Parkinson's Disease Tremor Suppression
A Double Approach Study - Part 1

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Abstract: Parkinson's Disease (PD) is a neurodegenerative disorder that affects mostly elderly people. Approximately 2% of world population, over 60 years old, lives with PD. This pathology is recognized not only by motor symptoms such as tremor, postural gait and rigidity, but also, nonmotor symptoms as depression and sleep abnormalities may be developed as well. In Brazil, according to the Ministry of Health, 200,000 people face the challenge to develop day-by-day activities due to PD. More than just a disease causing motor disturbances, PD brings to patients uncertainties about their ability to take care of themselves independently. In this context, assistive technologies assume an important position in order to bring back life quality and self-trust to PD patients. This work aims to study techniques, develop hardware and software for a better approach in tremor suppression in order to bring back life quality to PD patients. This study approaches the problem of flexion/extension carpi radialis tremor suppression using two different strategies. The first is a mechanical suppression based on a servomotor opposing to tremor movement. The second strategy is a functional electrical stimulator. Both systems are triggered by electromyogram (EMG).

1 INTRODUCTION

Parkinson's disease is the second most common neurodegenerative disorder in the world, loosing only to Alzheimer's. According to Dexter and Jenner (2013) 2% of the world population, over 60 years old, lives with PD. In Brazil, numbers from Ministry of Health estimates that 200,000 Brazilians are living with PD, among those 75% have tremors as a main symptom (Helmich et al., 2012). As a matter of fact, the increasing life expectancy rates, also increases PD prevalence. Projections from United Nations (UN) indicate that in six decades the elderly population will be 3 times bigger than now, achieving 2 billion people world wide. The Brazilian Institute of Geography and Statistics (IBGE) estimates that in 2050 Brazilian aged population will be around 54.8 million people. Economic related aspects of Parkinson's disease are also relevant. According to Findley (2007), just in the United States, PD moves the economy in 23 billion dollars yearly, considering direct and indirect costs. A PD patient costs on average US$ 10,000 every year in the United States (Dexter and Jenner, 2013).

In this context, assistive technology has a crucial role, not only because market growing projections, but also to help an increasing portion of world population to live without all impairments imposed by PD. This work focus on action tremor and presents two methods of tremor suppression based on a mechanical orthosis controlled by a servomotor and a functional electrical stimulation (FES) system, both of them triggered by eletromyography (EMG). It is organized as follow: Section 1 presents an introductory view and clinical aspects of PD. Section 2 presents alternatives for PD symptoms control. Section 3 presents materials and methods. Section 4 introduces hardware development. Section 5 shows signal processing strategies applied to EMG signal of PD. Finally, section 6 presents results of hardware and software development and tests.

1.1 Clinical Aspects

The central nervous system (CNS) consists of neurons interconnected as a network through synapses

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which includes dendrites and axons. Communication neuron to neuron takes place using neurotransmitters. Neurotransmitters are brain chemical signaling, with inhibitory and excitatory function, which is released at synaptic gap. In this context, substantia nigra pars compacta (SNpc) has as its role dopamine production, a inhibitory neurotransmitter. SNpc is connected with other neuronal structures such as striatum (caudate and putamen), globus pallidus internal and external and subthalamic nucleus, together called basal ganglia as shown in figure 1 (Jankovic and Tolosa, 2006).

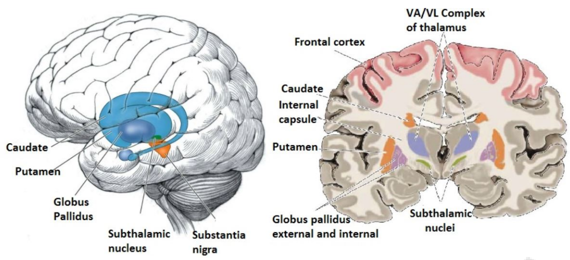


Figure 1: Sagittal and Coronal view. Adapted from Purves et al. (2011).

For PD these structures are quite important because when a ”movement command” is started at motor cortex, the electrical impulses are transmitted through the striatum, which works like a filter. In the case of an voluntary movement, the striatum increases thalamic and cortical neuronal activity making the movement more likely to happen. However, if it is an involuntary movement, SNpc neurons are activated, that in turn use dopamine as inhibitory neurotransmitter, diminishing thalamic and cortical activity suppressing undesired movements. Parkinson’s disease, among many other problems, affects dopamine production causing its diminishment, consequently making striatum hyperactivated and difficulting movement control (Jankovic and Tolosa, 2006).

Some motor symptoms are classically used to diagnose PD such as bradykinesia, tremor, rigidity, postural problems, difficult to speak or swallow. However, there are also some important nonmotor symptoms, even though it is hard to associate them with PD at the first sight, symptoms such as sleep deprivation, depression and cognitive impairment may be observed as well (Helmich et al., 2012).

1.2 Classification and Definitions of Tremor

Tremor can be defined as an oscillatory rhythmic activity, even though many pathologies may cause tremor as a symptom, it is important to emphasize that voluntary movements is accompanied with tremors, and the boundary between normal and pathological tremor is hard to define (Jankovic and Tolosa, 2006).

According to Jankovic and Tolosa (2006) tremors can be largely classified into three categories as resting tremor, action tremor and postural tremor. Resting tremor is defined as the oscillatory manifestation when a limb is not voluntarily activated and completely supported against gravity action. The postural variant is defined when tremor happen on an individual maintaining a position opposed to gravity action. Action tremor is the one which occur concomitantly to muscular contraction for voluntary movement. This work focus on action tremor because it is more disabling than rest and postural tremors (Rahimi et al., 2009).

Another important factor is tremor frequency, also in agreement with Jankovic and Tolosa (2006) it is classified as low, medium and high frequency tremor. Low frequency are tremors with oscillation frequency lower than 4Hz, medium frequency 4 to 10Hz, and high frequency bigger than 10Hz.

2 ALTERNATIVES FOR PD TREMOR SUPPRESSION

Regular treatment for PD has not change too much over the last decades. It is based on dopaminergic drugs intake, due to inefficiency in some cases, or even side effect, new technologies have been developed to reduce Parkinson’s disease effects on daily life. Some initiatives are extremely invasive, such as Deep Brain Stimulation (DBS), and presents inherent risks of a surgical procedures and promising results. Others are non-invasive technologies some for tremor suppression on the limbs such as FES and orthoses, or for tremor handling devices such as Lyftware and Gyroglove, trying to avoid tremor related inconveniences. It is important to emphasize that until present moment all approaches, pharmaceuticals or not, treat just PD symptoms and do not avoid disease progression, and consequently worsen of associated symptoms.

2.1 Deep Brain Stimulation (DBS)

Deep Brain Stimulation (DBS) is one of the most sophisticated neuromodulation techniques in the world today. It is analogous to a pacemaker as presented in figure 2, but differently from a pacemaker it applies electrical impulses to deep structures into the brain, with the objective of change or modulate electrical activity in important structures for motor disorders

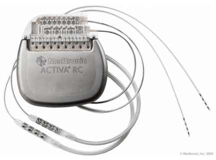


Figure 2: Deep Brain Stimulation Device - Illustrative figure adapted from Medtronic Catalog.

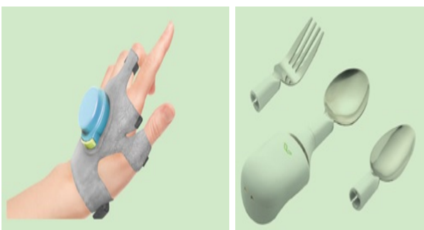
(Oluigbo et al., 2012). It is an alternative for drug resistant patients.

Although DBS has been considered a highly efficient method (70-90% successful rate), a large list of cons must be considered. First of all surgery for DBS implantation are highly invasive, and also two surgical procedures are needed for implantation. Its surgery risks, may include infection, hemorrhage or even implant rejection. These risks may be increased with patient's age and previous health conditions. Secondly, DBS surgery is not yet an world wide affordable treatment.

2.2 Lyftware and Gyroglove

Fortunately not all tremor handling technologies are invasive or risky. Utensils for daily routine improvement are also being developed. Technologies such as Liftware 3(b) or Gyroglove 3(a) may be one step in direction to PD patient life quality. According to Mertz (2016), the idea behind lyftware was not only create a technology which compensate tremors while people are eating, but also that patients had the experience of using fork and spoon as any other person. All sensors and processing are placed at the spoon handle, and the implemented algorithm compensates tremor through mechanical actuators continuosly.

Another initiative is Gyroglove. The project consists of a glove equipped with gyroscope, and through the angular momentum conservation principle oppose to tremor. It is achieved varying gyroscope spin velocity. After tests in July 2015 in an essential tremor patient with positive results, Gyroglove's team believe clinical trials will begin at the end of 2016.



(a) GyroGlove (b) Liftware

Figure 3: Assistive new technologies for tremor handling (Mertz, 2016).

2.3 Functional Electrical Stimulation - FES

Functional electrical stimulation has been defined by Sujith (2008) as the electrical stimulation of muscles deprived of nervous control in order to improve impaired motor function. According to Lynch and Popovic (2008) contractions generated using FES can be coordinated to actuate joints by stimulating muscles that exert torque about the joint. In this technology, electrical stimuli is delivered to the patient through surface or implanted electrodes. Other studies such as Maneski et al. (2011) and Zhang and Ang (2007) have used FES as a tremor suppression alternative.

2.4 Orthoses

Orthoses are devices used to imobilize, mobilize, adjust, alleviate or stabilize limbs affected by motor disorders or accidents with motor impairment. As any other medical treatment, they must be prescribed by an specialized physician (Ottobock, 2016). As biomedical engineering advances, orthoses perform an important role in rehabilitation, being applied for a large number of health problems. According to Rocon et al. (2005), upper limbs rehabilitation is based on affected joint stabilization. Orthoses can be considered rehab robots used to apply forces or mechanical charges to determined limb. Studies developed by Hogan (1984), and clinical observations made in the following years have shown that tremor answers in different ways to biomechanical charges, acting as a parallel impedance to the affected limb. This impedance change has direct effect on tremor. This property of biomechanical systems brings the possibility to satisfactory handle upper limb tremors using an orthoses approach (Hogan, 1984; Rocon et al., 2005). Some works such as those from Taheri et al. (2014), Seki et al. (2011), Rahimi et al. (2009) and Rocon et al. (2005) were developed for tremor handling with application of orthoses.

3 MATERIALS AND METHODS

This work was divided into three parts consisting of candidates selection, electromyography (EMG) signal acquisition for prototyping purposes and clinical tests. All procedures described in this section were submitted and approved by Plataforma Brasil ethical committee. Medical aspects such as patient selection were performed by neurologists from Federal University of São Paulo (UNIFESP).

As part of the first stage of this work three PD patients, with tremor as main symptom, were selected in accordance with Hughes et al. (1992) and United Kingdom Parkinson's Disease Society Brain Bank criteria, and one healthy volunteer was selected for control purposes. Initially, all four volunteers were clarified about this work risks, tests and possible achievements. After their agreement and signature of control documentation a questionnaire was applied to each one individually, in order to assess any other medical conditions that might be relevant to this work. After that, all patients were familiarized with the procedure for EMG acquisition and aspects related to both systems in development, FES and mechanical orthosis based suppression.

At the second section, which occurred later at the same day, four surface electrodes were positioned in agreement with protocols established by "Surface EMG for Non-Invasive Assessment of Muscles" (SENIAM), two on wrist flexor muscle, and two on wrist extensor muscle, to record EMG activity in PD patients and the control volunteer. The protocol followed the sequence of movements previewed in figure 4.

(a) Isometric (b) Grabbing a cup (c) Pinch

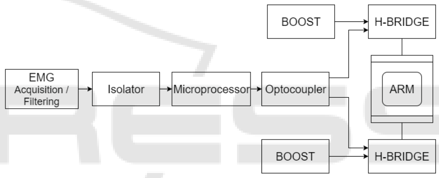
Figure 4: Applied protocol for signal acquisition.

First of all, PD patients were oriented to keep both arms extended in front of the body in isometric position as shown in figure 4(a) then the first EMG data set was recorded. The second EMG acquisition was performed based on figure 4(b) where PD patients were challenged to develop a small movement of grab a cup and move it to the mouth. The third and last set of EMG data was recorded with the patient doing repeatedly the pinch movement as represented in figure 4(c). The equipment used for all acquisition during this stage was DELSYS Trigno EMG system.

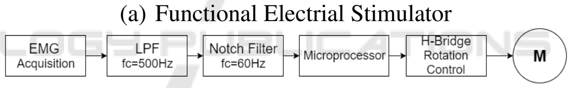
4 HARDWARE DEVELOPMENT

Following the acquisition stage, the hardware and software development stage had started. The goal here was to develop an EMG acquisition and stimulation hardware and a software responsible for tremor detection and suppression.

The hardware was developed inspired by arduino's shields. In order to achieve a modular project, each one of projects represented by 5(a) and 5(b) were built by modules. The first module is a preprocessing board which integrates a differential amplifier (INA121P) for EMG signal acquisition, a low pass filter with cut-off frequency of 500Hz in order to attenuate signals other than EMG, and a notch filter tuned in 60Hz to attenuate power-line noise. Both implemented with UAF42 IC. As a second step EMG signal is digitalized by the microprocessor A/D converter, buffered and processed to assess tremor frequency. The microprocessor chosen was STM32F407. The H-bridge circuit is used in both alternatives FES and mechanical. In the FES system it is responsible for apply a biphasic current-controlled impulse to patient's wrist extensor or flexor muscle. For the orthosis system, H-bridge is responsible for change direction of motor torque. The boost circuit is used only for FES system, because its need for a higher voltage to apply stimuli to the arm.



(a) Functional Electrial Stimulator



(b) Orthosis

Figure 5: Block Diagram of both approaches studied.

An orthosis was also developed using 3D printing technology as shown in figure 6.

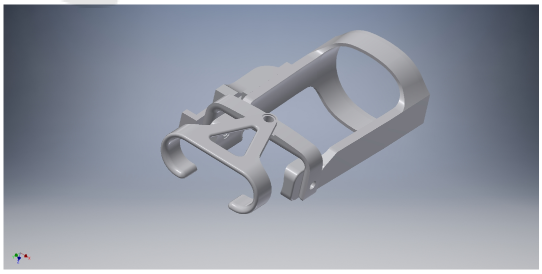


Figure 6: Mechanical prototype for wrist flexor/extensor tremor suppression.

5 SIGNAL PROCESSING STRATEGY

EMG raw signal from volunteers was first treated at at a preprocessing board. EMG signal was passed through a low pass filter with cut-off frequency of 500Hz, at this step the goal was attenuate frequencies higher than those that characteristically compose EMG signals. After that EMG signal was treated with a notch filter in order to attenuate 60Hz component from power line. Convert analog EMG into digital was next step as shown in figure 7 flowchart. The digitalized EMG signal was then stored into a buffer in order to be offline processed. The choice of an offline processing was to avoid stimulus related artifacts and muscle response artifacts mentioned by Widjaja et al. (2009).

As the flowchart indicates, signal was normalized and passed through a Fast Fourier Transform (FFT) in order to assess tremor frequency. According to Jankovic and Tolosa (2006), Ruonala et al. (2013), and Helmich et al. (2012) tremor frequency may vary from patient to patient, but the most common range is 4-10Hz. FFT results were analyzed in the interval 4-10Hz to find the maximum value that FFT assumed, and for consequence tremor frequency.

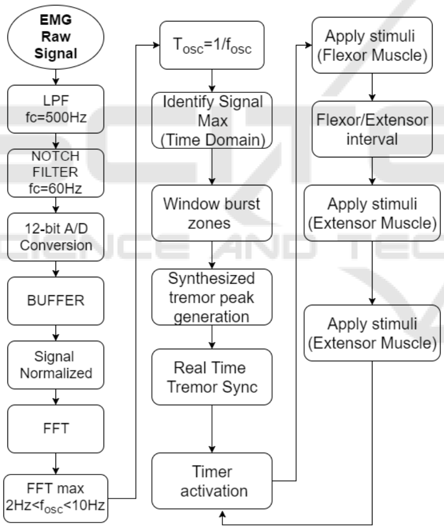


Figure 7: EMG signal processing flow chart.

Using the EMG signal in time domain, the maximum point was identified, and using tremor period calculated through FFT previous steps, impulses were synthesized based on maximum position and tremor period. After that the goal was to synchronize either FES or orthoses actuator with tremor manifestation. It was achieved using an interruption port and timers from STM32F407 discovery microprocessor board.

For FES system, circuits were designed to apply electrical stimulus to wrist flexor muscle, a count-down timer was implemented and stimulus was applied to wrist extensor muscle 90ms later. To orthosis system, circuits implemented change rotation direction of an electrical motor to oppose wrist movement cause by flexor contraction and 90ms later due to extensor contraction.

6 RESULTS

During the signal analysis developed to better understand PD dynamics, EMG signals from wrist extensor and flexor muscles were acquired with DELSYS Trigno EMG system. Considering first a time domain approach, as presented in figure 8, exists a delay in activation between flexor and extensor muscles which for our three volunteers is approximately 90ms.

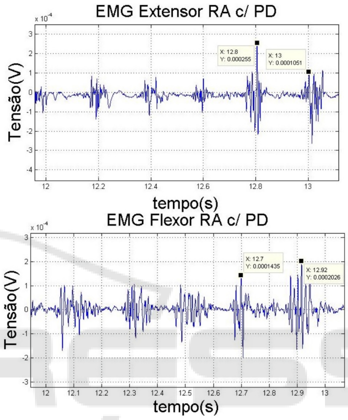


Figure 8: Delay between extensor and flexor electrical activity in the right arm (RA).

For the development of an orthosis or a FES system was important to figure out tremor oscillation frequency which was assessed through a FFT. Figure 9 represents FFT analysis of an volunteer with PD and a control volunteer. Although signal on the time domain (bottom) analysis is unclear, on the frequency domain is possible to verify the existence of a 4.55 Hz which was called oscillation frequency. The frequency found is also supported by other studies presented before.

EMG signal was then squared in order to study energy features and to establish tremor zones as presented in figure 10. One important aspect considered was how consistent signal was in time, keeping through relatively long periods of 20 to 30 seconds tremor pattern. To test graphically this consistence, impulses were synthesized and placed based on the period of oscillation, in this case calculated by $T_{osc} = \frac{1}{f_{osc}}$. The result can be seen in figure 11.

In this analysis was possible to identify that synthesized impulses placed every T_{osc} interval were consistently into tremor zone, which is an indicator of

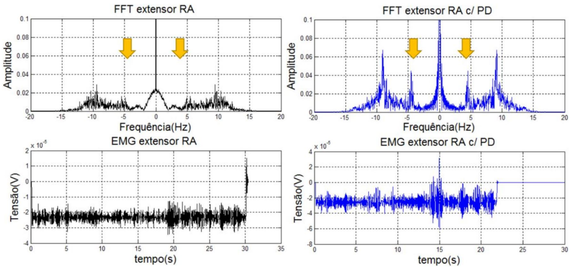


Figure 9: Fast Fourier Transform Analysis wrist extensor right arm (RA).

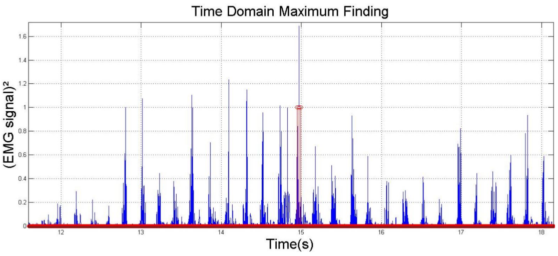


Figure 10: Tremor zones definition based on EMG energy.

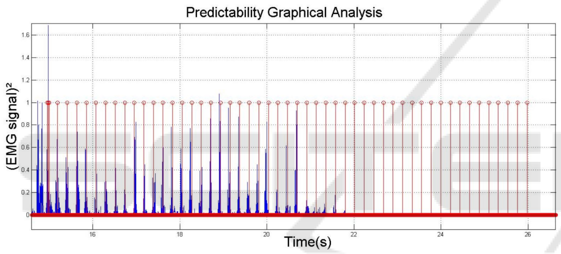


Figure 11: EMG signal power and predictability analysis.

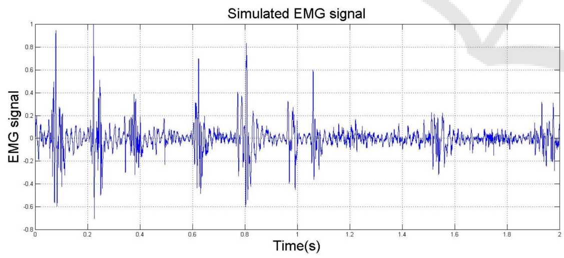


Figure 12: Simulated tremor EMG acquired with developed hardware.

consistence and predictability. Based on this result the synchronization strategy chosen was a peak detection of EMG signal. This peak detection start all timers in order to apply stimulus on FES case, or apply opposed torque for orthosis case. Figure 12 represents a simulated tremor EMG acquired with hardware developed by our team and it presents all requisites for the following stages of this work.

The project is now entering in final stage with clinical tests in partnership with neurology department of Federal University of São Paulo. In this stage the goal is to test the prototype in real PD patients with medical supervision. Fine adjust are expected to be necessary due to each volunteer characteristics and sensibility to electrical stimulus. Variables such as stimulus frequency and applied torque to wrist joint can be easily adapted to each patient through software coding.

It is also important to emphasize some differences among this work and approaches studied before. Differently from Zhang and Ang (2007) on FES, this work is focused on wrist flexion/extension tremor instead of elbow joint related tremors, and uses an offline processing in order to avoid EMG stimulation artifacts. Filters for artifact suppression as proposed by Zhang and Ang (2007) are planned for a next stage. Some works such as Maneski et al. (2011) consider essential tremor (ET) and PD as targeted diseases. However, this work focus only in PD in order to keep the boundary conditions well established, once according to Thenganatt and Louis (2012) tremors amplitude may be 2.7 times higher in PD. Diferently from all cited works, our team is also developing an electrical stimulator and that will bring more flexibility to develop stimuation protocols.

Considering the mechanical approach for tremor suppression some differences are also important. Rocon et al. (2005) in his study did not use EMG as signal for controlling orthosis. Later Maneski et al. (2011) discussed that only motion sensors may not be enough to assess frequency and phase of a tremor during tremor suppression stage. Therefore, our work in the first stage uses EMG as a control signal, and for modeling purposes.

In conclusion, completely customized hardware and software were developed to bring flexibility to PD tremor suppression protocols. A processing algorithm was implemented to control FES and mechanical orthosis. The clinical tests will begin soon, then fine adjustments may be needed for each patient and all hypothesis related to PD dynamics can be validated.

Future work comprehends insertion of an accelerometer for both approaches (orthosis and FES) to close the control loop and possibly achieve better results through tremor energy analysis.

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