tremor frequency. The same procedure was performed at the frequency of 1-3 Hz to reflect the MU activities at the voluntary drive frequency. This small bandwidth was chosen as it enhances sampling efficiency [Negro and Farina, 2012]. Circular phase histograms of the instantaneous phases were produced with 20° per bin resolution and the mean delays between neural drives were calculated by the following equation:

$$delay = \frac{|\overline{\phi_{nd}}|}{2\pi f_i}, \quad (3.2)$$

where $|\overline{\phi_{nd}}|$ is the absolute circular mean of the instantaneous phase difference, and $f_i = f_{tr}$ and $f_i = f_{vol}$ are the tremor and voluntary drive frequency, respectively.

3.3.7 Shared common synaptic input

The coherence analysis was performed with MU spike trains separately at the voluntary drive and tremor frequencies to investigate whether there were shared intra- and intermuscular synaptic inputs in those relevant frequency ranges. The coherence analysis was applied to all pairs of CSTs, generated as described above. For each patient, the autospectral density and cross-spectral density were computed for determining the coherence value. The confidence level (CL) of each coherence profile was calculated by the following equation [Rosenberg et al., 1989]:

$$CL = 1 - (1 - \alpha) \frac{1}{N - 1}, \quad (3.3)$$

where N is the number of data segments and α is the level of confidence, which was set to 0.95. This implies that the coherence values were considered significant if they were greater than 95% of CL .

3.3.8 Proportions of common synaptic input

The coherence function provides an indication of the extent of tremor input that is sampled by the MUs. To study the strength of common input to the MNs, we investigated changes in the coherence magnitude at the tremor and voluntary drive frequencies as a function of the number of MUs in CSTs. For this purpose, we created CSTs by randomly selecting k of all the MUs identified for each muscle, with k varying from one to the maximum number of MU spike trains detected in

that muscle.

3.3.9 Statistical analysis

Normality of the data was visually observed and assessed using the quantile-quantile plot and the Shapiro–Wilk test, respectively. Pairs of normally distributed variables were compared using paired t tests, whereas the Mann–Whitney–Wilcoxon test was used to compare non-normal data. The correlations between two variables were measured using Pearson’s correlation test for normally distributed data and Spearman’s correlation test for nonnormal data. We investigated how the coherence peak value (in the voluntary drive and tremor frequency bandwidths) changed as a function of the number of MUs used in the analysis using either ANOVA or the Kruskal–Wallis test, depending on the data distribution, followed by pairwise comparisons to compare individual differences. Four separate analyses were performed for intramuscular and intermuscular coherence in the voluntary and tremor frequency bands. Also, for the voluntary and tremor bands separately, we compared the intramuscular and intermuscular coherence with the same number of MUs. In all cases, the null hypothesis was rejected for P values < 0.05 . The results are means $\pm$ SD.

3.4 Results

3.4.1 Motor unit activities

The total number of MU spike trains that were analyzed from the 15 subjects was 211 (6.8 ± 4.0 MUs per muscle group). Average discharge rate was 14.3 ± 5.0 Hz. *Power spectral densities* (PSDs) of the MU spike trains were computed to identify the tremor frequencies. Figure 3.1a illustrates a subset of the identified MU spike trains and their CST for one muscle group from a representative subject. The PSDs of each MU and of the CST are compared in Figure 3.1b. The PSDs of the individual MUs showed high power at the frequency of discharge, the tremor frequency (5.6 ± 1.8 Hz) and its harmonics. Conversely, the PSD of the CST showed a single peak at the tremor frequency (5.0 Hz). Across patients, the average frequency of the power peak for the CST was 6.9 ± 1.8 Hz, ranging from 4.8 to 10.0 Hz (2 muscle groups $\times$ 14 patients and 3 muscle groups $\times$ 1 patient). In most patients (11 of 15), the MUs in at least one group of muscles also showed a power peak at the voluntary drive frequency (not evident in the example represented in Figure 3.1b), and in 5 of 31 cases, the peak of the power spectrum at the voluntary drive frequency was higher than the peak at the tremor frequency.

The normalized power peaks of the CST at the voluntary drive and tremor frequencies were also compared to investigate whether the voluntary drive could potentially contribute to the tremor input. The Mann–Whitney–Wilcoxon and Spearman’s correlation tests were used to search for

associations between the power peaks. The results showed that the power peak at the voluntary drive was statistically lower than the power peak at the tremor frequency during postural tremor ($P < 0.001$; Figure 3.2a). Moreover, the peaks in the two frequency bands showed significant positive correlation ($r = 0.6$, $P < 0.001$, Spearman's rank correlation; Figure 3.2b).

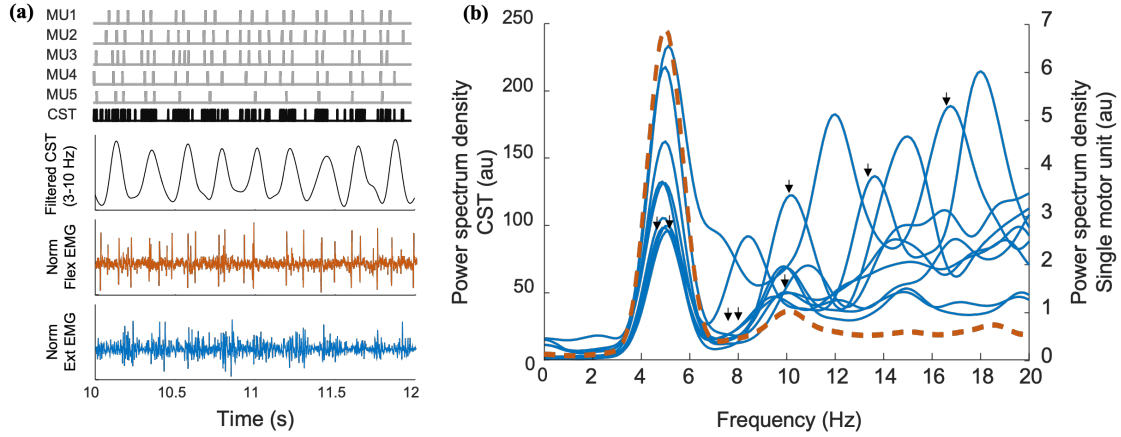


Figure 3.1: Comparison of the PSD of single-MU spike trains and CST. (a) Representative example of 5 MU spike trains (gray) and the CST (black), the CST bandpass filtered at the tremor frequency (3–10 Hz), and the central EMG channel of the surface grid positioned over the flexor (Flex) and extensor (Ext) muscle groups, respectively. (b) The PSDs of each spike train (blue solid lines) and the PSD of their CST (red dashed line). The PSDs of the individual MUs showed high power at the frequency of discharge (black arrows), the tremor frequency (3–10 Hz), and its harmonics, whereas the PSD of the CST showed a single peak at the tremor frequency reflecting population coding of the MUs. au, Arbitrary units; Norm, normalized.

Table 3.1: Summary of analysis results. The data was analyzed from 31 muscle groups of 15 ET patients (15 flexor muscle groups and 16 extensor muscle groups). The number of MU spike trains decomposed from these muscles is 211 ($N = 211$).

	Intramuscular		Intermuscular	
	Voluntary (1–3 Hz)	Tremor (3–10 Hz)	Voluntary (1–3 Hz)	Tremor (3–10 Hz)
Magnitude of coherence peak				
Mean $\pm$ SD	0.24 ± 0.16	0.63 ± 0.30	0.12 ± 0.08	0.44 ± 0.28
Range	0.04–0.52	0.04–0.95	0.03–0.27	0.06–0.88
Frequency of coherence peak, Hz				
Mean $\pm$ SD	0.46 ± 0.62	6.34 ± 1.43	0.05 ± 0.03	5.75 ± 1.58
Range	0.00–3.00	3.65–10.00	0.00–0.12	3.13–8.13
Phase difference, $^{\circ}$				
Mean $\pm$ SD	3.89 ± 22.05	3.89 ± 22.05	0.59 ± 48.79	126.9 ± 75.60
Range	-96.54–92.94	-92.79–92.01	-153.51–93.28	-174.73–177.33
Delay, ms				
Mean $\pm$ SD	4.31 ± 8.71	4.86 ± 9.94	18.08 ± 17.84	50.33 ± 34.83
Range	0.02–34.99	0.04–48.68	0.59–65.60	3.08–120.45

3.4.2 Common synaptic inputs to motor neuron pools

We first investigated whether all recorded muscles received a common tremor-related synaptic input [Gallego et al., 2015a]. Table 3.1 summarizes the results on common synaptic input to a muscle and shared common input across muscles. Figure 3.3a illustrates a representative example of common synaptic input to a muscle at the voluntary drive and tremor frequencies. From the group data analysis, the coherence peaks of all pairs of spike trains in each muscle averaged 0.2 ± 0.2 at the voluntary drive frequency and 0.6 ± 0.3 at the tremor frequency (Table 3.1). The average intramuscular coherence, calculated from all permutations of the CSTs within agonist muscles, showed relatively high peak within the tremor frequency band (see representative example in Figure 3.3a). Therefore, all examined muscles received a tremor-related common synaptic input. The intramuscular coherence was significantly lower at the voluntary drive frequency compared with the tremor frequency band (Figure 3.3a; $P < 0.001$, Mann–Whitney–Wilcoxon test). Similarly, we found that all groups of antagonistic muscles received a shared common synaptic input at the tremor frequency, as indicated by the coherence analysis of the CSTs from antagonist groups of muscles (intermuscular coherence, Figure 3.3b and Table 3.1). The intermuscular coherence values at the tremor frequency (0.4 ± 0.3) were significantly higher than those at the voluntary drive frequency (0.1 ± 0.1 ; $P < 0.001$, Mann–Whitney–Wilcoxon test).

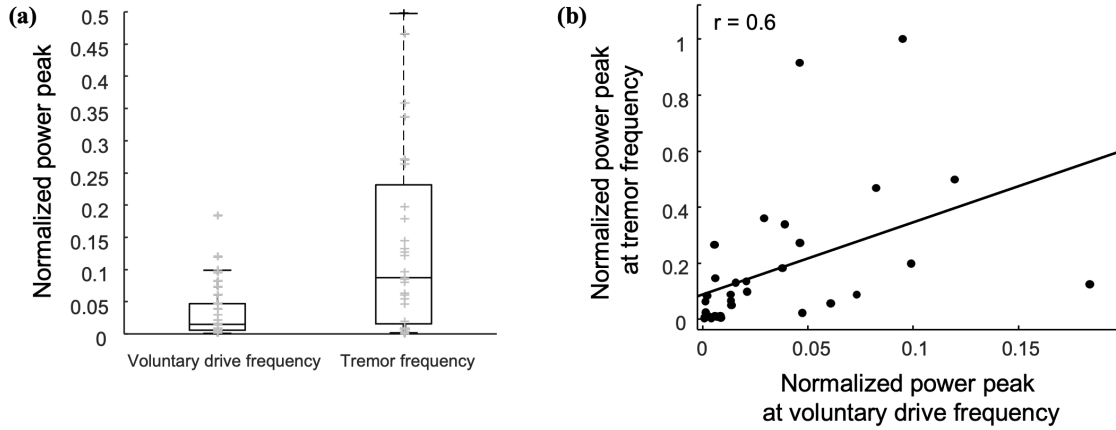


Figure 3.2: Comparison between power peak at the voluntary drive and tremor frequencies and their correlation. The power peaks were normalized with respect to the maximum peak across patients. (a) The boxplot shows that the normalized power peaks at the voluntary drive frequency were lower than those at the tremor frequency. Two outliers at 0.9 and 1 on the boxplot of the tremor frequency are not visible because the y-axis was limited to 0.5 for better visualization. Gray symbols represent the power peak of each patient. (b) The scatter plot shows that these peaks from two frequency bands were correlated, indicating the influence of the strength of the voluntary command on the strength of the tremor.

3.4.3 Delay between neural drives to muscles

We investigated the temporal differences between MU activations in agonist/antagonist groups of muscles at the voluntary drive and tremor frequency bands by calculating their phase difference. The phase difference between the voluntary and tremor-related drives to pools of MUs in agonist muscles (detected by the same surface EMG grid of electrodes) showed in most cases (voluntary drive: 28 of 31 muscles; tremor: 27 of 31 muscles) an in-phase pattern (average phase difference $< 10^\circ$) with relatively narrow variation. Figure 3.4a–3.4h shows representative examples of the phase differences in agonist muscles for a representative patient at the voluntary drive and tremor frequencies. These were in agreement with the overall trend shown in Figure 3.5.

Similarly, the phase difference between voluntary drives to groups of antagonist muscles (intermuscular phase difference) were, on average, also approximately in phase (Figure 3.5b). In stark contrast, the intermuscular phase difference at the tremor frequency showed nearly out-of-phase patterns across all sample data (Figure 3.5b). However, the intermuscular phase difference in both frequencies often varied over time (Figure 3.4i–3.4t), from almost in phase (Figure 3.4m and 3.4n) to out of phase (Figure 3.4s and 3.4t), resulting in a large spread of the circular histograms

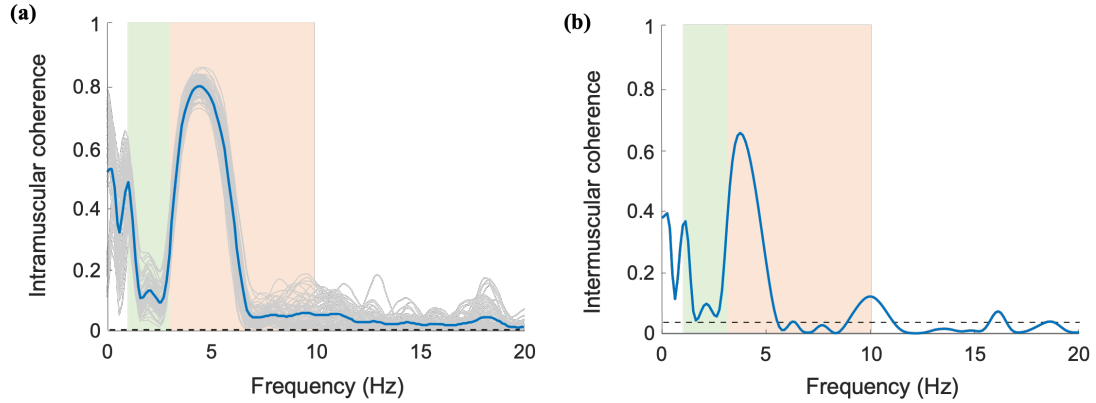


Figure 3.3: Representative example of intramuscular and intermuscular coherence at the tremor frequency of a patient with ET. (a) Intramuscular coherence of extensor muscles. Coherence between combinations of CSTs containing half the maximum number of motor units detected within the muscle (gray lines) and the averaged intramuscular coherence (blue line) is shown. The total number of MUs detected from extensor muscles was 7; therefore, pairs of CSTs of 3 MUs and 4 MUs were used for coherence analysis in this representative example. (b) Intermuscular coherence of the antagonist groups of muscles in the left wrist. Black dashed line is the confidence limit. Green and orange bands indicate the voluntary drive and tremor frequencies, respectively. Both intramuscular and intermuscular coherence graphs contain significant peaks at the tremor frequency and smaller peaks at the voluntary drive frequency. However, these peaks in the intermuscular case (b) are smaller, indicating the reduction in correlation of MU spike trains of antagonist groups of muscles.

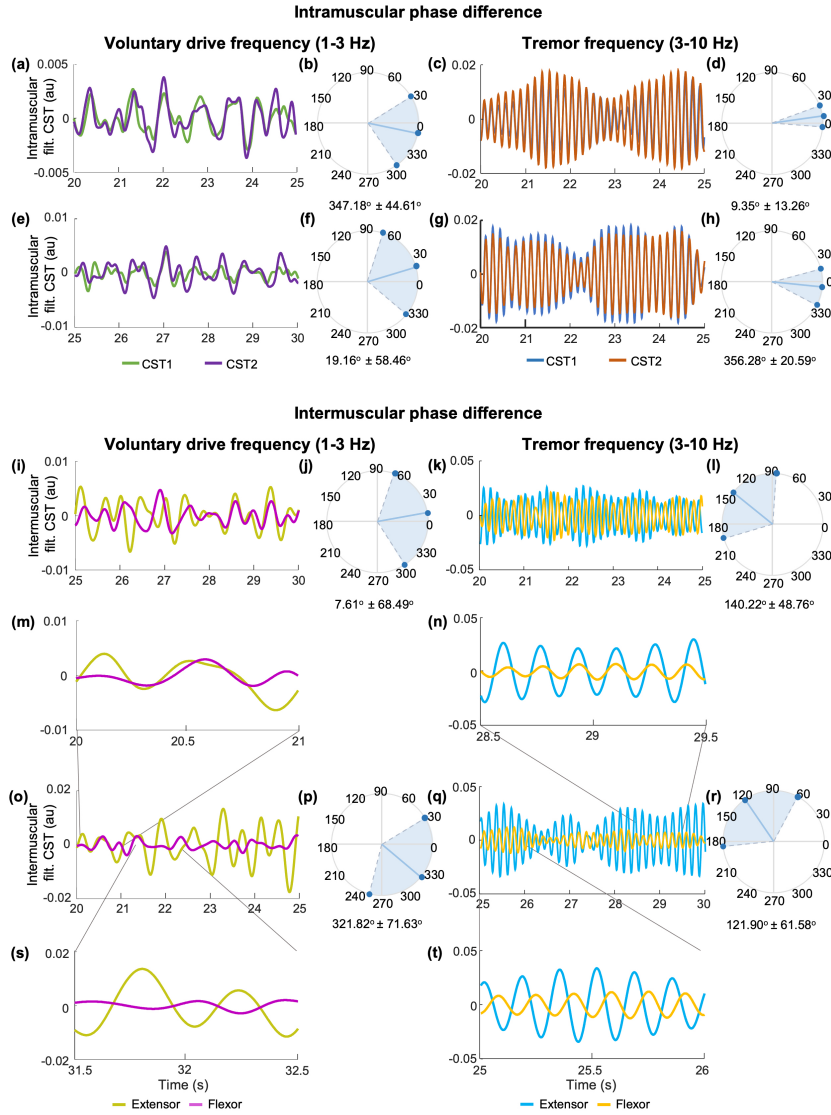


Figure 3.4: Representative phase difference between the neural drive to agonist muscles (a–h) and antagonist muscles (i–t) at the voluntary drive and tremor frequencies of a patient. a–h: phase difference between neural drive to extensor (a, c) and flexor (e, g) muscles of the left wrist. The phase differences were compared using the filtered CSTs [filt CST; groups of half the maximum number of motor units] at the voluntary drive frequency (1–3 Hz) and the tremor frequency (± 1 Hz with respect to the dominant tremor frequency). b, d, f, and h: circular histograms of the intramuscular phase difference showing relatively in-phase patterns of the MU activations in both frequency ranges. i–t: phase difference between the neural drive to antagonist muscles of the left (i, k) and right (o, q) wrists and their circular histograms (j, l, p, r). The average (over time) intermuscular phase difference at the voluntary drive frequency was relatively in phase (i, o), whereas that at the tremor frequency was relatively out of phase (k, q). As shown by this representative patient data, the phase difference varied over time from in-phase to out-of-phase patterns in both frequencies (m, n, s, t). au, arbitrary units.

(Figure 3.4j, 3.4l, 3.4p, 3.4r). The standard deviation of the intermuscular phase difference at both frequencies was negatively correlated to the coherence values (voluntary: $r = -0.7, P < 0.001$, tremor: $r = -0.8, P < 0.001$, Spearman's correlation test), because the larger variability in phase corresponded to lower coherence. These results show that the MNs concurrently received synaptic inputs with different phase relations between agonist and antagonist muscles.

Because the in-phase voluntary drives to agonist-antagonist muscle groups might serve to stabilize the limb, we investigated a potential association between the voluntary intermuscular coherence and tremor severity (estimated by the Fahn–Tolosa scale). However, these two variables were not correlated ($P = 0.21$ and $r = -0.36$, Spearman's correlation test).

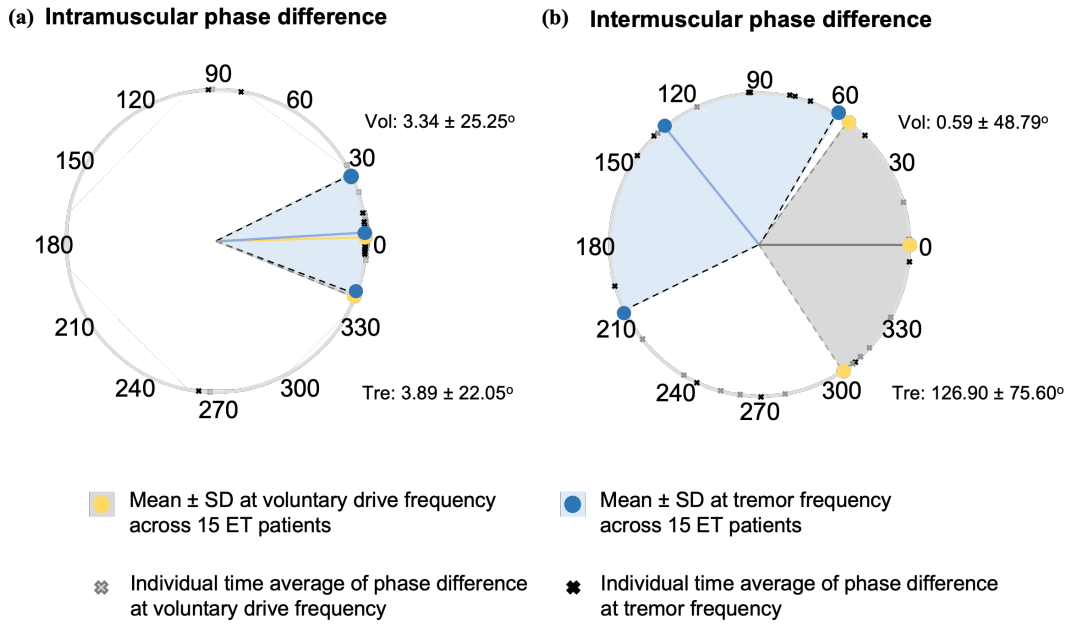


Figure 3.5: Means and variations of the phase differences between agonist (a) and antagonist (b) motor unit activations at the voluntary drive (yellow circles and light gray area) and the tremor frequencies (blue circles and light blue area) of all the patients with ET. The cross symbols show averages over time of the phase difference of each muscle from 15 patients. During postural tremor, MUs within agonist muscles (a) showed small average phase difference (close to 0) with relatively narrow variation, indicating that these MUs were activated almost simultaneously at both frequencies. However, the activations of the MUs within antagonist muscles were significantly different between two frequency bands (b). At the voluntary drive frequency, the MUs in antagonist muscle groups showed an in-phase activation with slightly wider variation, whereas at the tremor frequency, the average phase difference increased to a higher degree (close to out-of-phase) with great variation. Vol, voluntary drive frequency; Tre, tremor-related frequency.

3.4.4 Proportion of common input

To study the strength of common input to muscles, we investigated how coherence magnitude changed as a function of the number of MUs. We performed this analysis both within a muscle and across groups of antagonist muscles. The coherence values of all the permutations of subgroups comprising one to the maximum number of MU spike trains were computed and averaged per group.

Figure 3.6 shows the trend of the increment in the coherence peak values due to the inclusion of additional MUs at the voluntary drive and tremor frequencies of all patients. The Kruskal–Wallis test was used to investigate the increment of the coherence values at the voluntary drive frequency because they were nonparametric, whereas ANOVA was used for the coherence values at the tremor frequency because they were normally distributed. Both statistical analyses were followed by pairwise comparisons (t test for normally distributed data and Wilcoxon test for non-normal data). The intramuscular coherence values of the CSTs comprising one to four MUs at the voluntary drive and tremor frequency ranges were significantly different ($P = 0.04$ and $P < 0.001$, respectively). Pairwise comparisons revealed that the coherence of the CSTs comprising three and four MUs were significantly different from those with only one MU (voluntary drive: $P = 0.003$ and 0.001 ; tremor: $P = 0.004$ and 0.007 , respectively), but the increment of intramuscular coherence was not significant when three-MU CSTs and four-MU CSTs were compared ($P = 0.51$ and 1.00 for the voluntary drive and tremor frequencies, respectively). Therefore, only three to four MUs were sufficient to accurately sample the voluntary and tremor inputs to agonist muscle groups. In contrast, the increase of the inter-muscular coherence at both frequencies were never significant ($P = 0.21$ and 0.69 , Kruskal–Wallis test and ANOVA for the voluntary drive and tremor frequency, respectively).

We then compared the intramuscular and intermuscular peak coherence values of the CSTs comprising one to four MUs. We found that, for the voluntary drive frequency, the intermuscular coherence values were lower than the intramuscular coherence values when more than two MUs were considered ($P = 0.007$ and 0.007 for 3 and 4 MUs, respectively; Kruskal–Wallis test). For the tremor frequency, the intermuscular coherence values were lower than those of the intramuscular case even when only two MUs were included in the analysis ($P = 0.004$, $P < 0.001$, $P = 0.001$ for 2, 3, and 4 MUs, respectively; ANOVA).

The relative increment in coherence values for each MU added in the calculation of the CST were also calculated to estimate their trends. The averaged relative increment of the intramuscular coherence at voluntary drive and tremor frequencies monotonically decreased from 27.7% to 3.3% and from 33.6% to 11.2% when the number of MUs increased from one to seven, respectively (Figure 3.6a and 3.6b). For the coherence values between groups of antagonist muscles (Figure 3.6c and 3.6d), the relative increment of the intermuscular coherence values did not decrease monotonically. Together, these results indicate that common inputs are less shared across antagonist muscles than they are across agonist muscles and that there may be differences between the voluntary and tremor

drives in the extent of their sharing.

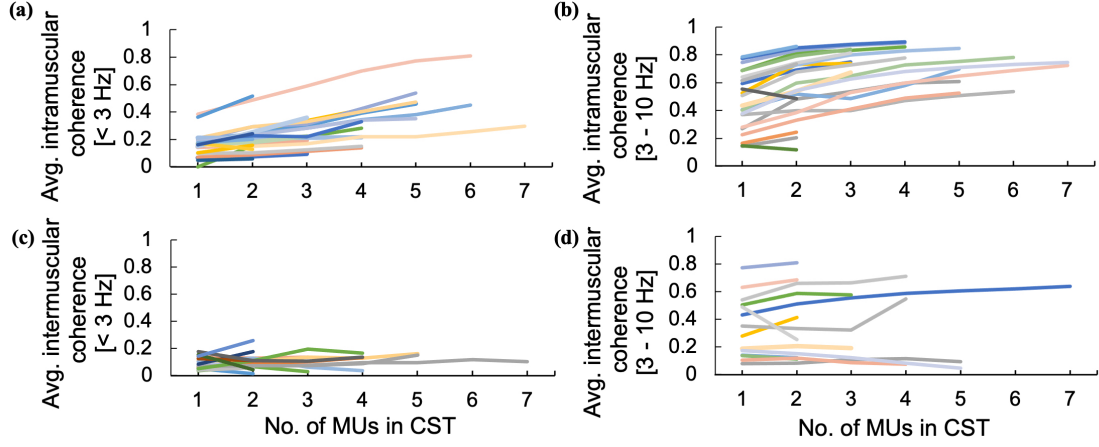


Figure 3.6: Change in magnitude of maximum coherence as a function of the number of motor units of all patients with ET. (a) and (c): intramuscular and intermuscular coherence, respectively, at the voluntary movement frequency. (b) and (d): intramuscular and intermuscular coherence, respectively, at the tremor frequency. The intramuscular coherence values slightly increased toward plateau when more MUs were added to the CSTs in both frequency ranges. However, the intermuscular coherence ((c) and (d)), on average, was lower than the intramuscular coherence ((a) and (b)) in both the voluntary drive and tremor frequencies, and their increments were not statistically significant. Avg., average.

3.5 Discussion

In this study, we investigated the behavior of MUs in agonist/antagonist groups of muscles of 15 patients with ET during postural tremor, focusing on the relation between their voluntary and tremor-related inputs. We found that, within each muscle, coherence peaks at the voluntary drive frequency were lower than at the tremor frequency (Figure 3.3a), likely reflecting that voluntary inputs are less shared across motor neurons than tremor-related inputs. Coherence values between groups of MUs from antagonist muscles were smaller, suggesting that motor neurons innervating antagonist muscle groups may be influenced by common inputs and also by independent inputs projected individually to each MN pool. We also observed that through the task, the relative phase of MUs from antagonist muscles varied randomly from in phase to out of phase at both the voluntary drive and tremor frequencies. However, the phase difference at the voluntary drive frequency was, on average, lower than at the tremor frequency, perhaps reflecting muscle co-contraction to maintain postural position. Taken together, these results imply that in patients with ET, MUs in antagonist muscle groups were activated differently in different frequency bands.

3.5.1 Tremor characteristics

During tremor, the MNs fire in discrete patterns with an occurrence of short interspike intervals (paired or tripled discharges; Figure 3.1a) [Dietz et al., 1976, Holobar et al., 2012], unlike MU spike trains of healthy individuals that fire more regularly. Although the power spectrum of a single MU showed several peaks at various frequencies (Figure 3.1b), all of them exhibited a peak in the tremor frequency band (3–10 Hz) and, in some patients also in the voluntary drive frequency band (1–3 Hz). When these MUs were pooled together to create CSTs, the spectral peaks at the voluntary drive and tremor frequencies were enhanced, whereas the power of other frequency components was reduced. This demonstrated an averaging process of the neural outputs where only the common inputs to the pools of MNs were emphasized (population coding) [Farina and Holobar, 2016, Negro and Farina, 2012]. In fact, MN populations (CST) sample the input signals at a higher rate compared with single MUs and, therefore, optimize the neural input detection. The existence of a significant peak at the tremor frequency extracted from the CST (Figure 3.1b) indicates that the MN pools received strong neural input at this frequency [Farina et al., 2014]. Apart from the peaks at the voluntary drive and tremor frequencies, the PSDs showed smaller peaks in the first harmonic of the tremor, previously attributed to mechanical resonance [Raethjen et al., 2009]. The two main peaks in the PSDs of the CSTs were at the voluntary drive and tremor frequencies, but their magnitudes varied among patients. In some cases, the peak of PSDs at the voluntary drive frequency was greater than the tremor peak. However, the greater the voluntary contraction, quantified by the power peak at the voluntary drive frequency, the higher the tremor power. This positive correlation may indicate an inter-dependency of the tremor and voluntary drives. In fact, Schmied and Descarreaux [Schmied and Descarreaux, 2010] suggested that contributions of common inputs can be enhanced by stronger voluntary contractions: higher force would increase the number of MNs recruited, and these MNs would sample better the tremor-related neural input. However, even though there was a statistically significant association between voluntary and tremor power, the model did not capture a lot of variance, weakening this interpretation.

3.5.2 Common input drive to agonist and antagonist groups of muscles

MNs receiving the same inputs have high statistical tendency to discharge synchronously, leading to an increase in correlation between neural output of the MNs (MU spike trains). Specifically, the shared synaptic inputs equally enhance electrical potential at the membrane of the neurons receiving them, which increases their probability of firing simultaneously [De La Rocha et al., 2007, Negro and Farina, 2011, Raethjen et al., 2007]. This correlation in MU activations can be quantified using coherence analysis [Farina and Holobar, 2016, Negro and Farina, 2011, Negro and Farina, 2012]. In turn, the measured CST coherence values reflect the strength of the shared neural drives [Christakos et al., 2009, Gallego et al., 2015b]. The relatively high intramuscular coherence

and in-phase pattern of the MU activations observed at the voluntary drive and tremor frequencies (Figure 3.3a and Figure 3.5a) thus indicate that MNs within agonist muscles shared a large amount of both inputs [Gallego et al., 2015b]. The tremor movements were mainly controlled by common inputs, which possibly include central oscillators in the primary motor cortex, pontomedullary reticular formation, and cerebellum given that these neural commands oscillate at an approximate frequency of 3–10 Hz [Williams et al., 2010]. The tremor-related input was partly modulated by the level of force exertion (voluntary command). Although significant tremor peaks were also present in the intermuscular coherence spectra (Figure 3.3b), indicating the presence of common tremor-related inputs to MNs of antagonist muscle groups, the averaged intermuscular coherence was lower compared with the intramuscular coherence, reflecting the presence of other inputs independently projected to the MN pools of the two muscle groups [Farina and Holobar, 2016, Lemon, 2008]. These inputs could relate to afferent feedbacks from the muscle spindles in the antagonist muscle, which are activated when the muscle rapidly changes its length. These oscillations create resonance [Deuschl et al., 2001, Lakie et al., 2012], which corresponded to the harmonic frequency found in the PSDs of the individual MUs.

Our phase difference analysis also suggested that voluntary and tremor-related inputs could influence muscle contraction independently from each other: MU activity at the voluntary frequency tended to have small averaged phase difference (in phase: phase difference $< 10^\circ$), likely reflecting muscle co-contraction (Figure 3.4i, 3.4j, 3.4o, 3.4p, and Figure 3.5). Based on the assumption that the tremor oscillations are also transmitted to the antagonist muscle via afferent feedbacks in opposite phase, the phases of the muscle activations could increase toward 180° due to out-of-phase activations. This behavior can be observed in Figure 3.4k, 3.4l, 3.4q, 3.4r, and Figure 3.5, where the phase difference of antagonist MU spike trains at the tremor frequency increased. The difference in phase values within two bandwidths shows that MNs of agonist-antagonist muscle pairs may be concurrently present in-phase and out-of-phase oscillatory components during the same motor task.

In addition, we observed that the phase differences in both frequencies varied greatly during the recording time (Figure 3.4j, 3.4l, 3.4p, 3.4r). This was possibly due to the instability of limb movements determined by the stretch reflex arc and mechanical resonance of the limb [Gallego et al., 2015b, Raethjen et al., 2000, Zhang et al., 2009]. This MU firing modulation leads to variations in MU discharge patterns and inconsistent phase differences over time. This variation of the phase difference over time could explain the limited effectiveness of tremor suppression strategies that apply out-of-phase stimulation to antagonist muscle groups [Dosen et al., 2015, Maneski et al., 2011].

3.5.3 Saturation in coherence value as a measure of shared input

Theoretical and experimental analyses [Negro and Farina, 2011, Negro and Farina, 2012] show that when the number of activated MNs is sufficient and the sampling rate is high enough to effectively sample the common input, linear transmission of this common input will saturate [Farina et al., 2014]. We have shown that the saturation in the coherence values at the tremor frequency can be observed by just examining the MU activity itself. The intramuscular coherence values monotonically increased (Figure 3.6a and 3.6b), and the increment was progressively smaller with increasing numbers of MUs. In fact, the coherence values of three-MU CSTs and four-MU CSTs were not statistically different, suggesting the saturation stage of the coherence peak. This saturated coherence value can be interpreted as the true strength of the common tremor-related inputs [Farina and Negro, 2015, Negro and Farina, 2011, Negro and Farina, 2012]. This intramuscular coherence probably does not saturate at 1 for a number of reasons, including that we recorded from several agonist muscles (not just one), that motor neurons may not be perfectly linear, that there are likely other sources of common input, e.g., from spinal afferents [Gallego et al., 2015a], and the presence of independent inputs.

3.5.4 Limitations

Our study patients held their hands outstretched against gravity with the forearms fully supported. Given this limited effort, it is expected that fatigue did not play a major role. However, further studies are needed to investigate how our phase difference and coherence results may change at higher force levels, since in healthy individuals, a fatiguing contraction involves differential control of agonist and antagonist muscles [Lévênez et al., 2008]. Also, it would be relevant to examine whether the results change depending on the hand position (e.g., with the hands in a palms-up position).

3.6 Conclusion

The study of coherence between MU spike trains of patients with ET indicated that both the voluntary drive- and tremor-related inputs are common to antagonist muscle groups during postural tremor. When patients were maintaining posture, the MNs in these muscles were activated simultaneously and predominantly in an in-phase pattern at the voluntary frequency band. However, the time shifts (phase differences) in these MN activations increased at the tremor frequency band, which may be due to the projection of tremor-related input transmitted through afferent feedbacks in an out-of-phase pattern. These shifts in the MN activations could be modulated by 1) level of force exertion that determines the sampling of tremor-related input to each muscle and 2) influences of the afferent feedbacks (resonance).

In addition, the phase shift of the MN activation varied over time possibly due to the delay in the afferent feedback and reflex loops. If this rationale is verifiable, we may be able to accurately counteract the tremor related-neural commands by tracking the phase of the MN activity in pairs of antagonist muscles and cancel out the commands before they produce the muscle oscillations.

Chapter 4

Online tracking of the phase difference between neural drives to antagonist muscle pairs in essential tremor patients

An antagonist pair of muscle plays a crucial role in regulating tremor movement by alternately activate extensor and flexor muscle groups. In Chapter 3, we have found that both voluntary command and tremor-related inputs are common to antagonist muscle groups. During postural tremor, the phase of their activation varies over time which is a potential challenge for the design of tremor suppression system. In this chapter, we therefore focused on developing and validating a technique to track the changes in the phase of muscle activity which can be implemented for real-time tremor suppression. The chapter is presented in order of Abstract, Introduction of recent development of tremor suppression techniques and our implementation of phase-locked loop system in tremor signal phase detection, Material and methods, Statistical Analysis, Results and Discussion. Part of this chapter was published in [\[Puttaraksa et al., 2022\]](#)

4.1 Abstract

Transcutaneous electrical stimulation has been applied in tremor suppression applications. Out-of-phase stimulation strategies applied above or below motor threshold result in a significant attenuation of pathological tremor. For stimulation to be properly timed, the varying phase relationship between agonist-antagonist muscle activity during tremor needs to be accurately estimated in real-time. Here we propose an online tremor phase and frequency tracking technique for the customized control of electrical stimulation, based on a PLL system applied to the estimated neural drive to muscles. Surface EMG signals were recorded from the wrist extensor and flexor

muscle groups of 13 ET patients during postural tremor. The EMG signals were pre-processed and decomposed online and offline via the convolution kernel compensation algorithm to discriminate MU spike trains. The summation of MU spike trains detected for each muscle was bandpass filtered between 3 to 10 Hz to isolate the tremor related components of the neural drive to muscles. The estimated tremorogenic neural drive was used as input to a PLL that tracked the phase differences between the two muscle groups. The online estimated phase difference was compared with the phase calculated offline using a Hilbert Transform as a ground truth. The results showed a rate of agreement of 0.88 ± 0.22 between offline and online EMG decomposition. The PLL tracked the phase difference of tremor signals in real-time with an average correlation of 0.86 ± 0.16 with the ground truth (average error of $6.40^\circ \pm 3.49^\circ$). Finally, the online decomposition and phase estimation components were integrated with an electrical stimulator and applied in closed-loop on one patient, to representatively demonstrate the working principle of the full tremor suppression system. The results of this study support the feasibility of real-time estimation of the phase of tremorogenic neural drive to muscles, providing a methodology for future tremor-suppression neuroprostheses.

4.2 Introduction

Tremor is characterized by rhythmic oscillations of body parts around joints [Lyons and Pahwa, 2005, Deuschl et al., 1998]. It is a common phenomenon that is experienced by healthy individuals (physiological tremor) or by people with movement disorders, such as ET and Parkinson’s disease (or PT). Physiological tremor is a low-amplitude, and high-frequency oscillation ranging from 8 to 12 Hz [Elble and Randall, 1976, Elble, 2003] and is inherently present in the activation of healthy muscles during voluntary contractions and in particular during fatigue. Unlike physiological tremor, pathological tremor has a broader frequency range (1 to 25 Hz), and higher oscillatory amplitude [Hess and Pullman, 2012, Zhang et al., 2009]. This type of tremor is likely to be caused by abnormalities in either the CNS, PNS, their pathways to muscles, or all of them together. The involvement of this assembled structure at different frequencies of tremor activities has been investigated using spectral coherence, and phase analysis [Yang et al., 2016, Raethjen et al., 2009, Gallego et al., 2015b, Raethjen et al., 2007, Hellwig et al., 2003, Puttaraksa et al., 2019, Amjad et al., 1997].

Among different types of pathological tremor, ET is the most common tremor disease, affecting 4% of people aged over 50 [Wenning et al., 2005]. ET is characterized by postural tremor that occurs whilst maintaining a limb position against gravity [Lorenz and Deuschl, 2007] and kinetic tremor that occurs when a body part is moving [Pigg et al., 2020, Louis, 2013]. Although pharmacotherapy and thalamic surgery or *deep brain stimulation* (DBS) surgery are the most common and effective treatments for pathological tremors, these approaches have several limitations, and they are not always effective [Zesiewicz et al., 2005].

4.2.1 Treatments for tremor

Pharmacologic treatment is the most common method used to treat ET. Propranolol and primidone provide a similar variable level of tremor treatment by reducing the amplitude of tremor at around 50% [Zesiewicz et al., 2002, Zesiewicz et al., 2005, Benito-León and Louis, 2006, Louis, 2012]. However, not all of the patients would respond to the treatment at the same dose, and increasing the dose is needed to maintain the level of treatment. Ten to 60% of patients could experience side effects such as fatigue, dizziness, impaired balance, slow heart rate or blood pressure, and nausea. Although the mental effect of the medicine is less common among patients, the patients might experience depression, insomnia, or loss of memory.

Surgical treatment is another effective treatment for ET. Thalamus and ventral intermediate nucleus are the typical locations for brain surgery. Reduction of tremor has been observed in 69% of 65 patients after undergoing stereotactic thalamotomy at the ventral intermediate nucleus, which is related to creating ventral intermediate nucleus lesion using ultrasound [Fishman, 2017]. This lesion destroys and blocks the abnormal signal from the inner brain before it goes to a contralateral muscle. However, this technique is less popular than the DBS as it has the potential risk of serious side effects such as infection, cognitive, speech, and balance problems [Tasker, 1998]. The DBS is usually targeted to the thalamus or cerebellar outflow pathways of the brain. The DBS is a preferred treatment if the patients pass surgical criteria and are drug-resistant as it provides marked tremor reduction of 80% with mild side effects of speech, gait, and balance problems. However, the DBS is expensive, and it requires insertion of a pre-programmed pacemaker and battery. Replacement of this device might be needed in case of failure or battery run out (usually every 4 years), which could cause pain and infection [Iorio-Morin et al., 2020].

As an alternative, the tremor rhythm can be attenuated by applying mechanical perturbation [Elble et al., 1987, Britton et al., 1992], transcranial magnetic stimulation [Pascual-Leone et al., 1994, Hallett, 2007, Lu et al., 2015], or electrical stimulation to peripheral nerves [Britton et al., 1993, Lin et al., 2018b, Pahwa et al., 2019, Isaacson et al., 2020]. These techniques have been validated in subjects with physiological tremors, Parkinson’s patients with postural tremors, and ET patients [Britton et al., 1993, Elble et al., 1987, Pascual-Leone et al., 1994, Lu et al., 2015, Britton et al., 1993, Lin et al., 2018b, Pahwa et al., 2019, Isaacson et al., 2020]. Among these techniques, the use of electrical stimulation of peripheral nerves seems to be the most viable for wide clinical/home use since it involves stimulation of distal parts of the body where it is less likely to cause discomfort or side effects.

Electrical stimulation is used to generate muscle activation by providing impulses that excite the nerves supplying muscles. Closed-loop electrical stimulation for tremor suppression has been implemented in association with various sensors, such as displacement sensors [Prochazka et al., 1992], inertial sensors [Dideriksen et al., 2015, Maneski et al., 2011], and surface and intramuscular

EMG [Dideriksen et al., 2017, Zhang et al., 2011, Muceli et al., 2019, Pascual Valdunciel et al., 2020]. In the literature, several strategies have been proposed to achieve tremor control, such as simultaneous stimulation (to produce co-contraction of the antagonist muscles) [Gallego et al., 2013] and out-of-phase stimulation [Maneski et al., 2011, Dideriksen et al., 2017, Dosen et al., 2015] with currents either above or below the threshold for muscle activation [Pascual-Valdunciel et al., 2021].

Zhang and team demonstrated significant tremor suppression, using artificial EMG-regulated neuronal oscillators to control electrical stimulation, with stimulation parameters tuned by a proportional-integral-differential controller of motion signals [Zhang et al., 2011]. This technique achieved a 94% of tremor amplitude suppression but has not been practically validated in patients. Maneski et al. used an inertial sensor (gyroscope) to time the electrical stimulation in an out-of-phase manner and tested the system on healthy subjects, Parkinson’s patients, and ET patients [Maneski et al., 2011]. Although a tremor suppression of 67% was observed, the phase tracking by motion sensors was associated with relatively large delays, which would make practical adoption difficult.

Tremor suppression systems based on EMG have also been extensively investigated. Dideriksen et al. [Dideriksen et al., 2017] and Dosen et al. [Dosen et al., 2015] have shown that out-of-phase subthreshold stimulation (below the threshold of muscle activation) could reduce tremor, as measured by the oscillations of the affected joint (the wrist). Although the out-of-phase stimulation strategy produces significant levels of tremor attenuation, recent studies have demonstrated that the phase differences between a pair of antagonist muscle activities at the tremor frequency of 3 to 10 Hz vary greatly and rapidly over time [Gallego et al., 2015a, Puttaraksa et al., 2019], meaning an accurate real-time estimation of muscle activity phase during tremor is needed for continuous control. For this reason, we propose a system for real-time estimation of the phase difference in the neural drive to agonist and antagonist muscles during the tremor. The neural drives are estimated by the online decomposition of EMG signals into individual MUs because they are the best representatives of the neural command from the central nervous system through their pathways to muscles [Gallego et al., 2015b, Gallego et al., 2015a, Dideriksen et al., 2011c]. The phase of the neural drives is tracked by a PLL system and used to control the stimulation timing. We provide extensive results on validation of all parts of the system, both offline and online, on patients’ data. Following this validation, we show the working principle of the full system in a closed-loop in one ET patient as a proof-of-concept demonstration.

4.3 Material and Methods

4.3.1 Patients

Data for the validation of the system components were recorded from 13 ET patients (5 women; age 68.9 ± 11.3 yrs) with a diagnosis of ET according to the Movement Disorder Society consensus criteria [Deuschl et al., 1998]. All patients had a prominent postural forearm tremor. Tremor severity in the most affected limb was 28.9 ± 10.3 (ranging from 10 to 51 on the Fahn - Tolosa - Marin tremor rating scale which has the maximum possible score of 144 [Fahn et al., 1988, Lyons and Pahwa, 2005]). Average disease duration was 17.3 ± 9.5 yrs, ranging from 2 to 43 yrs. Seven patients had left tremor predominance, five patients had right tremor predominance and one patient had bilateral tremor. Three of the patients were not on medical treatment while the rest of the patients used medications to treat tremor. All the patients were asked to discontinue their treatment prior to the experiment and none of them had been treated with DBS. Following the validation of all system components on the 13 patients, an additional ET patient (male, 79 yrs) with prominent postural forearm tremor on the right side was recruited for the proof-of-concept real-time demonstration of the full closed-loop tremor suppression system. All procedures were approved by the Ethical Committee at the University Hospital “12 de Octubre” (Madrid) (for the tests on the 13 patients) and by the Imperial College Ethical Committee (for the proof-of-concept demonstration), in compliance with the Declaration of Helsinki. Written and signed informed consent was obtained from all study participants.

4.3.2 Closed - loop tremor suppression system

Figure 4.1 illustrates the process of estimating the phase difference of an antagonist pair of muscle activity to control the timing of electrical stimulation using cumulative spike train. The process includes high-density surface EMG recordings from the extensor and flexor muscle groups (1), online EMG decomposition using the convolution kernel compensation algorithm (2), low-pass filter of the cumulative spike trains (3), phase estimation using a PLL system (4), and stimulation controller (5). The EMG signals from the two muscle groups were separately decomposed into MU spike trains before summation to create the cumulative spike trains and low-pass filtered at the tremor frequency (3 to 10 Hz). The phases of these filtered signals were then estimated using a PLL system which generated phase-locked signals of both muscles. Finally, the phases of the signals were used to control the stimulator in an out-of-phase manner. Specifically, the stimulation for the extensor muscle group was timed based on the phase of the flexor muscle activity and vice versa.

4.3.3 EMG recording and decomposition

For offline validation of the system, recorded tremor data were used to assess the accuracy of the proposed online decomposition and the phase-locked loop system. During the recording, the patients were seated on a comfortable armchair with their forearms fully supported. Postural tremor was provoked by asking the patients to stretch their dominant hand against gravity. Two 30-s recordings of 64 channels of the EMG data (grids of 13 x 5 electrodes -1 missing at the corner, inter-electrode distance 8 mm, single differential configuration) were acquired (EMG-USB2; OT-Bioelettronica, Italy, 2048-Hz sampling frequency and 12-bit analog-to-digital conversion) from the extensor and flexor muscle groups, providing 26 data sets from 13 patients.

The multi-channel EMG signal (X_i) can be mathematically described as a convolutive mixture of the impulse responses of filters representing MUAP shapes, h_{ij} with a series of MU discharge timing (MU spike trains, S_j) as described in eq. 4.1 [Glaser et al., 2013]

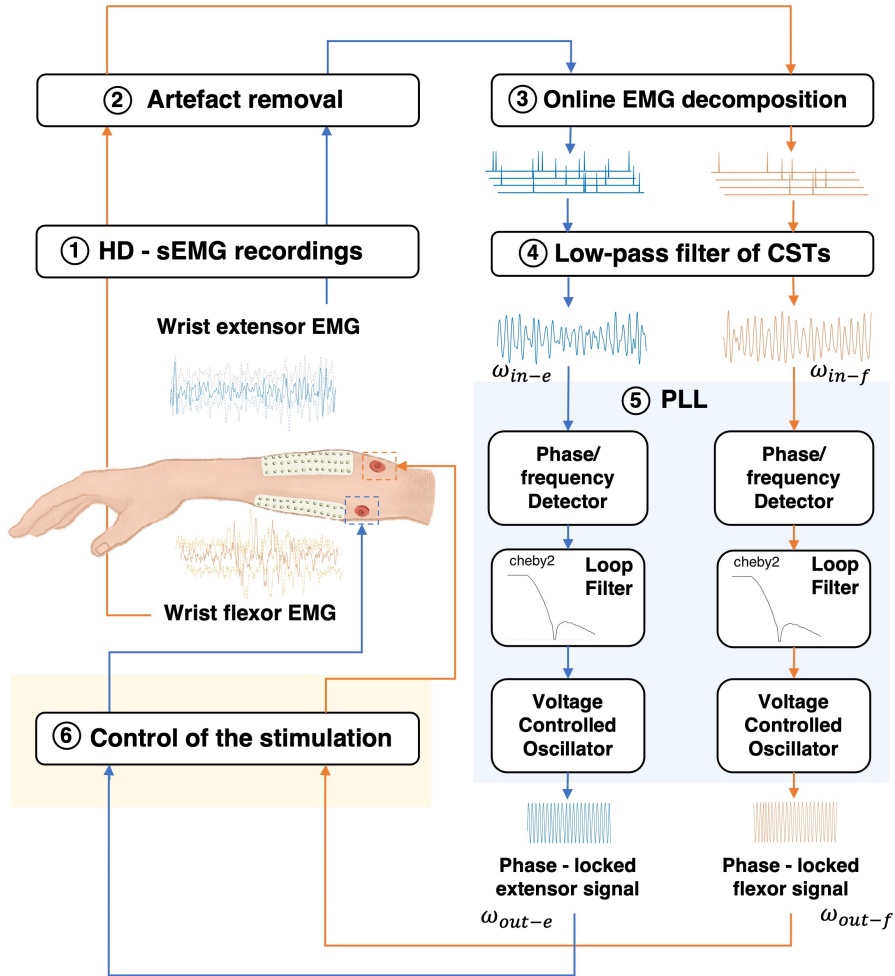


Figure 4.1: Closed-loop tremor suppression system flow chart.

$$x_i(n) = \sum_{j=1}^N \sum_{l=0}^{L-1} h_{ij}[l] S_j(n-l), i = 1, \dots, M, \quad (4.1)$$

where N and M are the number of MUs (sources) and EMG channels, respectively. From this model, the MU spike trains (S_j) were discriminated from the EMG signals using the convolution kernel compensation decomposition algorithm [Farina et al., 2010, Holobar and Zazula, 2003, Holobar and Zazula, 2007].

S_j was calculated using the correlation matrix of the extended (delayed repetitions) observations (EMG signals) [Holobar and Zazula, 2007], and the cross-correlation vector between the EMG signals and the estimated MU spike trains. The product of the cross-correlation vectors and the correlation matrix were multiplied by the extended EMGs yielding MU spike trains (equation (17) in [Holobar and Zazula, 2007]). In the offline decomposition, cross-correlation vectors were calculated from the whole recording period whereas for the online decomposition they were initialized from the first 10 s of the 30 s-long EMG recordings and applied to the remaining 20 s for online validation [Glaser et al., 2013].

We have assessed that 10 s is a sufficient period for estimating the MUAP shapes of individual MUs of tremor EMGs as the spike triggered averaging [Fetz and Cheney, 1980] of the first 10 s or the whole 30 s of data yielded similar multi-channel MUAP templates (Figure 4.2). The likelihood of estimated MU spike trains to be genuine were estimated using a validated metric, the *pulse-to-noise ratio* (PNR) [Holobar et al., 2014]. Although PNR value of 30 dB is recommended for identification of individual MU spike trains [Glaser et al., 2013], we accepted the spike trains with $\text{PNR} \geq 26$ dB. Namely, we were not using individual spike trains in this study. Instead, all of the retained MU spike trains of each muscle were summed to create cumulative spike trains. Note that the quality of cumulative spike trains increases with the number of included MUs [Negro and Farina, 2012], whereas slightly increased rate of errors in estimation of individual MU discharges was not detrimental for the performance of our phase-locked loop system. The cumulative spike trains were then bandpass filtered (third-order Butterworth) at 3 to 10 Hz to isolate the tremor-related components of the neural drive [Puttaraksa et al., 2019].

4.3.4 Phase-locked loop system (PLL)

PLL is a feedback system capable of synchronizing phase and frequency of two waveforms. It consists of three components: a phase/frequency detector, a low-pass filter and a voltage control oscillator (VCO, Figure 4.3). The PLL tracks phase and frequency shift of an input signal by proportionally varying the frequency of the VCO to match the input frequency which, thereby, induces phase locking between them [Razavi, 2005].

There are several models of the PLL such as the linearized PLL which is the simplest model

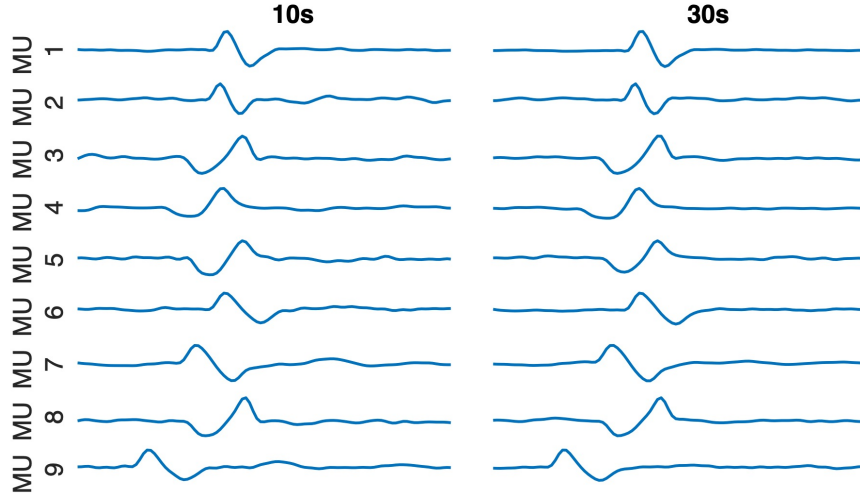


Figure 4.2: Representative example of a comparison of the MUAP shapes of extensor muscles detected using the first 10 s-long EMG signals and the whole length of the signals (30 s). The MUAP shapes detected using 10 s were similar to those detected from the 30 s-long signals.

(used for example in [Ong et al., 2016]) and the digital CP PLL which is modified by replacing one or more components with digital circuitries. In this study, we used a digital charge pump PLL due to its large capture phase range (up to 4π) and the use of edge-triggered flipflop which produces no phase offset and makes the system insensitive to duty cycle of input signals [Gardner, 1980].

The phase and frequency of the filtered cumulative spike trains were identified by a tri-stage detector comprising of two D-flipflops and NAND gate, *Phase/Frequency Detector* (PFD, Figure 4.4a). The PFD differentiates the zero-crossing state of the input (cumulative spike trains) signal and the signal estimated from the VCO which initially generates synthesized signal at the quiescent frequency. Specifically, if the input signal crosses zero before the VCO synthesized signal (phase lead), the “Up” stage will be on (logic 1) and open until the VCO synthesized signal crosses the zero line, the Up state is then reset to zero (clear). Conversely, if the input signal lag the VCO synthesized signal, the “Down” state will be on until the input signal crosses zero. The PFD provides sequences of two outputs (Up and Down) to the *Charge pump* (CP) which are then subtracted by a subtracting node. The state difference was then multiplied with the pump current gain (I_p) to produce a square sequence of control voltage (Figure 4.4b) that adjusts the quiescent frequency (Q_s) and minimizes the phase error between the cumulative spike trains signal and the estimated

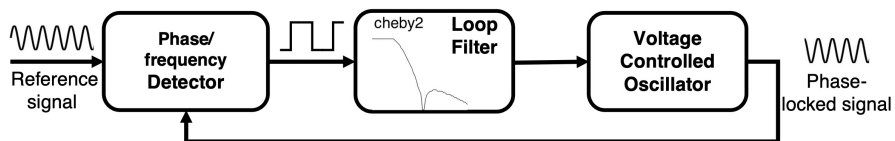


Figure 4.3: The diagram of phase-locked-loop system.

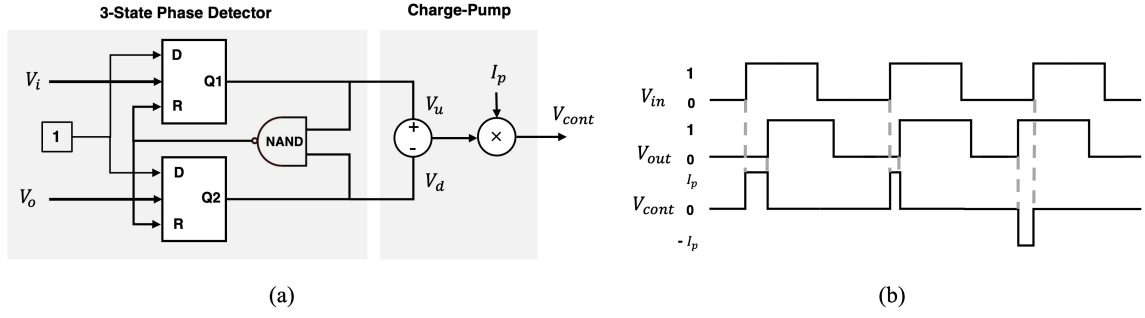


Figure 4.4: Tri-state phase detector and charge-pump diagram (a), and the waveform of the Phase/frequency detector and the charge-pump output (V_{cont} ; b).

signals until their phases are locked. In order to reduce the ripple of the logical control voltage signal (V_{cont}) and discard its harmonics, the V_{cont} was low-pass filtered using a Chebyshev filter (type II, third order).

The VCO is in charge of generating synthesized signal at Q_s . This preassigned Q_s is regulated by filtered V_{cont} from the loop filter. The output frequency (hence the phase) of the VCO synthesized signal is proportional to the applied control voltage. Specifically, if the control voltage is zero, VCO will produce a signal with Q_s frequency (Free-Running state)). Otherwise the frequency is proportionally adjusted according to the V_{cont} with a frequency change rate (VCO sensitivity) of K_{vco} (radian/second/volt) and reduces the error between the frequency of synthesized signal and frequency of input signal until the phase is locked.

The linear function which relates the VCO output frequency to V_{cont} is

$$\omega_{out}(t) = Q_s + K_{vco}V_{cont}(t), \quad (4.2)$$

where K_{vco} is the VCO sensitivity in radian/second/volt.

The charge-pump PLL was simulated in MATLAB Simulink (2020b). The Q_s and the K_{vco} of the PLL were simulated using Mixed-Signal Blockset. These parameters were determined to allow the VCO to vary its frequency around the tremor frequency range of 3 to 10 Hz. The following specific values were selected: low-pass cut-off frequency = 18 Hz, VCO gain = 0.4, $I_p = 1$, $K_{vco} = 3.5$ radian/second/volt and $Q_s = 6.5$ radian/second. The same parameters were used for all the data sets.

4.3.5 Proof-of-concept demonstration of the online tremor suppression system

Following the extensive offline and online validation, the proposed system was further tested on one ET patient in closed loop. EMG high-density electrode type and position follow the

description is Section II-C. A portable multichannel amplifier (Quattrocento, OT-Bioelettronica, Italy) was used to acquire the EMG signals, which were amplified with gain of 150, sampled at 2048 Hz, and AD converted on 16 bits. The stimulation was delivered online with the stimulation timing corresponding to the phase of the neural drive to its antagonist muscle to counteract tremor. The stimulation artefacts that contaminated the EMGs were blanked before the decomposition and phase estimation processes. The threshold for the artefact removal was set at 95% of the average artefact peaks in the first 2 s of the recordings obtained during stimulation. Twenty-five samples of EMG (5 before and 20 after the artefact peaks) were blanked. Blanked EMG recordings were then decomposed online to extract MU spike trains.

During the real-time proof-of-concept demonstration, a dual-phase approach to online decomposition was used [Barsakcioglu et al., 2020]. During the training phase, the subject was provided with visual feedback using the average of the root mean square amplitude of all the EMG channels (128 channels). The subject was seated in a comfortable position (with elbow supported) and the forearm in postural position. The training phase started with estimation of the maximum voluntary contraction during a palmar grasp. The subject was then presented and asked to follow (by performing a palmar grasp) a 4-s ramp trajectory (3.75% MVC/s) followed by a 45 s constant trajectory at 15% of the MVC. The data acquired during the training phase was then used to compute the real-time decomposition parameters. The rationale for choosing the palmar grasp during training was to co-activate both extensor and flexor muscle groups allowing the simultaneous training of the agonist and antagonist muscles. During the online decomposition phase, the subject was provided with the real-time raster plots of the MU spiking.

EAST, a portable multichannel stimulator (OT-Bioelettronica, Italy) was used to deliver positive electrical pulses with $300\mu\text{s}$ pulse width and 100 Hz frequency [Dosen et al., 2015]. Two circular ValuTrobe cloth neurostimulation electrodes (3.2 cm $\varnothing$) were attached close to the later epicondyle of the elbow and proximal to the elbow crease to stimulate the extensor muscle and flexor muscle groups, respectively [Dosen et al., 2015]. A rectangular cloth neurostimulation electrodes (5 cm $\times$ 9 cm) was positioned over the olecranon to act as common anode. To determine electrode positions prior to the start of the experiment, a sponge-attached stimulation electrode was slightly moved around the areas to determine where the motor response, slight flexion and extension of the wrist, could be activated. The stimulation frequency was set to 100 Hz and the pulse width to $300\mu\text{s}$ as during the probing phase. As afferent stimulation (below the motor threshold) is as effective as motor stimulation (above the motor threshold) in suppressing tremor [Dosen et al., 2015], we opted for afferent stimulation that prevents muscle fatigue and discomfort for the patients. The intensity of the stimulation was gradually increased from 1 mA in 1 mA step to determine the motor threshold. The intensity 1 mA below this motor threshold was selected for the afferent stimulation. In this study, the intensity used for the extensor and flexor muscle stimulation was 14 mA and 8 mA, respectively.

The signal outputs (estimated phase of the filtered cumulative spike train during tremor) from the PLL were used to control the stimulation in an out-of-phase manner. Specifically, the estimated phase of the flexor muscle activity was used to time the stimulation of the extensor muscle group and vice versa. Each stimulation was activated when the instantaneous phase of the signal output was larger than 63° (70% of the PLL output amplitude). The activation of the stimulation, therefore, was adjusted according to the phase of the muscle activity. If the phases of the muscle activity from the extensor and flexor muscles was fully overlapped, the stimulation was not activated.

4.3.6 Data Analysis.

We assessed the accuracy of the online EMG decomposition on the tremor recordings by comparing their extracted MU spike trains with those decomposed from the offline decomposition using the Rate of Agreement (RoA) metric [Glaser et al., 2013]

$$RoA_j = \frac{C_i}{C_j + A_j + B_j} \times 100 \quad (4.3)$$

where C_j is the number of discharges of the j MU spike train that was identified by both decompositions (tolerance set to 0.5 ms), A_j is the number of unmatched discharges of the j MU spike train identified from the offline decomposition and B_j is the number of unmatched discharges identified by the online decomposition.

The performance of the PLL was validated using the cumulative spike trains decomposed from the online and offline techniques. The groups of MU spike trains extracted from both techniques were used as inputs of the PLL system to assess their phases. The PLL separately estimates the phase of antagonist pair of muscles (extensors and flexors) before their phases were subtracted to obtain the estimated phase difference (PD_{EST}).

To evaluate the system performance in tracking the agonist-antagonist phase difference, a ground truth phase difference (PD_{GT}) is required for the comparison. The PD_{GT} was calculated offline from the Hilbert Transform, a commonly used technique to calculate phase [Dideriksen et al., 2011c, Liu, 2012], from 30 s-long cumulative spike trains of antagonist muscle pairs decomposed offline and filtered at the tremor frequency. We used the MU spike trains decomposed using the offline convolution kernel compensation method as the ground truth to calculate the PD_{GT} because this technique has been validated with simulated tremor signals with added voluntary movement and experimental data from Parkinson's patients and ET patients performing isometric contractions [Holobar et al., 2012]. This technique has high accuracy in decomposing simulation signals compared with their reference and is able to identify the main characteristics of tremor-related MU activity similar to the observation via intramuscular EMG recordings [Christakos et al., 2009, Das Gupta,

1963]. The correlation between the PD_{EST} (using offline or online decompositions) and the PD_{GT} was then calculated using cross-correlation analysis. Circular histograms with 40-bin were used to plot the PD_{EST} and PD_{GT} and the error between them. The mean phase difference and their standard variation were compared. For the proof-of-concept demonstration, the experiment started with 30 s of baseline (stimulation off) followed by 30 s of stimulation on and repeated for 5 trials for each condition. To assess the tremor during the stimulation as well as no-stimulation phases, a camera system was used. Three green markers (1.2 cm x 1.2 cm) were attached to the ulnar head of the fifth metacarpal bone (M1), the ulnar styloid process (M2), and in correspondence of the ulnar bone, 1/3 of the forearm distally (M3). A custom script written in Python 3.8 was used to manage video capture (30 frames per second) and marker position recognition for later post-processing to compute the wrist joint angle. The wrist flexion/extension angle was estimated as the acute angle between the directions identified by (M1, M2) and (M2, M3).

4.3.7 Statistical analysis.

The normality of variables including the average phase difference and the correlation values were visually observed using histogram plot and assessed using the Shapiro–Wilk test. To compare the estimated variables with their ground truths, pairs of normally distributed variables were compared using paired t-tests, whereas the Mann–Whitney–Wilcoxon test was used to compare non-normal data. The correlations between two variables were measured using the Pearson’s correlation test for normally distributed data and the Spearman’s correlation test for non-normal data. In all cases, the null hypothesis was rejected for $P-values < 0.05$. The results are represented as means $\pm$ SD and median (IQR).

4.4 Results

4.4.1 Validation of the online decomposition.

Decomposition accuracy was validated on the pre-recorded data of the 13 patients, which were processed simulating an online decomposition. The average number of identified MUs for offline and online identification (MU tracking with PNR > 26 dB) were 11.6 ± 5.2 and 10.8 ± 5.5 for extensor muscles, and 4.9 ± 2.6 and 4.7 ± 2.4 for flexor muscles, respectively.

Figure 4.2 shows the MUAP shapes of the MUs decomposed in the first 10 s of a representative subject and the MUAP shapes of the MUs decomposed from the whole duration of the signals. The mean discharge rates were 11.4 ± 2.3 Hz and 11.5 ± 2.8 Hz for the MUs decomposed offline and online, respectively. The averaged RoA was 0.88 ± 0.22 across all the MUs detected from both algorithms. Across patients, the mean tremor frequency as estimated by the power peak frequency

of PSD within the tremor frequency range (3 to 10 Hz, Welch’s method) was 6.8 ± 0.9 Hz, ranging from 5.5 to 8.8 Hz. Figure 4.5 illustrates a subset of the identified MU spike trains using online and offline decomposition and their cumulative spike train of extensor muscles of a representative subject. The vertical lines indicate the discharges of each MU and the dots denote disagreement of the discharges.

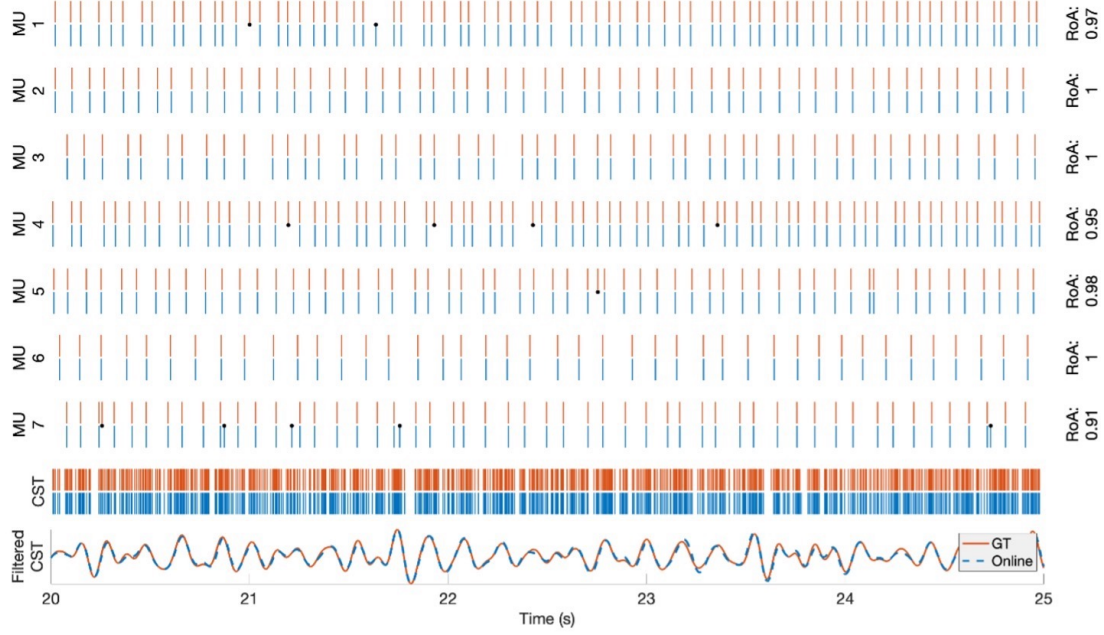


Figure 4.5: The first seven panels depict representative examples of 7 individual MU spike trains identified by the offline decomposition (red line) and online decomposition (blue dashed line) from extensor muscles. The following panels are their cumulative spike trains and the filtered cumulative spike trains at 3 to 10 Hz, respectively. Each vertical line represents an MU discharge and disagreements between the online and offline decomposition are denoted by small black dots. The RoAs indicate the similarity of the discharge of each MU between offline and online decomposition.

4.4.2 Validation of the PLL system.

Hereafter, the ground truth variables will be indicated with the subscript ‘GT’ and the estimated variables with the subscript ‘E’. We will add ‘off’ and ‘on’ for the variables estimated from the MU spike train decomposed offline and online, respectively. Note that the figures show the comparison of analysis obtained from the cumulative spike train decomposed online and the GT. The comparison of the analysis obtained from cumulative spike train decomposed offline with the GT can be found in the text.

- **Performance of PLL in detecting the phase of neural drive in individual muscles**

Phase estimates for individual muscles were assessed to ensure that the PLL could follow the frequency and phase of the reference signals. Figure 4.6a illustrates the reference signal (red line) and the estimated signal from the PLL (blue dashed line) of the extensor muscle group of a representative patient. In theory, the phase of two signals will be locked when the frequencies of the two are equal. We have assessed the instantaneous frequency

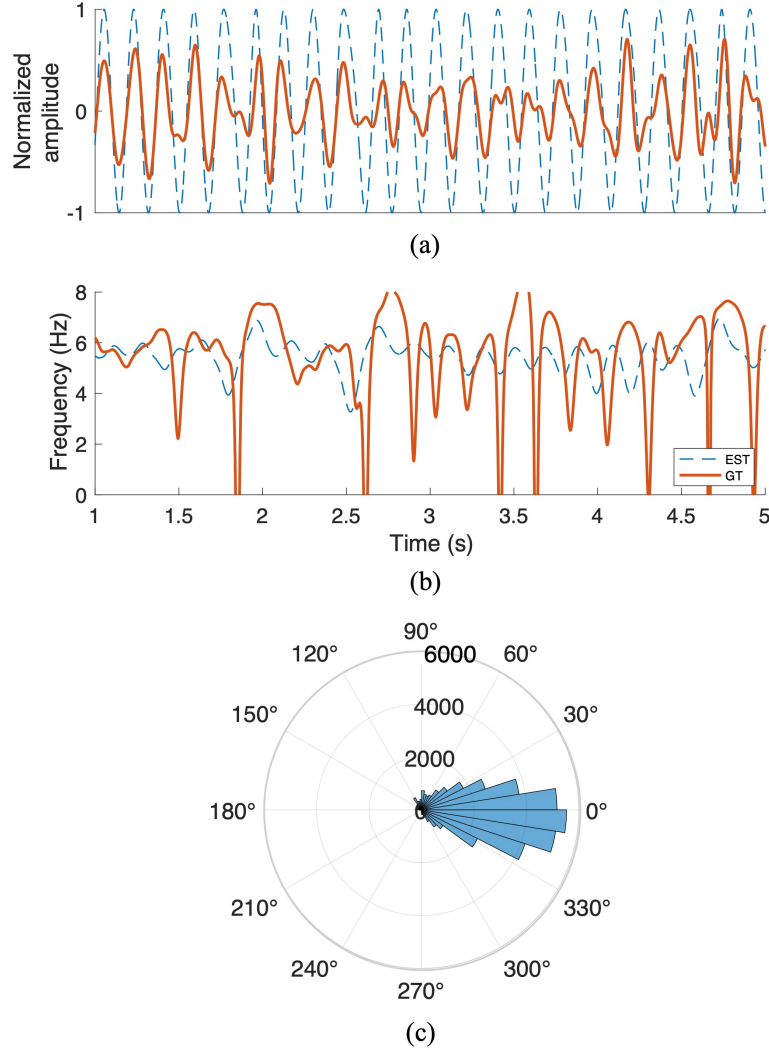


Figure 4.6: Comparison of the estimated signal with the reference extensor signal of MU spike train decomposed online of a representative patient (a). The instantaneous frequency of the estimated signal and the reference is shown in b. The circular histogram shows the error between the $\phi_{(E-on)}$ and the ϕ_{GT} of the extensor signals (c). The estimated signal shows high instantaneous frequency correlation value of 0.89 and difference in phase compared to the ϕ_{GT} concentrated at -0.99° showing the ability of the PLL in tracking the frequency and the main phase of individual muscle activations.

of the estimated signal to investigate if the PLL could follow the changes of the reference instantaneous frequency (ω_{GT}) within the tremor range. The median of the correlation with the ω_{GT} of both muscles was 0.86 (0.17) and 0.86 (0.11) for $\omega_{(E-off)}$ and $\omega_{(E-on)}$, respectively. This shows high similarity of the estimated instantaneous frequency and the ground truth. Figure 4.6b shows the comparison of the $\omega_{(E-on)}$ (blue dashed line) with their ω_{GT} (red line) of the same muscle. Similarly, the correlation of instantaneous phase of all patients compared with the GT were 0.88 (0.09) and 0.88 (0.08) for $\phi_{(E-off)}$ and $\phi_{(E-on)}$, respectively. The circular histogram shown in Figure 4.6c, illustrates high similarity between ϕ_{GT} and $\phi_{(E-on)}$.

- **Performance of PLL in tracking the phase difference between neural drives to antagonist muscle pairs**

The phase difference (PD) between the activations of antagonist muscle pairs was calculated by subtracting the instantaneous phase of extensor with those of flexor muscles. We assessed the performance of the PLL in estimating the phase difference by calculating the correlation between the PD_E and the PD_{GT} . Figure 4.7 illustrates the circular histograms of the antagonist $PD_{(E-on)}$ (a) and PD_{GT} (b), respectively, whereas the differences between them is shown in Figure 4.7c. Figure 4.7d shows the ground truth extensor and flexor muscle

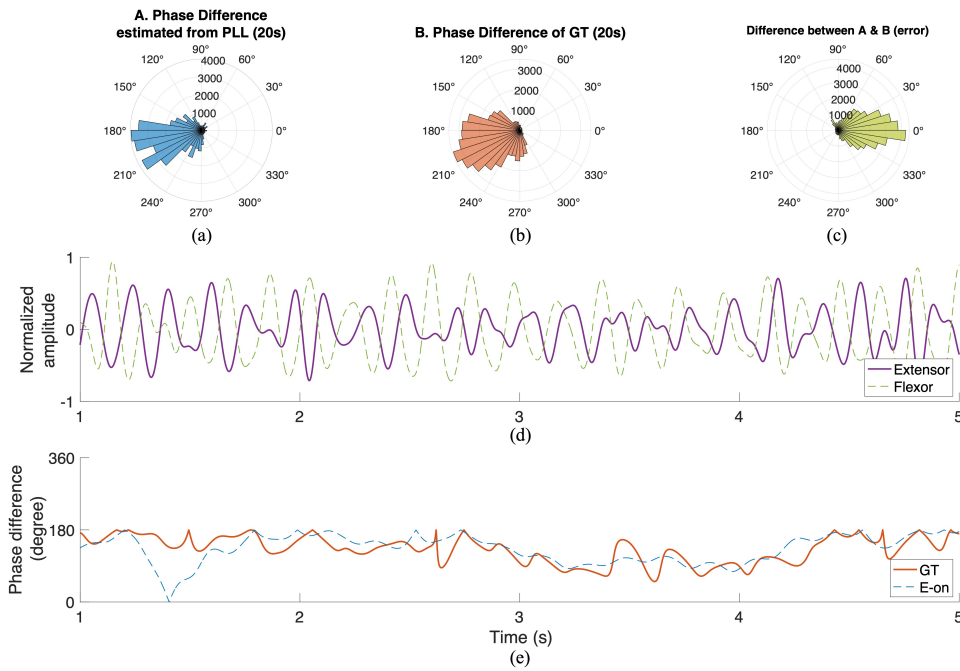


Figure 4.7: The circular histogram shows the antagonist phase difference estimated from the PLL ($PD_{(E-on)}$; a) and the estimated phase difference of the ground truth ($PD_{(GT)}$; b). The error between the $PD_{(GT)}$ and $PD_{(E-on)}$ was shown in (c). The small difference between the $PD_{(GT)}$ and the $PD_{(E-on)}$ indicates that the phase of the PLL estimated signal is similar to the GT. Panel d depicts the tremor signals of extensor (purple line) and flexor (green dashed line) muscle groups. Panel e shows the comparison of $PD_{(GT)}$ (red line) and $PD_{(E-on)}$ (blue dashed line).

activities reflecting the alternate bursts of tremor-related activations of the antagonist pair of muscles. A relatively low difference (error) between the PD_E and the PD_{GT} of 6.10° and a correlation of 0.95 indicated a high similarity between them.

The time-varying PD_{GT} (red line) and $PD_{(E-on)}$ (blue dashed line) were compared in Figure 4.7e. The median of the absolute error and the correlation values across all subjects were 2.32° (6.77°) and 0.90 (0.12), respectively, for the estimation using MU spike trains decomposed offline and 6.40° (3.49°) and 0.86 (0.16) for the estimation using MUs from online decomposition technique. Statistical analysis showed that the estimates of phase difference using either online or offline techniques were not significantly different (P -value = 0.1, Wilcoxon rank sum test, Figure 4.8). However, the phase difference showed no significant correlation between offline and online decomposition ($R = 0.52$, P -value = 0.07, Spearman's correlation test).

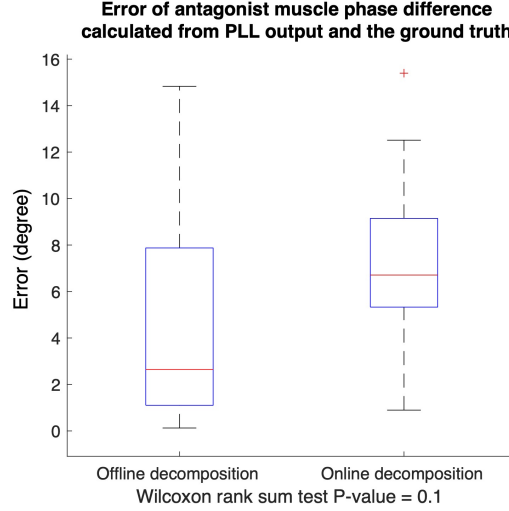


Figure 4.8: The error between the estimated phase difference from the PLL using MU spike trains decomposed from the offline and online techniques, and the phase difference of the ground truth signals calculated using the Hilbert transform. The P -value of 0.1 (Wilcoxon rank sum test) shows no significant difference in the use of offline or online decomposed MU spike trains in estimating the antagonist muscles phase difference via PLL.

4.4.3 Proof-of-concept demonstration of the online tremor suppression system

The system was preliminarily tested online on an ET patient. Figure 4.9a illustrates the patient's forearm with HD-EMG matrices, stimulation electrodes and three markers on. The tremor frequency was 5.5 ± 1.4 Hz (average of the frequency corresponding to the peak of the PSD of the cumulative spike train filtered in the bandwidth 3 to 10 Hz across the 5 “stimulation off” trials). 21 and 11 MUs were decomposed from extensor and flexor muscles with firing rates of

11.7 ± 2.9 and 11.8 ± 2.5 pulse per second, respectively. Figure 4.9 shows the cumulative spike trains decomposed online and the stimulation timings to extensor (Figure 4.9b) and flexor (Figure 4.9c) muscles during the “stimulation on” condition. The wrist angle is qualitatively compared for the case of stimulation and absence of stimulation in Figure 4.9d. Overall, the closed-loop online test preliminarily demonstrated the potential and feasibility of the full recording system. While it is not possible from these representative results to draw conclusions on the level of tremor suppression, the provided demonstration shows that all system parts correctly work when applied in conditions similar to the target clinical application.

4.5 discussion

We have presented a real-time system (EMG decomposition followed by PLL on cumulative spike trains) that estimates the phase difference over time between tremorogenic neural drives to agonist-antagonist muscle pairs. This system can be used to drive electrical stimulation in closed loop to suppress tremor.

Various tremor suppression systems have exploited mechanical and inertial systems [Dideriksen et al., 2011c, Maneski et al., 2011], as well as EMG recordings [Dideriksen et al., 2017, Zhang et al., 2011, Muceli et al., 2019, Pascual Valdunciel et al., 2020], in order to tune the stimulation parameters (e.g. timing and frequency). Although the surface EMG enhances the accuracy of stimulation timing, estimating the phase of the signal from the surface EMG might not be reliable since it is not a perfect representative of the neural activation to the muscles [Dideriksen et al., 2011c, Das Gupta, 1963, KG, Keenan, Farina D, Maluf KS, Merletti R, 2005, Alcazar et al., 2019, Yavuz et al., 2010]. A better control of the stimulation parameters can be obtained by accurately identifying the discharge timings of MUs found by applying blind source separation algorithms to high-density surface EMG [Holobar and Zazula, 2003, Holobar and Zazula, 2007, Drost et al., 2006, Farina et al., 2016, Merletti et al., 2008, Chen et al., 2016, Negro et al., 2016]. In this study, the validated offline [Holobar and Zazula, 2007, Holobar et al., 2010, Negro et al., 2016] and online convolution kernel compensation decomposition [Glaser et al., 2013] were used to discriminate the spike trains of each MU from the EMG of ET patients. The results show that the online decomposition has equivalent performance to the offline decomposition as calculated by the popular convolution kernel compensation source-separation algorithm. It is worth noting that the online decomposition was previously validated with data recorded from healthy subject [Glaser et al., 2013] and the MU activities during tremor are highly correlated due to enhanced short-term synchronization [Holobar et al., 2012]. Therefore, a further validation of online decomposition in data collected from this patient population was missing and it was carried out in this study.

In order to track the phase of muscle activity during tremor, a PLL (which is generally used to synchronize phase and frequency of two waveforms) was implemented and tuned by the discharge

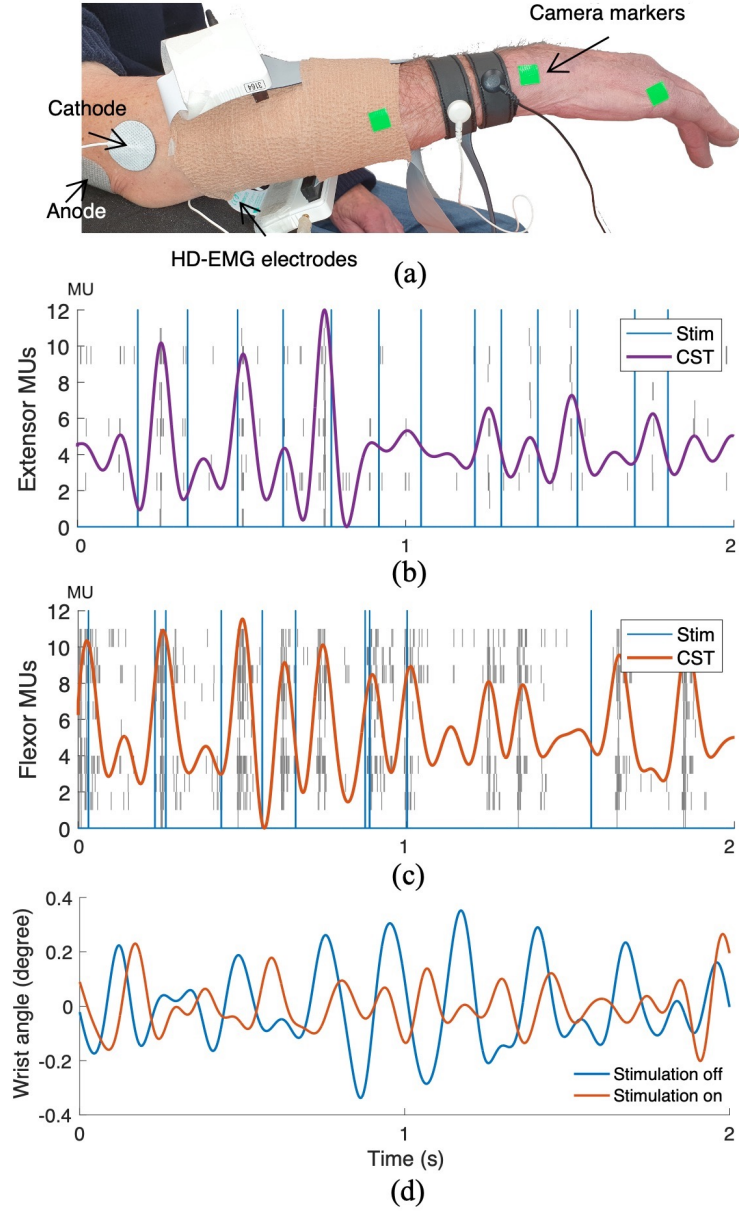


Figure 4.9: Example of discharge timings of 12 and 11 identified MUs (gray lines) with corresponding cumulative spike trains from extensor (b) and flexor (c) muscles, respectively. The stimulation timings are indicated by the vertical lines. The wrist angles in two representative intervals of stimulation off (blue line) and on (red line) are compared in (d) and the positions of the electrodes and markers are shown in (a). Note that the plots of discharge times are not aligned to those of wrist angle (all of them are representative plots extracted from different intervals during the proof-of-concept experiment). Since the stimulation frequency was set at 100 Hz and the stimulator can deliver a certain number of stimulation pulses as long as it is in the windows that the antagonist muscle was active (in this case, the extensor muscle activity was used to control the stimulations to flexor muscle.), double stimulation pulses such as in the period of 1 second of Figure 4.9c could occur.

timing of the decomposed MU spike trains. Compared with the phase calculated offline using the Hilbert transform, the PLL provided highly accurate tracking of the phase difference. The PLL was also able to provide comparable estimation using either MU spike train decomposed offline or online to estimate the phases (no significant difference in the average phase difference of the estimated and the ground truth).

The advantage of implementing the PLL in the tremor suppression system is its ability to continuously produce a voltage oscillation closely following the phase of the reference tremor signals in real-time, as well as strictly following the frequency of the reference signals in a predefined frequency band (in this case, the tremor frequency between 3 and 10 Hz). This ensures that only the tremor-related components of the reference signal are tracked and used to activate an electrical stimulator. This voltage oscillation signal could be used in real-time to modify the stimulator activation timing. A challenging limitation of PLL in tracking the phase is that the control signal produced by the PLL starts its phase at a pre-defined angle and needs a few milliseconds to adjust its initial phase to match the reference signal. Specifically, if the tremor oscillates at around 6 Hz, which is equivalent to 0.16 s per cycle, the PLL will need at least this time to change its frequency in order to follow the phase of the reference signal in a following waveform. This may have an effect when designing the stimulation of the tremor suppression system, as operation needs to be divided into stimulation periods and recording periods due to unavoidable stimulation artefacts in the EMG signal [Dideriksen et al., 2017, Dosen et al., 2015]. To overcome this limitation, we have integrated the blanking algorithm to the EMG before the decomposition. For every stimulation pulse, 25 samples of the EMG were blanked. As the decomposition template was created during the training phase when the stimulation is not activated, the blanking did not significantly affect the performance of the decomposition. This allowed the same number of MUs to be identified between the training, “stimulation off” and “stimulation on” and the burst of the tremor to be distinguished. The full closed-loop system was tested on only one ET patient. For this patient, the proposed system worked correctly in all parts. However, the reduction of tremor varied among trials as the patient had very mild wrist tremor with intermittent tremor absence during the recordings. Therefore, it is not possible to draw general conclusions from this single case study. More patients with different tremor severity are required for further validation. Nonetheless, the proof-of-concept demonstration showed the proper functioning of the system in a relevant clinical application. The validation of the online tremor suppression on more patients with broader range of tremor severity is still required.

4.6 Conclusion

In conclusion, the online decomposition-based convolution kernel compensation algorithm was validated with high-density surface EMG recordings of ET patients showing equivalent accuracy of the MU spike trains discrimination to the use of the offline decomposition technique. The

application of the PLL to those decomposed MU spike trains shows a promising performance for the tracking of the antagonist muscles phase difference during postural tremor. The proposed system was preliminarily integrated with a stimulator for a complete verification of the closed-loop working principle.

Chapter 5

Postural tremor modulation via continuous transcutaneous spinal cord stimulation

In Chapter 4, we have utilized peripheral nerve stimulation to counteract the tremor under the hypothesis that the excitation of the afferent neurons may modulate the excitability of the inhibitory interneurons located in the spinal cord resulting in an inhibition of its antagonist muscle activity. During that study, another question has raised. Since the spinal cord is the location where neural commands from the brain are integrated with afferent feedback from muscles, electrical interference at this location may be able to modulate the tremor-related neural drive to the muscles.

In this chapter, we intend to validate this hypothesis by assessing the modulation level of tremor oscillation of ET patients using an accelerometer when the patients were electrically stimulated at C5-C6 of the cervical spine. The chapter is presented in order of Abstract, Introduction of the applications of invasive and non-invasive electrical or magnetic stimulations at cortical and subcortical levels, Material and Methods, Statistical Analysis, Results, Discussion and Conclusion.

5.1 Abstract

Transcutaneous electrical spinal cord stimulation (tESS), a non-invasive spinal cord stimulation technique, is beneficial for promoting the excitation of neurons located in the spinal cord. In this study, effects of the tESS on tremor modulation of ET patients have been observed. The tESS was used to deliver a burst-modulated alternating current (Russian currents) of 5 kHz carrier frequency at C5-C6 of the cervical spine of the patients. The high frequency of the stimulation was modulated by slow burst within the tremor frequency (3 to 10 Hz) and beta bands (21 Hz). The degree of hand tremor was assessed using a triaxial accelerometer placed on the dorsal surface of

the patients' most affected hand. Spectral analysis revealed that the power of the wrist tremor reduced when the patients were stimulated with the slow burst at their specific tremor frequencies ($P - value = 0.048$). The phase difference between the stimulation and the tremor phases may non-linearly correlate to the tremor amplitude ($R = 0.05$, $P - value = 0.06$), implying that the stimulation timing might not be relevant to the reduction in the amplitude of the tremor. Our results suggested that the use of slow burst stimulation with high carrier frequency could influence the modulation of the tremor-related neural activities, possibly by increasing the excitability of inhibitory interneuron in the spinal cord, which concurrently inhibits the activity of antagonist muscles canceling out the oscillation specifically at the tremor frequency.

5.2 Introduction

It is suggested that the origin of involuntary oscillations involves the CNS [Lyons and Pahwa, 2005, Shaikh et al., 2008]. The abnormal oscillations could be due to lesions in brain regions such as the primary motor cortex, the sensorimotor cortex [Raethjen et al., 2007] and the thalamus [Elble, 1996, Hua et al., 1998, Deuschl et al., 2001, Lyons and Pahwa, 2005]. Evidence has also shown that loss in neurochemical substances, such as GABAergic neurotransmitters (produced by cerebellar Purkinje cells) or dopamine, serotonin, and noradrenaline (produced from the brain stem) could generate abnormal oscillations [Helmich et al., 2013]. It was demonstrated by [Jones, 1993] that the level of GABAergic neurotransmitter was reduced in ET patients. While the loss of GABAergic neurotransmitters leads to oscillations in the cerebello-thalamo-cortical network, the loss of dopamine, serotonin, and noradrenaline could lead to the basal ganglia and thalamic oscillations [Barrière et al., 2008, Hammond et al., 2007, Hua et al., 1998]. These pathological oscillations and voluntary commands propagate from the brain through corticospinal and other pathways to the spinal cord, where the neural commands are further modulated by afferent sensory neurons to produce compound movements. These afferent neurons include Ia afferent neurons in muscle spindles and Ib afferent from Golgi tendon, which were suggested to be involved in tremor enhancement [Deuschl et al., 2001, Elble et al., 1987, Stiles and Pozos, 1976]. Neurons in the dorsal horn of the spinal cord, therefore, play a crucial role in integrating and modulating these descending and ascending commands. This leads to a hypothesis that electrical disturbance of the spinal cord could influence motor neuron excitability and could change MU activity during tremor.

In this chapter, a brief literature review of CNS stimulation for clinical treatments via primary motor cortex and spinal cord stimulations using magnetic and electrical stimulation is presented, followed by a demonstration of tremor modulation by tESS using continuous burst-modulated alternating current on C5-C6 of cervical spine process of ET patients during the postural tremor.

5.2.1 Primary motor cortex stimulation

Motor cortex stimulation for pain treatment has been intensively studied since the late 1900s, possibly started in Japan as the studies were written in Japanese [Yamamoto et al., 1990, Muramatsu et al., 2000] until a few years later, more studies were published internationally [Katayama et al., 2002b, Katayama et al., 2002a]. The motor cortex stimulation for pain treatment, such as chronic neurogenic pain or post-stroke pain, were delivered using epidural or subdural electrical stimulation [Rasche et al., 2006, Sokal et al., 2015, Honey et al., 2016, Ramos-Fresnedo et al., 2022]. Mechanisms that underlie the motor cortex stimulation are out of the scope of this study, but it was proposed recently in [Kim et al., 2016, Henssen et al., 2020]. In brief, it is suggested that motor cortex stimulation modulates subcortical circuitry and pain system by inhibiting the primary somatosensory cortex, thalamus and spinothalamic tract via reciprocal pathways between the motor cortex and sensory cortex.

Electrical motor cortex stimulation was also reported to be beneficial for tremor treatment. In 1998, [Nguyen et al., 1998] demonstrated long-term improvement of facial pain and upper limb action tremor in a PD patient using chronic cortical stimulation at the precentral and postcentral gyrus. They suggested that the oscillation of action tremor, which is caused by lesions in the superior cerebellar peduncle and interruption in its pathways, could be blocked by the stimulation of the motor cortex. More recent long-term tremor improvement has been reported from a study using similar motor cortex stimulation [Moro et al., 2011]. This study used unilateral subdural motor cortex electrical stimulation through four contact electrodes to treat contralateral tremors in ET and PD patients. Since epidural or subdural electrical stimulation requires opened-brain surgery to insert the electrodes, it could increase inflammation risk. In addition, difficulty in selecting accurate stimulation electrode placement and stimulation intensity limit the use of invasive motor cortex stimulation.

Similar to electrical motor cortex stimulation, *transcranial magnetic stimulation* (TMS) can also induce a transient perturbation in physiological and pathological neurocircuits with no surgical requirement [Lin et al., 2018a]. The TMS has been used to stimulate the primary motor cortex for corticomotor partway evaluation. Since a brief single pulse of the TMS can evoke a *motor evoked potentials* (MEPs), a brief muscle response, in the contralateral muscles, it is a medium for measuring corticospinal excitability in healthy individuals or individuals with pathological conditions. The TMS evokes MEPs by generating magnetic pulses that induce an electrical field in the area underneath the TMS coil. The effect of TMS on neural activity in the corticospinal partway has been demonstrated using single [Pascual-Leone et al., 1994, Hallett, 2007, Rocchi et al., 2021], paired-pulse [Lu et al., 2015] and continuous (repetitive) stimulation [Hellriegel et al., 2012, Hellriegel et al., 2012, Batra et al., 2022]. The single stimulation allows elucidation of the cortical pathway to the muscle by assessing the change in MEPs amplitudes. The paired-pulse stimulation was used to assess facilitation and inhibition mechanisms (homosynaptic depression) of

the intracortical process as different inter-pulse intervals of the paired-pulse stimulation differently alter the amplitude of MEPs responded to each stimulation pulse. The repetitive stimulation was also used to study the neuromodulation effect of the TMS on a central oscillatory network for tremor suppression.

On the tremor aspect, it was demonstrated that high intensity of TMS of the motor cortex was able to reset the onset of the tremor. [Pascual-Leone et al., 1994] has tested the effect of TMS on the change in tremor bursts measured by EMG recordings of wrist flexor/extensor muscles of ET and postural tremor of PD patients. The tremor resetting was observed by comparing the timing of the tremor bursts that were modulated by the stimulation to the timing before the stimulation. Their results have shown that bilateral and unilateral TMS induce bilateral tremor resetting. However, the bilateral TMS produces synchronized reset in both limbs, while unilateral TMS evoked asynchronous tremor patterns. This asymmetry shows that the muscles of bilateral limbs may not entirely share the same input from the CNS but are somewhat influenced by independent inputs. In contrast, the antagonist pair of muscles in the unilateral limb partially shared the same input. The resetting of the tremor patterns after TMS supports the rationale that descending input from cortical and subcortical mechanisms is involved in the tremor [Pascual-Leone et al., 1994, Hellriegel et al., 2012]. Although there was an argument that the tremor resetting may be due to a muscle twitch evoked by the stimulation that disturbed the stretch reflex loop and altered the tremor rhythm to a certain degree [Britton et al., 1992, Lu et al., 2015], [Pascual-Leone et al., 1994] has shown that the extent to which the muscle twitch could involve might be weaker than the cortical and subcortical effect as the tremor resetting degree is not significantly correlated with the strength of the muscle twitch.

More recent research where the effect of localized single and paired-pulse TMS of the primary motor cortex was recorded using EMG also suggests that TMS could promote tremor reduction [Lu et al., 2015]. They observed that the EMGs recorded during voluntary contraction showed a silence period (EMG suppression) after a single TMS stimulation, suggesting inhibitory effect of the cortical stimulation on subcortical tremor mechanisms. [Hellriegel et al., 2012, Batra et al., 2022] used short repeated TMS in theta-burst frequency (50 Hz stimulation bursts with three pulses of 5 Hz carrier frequency) on the primary motor cortex of ET patients. They observed a short-term tremor amplitude reduction caused by long-term depression of postsynaptic neurons. They suggested that the stimulation may increase the level of inhibitory neurotransmitters like GABAergic generating inhibition effects in the cortical pathways.

5.2.2 Spinal cord stimulation

The dorsal horn is an important place where cortical and sensory inputs are integrated to generate reliable output to muscles, from simple movements like flexing a single joint to complex

movements requiring activation of synergistic muscles. The dorsal horn acts as an assembly point where descending inputs from supraspinal tracts such as corticospinal and rubrospinal tracts [Asante and Martin, 2013] are gathered with ascending sensory inputs from peripheral afferents. Neurons in different laminae of the dorsal horn transform the required motor adjustment from cortical and subcortical regions and estimate the command needed to change the current muscle position to the desired position. The muscle current position is estimated by the feedback information from the muscle-specific proprioceptive afferent. Then the neurons orderly organize and assign the command to interneurons, or motor neuron pools innervating synergistic muscles to archive the desired position or tasks [Todd, 2002, Todd, 2010, Harding et al., 2020]. Stimulation of the dorsal horn could, therefore, modulate the spinal efferent outputs projected to muscles or ascending input going back to the brain.

Apart from the investigation of the effects of TMS over the motor cortex, Pascual-Leone and his team have also primarily given an insight into the effect of TMS centered at the C7 spinous process on peripheral nerves. However, they rarely observed the effect on the tremor resetting [Pascual-Leone et al., 1994]. Study by [Ugawa et al., 1989] has suggested that the TMS over the cervical spine was able to produce *compound muscle action potentials* (CMAPs), summation of the active motor neuron potentials, in the upper limb regarding to the coil position and direction of the stimulation current.

Epidural spinal cord stimulation (ESCS) has been intensively used for therapeutic purposes including pain relief [Jensen and Brownstone, 2019, Tapias Pérez, 2021] and treatment for movement disorders such as dystonia [Shimizu et al., 2020], *spinal cord injury* (SCI) [Eisdorfer et al., 2020, Seáñez and Capogrosso, 2021] and tremor [Fénelon et al., 2012, Thiriez et al., 2014, Russo et al., 2018]. ESCS is beneficial for SCI patients as it could strengthen monosynaptic connections between sensory and motor neurons [Eisdorfer et al., 2020]. ESCS consists of multiple silicone-based stimulation electrodes in the form of percutaneous or paddle leads connected to a pre-program pulse generator. The leads are typically implanted into the epidural space between dura matter and deliver a continuous electrical pulse to the dorsal column. As the stimulation electrodes are implanted near the dorsal root of the spinal cord, which is the termination of afferent sensory neurons from the trunk and limbs, the ESCS could affect the sensory partway. The sensory neurons send the signal to the thalamus and sensory cortex for cortical processing while concurrently, post-synapse to the spinal motor neurons via mono- and poly-synaptic connections to produce CMAPs [Thiriez et al., 2014]. It is suggested that the ESCS influences recruitment of medium-large diameter sensory neurons in the dorsal column, including proprioceptive afferent neurons that provide information on muscle force, length, velocity like group Ia afferent, and cutaneous afferent neurons that provide tactile feedback from the skin due to external stimuli [Strzalkowski et al., 2018]. Contrary, it could inhibit the response of small-diameter neurons carrying pain stimuli, therefore, reducing painfulness preserved from the patient [Rattay et al., 2000, Mendell, 2014, Jensen and Brownstone, 2019]. The involvement of the dorsal column nuclei from epidural stimulation over the cervical (C2) spine

was suggested by Qin and team when they found an increase in cerebral blood flow in male rats implying modulation of the activity in that areas due to the ESCS. In addition, the stimulation could alter a majority of neurons in the the dorsal column nuclei of rats providing excitability or inhibitory patterns of responses depending on the types of the neuron activated (high or low threshold neurons) by mechanical somatic stimuli [Qin et al., 2009]. Like the TMS, the ESCS also affects the inhibition system associated with GABAergic neurotransmitters and other substances such as serotonin. Apart from the effect of the ESCS on peripheral limbs, [Stančák et al., 2008] has shown that the ESCS also affects the central regions. The ESCS on lower back spinal (T9-T10) increases activation of primary motor cortex observed via functional magnetic resonance imaging of patients with lower back and legs pain [Stančák et al., 2008].

Using the finite element method to simulate the distribution of ESCS on a computational model of monkey cervical spinal cord and nerve fibers, [Greiner et al., 2021] suggested that the ESCS could conduct electrical potential in dorsal root, spinocerebellar tract, corticospinal tract, and dorsal column. However, it barely directly recruited motor neurons even though the high stimulation amplitude was used. Their experimental results of epidural stimulation at C5-T1 suggested that a single pulse of ESCS could recruit motor neurons during resting, and placing electrodes lateral to the spine provided higher segmental specificity than medial position. They also suggested that stimulation around C5-C6 could induce muscle fiber activity in the deltoid, biceps, and extensor carpi radialis muscles, while caudal stimulation around C8-T1 level mainly recruited fibers in the extensor digitorum communis, flexor digitorum profundis, flexor carpi radialis, and abductor pollicis brevis muscles. They pointed out that stimulating on C6 may target better the Ia-afferent fibers than other segments at low stimulation intensity.

For tremors, an implant spinal cord stimulation at T9-T10 was validated with a chronic pain patient who developed parkinsonian tremors after eight years of surgery. The study suggested that ESCS provided equivalent tremor improvement as the effect of levodopa. The reduction of the EMG amplitude with unchanged tremor frequency was reported [Fénelon et al., 2012]. In a more recent study, the ESCS was used to treat hand tremors in an ET patient. The pre-programmed stimulation patterns with the pulse width of 120 μ s and 100 Hz frequency were stimulated through two 8-contact electrodes implanted in the C2-C5 epidural space. In this longitudinal test, the tremor in the head, neck and hands was significantly suppressed, and the tremor in handwriting was improved [Russo et al., 2018]. Although the ESCS is minimally invasive and the electrodes are reversible, it still has potential concerns regarding lead migration and fractures. Especially, the implant of the pulse makers could be painful and inflammable.

tESS, which is a non-invasive alternative to ESCS of the cervicothoracic spine, could produce CMAPs in the upper and lower limbs of humans [Sabbahi and Sengul, 2011, Einhorn et al., 2013, Knikou, 2013]. It was suggested that tESS could also facilitate recovery in subjects with SCI. The tESS could evoke CMAPs at equivalent amplitudes to those produced by low-frequency ESCS,

suggesting that they may activate the same set or subset of the neural structure. Specifically, tESS also evokes CMAPs via recruitment of medium to large diameter proprioceptive neurons within the dorsal root, and repetition of tESS could increase the excitability of the motor pathway and increase the effect of GABAergic neurotransmitter in inhibiting the neural command. However, the tESS is different from the ESCS in terms that it has low segmental selectivity and its effect partially relies on the conductivity of the tissues and the distance of skin to the cutaneous (afferent) fibers [Hofstoetter et al., 2018].

The electrically induced CMAPs consist of a direct response to the stimulation (M-wave) and a reflex-related component whose amplitude may be altered with the stimulation frequency due to homosynaptic depression. [Hofstoetter et al., 2018] demonstrated that a single tESS promotes excitation of monosynaptic neurons of the same muscle or synergistic muscles and may partially excite Ia afferent of its antagonist muscle. They further suggested that the effect of tESS can be enhanced by increased voluntary contraction as the summation of electrically induced potentials and the ongoing descending command enhances the baseline potential of the neural membrane, increasing the possibility to reach its recruitment threshold. The tESS, therefore, makes it easier to elicit the muscle response during voluntary contraction than stimulating at rest [Milosevic et al., 2019].

The tESS applied over the C5-C6 spinous process of subjects with chronic incomplete cervical SCI, and healthy individuals facilitated increased CMAPs of biceps brachii but did not promote MEPs elicited by TMS at the primary motor cortex. In addition, the tESS promoted intracortical inhibition effects on paired-pulse TMS stimulation [Benavides et al., 2020]. These results suggested that the tESS may differently affect cortical and spinal networks. [Milosevic et al., 2019] used cervical tESS to stimulate around the C7-T1 at 30 Hz slow burst with 5kHz carrier frequency. Suppression of second response observed from all muscles after pair-pulse 50-ms inter-stimulus interval suggests an involvement of homosynaptic depression and inhibition effect of GABAergic neurotransmitter. The second reduction of the second muscle response implies a reflex inhibition after the first stimulation, which supports the involvement of Ia afferent and motor neurons in the tESS loop.

Possible mechanisms underlying the tremor reduction by tESS are similar to those of the ESCS. It increases excitation of the proprioceptive afferent fibers located in the dorsal root and strengthens the connection between the proprioceptive sensory and synapsed motor neurons. Increment of the proprioceptive sensory neuron excitability could also activate inhibitory interneurons inhibiting the antagonist muscle activity, which in turn stabilizes activation of the antagonist pair of muscles [Proske and Gandevia, 2012]. In addition, there is evidence that tESS may interfere with the neural activity in reticulospinal and spinocerebellar tracts associated with stabilization of the body [Kim et al., 2017, Eisdorfer et al., 2020].

From all the possibility that non-invasive electrical stimulation of the spinal cord could

promote neuromodulation of neural activity at the cortical level, we hypothesize that the postural tremor of ET could also be modified by the tESS over C5-C6 using slow burst-modulated alternating current (Russian currents) of 5 kHz carrier frequency.

5.3 Material and methods

5.3.1 Patients.

Data were recorded from 9 male ET patients aged 71.3 ± 11.8 yrs ranging from 43 to 86 yrs with the duration of diseases of 18.3 ± 9.8 yrs (5 to 35 yrs). All patients had a prominent postural forearm tremor, at 34.2 ± 11.1 (14 to 67) severity measured by the Fahn - Tolosa - Marin tremor rating scale (Table. 5.1). Seven patients had a tremor predominance on the right hand, and two patients had a left tremor predominance. Four of the patients were not on medical treatment, while the rest used medications such as Clonazepam, Botulinum toxin and Propranolol to treat tremors. All the patients did not discontinue their treatment prior to the experiment. The experiment was performed at the National Hospital for Neurology and Neurosurgery, London. All procedures were approved by the University College London Research Ethics Committee, in compliance with the Declaration of Helsinki and according to international safety guidelines. Written and signed informed consent was obtained from all study participants.

Clinical data such as age, tremor duration, bodyside most affected by tremor and medical treatments were collected by Anna Latorre, a doctor at the Sobell Department of Motor Neuroscience and Movement Disorders, University College London Institute of Neurology.

5.3.2 Spinal cord stimulation, EMG and tremor recordings.

Before each experiment, we started with motor threshold measurement, selecting optimum stimulation electrode positions and measuring tremor frequency as a pre-session procedure before continuing to the main experiment of HD-sEMG and acceleration recordings of wrist tremor during cervical electrical stimulation (Figure 5.1).

During the pre-session procedure, the patients were seated comfortably on an armchair resting their arms on their laps. The motor threshold was defined as the minimal intensity of a single electrical stimulation pulse required to evoke a muscle response in a relaxed muscle in 10 consecutive stimulation. The motor threshold was assessed using bipolar sEMG recording using Ag-AgCl electrodes. The bipolar sEMG electrodes were placed on the center of the muscle belly of *anterior deltoid* (DelA), *biceps brachii* (BB), *flexor carpi radialis* (FCR), *extensor carpi radialis* (ECR), and *first dorsal interosseous* (FDI) muscles to ensure that the stimulation intensity delivered

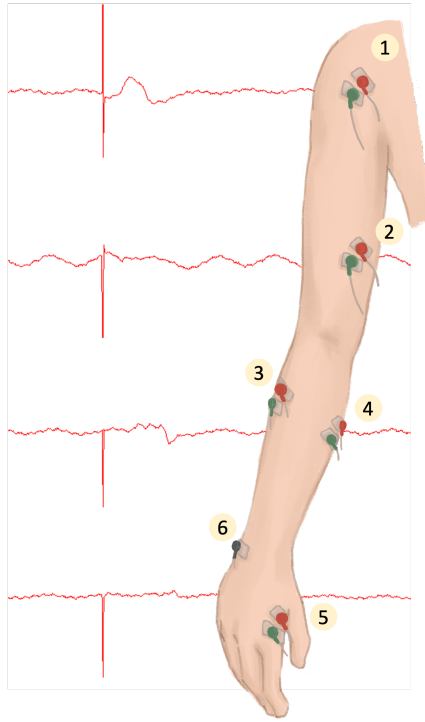


Figure 5.1: Bipolar sEMG electrodes were attached on DelA (1), BB (2), FCR (3), ECR (4) and FDI (5) for motor threshold measurement. The red lines are examples of bipolar sEMG recordings of muscle responds to a single stimulation at C5-C6 of the cervical spine. The respond was strongest at DelA, followed by BB, ECR and FDI, respectively

on the selected segments of spinal cord (C5-C6) could evoke muscle contraction from proximal (DelA) to distal end (FDI) of the upper limb (Figure 5.1). Noted that the amplitude of the EMG recordings may significantly reduce when the electrodes are placed close to the innervation zone. The innervation zone could be concentrated in a narrow band around the muscle belly such as in BB or scattered in wide areas as in DelA, FCR and ECR [Saitou et al., 2000, Nishihara et al., 2010]. Pre-assessment of the sEMG amplitude at the muscle belly could ensure that the selected stimulation intensities were capable for evoking muscle contractions even when the electrodes were coincidentally place on the innervation zone. The Motor threshold was determined by gradually increasing the peak stimulation current from 10 mA to 100 mA in a ten mA-increment step; then, the step was finer when the motor threshold was nearly reached to obtain a recruitment curve of all the muscle responses simultaneously. A circular stimulation electrode (cathode, 3.2 cm diameter ValuTrobe Cloth, Axelgaard Manufacturing) was placed between C5 and C6 spinous processes. The position was selected based on the location that elicited a motor response in DelA, BB, FCR, ECR and FDI. Two rectangular anodes (5x9 cm ValuTrobe Cloth, Axelgaard Manufacturing) were bilaterally attached to clavicolae to induce a posteroanterior directed current perpendicular to the spine.

During the main experiment of the spinal cord stimulation, the patients were asked to induce

postural tremor by stretching their most affected arm outstretched against gravity at the shoulder level, as postural tremor is one of the common characteristics of the ET. If the tremor disappeared, the patients were asked to count backwards or answer experimenters' questions to distract and trigger the tremor.

One of the burst-modulated alternating current forms, Russian currents, was used for the stimulation. Russian currents are alternating currents of high kilohertz-frequency delivered in slow bursts in the physiological frequency range of up to 100 Hz. We utilized the Russian currents as it was suggested that modulation of high frequency by delivering them at a slower frequency could reduce pain and discomfort occurring during the stimulation since the high frequency of the applied current is inversely correlated with the skin impedance [Ward and Robertson, 1998, Ward, 2009]. As applying the high-frequency alternating currents could reduce the skin impedance, it also increase electrical energy reaching the nerve underneath skin tissue. This high-frequency stimulation therefore, could be more beneficial than electrical stimulation at low-frequency currents as it is essential for stimulating deep muscle nerves and could improve muscle strength [Eisdorfer et al., 2020, Seáñez and Capogrosso, 2021].

Study of [Currier and Mann, 1983] has suggested that Russian current stimulation with 2.5 kHz frequency and modulated at 50 Hz could improve torque when the stimulation was combined with exercise compared to control (no stimulation and no exercise). Furthermore, [Cittadin et al., 2021] has investigated and compared the Russian current of 2.5 kHz modulated at 50 Hz and Aussie currents, which utilized medium-frequency currents of 1 kHz carrier frequency modulated at 50 Hz with pulse duration of 2 ms, in the force gain of the women forearm muscles responsible for the grip. The results show that the Russian current is proven to be optimal for increasing force gain and muscle thickness. In addition, the high-frequency stimulation does not directly generate nerve firings at that high frequency, but the effect of the stimulation is instead a result of the summation of the high-frequency pulses that modulates the depolarization of the nerve fibers. The muscle nerves, therefore, did not respond at high frequency but at the slow burst frequency in the physiological frequency range. Thus, the effect of the high-frequency stimulation should not variate much from the effect of slow burst frequency stimulation.

We used 5 kHz as the carrier frequency, and the stimulation burst frequencies were set at patient-specific tremor frequency (alpha band) and 21 Hz (beta band) [Ward, 2009, Guiho et al., 2021]. The five-kilohertz carrier frequency was selected as it was demonstrated that setting carrier frequencies between 1 to 10 kHz could reduce pain, sensory and motor threshold of arm muscles [Ward and Robertson, 1998]. The burst frequencies were selected based on the hypothesis that the tremor frequency stimulation could activate the inhibitory interneurons at the tremor frequency and counteract the tremor. The stimulation of the beta band was selected as it is within the frequency range of frequently recorded cortico-muscular coherence, an approach for measuring synchrony between neural signals and associated muscles during voluntary tasks [Liu et al., 2019].

As shown in Figure 5.2, each burst of slow stimulation was filled with five biphasic pulses of 100 μs pulse width to generate a 5 kHz carrier frequency of 1 ms duration. In case the tremor frequency was 5 Hz, for example, each burst will be at a distance of 199 ms to another to deliver five stimulation bursts in 1 s. The stimulation intensity was determined as 10 mA lower than the patient's motor threshold or below the pain threshold of the patients. The stimulation was controlled using CED 1401 interface with Signal software (Cambridge Electronic Design) and delivered biphasic pulses through Digitimer DS8R (Digitimer, Welwyn Garden City, UK, Figure 5.3).

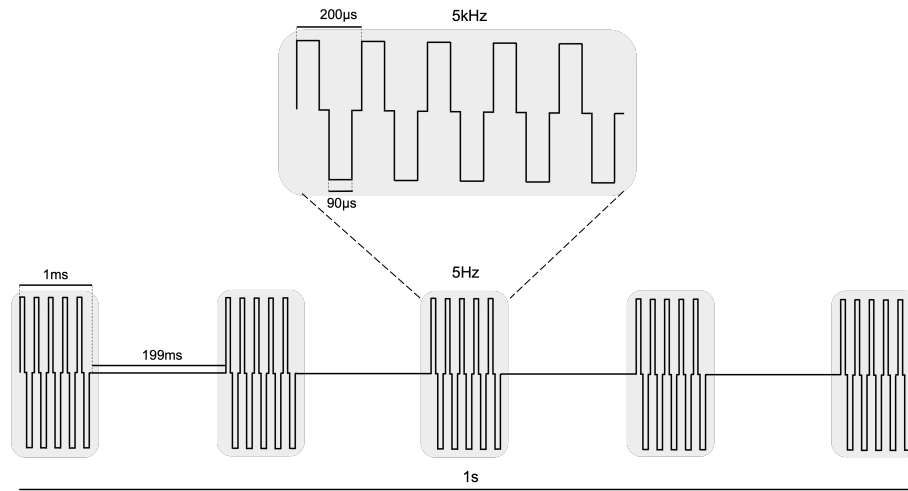


Figure 5.2: Example of Russian currents stimulation of 5 kHz carrier frequency with 5 Hz modulated frequency burst. Each burst of the stimulation consists of 5 biphasic pulses of 100 μs pulse width to generate a 5 kHz carrier frequency of 1 ms duration. The distance between bursts determines the modulation frequency of the stimulation. In case that the modulation frequency was 5 Hz, for example, each burst will be at a distance of 199 ms to another to deliver five stimulation bursts in 1 s.

High-density surface EMG of 64 channels (13x5 matrix Ag/AgCl electrodes with 8 mm inter-electrode distance) were used to record wrist extensor and flexor muscle groups of the most affected limb. Skin preparation was done using alcohol and scrub to reduce electrode shift and electro-skin resistance. The electrodes were placed parallel to muscle arrangement centered at the belly of extensor and flexor muscle groups. Two wet wrist braces were used as a common ground and patient reference. The signals were recorded using Quattrocento (OT -bioelettronica <http://www.otbioelettronica.it>). The signals were amplified, filtered (10–500 Hz), and sampled for offline analysis at a 2048 Hz sampling frequency. A medical ground pad is attached to the centre of the BB muscle referencing to the EMG reference to reduce the contamination of stimulation artefact on HD-EMG recordings. Tremor movement was recorded using triaxial *accelerometer* (ACC) placed on the dorsal surface of the most affected hand, digitized via the CED 1401 and sampled at 5 kHz (Figure 5.3).

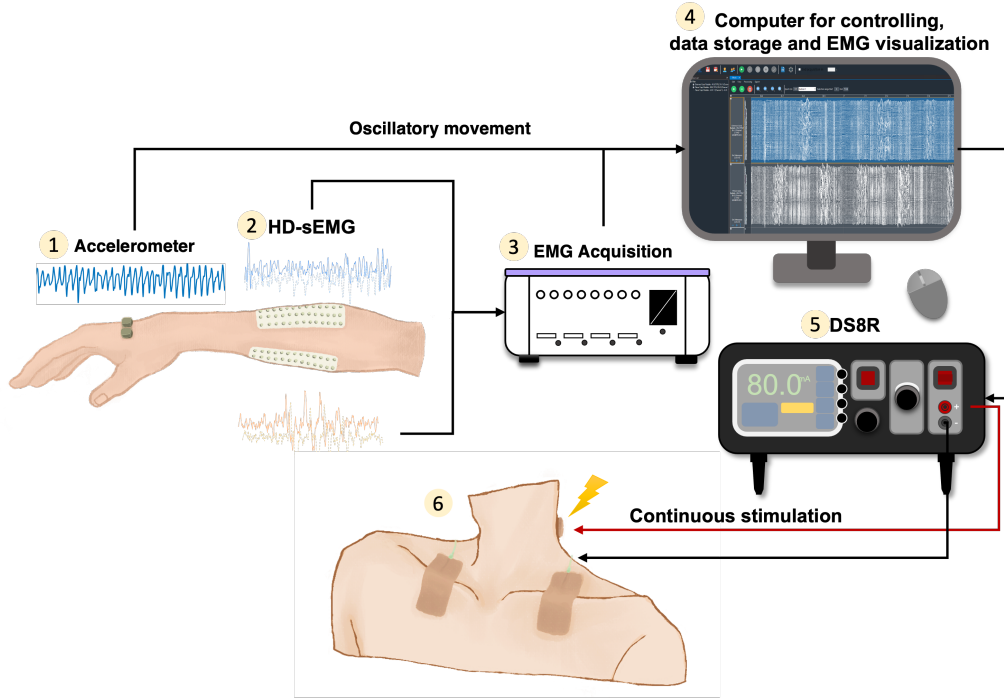


Figure 5.3: Experiment set up. The accelerometer and HD-sEMG were attached to the back of the hand, extensor and flexor muscle, respectively, to record hand and wrist movements. The ACC data was collected using Signal software, and the sEMG data was acquired and amplified via Quattrocento. The data was visualized and stored in a computer for further offline analysis. The stimulation was also programmed via the Signal and delivered through DS8R to the cervical spine at the C5-C6 level.

The patients were blind to the stimulation order. For each stimulation frequency, 60 s of EMG and ACC data were recorded after the patients lifted their affected arm outstretched and remained in the position at shoulder level. Four trials of baseline tremor movement without the stimulation and each stimulation frequency (randomly delivered) were recorded; thus, the total recording was 12 trials for baseline and two stimulation conditions. The patients were allowed to rest between each trial to prevent fatigue.

To estimate the dominant frequency of the tremor (DTF), the ACC data were filtered at 3 to 10 Hz (2nd Butterworth bandpass filter). Welch's PSD was used to decompose frequency contents of the data (Pwelch method: window = 10k samples, overlapped samples = 2.5k, nfft = 10k, sampling frequency = 5000, frequency resolution = 0.5 Hz). The DTF was determined as the frequency at the peak power of the PSD. Band power of the tremor during the baseline (no stimulation) and stimulation conditions, which were calculated as the integral of power spectrum over 2 Hz-frequency bandwidth around the DTF, were estimated and compared. We quantified the tremor power modulation by calculating the power ratio between the baseline and stimulation conditions in percentage. The ratios higher and lower than the baseline imply the facilitation and inhibition effect of the stimulation on the tremor, respectively.

We used phase difference analysis to investigate if the change in the tremor amplitude is related to the phase difference between the phase of the stimulation and those of tremor oscillation during baseline (stimulation off, PD_{SB}) and stimulation at the tremor frequency (stimulation on, PD_{ST}). Synthesis sinusoidal oscillations were generated at the same phase as the stimulation to compare with the phase of the tremor oscillation. Instantaneous phases of the sine wave and the filtered ACC recordings were calculated using the Hilbert transform and subtracted to acquire the phase difference. The relationship between the phase difference and instantaneous amplitudes of the ACC data, which were the absolute values of the Hilbert transform, was observed by plotting the phase difference against the instantaneous amplitude averaged over 10 degrees of the phase difference.

5.3.3 Statistical analysis

Shapiro-Wilk parametric hypothesis test was used to assess the normality of the data. Kruskal-Wallis analysis was used to compare the power of the tremor at baseline and after stimulation, if the data sets were non-parametric, followed by Wilcoxon Rank Sum Test to compare tremor power between individual conditions. The correlation between the PD_{SB} or PD_{ST} and the tremor amplitude was estimated using Spearman's correlation coefficient. The null hypothesis was rejected and accounted as significant when the p-values < 0.05 .

Table 5.1 Summary of patient data.

Patient	Age	Hand Tested	Disease Duration (years)	Treatment	Tremor Severity ¹	Motor Threshold (mA)	Stimulation Intensity (mA)	Tremor Frequency (Hz)
1	70	right	25	none	67	110	55	5
2	43	left	20	clonazepam 1mg	20	53	33	6
3	72	right	10	none	14	80	70	4.75
4	77	right	8	none	44	70	55	6
5	79	left	15	Botulinum toxin injections	40	90	40	6.05
6	70	right	20	Propranolol 20mg	18	100	30	4.75
7	71	right	5	propranolol 120mg	22	100	50	5.7
8	86	right	27	bisoprolol 2.5mg	39	90	70	5
9	74	right	35	Botulinum toxin injections	44	60	50	6.75

¹ Fahn - Tolosa - Marin tremor rating scale.

5.3.4 Results

Table. 5.1 summarizes the clinical information of the patients. The averaged motor threshold was 83.7 ± 19.4 mA ranging from 53 - 110 mA (peak values). The stimulation intensities which were determined by the motor and pain thresholds of the patients had the average of 50.3 ± 14.3 mA.

PSDs of all patients showed peaks within the tremor frequency range (3 to 10 Hz), with the average of 5.6 ± 0.7 Hz ranging from 4.8 to 6.8 Hz. Figure 5.4 shows comparison of ACC recordings of two representative patients during baseline (blue lines) and stimulation at the tremor frequency (Stim-Trm, red line) (Figure 5.4a, 5.4c). The PSDs from four trials of each condition were plotted in Figure 5.4b and 5.4d (dashed line) with their average (thick line). The comparison of the tremor band-power of all patients showed that there was a reduction in the power of the tremor when the spinal cord was stimulated at the tremor frequency ($P - value = 0.048$, Kruskal-Wallis analysis), but there was no significant difference between the power of the tremor at baseline and with 21Hz stimulation ($P - value = 0.41$, Kruskal-Wallis analysis). Figure 5.5 shows the comparison of the tremor power in three conditions: baseline, tremor frequency and 21-Hz stimulation. We have

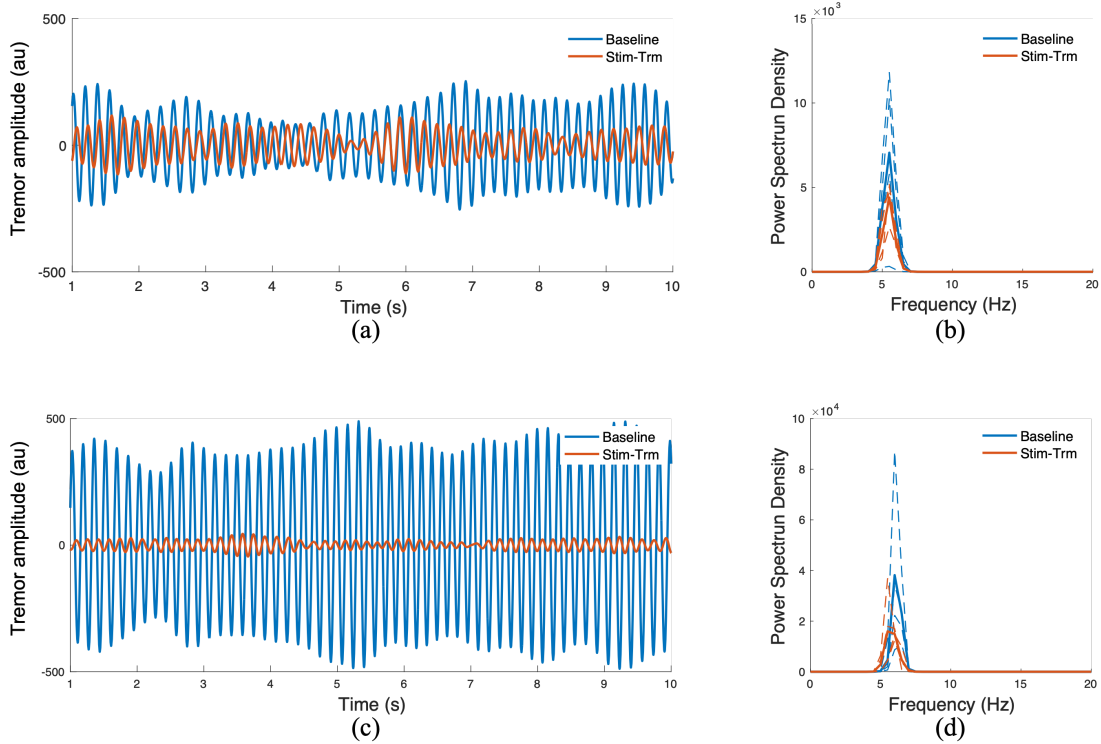


Figure 5.4: Comparison of ACC recordings of two representative subjects (a and c) and the PSDs from four trials of baseline (blue dashed lines in b and d) and stimulation at tremor frequency (red dashed line, Stim-Trm). The blue and red thick lines in b and d are the average PSDs of each case. The reduction percentages of these patients were 47.8% and 91.8%, respectively. The PSDs of all trials have a peak within the tremor frequency. au, Arbitrary units.

divided the tremor power of all conditions by the baseline to create a tremor power ratio for better visualization. The average reduction percentage from only 8 patients whose tremor reduced was $43.3 \pm 25.5\%$. It can be seen that the average tremor power of 8 out of 9 patients reduced after the stimulation at the tremor frequency, whereas there was no significant trend of tremor power after the 21-Hz stimulation. Figure 5.6 shows the histogram of the phase difference PD_{SB} (Figure 5.6a and 5.6c) and PD_{ST} (Figure 5.6b and 5.6d) in 36 bins of two representative patients. The red circle lines are the average instantaneous amplitude of the tremor corresponding to the phase difference in each bin. Although a correlation between PD_{ST} and the tremor amplitude can be observed such as in Figure 5.6b ($R = 0.7, P - value = 4.4 \times 10^{-7}$), on the average from all of the patients, there was weak correlation between amplitude and PD_{ST} ($R = 0.05, P - value = 0.06$) neither the correlation between amplitude and PD_{SB} ($R = 0.01, P - value = 0.72$).

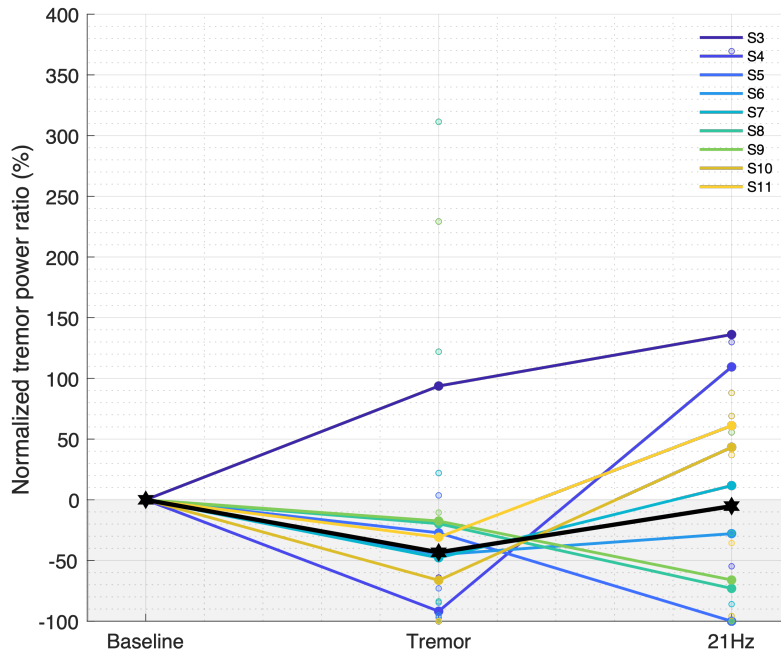


Figure 5.5: Comparison of tremor power ratio between baseline, stimulation at tremor frequency and stimulation at 21 Hz. In 8 patients, the average tremor power reduces compared to the baseline when the subjects were stimulated at their tremor specific frequencies ($43.3 \pm 25.5\%$ reduction, $P - value = 0.048$, black star line). However, the average tremor power showed no significant difference between the baseline and 21-Hz stimulation ($P - value = 0.41$).

5.3.5 Discussion

Postural tremor at the wrist of 9 ET patients was recorded during spinal cord stimulation at the C5-C6 cervical spine. The tremor oscillation was recorded using a triaxial ACC attached to the dorsal surface of the hand. Power spectrum analysis of the ACC recordings of all patients

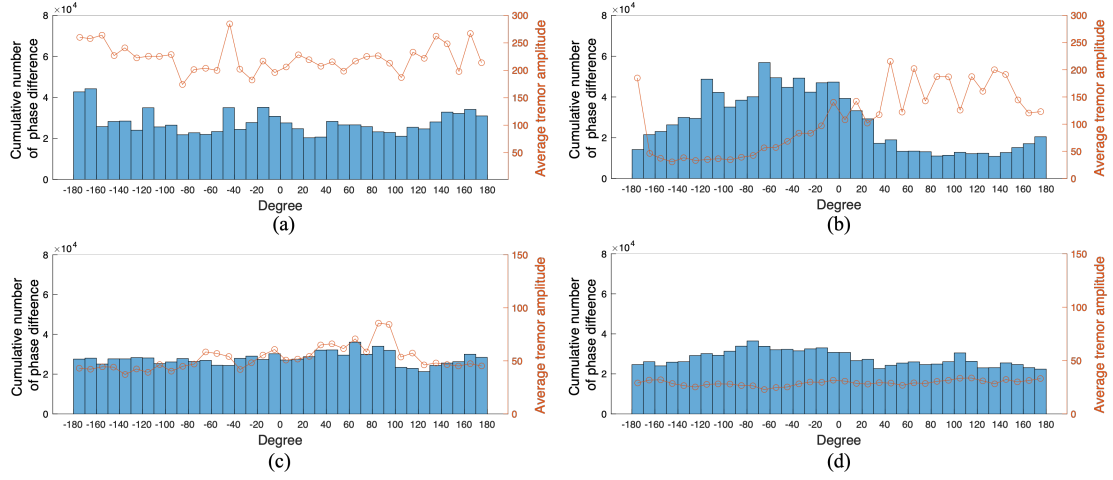


Figure 5.6: Histogram of the phase difference PD_{SB} (a and c) and PD_{ST} (b and d) in 36 bins of two representative patients. The red circle lines are the average instantaneous amplitude of the tremor corresponding to the phase difference in each bin. On the average, the phase difference are not related to the change in the tremor amplitude.

showed tremor peaks within the tremor frequency band (3 to 10 Hz). There was a reduction in the power of the tremor during spinal cord stimulation at tremor frequency compared to the baseline condition. Increasing of the stimulation frequency to the beta band provides variant effects to the tremor power.

As a convergence of upper motor neurons from the brain, interneurons, and lower motor neurons to the muscles, the spinal cord has been a target for neuromodulation of motor control. SCS has been intensively used for pain relief [Jensen and Brownstone, 2019, Tapias Pérez, 2021] and improving muscle strength in patients with SCI [Eisdorfer et al., 2020, Seáñez and Capogrosso, 2021]. The SCS was also beneficial in improving tremor [Fénelon et al., 2012, Thiriez et al., 2014, Russo et al., 2018]. While the mechanism of SCS associated with pain relief or motor disorder symptoms related to muscle weakening such as in cerebral palsy, SCI or dystonia have been revealed for decades, the effects of SCS on tremor is not very well understood. Most of the literature related to the SCS treatment for tremors was mainly focused on treating Parkinson's patients [Fuentes et al., 2009, Fénelon et al., 2012, Cai et al., 2020, Nishioka and Nakajima, 2015]. Only one recent studies have reported the use of SCS for ET treatment [Russo et al., 2018].

It was suggested that the SCS could initiate neuromodulation in the dorsal column, which is the closest spinal structure to the stimulation electrodes. The dorsal column is a termination point of afferent sensory neurons and is essential for sending the sensory information to the sensory cortex, and thalamus [Kleinfeld et al., 1999]. Proprioceptive sensory neurons peripherally project their axons to receptors like the Golgi tendon and the intrafusal muscle fibers of muscle spindles in a muscle. The neurons send information associated with the muscle dynamics such as muscle length,

velocity and tension centrally back to the brain and the spinal cord while also direct/indirectly synapse with motor neurons of the same muscle (homonymous motoneurons) or its antagonist muscle (heteronymous motor neurons) [Proske and Gandevia, 2012]. Proprioceptive sensory neurons include medium to large diameter neurons such as Ia, Ib and II afferent groups. These neurons play a significant role in coordinated motor output, controlling movement, stabilization and locomotion of the body [Fumiyasu and Yutaka, 2017]. Specifically, the SCS increases the activation of medium to large diameter sensory neurons. This increased sensory input subsequently facilitates the outputs from the motor cortex and thalamus, thus promoting the excitability of neurons in their pathways to muscle. In contrast, the SCS could inhibit the small-diameter sensory neurons conveying pain information. The SCS is therefore used for pain treatment [Rattay et al., 2000, Mendell, 2014, Jensen and Brownstone, 2019]. The SCS does not only affects the dorsal column but may modulate deeper to the dorsal column nuclei [Qin et al., 2009]. These neurons indirectly modulate the activity at the cortical level, such as the primary motor cortex and cerebral cortex [Stančák et al., 2008].

In addition, computational simulation of the SCS on animal spine suggested that the SCS could excite fibers in the dorsal root, spinocerebellar tract, and corticospinal tract [Greiner et al., 2021]. The cerebellum, spinocerebellar tracts, and reticulospinal tracts are crucial in adjusting and reducing predicted and actual movement errors for a task-specific movement. The motor command is estimated from the cerebellum to perform a refined movement. At the same time, those estimated motor commands are predicted and copied via the reticulospinal tract. This motor copy is fed back to the supraspinal to predict further the additional command required for achieving the remaining movement error through spinocerebellar tracts. The mechanism is real-time adjusted until the desired movement is reached and associated with generalization learning of the brain for the repetitive movements [Kawato, 1999, Zuccaro, 2013]. There is evidence that SCS may facilitate the motor copy of the reticulospinal tract while also enhancing the excitability of the afferent neuron as an Ia group. This could increase baseline potential to easily recruit interneuron and motor neuron activation [Kim et al., 2017, Eisdorfer et al., 2020].

In this study, we found a reduction in tremor power measured as the peak of the PSD of the ACC recordings during continuous tESS at tremor frequency. This is possibly due to various possible effects of SCS on the dorsal column and its pathways to the upper brain regions associated with the tremor, such as the motor cortex and thalamus. In an animal experiment where the PT was induced by dopamine depletion and lesion in 6-OHDA, a shift in neuron firings in the primary motor cortex to the state that the neurons were ready to initiate movements and improve in the locomotion was demonstrated after the animal received the dorsal column stimulation [Fuentes et al., 2009]. This study has revealed the involvement of the pathways between the dorsal column to basal ganglia and primary motor cortex in the SCS mechanism. Since the thalamus is also a target for the DBS, the SCS might indirectly interact in a similar mechanism as the DBS does to reduce tremors. Although the tESS has less segmental selectivity than the ESCS, and electrode-skin properties influence its effects, the neuromodulation mechanism of the tESS is likely to be the same

as the ESCS.

Stimulation parameters such as amplitude and frequency of the stimulation could play a crucial role in variation of tremor modulation effects. The frequency of the stimulation could range from 20 to 1000 Hz [Thiriez et al., 2014]. Our study used Russian currents of 5 kHz carrier frequency with modulated slow bursts at tremor and 21-Hz frequencies as the Russian currents induced less pain and discomfort even when high stimulation frequency was delivered [Ward and Robertson, 1998, Ward, 2009]. Furthermore, the summation of the high-frequency stimulation could significantly promote depolarization of the nerve fiber, enhancing the excitability of the system. We found that the stimulation of the slow burst at the tremor frequency reduced the power of the tremor oscillation. Unlike the stimulation at 21 Hz, the tremor power could increase or decrease from the baseline. We hypothesize that the stimulation at tremor frequency might interfere with the sensorimotor pathways and counteract the oscillation at the tremor frequency [Hellwig et al., 2001]. Precisely, the tESS may modulate the tremor activity by directly enhancing the excitability of proprioceptive sensory neurons of agonist muscle which in turn activates inhibitory interneurons that inhibit the antagonist muscle activity and compensate for the oscillation at the tremor frequency [Proske and Gandevia, 2012]. The tESS may also increase the release of GABAergic neurotransmitters, inhibiting the impaired neural activation in the cortical region at tremor frequency [Hofstoetter et al., 2018, Raethjen et al., 2000]. Whereas the higher-frequency stimulation at 21 Hz may enhance the tremor by promoting the excitation of neurons to increase the number of neurons recruited and their firing rate. 21-Hz stimulation might also synchronize with the descending inputs in the central brain regions facilitating the overall activity of the muscles. However, this study lacks the analysis of MU firing patterns weakening this hypothesis. The analysis of the MU firing patterns, especially a comparison of the behavior of the same MUs during baseline and stimulation conditions, could provide an assessment of the change in MU firing rate, depression or facilitation effects of the firings after each stimulation pulse, and modulation of the MU oscillation power during different stimulation timing (delay between the stimulation and the tremor). Further investigation of the changes in MU firing patterns after the stimulations are, therefore, required to support the suggested hypothesis.

We investigated the optimized timing of the stimulation by assessing the correlation between phase difference (between the stimulation phase and the phase of the tremor) and the tremor amplitude. We hypothesized that there might be a stimulation timing that could significantly reduce the tremor amplitude. However, we found that there was a weak relationship between the phase difference and the tremor amplitude and the relationship was non-linear. This might be interpreted that the stimulation timing may be to some extent relevant to the reduction of the tremor but the pattern of this relationship was unclear. Having a greater number of samples in each trial (longer recordings) may reveal more about the effect of the different stimulation timing.

In comparison to afferent stimulation at the peripheral nerves (utilized in Chapter 4), the

spinal cord stimulation could be more beneficial in modulating sensory and motor neuron excitation, possibly due to the stimulation site that is directly delivered close to the dorsal root connecting both ways toward the brain and the skeletal muscle fibers. Since the peripheral sensory nerves, the target of the afferent stimulation, have an anatomical feature that increases the chance of action potential propagation failure, i.e., the split axon at the soma (T-junction) makes the transmission unreliable [Gemes et al., 2013]. Avoiding the failure by stimulating directly on the spinal cord may preserve the possible effects of the stimulation. In addition, the patients were likely to be more tolerant to the higher stimulation intensities when they were delivered using the Russian currents at the spinal cord than at the peripheral nerves (the intensities used were in the level of 50 mA and 10 mA for the spinal cord and peripheral nerve stimulations, respectively). The spinal cord stimulation system could also provide a better appearance as it can be hidden underneath their clothes. However, significant improvement in the design of the spinal cord stimulation system is needed as it requires a high stimulation intensity generator and could be used as a closed-loop system as well.

Noted that this study lacks the analysis of the MU decomposed from the concurrently recorded HD-EMG during the stimulation. This is because the EMG recordings were contaminated by the high amplitude of the stimulation artefacts, allowing only a few MUs discriminated in each trial. Although the artefacts may have a more negligible effect on the analysis of the ACC recording as the stimulation position was at a distance to the ACC recording area, the artefacts severely affect the EMG recording as the large amplitude of the artefacts could eliminate the small MU action potential patterns recorded by the EMG. This low signal-to-noise ratio significantly reduces the decomposition performance. The small number of MU spike trains is insufficient to drive to a conclusion about MU behavior after the stimulation. An adequate number of MU spike trains is needed to ensure valid estimation of the analysis of MUAPs since individual MU is nonhomogeneous [Podnar and Mrkaic, 2003]. Even though we have used medical ground to help removing the amplitude of the artefact, a better artefact removal technique is required to improve the quality of the EMG recordings.

5.4 Conclusion

In conclusion, this study suggested that the tESS with the sub-threshold intensity at tremor frequency over the cervical spine might be another means for non-invasive tremor suppression preferable to the deep brain stimulation or ESCS. This study could not confirm the mechanism underlying this reduction but suggested the involvement of the cortical inhibition and sensory feedback agonist-antagonist muscles.

Chapter 6

Conclusion and Future Work

This chapter is a review of the studies presented in this thesis and a discussion of the research key points, limitations and suggestions for future work.

Chapter 1.

introduced the motivations and objectives of the thesis, followed by the structure of the thesis.

Chapter 2.

presented a brief review of important topics related to the theme of the thesis. It includes

1. Physiology of motor control and force generation.
 - How the CNS and PNS involve in muscle control and their connections to muscles through cortico-muscular tracts.
 - Communication between motor neurons, interneurons and muscle fibers via propagation of action potentials.
 - MU recruitment and rate coding for force modulation.
 - Linearity of motor neurons
 - EMG for recordings of MU activities and development of recording techniques and decompositions.
2. Physiology of tremor.
 - General characteristics of the tremor.
 - ET: Origins, prevalence and effects on ADL.
 - Possible causes of tremor and model of tremor generation.
 - Development of non-invasive treatments for tremor inspiring this research study.

Chapter 3.

is the physiological study of the tremor via the analysis of MU discharge timing. MU spike trains decomposed from EMGs of wrist extensor/flexor muscle of 13

ET patients were analyzed. Coherence and power spectrum analysis was used to investigate the features of the MU spike trains individually and as a pool of MUs by summation of all the MUs detected to represent their population behaviors. Relations between voluntary and involuntary (tremor) movements were estimated by comparing their phase differences.

1. **Main outcomes.**

- A motor neuron pool acts as an amplifier of shared inputs projected to individual motor neurons whilst it filters out other frequency components that are not common. This ensures that only the common command from the CNS will be emphasized and smooth out the less relevant neural activity.
- A few number of MUs are sufficient for capturing the strength of shared inputs projected to the muscle.
- MUs within an agonist muscle receive shared inputs from the CNS at voluntary and tremor frequencies. Whereas part of these inputs can be shared with its agonist muscle, the coherence analysis revealed that these shared inputs are less influenced between agonist-antagonist muscle pairs suggesting an involvement of other independent inputs projected individually to each muscle.
- Positive correlation between the power of the voluntary movement and tremor suggested that tremor-related neural inputs could be captured by the MUs in the same way as the voluntary command and are common to the MU neuron pools.
- Enhancing of the voluntary command to induce higher force increases the number of MUs recruited. More of the tremor-related inputs are, therefore, captured by those MUs increasing the power of the tremor.
- Power spectrum of the MU activities are concentrated between the frequency of 3-10 Hz, which is within the frequency range of central oscillator in the CNS, such as in the motor cortex and cerebellum, suggesting that the tremor might originate from these regions.
- Power spectrum of the MU activities also showed small peaks of harmonics suggesting the involvement of limb resonance due to stretch reflex loop, which may be projected to each muscle as an independent input.
- Phase analysis of muscle activities at the tremor frequency reveals that agonist-antagonist muscles are activating alternately with the average phase difference close to an out-of-phase during the postural tremor.

Whereas the phase difference of agonist-antagonist muscle activities at voluntary frequency were in-phase reflecting co-contraction of the muscle while maintaining the arm posture.

- Difference in the phase of MU activation during voluntary and tremor movements leads to a rationale that the MUs may respond independently to the voluntary and tremor commands but the sum of these commands generates the overall tremor movement.
- The phase analysis also showed that the phase of the tremor varies over time.

2. **Limitations.**

- This study was based on the EMG recordings alone without any concurrent EEG recordings limiting the interpretation of the study to confirm an involvement of a central oscillator.
- Relatively wide area of HD-EMG electrodes may record the influence of a group adjacent to muscles (crosstalk). The extensor and flexor muscles were referred to extensor and flexor muscle groups, respectively. The crosstalk may reduce the accuracy of the coherence analysis.
- The study was only investigated during postural tremors where the patients were asked to have their arms outstretch against gravity with the hand in pronation position. Changing the position of the hand to supination may affect muscle activity as there is a rotation of radius and ulna bones and muscle twitches. Gravity might also influence differently to extensor and flexor muscle groups during the tremor. It is interesting to investigate the differences in agonist-antagonist muscle activities during pronation/supination since the partway of the neural drive to the muscle are the same; the differences may lead to further elucidation of gravity and muscle spindle reflex effects on the tremor.
- Although the patient's forearms was supported with an armchair during the experiment to reduce fatigue and the force exerted was relatively low as the task was only to maintain the hand outstretched. However, at a higher force level, fatigue might play a crucial role in enhancing the tremor. Further investigation of phase and coherence analysis during high force levels is needed.

Chapter 4.

Design of close-loop tremor suppression system. A system of transcutaneous electrical stimulation for tremor suppression was designed. Sub-motor threshold stimulation was used, and stimulation time was estimated based on MU activities

during the tremor. The system consists of an online decomposition of HD-EMG recordings, which discriminate the signals into MU spike trains. The decomposed MUs were connected to a PLL system to track the phase of the MU activity in real-time. This phase was used to activate a portable stimulator to generate an electrical pulse. This chapter reports validations of the online decomposition algorithm and the phase estimated by the PLL system using 13 pre-recorded ET data. Later in the chapter, the test of the system on an ET patient was presented to prove the concept of the system.

1. **Main outcomes.**

- Approximately 10 s of the MU spike trains could represent the shape of the MU action potentials assessed using the spike trigger average technique.
- The validation of online decomposition in data collected from ET patients shows that the online decomposition using 10 s of the MUAP template provides equivalent performance as the offline decomposition.
- PPL system accurately estimates the phase of low-frequency signals.
- Preliminarily test of the closed-loop online test demonstrated that all system parts correctly work in conditions similar to the target clinical application.

2. **Limitations.**

- Electrical stimulation generates artefacts that hamper the EMG recorded. These artefacts could reduce the accuracy of the decomposition. The blanking technique used in the study might remove not only the artefacts but also the actual MU activities. In order to avoid this, a better artefact removal method should be added to the experimental protocol or in the pre-processing step. For example, by adding a ground electrode between stimulation electrode and the EMG electrodes may reduce the amplitude of the artifacts or adding an artefact filter to the EMG before the decomposition step.
- There was a minimum cycle needed for the PLL to estimate the phase of the signal. The PLL produces a synthesis signal with the phase at a pre-defined angle and needs at least a cycle to adjust its initial phase to match the reference signal. The stimulation timing of that cycle might not match with the phase of the tremor, influencing the level of the tremor suppression.
- The PLL system with the set-up reported in the Material and methods section of the chapter was validated with the EMG recordings of

postural tremor when the patient maintains the arm outstretched. Changing the arm position or abrupt motion could lead to an error in the estimation of the phase of the MU activities.

- Pulse width and frequency of the stimulation used in this study were selected from the literature. Modification of these parameters could change the performance of the suppression system. Further study is required to compare the results after the variation of the parameters. A personalized stimulation setting might be required to improve the performance of the system.
- This study has been tested with only one patient. We could not conclude if the system was effective for tremor suppression. Further validation of the system with more patients and different types of tremors is required.

Chapter 5.

is the study of the effects of tESS on the amplitude of the tremor in ET patients. The tremor was measured by a triaxial accelerometer placed on the dorsal surface of the hand. A Russian currents stimulation of 5 kHz modulated at tremor and beta frequency was used to stimulate the cervical spine of the patients at the C5-C6 level.

1. Main outcomes.

- In 8 out of 9 patients, the tremor amplitude was reduced when they were continuously stimulated at patient-specific tremor frequency. While the stimulation at the beta band provided inconclusive effect on the tremor amplitude.
- The phase of the tremor oscillation varies over time, according to our study in Chapter 2.
- The phase difference between the phase of the stimulation and those of tremor were not correlated, suggesting that the stimulation timing may not be an essential concern when continuous stimulation was used.
- The tESS at the tremor frequency may counteract the impaired neural activity at peripheral and cortical levels reducing the amplitude of oscillation specifically in that frequency band.

2. Limitations.

- Position of the stimulation electrodes on the cervical spine was estimated by the experimenter without an evaluation of correct positioning via imaging techniques.

- Analyzing of the ACC recording without the analysis of the MU firing pattern after the stimulation limited the interpretation of the neural mechanism underlying the tremor suppression effect of the tESS.
- High amplitude of the stimulation produced artefacts contaminating the tremor recordings. A better artefacts removal is needed to increase the signal-to-noise ratio and help improving the MU decomposition performance.

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